PEN

inside

CLOTTING FACTORS:

Aren't They Basically All the Same?

Paul Clement

In the past 50 years, we've seen remarkable advances in the development of therapies to treat or prevent bleeding in hemophilia. We've progressed from fresh frozen plasma in the 1950s and early 1960s, which contained very little factor and required risky, large-volume infusions, to the more concentrated and effective cryoprecipitate, to the first commercial freeze-dried clotting factor concentrate in 1968.

In the US, we now have the choice of 15 different factor VIII products and 10 factor IX products, as well as a new non-factor treatment and more products in the pipeline (see chart, p. 10). There's a dizzying array of choices: plasma-derived or recombinant? First-, second-, or third-generation recombinant? Standard half-life or extended half-life? Extended half-life factor using PEGylation or fusion? Factor VIII with von Willebrand factor (VWF) or without? Recombinant factor produced from a human cell line or animal cell line? Full-length factor VIII or B-domain deleted? Why do we even have all these differences?

Aren't all factor products basically the same?

If you're considering switching products or preparing to discuss with your hematologist what factor your newborn should use, you must get informed. Read on to learn about some of the differences—some subtle, some not so subtle—between clotting factors. And find out what questions to ask your hematologist when choosing a factor product.

Plasma-derived or recombinant?

This is probably the most basic question when choosing a clotting factor. Until a few years ago, the automatic answer would have been "recombinant." Roughly 80% of Americans with hemophilia use recombinant clotting factor. But people are now taking a second look at plasma-derived products, specifically those containing von Willebrand factor. Why?

In May 2016, the results of the Survey of Inhibitors in Plasma-Products Exposed Toddlers (SIPPET) were published in the *New England Journal of Medicine*.[1] These results suggested that in previously untreated patients (PUPs), the risk of developing an inhibitor when using recombinant factor VIII products is higher than when using plasma-derived factor VIII concentrates containing VWF. (There is no evidence of a higher risk of inhibitors with recombinant factor VIII in previously treated patients.) This begs the question: Should newly diagnosed patients with severe hemophilia A be treated with a plasma-derived product containing VWF?

Your hematologist probably won't automatically prescribe a plasma-derived factor VIII with VWF for your newly diagnosed baby with hemophilia A. SIPPET has been controversial: the results contradict several other studies that have found no increased risk of inhibitors when using recombinant factor VIII.[2] And people with hemophilia maybe feel uncomfortable choosing a plasma-derived clotting factor for two reasons: one has to do with the history of clotting factor, and the other has to do with fear of viral transmission. Are these concerns still valid?

1. Flora Peyvandi, Pier Mannucci, Isabella Garagiola, et. al., "A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A," *New England Journal of Medicine* 374 (May 26, 2016): 2054–64. 2. For more info on SIPPET, see the May 2016 and August 2018 issues of *PEN*.

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welcome

When my son was diagnosed in 1987, my hemophilia treatment center told me about only one factor concentrate product. I had no idea I had a choice. I had no idea there were other products to choose from. So we used that one product for years. I was too preoccupied with handling my own turbulent emotions, learning about hemophilia, learning how to do an infusion, and trying to prevent bleeds to research or even question our product. Then in 1992, a new product was introduced. Our hematologist told me about it, and I wondered: Should we switch? Eventually, I started hearing about other products. The more I learned, the more I wanted to choose my own product. It was hard work—remember, we had no internet, Facebook, or even email at that time!

It's so much easier now to learn about product choice. Every manufacturer has a website with full information about its products. You can ask other parents on Facebook groups about their experiences. And you get emails from us, notifying you about various products, with links to websites for more info. In fact, I was the first person to write about product choice, in the 1990 edition of *Raising a Child with Hemophilia*. And we always provide questions for you to ask your hematologist, to help get the answers you need. Our tools are yours, free of charge.

But remember, you *must* be a proactive, informed consumer. You need to make your own choices about what you inject into your loved one with a bleeding disorder. And your choices are rapidly changing, faster than at any other time in our community's history. Read Paul Clement's excellent feature article reviewing product types and history. Compare factor products using the chart on page 10. It's also available as a download on our website, and is constantly updated. Know what you use, and why. You do it with your shampoo, toothpaste, clothes, car—but your factor is most important of all.

In the past, it was incorrectly believed that only men could have hemophilia, and women with the gene were labeled asymptomatic "carriers." It's now recognized that women are not just carriers of hemophilia, but can also have hemophilia and experience symptoms if less than 50% of their factor is active. Most diagnosed patients are male. For editorial simplicity in PEN articles, when we refer to a person with hemophilia, we may alternately use "he" or "she," or just "he."

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as i see it

You Be the Judge

Mily Cepeda

Omar and Mily

When I share with people that my son has hemophilia, I often hear comments like these: "Hemophilia, what?" "Are you kidding me?" "Does it affect his brain, his learning?" "Is it contagious?" "But your son was just limping yesterday, and not today." "But I can't see the disability." I am mother to Omar, a 14-year-old with severe hemophilia, and his disorder is not always apparent. Handling these comments from others can be tough when it comes to a chronic disorder like hemophilia. It's especially challenging when the disorder doesn't have consistent visible symptoms, and you are often confronted with more questions.

Parenting a child with a chronic disorder has a whole new set of challenges and worries. Hemophilia is unpredictable, inconsistent, and some sometimes invisible. One time when we lived in south Florida, my son received a handicap decal for our car because he was unable to walk due to his ankle bleed. We received stares in the parking lot of our local grocery store. A woman questioned, "Why the decal? You both look fine. Do you have that handicap card illegally?" I was floored. But I responded politely, "We are okay, and have a nice day, ma'am."

Some chronic conditions are not always obvious, and many patients are limited in their work or daily activities; sometimes they're labeled lazy, overdramatic, or even a liar. Many patients try to explain their disability after hearing, "But you look so good." It's crucial that we spread awareness about invisible disorders to everyone we encounter and dispel any judgment calls.

Here are three incidents our family experienced with our invisible disorder—hemophilia:

Story 1. Omar was in fifth grade when he had a little sprain in his ankle, which happens to be his target joint. Just to be safe, my husband and I took Omar to the hemophilia treatment center (HTC) to get examined. The very next day, Omar went to school with crutches to avoid permanent damage. With high levels of factor in him, Omar decided not to use crutches at school for the next three days. He was fine, walking normally. Judging started right away. When Omar returned home, he said that his teacher and friends had called him a liar, and had assumed that all of this was made up. The next day, I visited school and clearly explained again about Omar's bleeding condition, distributed additional information, and stated that this invisible illness is something to take seriously.

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Cazandra Campos-MacDonald

Life After Immune Tolerance

There are many different treatment options for people with hemophilia. Individual variables like severity level, lifestyle, and how the patient's body reacts to certain products help determine the best treatment option. But when you throw an inhibitor into the mix, treatment options are fewer. You can treat the bleed with bypassing agents, try Hemlibra®, or try to eradicate the inhibitor through immune tolerance therapy (ITT). When ITT is successful, and the inhibitor is gone, what is life like then?

My oldest son Julian has severe hemophilia A and is now 22. He infuses twice a week and has been inhibitor-free since age four. His inhibitor was detected at age 11 months, after a torn frenulum would not stop bleeding. Fortunately, Julian's titer was below 10 BU, and we were able to start ITT immediately. A port was placed within a matter of days, which his father and I began learning how to access. For two and a half years, we gave Julian large doses of factor VIII through his port per our ITT protocol. This was a huge change in how we managed hemophilia. We went from infusing on demand to daily port access. Having a toddler with a bleeding disorder isn't easy, and wrangling him to sit still for daily infusions early in the morning before daycare became part of our routine.

Rich Pezzillo

When we received the news that Julian's inhibitor was tolerized, it was as if we had won the lottery! The protocol from the hemophilia treatment center was now to lower his factor VIII dosage and infuse three times a week. Infusing early in the morning before work wasn't easy, but now we had some relief. If extra activities were on the schedule, we now had control over deciding if Julian needed extra preventative infusions. Gaining more control over hemophilia gave my family a huge part of our lives back, and that was empowering. We moved from hemophilia being the focus of our lives to having it simply be part of what we did. Life after ITT was filled with adventures, and bumps and bruises. Infusing three times per week gave us a brand-new outlook on managing hemophilia.

