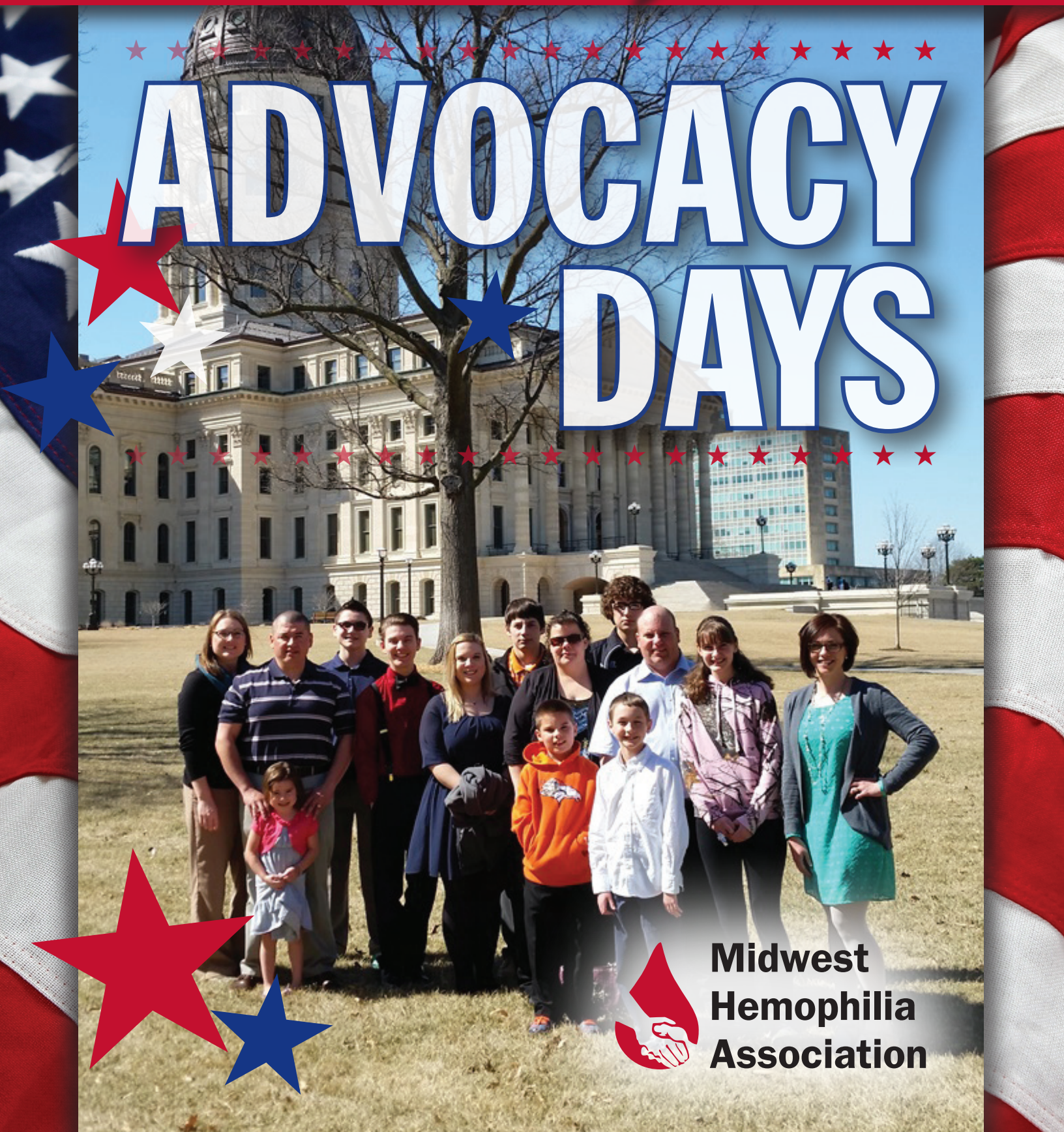
CHAPTER Factors

SPRING 2015



ADVOCACY DAYS

Midwest Hemophilia Association

Chapter Factors is published by:

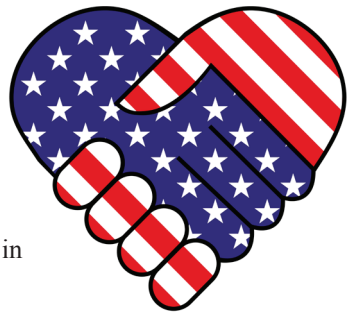
The Midwest Hemophilia Association

PO Box 412866
Kansas City, MO 64141
816-479-5900
www.midwesthemophilia.org

News and Notes

Advocacy is an often used word in our community. There are sessions at conferences, webinars are held and many articles written about it. In the past months, I have had the privilege of witnessing it. First, in Washington D.C., then on back-to-back days at the Missouri and Kansas Capitols.

