Interviews with the Experts

Pediatric MDS: A Primer for Parents

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Although rare, pediatric myelodysplastic syndromes (MDS) can be a bewildering challenge for parents. Dr. Inga Hofmann applies her expertise to this subject with information and advice for parents of pediatric MDS patients.

Are the symptoms of pediatric MDS the same as MDS that normally strikes older patients?

There can be some similarity, but the large majority of pediatric MDS patients are at first asymptomatic. Their diagnosis is made as an incidental finding, meaning they go to a pediatrician for a checkup or sports physical and are found to have low blood counts that are worked up further, and from that, an MDS diagnosis may be given, after other possibilities have been ruled out. There is a subset that does present with symptoms, often related to cytopenias (low blood cell counts) that are seen in adults. Whereas the most commonly seen adult or elderly patient symptom is anemia, with the pediatric population, it is low platelet counts (thrombocytopenia) followed by low white blood cell counts (neutropenia). Anemia can be seen as well, but less commonly than in the adult.

Are certain MDS subtypes seen more often in children than in the older population?

Most pediatric MDS present as a low-grade subtype called refractory cytopenia in childhood (RCC), which shows marrow dysplasia (abnormal blood cells the bone marrow), but no increase in blasts, which are the leukemic cells that give us an indication that there could be potential for disease progression and transformation into leukemia. Some pediatric patients present with more advanced disease, including refractory anemia with excess blasts (RAEB-1 or RAEB-2) or progression to acute myeloid leukemia (AML), but that is less common than those who present with RCC. Most of the time, newly diagnosed patients are older children or teenagers, but MDS can present at any age, and we see cases in infants and very young children.

Is it possible for pediatric MDS to be overlooked as a diagnosis because it is rare in the general population and even rarer in children?

It is possible, and often it is not an easy diagnosis to make. Being a rare condition, there are quite a few doctors and other health care practitioners who have never seen pediatric MDS. It could be mistaken for other bone marrow failure disorders including aplastic anemia or other inherited bone marrow failure syndromes. A very detailed diagnostic workup including laboratory tests and a detailed review of the bone marrow aspirate and biopsy slides by an experienced pathologist is very important.

Is pediatric MDS more often linked to inherited genetic factors than MDS in the older population?

There is a significant subset of pediatric patients where this may apply. Through research efforts, we recently discovered that patients with a mutation in a gene called GATA-2 have a familial predisposition to MDS. They might have inherited this genetic defect from either parent or it might have occurred in the patient de novo, meaning none of the parents have it. In either case, the patient with the GATA-2
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continued from cover

mutation can pass the mutation on to their offspring. Therefore, genetic counseling for these patients is very important.

It is important to remember that a familial predisposition is not always obvious by a routine examination or family history. Therefore, a very detailed family history can be very helpful in uncovering potential clues. A genetic counselor can help with this. Given the significant health implications of GATA-2 mutations for the patient and family members, testing for this mutation should be considered in all pediatric patients with MDS or bone marrow failure conditions of unknown etiology.

Is the treatment approach the same as used for adult MDS patients, or are there any treatments that have a designated use for pediatric MDS?

A hematopoietic stem cell transplant is the only potential curative therapy, but that is not always possible in adults. With children, we almost always consider a stem cell transplant, as it is the only curative treatment. Children have the potential of a long life ahead them and are much more likely to tolerate the transplantation process better than an adult or elderly patient. The other difference is that the adult population is frequently getting therapy with hypomethylating agents, such as azacitidine (Vidaza®) or decitabine (Dacogen®), and while that often leads to longer survival in these patients, it is not a curative therapy. Most of the time, pediatric MDS would be treated with hypomethylating agents only in very special circumstances, or as a palliative care treatment option or clinical trial.

Is there a better chance of finding a matched or partially matched donor for a stem cell transplant for a pediatric MDS patient, and are complications from a transplant more or less common?

