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Parent Empowerment Newsletter

Part 2 of the 3-part series
Crossroads

BY PAUL CLEMENT

Plasma-Derived and Recombinant Factor: **Historical Perspective, Matter of Choice**

Salinder's mind was reeling. She was still grappling with the implications of her 16-month-old son Eshaan's recent diagnosis with a low-titer, low-responding inhibitor. Now, Eshaan's hematologist was recommending immune tolerance induction (ITI), a port, and a switch from recombinant to plasma-derived factor concentrate. A hundred and one questions flooded Sal's mind, but above all, why did the doctor want to use a plasma-derived product? Sal recalled that plasma-derived products had transmitted HIV and hepatitis in the past. Were the products safe? Would Eshaan risk contracting a disease if they switched?

Plasma-derived (PD) products are getting more attention lately, particularly factor VIII products that also contain von Willebrand factor (VWF). Why? Mainly because they may have a higher success rate when used for ITI. The US hemophilia community is giving PD products a closer look. Insurance companies view them as a potential lower-cost alternative to treatment – some have even suggested forced switching for some patients.

Yet parents like Salinder are concerned about this trend. The early 1980s left an indelible impression on our community. Thousands of people with hemophilia were infected with deadly viruses through PD clotting factor – viruses including hepatitis C (HCV) and the human immunodeficiency virus (HIV), which causes acquired immune deficiency syndrome (AIDS). Although infection with these viruses is no longer a concern with today's PD concentrates, fears persist.

Fears can cloud decisions about which treatment is best for your child and how to advocate for that treatment. Do you know enough about the different product types to have an informed conversation with your doctor? With your insurance company? Change is rapid in the health insurance industry,

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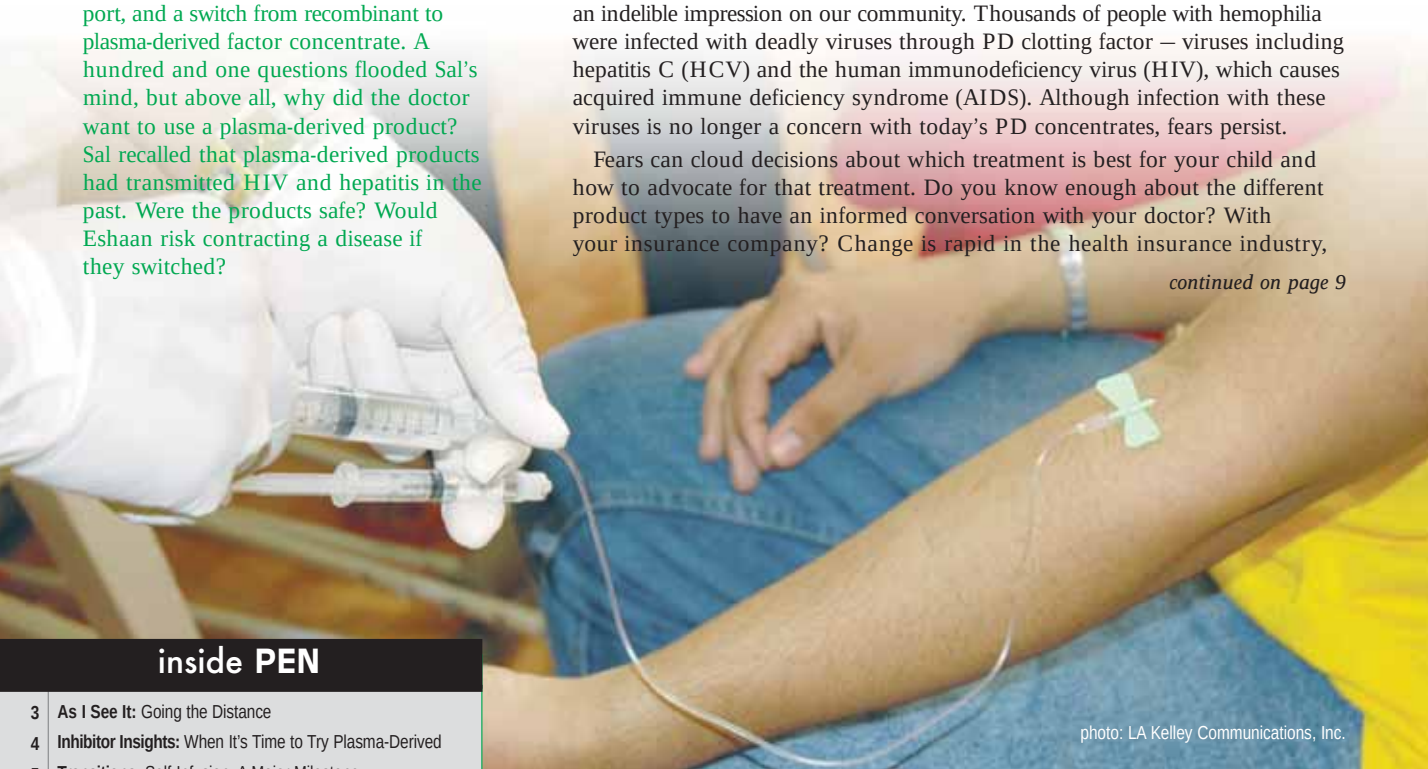

