PEN

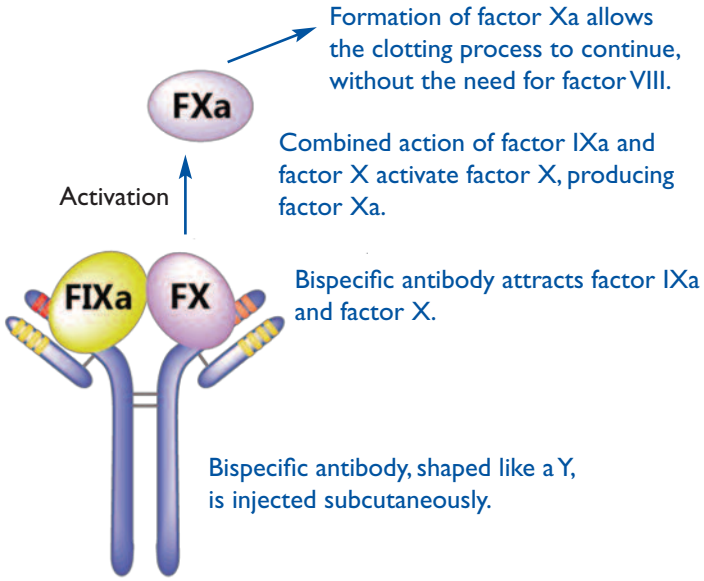
inside

What Are the Facts on HEMLIBRA?

Paul Clement

Social media was abuzz with elation and speculation when the US FDA approved Genentech/Roche's Hemlibra® on November 16, 2017.[1]

Why elation? Many reasons. Hemlibra is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A with factor VIII inhibitors. Hemlibra is the first drug of its kind for people with hemophilia: it is not a factor product; instead, it's a *bispecific monoclonal antibody* that mimics the function of factor VIII.[2] And unlike factor, instead of being administered through the veins, Hemlibra is administered as a weekly subcutaneous (under the skin) injection.[3] It has produced remarkable results: 65% of children with inhibitors on Hemlibra prophylaxis experienced zero bleeds, and 95% experienced zero treated bleeds after an observation time of ten months.



Hemlibra, a bispecific antibody, mimics the function of factor VIII by bringing together factors IXa and X to activate factor X (making Xa). This restores the clotting process, so a blood clot can form.

And the speculation? Hemlibra has generated lots of discussion—helpful and unhelpful—on social media. For example, in one discussion thread, while some good questions were posed, there was also misinformation and some fearmongering. Social media can stir up great discussions, but we need to be careful with the information provided. Here, we offer answers—well researched and fact-based—to some of the questions and comments posted on social media about Hemlibra.

"Hemlibra carries an FDA black box warning!"

This statement implies that all drugs with a black box warning are dangerous. Hemlibra does carry a black box warning, but this doesn't mean it shouldn't be used. All drugs have associated side effects and risks. FDA approval of a drug doesn't mean that the drug is safe in all circumstances; it means that the benefits of the drug, when properly used, outweigh the risks. A black box warning is the most serious warning the FDA can require of manufacturers. It warns consumers and physicians about serious or life-threatening risks ("adverse events") associated with a drug.[4] These warnings usually include information on how to avoid or reduce the severity of adverse events by using the drug appropriately: for example, avoiding the drug in specific situations; observing patients for signs of adverse events; educating patients on signs and symptoms of adverse events and side

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1. Hemlibra's generic name is emicizumab-kxwh. In clinical trials, it was called ACE910. 2. See the February 2018 issue of PEN for details on how Hemlibra works: www.kelleycom.com. 3. Weekly dosing of Hemlibra may be extended to once a month, pending the results of clinical trials currently underway. 4. Adverse events differ from side effects. An adverse event is usually a serious, unwanted, unexpected occurrence that results from taking a medication correctly. Side effects are usually foreseen, and are less serious than adverse events. Adverse events require medical intervention, but most side effects resolve on their own with time.

welcome

The cure to eliminate fake news is that people stop reading 140-character tweets and start reading 600-page books. —Piero Scaruffi

In December 2017, President Obama noted, "One of the dangers of the internet is that people can have entirely different realities. They can be cocooned in information that reinforces their current biases."

We see this daily on Facebook and Twitter. Some members of our community can be reactive on social media, due to what we have suffered. Our "different reality" was living through the horrors that HIV wrought on our community. We can understand, then, why families feel wary of new drugs in the marketplace. And we praise the watchdog consumer groups and individuals who safeguard those families by asking tough questions when new drugs appear.

But sometimes, our community reacts unfairly on social media. When CSL Behring announced that Helixate® FS would be discontinued, Facebook blew up with accusations, for example the "fake news" that the manufacturer was forcing people to switch to higher-cost products. The truth? A contract that had allowed CSL Behring to sell Bayer's Kogenate® FS as Helixate FS for many years had expired. Helixate FS *is the same product as* Kogenate FS. But without a contract, CSL Behring was left with no Helixate FS to sell. Simple as that.

When a discussion on Hemlibra® came up in March on Facebook, our team watched as interesting accusations, news, and some misinformation was posted. We investigated these posts to provide more in-depth information in our feature by Paul Clement. To our surprise, some of the news that was questioned by some, but not posted anywhere officially online, turned out to be correct.

As a publisher, I still love print media. It's more expensive, slower, and not as often read as electronic media, especially Facebook. But it requires fact checking, research, editing, and more editing. You can't delete it quickly once it's published. You need to release information you can stand by. Journalist Brit Hume wrote, "In the end, you make your reputation and you have your success based upon credibility and being able to provide people who are really hungry for information what they want." That's what we try to do here each quarter. We hope you get answers to your questions every time you read PEN.

Laurie Kelley

inbox

THANK YOU FOR sparing your precious time to visit Fiji, and for your unconditional support for setting up an organization for hemophilia patients. Your concern and dedication to these patients is truly appreciated. We are so grateful to have participated in your medical seminar on February 17, 2018.

Physicians of Smart Care Medical Centre
FIJI

THANK YOU FOR the book *Raising a Child with Hemophilia*, which was my first educational tool when my now 13-year-old was diagnosed with severe hemophilia A at 18 months. It helped me tremendously on our first trip to the ER for an infusion before we were self-infusing at home. I was actually prepared for staff that was clueless about hemophilia. I also have a 10-year-old-son with severe hemophilia A, so we're old pros now.

Ann Hodyl
ILLINOIS

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PARENT EMPOWERMENT NEWSLETTER | MAY 2018

EDITOR-IN-CHIEF Laureen A. Kelley
SENIOR EDITOR Sara P. Evangelos • SCIENCE EDITOR Paul Clement • CONTRIBUTING WRITER Richard J. Atwood
LAYOUT DESIGNER Tracy Brody • PUBLICATIONS MANAGER Jessica O'Donnell
DIRECTOR, PROJECT SHARE Zoraida Rosado

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Parents or patients with personal insurance questions should contact their employer's human resource department, Medicaid or Medicare caseworker, payer representative, or HTC social worker.

It's increasingly recognized that women are not just carriers of the hemophilia gene, but also can experience symptoms if they have less than 50% of their factor active, and they should be diagnosed with mild hemophilia. The majority of diagnosed patients are male. For editorial simplicity in PEN articles, whenever we refer to a person with hemophilia, we may alternately use "he" or "she," or just "he."

LA KELLEY communications, inc.
37–39 West Main Street #8
Georgetown MA 01833 USA
978-352-7657 • fax: 978-352-6254
info@kelleycom.com • www.kelleycom.com

as i see it

To Play or Not to Play?

Derek Markley

As a father, I will be the first to say that learning about hemophilia leads to a number of questions about the life your son will live. This is highly dependent on your own childhood. Hemophilia mainly affects boys. There are women who suffer from hemophilia and other bleeding disorders, but hemophilia often discriminates. It likes to live in boys.

No one can stereotype exactly what a boy's childhood will look like. Personally, I forecasted my son's future based on my own experiences. We lived out in the country, and growing up, our daughter was happy being outdoors. With a son, I expected that we'd have someone who was simply a replication of me as a child, and also loved being outdoors.

I like to be outside. As a youth I played outdoors, shot BB guns, fished, and often did things that resulted in falling, tripping, slipping, or sliding. None of this was out of the ordinary. Little boys come back in the house dirty, sweaty, and bleeding sometimes. I was no different.

My fondness for being outdoors also meant that I was constantly playing a sport. My parents enjoyed that, and let me play year-round. Baseball, soccer, and basketball took up most of my year. With all the sports seasons running end-to-end, I picked up a stream of kid injuries, such as broken fingers, twisted ankles, bloody noses, and all manner of bumps, bruises, cuts, and scrapes. Those things were just a fact of life. Rarely was anything bad enough to warrant a trip to the hospital or 24-hour clinic, but we did end up there a couple of times.

How do you raise a boy with hemophilia, based on that kind of a childhood?

Bubba's diagnosis immediately made me confront my own notions about what little boys "should" be able to do. Because of my own childhood, I had an irrational fear that he wouldn't ever have a fully "normal" childhood. I never had to be the kid who sat out of the game, avoided jumping off a slide or tree branch, or shied away from a backyard game of football.

Derek Markley

Bubba and Derek Markley

As boys, those are things we're supposed to do, right?

After the diagnosis, my brain was trying to immediately construct a vision of what Bubba's life would look like for his first 18 years. He'd miss everything that had made my childhood fun. He'd always be on the sidelines. He'd never get to enjoy the benefits, and the associated consequences, of taking the risks that little boys take when playing, fighting, or just being rough-and-tumble kids.