The chances of finding a possible matched related or unrelated donor for children or adults are similar. There is about a 20-25% chance that a sibling will be a match. One difference in children is that we prefer stem cells from bone marrow over peripheral blood, which means the donor’s cells have to be collected in the operating room under anesthesia. If no suitable living donor is found, we also consider cord blood transplants, and given that our patients are smaller, we might have better luck finding suitable cord blood with a sufficient number of cells.

Complications such as organ toxicities and graft versus host disease can be seen in children and adults. However, in general, children tolerate a stem cell transplant better than adults with lower rates of serious complications and death occurring from toxicity.

Is the likelihood of recurrent MDS or onset of a second bone marrow failure disease which sometimes occur with adult patients, also possible in children?

Most pediatric patients with low-grade MDS, prior to progression to a leukemic state, can be cured by the transplant. The main concern is the transplant toxicity they have to overcome. Pediatric patients who have advanced to pre-leukemia (RAEB) or AML are more difficult to treat, and we have seen relapses in those patients more often than with low grade RCC, who rarely relapse. We suspect that at least some patients with pediatric MDS have an underlying inherited condition that predisposes them to develop MDS. We also know that patients with inherited bone marrow failure syndromes such as Fanconi anemia, dyskeratosis congenita, or Shwachman-Diamond syndrome are at increased risk of developing MDS and AML. So, the inherited condition or predisposition happens first, then the patients develop MDS. For example, there could be MDS following aplastic anemia that did not respond to immunosuppressive therapy. This is rare, but can happen.

What should parents keep in mind about the promise and perils of using social media or the Internet for learning about pediatric MDS and for related online research?

All parents are different, and for some, online resources and social media are helpful for processing the large volume of information about the disease and the diagnosis and treatment problems they may encounter. I don’t discourage parents from using it, but I think it has to be viewed with some healthy skepticism. The best idea is to focus on acknowledged websites with reviewed, sound information. Anything seen on other websites or social media should be brought to the treating physician before it is accepted as an absolute truth. Patients, families, and health care providers should work through these questions together to make sure the information is applicable to the child. Following misinformation down the wrong track could lead to misconceptions about treatments, goals, and expectations. One of the most important things in the care of a child is building a good partnership and open communication between the patient, family, and clinical care team that understands the needs of the family and child.

What should parents remember about pediatric MDS?

It’s a rare disorder, so it is important to assure that an accurate diagnosis by an experienced team has been made. Pediatric MDS can be cured by a stem cell transplant. Novel technologies and ongoing research efforts will allow us to understand more about the etiologies of the disease and potential new therapies. It is important that the family feels comfortable with the level of experience and support they get from their health care team. Reaching out and asking questions will help them to better understand their specific situation and make the right decisions for the child.
MDS Clinical Research Consortium Presents at ASH 2014

The MDS Clinical Research Consortium (MDS CRC) is dedicated to advancing care for MDS patients through state-of-the-art collaborative clinical research. It combines the expertise of many leading MDS researchers with the capacity of their world-class institutions to share data and advance research. This unique research consortium is funded by the Edward P. Evans Foundation. Participating institutions include: Cleveland Clinic Taussig Cancer Institute, Dana-Farber Cancer Institute, MD Anderson Cancer Center, H. Lee Moffitt Cancer Center and Research Institute, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, and Weill Medical College of Cornell University.

At the recent 2014 American Society of Hematology (ASH) annual meeting, the six principal investigators at the participating institutions, along with 11 current and former Edward P. Evans Fellows who work with the principal investigators on MDS research, brought evidence of their scholarship to bear. CRC-funded principal investigators authored or co-authored 106 abstracts accepted for ASH 2014. Edward P. Evans Fellows authored/co-authored 32 accepted abstracts and one fellow was co-author on a plenary session, a prestigious position for an early career researcher.

Shown here is some of the work presented by the fellows that AA&MDSIF has profiled over the past year.

- **Akinori Yoda, MD, Dana-Farber Cancer Institute**
  Dr. Yoda presented work on genetic myeloid and lymphoid neoplasms and leukemia that have the potential to be targeted through application of inhibitors.