Rich Pezzillo, executive director of the New England Hemophilia Association (NEHA), is an active, healthy man who has moderate hemophilia A. His life changed dramatically when he developed an inhibitor following dental surgery at age 17. For ten years, he lived with an inhibitor that only reached 14 BU but proved persistent. Rich's doctors prescribed various factor products for his ITT. After each failed attempt at ITT, Rich continued to have breakthrough bleeds. The half-life of his factor was very low. He accepted that this would become his normal.

The inhibitor gravely impacted Rich's quality of life, and much time was spent in a wheelchair. He suffered numerous hospitalizations, surgeries, two PICC lines, and two ports. These were the days of receiving six to seven boxes containing factor and supplies for a month's worth of treatment, with a separate refrigerator at college. It proved to be too much. Rich took a year off from school, and eventually transferred to a college closer to home. He finished school four years later than he had planned.

Rich missed the physical part of his life while treating his inhibitor. He could no longer go to the gym and weight train, and even going up a flight of stairs was difficult.

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richard's review

Linda Weaver's Studio

Richard J. Atwood

Reading and Romancing with von Willebrand Disease

I'll never claim to be an expert on romance. In fact, I just recently discovered the literary genre called medical romance.

Yet I'm curious about any novel that opens a discussion on bleeding disorders. Regrettably, fictional characters with von Willebrand disease (VWD) are grossly underrepresented in all genres of literature, except, possibly, in recently published medical romance novels.

Check out the following selection of internationally set romance novels, either printed or e-published, that include some fictional characters who happen to have VWD.

Reclaiming Nick

Susan May Warren
Tyndale House, 2006

In Phillips, Montana, the lives of Nick Noble, a former cop, and Piper Sullivan, an investigative reporter, become intertwined. Nick shares the family ranch with his half-brother. Piper goes undercover to find justice for her convicted brother, who was arrested by Nick. This novel could be classified as Western Christian romance suspense: secrets are kept and revealed, and religion is lost and then found. Romance is limited to holding hands and kissing before a marriage proposal. Only after Nick nearly dies donating his liver for his half-brother's Wilson's disease does he learn that both he and his half-brother have VWD. The author seems to include VWD as an example of a shared genetic connection, and also as a way to complicate the brothers' medical conditions.

His Secret Love-Child

Marion Lennox
Harlequin, 2006

Gina Lopez, a compassionate American cardiologist, returns to Crocodile Creek in Queensland, Australia, with her four-year-old son after a five-year absence. Previously, while separated from her husband, Gina had an affair with Callum Jamieson, a surgeon. Gina never told Cal she was pregnant before leaving to care for her dying husband in Idaho. Another secret is her diabetes—remember, this is a medical romance, so it features medical conditions that boost the backstory. Gina finds an abandoned, premature newborn in Australia. Assisted by Cal, Gina performs lifesaving heart surgery, only to discover that the baby has VWD, complicating the baby's serious medical problems. The relationship between these two doctors is an awkward, unexpected rekindling of passion, followed by a marriage proposal.

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Where Does Your Factor Come From?

Laurie Kelley

You may know the brand name of the factor concentrate your child or other loved one uses to treat bleeds. And you may have chosen the brand with the help of your hematologist. But where do get your factor? Who provides it? Is your current brand the best way to meet your personal needs? Do you have choice of provider?

Pharmaceutical companies develop and manufacture factor. Then they sell the factor to a licensed pharmacy—a factor provider. You can't buy factor directly from the manufacturer, just as you can't buy a car directly from General Motors, or diapers from Kimberly-Clark. And you can't get factor from your local drug store. Your hematologist supplies a prescription to a factor provider, who delivers it to you. Who are factor providers?

Hospital Pharmacies

You want a factor provider that can meet your personal needs; this usually means being cost-effective and speedy, and supplying factor in the correct assay sizes with all the ancillaries (such as needles and syringes) you require. Unless you are a member of a health maintenance organization (HMO) and are required to buy factor from the hospital pharmacy, or your hospital runs a 340B program (see p. 18), obtaining your factor through a hospital pharmacy is usually not a good option. Why not? Hospital pharmacies are the least cost-effective factor provider, and often mark up the cost of factor several hundred percent to cover the high overhead costs of running the hospital. Also, hospital pharmacies are not set up for home delivery and unlike specialty pharmacies, do not offer any additional services, such as a home nurse. Factor is already very expensive without the hospital markup! You'll want a long-term solution, with a factor provider that ships to your home.

Specialty Pharmacies

Specialty pharmacies are one of the chief factor providers in the US. If your insurance payer approves a specialty pharmacy based on your physician's prescription, you make a phone call, order your factor, and receive the order at your home within 24 to 48 hours,

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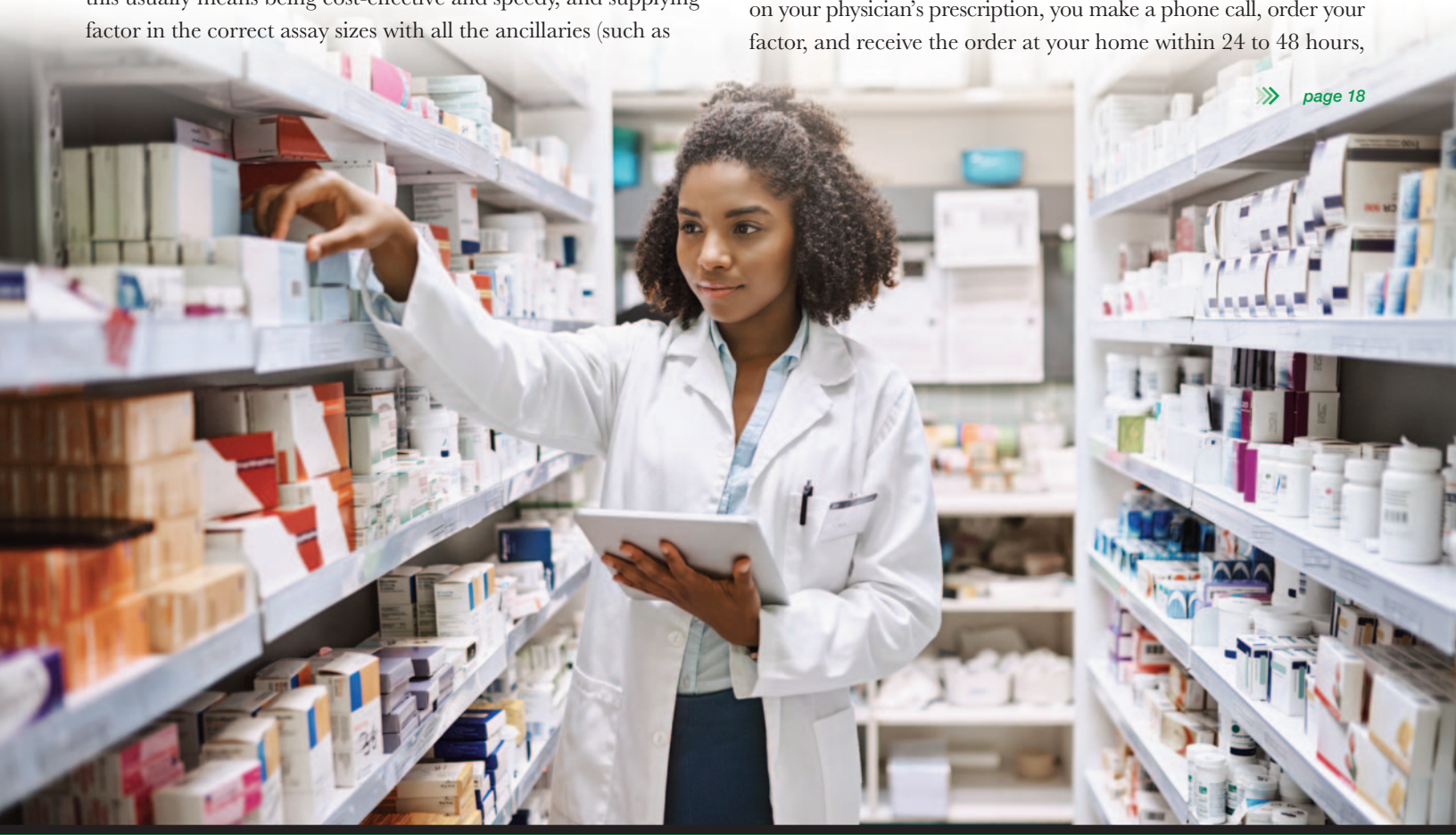


PROJECT SHARE

It's time to give back

Project SHARE (Supplying Hemophilia Aid and Relief) is now a Program of Save One Life!