The problem was that I'd already imposed my childhood on Bubba. I guess that's a natural reaction for some fathers. You are given someone you expect to be a little copy of yourself. The idea is that this little person will have to grow up to learn how to be a boy and later a man. Immediately, you begin using your own experiences as a model for how that might look.

Another problem arises when it begins to sink in that everything is not under your control. You didn't get to vote the genetic mutation occurrence up or down. It's something that just happened. It suddenly becomes apparent that you only have an illusion of control.

Life likes to make a point occasionally.

There are times when one of the worst things we can have is an active imagination. Of course, it's fantastic when you're a kid: without an imagination, floors cannot become lava and castles can be constructed with pillows. But grown-up life can turn an imagination against you. This was particularly true for my wife and me in the first few days post-diagnosis, as we tried

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Cazandra Campos-MacDonald

What Causes Inhibitors?

Part 2

When you receive an inhibitor diagnosis, you may feel overwhelmed by emotions that flood your mind and heart. Understanding why an inhibitor forms doesn't always bring comfort or relief, but knowing about certain risk factors may ease the blow of the diagnosis or prepare you if you plan to have more children. With an inhibitor diagnosis, take one step at a time: breathe deeply, and begin learning everything you can. Information can ease your mind and help lessen the feeling of being overwhelmed.

About one-third of people with hemophilia A are diagnosed with an inhibitor, and about 2% to 3% of people with hemophilia B. We know that genes play a deciding role in inhibitor development. In Part 1 of this series (November 2017), we discussed the genetic risk factors that can cause an inhibitor. Here in Part 2, we'll discuss additional genetic risk factors, such as ethnicity and family history, plus exposure to clotting factor and environmental risk factors for developing inhibitors.

Ethnicity

Ethnicity is a significant risk factor for developing inhibitors. As a Hispanic woman, the possibility of my sons developing inhibitors is twice the rate of Caucasians. African Americans with hemophilia A also develop inhibitors at twice the rate of Caucasians.[1]

Family History

The risk of developing an inhibitor is related to the type of genetic mutation causing the person's hemophilia. Because members of the same family share the same genetic variation that results in hemophilia, as well as the makeup of part of their immune systems, a family history of inhibitors is a strong indicator that siblings or children in later generations will also be at significant risk of an inhibitor. But even though genetics is the most important risk factor for developing inhibitors, having the same risk factors does not mean that you will necessarily develop inhibitors. In approximately 25% of cases of brothers with hemophilia, one will develop an inhibitor while the other will not.

My oldest son, Julian, now 21, was diagnosed with a low-titer inhibitor at age one, after a bleed due to a torn frenulum that we were unable to control over several weeks. Prior to this injury, Julian had several infusions for various bleeds, and this triggered the development of his inhibitor. Before we knew it, my husband and I had begun daily infusions for immune tolerance induction (ITI). It took two and a half years of daily infusions to eradicate Julian's inhibitor.

Julian's younger brother, Caeleb, was also diagnosed with severe hemophilia. With Julian's history of an inhibitor, the chance of Caeleb developing one was high. Caeleb was circumcised at age eleven months without prior testing for an inhibitor. The circumcision site oozed for two weeks. He received large amounts of factor VIII, but the bleeding would not stop. Unlike Julian, who has a low-titer inhibitor, Caeleb was diagnosed with a high-titer inhibitor.

Age at First Exposure

A patient's age at first exposure to factor concentrate is sometimes identified as a risk factor for developing inhibitors, but it's not clear whether the risk is associated with age or with early intensive therapy with factor. What is known is that most people who develop inhibitors do so at an early age. People with hemophilia A typically develop an inhibitor within the first 20 infusions. People with hemophilia B may develop an inhibitor after the first or second treatment. After 100 infusions, inhibitor development in those with hemophilia A is rare but can happen. Caveat: Parents should not delay treating a child's bleed because they believe that treating at a young age will cause an inhibitor.

Intensity of Exposure to Factor

Receiving high doses of factor for three days or more, usually after a surgical procedure, or receiving a continuous infusion of factor through a pump have been associated with inhibitor development. Why?

High doses of factor usually accompany or follow infections, surgery, or trauma. All of these situations stress cells and cause them to emit "danger signals"—compounds released by cells that are under stress, injured, or undergoing abnormal death. These danger signals put the immune system on high alert, when it is more likely to develop inhibitors. While the possibility of developing an inhibitor can be frightening, the patient should follow the hematologist's treatment plan post-surgery. Treating bleeds should always be the first priority.

Immunizations and illness also put the immune system on high alert and may be associated with an increased risk of developing inhibitors. Because of this, it is recommended that prophylactic factor infusions not be done close to immunizations.

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1. Ethnic differences in inhibitor rates are believed to be due to a mismatch of factor VIII proteins. Factor VIII molecules are not all the same: six different variations have been identified. Recombinant factor VIII products contain two forms of factor VIII that are found in all ethnic populations. But a significant portion (as much as 25%) of African Americans and Hispanics are likely to have one of three other forms of factor VIII. If the form of factor VIII you have is different from the form of factor VIII you receive in an infusion, then you may be at higher risk of developing antibodies (inhibitors) against it.

richard's review

Linda Weaver's Studio

Richard J. Atwood

Training Hemophilia Researchers: Dr. Thomas Addis

Thomas Addis, Stanford Medical History Center

You attend annual comprehensive visits at your hemophilia treatment center (HTC), confident that the staff members are specialists in diagnosing and treating bleeding disorders. Yet how do these dedicated healthcare professionals obtain and expand their expertise? For physicians, training in hematology lasts for around seven years, supplemented with ongoing continuing education. An extra opportunity, especially for young doctors who want to conduct research, is a postdoctoral fellowship, or postdoc.

I explored the history of one notable physician who held a hemophilia research fellowship over 100 years ago. You may not have heard of Thomas Addis, a Scotsman who enjoyed playing golf and who spent his medical career at Stanford University. I learned a lot from his 2010 biography by Frank Boulton, *Still Counting: The Life, Times and Continuing Influence of Dr. Thomas Addis MD 1881–1949*. I trust the medical content of the biography because a British clinical hematologist wrote the book.

Thomas Addis was born and raised in Edinburgh, Scotland. He was half American, part English, and part Scottish. From the University of Edinburgh, Addis earned the undergraduate degrees of MB, ChB, and LM in 1905, and the graduate degree of MRCP[1] with his MD thesis in 1908. Not all of these initials may be familiar to American readers, yet they indicate a highly trained physician.

Addis next worked at the laboratories of Edinburgh University, where he held a Carnegie Research Scholarship from 1908 to 1910. Then he moved to the Royal College of Physicians in Edinburgh for another Carnegie Research Fellowship. There he conducted blood-clotting research, with an emphasis on hemophilia. He also did similar research in Gloucester and Bristol in England, plus Berlin and Heidelberg in Germany. In all, Addis studied 12 cases of hemophilia from six different hemophilic stocks, or pedigrees. These individuals included three members of the Webb-Curtis pedigree from Bristol and three members of the Mampel pedigree from Heidelberg. From 1908 to 1911, Addis published numerous medical journal articles on his research into hereditary hemophilia, with a subsequent article in 1916.

Being more of a bench scientist than a clinician, Addis left the treatment of his 12 hemophilia cases to other clinicians. Instead, he took multiple finger-stabs for his blood samples, usually from the patient's thumb, because taking venous blood from a person with hemophilia was considered too dangerous at that time. Addis then measured the clotting times. These are considered *in vitro*[2] experiments, taking place outside the patient's body.

During his research period, Addis could have chosen among 11 different blood-clotting time testing methods. Instead, he developed his own complex apparatus—although compared to current methods, his was crude. For better results, he standardized his procedures, controlled multiple variables, and conducted carefully designed experiments. Addis was able to quantify his results for statistical analysis, which was not always done then.

Addis confirmed that the clotting time in hemophilia was prolonged—still a disputed observation in that era. He found that finger-stab blood-clotting times were longest in the most severely affected patients. Addis deduced that the primary inherited fault of hemophilia was in the blood, not in the vessels or tissues. He even anticipated the roles of PT (prothrombin time) and PTT (partial thromboplastin time) blood tests for diagnosing hemophilia when he found a normal PT and a long PTT to be characteristic of the disorder. And amazingly, over 100 years ago, Addis isolated the plasma component that allows blood to clot and is missing in people with hemophilia.

To announce his findings, Addis published in notable medical journals and presented at suitable medical conferences. Others acknowledged his work, but Addis had critics. One point of contention was that Addis attributed the plasma deficiency in hemophilia to a prothrombin molecule, which proved incorrect. It would have been safer had he just called it "something in the plasma" that current methods could not separate, purify, and identify. Also, Addis presented ideas that did not fit with the contemporary theory of blood clotting in hemophilia, so they were dismissed. Add to that his young age, and possibly his brashness, as fodder for his critics.

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1. Bachelor of Medicine (MB), University of Edinburgh; Bachelor of Surgery (ChB), University of Edinburgh; License in Midwifery (LM), Dublin Society of Apothecaries; Member of the Royal College of Physicians (MRCP).
2. Meaning "in glass," *in vitro* experiments are commonly called "test-tube" experiments.

Embracing the Unique

Laurie Kelley

When children are diagnosed with hemophilia, they are each given an essential diagnostic label: for example, hemophilia A or hemophilia B, severe, moderate, or mild. These labels originate from a lab analysis of the child's blood. The diagnosis determines what type of factor replacement therapy each child will get. Labels like these can help draw a picture of who your child is and what he or she needs. But when it comes to dosing and prophylaxis regimen, sport choices and bleeding patterns, and even pain management, your child with hemophilia is unique. Diagnostic labels don't adequately explain a person's individuality and needs.