- **Lukasz Gondek, MD, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins**
  Dr. Gondek presented his work on genetic complications in the ‘hedgehog’ signaling pathway that indicates progression of MDS and the potential for leukemia.

- **Yue Wei, MD Anderson Cancer Center**
  Dr. Wei presented her work on down-regulation of various genetic expressions and patients’ responses to hypomethylating agent (HMA) treatment, linked with patient survival in MDS. She was also involved in work presenting a mouse model of telomere dysfunction within MDS.

- **Eric Padron, MD, H. Lee Moffitt Cancer Center and Research Institute**
  Dr. Padron presented work on malignancies among MDS patients, comparing treatment with or without lenalidomide (Revlimid®) and contributed to a study looking at prognostic factors and outcomes of thrombocytopenia related to MDS and AML.

- **Amer Zeidan, MD, former Fellow, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins**
  Dr. Zeidan presented the work of the MDS Clinical Research Consortium that evaluated risk models in predicting outcomes of patients with higher-risk MDS treated with HMA.

- **Coleman Lindsley, MD, former Fellow, Dana-Farber Cancer Institute**
  Dr. Lindsley presented work on genetic alternations in AML and the age related adverse outcomes of clonal hematopoiesis.

ASH 2014 – Bringing the Latest in MDS Research to You

**Scientific Symposium**
AA&MDIF and Cleveland Clinic cosponsored “MDS and MDS/MPN: Past, Present, and Future.” This event featured an internationally renowned faculty and drew an audience of nearly 500 hematologists and other allied health professionals.

**Poster Presentation**
Dr. Aaron T. Gerds with the Cleveland Clinic provided an oral poster presentation of the collaborative study on communication conducted by AA&MDSIF and Cleveland Clinic. The poster described differences between how patients and their physicians view reasons for treatment discontinuation.

**Research Summary**
Read our patient-friendly summaries on the most important new MDS research reported at ASH.

**Interviews with the Experts**
Dr. Benjamin Ebert highlighted several studies further defining the role of genetic mutations in determining treatment options for MDS and how genetic information may be used to predict which MDS patients would benefit most from bone marrow transplantation.

Learn more at www.AAMDS.org/ASH2014
Dealing with End-of-Life Challenges

AA&MDSIF focuses much of our energy on providing answers to your questions about your bone marrow failure disease. We are here to connect you to sources of support to help you on your journey with aplastic anemia, MDS, or PNH. And to offer a sense of hope for the future, we encourage and support research to find better treatments and possible cures. Yet we are acutely aware that these diseases are life threatening, and sometimes, those we have come to love and consider part of our greater “family”, our patients, die. We have added new resources to our website (visit www.AAMDS.org/EndLife) to help you find the answers and support you need when you or your loved one is facing the end of life.

Are You Tired?

AA&MDSIF is working with the MD Anderson Cancer Center to study “Fatigue, Symptom Burden and Health-Related Quality of Life of Patients with Bone Marrow Failure Diseases.”

We know patients with bone marrow failure diseases experience fatigue. However, most of the scientific studies about fatigue are based on research with patients that have solid tumor cancers, not MDS. We to learn more about your experience with fatigue so we can better meet your needs. Working with Dr. Carmen Escalante at MD Anderson, AA&MDSIF is conducting a research study to learn about fatigue and other symptoms in our patient community. This information will help us improve patient services and programs. Interested in sharing your experience? Participants can go to www.AAMDS.org/FatigueStudy to complete the online questionnaire.

MDS timeline

A look at the emerging awareness and classification of myelodysplastic syndromes over past 40 years

What do you remember from the 1970’s? The end of the Vietnam War? Watergate? Disco music? You may be surprised to learn that our current understanding of MDS began in the ‘70s. Although related studies were conducted for many decades prior, the myelodysplastic syndromes (MDS) were not well known. In the early years, it was further complicated by common use of the term ‘pre-leukemia’ to describe it. The relationship of MDS to similar hematologic conditions was poorly understood. “You’ve come a long way baby” was a marketing slogan introduced in the late 1960s. Looking back, we could say the same for our understanding of MDS today.