It was inspiring to see our community members, adults and children, roaming around the legislative offices and Capitol halls meeting with legislators and sitting in on the general assembly learning more about how our legislative branches conduct business. It's one thing to attend a meeting on Advocacy at a conference but a completely different animal when you are sitting in a legislator's office telling your story. Some of our first-time attendees were nervous, and that is to be expected. But once they got it in their heads that the legislators they were meeting with were just people like them, it was easier for them to tell their own personal story and ADVOCATE for their family and others in the hemophilia community.



You will read two different articles in this edition regarding our Advocacy Days. I hope, after you read the articles, that you too will be inspired to attend next year's Advocacy Days. And as I have said many times before, Advocacy is more than just meeting at the Capitol one day a year. Advocacy is building a relationship with your elected official so that your message can be heard year-round. MHA is working on a comprehensive Advocacy Strategic Plan that will provide an avenue for our community members to get involved. The first step is for you to know who your legislator is in your district. Take a second now and go online to *www.openstates.org*. Type in your local information and voila, up comes all your elected officials. It's that easy.

In the coming months, we will provide you with a series of strategic measures to help you establish yourself with your local legislator, as well as provide you with information about the issues that affect you and your family. Finally, a very sincere thank you to everyone who attended our Advocacy Days. You are to be commended for taking time from your busy schedules.

Mark Cox
Executive Director

2015 MEMBERSHIP APPLICATION

Name: _____

Address: _____

Phone: _____ Email: _____

☐ Individual/Family ($25) ☐ Corporate ($100)
☐ Additional Contribution: $_____

Amount Enclosed: $_____

Please mail this form and your membership fee to:
Midwest Hemophilia Association • PO Box 412866 • Kansas City, MO 64141

Or pay online at: ***www.midwesthemophilia.org***

THANK YOU FOR YOUR SUPPORT!

QUICK NOTES

Message from the President

Hello everyone! First of all, I would like to introduce myself and tell you a little bit about my background. My name is Aimee Tempera and I have been part of MHA for many years. I have an uncle, cousin, two brothers and now a son with Hemophilia A. Growing up around hemophilia I thought I was able to handle everything that came with it, after all, just infuse and you're done right? I was pretty confident with what to look for, dealing with doctors and the difficulties that might come along with it. However, no one told me all the emotions were different when it was your own son. I felt like a novice, like I had just found out about hemophilia and what it all entailed. Even with all my years with family members, my brothers never went through what my son just went through. Talk about your world being upside down. Fortunately, I had and still have an amazing support system through family, friends and MHA. So let me tell you my MHA beginnings.

At first I was a participant. I went to Family Fun Fair (FFF) and the local events. Then as time started to go on, I decided to do my own thing. I didn't go to FFF or events as often because there was college, and guys of course. Then cycle back around to post BA (in business Management) I started to come back around again. After one FFF someone mentioned I should run for the Board. Well folks, here I am! I have been on the Board of Directors for 5 years and have watched this Board transform. We have grown as a Board and an area. Did you know that we even have events in western Kansas now?

I am here to tell you that I have seen first-hand what a small group of people that care can do... which made me think, "if just a few people can make this big of a difference, what could the community as a whole do?" There are so many people with talents that we don't even know about. I am not asking for monetary contributions, I am asking for your time, your stories, your passion, your involvement, anything to make a difference. Show the outside world your struggles and how you have overcome them. Show them your strength, your courage, and your discipline. Because whether you choose to acknowledge it or not, you have accomplished it all!

I love everything about this community, and have so much passion for this organization. I have made a commitment to give whatever talents I could to help this organization thrive. I want MHA to be around for my son when it is his time and for his children after that, and the work starts with us. I am asking that everyone take this journey with me and together, let's show the world what we are made of! If you would like to reach me my contact information is on the first page of this newsletter.

— By Aimee Tempera, President

Scholarship Applications Now Available

They say nothing in life is free, however I would disagree, as there are some things that only take a little effort on your part. If you are planning on sending a child to college or you are attending college, please make note of the offers detailed here for possible scholarship money available.