We asked parents from Facebook about their children with hemophilia: Has anyone ever used the labels of hemophilia to categorize your child, which resulted in limiting treatment options, or limiting what people think your child can do? What is it about your child that is not "typical" for someone with hemophilia? The responses poured in. While a child's uniqueness may be revealed in a preference for certain sports or a physiological reaction to a particular product, most of the parental responses we received were about each child's unique half-life, and about subsequent bleeding patterns.

Half-life was barely mentioned when my son was born. In the late 1980s and early 1990s, we dosed his factor using a chart based on his weight; it was very mathematical. We took one-half of his weight in kilograms times the factor level we desired, and this equaled the number of units of factor VIII we needed to infuse. Over time, as parents, we developed intuition about how much or how little factor our son needed based on his response to factor and his bleeding patterns, and we could adjust his dosage ourselves.

Up until about the last 10 years, hemophilia treatment centers (HTCs) often prescribed factor dosages based on weight, and determined a prophylaxis regimen based on a strict protocol from clinical studies. We now know that every child needs to have a pharmacokinetic (PK) or recovery study done to determine his or her individual, unique half-life response to a specific factor VIII product. Determining the unique half-life can help hone the amount of factor a child should receive, or indicate the best prophy regimen. A short half-life may mean more frequent infusions, higher doses, or the use of extended half-life products.

If anyone knows about the uniqueness of factor half-lives in children with hemophilia, it's June Reese, who has four sons with hemophilia. She says, "One son has always had a short half-life and has really struggled with bleeds. His teachers often compare him to his brothers, one of whom never bleeds." And this was a problem for the Reese family: in categorizing two brothers with textbook half-lives as "normal" for hemophilia, teachers dismissed the third brother's frequent bleeds—they thought he was being careless, or worse, that he was imagining the bleeds.

Crystal Eskine has two sons with severe hemophilia A, ages 9 and 10. "I expected two similar stories," she laughs. Despite having the same diagnosis as his brother, Crystal's 10-year-old bleeds spontaneously, "if you look at him too hard." Her younger son "never needs factor," and "he isn't even on prophy he bleeds so little!" When Crystal's doctor wanted her to adhere to a traditional dosage and infusion schedule with her older son, her gut instinct told her it wasn't good enough. She knew her children's unique responses to factor. "I started giving my older son double doses. I took notes, showed our doctor, but he still he thinks I'm worrying too much, while I still don't think the dosing regimen is good enough." Crystal continues, "I've asked for a PK test, with blood samples taken over a much longer time period, but he has said no."

And then there is Jen Miller's five-year-old with severe hemophilia A. Jen calls him a "typical boy" who enjoys video games, swimming, T-ball, and playing with his friends. His factor half-life is very short, which is not typical, but this doesn't seem to impact his bleeding patterns.

When a shorter half-life does impact bleeding patterns, and parents instinctively know something isn't right, they need to alert their HTC staff, sometimes to prove that their child does not fit a category or label. In these cases, parents should request

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PROJECT SHARE

From Pain to Promise: Lerroy's Story

In 1990 my twin brother Luigi, age one, had a swollen left knee. Our parents had him tested, and he was diagnosed with severe hemophilia A. Because we are twins, I was tested too, and also diagnosed. It was very tough living with hemophilia, especially without access to factor VIII. We just took pain medication when we were in pain.

My worst, most painful bleed was in 2008. I was coughing hard for days, and then I felt a small pain in my lower abdomen. Ignoring it, I went to school. There I felt the pain worsen, and I had trouble urinating. It seemed that something was blocked inside me, and my lower abdomen was swelling. I went to the hospital and was confined for seven days. The doctors did an ultrasound and inserted a catheter so I could urinate. I was told it was good that we rushed to the hospital, as the internal bleeding was worsening and might have been fatal. I was infused with factor VIII for five days. That cost a lot, and we had no money then, so my parents went fully into debt. A year later, Blood Brothers Aid was established by a group of men with hemophilia in Manila. My brother and I were among the first board members!

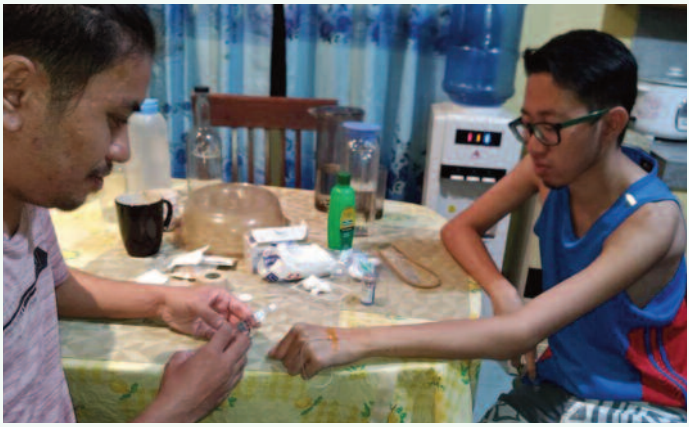
I was able to finish college, with the assistance of Blood Brothers and Father Don Kill, who volunteers to help people with hemophilia in the Philippines. Now I'm employed, and I'm still a member of Blood Brothers after nine years. I participate in their activities, including Christmas parties and summer camp. I've learned from my past bleeding; the pain I experience now is less severe, and my joint bleeding episodes are fewer. I'm getting infused with factor VIII that is donated to Blood Brothers from Project SHARE, but I take it only when the bleeding and pain are not tolerable.

Without Blood Brothers, I would not be able to work. I'm very thankful to Blood Brothers, Father Donald Kill, and Project SHARE!

Lerroy Atanacio
PHILIPPINES

Blood Brothers Aid

Lerroy (with hat) with members of Blood Brothers Aid



Lerroy getting an infusion of factor

Facts on Hemlibra... from cover

effects; selecting patients carefully; and avoiding certain other medications while taking the drug.

In the clinical trials of Hemlibra, two patients out of 189 in pooled clinical trials suffered a blood clot, or "thrombotic event" (a thrombosis is a blood clot), while also taking FEIBA. One of the two patients also suffered skin necrosis (skin death) associated with superficial thrombophlebitis (blood clots in surface veins). Hemlibra prophylaxis with FEIBA therapy was discontinued, and the blood clot resolved within a month in both patients without needing treatment for the clot. One patient resumed prophylaxis with Hemlibra after the clot was resolved. Neither of these patients suffered serious consequences, but blood clots *are* potentially serious. Blood clots that develop in the brain or in the deep veins of the leg (which can break loose and travel to the lungs) can be life-threatening.

Another three of the 189 patients suffered thrombotic microangiopathy (TMA). TMA is a serious and potentially life-threatening condition in which blood clots form in the smallest blood vessels, causing damage to the kidney, brain, and other organs. In Hemlibra clinical trials, the three patients who developed TMA stopped using Hemlibra and FEIBA. Two were treated for TMA using plasma exchange therapy, and the TMA resolved in all three patients within a week. One of the three patients resumed Hemlibra after the TMA resolved.

In reviewing these five adverse events, investigators found a common denominator: all of the patients were using FEIBA to treat breakthrough bleeds at average cumulative doses greater than 100 U/kg for 24 hours or more.[5] So Genentech issued a new protocol, recommending that if FEIBA must be used to control breakthrough bleeds, then patients should use less than 100 U/kg total. After implementation of this protocol, no further cases of TMA or thrombotic adverse events have occurred.

5. Recommended maximum single dose of FEIBA is 100 U/kg, not to exceed 200 U/kg per day.

Some social media participants questioned why anyone would switch from a "safe" drug like FEIBA or recombinant factor VIIa (rFVIIa) to a "dangerous" drug like Hemlibra. But these participants seemed unaware that the bypassing agents FEIBA and NovoSeven® RT,[6] as well as other rFVIIa products, also carry a black box warning and have been associated with serious adverse events, including excessive clotting and deaths. In fact, it's not unusual for inhibitor patients to use both FEIBA and rFVIIa, in sequence, to control a difficult bleed—a high-risk practice that manufacturers of both these bypassing agents specifically warn against in their prescribing information because it is associated with a higher risk of blood clots.

Over 500 FDA-approved drugs in the US carry black box warnings, yet most consumers and many physicians aren't aware of these warnings or simply ignore them. And that's dangerous: a drug may be perfectly safe if warnings and precautions are followed, but ignoring warnings and not following precautions can be fatal. As a consumer, you must be proactive. Don't assume your doctor is aware or will inform you of all risks associated with every drug you are prescribed. *Always read the prescribing information (package insert) for every medication you take*. Read about the side effects and especially any black box warnings, and ask your physician to discuss them with you.[7] It may save your life.

"People on Hemlibra have died."

This statement is true, but the context in which it was written implies that the drug caused the deaths and is therefore unsafe. Although the attending physicians have stated that Hemlibra was not the cause of death, some patients still have questions.

As of this writing, five adults who were on Hemlibra have died. One of the patients was in a clinical trial of Hemlibra, and the other four obtained the drug through a compassionate use program.[8] Here's a summary of what we know about these deaths:

A 41-year-old in a Hemlibra clinical trial died in February 2017 from a serious rectal bleed; he had a history of GI problems and an ileostomy. Acute rectal bleeds are potentially serious (up to 25% of people with acute lower GI bleeds and without hemophilia die from the hemorrhage), and a lot of blood can be lost in a few hours. Initial treatment involves maintaining blood volume by administering IV fluids. Significant blood loss requires administering packed red blood cells (RBCs), which the patient refused. Bleeding that does not stop often requires surgical intervention—not an option in this case, because the patient refused to accept a transfusion.