1976: In the beginning, there was FAB

About 40 years ago, a group of of seven researchers began to study differences in leukemia cases. In 1976, this group–(known as FAB, for French, American, British) published research on two conditions (CMML and RAEB) that could be confused with acute leukemia. These conditions were considered pre-leukemic states and were called ‘dysmyeloipoietic syndromes.’

1982: FAB - MDS is first formally defined and classified

In 1982, the FAB group established the term ‘myelodysplastic syndromes.’ They introduced classification categories used to assess MDS that endured until the end of the century. Based on the percentage of blasts (young, immature blood cells) in bone marrow and blood, the FAB system had five MDS categories, or subtypes. Yet investigators soon realized there was a need to better predict how MDS will act as time passes.

1997: IPSS points to prognosis

A study of over 800 patients published in 1997 was the basis for the International Prognostic Scoring System (IPSS). Even today, the IPSS remains the most widely used system to estimate severity of MDS and probable survival terms.

IPSS is based on three criteria: like FAB, it includes percentage of blasts in bone marrow, but it also includes two other measures. One is karyotype (also known as cytogenetics) or abnormalities in bone marrow chromosomes. The other is cytopenias, which are low blood cell counts of any or all three types of blood cells (red blood cells, white blood cells, or platelets). From these combined criteria, a numerical score is drawn.
That score is associated with one of four risk categories: low, intermediate-1 (grouped together as low-risk MDS), and intermediate-2 and high (which are grouped as high-risk MDS).

2001: WHO introduces a highly refined MDS classification

The World Health Organization (WHO) first introduced their classification system in 2001. This described additional MDS subtypes (removing and adding some categories to the original FAB group). This resulted in a total of ten MDS classification categories.

2008: Researchers further refine the WHO classification to the current standard for distinguishing and describing MDS subtypes

Less than ten years after it was first produced, the WHO classification system now has 11 subtypes, including one for MDS that does not fit any classification and one for rare pediatric MDS cases. This remains a widely used classification of MDS.

2012: A revisitation leads to a revision, and the IPSS-R is launched

Based on a large study of over 7,000 patients, the most recent MDS classification system is the Revised International Prognostic Scoring System (IPSS-R). The IPSS-R includes increased importance assigned to cytogenetics. Risk categories expand from four to five with this revised system. However, both IPSS and IPSS-R are limited in the respects that they only account for newly diagnosed cases that have not received any treatment. Neither account for the effect of other diseases or conditions a patient may have. As more patients and physicians become familiar with it, it is anticipated that IPSS-R will replace IPSS.

2015 and beyond

As research continues, the standards for describing the many MDS subtypes and systems for comparing their relative severity continues to evolve. Yes, we have come a long way in understanding and classifying MDS. Using these advances in classification allows more precise treatments to be developed.

“MDS research is more exciting than it has ever been by far. We have more good science occurring right now than we have ever had.” – Dr. Benjamin Ebert, Dana-Farber Cancer Institute

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Story of Hope
Linda Dans-Zagami - Stem Cell Transplant Survivor Endures Setbacks and Finds Strength

Who would have thought that my journey would begin with a stroll through the park! On a beautiful spring night in 2010, I twisted my ankle while walking through the park. When the swelling persisted, I went to my doctor, who conducted a routine blood test and determined that I was anemic, and I was instructed to take iron. The rest of the year was spent trying to figure out why my ankle was still swollen.

Other issues surfaced. I was very tired -- not just tired, but bone weary. Why did I have to stop and catch my breath while walking through the airport? Why was I becoming overly emotional? Why was I getting palpitations, why did I have no appetite, and why was I losing weight? I began making excuses – I’m getting older, I’m working too hard, I’m not sleeping well.

