Joint Disease, Prophylaxis, and Microbleeds: Are We Getting It Right?

Paul Clement

So, you’re doing everything right: You infuse factor concentrate regularly according to your prophylaxis schedule. You eat healthy and exercise. You go for your annual HTC visit. But…you still develop an arthritic joint. What gives?

Joint disease is the most common complication in severe hemophilia. You already know that repeated bleeding into joints causes degenerative joint disease—slow deterioration of the cartilage in the joint resulting in a painful form of arthritis and eventual destruction of the joint. But isn’t prophylaxis, along with all the other general healthy habits, supposed to prevent that? Is there something about prophylaxis we’re not getting? Really, what gives?

The Culprit?

From fresh frozen plasma to cryoprecipitate to factor concentrate, the past fifty years have seen dramatic improvement in the products we use to treat hemophilia.

The mid-1990s brought a new treatment regimen in the US: prophylaxis. The goal of prophylaxis was to prevent bleeds from occurring by infusing factor one to three times a week; this would keep some factor circulating in the bloodstream to help stop bleeding. And it was hoped that prophylaxis would greatly reduce or prevent joint disease. Prophylaxis promised that children with severe hemophilia could mature into physically active adults, free of the crippling effects of arthritis.

Although the promises of prophylaxis have largely proved true, joint disease has not been completely prevented. Now, young men who have been on prophylaxis all of their lives are showing some signs of degenerative joint disease, sometimes in joints where they haven’t reported any major bleeds. Why?

One of the possible culprits is microbleeds. Microbleeds are tiny bleeds into joints that do not produce the typical signs and symptoms of a bleed. Because they go unnoticed, they are sometimes called subclinical bleeds. Over time, often many years, these tiny undetected bleeds may contribute to changes
Call it “Revenge of the Nerds.” After a 24-year marriage ended, I entered the dating game relatively intact and healthy: at my high school weight, and able to ride 100 miles on my bike, mountain climb, and bend over and tie my shoes. You laugh, but the truth is, many of the men I am meeting at age 56 have joints that are battered, weak, stiff, and in need of replacement. And those are the ones without hemophilia.

Part of the dating screening process is finding someone who likes to do what you enjoy, and is able to do it. So I’m looking for someone to hike, bike, climb, and run with me. Preferably in my age group—who knows who Herman’s Hermits were and recalls when man first stepped on the moon. But guys this age come with baggage, and I don’t mean emotional and marital. Turns out the guys who were jocks in their high school years and beyond—tennis champs, track stars—put tremendous stress on their joints and did some damage, even if it wasn’t apparent then. It sure is now. I watch them hobble into a restaurant or offer an excuse for not keeping up on a bike (“I’m tired”). But there it is: they face joint replacements at age 55, 60, and beyond. One guy I met who didn’t have joint damage laughed, “It pays to have been a nerd!”

Well, not really: he was a nerd and didn’t last past date two.

Meeting these men, I’ve wondered if the joint damage was done by microbleeds. I read in my favorite magazine, Outside, that over 2% of Americans have artificial joints (wonder how many of those are mid-50’s and dating?), and those numbers are expected to climb.* In 2012, a study in Journal of Bone and Joint Surgery predicted a 670% increase in total knee replacements by 2030.

I asked Paul Clement, our marvelous science writer, to look into this topic (for hemophilia, not for my dating purposes). He has written an excellent feature on why some people with bleeding disorders still face joint damage even after years of prophylaxis. Please read it carefully, and discuss this important new area of research with your HTC doctor. All the great products in the world, including those in the pipeline, still may not protect from bleeds if we are missing some of the complex pieces of knowledge about how joints bleed.

As for me, I’ve rearranged my sequence of dating screener questions: 1. Do you still live with your mother? 2. Are you a cat person? 3. How are your joints?

* Outside Online, March 17, 2014
Chances are, if you have hemophilia and can self-infuse, you’ve had to do it in less-than-ideal surroundings. For someone (like me) who is terrified of needles, infusing anywhere can be a challenge. Here are some tips I’ve learned infusing on the sides of mountains, in the backs of vans, on a sailboat, and even in a moving car!

1. Infusions are infusions. No matter where you are, you are putting a needle into your vein. Most of us have done this thousands of times, so that’s the easy part. You know the drill already.

2. Take a step back and a deep breath. Sometimes when you feel rushed, you can miss a vein. As you’re about to stick yourself, take a deep, relaxing breath. That two-second breath will save you more time than a miss, as I have learned. I once pulled my quadriceps on a 2011 trip up Mt. Kilimanjaro in Tanzania. As soon as I got to the next camp, I worked as fast as I could to infuse—and blew right through my vein. I was so disappointed in myself, but as I regrouped and tried it the second time, I took a deep breath and nailed it!

3. Try to have several options for veins. When infusing in a familiar environment, try a different vein, especially if you have some extra time. Having several options will come in handy if you’re ever standing on the side of a mountain and need to infuse. Before I get any comments from my girlfriend: I admit that this is still something I am pretty terrible at. I have a favorite vein that I use over and over. It’s my comfort spot to get my infusion done. But I do use other veins occasionally that I know I can hit. I just need to practice more.

4. Stay hydrated! One of the keys to successful mountaineering is drinking water, and this also helps a ton with infusions: being hydrated makes your veins easier to stick. Any physical activity you do, from walking to running to hiking, requires plenty of water. When traveling abroad, clean water isn’t always easy to obtain, so take advantage of clean water when you can. Or bring purifying tablets or use a backpacker’s water filter, available at most outdoor sports stores.

5. Sometimes you just have to go for it. When I had a bleed on a sailing trip in the British Virgin Islands, I had only one option: infuse on a rocking boat. I had nowhere else to go, so I just sucked it up and went for it. It was exciting and a little terrifying, but it worked!

6. Teach someone else. It never hurts to have help infusing; and many people are open to the idea. Because I travel hours, even days from civilization, this is really a must for me. If something happened where I couldn’t infuse, I would need help.

7. Sanitize! Just because you’re filthy dirty and stink from being in some crazy place, don’t forget to be clean when infusing. Wash as well as possible, use gloves, and use as many alcohol wipes as necessary to get the infusion site clean. Getting an infection from an infusion should never happen.