A Proper Diagnosis Saves a Life, and Changes a Life

Dr. Shahla Soheil
Hemophilia Foundation–Pakistan (HFP)

Help us improve the quality of life of people with bleeding disorders in developing countries

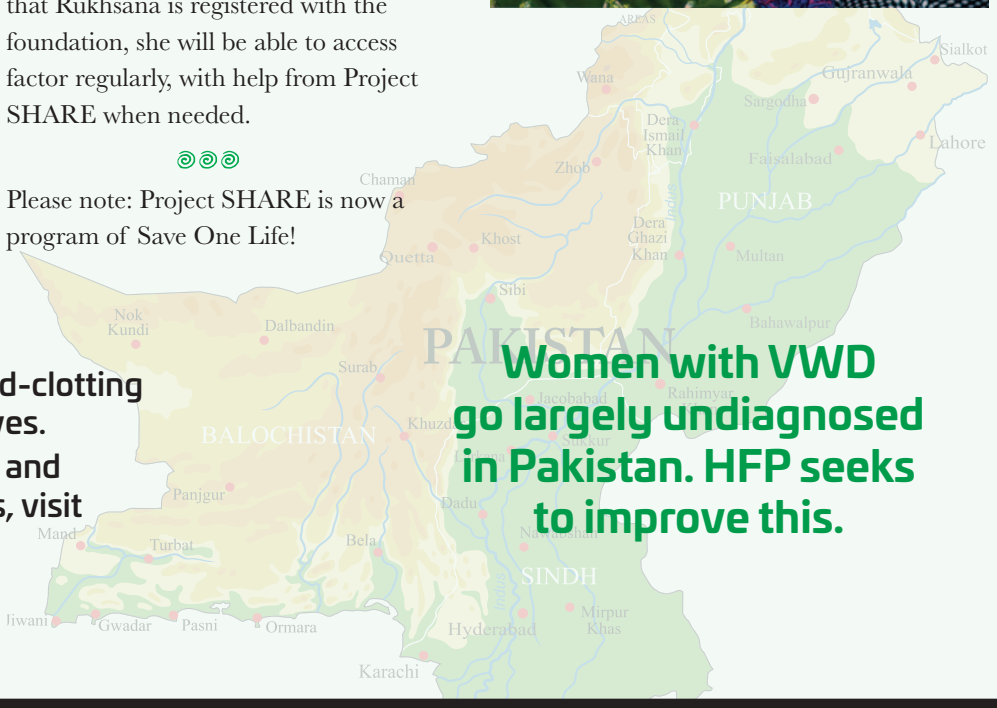
Rukhsana Asif grew up in a rural village in Pakistan, always vaguely knowing that there was something wrong with her. Now age 42, Rukhsana was married 15 years ago, and soon after, she had her first and only child via cesarean section. She bled profusely. She was transported to a hemophilia treatment center (HTC) in Sialkot City, 124 miles away. Her uterus was removed, using fresh frozen plasma and blood transfusions to control the bleeding. She survived, but still did not have a diagnosis.

In July 2018, Rukhsana developed a gastrointestinal bleed; her hemoglobin dropped to a dangerous level. She was brought to Lahore, where Hemophilia Foundation–Pakistan is located, to a private hospital. The hospital staff gave us an emergency call at our HTC.

We visited Rukhsana on October 27, 2018. We registered her and diagnosed her with type 3 von Willebrand disease (VWD). We started her treatment with clotting factor concentrate donated by Project SHARE. After an endoscopy, the source of the bleeding was identified, and she was treated. She is well now and is home.

All in all, Rukhsana used over 40,000 IU of factor, normally not available in Pakistan. All of this factor was donated by Project SHARE only. Now that Rukhsana is registered with the foundation, she will be able to access factor regularly, with help from Project SHARE when needed.

Please note: Project SHARE is now a program of Save One Life!



Women with VWD go largely undiagnosed in Pakistan. HFP seeks to improve this.

Donate unused or unwanted blood-clotting medicine to help us save lives.

To learn more about SHARE and other Save One Life programs, visit www.saveonelife.net or call 978-352-7652

History of clotting factor

It's good to know and appreciate the history of your clotting factor. The development of clotting factor concentrates in 1968 was life-changing for people with hemophilia. It allowed rapid home self-infusion, without a trip to the hospital to receive cryoprecipitate. It prevented crippling pain and long stays in the hospital, and it greatly improved quality of life. Factor concentrates quickly replaced cryoprecipitate and became the standard of care for hemophilia in the 1970s. The future for people with hemophilia seemed bright, but there were dark clouds on the horizon.

Early factor concentrates were not treated to inactivate viruses. Patients were at great risk of contracting hepatitis, HIV, and other viral diseases. Pharmaceutical manufacturers had tried dozens of methods to destroy blood-borne viruses, but the factor VIII molecule is very fragile. And initial studies of methods that successfully destroyed viruses, like heat treatments, also destroyed 50% to over 90% of the factor. This huge loss of factor was considered unacceptable, so during the 1970s and early 1980s, clotting factor remained untreated.

Clotting factor concentrates also exposed patients to plasma from many donors, increasing the risk of viral infection. Each lot of factor was produced from the pooled plasma of 10,000 to 60,000 donors; and after stabilizer was added, the final product could contain plasma from as many as 400,000 donors.[3] To make things worse, in the course of a year, a patient might use factor from several different lots and possibly be exposed to plasma from millions of donors. Just one contaminated donation could contaminate the entire lot, and the larger the pool of plasma donations, the greater the risk that the pool contained plasma from an infected donor. The risk was further increased by plasma collection practices: blood plasma was often collected from prisoners and homeless populations, many of whom were IV drug users at high risk of viral diseases. People with hemophilia unwittingly became the canary in the coal mine for blood-borne viral diseases.

The decision to *not* treat factor concentrate would prove disastrous to the hemophilia community. Two yet-to-be-discovered viruses—hepatitis C (HCV) and the human immunodeficiency virus (HIV)—would eventually kill thousands.

Fast-forward to today: hepatitis and HIV infections from plasma-derived clotting factor are now a thing of the past. In 1997, manufacturers of plasma products voluntarily adopted measures to ensure the safety of plasma products, called the Quality Standards of Excellence, Assurance and Leadership (QSEAL) program.[4] And today, plasma donation centers are no longer located in high-risk areas or accepting donations from prisoners. Here are some of the quality standards adopted:

- *Qualified Donor Standard* requires a donor to return for a second donation and pass all health and blood tests again before his or her plasma can be used. This allows identification of donors who are in the early stages of an infection (the "window period") when some tests can't detect the infection.
- *60-Day Inventory Hold Standard* requires source plasma (donated plasma, as opposed to plasma recovered from a blood donation) to be frozen and held in inventory for a minimum of 60 days. This allows any suspect donations to be retrieved and discarded before being considered for use in fractionated blood products.
- *Implementation of more sensitive viral blood tests*, such as nucleic acid tests (NAT), allowing contaminated donations to be detected earlier and removed from the plasma pool.

Although all FDA-approved clotting factors are now considered safe, the tragic failure of the healthcare system made a lasting scar on the psyche of the hemophilia community, and many people still deeply distrust pharmaceutical companies.