The Midwest Hemophilia Association is pleased to offer a $1,000 scholarship for post secondary education to a person with a bleeding disorder who lives in the organization's service area of western Missouri and eastern Kansas. The scholarship is for continuing education at a college or trade school. The scholarship will be applicable to the 2015-2016 school year. The funds may be used at the discretion of the recipient (i.e., books, tuition, room and board, etc.)

The application is available online at

www.midwesthemophilia.org. Completed applications must be received no later than June 1, 2015.

Additional scholarship opportunities are available for persons with bleeding disorders such as hemophilia and von Willebrand disease. Information about them is available at the National Hemophilia Foundation (NHF) at 1-800-424-2634 or check their website *www.hemophilia.org* for more information. Many of these scholarships are time sensitive so don't delay.

Pull for a Cure Coming to Ozarks

Guess what is coming to the Ozarks? Another walk? No. Another educational dinner? No. Pull for a Cure? YES!! The first annual Pull for a Cure!

This will be my first sporting clay event so I am excited to practice and help the hemophilia community raise funds for programs that help our families. I have three boys and two have severe hemophilia B. I love living here in the Ozarks, but sometimes we can feel left out or isolated when it comes to dealing with hemophilia, no HTCs, no knowledgeable medics, events that take place 3-4 hours away, etc. So when we have an event as cool as this one it gets me excited to be a part of it so that we can reach out to the surrounding community and also get the word out to the public about hemophilia. Plus, what a fitting event for this area.

The event will be held at the Ozark Shooters Sports Complex located at 759 US Hwy. 65, Walnut Shade, MO. The event will be June 6th with registration starting at 8:30 and the shoot starts at 10. If you need shells, the shop will have some to sell. Participants will have 100 targets to shoot. A continental breakfast will be provided, as well as lunch. There will also be prizes, raffles and awards! Create a team or come alone. You can reserve a hotel room at Hampton Inn at 200 Payne Stewart Drive located just 11 miles south of Ozark Shooters in Branson, MO. Bring the whole family and make a weekend out of it and enjoy Branson while you are here!!

So grab a shot gun, some shells, a few friends and head to Ozark Shooters to help raise awareness for hemophilia and support Midwest Hemophilia Association. You can find more details at *www.midwesthemophilia.org*. This will be an exciting event and we hope to see everyone there!!

— By Charity Meadows

HELPFUL NUMBERS

KANSAS CITY REGIONAL HEMOPHILIA CENTER
1-816-302-6869 • 1-800-236-1713
Dr. Shannon Carpenter • Dr. William Jennings • Dr. Brian Wicklund • Dr. Jill Moormeier
Katie Foote, LMSW • Andrew Wilson, RN, CFNP • Melissa Armanees, RN, CPNP

UNIVERSITY OF MISSOURI HOSPITAL AND CLINICS
HEMOPHILIA TREATMENT CENTER
1-573-882-9355
Dr. Barbara Gruner • Dr. Carl Freter • Dr. Tamara Hopkin • Lauren Grana, MSW

NATIONAL HEMOPHILIA FOUNDATION (NHF)
1-800-42-HANDI • www.hemophilia.org

2015 MHA CALENDAR

June 6, 2015
Ozarks Pull for a Cure – A Sporting Clay Event
Walnut Shade, MO

June 20, 2015
Springfield Education Event
Springfield, MO

August 2-7, 2015
25th Annual Summer Camp
Lake Doniphan Conference and Retreat Center
Excelsior Springs, MO

August 12-16, 2015
NHF Annual Meeting
Dallas, TX

August 28-30, 2015
Men's Retreat
Location to be announced

September 18, 2015
17th Annual MHA Golf Tournament
Drumm Farm Golf Club
Independence, MO

September 19-20, 2015
21st Annual MHA Family Fun Fair
Kansas City, MO

October 10, 2015
Kansas City Hemophilia Walk
Shawnee Mission Park
Shawnee, KS

October 17, 2015
Springfield Hemophilia Walk
Botanical Gardens
Springfield, MO

October 25, 2015
Wichita Hemophilia Walk
Exploration Place
Wichita, KS

Date TBD
19th Annual MHA Banquet and MHA Board Meeting
Kansas City, MO

Make plans now to join us!