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inside PEN

LA Kelley Communications, Inc.

welcome

Sherrell Portrait Design

When Tommy turned 18, I gave him an important choice, one of the most important ones he will ever make.

Another milestone in Tommy's life, like earning his driver's license, applying for colleges, and signing with the Selective Service System: he needed to select his brand of factor. For the first few years after Tommy was born, his doctor chose his factor brand. When I became better informed about the wide array of brands available, I selected his factor brand. Now that Tommy was 18, it was time for him to choose.

But I didn't want this crucial choice to be based on gadgets or pretty-colored vials, or be limited to one or two brands. So I asked Tommy's home care company rep to visit, and without me in the house, she reviewed the various choices and helped Tommy select the one he felt best met his needs – all approved by his hematologist.

What was important to him in making his selection? Convenience: achieved with small diluent volume. Needleless transfer: not so important at age 18. Most important? Safety.

I was happy to reassure Tommy that all factor products licensed in the US are considered safe by the FDA. But many in our community still do not believe this – at least, not at gut level. And that's why we decided to focus this issue of *PEN* on the choices available in plasma-derived and recombinant products. To make an informed decision about product choice, as a parent or as a patient transitioning to adulthood, you need to know the facts about plasma-derived and recombinant factor. You need to know how they are both manufactured. You need to know their history. Ultimately, you need to make your own choice.

Choice of factor product. Access to all types of factor, both plasma-derived and recombinant. That's what we've been rallying for these many years – while rallying against the "current storm" of reimbursement cuts. Tommy represents a new generation: those born after the HIV holocaust, who were not infected. This generation may have been raised with a sense of security, but as you will read, we must always be vigilant. This issue of *PEN*, second in our Crossroads series, will remind you why so many in our community are still concerned about safety. And it will explain why all factor products in the US today are considered safe.

PARENT EMPOWERMENT NEWSLETTER AUGUST 2009

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inbox

The [May] issue of *PEN* was great! I stayed up late reading it cover to cover. The article about communication with the HTC was helpful. I really related to the section dealing with insurance dictating so much of our care. I have Anthem insurance and had to leave our home care company to use PrecisionRx. I spent hours on the phone last week with the insurance company to see what I'd need to do to use our previous home care company. That was the first time in 13 years that I've been without factor in my home. It was a terrible feeling! I had been trying to place an order for over two weeks. The people at PrecisionRx are kind, but their computer system is a mess. The system lost our order twice, and there was no record of us calling and emailing repeatedly. I could go on and on about dealing with them as opposed to a home care company that really knows hemophilia. I hope to have the issues resolved soon, and I pray I can return to our previous company. On a positive note, I finally received our factor order.

Becky VanSant
MISSOURI

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Going the Distance

How I "Live Strong" with Hemophilia

BY BARRY HAARDE

Barry Haarde

As hemophilia patients and their families know, living with hemophilia brings uncertainty into our lives. As one of the "older generation," I can well remember the days before clotting factor concentrates, when almost every bleed led to a trip to the emergency room and perhaps a few days in the hospital. Our lives improved dramatically with the advent of factor concentrates and the ease afforded by home delivery and self-infusion of our new "miracle drug."

Regrettably for many, our new lease on life was short-lived. I am one of the nearly 10,000 people with hemophilia infected with both HIV and hepatitis C contracted through the use of factor products before viral inactivation methods were employed. Many in our community were lost to AIDS, and many more are now succumbing to liver failure from hepatitis C. Among those lost are my brother John Haarde (1952–2007) and my brother-in-law Joseph Patrick Grant (1943–1990), who had factor VIII and IX deficiency, respectively.