3. "FDA Oversight: Blood Safety and the Implications of Pool Sizes in the Manufacture of Plasma Derivatives," www.gpo.gov/fdsys/pkg/CHRG-105hhrg45902/pdf/CHRG-105hhrg45902.pdf. 4. For more on the Plasma Protein Therapeutics Association (PPTA) QSEAL voluntary standards program, see www.pptaglobal.org/safety-quality/standards/qseal.

Fear of viral transmission

Current plasma-derived factor concentrates are very safe. Plasma donors and plasma donations are screened, plasma pools are tested, and factor products undergo various purification methods to reduce or eliminate unwanted proteins, including some viruses. No cases of hepatitis or HIV have been transmitted by plasma-derived products since the late 1980s. Even so, no plasma-derived product can be made 100% safe from viral contamination.

Viruses are divided into two groups: (1) enveloped viruses, surrounded by an outer fatty membrane; and (2) non-enveloped viruses, lacking this membrane. Enveloped viruses, like HIV, are relatively easy to inactivate using solvent-detergent or heat viral inactivation processes. On the other hand, non-enveloped viruses, such as HAV and parvovirus B19, are not affected by solvent-detergent viral inactivation processes and are highly resistant to heat treatment. Also, some non-enveloped viruses, such as HAV, are very small—smaller than the factor VIII molecule—and can't be filtered out of factor VIII products.[5] This means that some viruses might be transmitted through plasma-derived factor. So far, we're lucky that current screening and purification methods have prevented this, but we can't screen or test for viruses if we don't know they exist. New, or "emergent" viruses constantly threaten our blood supply, and possibly threaten factor concentrates.

It's partly a matter of luck that current viral inactivation and purification processes have successfully removed new pathogens such as West Nile virus, Dengue fever virus, and Creutzfeldt-Jakob disease (CJD) prions (not a virus, and can't be inactivated) from factor concentrates. But it's only a matter of time before some new infectious disease slips past our defenses. Although this risk is considered very small, some people would rather not take any risk at all. The fear of viral contamination was one thing that led to the development of recombinant clotting factor concentrates.

Recombinant clotting factor concentrates

The successful cloning of factor IX in 1982 and the factor VIII gene in 1984 were major breakthroughs, allowing the production of recombinant human factor concentrates—with the goal of producing a factor that would be free of the risk of transmitting infections or other pathogens. Recombinant factor is not made from blood plasma. Instead, it's produced by mammalian cells that have been genetically modified to produce human clotting factor. The cells—tens to hundreds of millions of them—are grown in a liquid growth medium housed in large stainless steel tanks called bioreactors. The cells produce human clotting factor, and then discharge it into the growth medium. Periodically, some of the growth medium containing the factor is extracted and processed into clotting factor concentrate.

The first recombinant factor VIII product was Recombinate (Baxter), licensed in the US in 1992. The first recombinant factor IX product was BeneFIX (Wyeth), in 1997. In the US, there are now about 20 recombinant factor products on the market.

Recombinant "generations"

There are three generations of recombinant clotting factor. First-generation recombinant factors use animal proteins in the

5. Filtration, as a viral removal process, is more suitable for factor IX products, because the factor IX molecule is very small, and the filter can remove small viruses but still allow the factor to pass through.

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®* *Jivi®*					
CSL Behring	*Afstyla®*	*Idelvion®*		Humate-P®	Mononine®	
Grifols				Alphanate	AlphaNine®S/D Profilnine®	
Kedrion*				Koate®-DVI		
Novo Nordisk	Novoeight®	*Rebinyn®*	NovoSeven®RT			
Octapharma	Nuwiq®					
Pfizer	Xyntha®	BeneFix®				
Sanofi Genzyme	*Eloctate®*	*Alprolix®*				
Takeda	Advate *Adynovate* Recombinate	Rixubis		Hemofil M	Proplex-T	FEIBA VH

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

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 is a second-generation product. Advate, Adynovate, Afstyla, Alprolix, BeneFix, Eloctate, Idelvion, Ixinity, Jivi, Kovaltry, Novoeight, Nuwiq, Rebinyn, Rixubis, Vonvendi, and Xyntha are third-generation products.

Shire was acquired by Takeda, and Sanofi acquired Bioverativ.

growth medium (such as calf serum or human plasma protein solution). Then albumin, a human plasma protein, is added to the final formulation to stabilize the fragile factor VIII protein. Growing the cells in plasma and then adding albumin to the final step is often seen as defeating the main goal of producing recombinant factor: to develop a factor concentrate that contains no blood products and is free of the risk of transmitting pathogens.

Research continued into removing animal and human proteins from the production of recombinant factor. The first second-generation recombinant factor, made without albumin, was released in 1999. These products still used human or animal proteins in the culture medium, but used sugars and traces of other compounds as stabilizers in the final product. (Almost all the white powder you see in a vial of factor is stabilizer.) Because it had no added human albumin, second-generation recombinant factor was considered a significant advance in removing the risk of blood-borne pathogens.

Factor made with no extra human or animal proteins in the production process or in the final product are called third generation. Third-generation recombinant factor VIII products were licensed in the US in 2003. Today, all factor VIII products are third generation, with the exception of Recombinate (first generation) and Kogenate FS (second generation).

Animal or human cell line?

Factor VIII is a very large and complex molecule. It's hard to find cells that can synthesize—make—factor VIII, or produce enough of it to make the process commercially practical. Mammalian cells are best adapted to synthesize factor VIII. And almost all recombinant factor products use one of two hamster cell lines to synthesize factor VIII: either Chinese hamster ovary (CHO) cells or baby hamster kidney cells (BHK).

Although CHO and BHK cell lines are efficient at synthesizing factor VIII, they're not so good at "finishing" the protein, which means attaching carbohydrates and other compounds to the factor molecule and folding it into the proper shape. The correct finishing of a protein is an important step, because it affects the functioning of the protein. Current recombinant factor products produced from CHO or BHK cell lines are not identical to human

plasma-derived factor, and they also contain some inactive factor, probably due to inefficient finishing of the protein. Perhaps more important to consumers, these factors also have some hamster compounds attached to the factor. Since these compounds are not human, they are "potentially immunogenic": in other words, they might trigger the immune system to produce inhibitors.

So why don't we just use human cell lines to produce factor? This has proved difficult, but two companies have done it: Sanofi Genzyme and Octapharma both produce factor using a human embryonic kidney cell line. Do these have a lower inhibitor rate? Right now, we don't know. Clinical trials to answer this question are either underway or soon to begin: Octapharma enrolled 110 PUPs in a study called NuProtect, which started in 2014, to find out if the inhibitor rate is comparable to that of plasma-derived factor. Sanofi Genzyme is enrolling PUPs in a trial called INHIBIT, set to begin in 2020 with results expected in 2024.[6] Although preliminary results of Octapharma's study indicate a lower inhibitor rate than that of standard recombinant factor, final study results won't be available until later this year; also, one epidemiologist has written that the study has a selection bias that might skew the results.[7] You'll need to discuss with your hematologist whether these products offer lower inhibitor rates as compared to other recombinant products, after final results of the studies are released.

Standard half-life factor or extended half-life factor?

Should you switch to an extended half-life factor? Many variables might influence your decision: Do you have hemophilia A or B? What benefits do you expect from extended half-life factor? What are your reasons for switching? What is your current bleeding pattern? Are you having regular breakthrough bleeds while on prophylaxis? Do you follow your prophy schedule, or do you often miss or skip infusions? How old are you (or your child)? Have you had a recent pharmacokinetic (PK) study done to determine the half-life of factor in your body? What's your activity level? You and your hematologist will have to weigh all of these questions, and more, before deciding to switch to an extended half-life factor.

First, note that there is no rule for what defines an extended half-life factor. The half-life of standard factor VIII is normally considered to be about 12 hours, give or take 4 hours. The half-life of factor IX is longer, about 18 hours, give or take 5 hours. Half-life is highly variable from one person to the next, and is heavily influenced by age: young children clear factor more quickly, and older adults clear factor more slowly. A young child may have a factor VIII half-life of only 4 hours, and an elderly person may have a factor VIII half-life of 25 hours. (This wide range is one of the reasons that PK studies to determine your individual half-life are so important.)