September 18, 2015

17th Annual Golf Tournament

Drumm Farm Golf Club
Independence

September 19-20, 2015

Family Fun Fair

Sheraton Kansas City Hotel at Crown Center
Kansas City, Missouri

*Visit **www.midwesthemophilia.org** for more information on these events*

Midwest Hemophilia Association

SAVE THE DATE

WALK LOCATIONS AND DATES

KANSAS CITY, MO
Shawnee Mission Park, Shawnee, KS
Saturday, October 10, 2015

SPRINGFIELD, MO
Botanical Gardens, Springfield, MO
Saturday, October 17, 2015

WICHITA, KS
Exploration Place, Wichita, KS
Sunday, October 25, 2015

Join us at any one of the three Hemophilia Walks. We walk to raise Funds and Awareness for the bleeding disorder community. Your support is vital to our success. To form a team or donate go to:
www.hemophilia.org/walk and click on the MO icon

National Hemophilia Foundation and Midwest Hemophilia Association Present
HEMOPHILIA walk '15
Every step makes a difference
National Presenting Sponsor
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ADVOCACY

Coming Together as One Voice at Washington Days

By Brooke Connell

February 25-27 I was fortunate to join more than 300 attendees from 45 states in Washington, D.C. for the annual National Hemophilia Foundation (NHF) Washington Days. With this being my first time in D.C. and my first time speaking to senators and representatives about life with a bleeding disorder, I was excited and nervous, and really had no idea what to expect.

At six months old, I was diagnosed with Severe von Willebrand Disease. I have faced similar challenges as most in our community, but by educating myself, staying engaged with my hemophilia treatment center and actively managing my disease, I have faced those challenges with optimism. I hope by serving on the Midwest Hemophilia Association Board, I can encourage and inspire others with a bleeding disorder, and give them hope for their future.

The first day in D.C. was spent in training with the staff of NHF about the issues we would need to address in our meetings on the Hill. In addition to telling our individual story, we were also asking for:

Support in maintaining (not increasing, which the representatives appreciated) funding for the federal hemophilia programs;

Co-sponsoring legislation to improve access to skilled nursing facilities for hemophilia patients; and

Co-sponsoring the Patients' Access to Treatment Act (House) or introducing companion legislation (Senate) to increase access to life-saving drugs on specialty tiers by prohibiting insurers from imposing exorbitant co-insurance requirements on patients.

I was joined by MHA Executive Director Mark Cox and fellow board member Jennifer Rentschler for our day of meetings with Representatives Kevin Yoder and Mike Pompeo, and Senators Jerry Moran and Pat Roberts. We all left the Hill feeling encouraged and motivated to continue our advocacy efforts at the local level.

Washington Days concluded with a State Advocacy Workshop on Friday. We discussed the emerging trends and corresponding legislative efforts related to each that have the potential to affect the bleeding disorders community: out-of-pocket costs, preferred drug lists and standardization of prior authorization.

Wondering how you can become involved? Stay informed of legislative issues that will affect our community by engaging with NHF and MHA on social media, and watch for local advocacy efforts in Kansas and Missouri that you can participate in. Also, start planning now to attend Washington Days in 2016, and have your voice be heard!

Washington Days with NHF… A Dad's Perspective

By Matt Brown

So there I was sitting in Senator Roy Blunt's office in the Russell Senate Office Building smack in the middle of Washington, D.C. My son, Spencer, was beside me answering a question from Connor McGrath, Senator Blunt's legislative correspondent. Besides the feeling of pride at seeing my now 13-year-old son engaged in a meaningful adult conversation, I was also feeling a little awe struck. I had to ask myself, "How did you get here?"

"With a whole lot of walking" was the first thing that came to mind. My feet were feeling like lead weights and I was trying to catch my breath. (A little

DAYS

word of advice to insert here. If you only have 20 minutes to make it from Representative Billy Long's office in the House of Representatives to the Russell building, remember to grab your jacket before you leave. It is a long distance. And don't wear a belt or carry change in your pockets through security check points. They are easily forgotten when you are in a hurry--I hope someone gets good use out of my brown leather belt).

But seriously, my journey to Washington, D.C. started when my wife asked me if I would be interested in attending the annual NHF Washington Days with the Midwest Hemophilia Association. I felt honored to be asked and immediately chose to take my son along. After all, he was the one with hemophilia and this opportunity would never have existed had he been born without this particular bleeding disorder. Kind of ironic, isn't it?

Since the day our son was born it has been our motto that though Spencer has hemophilia, we will never let hemophilia have Spencer. That meant educating ourselves to become consumer experts in his bleeding disorder. And in time, educating our son on how to manage his health and advocating for himself. So there we were... doing just that. He and I were learning and advocating together.

We also believe we should respect those who went before us who have not had it so well…those 'hemophilia soldiers' who sacrificed their health and sometimes their lives for the treatment opportunities we have today. And now that we find our community in such a promising place, the question becomes how will we honor the past and make improvements for the future?