Whether you’re climbing mountains, taking a vacation far from home, or just stuck somewhere away from your usual infusion spot, I hope these tips will help ease some tension about infusing out of your comfort zone, whatever that means for you. Don’t miss what this amazing world has to offer just because of your hemophilia. Own it!

Chris Bombardier, age 28, has severe hemophilia B. He graduated from Doane College in 2007 with a BS in biology. He is currently a board member of Save One Life, and is attempting to become the first person with hemophilia to climb the highest mountain on each continent, known as the 7 Summits. Chris volunteers with the hemophilia community in Kenya and also in his local community.
In Part 1 of “Beating the Odds,” we introduced Deena Lipinski of Arizona, single mother of Tyler. Tyler has hemophilia B, and developed a high-titer inhibitor. This is a dangerous complication for people with hemophilia B because normal infusions of factor IX no longer work, and Tyler has faced numerous medical emergencies and challenges. Somehow, Deena has maintained strength, grace, and humor through it all.

Q: When we left off at the end of Part 1, Tyler had just learned to self-infuse at age seven. What happened next?

Tyler was successfully desensitized to factor IX concentrate when he was seven. For five years we were able to use factor IX daily and keep his bleeds to about once a month. In 2011 Tyler turned 12, and he started getting hives after receiving his daily infusions. This escalated to anaphylactic reactions (severe allergic reactions). Even though we had been through all this before—the hives, throwing up, trouble breathing after receiving his factor—I had forgotten how stressful things could be. We were frequently running to the ER and calling paramedics. It was a very scary time, and Tyler dreaded each infusion. I was not expecting that he would relapse after using factor IX concentrate for years.

During the next two years, Tyler was bleeding constantly. With no prophylactic factor IX treatment, we again had to deal with the bleeds as they happened, rather than prevent them. Life became crazy again. I was really confused about why, after so many years, his allergic reactions had returned. The thought of going through the 18-month desensitization process again was depressing. Tyler was equally frustrated. He seemed to be always bleeding. Every week he had a new bleed. His ankles, knees, elbow, forearm, and iliopsoas muscle [a muscle group running from the inner thigh into the lower abdomen] were the most common sites for bleeds. It became hard for him to attend school because if he had a knee bleed and used his wheelchair, he would get a bleed in his elbow from wheeling himself. Crutches caused forearm bleeds. Even his Xbox could cause a bleed in his arm if he played too long. And we gave up on the Wii due to what I called “Wii bleeds.” Tyler could not just be a regular kid. As before, things were spiraling out of control.

For me, maintaining a job was difficult. Fortunately, a friend offered me a part-time position with flexible hours. This was a lifesaver, as I’m a single mom and Tyler’s only caregiver. The job turned out to be exactly what I needed. If I had an emergency at the beginning of the week, I worked at the end of the week, and vice versa. Having a place to go gave me a break and helped maintain my sanity, not to mention the much-needed income. I’m lucky that my family lives in town, too. My sister has been a great help if I need a place for Tyler to go, and have someone help wait on him when he’s laid up. I am so grateful to have my brother’s family giving me breaks as well.

Deena and Tyler

1. PEN, Feb/Mar 2014 2. In this article, the word desensitization is used interchangeably with immune tolerance induction (ITI).
I enjoy reading mysteries. Solving the crime with the hidden clues gives me a sense of accomplishment when I’m right, or it frustrates me when I fail.

I am seriously conflicted—almost to the brink of screaming—about mystery writers who include a character with hemophilia. I’m happy that hemophilia is actually part of a plot. I like that hemophilia, even when fictional, is acknowledged. But I’m also disappointed because these characters are often the victims. So many characters with hemophilia have died of unnatural causes! And to complicate matters, the unrevealed hemophilia diagnosis and the slowly coagulating blood are often red herrings, clues that are meant to confuse both the detective and the readers. These clues alter the time of death and the list of possible suspects. But those of us in the bleeding disorder community are savvy: we know something about blood coagulation.

Hematologists were determining hemophilic blood coagulation times from the 1890s onward. And mystery writers began using blood coagulation as a plot device to determine the time of death. In the first Miss Marple mystery, Murder at the Vicarage (1930), Agatha Christie (1890–1976) incorporated the clue of congealing blood to help the village physician determine the time of death after Colonel Protheroe was shot in the head. In this case, the murder victim did not have hemophilia.

But mystery writers eventually began to include the delayed coagulation of hemophilic blood. And they began creating murder victims with hemophilia. In 1930, the BBC commissioned six writers (Dorothy Sayers, Hugh Walpole, Agatha Christie, Anthony Berkeley, E. C. Bentley, and Ronald Knox) to collaborate on a radio play called Behind the Screen. In their group discussion on a possible plot, one writer suggested that a game of bridge be interrupted by a river of blood, originating from behind a curtain and surrounding the bridge players. A second writer stated that blood clots rather than flows, unless the victim has hemophilia. But this plot idea was abandoned. The radio series using another plot line was eventually broadcast, and then published in the Listener.

For the Lord Peter Wimsey murder mystery Have His Carcase (1932), Dorothy Sayers (1893–1957) included a character with hemophilia. When Harriet Vane discovers the corpse of Paul Goldschmidt, blood is still flowing from his slit neck. The time of his death is miscalculated because his hemophilic blood has not congealed, implicating innocent suspects rather than guilty parties. Not until late in the investigation is the hemophilia diagnosis revealed.

Sayers accurately described the condition of hemophilia, its bleeding manifestations, and its genetics. She creatively used different murder methods in each of her novels, and probably learned about hemophilia from several sources. She followed the news about hemophilia in the Russian and Spanish royal families. And during 1930 and 1931, she received technical assistance on medical details from two writers: Robert Eustace, the pen name for Dr. Eustace Robert Barton (1868–1943), and John Rhode, the pen name for Cecil John Charles Street (1884–1964).

Sayers may be the first mystery writer to include a fictional character with hemophilia as the murder victim. All subsequent mystery writers—and many over the past century have copied this plot device—should acknowledge Sayers for her attention to detail in believably portraying a character with hemophilia. Have His Carcase remains in print, and is available at your local library along with Sayers’s other wonderful mysteries.