The lengthening, or extension, of the half-life for factor VIII and factor IX are very different. For factor VIII, the half-life of an extended product may be almost the same as the half-life of a different standard factor VIII—meaning there may not be much extension! The half-life extension for factor VIII ranges from about 1.1 to 1.8 times that of standard factor VIII. For factor IX, the half-life extension is much greater: from 3 to 5 times that of standard factor IX. This means that if you have hemophilia B, you're likely to gain a major benefit by switching to an extended half-life product: you can extend infusion times and/or increase your trough level (the lowest level of factor in your body before your next infusion) using the same dose you used of standard factor IX. For hemophilia A patients, the benefit is less clear and depends on what product you choose.

If you're considering switching to an extended half-life product, you and your hematologist should look at your activity level, especially if there are days when you're more active and at increased risk of having a joint bleed. If you look at a graph of the half-life of an extended half-life factor product, there is a long "tail" on the right of the graph where your factor level is close to trough level for a lengthy period, and where you have less protection. (This is in contrast to a standard half-life product,

6. INHIBIT is also looking at whether "preemptive prophylaxis"–infusions before the first bleed–can also lower the inhibitor rate. 7. K. Fischer, "Interpreting Data on Inhibitor Development from Previously Untreated Patient Studies, Beware of Premature Conclusions," *Haemophilia* 24 (2018): 177–79.

where you're likely to have more frequent infusions, so you'll have more frequent high-factor levels or "peaks" providing more protection against bleeds.) If you're very active and switch to an extended half-life product, and you have a low trough level between infusions, you may want to consider additional treatment with a low dose of a standard half-life product on high-risk days that fall near the end of your infusion interval, to give yourself additional protection against bleeds.

Why do you want to switch? Your answer and your hematologist's may differ, especially if you're having breakthrough bleeds while on prophy. Consumers often look at reducing the number of infusions as a reason to switch, while your hematologist may view switching as a way to increase your trough level to reduce bleeding. Studies of factor IX patients who switched to an extended half-life product indicate that there's some of both going on: patients used one-third to one-half the factor they used previously (but not three to five times less), suggesting that they increased the interval between prophylactic infusions, but also increased their trough level. What insurers are concerned about is the finding that even though consumers used fewer units of factor on extended half-life products, the yearly cost of the factor almost doubled.[8]

PEGylation, fusion, or single-chain?

Extended half-life factor products usually have another molecule attached to the factor to extend its half-life. This extra molecule may be PEG (polyethylene glycol), or fusion of Fc or albumin (two human compounds). One product doesn't use another molecule to extend the half-life. Instead, it changes the factor VIII molecule from its normal double-chain structure to a single chain, slightly increasing half-life.

Why is the method of half-life extension important? Some researchers are concerned about the long-term effects of PEG. PEG is categorized by its molecular weight. Low molecular weight PEG weighs less than 5,000 and is used in many products, including drugs and cosmetics.[9] It has a good safety record, and even though the body can't break it down, the kidneys can remove this PEG and excrete it in urine. This isn't true of the very high molecular weight PEG used in extending the half-life of factor; it weighs 20,000 to 60,000. This PEG is not broken down, and is too large to be excreted by the kidneys. Some is removed from circulation by the liver and excreted into the bowel with bile, but much of it seems to be held in the body, accumulating in various organs, including part of the brain.

What happens to this PEG and how it affects the body is unknown. We'll need long-term studies to assess the risk. But studies showing negative effects of high levels of PEG on animals have raised concerns. When reading literature on extended half-life products using PEG, beware of arguments citing the safety of PEG—these studies are of low molecular weight PEG, and are not comparable to the PEG used in factor. Also watch out for statements like "There is no evidence of any risk." Lack of evidence is not proof of absence. Finally, the use of PEG to extend half-life is also a double-edged sword: on one hand, it may decrease the risk of inhibitors against the factor; on the other hand, the PEG itself can produce an immune response.

Be an informed consumer!

Sadly, some people don't know the name of their clotting factor, much less who produces it or whether it's plasma-derived or recombinant. Don't be one of those people. Be an informed consumer. Learn all you can about your factor product, and stay current on developments in other factor products and new therapies. Know the right questions to ask your hematologist about the best treatment for your personal situation. This may help you if you need to justify to your insurance company why you want to switch products. Being informed may help you choose a therapy that reduces your risk of joint bleeds or inhibitors, improving your quality of life.

And no, clotting factors are not all the same!

8. J. Tortella Bartholomew, José Alvir, Margaret McDonald, et. al., "Real-World Analysis of Dispensed IUs of Coagulation Factor IX and Resultant Expenditures in Hemophilia B Patients Receiving Standard Half-Life Versus Extended Half-Life Products and Those Switching from Standard Half-Life to Extended Half-Life Products," *Journal of Managed Care & Specialty Pharmacy* 24 (7) (2018): 643–53. 9. Masses (molecular weight) of proteins are often expressed in a unit called a dalton (Da). One Da = 1 gram/mole.

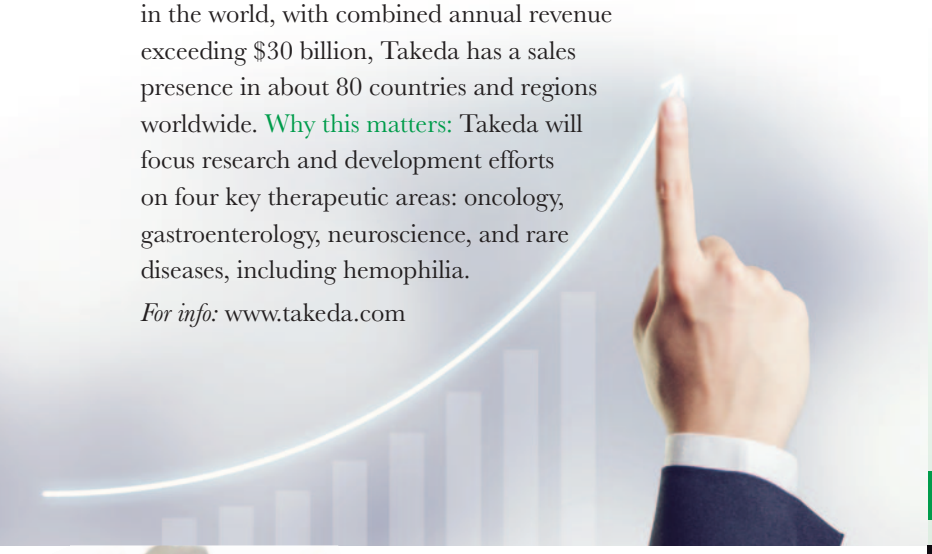
headlines

manufacturer

Takeda Takes Over

Osaka-based Takeda Pharmaceutical announced the completion of its acquisition of Shire, manufacturer of products including Advate, Adynovate, and Recombinate, eight months after entering into the $62 billion agreement in May 2018. Now one of the 10 largest drug manufacturers in the world, with combined annual revenue exceeding $30 billion, Takeda has a sales presence in about 80 countries and regions worldwide. Why this matters: Takeda will focus research and development efforts on four key therapeutic areas: oncology, gastroenterology, neuroscience, and rare diseases, including hemophilia.

For info: www.takeda.com



Good News Continues for Hemlibra®

Findings from the HAVEN 2 study, the largest-ever clinical trial in pediatric patients with hemophilia A and inhibitors: weekly prophylaxis with Roche's Hemlibra dramatically reduced the annualized bleeding rate (ABR) in relation to previous prophylactic or episodic treatment with a bypassing agent in children under age 12. Of the 88 patients enrolled, zero treated bleeds were reported in 77% of patients on weekly prophy, 90% on biweekly, and 60% on monthly. Of the 13% who required treatment for a bleed, 83.3% of those bleeds were associated with trauma and just 16.7% were spontaneous. Why this matters: Investigators concluded that in children with hemophilia A and inhibitors, Hemlibra prophy is well tolerated and can prevent or reduce bleeds with less frequent dosing and with no new safety issues.