6. FEIBA and NovoSeven, along with other rFVIIa products, are called bypassing agents. They are used to treat bleeds in people with hemophilia A and inhibitors. 7. Package inserts (PIs) are available on manufacturer websites. 8. Compassionate use (or expanded access) programs in the US allow patients not in a clinical trial to access drugs before FDA approval. Compassionate use must be requested by the patient's doctor and endorsed by the company that makes the drug. FDA calls compassionate use "expanded access," and identifies three categories: (1) individual, (2) small group, and (3) widespread access. Genentech distinguishes between individual and small group access, calling individual access "compassionate use" and small group "expanded access." Of the four patients who died and were not in a clinical trial, one was in the FDA Expanded Access Program.

In an attempt to control the bleeding, the patient was given 11 doses of rFVIIa (87 µg/kg) over three consecutive days. When this was unsuccessful, he was switched to FEIBA and given 12 doses over four days (228 U/kg total the first day, and 195 U/kg total per day for the next three days). But this treatment was also unsuccessful, and the bleeding continued. On the fourth day after beginning FEIBA treatment, the patient began showing signs of TMA. FEIBA was stopped to help resolve the TMA, and the patient received plasma exchange therapy with albumin to treat the TMA. Although the TMA was resolving, the patient's condition continued deteriorating due to severe anemia as a result of the bleed. The patient repeatedly refused blood transfusions, and died nine days after the bleed began.

It was claimed in the online discussion thread that a blood transfusion may not have saved this patient's life. But the patient's refusal to accept one certainly did cause his death and obstructed his physicians' efforts to save his life. Investigators concluded that Hemlibra was not responsible for the patient's rectal bleed.

We also know a little about two of the four patients who died while on the compassionate use program. One, a physician and assistant professor of oncology, obtained the therapy through a compassionate use program in Belgium.[9] He was vacationing in the Caribbean when he developed a staph infection that entered his blood (sepsis). He was flown to Miami for treatment, developed a brain bleed, and died two days later (February 2016).[10] The treating physician assessed an intracranial hemorrhage (ICH) and sepsis as the cause of death, which was unrelated to Hemlibra. It's important to remember that in his position as a cancer researcher, this professor was investigating the use of antibodies to fight cancer and had no qualms about using Hemlibra, an antibody drug. He went to great lengths to obtain the drug, flying from the US to Belgium weekly for injections.

A second patient who received Hemlibra through a compassionate use program also died as a result of ICH, in November 2017. This patient had a history of multiple ICH, before starting Hemlibra.

As of this writing, little is known about the other two deaths of patients on compassionate use, in early 2018, though Genentech has requested medical records. Genentech is thoroughly investigating these two recent cases, but in all four compassionate use deaths, the patients' physicians determined that death was not due to Hemlibra.

Genentech is developing a website for healthcare professionals, to keep them informed about new adverse events related to Hemlibra. This site should be ready by the time you receive PEN. For medical inquiries about Hemlibra: patients, caregivers, and healthcare professionals can call Genentech's Medical Communications team at 800-821-8590 between 5:00 am and 5:00 pm PT Monday–Friday.

Bottom line? Three things to remember when discussing drugs and patient deaths:

1. When a patient dies in a clinical trial or while taking a drug, it's reported as an adverse event, but this doesn't automatically mean that the drug caused the death. A person died during the first clinical trials of FEIBA, and two people died during a recent clinical trial on the use of FEIBA for prophylaxis, but none of these deaths resulted from using FEIBA. In fact, hemorrhage is the leading cause of death for hemophilia A inhibitor patients (and up to 70% of these deaths are caused by ICH). Also, almost all who have died were taking bypassing agents before they died—yet we don't blame the bypassing agents for their deaths. Be careful not to jump to conclusions and assume a cause-and-effect relationship where none exists.
2. Having an inhibitor increases the chance of death by as much as 70%, *regardless of type of treatment*. FEIBA and rFVIIa are not 100% effective at controlling bleeding in inhibitor patients, so these patients are at higher risk for severe bleeds and occasionally death, when compared to people with hemophilia who do not have inhibitors.
3. Four of the five deaths of patients on Hemlibra happened on a compassionate use program. To obtain a drug through such a program, applicants must meet several requirements, including that the patient must have "exhausted all available treatment options." In other words, for hemophilia A inhibitor patients to be approved for compassionate use, treatment with bypassing agents must have failed. This puts these patients at great risk of death due to hemorrhage, regardless of the treatment used.

"Clinical trials of Hemlibra were very tiny and fast-tracked."

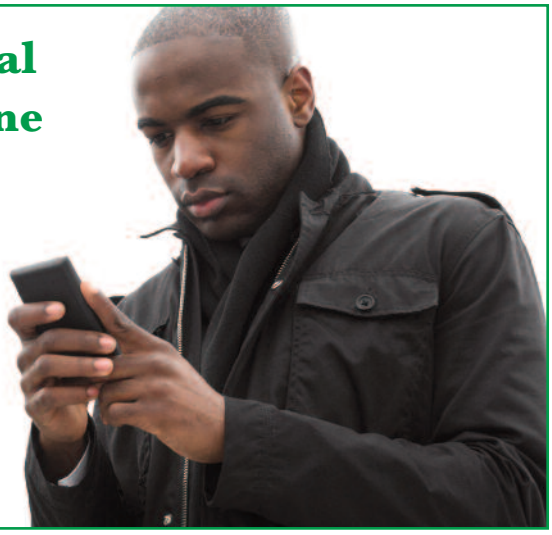
This statement implies that the drug was not properly studied and is therefore unsafe. But this is misleading. Clinical trials of Hemlibra are "tiny" only if compared to clinical trials of drugs

Genentech's Medical Communication Line

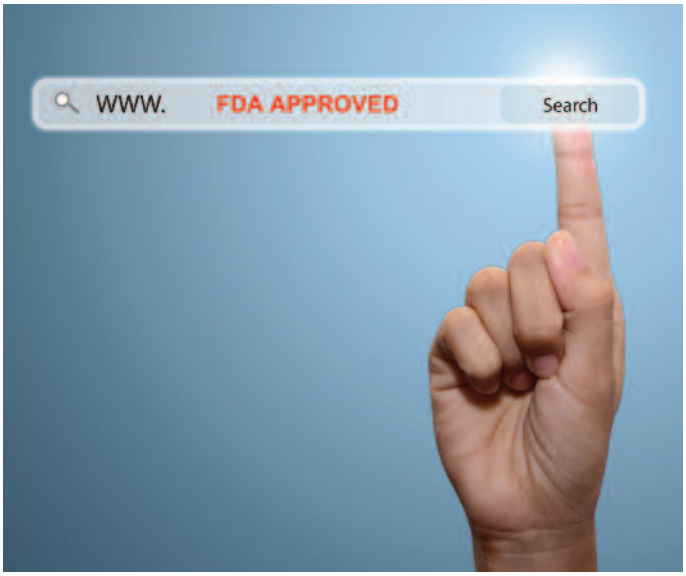
If a physician, parent, or patient has a question about Hemlibra, including its efficacy, clinical trials, complications, and adverse events, please call to speak directly to Genentech's medical team:

800-821-8590

5 am to 5 pm PT
Monday–Friday



9. See wwwforevermissed.com/holbrook. 10. Sepsis with staph is a high-risk contributing factor in the development of acute disseminated intravascular coagulation (DIC), which initially causes widespread clotting in small blood vessels, followed by spontaneous bleeding as blood-clotting factors are depleted.



intended for use by the general population. The numbers of patients enrolled in clinical trials of drugs being developed for orphan diseases[11] are always smaller than those in trials of drugs being developed for the general population. Why? Because there are fewer people with the disease or disorder, so there are fewer people to recruit for clinical trials. The phase III clinical trials of Hemlibra were, in fact, significantly larger than those for either FEIBA or rFVIIa products such as NovoSeven.

Were the trials rushed? No. Development of Hemlibra started in 2008, and the first clinical trial began in July 2013. One reason that clinical trials of orphan drugs may seem rushed is that because of the small pool of potential participants, these trials often combine phase I (testing of safety) and phase II (testing of safety and efficacy). This shortens the overall time in clinical trials.

In recent years, the FDA has also implemented four programs designed to shave time off the FDA review process for drugs that, if approved, "would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications." Genentech/Roche applied for, and was approved to participate in, two of these FDA accelerated review programs for Hemlibra: Breakthrough Therapy Status, and Priority Review. Participation in these programs shaved several months off the typical FDA review process. The FDA states, "Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval."[12] In other words, the safety of a drug under review is not compromised by a company's participation in the programs.

"Will my immune system be altered or compromised while using Hemlibra?"

This a misplaced concern: we've all sat through TV commercials for drugs where half the commercial time is used to list a wide array of serious side effects. Many of the drugs advertised on TV for arthritis, Crohn's disease, colitis, and cancer—Humira, Remicade, Enbrel, Avastin, Herceptin, and others—are monoclonal antibodies. In fact, many people with inhibitors are already familiar with the monoclonal antibody drug rituximab (brand name Rituxan), used to depress the immune system and sometimes used in immune tolerance induction (ITI) therapy for factor inhibitors. Rituximab, developed in 1997 by Genentech, was the first monoclonal antibody approved for treating cancer.[13]

Monoclonal antibody drugs aren't like other drugs, such as NSAIDs or factor VIII, where there may be several different brand names and formulations but each drug has a similar effect. Each monoclonal antibody drug is a completely different drug, with completely different mechanisms of action. So even if one antibody drug has certain side effects, this doesn't mean that other antibody drugs for different disorders—designed to attach to different molecules and with a different mechanism of action—will have similar side effects. In other words, the side effects of an antibody drug are related to the type of molecule it attaches to, or the drug it carries, not the fact that it is an antibody.