Today there are still more mysteries to solve. If you watch detective shows, you’ll know that DNA samples provide vital forensic evidence. Yet all of the genetic variations for bleeding disorders are not yet documented. You can help unravel the genetic mystery of hemophilia—and without all the drama of being a victim—by participating in a National Hemophilia Foundation genotype testing program called My Life, Our Future. Your unique genotype is an important clue in solving this puzzle.

To learn how to get involved at little or no cost, contact your hemophilia treatment center or visit mylifeourfuture.org for information on this confidential program.
Fatima, a 45-year-old woman in Ghana, Africa, has sole custody of Kadir, now 13, after a bitter divorce from Kadir’s father six years ago. Kadir has hemophilia A, and suddenly became ill in June 2013. He had a brain bleed, which temporarily paralyzed him, keeping him hospitalized for most of June and July. As in most African countries, the prescribed factor VIII to help with Kadir’s recovery was not available in Ghana. Even if it were, Fatima would never have been able to afford it.

But Fatima found help through international channels. Her son was already being sponsored by Africana Children’s Education Fund (ACEF), based in Kansas City, Missouri. ACEF is a non-profit organization that facilitates the education of orphans, the poor, and the abandoned children in Ghana through sponsorships. A family in Tulsa, Oklahoma, sponsors Kadir and pays for his books, tuition, school uniforms, medical insurance, and school lunches. Together with ACEF, the family reached out to the US hemophilia community to get factor for Kadir.

A doctor in Kansas City referred ACEF to Project SHARE. Director Zoraida Rosado immediately shipped the prescribed medication to Dr. Vivian Paintsil, a pediatric hematologist, of Komfo Anokye Teaching Hospital (KATH) in Kumasi, Ghana.

The shipment took eight days to reach Ghana and was held up in customs for several more. But it reached Kadir in time, and he survived. During Kadir’s recovery, he showed signs of hearing and speech loss, and will need a hearing aid and speech therapy.

Now, Kadir is showing incremental improvements in his walking and hand movements. He is still unable to hold a pencil to write, but he is eating well and responding to treatment. His current hearing and speech loss will be managed by working with other medical specialists at KATH. Kadir is currently under treatment as an outpatient, and doctors hope that he will make progress and be able to return to school.

“It takes a whole village to raise a child,” according to the African saying, but Dr. Paintsil believes that it takes the whole world to help a sick child—from America to Africa.

Initial report submitted by Peter Osei-Kwame, PhD, president of Africana Children’s Education Fund Inc., Kansas City, Missouri, and Dr. Vivian Paintsil, MD, pediatrician, Department of Child Health, Komfo Anokye Teaching Hospital, PO Box 1934, Kumasi, Ghana.
in the joint cartilage, making the joint feel stiff or achy.

Why do microbleeds escape detection, and why doesn’t prophylaxis always work to stop them?

**Anatomy of a Joint Bleed**

It helps to review what happens when a joint bleeds. A joint is where two bones meet. There are several types of joints: some are immovable, such as the fibrous joints in the skull, and others are freely movable, such as the knee or hip.

A freely movable joint is covered by a thick sheath of connective tissue called a **joint capsule**. Lining the capsule is a thin layer called the **synovial membrane** or **synovium**, which is normally clear and colorless. The synovium secretes a small amount of **synovial fluid**, a slimy liquid with the consistency of egg yolk. Synovial fluid coats the bone ends within the joint capsule and serves as a lubricant to reduce friction between the moving bones. The fluid also absorbs shock, and transports nutrients and oxygen to cartilage cells on the ends of the bones as well as removing their waste. Friction in the joint is further reduced by the **hyaline cartilage**, a layer of smooth rubbery cartilage covering the ends of the bones.

Joint bleeds (**acute hemarthrosis** in medical lingo) originate when one of the many tiny blood vessels of the synovium ruptures, spilling blood into the joint capsule. Untreated, the ruptured blood vessel fills the joint cavity with blood. The increasing pressure of the blood inside the joint capsule equalizes with the pressure inside the blood vessel, and eventually the bleeding stops. In the first stages of a bleed, the joint may feel warm, bubbling, or tingling. Some people report feeling an **aura**, an unusual sensation in the joint when a bleed begins. As the pressure of the blood within the joint increases, the swelling joint becomes more painful. Later symptoms of a joint bleed often include stiffness, warmth to the touch, reduced range of motion, and inability to bear weight.

After a bleed, the body begins to remove the blood from the joint. Cells in the synovium secrete enzymes that break down the blood, allowing it to be absorbed. These enzymes also irritate the synovium itself and the cartilage, stimulating an inflammatory response. It may take four to six weeks after
a joint has had a bleed for the blood inside the joint to be removed. But some of the breakdown products of the blood remain in the joint, especially hemosiderin—iron from red blood cells—which stains the synovium a brown or rust color. Hemosiderin has been blamed for causing the synovium to overgrow and thicken, and for causing damage to cartilage cells.

For several weeks after a bleed, a joint is susceptible to re-bleeding. Repeated bleeding into the same joint may produce a target joint—a joint that bleeds with increasing frequency and also bleeds spontaneously, with no apparent trauma. Repeated bleeding into a target joint further irritates the synovium, causing it to thicken and grow more blood vessels. This sets the stage for a vicious cycle: the thickened and inflamed synovium bleeds more easily, causing more irritation and inflammation, resulting in more frequent bleeds.

An enlarged and chronically inflamed synovial membrane is called synovitis. Synovitis causes the joint to remain swollen and “spongy,” even after treatment. Chronic synovitis contributes to more frequent bleeding into the joint, accelerating the damage to the cartilage on the ends of the bones, and eventually resulting in hemophilic arthropathy, a crippling form of arthritis. As if these destructive changes in the joint weren’t enough, the muscles surrounding the joint often atrophy because of decreased use. Weak muscles provide less support for the joint, which leads to more frequent bleeding, adding to the painful cycle of joint bleeds.