Whether we're the older guys or those born after 1986, members of our community are still faced with a fundamental question: How do we respond to the many uncertainties, physical challenges, and financial burdens of living with hemophilia? I have always relied on my Christian faith and the support of my family to get through the tough times, but I've also found inspiration in an unlikely area for someone with severe hemophilia – bicycle racing!

In 1999 I had a total knee replacement due to joint deterioration that resulted from many years of repeated hemorrhaging. My orthopedic surgeon informed me that my surgery and rehab would be more successful if I could get the muscles around the joint in better shape, so off I went to the local bike shop. I began with casual riding on the neighborhood bike trails – nothing too strenuous. Then, after my surgery and a few months of physical therapy, I began taking longer rides of about 20 miles.

After a lifetime as a confirmed couch potato, I enjoyed the exercise! My transformation into fitness junkie really took off when I purchased my first road-racing bike and joined a local bike club. With consistent, fairly rigorous training, four years after my knee surgery I was able to complete 100-mile rides in five hours, or less on a good day. I was putting more miles on my bike than on my car!

I knew I was taking a risk riding in tightly grouped packs of riders, who often reached speeds of 30 mph. I had seen enough bike crashes to know what the consequences would be if I ever went down hard. But somehow, the thrill of competing in an athletic endeavor – something I was unable to do as a kid with hemophilia – made it worth taking the chance.

My involvement in cycling paid off in other ways. In 2007 I learned that my liver disease had progressed to cirrhosis, caused by the hepatitis C virus. I began interferon treatment, which can cause severe side effects, including fatigue and depression. Like many others with hepatitis C, I had delayed treatment because I "felt fine" and thought I was in the best shape of my life. During my treatment, I've experienced weight loss, anemia, and allergic rash problems, but I've been able to continue working and riding my bike. Studies show that regular exercise is as beneficial for the liver as it is for the heart, especially for those living with liver disease. I believe that being in the best possible physical condition helps me manage the many potential side effects of my antiviral therapy.

I also use my cycling activities to raise awareness of HIV/hepatitis C in my local community, and to inspire others to go on "living strong" in spite of their medical problems. Specifically, I encourage those living with hepatitis C to take their diagnosis seriously and learn about their treatment options.

Recently, I rode in my seventh MS 150 bike ride from Houston to Austin, Texas. This 175-mile, two-day event attracts 13,000 cyclists from around the country. It's the largest charity bike ride in America, benefiting the National Multiple Sclerosis Society, which offers MS bike rides across the country. I rode this year in memory of my brother, brother-in-law, and all the others with hemophilia who have lost their lives to AIDS and hepatitis C.

Barry Haarde, 43, has severe hemophilia A. He lives and works in Houston and participates in many area cycling events. He is active in an HIV/AIDS ministry and support group at Fellowship of the Woodlands Church, and is involved with the Blood Brothers program through the Gulf States Hemophilia Center. Barry invites *PEN* readers to visit his bike team website at www.tlsports.org or email him at redsaleen97@yahoo.com

BY SONJI WILKES

When It's Time to Try Plasma-Derived

Imagine this: You have been conscientiously following your child's immune tolerance induction therapy (ITI, sometimes called immune tolerance therapy or ITT) for over a year, using a recombinant clotting factor. But his Bethesda Unit (BU) titers are not progressing toward zero. In fact, his BU titers are all over the place – when charted out, they look like a roller-coaster ride. Six months ago, you weren't too worried about his titer levels, but in the past two months, he's had multiple joint and muscle bleeds. During a recent trip to the hemophilia treatment center, his hematologist proposed trying a plasma-derived product. Why?

Why Consider a Product with von Willebrand Factor?

Dr. Guy Young, director, Thrombosis and Hemostasis Center Division of Hematology/Oncology, Children's Hospital Los Angeles, explains: "Currently, the US standard of care is to use recombinant factor VIII for ITI. Generally patients start ITI with the same product they had already been on [before developing the inhibitor]. During the course of ITI, inhibitor titers should be monitored closely, and if the inhibitor titer isn't coming down as expected, or plateaus after at least a six-month trial with recombinant factor VIII, then switching to a [plasma-derived] factor VIII product containing von Willebrand factor [VWF] should be considered, as this may be effective when recombinant factor VIII was not."