Almost all antibody drugs on the market today target the immune system or attach to cells. But Hemlibra's mechanism of action is unlike that of most antibody drugs. Hemlibra does not target the immune system, so it does not increase the risk of infections, cancer, or severe allergic immune reactions. And it does not attach to any cell. Hemlibra's only function is to attract factors IXa and X, bringing them close together so that factor X becomes activated. This allows the clotting process to proceed without the need for factor VIII (see diagram on cover). In other words, because of its mechanism of action, Hemlibra is unlikely to affect your immune system. Even before clinical trials were initiated, Hemlibra was subjected to a battery of tests to measure its *immunogenicity*, or the likelihood of eliciting an immune response. And it showed no signs of stimulating *neutralizing antibodies* against itself. (In hemophilia, neutralizing antibodies against factor are called "inhibitors.")

"Hemlibra may interfere with laboratory tests, so how can I manage my bleeding disorder with blood tests that measure blood clotting?"

It's true that Hemlibra affects the results of some blood tests that measure clotting activity, but this is no different for FEIBA or rFVIIa. Both bypassing agents also skew some lab tests that measure clotting activity. Also, there is no lab assay to monitor the efficacy of either bypassing agent: efficacy is determined by observing how quickly bleeding slows or stops. And there are no blood tests for bypassing agents to determine optimal dosing, partly because these drugs have highly unpredictable "hemostatic effect"—meaning the same dose will work for one person but not for another.

"How will I treat breakthrough bleeds?"

Hemlibra is used for prophylaxis only, so patients will still need to stock a bypassing agent, or possibly factor VIII, to treat breakthrough bleeds. But using Hemlibra may restrict your

» page 14

11. Orphan diseases affect fewer than 200,000 people nationwide. Hemophilia affects about 20,000 in the US, and only a few hundred have inhibitors. 12. Find details of FDA accelerated approval programs in "Guidance for Industry Expedited Programs for Serious Conditions–Drugs and Biologics," www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf. 13. Monoclonal antibody drugs can be identified by the "mab" ending of their generic names. The generic name of Hemlibra is emicizumab, identifying it as a monoclonal antibody.

headlines

manufacturer

SubQ for Hemophilia B?

Catalyst Biosciences announced the phase II part of its phase II/III clinical trial program to evaluate marzeptacog alfa (activated) (MarzAA), a subcutaneously administered factor VIIa therapy being developed for prophylaxis in hemophilia A or B with inhibitors. The trial is set to enroll up to 12 patients across 10 clinical study sites globally. The goal is a reduction in annualized bleeding rate (ABR) that will be compared with each patient's historical ABR as the control. Safety and tolerability of daily subQ dosing and potential inhibitor formation will also be monitored. Interim data are expected in the first half of 2018. **Why this matters:** If successful, this product would be the first subQ therapy for hemophilia B patients with inhibitors.

For info: www.catalystbiosciences.com

Know Your PK!

Shire is now providing myPKFit, a new pharmacokinetic (PK) dosing software for use with Advate, a treatment for hemophilia A. This free, web-based Rx software can be used by healthcare professionals to create personalized treatment regimens in patients aged 16 or older. **Why this matters:** This software allows clinicians to determine PK of patients on Advate with only two to three blood samples, reducing the burden of collecting 10–11 blood samples over 32–48 hours as required for typical PK testing.

For info: www.mypkfit.com

New Factor IX Rebinyn® Available

Novo Nordisk's Rebinyn, Coagulation Factor IX (Recombinant), GlycoPE-Gylated, is now available in the US for treating hemophilia B. Rebinyn is an extended half-life factor IX for treating and controlling bleeding in adults and children with hemophilia B. It can be used to treat bleeds when they occur and to help manage bleeding during surgery. Rebinyn is not for routine prophylaxis, or for immune tolerance induction to treat inhibitors in patients with hemophilia B. **Why this matters:** Unlike extended half-life factor VIII products, extended half-life factor IX products offer a significantly longer half-life and are a game-changer.

For info: www.novonordisk-us.com

Bioverativ Sold

French drug maker Sanofi has acquired Bioverativ, manufacturer of Eloctate and Alprolix, for $11.6 billion. Sanofi has sought acquisitions to bolster its portfolio of drugs because it faces declining sales of its diabetes drug, Lantus, which has lost its patent protection. Bioverativ, based in Waltham, Massachusetts, began as a Biogen spinoff in 2016. **Why this matters:** Large drug makers have a renewed interest in smaller biotech firms, and some experts predict that 2018 will see a substantial increase in mergers and acquisitions.

For info: www.bioverativ.com

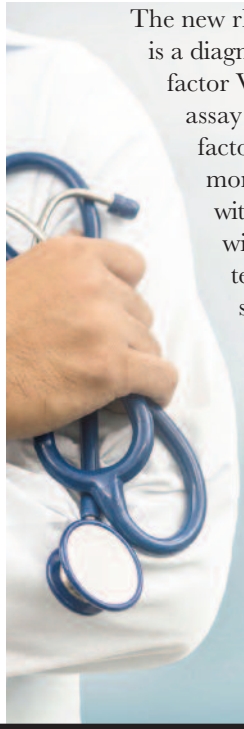
global

Going Green

GreenGene-F, the Korean Green Cross recombinant factor VIII product, is currently in phase III clinical trial in China. The company is also developing a prolonged half-life recombinant factor VIII and an anti-TFPI antibody for subcutaneous administration to treat hemophilia A patients with or without an inhibitor. **Why this matters:** Green Cross has been interested in the US as a market and could eventually introduce GreenGene-F here.

For info: www.rhealth.com

Easier Diagnosis of Hemophilia



The new rHealth Fluorogenic FVIII Kit is a diagnostic assay intended to quantify factor VIII levels in human plasma. The assay may be used to help identify factor VIII-deficient patients and monitor factor VIII levels in people with hemophilia. The kit is compatible with rHealth diagnostic platform technology, and is approved for sale in Europe but not in the US. **Why this matters:** rHealth Fluorogenic FVIII Kit offers a method requiring fewer steps compared to similarly sensitive factor assays—which tradition-ally have complicated protocols with multiple steps.

For info: www.rhealth.com

soundbites

A single administration of an investigational **hemophilia B gene therapy** (AMT-060) developed by uniQure reduced the mean annualized spontaneous bleeding rate (AsBR) from 9.8 to 4.6 in 10 adult subjects with severe factor IX deficiency.

BioMarin Pharmaceutical has dosed the first patient in the **global GENEr8-1** phase III study using a high dose of valoctocogene roxaparvovec (VR, formerly BMN 270), an investigational gene therapy for treating patients with severe hemophilia A.

The global hemophilia market is currently estimated to be worth **$10 billion** in factor sales.

CSL Behring has officially launched **a new website**, www.cslbehring.com, which includes a storytelling hub named Vita (Latin for "life") to inform and inspire people living with hemophilia and other rare diseases.

The Republic of **Ireland** has become the first country in Europe where all people with hemophilia will have their treatment switched to the extended half-life therapies Eloctate (factor VIII) and Alprolix (factor IX).

Check out the February issue of NHF's *HemAware* (hemaware.org), which features mountaineer Chris Bombardier and his successful **Seven Summits Quest**.

Read the February issue of PEN, which helps readers get motivated to set goals for 2018, using **Chris Bombardier's historic climbs** as a guide for successfully reaching goals. www.kelleycom.com

After more than a decade, National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC) issued new, updated ***Guidelines for Emergency Department*** *Management of Individuals with Hemophilia and Other Bleeding Disorders*, 252, in September 2017.

CSL Behring has **discontinued production** of its plasma-derived factor VIII product Monoclate-P, which should still be available through distributors until December 2018.

nonprofit

NHF 70th Annual Meeting in Orlando!

October 11–13, 2018

National Hemophilia Foundation welcomes all attendees to sunny Orlando for three days of learning, fun, and networking with the national bleeding disorder community. Guest speakers, games, and social events make this a valuable time for new families and regular attendees. Registration opens February 1, 2018. **Why this matters:** This is the largest national hemophilia meeting in the world.

For info: www.hemophilia.org

in memoriam

Barry D. Haarde passed away February 17, 2018, at age 52, at his home in the Woodlands, Texas. Barry skyrocketed to stardom in the hemophilia community for his intrepid bike rides to raise money for charity, despite having hemophilia A, HIV, and a contracted knee. Barry traveled across the US on his Cervélo bicycle six different times spanning six years, raising over $250,000 for Save One Life, a child sponsorship nonprofit that provides direct financial aid to children with bleeding disorders in developing countries. He was a frequent speaker at hemophilia events, and was popular with parents and patients. He won special awards throughout his brief riding career. Barry was an accomplished trombone player, and toured professionally with the Tommy Dorsey band. He was an avid stamp collector, and loved lighthouses. Shortly before he died, he took a long tour to photograph lighthouses in the US. He worked for Hewlett-Packard for 27 years in the IT department, until the office was closed due to Hurricane Harvey in 2017. Barry will be remembered for his humble and self-deprecating manner, incredible athleticism, and dedication to people with hemophilia. He is survived by his sister Emily Cobb and brother Ed Haarde of Florida. The family asks that donations be made in Barry's name to Save One Life, www.saveonelife.net.