**Treatment for Chronic Synovitis and Joint Disease**

Treatment for early stages of chronic synovitis involves secondary prophylaxis (often at higher doses than for primary prophylaxis), usually for three to six months, and physical therapy. The goal is to break the vicious cycle of bleeding and allow the synovium to return to normal. If the synovium doesn’t return to normal after this initial prophylaxis program, the treatment may be repeated for another three to six months.

What then? If you don’t respond to prophylaxis, surgery is next. A synovectomy removes the overgrown synovium, allowing the joint capsule to grow a new, more normal synovium, usually within six months. The goal of a synovectomy is to reduce the frequency of joint bleeds. When performed early, synovectomies often effectively break the cycle of bleeds and significantly slow the progression of joint disease. Synovectomies performed at a later stage of synovitis, after joint damage has occurred, may reduce the frequency of bleeding and slow the progression of joint disease, but the procedure will not stop joint disease from progressing—joint damage will continue, though more slowly, even without new bleeds.

Surgical intervention can’t make your joint like new. It can’t reverse joint damage already caused by repeated bleeds into a joint. And it can’t restore lost range of motion. The major benefit of surgery is to reduce the number of bleeds, reducing pain and making your joint work better. Fewer bleeds also means slower progression of joint disease.

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1. Secondary prophylaxis is a short-term infusion program usually begun after repeated bleeds into a joint. Primary prophylaxis is usually a lifelong infusion regimen begun before age two. 2. Unfortunately, once someone has developed chronic synovitis, secondary prophylaxis often fails to break the cycle of bleeding, with only about 40% of patients showing clear improvement.
Preventing Joint Bleeds through Prophylaxis

The only way you can prevent degenerative joint disease or hemophiliac arthropathy is to prevent joint bleeds.

This means primary prophylaxis, which is a long-term preventive treatment approach: young patients (usually, starting at one to two years old) receive regular factor replacement either before or after their first joint bleed. This regimen is recommended for life. There are several protocols for primary prophylaxis, but most US regimens call for maintaining factor levels always above 1%. If you have severe hemophilia A, this usually means about three factor infusions per week; if you have severe hemophilia B, only two infusions per week. By keeping factor levels always above 1%, primary prophylaxis essentially converts a person with severe hemophilia into one with moderate hemophilia. For most people, this is usually enough to prevent most joint bleeds not caused by trauma.

Studies have shown that primary prophylaxis has dramatically decreased joint damage in people with severe hemophilia. The first phase of the Joint Outcome Study (1995–2005), a randomized clinical trial funded by the US Centers for Disease Control and Prevention (CDC), found that primary prophylaxis provided an 84% risk reduction in “structural bone disease,” in other words, a reduction in arthritic changes to the joint. The study also found that by age six, 93% of the boys on prophylaxis maintained normal joint cartilage with no defects detected by MRI of the elbows, knees, and ankles. This is compared to only 58% of the boys using on-demand therapy.

Prophylaxis helps reduce bleeds, but does not prevent all bleeds. You may have spontaneous breakthrough bleeds, or have bleeds from trauma. Unfortunately, it may take only one major bleed into a joint to set the stage for slow degenerative joint disease, with effects that may not show up for several years. How can you minimize the risk of joint damage?

• Stick to your prophylaxis schedule. Don’t skip days!
• Tailor your infusion schedule to meet your needs. If you or your child participate in a sport, infuse on practice days to have higher factor levels on those days.
• Always infuse in the morning so factor levels will be highest during the day when activity levels are highest. Don’t infuse prophylactically at night.
• See your hematologist if you experience breakthrough bleeds. You may need a higher dose of factor. Everyone metabolizes factor differently, so a dosage that works for one person may not work for another.
• If you have a bleed, always treat early and aggressively. Never “wait and see” or wait until symptoms worsen before infusing. Early treatment reduces the risk of joint damage. Applying ice or compression bandages to a joint bleed may slow the bleed and help relieve pain, but this does not stop the bleed and does not take the place of factor replacement therapy.
• If you must visit a local emergency room, go prepared with a treatment letter from your hematologist stressing the need to infuse without delay and before any diagnostic tests are done.

Other Ways to Prevent Joint Bleeds

Besides primary prophylaxis, stay physically fit. There is overwhelming evidence that strong, flexible muscles help stabilize joints and decrease the incidence of joint and muscle bleeds. Stretching properly, warming up before exercising, and cooling down afterward are equally important and help prevent muscle bleeds. Check with your hemophilia treatment center (HTC) team before starting any physical fitness routine.

There’s a lot of anecdotal evidence that boys with hemophilia who swim competitively and train for several hours a week have significantly fewer bleeds than their peers who do not swim. John Schmitke, a young man with severe hemophilia A, spoke recently at the Canadian Hemophilia Society’s annual meeting. John told a story familiar to boys with hemophilia who swim regularly, noting that by age 16, he was
swimming competitively and training 14 hours a week. “I started to notice that I bled less irregularly and less seriously than many of my peers also treating prophylactically,” said John, adding that not only did he have fewer bleeds than his peers, but he was able to decrease the dose he used for prophylaxis without an increase in bleeds!

If you suffer a severe joint bleed, call your hematologist and physical therapist before resuming your normal exercise program. After a severe joint bleed, your physician or physical therapist may advise prophylactic factor therapy using a higher dose during the recovery period (to prevent re-bleeding), plus a physical therapy and rehabilitation program to strengthen the muscles around the joint and help increase range of motion.

And watch your weight. Statistics from the CDC show obesity now affects 17% of all US children and adolescents—triple the rate of just one generation ago. Almost 70% of American adults are overweight, with one-third classified as obese. Obesity has serious health effects: it increases your risk of heart disease, high blood pressure, stroke, diabetes, cancer, and many other disorders. And it also affects your joints. If you’re overweight, your hip, knee, and ankle joints bear a heavier load, contributing to joint bleeds. One study found that for each pound of body weight lost, there is a four-pound reduction in knee joint stress among overweight and obese people with osteoarthritis of the knee.3

Remember to wear protective gear. When a toddler is first getting his “land legs,” knee and elbow pads can help prevent joint bleeds caused by falling. As he grows and begins to participate in sports, he needs appropriate protective athletic gear.