To understand this, it helps to know how factor VIII circulates in the body. While moving in the bloodstream, factor VIII is naturally found tightly bound with VWF. Not only does VWF participate in the clotting cascade when there is an injury, but it protects factor VIII from being broken down by enzymes in the blood. It also covers some areas on the factor VIII molecule that are binding sites for inhibitors. Current recombinant clotting factors don't contain VWF, which is removed during the purification process. Experts speculate that plasma-derived factor VIII with VWF may have an advantage for ITI because it may be less immunogenic – less likely to appear to the immune system as a foreign protein.

Is plasma-derived with VWF better for ITI? "The short answer is we don't know," admits Dr. Young. "We are not suggesting [just] any plasma-derived factor VIII, but rather a factor VIII product that has von Willebrand factor in it. The notion is that the VWF presents the factor VIII to the immune system in a more natural state. Or, alternatively, the VWF shields the factor VIII from the inhibitory antibodies, so the immune system can see it better and then develop tolerance." But, Dr. Young stresses, "These are both merely unproven theories."

Dr. Donna M. DiMichele is professor of pediatrics and public health at Weill Cornell Medical College and attending pediatrician at New York–Presbyterian Hospital. She voiced a similar position in her 2008 monograph on inhibitors for the World Federation of Hemophilia (WFH): "The impact of factor VIII dose and product type on ITI outcome remains unclear. In the absence of information suggesting otherwise, the major consensus opinion is that ITI should be performed using the product on which the inhibitor developed. A plasma-derived factor VIII containing von Willebrand factor may be preferentially used in some circumstances."[1]

Choosing the Most Effective Product for You

The global medical community has not reached agreement about which, if any, product type is better for ITI. In the US, plasma-derived factor VIII with VWF is more commonly chosen for a second round of ITI *after* the first round using recombinant fails. As many inhibitor patients know, ITI is individualized, and treatment options must be considered case by case. Most inhibitor patients achieve tolerance using one product, often a recombinant factor, throughout ITI without incident. Others decide to try plasma-derived products with VWF to optimize their child's chances for a successful ITI program.

Rachel Katzman recalls the uncertainty of ITI success while continuing to use a recombinant product for her son Blake. "In the back of my mind, I began to think about switching products just to get rid of his inhibitor, since it was sticking around. I wanted it gone." When Blake, now age six, started bruising more and ended up with a bad calf bleed, Rachel had his titer level checked again. It had tripled. "At one point, he had a bleed in every extremity." Rachel sought a second opinion and made the decision with Blake's hematologist to switch to a plasma-derived factor containing VWF.

Today Rachel believes, "Now that the inhibitor titer has dropped, there couldn't really be any other choice [for us] but to use a plasma-derived product." But when making the decision to switch, Rachel wasn't so sure. "The inhibitor made the

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1. DiMichele, Donna M. "Inhibitors in Hemophilia: A Primer." 4th ed. World Federation of Hemophilia, 2008. Web. June 7, 2009. <http://www.wfh.org/2/docs/Publications/Inhibitors/TOH-7%20Inhibitor-Primer-Revised2008.pdf>

Transitions is a *PEN* column sponsored by Baxter BioScience

Self-Infusion: *A Major Milestone*

BY KEVIN CORREA

For a child with hemophilia, the transition to self-infusion is one of the greatest steps on the road to healthcare independence. This transition holds important medical and emotional components. And while there are different paths toward the goal of self-infusion, parents should start the transition when their children are young.

Maria Santaella, nurse coordinator at the University of Miami's Bleeding Disorders Program, co-developed the nationally recognized workshop Infusion 101. "From a medical perspective, prompt treatment is essential to avoid long-term injury," says Santaella. But the importance of self-infusion, she explains, goes beyond medical concerns. "The boys get a great sense of accomplishment and independence once they've learned to self-infuse."

The staff at the University of Miami's hemophilia treatment center expects patients to self-infuse by age 14. To achieve this goal, the transition starts much earlier, beginning with parent education. More than 70% of the HTC's parents have learned to prepare a work area and mix factor before their child is six years old.

STAR Children Relief

Cosmin, a young Romanian, self-infusing

"Obviously every family is different," notes Santaella, "and we have to make sure both child and parents are ready for the process."