Creating Fiji's First Hemophilia Organization

Laurie Kelley and Dr. Julia Phillips, New Zealand, celebrate the new FHF

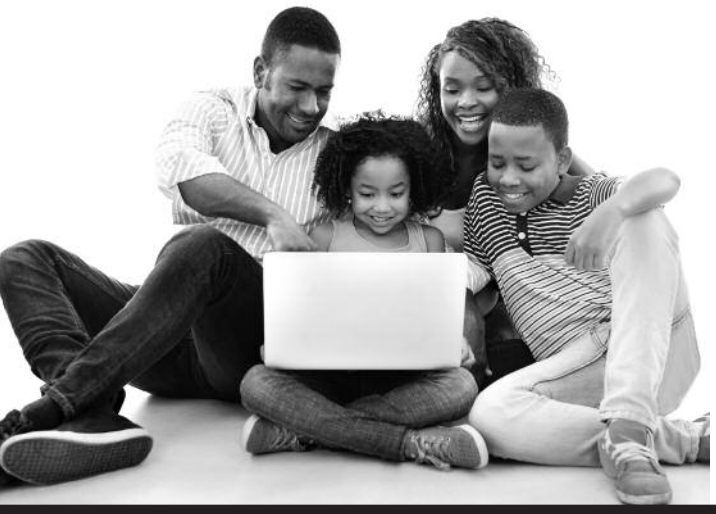
LA Kelley Communications president Laurie Kelley visited the South Pacific island nation of Fiji in February, to help start the first national hemophilia organization. Contacted initially via Facebook by patient Kunaal Prasad, age 23, Kelley authorized the first shipment of factor concentrate for some families through Project SHARE. Recognizing the need to train Fiji physicians in hemophilia and infusion, she invited hematologist Julia Phillips from New Zealand, and was accompanied by Randall Curtis, a man with hemophilia from California who is an advocate for the community and developer of an internationally respected hemophilia database. The three visitors met with physicians at three main hospitals, and held a medical training workshop on February 10, inviting medical teams from across the island of Viti Levu. A workshop the next day focused on creating the Fiji Haemophilia Foundation (FHF), with elections for leaders and forming a constitution. Prasad was unanimously elected president of the new foundation.

patient programs

Visit an HTC—Virtually!

Believe Ltd.'s new website offers the first online guided tour of a hemophilia treatment center (HTC). The five-minute video gives families a clear look at the value of the comprehensive care model at their HTC, and concrete ideas for engaging with key staff members. In fun vignettes, families are introduced to the roles of key staff: hematologist, nurse, physical therapist, social worker. Available in Spanish. **Why this matters:** HTCs are centers of excellence in providing hemophilia care, and families can learn about HTCs before they visit, to make their trip more productive.

For info: www.HTCTour.org



Facts on Hemlibra... from page 10

use of FEIBA to treat breakthrough bleeds because of the risk of unwanted clotting. Because of adverse events that occurred during clinical trials, Genentech recommends that if FEIBA must be used to control breakthrough bleeds, then patients should use less than 100 U/kg of FEIBA total. National Hemophilia Foundation's Medical and Scientific Advisory Council (NHF's MASAC) goes one step further, advising that "use of aPCC (FEIBA) for breakthrough bleed treatment for patients on emicizumab (Hemlibra) should be avoided if possible."[14] This may be a problem for some patients, because not everyone responds equally well to FEIBA and rFVIIa. For some people, one works better than the other. And some patients need both products to control bleeds.

If you know you don't respond well to rFVIIa, and you depend on FEIBA to treat bleeds, discuss with your hematologist how to treat breakthrough bleeds if you decide to use Hemlibra. And even though there were no problems with using rFVIIa to treat breakthrough bleeds in clinical trials of Hemlibra, preclinical experiments indicated a possibility of "hypercoagulability" (blood clots) when Hemlibra and rFVIIa are used together. The risk of developing a blood clot while on Hemlibra and using rFVIIa was too small to measure in the clinical trials (none were found), so determining the risk will take post-marketing surveillance in a much larger population of patients and reports to the FDA Adverse Event Reporting System.[15]

The good news? When following manufacturer recommendations to minimize FEIBA dosing, no thrombotic events or TMA have been associated with using Hemlibra prophylactically.

"Can I use Hemlibra while on immune tolerance induction therapy?"

That's a good question, with no definitive answer yet. Along with a possibility of hypercoagulability when Hemlibra is used with rFVIIa, the preclinical experiments showed the same possibility when factor VIII and Hemlibra are used together. Still, in the phase I clinical trial of Hemlibra on 48 people without hemophilia, there were no observed "hypercoagulable effects" over the four-month observation period. But given that ITI often requires daily high doses of factor over several weeks to more than a year, studies using Hemlibra in combination with ITI are needed to determine the safest regimen in which to use both.

Currently, some people on ITI who continue to have bleeds are often put on prophylaxis with bypassing agents. In these cases, Hemlibra instead of bypassing agents might be used for prophylaxis. But there is disagreement on this. ITI is very expensive and time-consuming, and many patients continue to have spontaneous bleeds. Some physicians wonder whether ITI is even necessary if prophylaxis with Hemlibra is better than prophylaxis with factor VIII. They also point out that the inhibitor titer (level) decreases over time when a patient is not exposed to factor VIII—meaning that if you have only infrequent bleeds while on Hemlibra, then you could use factor VIII to treat bleeds or for surgery for a short time until inhibitor levels rebound. The use of ITI while on Hemlibra is a great question for your hematologist.

"Can I take Amicar while on Hemlibra?"

This is another unanswered question. Antifibrinolytics such as aminocaproic acid (brand name Amicar) and tranexamic acid (brand names Lysteda, Cyklokapron) are designed to slow the breakdown of clots. They're sometimes used in treating mucous membrane bleeds, including mouth or nose bleeds. The Hemlibra package insert and promotional materials do not mention antifibrinolytics, and their use was not addressed in clinical trials.

Antifibrinolytics increase the risk of unwanted blood clots when used with bypassing agents. FEIBA's package insert warns of the possibility of thrombotic events when the drug is used with antifibrinolytics. NovoSeven's package insert includes no such warning, but adverse thrombotic events when the drug was used with antifibrinolytics were reported to the FDA in post-marketing surveillance. The increased risk of blood clots while taking antifibrinolytics and bypassing agents may have no bearing on Hemlibra prophylaxis, but again, this is unknown and a question for your hematologist.

"Can I develop antibodies to Hemlibra?"

Yes, you can develop antibodies to any substance introduced into the body. Antibodies against Hemlibra were detected in five patients in phase I trials, and were suspected but not identified in two patients in Genentech's HAVEN 1 (adult) phase III trial. None were detected in the HAVEN 2 (pediatric) phase III trial. One of the patients in the phase I trial tested positive for antibodies against Hemlibra even before taking the drug. None of the antibodies were neutralizing antibodies, so they did not affect the drug's function. But for one of the patients, the non-neutralizing antibodies significantly reduced the half-life of Hemlibra from about 30 days to about seven days. These patients remained in the trial and continue to be followed; this will provide more information on how the antibodies affect the drug and bleeding patterns.[16]

The risk of developing antibodies differs with the type of monoclonal antibody being used. Historically, monoclonal antibodies were produced in mice, and these antibodies carried a significant risk of an immune response when injected into humans. With advances in recombinant DNA technology, we can now direct mice, rabbits, or other organisms to produce partly or fully *human* antibodies, which are much less immunogenic—less likely to produce an immune response and stimulate the production of anti-drug antibodies.

Antibodies are often classified into four broad groups based on how "humanized" they are. Each group carries a different risk for the development of anti-drug antibodies. The four groups are mouse (non-primate, including rabbit), chimeric (from two different animals; about 65% human), humanized (98%–99% human), and human (100% human). As you might expect, mouse antibodies have the highest risk of developing anti-drug antibodies, over 40%. Humanized and human antibodies have the lowest risk, less than 10%.

14. For NHF MASAC guidance on Hemlibra, see http://files.constantcontact.com/a950483b501/8c82455c-1db2-47aa-9b5a-03971e56da76.pdf. 15. Report all drug-related adverse events to your physician, who can inform the FDA. You can also log your adverse event yourself, using the FDA Adverse Event Reporting System: www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ 16. Johannes Oldenburg, Johnny N. Mahlangu, et al., "Emicizumab Prophylaxis in Hemophilia A with Inhibitors," *New England Journal of Medicine* 377 (2017): 809–18.

Hemlibra is a humanized antibody with a relatively low risk of anti-drug antibody development. So far, no neutralizing (anti-Hemlibra) antibodies have been detected in patients. Because the risk of developing anti-Hemlibra antibodies seems very small, this risk can't be accurately predicted by relatively small clinical trials; we'll have to wait for results from post-marketing surveillance. The issue of anti-Hemlibra antibodies will also be addressed in two additional phase III clinical trials of Hemlibra, currently underway: HAVEN 3 is evaluating prophylactic use of Hemlibra versus no prophylaxis in people with hemophilia A and no inhibitors (data to be reported at the upcoming World Federation of Hemophilia medical meeting). And HAVEN 4 is looking at higher doses of Hemlibra, but less frequent monthly dosing as opposed to weekly dosing (to be completed in July 2018).

"Genentech is bribing researchers and physicians to hype Hemlibra."

This misinformation might best be described as a conspiracy theory. There *has* been great interest in Hemlibra in the hemophilia community, not because physicians are being bribed, but because people want a more effective and less burdensome therapy for hemophilia A with inhibitors. They want a therapy that will reduce or eliminate bleeds, help preserve joints, and improve quality of life—it's a simple as that.