We, as an entire hemophilia community, need to learn how to exercise our voice and get people to listen. That is what Washington Days is all about. If we sit idly by, do we believe things will get better? If we are not involved in the legislative process, if we are not sure that our voices are heard, the past could easily repeat itself. I can live with Hawaiian shirts or bell bottoms coming back again. My son can't live with the tragedies of the past being repeated in the hemophilia community, and neither should you or I. Let's be real here. There are many things we can do, and would do, to keep ourselves and our children healthy. I would die for my son and I know many feel the same way about their children. But, the one thing that keeps me up at night is what happens to Spencer if he no longer has access to the medicine that allows him to live a mostly normal life. It's not a sure thing. Without due diligence on our part things could change. That's a call to action if I ever heard one.

For those of you, who like me, find yourself forever a part of the bleeding disorder community, don't sit idly by. Do your part. It doesn't matter what life has dealt you. It's not about what you can get and keep. It's not about how much 'swag' your kids bring home from events. (Don't get me wrong, I love branded water bottles just as much as the next guy.) But it IS about your voice and your participation in event opportunities that help ensure the past is not repeated and progress continues to be made. Let your voice be heard. Do something to make a difference. "Ask not what you hemophilia community can do for you, but what..." Okay, that's too cheesy. You get what I mean. I truly believe there are reasons for everything that happens. You are in this community of "bleeders" for a reason. There is still much work to be done. My trip to Washington opened my eyes to that fact. ■

Gene Therapy Study in Dogs Shows Markedly Lower Bleeding Rates

In a recently published paper, an international team of researchers report effectively administering gene therapy to three dogs with hemophilia B in an ongoing study. The report, "Liver-Directed Lentiviral Gene Therapy in a Dog Model of Hemophilia B," was published March 4, 2015, in the journal Science Translational Medicine. The lead author of the paper was Luigi Naldini, MD, PhD, director of the San Raffaele Telethon Institute for Gene Therapy at the San Raffaele Scientific Institute in Milan, Italy.

The three dogs in the study were administered the gene therapy either through direct injection into the liver, a primary source of clotting factor protein production, or intravenously. The therapy was housed in repurposed retroviruses called lentiviral vectors. These vectors act as vehicles, carrying customized genetic material to elicit the production of factor IX (FIX). One advantage in using lentiviruses is that a majority of patients do not generate antibodies to this type of vector, avoiding an immune response that would otherwise render the treatment ineffective. Another benefit of using lentiviral vectors is their large size, enabling them to deliver greater concentrations of the FIX gene, resulting in a more optimal therapeutic effect.

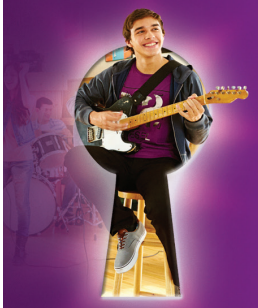
Three years after administering the treatment, Naldini and his colleagues report significant symptomatic improvement. Prior to receiving the therapy, the dogs experienced approximately five spontaneous bleeds per year. In contrast, in the three years since receiving therapy, the dogs have averaged 0 to 1 bleed per year. This notable decrease in spontaneous bleeding events was achieved because the gene therapy boosted FIX generation in the dogs from virtually 0 to 1%-3%. This seemingly modest increase was enough to dramatically lower bleeding rates.

"The result was stunning," said Timothy Nichols, MD, director of the Francis Owen Blood Research Laboratory at the University of North Carolina School of Medicine and co-senior author of the paper. "Just a small amount of new factor IX necessary for proper clotting produced a major reduction in bleeding events. It was extraordinarily powerful."

Investigators have also reported no harmful side effects. Safety being a primary concern, Naldini and his team performed additional studies in types of mice that are more likely to develop complications from lentiviruses, such as malignancies. No hazardous responses to the therapy were reported. "Considering the mouse model data and the absence of detectable genotoxicity during long-term expression in the hemophilia B dogs, the lentiviral vectors have a very encouraging safety profile in this case," said Nichols.