For info: www.emicizumabinfo.com

soundbites

Genentech's web portal for patients and caregivers provides accurate info on any serious adverse events for **Hemlibra**: www.emicizumabinfo.com

The FDA has approved **Esperoct** (turoctocog alfa pegol, N8-GP), an extended half-life factor VIII molecule for treating patients with hemophilia A for routine prophylaxis, on-demand treatment, and perioperative management of bleeding. The product won't be available commercially until 2020.

David Quinn, a person with hemophilia B, is now head coach of the New York Rangers hockey team. Quinn became famous in 1980 for missing out on being part of the US Olympic Hockey "Dream" Team, known as "Miracle on Ice," because of a bleed that almost cost him his life.

Swiss pharma giant **Roche** bought gene therapy specialist Spark Therapeutics for $4.3 billion. Spark's hemophilia A gene therapy (SPK-8011) is expected to start phase III clinical trials this year.

nonprofit

NHF Annual Conference

October 3–5, 2019
Anaheim, California

National Hemophilia Foundation will hold its 71st national bleeding disorder conference this fall. Registration includes three days of educational sessions, networking opportunities, and access to the Exhibit Hall, where dozens of companies and nonprofits display booths. Thousands of participants in the bleeding disorder community are expected to attend. Why this matters: NHF Annual Conferences provide one of the largest gatherings of community members in the world.

For info: www.hemophilia.org

news from LA Kelley Communications

Project SHARE Joins Save One Life!

The lifesaving program Project SHARE, founded by Laurie Kelley in 2002, has moved over to Save One Life. Originally created to handle a few donations when Laurie traveled overseas, the program ballooned from 30,000 IU per year to over 7 million IU. Save One Life is a registered nonprofit with a board of directors, and ideally designed to handle Project SHARE. Why this matters: Save One Life will now provide a more holistic approach to patients in developing countries by offering factor to the nonprofit's beneficiaries, in addition to patients not enrolled as beneficiaries of the sponsorship program.

For info: www.saveonelife.net

Sponsor a Child!

You can improve the life of a child with a bleeding disorder.

Our sponsorship program provides direct assistance to children in developing countries, who suffer the double burden of a bleeding disorder and poverty.

To sponsor a child:
contact@saveonelife.net
or 978-352-7652

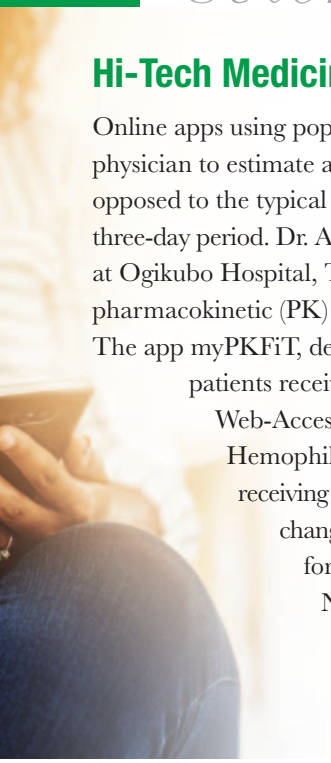
Sponsorships are
$420 per year
(just $35 a month!)

SAVE ONE LIFE

saveonelife.net

science

Hi-Tech Medicine Works



Online apps using population pharmacokinetics (popPK) allow a physician to estimate a patient's PK with only 2 blood draws, as opposed to the typical 5–11 blood draws taken over a two- to three-day period. Dr. Azusa Nagao, a researcher in blood coagulation at Ogikubo Hospital, Tokyo, and colleagues calculated individual pharmacokinetic (PK) profiles for 39 patients using two apps. The app myPKFiT, developed by Takeda for Advate, was used for patients receiving recombinant factor VIII, and the Web-Accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-Hemo) app was used for patients receiving other factor VIII concentrates. Based on results, changes to prophy regimens were recommended for 20 of the 39 patients. Why this matters: New online popPK tools will greatly decrease the burden on patients of having a PK study done—allowing for more PK studies and more individualized treatment.

For info: www.thrombosisresearch.com

uniQure's High Hopes

A phase III clinical trial of AMT-061, a gene therapy candidate for severe and moderately severe hemophilia B, has treated its first patient. The HOPE-B study is testing the safety and effectiveness of AMT-061 in adult men with hemophilia B. Patient recruitment is continuing for an estimated total of 56 participants at sites in the US and UK. Why this matters: Successful administration of AMT-061 in the first patient enrolled in the trial is a milestone in advancing a possible one-time treatment for hemophilia B.

For info: www.uniqure.com

CRISPR Patent Goes to Berkeley

On February 9, the University of California–Berkeley, along with Emmanuelle Charpentier of Umeå University and Krzysztof Chylinski of the University of Vienna, was awarded a second patent for CRISPR-Cas9 technology, which may be useful in gene therapy. CRISPR allows scientists to target a specific area of a gene, cut out the gene sequence, and insert another gene. The patent ends four years of litigation with Harvard/MIT's Broad Institute, which received a similar patent in 2018 for using CRISPR in mammalian cells. Because the two patents overlap, commercial users of the technology may need to secure licenses from both organizations. Why this matters: Critics argue that the technology should remain in public domain since the research used public funds, and that licensing may slow commercial development of gene therapies using CRISPR.

For info: www.kqed.org/science

global

WFH
WORLD FEDERATION OF HEMOPHILIA

Roche Joins WFH Humanitarian Program

Roche/Genentech has joined the WFH humanitarian aid program and will be donating Hemlibra to 1,000 people with hemophilia A over five years in countries with little or no access to hemophilia treatment. Why this matters: About 75% of the world's population with hemophilia receives little or no treatment.

For info: www.roche.com

From Mountaineer to Executive Director

Chris Bombardier, who made history a year ago by being the first person with hemophilia to complete the Seven Summits, takes on a new challenge as executive director of Save One Life. The international child sponsorship nonprofit, founded by Laurie Kelley, offers direct financial assistance to over 1,400 patients in 13 developing countries. Why this matters: Chris has hemophilia B and has worked in Kenya; his high profile and overseas experience will grow the nonprofit and help more patients in developing countries secure aid and factor.

The rocks in the water don't know how the rocks in the sun feel.
—*Haitian proverb*

Have you visited HemaBlog lately?

Laurie Kelley

Haiti is the poorest country in the Western hemisphere, and even during good times is never easy to visit or work in. A government that seems perpetually corrupt, combined with natural disasters (most notably the earthquake of 2010), difficult topography, lack of infrastructure, and massive inflows of foreign aid have left this island nation dependent, poor and frustrated.

The frustration reached a peak last week, when riots erupted in the capital, Port-au-Prince, and the second largest city, Cap Haitien—right where I was. I flew from Boston on Sunday, February 10, after at least seven months of planning, and 16 years in the making. At last, I was going to start a hemophilia program in the country. *Yes, 16 years in the making.* That's a story for another blog.

I landed on Sunday and was home Monday night. Only 24 hours in Haiti. Almost all our plans foiled. But it was not a total loss. I was able to meet two of the 11 boys I know with hemophilia. And that made the whole adventure worthwhile.

I met up in Miami on layover with Barbara Campbell, executive director of the Dalton Foundation, which does a lot of great healthcare work in Haiti. Her group is connected with the Cap Haitien Health Network (CHHN), a nonprofit based in Orlando, which has guided me for the past 11 years in trying to establish hemophilia care. Barbara is competent and energetic, and obviously loves Haiti.

This is the irony of Haiti: as bad as it gets, as frustrating as it can be, there is something compelling about the country and its people, especially to Americans and American missionary groups. Perhaps because it is only a 90-minute flight from our shore: we feel a kinship with this sad piece of earth. Perhaps it's because we know there must be a solution; I mean, it's a tiny country—how hard can it be to fix? It's right in our backyard. Let's bring in the help, the food, the seeds, the money, the medicine, the manpower—let's fix this place up! It hasn't quite worked out. For all we have invested in Haiti, it festers in the heat. And still we want to make it the beautiful country it should be.