The Insidious Microbleed

Even though you’ve been following your prophylaxis schedule, eating well, and exercising, you’ve developed an arthritic joint. Why?

Enter the microbleed. Microbleeds are tiny bleeds from the capillaries, the smallest blood vessels. Typically, microbleeds are self-limiting: only a minuscule amount of blood leaks out of the blood vessel before the clotting system kicks in and stops the bleeding—which is why they go unnoticed. Microbleeds are thought to happen regularly, in everyone. Over the past decade, we’ve dramatically improved our ability to detect microbleeds in the brain: technicians are now able to see microbleeds on brain scans using specialized MRI scans from sophisticated high-resolution MRI machines and image-processing techniques. Surprisingly, neurologists have found microbleeds in the brain in 20% of healthy people over age 45 and up to 40% of people over age 80.

In a person with hemophilia on prophylaxis, a microbleed is more likely to bleed just a little longer than it would in someone without a bleeding disorder, especially if that person has a low factor level just before the next infusion. Recent research on the effect of microbleeds in the joints of dogs found that microbleeds don’t stimulate an inflammatory response, as acute joint bleeds do.

But these were short-term studies. Research into microbleeds in hemophilia is just getting under way—scientists want to know how common microbleeds in joints are, and how they might affect long-term joint health. Researchers speculate that over

time, the buildup of blood breakdown products from repeated microbleeds may initiate an inflammatory response in the synovium and cause arthritic changes similar to an acute joint bleed.

Given that we aren’t sure how microbleeds affect joints in the long term, what can be done to treat and prevent degenerative joint disease?

Microbleeds: Do We Need a New Prophy Regimen?

Currently we really don’t know how microbleeds affect joints. But it’s a good idea to be cautious, and assume that they do have a negative long-term effect on the joints of people with bleeding disorders. There’s no way to eliminate microbleeds, but we can potentially decrease the number of microbleeds and their duration, and reduce their impact on joint health, by increasing factor levels circulating in the blood.

Microbleeds are gaining attention in the bleeding disorder community: they were discussed in September 2013 at the World Federation of Hemophilia (WFH) Eighth Global Forum on the Safety and Supply of Treatment Products for Bleeding Disorders, in Montreal, Canada. One of the topics presented was the trough level as used in primary prophylaxis. In the US, the targeted trough level is usually 1%, meaning that at its lowest point between infusions, the level of factor in the blood would be close to, but not fall below, 1%.

At the Global Forum, Dr. Albert Farrugia of Plasma Protein Therapeutics Association (PPTA) reported that recent studies have shown that a 1% trough level is not adequate to completely prevent joint bleeds in prophylaxis. He suggests, based on current research, that 15%–20% factor VIII activity levels are needed to adequately prevent bleeds.

This raises a question: Are the trough levels we use for primary prophylaxis in the US today enough—that is, should we be infusing higher doses in prophylaxis to prevent bleeding?

Studies have shown that higher trough levels decrease joint bleeds, but also that closer monitoring of trough levels and peak factor levels are key factors to consider when designing a prophylaxis regimen. This raises another question: Do you really know what your trough level is? Most people might say “Yes, my factor trough level is about 1% or more,” but do you really know? Most people haven’t had half-life studies (pharmacokinetic studies) of how long factor lasts in their system. This is especially true for the 30% of people with bleeding disorders in the US who are not seen at an HTC. Several studies have shown that half-life varies widely among patients and age groups; as a rule, factor tends to have a shorter half-life in children than in adults. That means that some people might unknowingly be spending a lot of time at or below 1%, increasing their risk of bleeding. This suggests that one prophy treatment regimen may not fit all.

One prophylaxis clinical study showed that some patients had a half-life four times longer than those with the lowest half-life, and that half-life varied significantly from person to person. The

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N ot all joints are affected equally by joint bleeds. Hinge joints, such as the knee, ankle, and elbow, bleed more frequently than ball-and-socket joints, such as the hip and shoulder. The two joints most commonly affected by bleeds are the knee and ankle, followed by the elbow. Ball-and-socket joints bleed infrequently.

study also found that even though all patients studied had a 1% trough level, there was wide variation in the factor dose required to keep individual patients above the 1% threshold. People who had a shorter half-life needed higher dosing to maintain a 1% trough level. And because of this, they had higher peak factor levels and fewer bleeds per year than people with a longer half-life (presumably because they spent more time with higher factor levels in their system as a result of their higher dosing).

Conversely, people with a longer half-life required less factor to maintain a 1% trough level, but had more bleeds per year (presumably because they spent more time with lower factor levels). John Schmitke, the Canadian swimmer, added an interesting take on this: while he was swimming competitively, he significantly reduced his factor usage—with no increase in bleeds—by infusing less factor but infusing daily; this may have kept his time near peak levels higher, resulting in fewer bleeds.

The prophylaxis clinical study demonstrates that although trough level is important, it isn’t the only thing to consider when designing a prophylaxis regimen. The amount of time spent near peak levels between infusions is also important. For many people with hemophilia, the initial dose of factor needed to maintain a 1% trough level is calculated based on weight and on an average half-life for the product being used—but, as studies have shown, neither of these may be accurate.

The bottom line? Many clinicians are using seat-of-the-pants estimates for initial dosing of their patients, and adjust the dosing upward if the patient has multiple breakthrough bleeds. As a result, some patients start off being dosed inappropriately and have several joint bleeds before their factor dose is adjusted upward—and they may suffer joint damage as a result.

**An Alternative to Standard Prophylaxis Regimens?**

Dr. Steven Pipe, of CS Mott Children’s Hospital at the University of Michigan, speaking at the Global Forum, believes that HTCs will be changing their treatment paradigms in future and moving toward more individualized, “tailored” therapy. Tailored therapy aims to improve effectiveness of hemophilia treatment by individualizing a person’s treatment according to how factor works in his body and raising prophylaxis trough levels, possibly through the use of new longer-acting factor products.6

Perhaps tailored therapy would reduce bleeds (and microbleeds!) and finally deliver on the original promise of prophylaxis: that children with severe hemophilia can look forward to maturing into physically active adults, free of the crippling effects of arthritis. And that’s when we get it right.