Ideally, Naldini, Nichols and their team would like to increase FIX production to 5%-10% to essentially eradicate spontaneous bleeding in patients with hemophilia B. To reach this endpoint, several years of additional investigation, including larger animal studies and eventual human clinical trials, will need to occur. ■

— Source: ScienceDaily, March 12, 2015



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ADVATE SUPPORTS YOU BY IMPROVING YOUR PERSONAL INFUSION EXPERIENCE WITH THE BAXJECT III SYSTEM

The reconstitution process with the BAXJECT III system is easier, faster, and designed for you*

- An all-in-one, connected design[1]
- Broad selection of doses, providing opportunities for single-vial options[1]
- One-step activation with fewer steps for **faster** reconstitution—just press, swirl, flip and withdraw*[1,2]
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Share your experience using the ADVATE with BAXJECT III system at **www.BAXJECT3Survey.com**

ADVATE [Antihemophilic Factor (Recombinant)] Important Information

Indications

ADVATE is a medicine used to replace clotting factor (factor VIII or antihemophilic factor) that is missing in people with hemophilia A (also called "classic" hemophilia).
ADVATE is used to prevent and control bleeding in adults and children (0-16 years) with hemophilia A.
Your healthcare provider may give you ADVATE when you have surgery.
ADVATE can reduce the number of bleeding episodes in adults and children (0-16 years) when used regularly (prophylaxis).

ADVATE is not used to treat von Willebrand disease.

DETAILED IMPORTANT RISK INFORMATION

You should not use ADVATE if you:
- Are allergic to mice or hamsters.
- Are allergic to any ingredients in ADVATE.

Tell your healthcare provider if you are pregnant or breastfeeding because ADVATE may not be right for you.

You should tell your healthcare provider if you:
- Have or have had any medical problems.
- Take any medicines, including prescription and non-prescription medicines, such as over-the-counter medicines, supplements or herbal remedies.
- Have any allergies, including allergies to mice or hamsters.
- Have been told that you have inhibitors to factor VIII (because ADVATE may not work for you).

Your body may form inhibitors to factor VIII. An inhibitor is part of the body's normal defense system. If you form inhibitors, it may stop ADVATE from working properly. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to factor VIII.

You can have an allergic reaction to ADVATE.

Call your healthcare provider right away and stop treatment if you get a rash or hives, itching, tightness of the throat, chest pain or tightness, difficulty breathing, lightheadedness, dizziness, nausea or fainting.

Side effects that have been reported with ADVATE include: cough, headache, joint swelling/aching, sore throat, fever, itching, unusual taste, dizziness, hematoma, abdominal pain, hot flashes, swelling of legs, diarrhea, chills, runny nose/congestion, nausea/vomiting, sweating, and rash.

Tell your healthcare provider about any side effects that bother you or do not go away or if your bleeding does not stop after taking ADVATE.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see following page for Brief Summary of ADVATE full Prescribing Information.

References: 1. ADVATE Prescribing Information. Westlake Village, CA: Baxter Healthcare Corporation; April 2014. **2.** Data on file.

Baxter

ADVATE [Antihemophilic Factor (Recombinant)]
Lyophilized Powder for Reconstitution for Intravenous Injection
Brief Summary of Prescribing Information: Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

ADVATE [Antihemophilic Factor (Recombinant)] is a recombinant antihemophilic factor indicated for use in children and adults with hemophilia A (congenital factor VIII deficiency or classic hemophilia) for:

- Control and prevention of bleeding episodes.
- Perioperative management.
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

ADVATE is not indicated for the treatment of von Willebrand disease.

CONTRAINDICATIONS

ADVATE is contraindicated in patients who have life-threatening hypersensitivity reactions, including anaphylaxis, to mouse or hamster protein or other constituents of the product (mannitol, trehalose, sodium chloride, histidine, Tris, calcium chloride, polysorbate 80, and/or glutathione).

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with ADVATE. Symptoms include dizziness, paresthesia, rash, flushing, facial swelling, urticaria, dyspnea, and pruritus.

ADVATE contains trace amounts of mouse immunoglobulin G (MuIgG) ≤0.1 ng/IU ADVATE, and hamster proteins ≤1.5 ng/IU ADVATE. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

Discontinue ADVATE if hypersensitivity symptoms occur and administer appropriate emergency treatment.

Neutralizing Antibodies

Neutralizing antibodies (inhibitors) have been reported following administration of ADVATE predominantly in previously untreated patients (PUPs) and previously minimally treated patients (MTPs). Monitor all patients for the development of factor VIII inhibitors by appropriate clinical observation and laboratory testing. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, perform an assay that measures factor VIII inhibitor concentration. [see *Warnings and Precautions*]

Monitoring Laboratory Tests

- Monitor plasma factor VIII activity levels by the one-stage clotting assay to confirm the adequate factor VIII levels have been achieved and maintained when clinically indicated. [see *Dosage and Administration*]
- Perform the Bethesda assay to determine if factor VIII inhibitor is present. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with the expected dose of ADVATE, use Bethesda Units (BU) to titer inhibitors.
  - If the inhibitor titer is less than 10 BU per mL, the administration of additional antihemophilic factor concentrate may neutralize the inhibitor and may permit an appropriate hemostatic response.
  - If the inhibitor titer is above 10 BU per mL, adequate hemostasis may not be achieved. The inhibitor titer may rise following ADVATE infusion as a result of an anamnestic response to factor VIII. The treatment or prevention of bleeding in such patients requires the use of alternative therapeutic approaches and agents.