Hemophilia Camp and Self-Infusion

For many young children with hemophilia, summer camp provides the most exposure to other children who are self-infusing. Caroline[1] had always infused her son Connor, an eight-year-old with hemophilia, but she began teaching him the process when he was four. "By age five," says Caroline, "he could participate by picking the vein we would use." By age six, Connor could mix factor under her supervision. At age seven, he was ready to infuse himself. Camp gave him the opportunity and camaraderie to take the next step.

Caroline recounts Connor's story with pride: "The boys in his cabin made a pact. The following day they would all try to self-infuse. They each gave it a shot, and Connor was successful. He's been self-infusing ever since."[2]

Santaella believes that the group setting – camp or a workshop – is ideal for children to learn self-infusion: "The boys think, 'If he can do it, I can do it.' And they'll at least give it a try."

Manasa recalls the camp experience of Arjun, her hemophilic son. "When Arjun was seven, he returned home from camp, and having seen so many kids self-infusing, he decided he wanted to learn," says Manasa. "So I taught him sterile technique at home, and he infused through his port for four years."

Now age 11, Arjun recently had his port removed and learned the process of venous access with the help of his mother and home care nurse.

Grin and Bear It

One piece of advice offered repeatedly by those who have successfully transitioned to self-infusion: everybody should try to remain calm during the process. Things won't always go smoothly.

"Try not to let the child see any apprehension," Caroline suggests. "If you're nervous about the process, your child will be nervous too."

Manasa agrees. "The worst thing you can do is stress your child out. Parents have to project calmness."

At her workshop, Santaella tells parents to be prepared for setbacks. "Parents need to understand that the transition is a process. It's not an immediate changing of the guard," she explains. "They shouldn't expect that just because their children know the procedure, they're going to be able to do it right every time."

Manasa had to get used to biting her tongue while Arjun learned to self-infuse. "I've had to stop myself from overreacting," she admits. "You have to let them do things their own way. So maybe he holds the needle differently than I would. As long as everything's sterile, I let him do it."

To his peers just learning to self-infuse, Arjun advises, "It's just one little poke. If you try and it doesn't work, don't panic. Just stay calm and try again."

Knowing When to Start

There are many factors to weigh when determining if a child is ready to begin the transition to self-infusion. Is his factor deficiency mild, moderate or severe? Does he watch other family members who self-infuse? Has he shown interest in self-infusing? And equally important:

1. The names of patients and their families have been changed for anonymity.
2. Doctors and nurses at hemophilia camps hold training sessions on self-infusion and supervise the entire process. As an incentive for boys to learn, many camps give awards to boys after their first successful stick.

are the parents ready for the transition?

"Our HTC's motto was 'the more independent, the earlier, the better,'" recalls Caroline. "They pushed me to do it early. As a mom, I wasn't sure I was ready, but now I'm grateful that they got us going when they did."

The best way to determine if your child is ready is to speak with your HTC nurse coordinator or hematologist. And keep in mind that even if a child can physically perform the steps of self-infusion, he may be years away from being able to properly self-diagnose a bleed.

Quality of Life

Regardless of when your child makes this transition, it's a big milestone for the family. "Prompt treatment is a big benefit, but families also see a change in quality of life," Santaella notes. "They can reduce the amount of time they have to sit around the ER, and now the boy can go on that weekend fishing trip with his friend without everyone worrying."

For Manasa, Arjun's self-infusing provides peace of mind. "We go on a lot of road trips. Often the nearest hospital is two hours away. I'm not as paranoid anymore, knowing that we can at least get factor on board in the event of an accident."

Perhaps most valuable in mastering skills like self-infusion, children with hemophilia develop the confidence they'll need to eventually tackle complex issues like choosing their brand of factor concentrate, or fighting for better insurance coverage. Caroline has seen this confidence grow in Connor. "He's a completely different kid," she smiles. "It's given him a sense of control over his hemophilia. He doesn't fear it anymore."

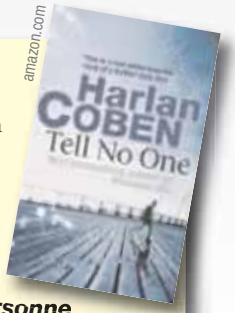
Getting Started

The first place to seek guidance on self-infusion is your HTC. They can help you assess your child's readiness. You should also investigate...

- workshops and events sponsored by your local National Hemophilia Foundation chapter,
- the comprehensive directory of camps for the bleeding disorder community compiled by NHF,
- educational self-infusion kits developed by the pharmaceutical companies.