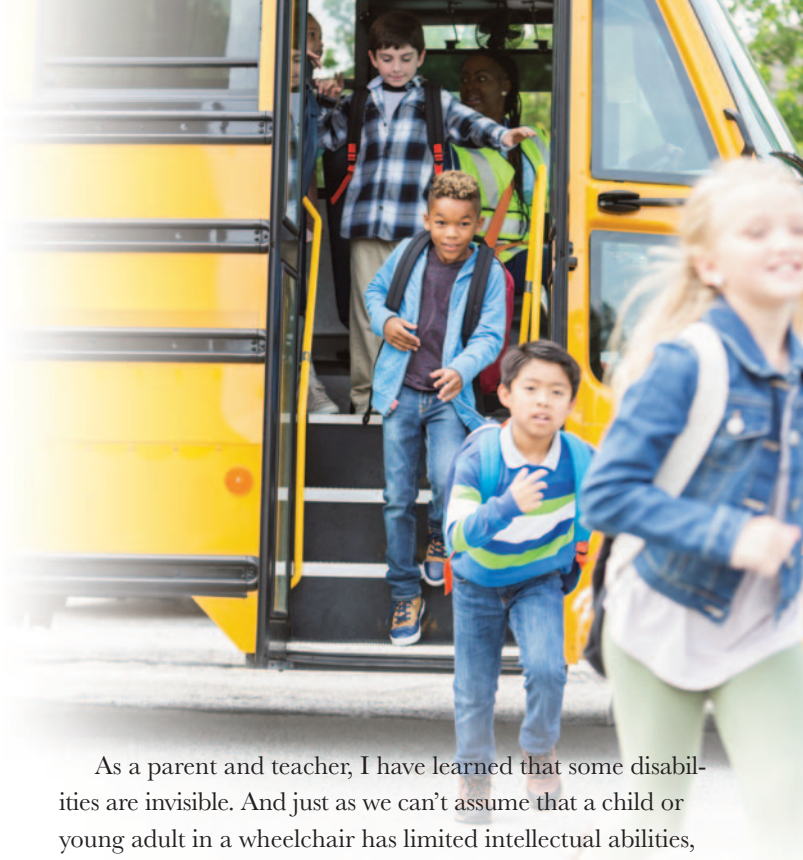
Two hours later, Barbara and I landed in Cap Haitien, and were met by our driver, "Charles," who also happens to be a lawyer and CPA. The day was sunny and surprisingly dry, and I looked forward to an afternoon with two brothers with hemophilia. But Charles told us we were not going to the hotel first, as planned; it would be too dangerous to drive in and out of that area twice. There were roadblocks and bonfires in the streets, and protests. Better to go see the boys now, and make only one trip into the gated Hotel de Roi Christophe. We piled all our luggage (mostly gifts) into the small van and took off. We got lost a few times, but it was a quick 30-minute ride to the boys' home. The roads were worn and torn, and traffic was light. We finally pulled up to a quaint, deep turquoise-colored single level house on a packed dirt road...

Read the rest of the adventure at Kelleycom.com/HemaBlog

As I See It... from page 3

Story 2. In the fall of 2015, I was assigned to teach at a special needs school in Livingston, New Jersey. I was so excited to teach this population and wanted to take up the challenge. At the time, it was my 15th year teaching special needs, ranging from age six months to 72 years. But I too judged someone, something I had never done in 15 years of teaching. I judged one of my students because he was not in a wheelchair; *all* of my students were in wheelchairs. I assumed that he didn't have an intellectual disability. I thought, "Why is he in this school? He looks perfectly fine, and he is walking well." I then discovered that this student had a major visual problem and indeed did have an intellectual disability. He was 14, and was learning at a third-grade level. This was a reminder to not judge others, even as a parent of a child with a chronic disorder. It was a learning moment for me.

Story 3. Omar's wish was granted by the Make-A-Wish Foundation in 2014 to attend WrestleMania 30 in New Orleans, Louisiana, at the Mercedes-Benz Superdome. On the third day of the trip, we were invited to attend one of the six WWE WrestleMania Axxess sessions at the Moral Convention Center. At the session, there was a replica of the WWE stage, complete with music and video screen. All of the Make-A-Wish children lined up to make their special appearances on stage as if they were wrestlers. Omar decided he would walk in with the music and video of wrestler John Cena. As we approached the beginning of the line, an attendant stopped us and said, "He can't go in." I quickly responded, "And why not?" The attendant continued to stare at our son and at us. He said, "This line is for the Make-A-Wish kids only, and he is not in a wheelchair." I replied, "Oh, you don't see his illness, but can *you see his badge* that says 'Make-A-Wish.'" I finished by saying, "He *is* making his entrance."



As a parent and teacher, I have learned that some disabilities are invisible. And just as we can't assume that a child or young adult in a wheelchair has limited intellectual abilities, we can't assume that a child or young adult who is walking normally doesn't have a chronic disorder like hemophilia.

I work closely with my students and take inventory of their strengths, weaknesses, likes, and dislikes—whether visible or not. At times, our disorders may be invisible, but we need to speak up and dispel any misconceptions and misunderstandings by sharing our knowledge. Folks, continue to advocate for yourself, for your children, and for others. Knowledge is power and empowering!

Mily Cepeda lives in New Jersey. She is a special education teacher and motivational speaker. Mily has an MA in special education and a BA in psychology. She is currently a doctoral student in education, dedicating her degree to her son and her father.

Inhibitor Insights... from page 4

After other attempts at ITT, Rich was finally placed on a plasma-derived product with von Willebrand factor. It worked. Finally, he was able to successfully tolerize, and his inhibitor was defeated.

Life after ITT has been very fulfilling for Rich. He has run a full marathon as well as six half marathons, despite admitting that running may not have been the best form of physical activity for his joints! These days, life after ITT is not filled with a big physical goal in mind—except for being determined to meet his personal challenge of 10,000 steps daily. Keeping as active as possible is important to Rich, and he goes out of his way to make sure he meets his step count. He wants people to understand that it's not so much about training for an event as about changing your lifestyle.

Rich is passionate about his work at NEHA. When he leaves the chapter one day, he wants the organization to be thriving and working to reach everyone affected by a bleeding disorder. "There is still not a cure," he says. Despite the many advances in treating hemophilia and inhibitors, Rich stresses, "We need to stay vigilant."

When we hear the stories of people who have been through the worst of the worst—the ones who understand firsthand the pain and suffering that hemophilia and inhibitors can cause—our community can be reminded of the significant complications of inhibitors, and how wonderful life can be after treatments like ITT.

YOU... from page 6

along with all necessary ancillaries and supplies. Reimbursement specialists handle your insurance paperwork. Specialty pharmacies stock most brands of factor, and usually can provide a size or assay that closely mirrors what you need for your child's infusions. Some specialty pharmacies will send a nurse to your home to perform or assist in the infusion process. There are many specialty pharmacies and home care companies that service hemophilia, and some are devoted only to hemophilia.

Your HTC

Did you know your hemophilia treatment center might sell factor? There are about 140 HTCs in America as of this writing, and over 100 participate in the 340B program; all are licensed distributors of factor. So you also have the option—if your payer permits—to purchase factor from your HTC. Why and when would you consider buying from your HTC? Federally funded HTCs can take advantage of the federal Public Health Service (PHS) Act known as the 340B Drug Pricing Program. The PHS Act allows certain federally funded entities and public hospitals to purchase prescription outpatient drugs (including factor) at steeply discounted prices. So federally funded HTCs can buy factor from pharmaceutical companies at rock-bottom prices, and then sell it to you and make a profit.

In theory, 340B pricing is beneficial. It offers competition to help keep prices down, reduces costs for the government, and generates funds for the HTC to use for staff positions or overhead—which is truly needed. But not every eligible HTC uses the 340B program. And even when an HTC does offer factor through 340B, not all the HTC's hemophilia consumers take advantage of this. Why? Sometimes, 340B pricing doesn't guarantee lower prices to the consumer: some HTCs charge the same price per unit as specialty pharmacies. And some consumers simply prefer the personal relationship they have with their specialty pharmacy reps.