Paul Clement is a high school science teacher who has written extensively for the hemophilia community and, for the past 14 years, has been a contributing editor for PEN. Paul has a knack for translating complex topics into easily understood language. He holds a bachelor’s degree in biology and master’s in science education from California State Polytechnic University. He lives in Southern California with his wife Linda, and has two children: Erika (29) and Brett (27), who has severe hemophilia A.

6. As an interesting aside regarding longer-acting factor products, many patients look forward to longer-acting products to reduce the frequency of infusions. But a survey of clinicians at the Global Forum found that 61% believed patients should infuse the longer-acting products at the same frequency they are currently using, but maintain higher trough levels.

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**Parenting Moment**

“Never do for a child what he is capable of doing for himself.

— Elizabeth Hainstock

Educating the mind without educating the heart is no education at all.

— Aristotle
Warm weather greeted us in Omaha, Nebraska, on March 22, when Zoraida and I arrived from Boston to set up for our first Pulse on the Road workshop of 2014. POTR is a three-hour workshop, sponsored by Baxter Healthcare. POTR is held in tandem with National Hemophilia Foundation, which generously lends us the incomparable Michelle Rice, mother of two adult sons with hemophilia and director of public policy at NHF. Last year, Michelle hired more staff to help her because she is stretched thin visiting chapters, patients, insurance companies, and governments in all 50 states.

On this POTR trip, we were thrilled that Nicole Quinn-Gato, policy specialist at NHF, accompanied Michelle.

Nebraska Chapter of NHF executive director Kristi Harvey-Simi began the workshop with an enthusiastic welcome. Next, we received an update on the Affordable Care Act from Kim Isenberg, senior manager, reimbursement and advocacy, Baxter Healthcare. Kim covered the ACA in general and also as it affects hemophilia, citing exceptions for some groups. Nevada has elected not to expand state Medicaid, an important policy to note.

Then, I presented key points on the importance of choosing healthcare, because it is now mandated for almost everyone to have healthcare. We still need to watch for certain variables, such as out-of-pocket costs, which may increase as a result of changing policies and plans.

Finally, Michelle and Nicole did a great job providing a 90-minute, hands-on workshop on accessing the HealthCare.gov website, using laptops and iPads. Participants actually logged on to scope out choosing a plan. This was interesting—and frustrating at times! The most common problem for participants was difficulty finding their hemophilia treatment center.

After lunch, at our Q&A, the audience asked questions of all the experts.

Though I offered everyone a chance to go home an hour early, nobody took advantage. I think they were all soaking up the information Michelle, Nicole, and Kim had to offer! @

Next stop for POTR: Philadelphia in June!
Q: **How did Tyler feel about what was happening?**

Until now, Tyler had never said “Why me?” or “I wish I didn’t have hemophilia,” but around age 12, he remarked on how different he was from other kids. And he didn’t mean it in a good way. He was feeling isolated and depressed. After a year of no factor IX and countless bleeds, Tyler started questioning: Why didn’t we just desensitize him to factor IX like we did when he was six? And we wondered, too: If it had worked once, it should work again, right? Even if we had to desensitize him every six years, it was well worth it to get a few years of factor usage.

Factor IX concentrate has a half-life of 24 hours. After Tyler developed severe allergic reactions to factor IX, we could treat bleeds only with the inhibitor bypassing agent recombinant factor VII concentrate (NovoSeven), which has a half-life of two hours. I think the risk of Tyler having an anaphylactic reaction to the factor IX, which can be fatal, was making everyone very nervous about starting another round of immune tolerance induction (ITI) therapy using factor IX. Tyler’s nurses and doctor were open to the idea of starting ITI again, but the method we would use was still undecided. Hooking him up to a CADD pump for 18 months, as we did last time, seemed so extreme. Now we had more options, like using chemotherapy drugs in addition to factor IX to tolerize and desensitize him to factor IX. However it would be done, we felt an increasing sense of urgency as Tyler’s bleeds became more frequent and harder to control.

Q: **While you were still deciding about trying to desensitize Tyler, were you worried that he might have a major bleed that you couldn’t control?**

In September 2013, Tyler developed compartment syndrome in his right forearm. He had gone to a sleepover, and returned home the next day so exhausted that he crashed for eight hours. When he woke up at 9:00 pm, he complained that his arm was bleeding. We started treating with NovoSeven, but we couldn’t get the bleed under control. The HTC admitted Tyler to keep up with the infusions every two hours, and to control his pain. But things just kept getting worse. Tyler’s pain was intense. More and more narcotics were added, including a pain pump allowing him to dose himself every eight minutes with morphine, but nothing seemed to be working.

Finally, at the end of the third day, Tyler was rushed in for an emergency fasciotomy to save his hand. I was scared to death. I was told that he could have permanent damage to his hand, and muscle tissue might have to be removed from his forearm. The doctors wouldn’t know the extent of the damage until they cut open his forearm to relieve the pressure on his nerves. Then they leave the wound open for 48 hours to allow the swelling to go down. On day three, they would take a piece of skin from Tyler’s thigh and cover the forearm.

Q: **How did you cope?**

At this point, I just wanted Tyler to be out of pain. It was the longest wait of my life.

I’ve always chosen not to have my family come to the hospital when Tyler is having surgery. I just wanted to be alone. I didn’t want to have to put on my game face and act like I was doing okay when inside, I was so freaked out. I just couldn’t deal with small talk. So once again, I made the decision to be alone, but midway through, I started to regret that. What if I got awful news this time? Would I be able to hold up? I hit Facebook and started posting everything that was going on. I think the distraction helped me get through it all.

And then, finally some good news after the fasciotomy: all of Tyler’s muscle tissue was okay, and no visible damage had been done. We wouldn’t know about permanent damage for a while, but at this point things looked good.

But my happiness was short-lived: within hours of surgery, Tyler’s wound started bleeding profusely. The wound VAC (used to keep his wound clean and keep blood out) kept clogging. Surprisingly, his blood was clotting in the tubing. I thought, so now it wants to clot!