One group that may push for Hemlibra is insurance companies. Prophylaxis with bypassing agents to treat hemophilia with inhibitors can cost almost a million dollars a year. The wholesale acquisition cost (WAC) of Hemlibra is estimated at about $482,000 for the first year of treatment and $448,000 for subsequent years (cost varies because dosage is based on a person's weight). WAC is the "list price" of a drug, and insurance companies usually pay much less than WAC. This means that a patient on Hemlibra prophylaxis may save the insurance company anywhere from 33% to over 75% of the cost for a patient on prophylaxis with bypassing agents.

There is also speculation that the cost of Hemlibra might be reduced. Genentech is now conducting clinical trials of the drug in people with hemophilia A without inhibitors; in order to break into that market, the cost would have to be less than $300,000 a year—the average cost per year for prophylaxis with factor VIII. Otherwise, insurance companies, which are always watching the bottom line, would not be inclined to cover the drug because of patient treatment burden.

Risk versus Benefit

Missing from the fearmongering posts on social media was a fact-based discussion of Hemlibra's risks versus benefits. Many posts inflated the risks and minimized or did not mention the benefits. *All* drugs have risks, and the risks of Hemlibra seem to be equal to or lower than the risks associated with bypassing agents. At the same time, Hemlibra appears to be being significantly more effective, based on the published HAVEN 1 and HAVEN 2 phase III clinical trial data.

For people with hemophilia A and inhibitors, the benefits of Hemlibra are a game-changer. When Hemlibra use was compared to previous bypassing agent use in the HAVEN 1 trial (adults), the annual bleed rate for Hemlibra was 1.8 bleeds per year, with 15.7 for the bypassing agent prophylaxis—an 88% reduction. Hemlibra won, hands down. Overall, the percentage of adult patients with zero bleeds was 58% for Hemlibra, compared to 12% for prophylaxis with bypassing agents. And the HAVEN 2 phase III clinical trial (children) produced the most impressive results: a 99% reduction in bleed rate in those treated with Hemlibra prophylaxis, compared to prophylaxis or on-demand treatment with bypassing agents. A remarkable 95% had no treated bleeds, and 65% had no bleeds at all.

The Bottom Line

Hemlibra is the first of several innovative therapies for hemophilia to reach the market. Several others are in the pipeline and may be approved by the FDA within the next few years. All of these new therapies will carry some risk of adverse events as well as the potential for side effects. They may also carry benefits. Deciding whether to switch to a new product involves weighing the risks and the benefits of a new drug, with the benefits outweighing the risks. But the decision to move to a new product is personal: FDA approval assures you that the benefits of a drug, in general, outweigh the risks, but that doesn't mean the drug is the best choice for your particular situation.

So how do you decide? First, you need facts and impartial information tailored to you. What should be obvious after reading this article is that social media is *not* the place to get complete, accurate information! Posts on social media can be misinformed, and may involve conspiracy theories and emotional hype—none of which will help you make an informed decision.

NHF's MASAC is a good source of information, and its guidelines and recommendations represent a consensus of opinions of the top bleeding disorder experts in the US. PEN is another good source of information: we strive to present fact-based, unbiased information, and reading our articles will give you a good understanding of a topic and what questions to ask.

But no source of information from a newsletter, a magazine, or the internet is tailored to your specific situation. So talk to the person who may know you best—your hematologist! Don't wait for your annual clinic visit. Call today to ask questions about your current therapy, and to discuss new ones entering the marketplace. It's a new era in hemophilia treatment, so make your HTC your first stop for information.

US Hemophilia Factor Brands by Company and Type

MANUFACTURER	RECOMBINANT			PLASMA-DERIVED		
	FVIII	FIX	Inhibitor	FVIII	FIX	Inhibitor
Aptevo Therapeutics		Ixinity®				
Bayer	Kogenate®FS *Kovaltry®*					
Bioverativ	*Eloctate®*	*Alprolix®*				
CSL Behring	*Afstyla®* Helixate®FS	*Idelvion®*		Monoclate-P® Humate-P®	Mononine®	
Grifols				Alphanate	AlphaNine®S/D Profilnine®	
Kedrion*				Koate®-DVI		
Novo Nordisk	Novoeight®	*Rebinyn®*	NovoSeven®RT			
Octapharma	Nuwiq®					
Pfizer	Xyntha®	BeneFIX®				
Shire	Advate *Adynovate* Recombinate	Rixubis		Hemofil M	Proplex-T Bebulin VH	FEIBA VH

Italicized brand names indicate extended half-life products. Because there is no consensus on what constitutes an extended half-life product, check the package insert (PI) carefully. The half-life of a product may also vary widely from patient to patient, and may vary widely with age (younger = shorter half-life; older = longer half-life). Have a pharmacokinetic (PK) test to determine your individual factor half-life, and discuss with your HTC hematologist which product best meets your treatment needs.

Recombinate is a first-generation recombinant product. Kogenate FS and Helixate FS are second-generation products (they are the same product). Advate, Adynovate, Afstyla, Alprolix, BeneFIX, Eloctate, Idelvion, Ixinity, Kovaltry, Novoeight, Nuwiq, Rebinyn, Rixubis, Vonvendi and Xyntha are third-generation products. Helixate FS and Monoclate-P have been discontinued, but will still be in the US distribution pipeline until about December 2018.

* Kedrion distributes Koate-DVI in the US for Grifols, which is the manufacturer.

von Willebrand Factor Concentrates

Manufacturer	Product	Type	Indication
CSL Behring	Humate-P®	Plasma-derived FVIII/VWF Complex. Average ratio of VWF:RCo to FVIII is 2.4:1.	Adults and children with severe VWD (type 3), and patients with mild to moderate VWD where the response to desmopressin (DDAVP) is known or suspected to be inadequate. Not indicated for prophylaxis.
Grifols	Alphanate®	Plasma-derived FVIII/VWF Complex. Average ratio of VWF:RCo to FVIII is 1.3:1 (varies by lot).	Control and prevention of bleeding in patients with hemophilia A, and patients with VWD where desmopressin (DDAVP) is either ineffective or contraindicated. Not indicated for patients with type 3 VWD undergoing major surgery.
Octapharma	wilate®	Plasma-derived FVIII/VWF Complex. Ratio of VWF:RCo to FVIII is 1:1.	Adults and children with type 3 VWD, and patients with mild to moderate VWD where the response to desmopressin (DDAVP) is known or suspected to be inadequate. Not indicated for prophylaxis.
Shire	Vonvendi	Recombinant VWF (contains no FVIII).	On-demand treatment and control of bleeding episodes in adults with VWD. Administer first dose with a recombinant FVIII-only product if FVIII baseline levels are below 40% or are unknown (this applies to all type 3 patients).

VWD: von Willebrand disease. VWF: von Willebrand factor. RCo: von Willebrand ristocetin cofactor (VWF:RCo) assay. aPCC: activated prothrombin complex concentrate.

Small-Molecule Hemophilia Therapies

Manufacturer	Product	Type	Indication
Genentech	Hemlibra®	Bispecific antibody. Administered subcutaneously once a week. Not a factor product.	Routine prophylaxis in adults and children with hemophilia A with factor VIII inhibitors. Use of more than 100 U/kg total of aPCC (FEIBA) for treating breakthrough bleeds increases risk of blood clots. Consult your healthcare provider before using FEIBA.

As I See It... from page 3

to envision what life would be like for our son, a boy with blood that does not clot.

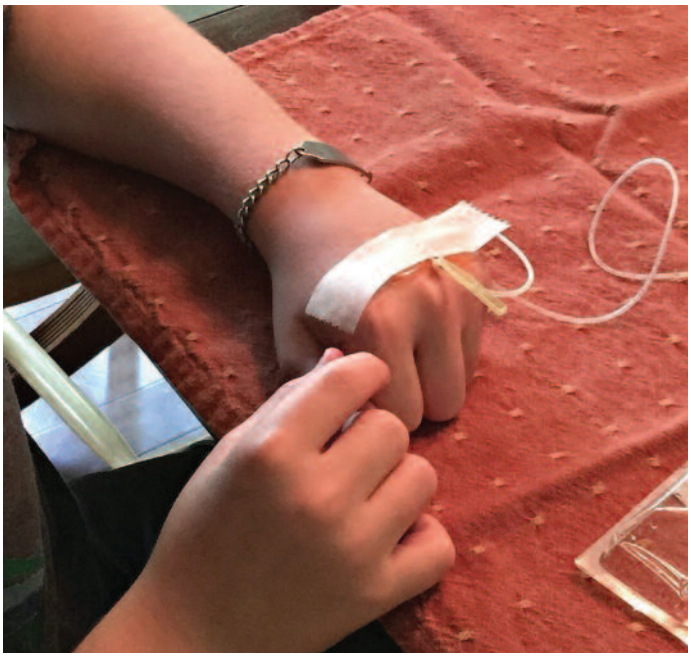
We would soon meet with doctors, nurses, physical therapists, and social workers who would help us manage Bubba's condition and our own fears, insecurities, and concerns. But prior to those incredibly helpful first meetings, we wondered exactly how we were supposed to raise a child who is different. We were desperate for someone to help us make sense of how we'd navigate the coming years.

As parents, we had to make a decision: either let Bubba play, or begin to guide his interests in a direction other than sports. When he started preschool in Tupelo, we learned that his teacher and her husband had lost a child at a young age. During one of our first discussions with this teacher, we found a common ground in our desire to make sure that Bubba was limited as little as possible by hemophilia. His teacher agreed fully, and told us that she and her husband had felt the same way about their son. I still remember her saying that she'd never regret the fact that they had always let him do as much as his medical condition would allow.