ADVERSE REACTIONS

The serious adverse reactions seen with ADVATE are hypersensitivity reactions and the development of high-titer inhibitors necessitating alternative treatments to factor VIII.

The most common adverse reactions observed in clinical trials (frequency ≥10% of subjects) were pyrexia, headache, cough, nasopharyngitis, vomiting, arthralgia, and limb injury.

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

ADVATE has been evaluated in five completed clinical trials in previously treated patients (PTPs) and one ongoing trial in previously untreated patients (PUPs) with severe to moderately severe hemophilia A (factor VIII ≤2% of normal). A total of 234 subjects have been treated with ADVATE as of March 2006. Total exposure to ADVATE was 44,926 infusions. The median duration of participation per subject was 370.5 (range: 1 to 1,256) days and the median number of exposure days to ADVATE per subject was 128 (range: 1 to 598).[3]

The summary of adverse reactions with a frequency ≥5% (defined as adverse events occurring within 24 hours of infusion or any adverse event causally related occurring within the trial period) is shown in Table 3.

No subject was withdrawn from a clinical trial due to an adverse reaction. There were no deaths in any of the clinical trials.

Table 3
Summary of Adverse Reactions[a] with a Frequency ≥5% (N = 234 Treated Subjects[b])

MedDRA[c] System Organ Class	MedDRA Preferred Term	Number of ADRs	Number of Subjects	Percent of Subjects
General disorders and administration site conditions	Pyrexia	78	50	21
Nervous system disorders	Headache	104	49	21
Respiratory, thoracic, and mediastinal disorders	Cough	75	44	19
Infections and infestations	Nasopharyngitis	61	40	17
Gastrointestinal disorders	Vomiting	35	27	12
Musculoskeletal and connective tissue disorders	Arthralgia	44	27	12
Injury, poisoning, and procedural complications	Limb injury	55	24	10
Infections and infestations	Upper respiratory tract infection	24	20	9
Respiratory, thoracic, and mediastinal disorders	Pharyngolaryngeal pain	23	20	9
Respiratory, thoracic, and mediastinal disorders	Nasal congestion	24	19	8
Gastrointestinal disorders	Diarrhea	24	18	8
Gastrointestinal disorders	Nausea	21	17	8
General disorders and administration site conditions	Pain	19	17	8
Skin and subcutaneous tissue disorders	Rash	16	13	6
Infections and infestations	Ear infection	16	12	5
Injury, poisoning, and procedural complications	Procedural pain	16	12	5
Respiratory, thoracic, and mediastinal disorders	Rhinorrhea	15	12	5

[a] Adverse reactions are defined as all adverse events that occurred (a) within 24 hours after being infused with investigational product, or (b) all adverse events assessed related or possibly related to investigational product, or (c) adverse events for which the investigator's or sponsor's opinion of causality was missing or indeterminate.

[b] The ADVATE clinical program included 234 treated subjects from 5 completed studies in PTPs and 1 ongoing trial in PUPs as of 27 March 2006.

[c] MedDRA version 8.1 was used.

Immunogenicity

The development of factor VIII inhibitors with the use of ADVATE was evaluated in clinical trials with pediatric PTPs (<6 years of age with >50 factor VIII exposures) and PTPs (>10 years of age with >150 factor VIII exposures). Of 198 subjects who were treated for at least 10 exposure days or on study for a minimum of 120 days, 1 adult developed a low-titer inhibitor (2 BU in the Bethesda assay) after 26 exposure days. Eight weeks later, the inhibitor was no longer detectable, and *in vivo* recovery was normal at 1 and 3 hours after infusion of another marketed recombinant factor VIII concentrate. This single event results in a factor VIII inhibitor frequency in PTPs of 0.51% (95% CI of 0.03 and 2.91% for the risk of any factor VIII inhibitor development).[3,4] No factor VIII inhibitors were detected in the 53 treated pediatric PTPs.