Q: **What happened then?**

Tyler had three more surgeries over the next three days in an attempt to get a wound vacuum working and to start closing up his arm. Finally, a fourth surgery was done on day five to close up his arm using his first skin graft.

After three weeks in the hospital, we were discharged. By then, Tyler had received 11 blood transfusions. He looked terrible and was in extreme pain. But thank goodness, he doesn’t remember any of this because of all the pain medication he was on.

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3. The success rate of ITI in hemophilia A is 70% to 85%; in hemophilia B it is 30% to 40%. 4. Sheets of connective tissue called fascia surround groups of muscles, nerves, and blood vessels to create a unit called a compartment. Pressure from a muscle bleed can cut off blood flow to the muscles within the compartment, causing muscle and nerve damage and other serious complications. Compartment syndrome is a medical emergency. 5. Fasciotomy is a surgical procedure in which the fascia of the compartment are cut open to release pressure from the accumulated blood in the compartment. 6. A wound VAC (vacuum assisted closure) is a device allowing people to conduct negative pressure wound therapy.
Our HTC doctors and nurses were incredible. I will be forever grateful for their support. I felt as if we’d gone to battle and just barely survived.

Tyler got a second skin graft a month later to complete the process. His scar is crazy, but he seems to think it’s cool. He decided to tell people it’s from a shark bite. I’m sure the story will grow with time!

Q: When did you return to the idea of desensitizing Tyler with factor IX?
Two months after Tyler’s second skin graft, we started the tolerization process again. Needless to say, our experience had made everyone feel that tolerizing Tyler again to factor IX was now a necessity. This time around, I decided to use Rixubi (Baxter’s new recombinant factor IX concentrate) rather than BeneFIX. I just felt, let’s try something different and see if he doesn’t relapse with this product.

So Tyler went back into the hospital at the beginning of 2014 after receiving a dose of chemotherapy. He was put in ICU, and then quickly moved to the hematology floor because he was doing so well. We began by giving him a dose of factor IX concentrate over ten hours, and then reduced that time daily. Every day I expected an anaphylactic reaction, and every day we had none. We were able to get the infusion down to 20 minutes with no problems. Tyler was in the hospital for only about a week.

It wasn’t until we tried to do a bolus of factor IX that Tyler finally had an allergic reaction. He got hives and had trouble breathing. Thank goodness we were at a Phoenix Children’s Hospital clinic when it happened. At this point, Tyler’s inhibitor spiked to 12 BU—a lifetime high for him. I guess his body wasn’t going to give in quite yet. Just when we thought it was all going so smoothly!

Q: How is Tyler doing now?
As of April, Tyler’s occasional allergic reactions consist of hives and itchiness. This we can deal with. Now I give Tyler 50 mg of Benadryl every morning before his infusion, which runs through an IV pump over 30 minutes. Soon we will wean that down to 20 minutes.

Tyler is still receiving Cytoxan, a chemotherapy drug, once a month to weaken his immune system. The goal is to get to a daily bolus and have his inhibitor and allergic reactions both gone. A month after his last bad reaction, his inhibitor had already dropped to 4 BU, and two months later it was down to 2.5 BU.

Q: How are you feeling about the future?
I know we will be successful; it will just take some time. Life is starting to calm down—a little. And the bleeds are becoming less frequent. I hope we will have a few years before the next big storm.

I never knew that a child could be so resilient and brave. Every day, Tyler makes me proud. He shows me strength I only wish I had. His story is a true testament to never giving up. I love you, Tyler, with all my heart. 😊
headlines

NONPROFIT

Washington Days a Record-Breaking Success

National Hemophilia Foundation’s (NHF) annual event, February 26–28, drew a record-breaking 300-plus attendees, from 43 states, participating in 220 Capitol Hill visits. Of the visits, 75 were meetings with senators (21) and representatives (54). Attendees asked Congress to maintain funding for federal hemophilia programs, and to co-sponsor HR 460, Patients’ Access to Treatments Act of 2013. Why this matters: HR 460 prohibits insurers from imposing exorbitant coinsurance requirements on patients using tier 4 drugs, which may include factor.

Steps for Living Videos

Steps for Living videos cover a variety of hemophilia topics: advice, treatment centers, disclosure, sports, camp. Made possible through US Centers for Disease Control and Prevention (CDC) and Pfizer Hemophilia. Why this matters: This is a fast, easy way to learn the basics of hemophilia.

For info: www.stepsforliving.hemophilia.org

HFA Celebrates 20 Years at Record-Breaking Meeting

At the 20th anniversary meeting of Hemophilia Federation of America (HFA) in Tampa, Florida, in March, a record number of attendees networked, heard expert speakers, and viewed a stunning History Room displaying the past 50 years in all its pain and triumph. Why this matters: HFA’s annual meeting offers the bleeding disorder community a grassroots approach with a strong emphasis on advocacy.

For info: www.hemofilafed.org

Summer Inhibitor Education Summits

For English speakers:
July 10–13, Albuquerque NM
July 24–27, Baltimore MD

For Spanish speakers:
May 30–June 1, Phoenix AZ

NHF is providing three educational summits for people living with inhibitors this summer, made possible through a grant from Novo Nordisk. Why this matters: These are the only national educational forums for inhibitor patients to meet and learn about their rare complication.