Nearly a year later in March 2011, another blood test was conducted, and I was referred to a hematologist. During the visit, the hematologist asked how I was functioning with a hemoglobin level of 6.6. This is almost half the normal number for females, and it turned out that day was the beginning of many transfusions. Additional tests were ordered – colonoscopy, endoscopy, small bowel series, liver MRI, and a bone marrow biopsy. Less than two weeks later, on April 28, 2011 came the diagnosis of myelodysplastic syndromes (MDS). I was numb… MD-what? Never heard of it! How could I get something I couldn’t even spell?

The next day found us at Hackensack Medical Center where the disease was explained to us, and, our questions were answered. I was only 58 and told I had a mild subtype of MDS, and so I probably wouldn’t need a transplant for three to five years. In the meantime, I was to meet the transplant team, receive shots to aid in blood cell production, and continue to get transfusions as needed. Those shots and transfusions continued throughout the summer. Although the diagnosis and subsequent treatment weighed heavily on our shoulders, my husband and I continued to go about our everyday routines.

When we weren’t getting the desired results with the shots, the treatment team was going to look into other drug options. Before we could explore these options, my spleen started to become enlarged, and it was apparent that it was time for a stem cell transplant. So much for the three to five year wait!

And so a whirlwind of activity began. On October 16, I was back at Hackensack Medical Center to begin the transplantation process. First, I needed a donor, and my brother and sister were more than willing to be tested. My brother Ray was disappointed that he wasn’t a match. But my sister Christina was a match – what wonderful news. My sister is 17 years younger than me, married, works as a teacher, has twin girls, and takes care of our father. She has a full plate, so was it too much to ask of her? Of course not!

On October 31, chemotherapy began, followed by radiation to shrink the spleen. Visits to various doctors took place before being admitted for the transplant, which was to take place on December 6, but, my sister’s cells had begun to coagulate, and they needed to be filtered before I could receive them. On December 7, 2011, I received the gift of life, courtesy of my sister. My hospital stay was not always a bed of roses. I had some very rough days and nights, but through it all I had faith – faith in myself, my doctors, and my God that I would make it. Then on December 26, I was allowed to go home. How wonderful, but also how scary!

The transplant was over, so things will be okay, right? Not so fast. My platelet levels were very low – below 30, and I still required frequent transfusions. I was so weak that I could not get out of bed without assistance. I also experienced graft-versus-host disease (GVHD) of the gut and skin. My doctor thought I might need a reduced intensity transplant. Fortunately, my platelet levels slowly rose, and the GVHD symptoms eased, so this additional transplant was not required. It has now been three years since my transplant. My platelet levels are still on the low side, but this might be my new normal. I still take a very low dose of steroids for GVHD.

My dear husband has been my rock throughout the whole process, making sure I did everything needed in order to ensure a speedy recovery. He begged me to eat when I had no appetite, encouraged me to get up and move, and endured my fits of anger. I couldn’t have done it without him.

My journey has hit several bumps along the way, such as a recent hospital stay for parainfluenza, but I have found that my MDS journey has been easier than some and tougher than others. My life will never be the same emotionally or physically, but there isn’t a day that goes by that I don’t thank God that I’m here today. As this journey continues, I try to have a full life by working full time, having sleep-overs with my six year old twin nieces, Nicole and Sophia, going on cruises, and spending time with family and friends, especially my adult niece Alicia and teenage nephew Kevin.
Meet Dr. Michael Greenberg, an AA&MDSIF Guardian of Hope

Michael Greenberg, MD, MPH, is committed to making an impact on the lives of people with bone marrow failure diseases like his young daughter, Alexandra Jane, who died from a form of aplastic anemia. His efforts helped to shape the Aplastic Anemia & MDS International Foundation into the world’s leading non-profit organization dedicated to supporting patients and families living with aplastic anemia, MDS, PNH, and related bone marrow failure diseases. Now, his generosity will help ensure that AA&MDSIF will continue to provide answers, support, and hope for many years to come.