BY RICHARD J. ATWOOD

Tell No One



Tell No One
by Harlan Coben
New York:
Dell Publishing,
2001

Ne le dis à personne
(Tell No One; available on DVD with English subtitles)

Music Box Films, 2006 (NR)
Directed by Guillaume Canet
Starring François Cluzet,
Marie-Josée Croze,
Kristin Scott Thomas

Although hemophilia plays only a minor role in the best-selling crime thriller *Tell No One*, the story demonstrates that a bleeding disorder can be misdiagnosed as abuse – with bad consequences. But it also shows that parents can be very protective of their children with hemophilia, and then form a strong bond with their physicians.

David Beck, a widowed pediatrician practicing in New York City in 2001, has grieved for eight years over the murder of his wife, Elizabeth. That is, until he receives a secretly coded email from her on the anniversary of her killing. The police and FBI reopen the murder case, suspecting Beck in Elizabeth's murder after uncovering other bodies and evidence. One of Beck's Medicaid patients is T.J., a six-year-old blind boy with hemophilia, the son of a drug dealer. Beck first encountered T.J. when the "erratically" behaving father brought the nine-month-old boy to the ER suffering from multiple retinal hemorrhages and heavy lethargy. T.J. was diagnosed with shaken baby syndrome until Beck checked hospital records to discover no bleeding at circumcision, yet umbilicus bleeding at two weeks. Beck ordered blood work, revealing a prolonged partial thromboplastin time with normal prothrombin time and normal platelet count. Based on these results, Beck diagnosed hemophilia. Now, six-year-old T.J. returns, after scraping his arm on a doorjamb, and must spend the night in the hospital hooked up to an IV, receiving blood products such as cryoprecipitate or fresh frozen plasma as treatment.

The many plot twists due to lies and secrets are intricately detailed, yet the description of hemophilia treatment using cryo and FFP is inexplicably outdated. There is no mention of factor concentrate, home therapy, or hemophilia treatment centers, which were certainly available in New York in 2001. But an interesting plot device is to test Beck's diagnostic skills by making shaken baby syndrome the initial diagnosis for T.J. in the ER, before hemophilia is clinically determined with blood tests. Unfortunately, T.J. is subsequently abducted and tortured when his father aids Beck during his escape from the law and the criminals, adding more suspense to the convoluted plot.

The award-winning French film version, set in Paris, successfully translates the gripping plot of the novel, with some minor changes. In the film, the drug dealer is indebted to Beck, who had diagnosed his heavily bruised son with hemophilia three years earlier, after an initial incorrect diagnosis of child abuse. The drug dealer now trusts only Beck, and becomes the doctor's protector.

The trauma of being falsely accused of child abuse when a child with hemophilia has multiple bruises cannot be underestimated. Finding a physician or other healthcare provider you can trust for hemophilia care is crucial for reassurance, comfort, and peace of mind – as most parents will attest.

Words of wisdom from our readers

I have a hard time getting my 16-year-old son Brandon to self-infuse. He has severe hemophilia and is on immune tolerance induction (ITI) so he needs factor every day. My husband or I have to mix the factor in the morning while Brandon gets ready for school. He had a PICC line, and we have to infuse just before he leaves or he won't give himself factor. He is so tired of having hemophilia and really wants a break. This is his first year of high school. I've talked to other parents who say that their children have been self-infusing since age 12 and younger. How can I encourage my son to infuse himself?

I RAISED THREE BOYS, TWO WITH hemophilia. My oldest son had more difficulty with self-infusion. It helped to send him to hemophilia summer camp, where he was for the first time with other boys his own age coping with the same issues. That support helped in his journey to care for himself. His younger brother helped, as he was eager to be like his big brother – so big brother wanted to be a hero. I suggest finding a teen hemophilic support group or summer camp for Brandon. Peer support is effective in moving forward. It also helped us to have emotional support from a therapist who understands hemophilia.

Suzanne Smith-Ellis, LMFT
CALIFORNIA

✦ ✦ ✦

I HAVE FOUR SONS WITH HEMOPHILIA A, ages 30, 21, 16 and 10. They have attended hemophilia camps, where they learned to self-infuse. They have their down days and occasionally wait too long to treat, but the pain always wins.

My sons are more willing to self-infuse if I allow them to do it on their schedule, not mine. Brandon might prefer to factor just before bedtime; mornings can be stressful enough just getting ready for school or work. It was tough on all of us, but they've learned to appreciate the freedom associated with taking care of their bodies.