Overcoming our initial fears was not easy, nor would those fears disappear immediately when Bubba's first soccer game ended without incident. So much of Bubba's life is defined by the fact that he has hemophilia, but that does not have to be a bad thing. Playing soccer has been great for him, and a few people have even learned more about hemophilia because of his presence. The biggest leap wasn't his to take; it was ours. Our decision to let him play sports ensures that we'll always feel apprehension at game time, but it also means that our son will make valuable memories as a member of a team, and as a little kid having fun on the soccer field.

Derek lives in Saltillo, Mississippi, with his wife Ashley and their children Abbey and Bubba. He is executive director of two University of Mississippi regional campuses and assistant professor in the School of Education. Ashley is a fifth grade math teacher in the Tupelo Public School District.

Inhibitor Insights... from page 4



Prophylaxis versus On-demand Factor Use

Some studies have shown that prophylaxis, as compared to on-demand factor use, is associated with a lower risk of inhibitors. Other studies have shown no such association, but if one exists, it may be because on-demand treatment with factor occurs after a bleed, when the immune system is already on high alert. On-demand treatment often involves infusing higher doses of factor and possibly for an extended period, which may increase the risk of inhibitors. There is also some debate about whether starting prophylaxis before any injury or when the child is very young would help induce tolerance to factor, potentially lowering the risk of inhibitors.

Type of Factor

The role of factor type (recombinant versus plasma-derived) in causing inhibitors has long been controversial. Multiple studies have found no correlation between factor type and inhibitor risk. However, the 2016 results of a large inhibitor study called SIPPET found a significantly higher inhibitor rate in people using recombinant factor products as compared to plasma-derived factor concentrates containing von Willebrand factor.[2] Research continues into the implications of these findings, and many questions remain to be answered by new research. The next issue of PEN will look at the European Medicines Agency review of the SIPPET study.

Understanding why inhibitors develop can be more important for some parents than for others. If you plan to have more children, consult with your hematologist and perhaps a geneticist; information about the risk of inhibitors in your family will help you be prepared. You might also consider delaying elective surgery or, in the case of circumcision, skipping the surgery altogether.

Having two sons with very different inhibitor results has been eye-opening. The key thing I have learned is that it's not the Bethesda unit (BU) level that is important. It's not even important to completely understand why an inhibitor showed up in my sons. The crucial part of living with an inhibitor is ensuring that a person's quality of life is the best it can be. Caeleb has been bleed-free for three years. Daily accessing and infusing isn't convenient, but if it gives us greater quality of life, then that's what we do.

Knowing why inhibitors develop can bring peace of mind, but sometimes we never truly understand the *why*. We simply embrace the fact that an inhibitor is part of our lives and move forward, resolute in our goal to give our children the best that life can offer.

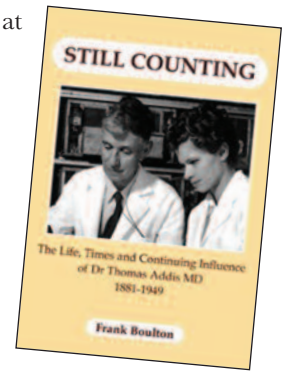
2. SIPPET, or Survey of Inhibitors in Plasma-Product Exposed Toddlers, was a prospective randomized study of inhibitor development in previously untreated patients. The study found a significantly higher incidence of inhibitors in patients treated with recombinant factor VIII than in those treated with plasma-derived factor VIII containing von Willebrand factor.

Richard's Review... from page 5

There was one exception in Addis's research: when he treated a patient with hemophilia for an *in vivo* experiment—inside the body. On May 10, 1910, Addis transfused about 300 cc of freshly drawn human phosphated blood[3] (probably his own anticoagulated whole blood), shortening the patient's blood-clotting time. Addis published his work only in 1916, after another physician reported a similar experience using a different chemical to prevent blood clotting. Addis's work is considered the first report of using phosphated blood in a transfusion to treat hemophilia. And remember, even though blood groups (A, B, AB, O) were discovered in 1901, blood group typing was not universally acknowledged in 1910.

Addis's work was not fully acknowledged and expanded on until the 1930s, when medical researchers at Thorndike Laboratories in Boston began to separate out the different components of plasma to identify the missing proteins in hemophilia. Would research into the cause of hemophilia have been accelerated if Addis's work had been fully recognized earlier, in 1910? Maybe not, because the laboratory methods to completely separate the blood components still needed to improve.

Stanford wanted to recruit an English physician with German medical training. So in 1911, Addis moved to San Francisco to become assistant professor of medicine at Stanford. He married, had two daughters, and eventually became a US citizen. In his laboratory, Addis worked on jaundice, diabetes, and blood circulation, but his most significant research was on the kidney. Unfortunately for the bleeding disorder community, Addis did not continue his blood-clotting research at Stanford.



Fellowship training in hemophilia was important for researchers like Addis a century ago, and today, postdoc fellowship training in bleeding disorders is just as important for medical researchers. Keeping these highly trained people in a research career is essential. This is how the science of bleeding disorder research is continually advanced. National Hemophilia Foundation (NHF) offers a variety of research fellowships, clinical fellowships, and career development awards not only for physicians, but also for nurses, social workers, and physical therapists. Please help support[4] these research efforts so that healthcare providers at your HTC continue to conduct research on what benefits all of us.

3. Blood clots rapidly after being removed from the body, making transfusions of whole, untreated blood impossible. Before 1900, researchers determined that certain chemicals (anticoagulants) binding calcium in the blood prevented coagulation, which could be countered with calcium chloride. They used potassium oxalate, though they feared toxicity if used in a transfusion. So they began adding phosphate for transfusion. Next came citrate, or sodium citrate, again with worries about toxicity. The goal was to keep the blood from coagulating by adding chemicals whose effects could be reversed. Finding the best additive in the best formula took some time and experimentation. 4. NHF funds a broad range of research, including Career Development Awards, Clinical Fellowship Programs, and Judith Graham Pool Postdoctoral Research Fellowships. See www.hemophilia.org.

YOU... from page 6

a PK study. Crystal laments, "My boys' hematologist makes me feel like I'm doing something wrong, but refuses to do a PK study." June adds, "For years, our medical staff acted as though we were to blame when he'd have bleeds—even though he was infusing regularly."

Kate Stotz, who has a 22-month-old with severe hemophilia A, felt she had to fight against the standard prophy infusion schedule of three times a week. "This was not working for our son," she explains. "He was having frequent bleeds on Sunday, the day he was unprotected. Trough levels indicated that in order to maintain a minimal 1% trough, we could not exceed 48 hours between infusions." Though Kate wanted to infuse every other day to keep him protected, her son's hematologist didn't want to break from the traditional schedule the HTC normally prescribed. "It took a lot of advocating on our part and ultimately finding a new doctor at a different HTC."

Sarah Hueston successfully advocated for a new prophy regimen for her 16-year-old son with severe hemophilia A, who plays two varsity sports. When they determined he had a short half-life, the HTC team, Sarah, and her son developed his treatment plan together. He now infuses standard factor daily. "It's what works for us," says Sarah, "and his doctors are so proud of him, as are we, his family! Never did we think he'd be doing the things he's doing even 10 years ago!"

By logging her son's bleeds, Stacey Mollinet was able to convince her HTC team to change the treatment schedule. When her son with severe hemophilia A was a young teenager, he didn't bleed like a typical severe and was not very active by nature. "I had to push the HTC," she recalls, "so he could treat only twice a week, instead of a standard prophy schedule." Around age 14, he started to bleed more like a typical severe. So Stacey worked with the HTC to adjust her son's dosing schedule, and ended up dosing every other day until he switched to extended half-life factor two years ago.

"There's not a one-size solution for everyone," Stacey has learned. "Keeping good infusion and bleed logs so you know what schedule works best to prevent bleeding is important."

Crystal laughs, "I could probably write a book about all the ways my boys 'differ' from the typical definition of hemophilia."

And in a community where boys "typically" have hemophilia while women are carriers, women are now advocating to redefine what it means to have hemophilia. Labels have their place, but when we define hemophilia and determine treatment plans, we sometimes need to look outside the box at hemophilia—and trust the parents and patients when they describe their own uniqueness and needs.

Inbox... from page 2

Project SHARE

I AM A HEMOPHILIA A patient. I have benefited a lot from the donated factor you gave Jose Memorial Haemophilia Society–Kenya. I am so grateful to Project SHARE since I am now able to control my bleeds and improve my knee joint mobility. My knee joint is a target bleed area and was badly damaged before, but now my knee joint has greatly improved. Thank God for Project SHARE! I am in a completely comfortable and safe space now since I don't have to worry about how I will get factor.

Kenneth Karanja
KENYA

I REALLY APPRECIATE Project SHARE for ensuring we have access to factor. I am in school almost every day now because when I get a bleed, I am able to infuse very easily. My heart and gratitude are with Project SHARE for making our lives easier!

Ephraim Wambugu
KENYA

ON MARCH 6, 2017, my wife brought me to the hospital because I could no longer endure the pain in the left side of my stomach. I learned I had a psoas bleed, and that, at age 54, I had acquired hemophilia. I was given cryoprecipitate and fresh frozen plasma every day. My doctors advised my family to look for Blood Brothers Aid Foundation, because I need factor VII and VIII to infuse. We met Raymund Naños by seeing BBAF advertised on TV. Raymund even visited me at the hospital many times, and gave me factor VII and VIII. I would like to give my snappy salute to the officers of BBAF for their unending support to all hemophilia patients like me. I give thanks to the partners of BBAF, including Project SHARE and Rev. Fr. Donald Kill. Thank you so much!

Hector Baccay
PHILIPPINES

AVAILABILITY OF FACTOR has really helped us, especially when I was circumcised. My knee joint was so damaged before, but now it is normal. Project SHARE has been transformative in my life; it is our life and hope.

Stephen Muiruri
KENYA

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