For info: 877-560-5833
First Long-Lasting Factor Approved

FDA has approved Biogen Idec’s long-acting hemophilia B treatment, Alprolix. Compared to several pre-study recombinant or plasma-based factor IX products, Alprolix showed a greater than threefold-longer circulating half-life, and a 60% reduction in clearance rate in children under age 12. Why this matters: Alprolix is the first recombinant treatment for this disorder, which affects 1 in every 3–5 million US births. For info: www.alprolix.com

New Factor VII in Pipeline

FDA has granted orphan drug designation to Opko Health’s longer-acting version of factor VIIa, called Factor VIIa-CPT, for treating bleeding in patients with hemophilia A or B with inhibitors to factor VIII or factor IX. Currently only NovoSeven, Novo Nordisk’s conventional recombinant factor VIIa with estimated worldwide sales of $1.7 billion in 2013, is commercially available. Why this matters: Factor VIIa-CPT should provide a longer half-life, and can be administered via IV and subcutaneously. For info: investor.opko.com

Meet Emergent

Emergent Biosolutions continues clinical studies to bring IB1001, a recombinant factor IX, to market. In 2014 Emergent acquired Cangene Corporation, which had previously acquired IB1001 from Inspiration Biotherapeutics. Why this matters: IB1001 was created with funding by two fathers with sons with hemophilia B to have another treatment option for hemophilia B patients. For info: www.emergentbiosolutions.com

Platelet Cells Could Benefit Inhibitor Patients

Investigators at University of North Carolina School of Medicine and Medical College of Wisconsin developed a gene therapy approach targeting blood platelets. Platelets are known to carry small amounts of factor VIII internally. When platelets are activated at the site of an injury, they discharge their contents, including FVIII. This gene therapy approach aims to put functional FVIII into platelets, where it appears to be protected from antibodies (inhibitors) to FVIII. Why this matters: The absence of antibodies to platelet-derived FVIII means that this approach may benefit patients who have inhibitors to FVIII. Source: “Platelet-targeted Gene Therapy with Human Factor VIII Establishes Haemostasis in Dogs with Haemophilia A,” Nature Communications, Nov. 2013

New Recombinant Factor XIII

US FDA has approved Tretten, Novo Nordisk’s recombinant factor XIII A-subunit product, for routine prophylaxis of bleeding in people with congenital factor XIII A-subunit deficiency. Patients have a lifelong susceptibility to bleeding, including spontaneous intracranial hemorrhage. Why this matters: Tretten is the first recombinant treatment for this disorder, which affects 1 in every 3–5 million US births. For info: www.novonordisk-us.com

Free Treatment for Indian Patient

Lok Nayak Hospital in Delhi, India, will provide free treatment as needed to Amit Ahuja, age 36, a hemophilia A patient with inhibitors who can’t afford expensive drugs. If he needs factor VIIa, the hospital will provide it free. Why this matters: Factor is only beginning to be funded in India, and cases like this are victories for Hemophilia Federation (India) and all patient groups.

MANUFACTURER
CSL Behring Launches My Access

My Access offers out-of-pocket payment assistance to eligible US patients using a CSL Behring therapy. Patients must have hemophilia A or von Willebrand disease, and have private insurance (up to $12,000) associated with treatment. Why this matters: Although My Access is for patients with private insurance using CSL Behring therapies only, rising out-of-pocket healthcare costs affect everyone, and these patients can greatly benefit from the program.

For info: www.mysourcecsl.com

Pfizer Offers Assistance with Copays

Pfizer RxPathways is a comprehensive assistance program that provides eligible patients with a range of support services, including insurance counseling, copay assistance, and access to medicines for free or at a savings. Why this matters: With new insurance rules and policies, bleeding disorder patients could face higher out-of-pocket costs.

For info: www.pfizerhelpfulanswers.com

Another Long-Acting Factor Product in Pipeline

Bayer’s long-acting recombinant factor VIII demonstrated prophylaxis with less frequent infusions in hemophilia A in a phase III trial. Why this matters: BAY 94-9027 helped protect against bleeds when used prophylactically with infusion intervals up to seven days.

For info: bayerhealthcare.com

CoRe Conversations Create Community

Core Conversations are bimonthly hour-long webinars and regular live presentations, sponsored by Biogen Idec, exploring topics of interest to the hemophilia community.

Mapping Your Future
Tips on choices and decision making after high school: selecting a college or vocational program, defining your path.
June 17, 8 pm ET / 7 pm CT / 5 pm PT

Setting Educational Expectations
Info on establishing clear goals and routines for school-aged children with bleeding disorders.
Aug. 19, 7 pm ET / 6 pm CT / 4 pm PT

Braving Change
Resources and possible approaches to informed decision making during times of change.
Oct. 21, 8 pm ET / 7 pm CT / 5 pm PT

Why this matters: Live discussions are often inconvenient to attend, but webinars make live presentations accessible to all.
For info: www.biogenidechemophilia.com
I read the new issue [“Donor Beware,” PEN, Feb/Mar 2014] and I am very glad you touched on the issue of concentrate being resold. I suspect that a large amount of concentrate, charged to US public or private insurance, has been mailed to other countries. In California, we have a lot of immigrants with families still in developing countries. In the 1990s, I had been corresponding with a man living in Shanghai who was bedridden for want of concentrate. When I finally visited Shanghai, he came to see me at my hotel, walking well. I asked him, how did you recover? He said, his hemophilic uncle in San Francisco mailed him little packages of concentrate, marked “vitamins,” and they got through customs. And that’s just one of many stories.

**CAROL KASPER, MD**
California

Thank you for helping my son, Elwayne Manabat. We requested factor VIII and you gave it to us. Thank you very much for your kindness and may you continue helping people like us who are in need.

**FELYNNE I. MANABAT**
Philippines

Though I sometimes complain about insurance, I never take it for granted. My son gets his medicine every time. Some don’t. I can’t imagine how helpless parents must feel knowing their child is suffering and can’t get access to his meds. Thanks to Project SHARE, [Patrick from the Philippines] is up and moving after three days of receiving his blood-clotting meds; he previously had not been mobile for a month due to a hip bleed.

**JEN HAMILTON LOVING**

**FACEBOOK**

Just want to say a million thanks for your help in getting factor to Milton Tomlinson for our son Zayden. He was released from the hospital last Friday and is recovering nicely. God bless you.

**RIKA MCINTOSH**
Jamaica

Nick Solomon is our recent recipient of factor VIII. He had pain and swelling over his right hip and has not been able to walk for about a month. This picture [right] was taken after three days of treatment. He can now stand up and walk with the aid of crutches. Thank you very much.

**FEDO GO, MD**
Philippines

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**Pfizer**
888-999-2349
www.hemophiliavillage.com
Mapping Your Future

June 17 | 8PM ET (5PM PT) | Webinar

Finishing high school marks a new beginning: we’ll examine some tips on choices and decision-making, from selecting a college or vocational program, to defining your career path.

BiogenIdecHemophilia.com/CoReConversations