PBM Pharmacies

Pharmacy benefit managers (PBMs) are powerful, multi-billion-dollar companies hired by insurance companies to manage the insurance benefits and prescription drug plans of private-sector entities, such as employers and labor unions. PBMs help determine the *formulary*—a limited list of preferred drugs that the payer will reimburse. PBMs also negotiate and manage contracts with pharmaceutical companies to buy the drugs needed by plan beneficiaries like you. The main function of a PBM is to keep prescription drug costs low for the insurance company.

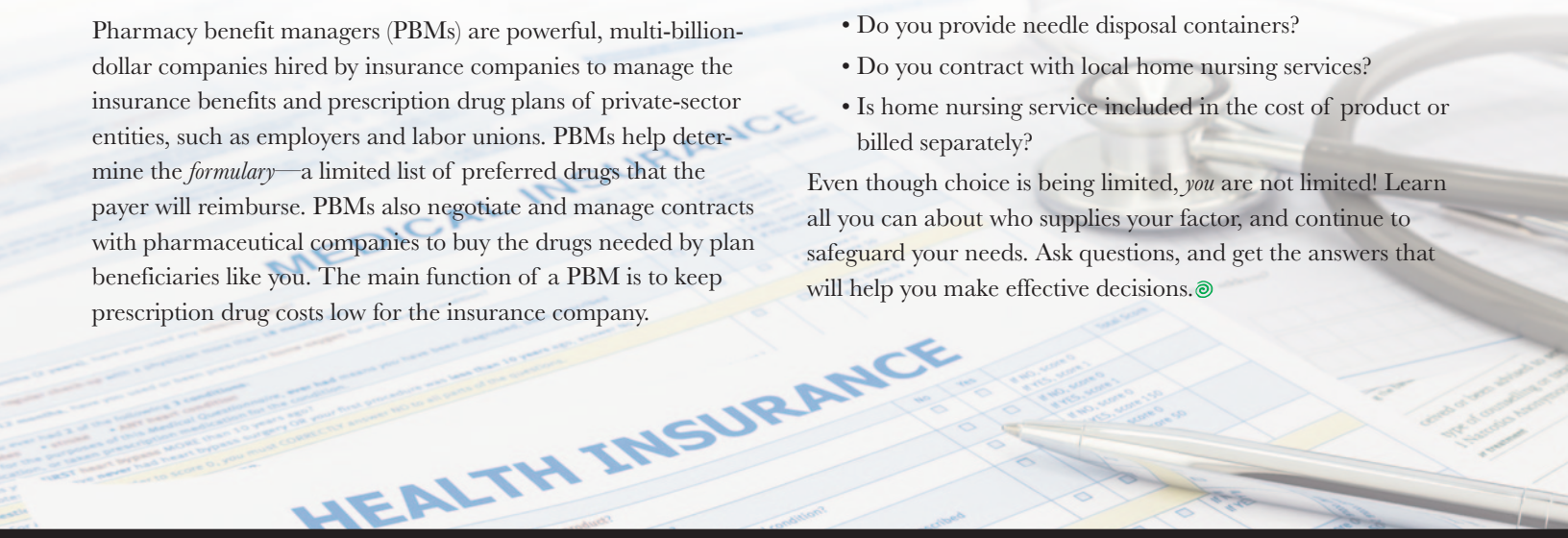
PBMs are able to make high-volume drug purchases to receive substantial discounts from pharmaceutical companies. With their vast resources and negotiating skills, PBMs such as Express Scripts and CVS Health now serve most of the hemophilia patients in the US. Some PBMs have started their own specialty pharmacies to sell factor; and because they have a direct line to the payer, these PBMs are able to switch families from the factor provider of their choice to the PBM's specialty pharmacy. They have incredible power over pricing, product availability, and your payer.

Based on this, can you even choose a factor provider? Unfortunately, your healthcare payer—insurance company or government program—often chooses for you. Find out if your insurance company reimburses for specialty pharmacy services. Then, learn which companies are in-network for you. Your choices might be limited, because for the payer, working with a single factor provider is one way to lower costs. More and more often, choice is being restricted. You may face a struggle when choosing a preferred factor provider.

If you can choose, use this list of questions to ask your factor provider to make sure your personal needs are met:

- Which brands of factor concentrate do you provide?
- How much product will you provide at one time?
- How are products delivered to me?
- Do you ship during emergencies?
- Do you supply the assay size I need as a single dose?
- How much will I pay per unit of product?
- Do you (the HTC) offer 340B pricing?
- Are you recognized as an in-network provider by my insurance company?
- What are your hours of operation?
- Are a pharmacist and registered nurse available 24/7?
- Can I use your regular HTC services even if I choose to use a specialty pharmacy as my factor provider?
- Do you supply ancillaries: needles, syringes, and bandages?
- Do you provide needle disposal containers?
- Do you contract with local home nursing services?
- Is home nursing service included in the cost of product or billed separately?

Even though choice is being limited, *you* are not limited! Learn all you can about who supplies your factor, and continue to safeguard your needs. Ask questions, and get the answers that will help you make effective decisions.



Richard's Review... from page 5

A Negative

L. C. Crichton

wattpad.com, 2014

Leaving Toronto, Ashley Pope returns to the family farm in Fairview, Ontario, to care for her widowed mother. After a horse knocks Ashley unconscious, Dr. Ryan Maxwell is concerned about her horrible bruises and nosebleeds. Despite being her doctor, Ryan takes Ashley out to dinner, followed by nightly dates. When Ashley has her period, she completely avoids discussing it with Ryan, her doctor/boyfriend. Ryan convinces Ashley to see a hematologist, who diagnoses VWD for Ashley and her mother. The Canadian Hemophilia Society published this short, young adult romance e-novella using an online social media platform.

Pregnant with His Royal Twins

Louisa Heaton

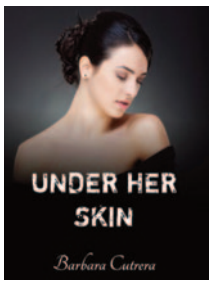
Harlequin, 2017

Freya MacFadden is a midwife in Chichester, England. Disfigured by a jealous ex-boyfriend at age 18, Freya hides her reconstructive facial surgeries with tattooed eyebrows and heavy makeup. After a costume charity ball, she has a one-night stand with Jamie Baker. Jamie doesn't tell Freya that he is Prince Jameel Al Bakhari, heir to the Majidar throne. Freya becomes pregnant with twins. Jamie honorably proposes marriage to protect his two royal sons, yet Freya declines. After falling on ice, Freya has a concussion. Jamie's older brother, who has VWD, suffers a stroke, so he abdicates the throne. Eventually, Jamie and Freya marry after the boys are born, and avoid the royal life—instead, Jamie's married sister assumes the crown.

Under Her Skin

Barbara Cutrera

On My Way Up, 2017



Everton, a paramedic, is widowed with a 24-year-old deaf daughter in Bradenton, Florida. He meets Citrine, who owns a hair studio and has VWD. Citrine was kidnapped as child and then reunited with her birth mother, who also has VWD. Because of Citrine's bruises and nosebleeds, Everton learns of her medical condition. Everton and Citrine begin an intense physical relationship. When a bookcase falls on Citrine, causing a concussion and broken bones, she is hospitalized for a week. Everton quickly learns to take care of her, and they eventually marry. *(Romance scenes in the novel are R-rated.)*

Bedding the Baby Daddy

Virna DePaul

self-published, 2017

Aurora LeMonde, a Louisiana Creole, is an executive assistant in Los Angeles. Aurora ignores the advances of Dante Callaghan, a playboy and financial analyst. Yet after a fundraising gala, their relationship changes and Aurora gets pregnant. She keeps it a secret from Dante, though she still wants to see him. Aurora learns that Dante has custody of his 11-year-old half-sister, who has VWD. After mutual misunderstandings and time apart, Aurora and Dante confess their love at a fundraising event for VWD, and marry after their son is born. *(Romance scenes in the novel are R-rated.)*

Von Willebrand disease is found worldwide. The same is true for romance. It seems only natural to combine them in medical romance novels as a way to increase readers' awareness with spiced-up education.

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