In clinical trials that enrolled previously untreated subjects (defined as having had up to 3 exposures to a factor VIII product at the time of enrollment) , 5 (20%) of 25 subjects who received ADVATE developed inhibitors to factor VIII.[3] Four subjects developed high titer (>5 BU) and one patient developed low-titer inhibitors. Inhibitors were detected at a median of 11 exposure days (range 7 to 13 exposure days) to investigational product.

Immunogenicity also was evaluated by measuring the development of antibodies to heterologous proteins. 182 treated subjects were assessed for anti-Chinese hamster ovary (CHO) cell protein antibodies. Of these subjects, 3 showed an upward trend in antibody titer over time and 4 showed repeated but transient elevations of antibodies. 182 treated subjects were assessed for mulgG protein antibodies. Of these, 10 showed an upward trend in anti-mulgG antibody titer over time and 2 showed repeated but transient elevations of antibodies. Four subjects who demonstrated antibody elevations reported isolated events of urticaria, pruritus, rash, and slightly elevated eosinophil counts. All of these subjects had numerous repeat exposures to the study product without recurrence of the events and a causal relationship between the antibody findings and these clinical events has not been established.

Of the 181 subjects who were treated and assessed for the presence of anti-human von Willebrand Factor (VWF) antibodies, none displayed laboratory evidence indicative of a positive serologic response.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ADVATE with the incidence of antibodies to other products may be misleading.

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of ADVATE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Among patients treated with ADVATE, cases of serious allergic/hypersensitivity reactions including anaphylaxis have been reported and factor VIII inhibitor formation (observed predominantly in PUPs). Table 4 represents the most frequently reported post-marketing adverse reactions as MedDRA Preferred Terms.

Table 4
Post-Marketing Experience

Organ System [MedDRA Primary SOC]	Preferred Term
Immune system disorders	Anaphylactic reaction[a]
	Hypersensitivity[a]
Blood and lymphatic system disorders	Factor VIII inhibition
General disorders and administration site conditions	Injection site reaction
	Chills
	Fatigue/Malaise
	Chest discomfort/pain
	Less-than-expected therapeutic effect

[a] These reactions have been manifested by dizziness, paresthesias, rash, flushing, face swelling, urticaria, and/or pruritus.

Plant-Based Inhibitor Therapy Continues to Evolve

Scientists from the University of Florida in Gainesville (UF-G) and the University of Pennsylvania (U-Penn) continue to investigate an experimental, plant cell-based approach to preventing inhibitors and allergic reactions (anaphylaxis) to clotting factor therapies in people with hemophilia. An update on their progress was published online, December 16, 2014, in Scientific American, a division of Nature America, Inc.

Lead investigator Henry Daniell, PhD, director of translational research at the U-Penn School of Dental Medicine, and Roland W. Herzog, PhD, a molecular biologist at UF-G, have, for several years, been working on a technique that involves encapsulating an orally administered "tolerance-inducing protein" such as factor IX (FIX) within plant cell walls. When ingested, the bio-encapsulated protein safely travels through the stomach before reaching the small intestines. The plant cell wall shields the FIX from being prematurely broken down by stomach acid. Eventually, microorganisms eat away the cell wall, gradually releasing the protein.

Building on earlier studies (2010) that successfully used bioengineered tobacco plant cells to prevent inhibitors and anaphylaxis in mice with hemophilia B (FIX deficiency), Daniell and Herzog are now turning to freeze-dried lettuce leaf cells engineered to trigger a high concentration of FIX. Each lettuce leaf cell contains approximately 10,000 chloroplasts, each structured in such a way to hold very large volumes of the FIX protein. Chloroplasts are subunits of plant cells, most often known as crucial components of photosynthesis. Although these chloroplast-rich plant cells are not equipped to prevent bleeding--plants are unable to make human clotting factors biologically active--they have shown an ability to induce tolerance in the immune system to FIX. Researchers have been developing this novel therapeutic approach for several years to create potential vaccines against malaria and cholera, and genetically engineered insulin to help prevent diabetes.

Daniell and Herzog recently took the next step and tested this approach in two dogs with hemophilia B. They fed both dogs their normal food along with the engineered lettuce cells converted into a green powder form. There have been no reports of anaphylaxis or inhibitors in the mice from the earlier study or in the dogs that recently received the plant-based therapy. "So far, it's going very well," reported Daniell. If this novel oral therapy continues to prevent treatment complications in animal models, the next step will be to replicate that success in human clinical studies. ■

— Source: Scientific American, December 16, 2014

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