I have noticed that with the new treatment protocols of prophylaxis, boys don't quite understand how to set their own limits to avoid injury or recognize bleeds early. So when they reach the teen years, they tire of treatments and may rebel against them.

Kathleen George
VIRGINIA

Ed. note: Infusing in the morning is preferable to infusing at night because the highest factor levels will correspond with the highest activity levels. Infusing at night provides less protection against bleeds because almost half the factor is gone by morning, when activity levels increase.

✦ ✦ ✦

TIRED OF HAVING HEMOPHILIA? Give me A break! I'm 43, with severe hemophilia. I've survived hepatitis A, B and C, been HIV positive since the 1980s, have limited range of motion in both elbows, and had my left ankle fused last year. And I'm one of the fortunate ones of my generation! My advice is to let Brandon experience what a bleed feels like. I'd guess he's had few bleeds, if any. I wish I'd had the quality of product, the convenience of today's factor, and prophylaxis treatment when I was younger. I must have been poked or poked myself at least 8,000 times. Back then, you had to wait in an ER; wait in a room at least 30 minutes for the factor to mix; and wait another 10 minutes for the infusion itself – it took two 50cc syringes to dispense because of the concentration. Yes, you have hemophilia and it sucks, I know. So deal with it, because it's better than having it 20 or 30 years ago. I've learned that there are only two types of people with hemophilia: the ones living with hemophilia, and the ones who make hemophilia live with *them*. Be the latter.

Mike Bembenek
ARIZONA

Ed. note: Parents should never alter any aspect of their child's treatment regimen without first checking with their hematologist.

✦ ✦ ✦

OUR DAUGHTER HAS BEEN RELUCTANT to infuse herself or to have peripheral infusions. I used to be so frustrated when I heard about people making a smooth transition from port to peripheral infusions. Our road has been anything but smooth! In fact, after a year without a port, we had a new port placed. Life without a port was too stressful, and it was so difficult to infuse. We felt like failures because so many parents have children younger than our daughter who are self-infusing successfully.

We took our daughter to a psychiatrist who deals with children with chronic and life-threatening illnesses. She helped our daughter understand her feeling of having no control and hating hemophilia, and helped her deal with the burden of having this for the rest of her life. The psychiatrist helped her deal with the emotional issues and realize what she needed to do, so we could move forward with her care. We sometimes overlook the emotional issues our children have in dealing with hemophilia because we've had longer to process all that hemophilia means. As our children mature, we should address their emotional as well as physical needs.

It's been five years since we began the process of learning to infuse peripherally and eventually have our daughter self-infuse. She had her first great success last summer at camp. Some older boys with hemophilia and an understanding, patient nurse mentored her and taught her their infusion methods. They worked on this twice a day for relatively short periods. She came home from camp ready to begin trying. We've agreed that we'll try only two pokes, and if we aren't successful, we'll use the port. We only try peripheral when it's her idea, and when she's comfortable and ready. We let her set some parameters and give her some control.

I advise Brandon's family to take it at their own pace. Everyone deals with things differently, and we shouldn't pressure our children to measure up to others. It would help Brandon to talk to a counselor about his fears and frustrations.

Becky VanSant
MISSOURI

✦ ✦ ✦

NICK STARTED INFUSING IN FIFTH GRADE with the help of Hole in the Wall Gang Camp and his HTC. We had a port inserted in Norfolk, Virginia, moved to Memphis, and then Nick started infusing himself within a couple of months.

Gail Staley
RHODE ISLAND

✦ ✦ ✦

OUR SON LEE STARTED SELF-INFUSING when he was 11. He had a goal, and this ultimately drove him to self-infuse. Thankfully, we had a wonderful nurse who Lee trusted and felt comfortable with, and he taught Lee in about three months. My advice to Brandon's family is to get involved with kids his age to advise, support, and listen. They can be role models and reassure Brandon that he can learn this task. Self-infusion allows you much more independence, and makes you feel you have more control of your life. Lee has never looked back and is still infusing in college – he's completely self-sufficient. Just set your mind to a challenge. It will really benefit you.

Eleth and Bob Ridenhour
KANSAS

✦ ✦ ✦

I'M A SOPHOMORE IN HIGH SCHOOL AND I self-infuse. I'm really glad I learned. It allows me a lot more freedom, and it's nice to know I can do it on my own. It's also very convenient: if you're going somewhere without your parents, or you need factor and your parents aren't home, you can self-infuse whenever you want and not need a parent. I don't do it all the time because sometimes I have a busy schedule in the morning with extracurricular activities, so it's easier and quicker just to have my parents do it then. I also don't like to be rushed when I'm doing it. I had to have factor every day at one point when I was younger, though now that inhibitor has gone away.