A medical toxicologist and tenured professor of emergency medicine at Drexel University College of Medicine in Philadelphia, Pennsylvania, Dr. Greenberg’s interest in AA&MDSIF began when he attended a patient and family conference in 1994 and met Marilyn Baker, the Foundation’s first executive director. “I found her to be so dedicated to making the organization a success. Her influence encouraged me to become involved, first as a member of the board, and then to serve as its Chairman,” said Dr. Greenberg. He began his eight years of service with AA&MDSIF in 1995 and served as Chairman from 1996 through 1999. “Our priorities at the time were to make sure that the organization would thrive. We set benchmarks: reorganize our finances, create a meaningful newsletter, develop a patient list, work with thought leaders and align our institutional priorities with them, and grow our constituency by working with community hematologists,” he said.

“Now the organization is first class. It’s gratifying to see what we did to help the organization come to the place it is now. The leadership is very insightful. The current Board of Directors and Executive Director, John Huber, are doing an outstanding job and are using the Foundation’s resources wisely,” Dr. Greenberg added. “It’s unusual to go from grassroots to the organization it is today. It’s a tribute to everyone who was there from the beginning, and to the hard work of everyone there today.”

Dr. Greenberg has also demonstrated his continuing commitment to the future of AA&MDSIF with a legacy gift through his estate. The gift, he says, is “a reflection of the need going forward and the continuing research that must follow. We will still need support, we will still need research. People who have these diseases, or who are touched by them – it is their hope that the result of our work will be better treatments and a cure.”

His legacy gift, along with his many other contributions to AA&MDSIF, serve as a tribute to his daughter. Says Dr. Greenberg, “I hope other people will be able to do the same because the organization needs it. There is a lot of work to do over the next decade or more, but AA&MDSIF is a tremendous resource for this effort. Prepare to be amazed in the future.”

How You Can Also Make a Difference
Learn how a gift in your will or estate can fulfill your charitable goals and help AA&MDSIF for generations to come. Visit www.AAMDS.org/Giving or contact Pam Spears at (301) 279-7202 x122 or spears@aamds.org. Request a free, no obligation booklet: Your Personal Estate Planning Record.

Always rely on your attorney or other qualified advisors to guide you through your estate planning process.

AA&MDSIF Executive Director Announces Retirement

Aplastic Anemia & MDS International Foundation (AA&MDSIF) Executive Director, John Huber, has announced that he will retire in July, 2015, after nearly eight years with the organization.

Huber became AA&MDSIF Executive Director in 2007. During his tenure, he developed a track record of creating and implementing new strategies, securing financial resources for patient education and research programs, expanding programs, and developing patient-centered, patient-focused services. He retires with more than four decades of leadership service with non-profit organizations.

“We are so thankful for John’s strong leadership and dedication to AA&MDSIF,” said AA&MDSIF Chairman Kevin Lyons-Tarr. “Under his leadership, the organization has grown five times in size since 2007, and he has laid a strong foundation on which the organization will continue to grow in support of our patients and their families,” said Lyons-Tarr.

“It has been an honor and a privilege to serve the thousands of patients, families, and caregivers who come to AA&MDSIF for answers, support, and hope. We are serving more people in more ways than ever before and I am extremely grateful to our Board of Directors, staff, supporters, donors, corporate partners, medical advisors, and our many volunteers who have made it possible for us to achieve this tremendous growth,” said Huber.

The AA&MDSIF Board of Directors will embark on a thorough and comprehensive search for Huber’s successor. The executive search firm, Korn Ferry, has been retained to conduct the nationwide search.
In Print

**Fact Sheets**
- AA&MDSIF Social Media
- Bone Marrow and Stem Cell Transplantation**
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- How to Evaluate Health Information on the Internet
- Iron Overload
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Support Connection

Our one-to-one Support Connection is a national network of trained volunteers, including patients, caregivers, and family members who offer information, personal experience, coping strategies, problem solving skills, and informational resources. To connect with a Support Connection volunteer, call (800) 747-2820, option 1 and speak with our patient educator, who will match you with one of our volunteers. You can also email info@aamds.org.