Here's an important example of convenience: last summer I decided to go to Mexico with my church on a mission trip. I didn't want my parents to go, but I hadn't been self-infusing lately. So I got back into it, and now I don't have to worry about my parents having to be there. It gives me the freedom to go on long trips with friends alone, which I enjoy. I hope this will help motivate Brandon to learn to self-infuse.

Jacob Gerhartz
MINNESOTA

✦ ✦ ✦

THIS QUESTION BRINGS BACK SO MANY memories for me and my husband. I have been married to Matty for 41 years, and it does get easier. In the beginning there was no help, and now there is so much – but you have to reach out and find it. Hang in there!

Matty, age 75, has severe hemophilia. He suggests that Brandon go to hemophilia camp and learn how to infuse with the group. Matty learned how to infuse with eight-year-olds and has been doing it ever since. The secret is accepting hemophilia, and then you can deal with it.

Eleanor and Matty Vieira
MASSACHUSETTS

✦ ✦ ✦

OUR SON, 16, HAS BEEN SELF-INFUSING since age 12. Our process: (1) we collaborated with the HTC; (2) our son practiced on us; (3) he treated himself the first time at his annual attendance at Paul Newman's Hole in the Wall Gang camp. He hasn't stopped since.

We all want a break, but we don't have a choice. I suggest setting a future date that allows everyone to prepare themselves, and then start. Take ownership of a task in the beginning – for example, Mom will mix, Brandon will infuse, Dad will clean up. Then, transition to where Brandon is accountable for the entire process. Consider rewards or benefits, such as driving permit options after six months of successful self-infusion.

Pat
PENNSYLVANIA

✦ ✦ ✦

I AM 29, WITH SEVERE HEMOPHILIA A. I've been self-infusing since I was 12.

I was encouraged to learn self-infusion at hemophilia camp. I had a huge supportive cast of peers, nurses, and doctors who reassured me that they would be there to assist if I had problems. This gave me the courage to do it that first time.

But when I came home from camp, I got really comfortable with my old routine – my nurse-mom treating me – and I lost that fire of self-sufficiency. It wasn't until my mom really laid the cards out on the table that things struck home for me.

When I reached high school and was playing more competitive sports, my mom gave me a fair ultimatum: since she was giving me the freedom to do the sports I liked, then I was responsible for my own well-being (and my clean jerseys and uniforms). This forced me to be accountable for my own body. That meant treating myself before a competition or daily practice, and learning to do my own laundry.

Brandon has to know that this is a huge step toward being an independent person. Hold Brandon accountable for following through with the whole process. Be sure that he knows why he has to do it, and that no one else is willing to do it for him. I know this is extremely hard for parents, since they have spent their entire lives protecting their children. It can be horribly tiresome for a child to bear the responsibility and inconvenience of hemophilia. But there is simply no other choice. Always stress that having the freedom to do what he wants, if he is willing to take care of his body, will help in his growth and development as his own person. Depending on anyone, whether a parent or spouse, won't last forever.

E. J. Villegas
PENNSYLVANIA

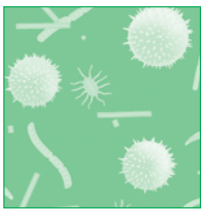
and new medical knowledge is coming to light. You need a better understanding of the history of hemophilia treatments and where current treatment is headed.

Progress, Hope and Disaster: Development of Factor Concentrates

The past 40 years have seen dramatic improvements in hemophilia treatment. Before 1965, having severe hemophilia meant frequent trips to the hospital, often for several days, to receive transfusions of blood or of fresh frozen plasma (FFP), derived from human blood donations. Because these treatments contained only tiny amounts of clotting factor, large volumes had to be infused to control a bleed. Along with the risk of allergic reactions, FFP infusion also carried the risk of overloading the body with fluid, which can result in death. Treatments with FFP were largely ineffective at controlling severe bleeds. Quality of life with hemophilia was poor. People faced frequent hospital trips, casts and splints, joint damage, crutches and wheelchairs, chronic joint pain, and the prospect of an early death.

A huge advancement soon changed this. In 1964 Dr. Judith Graham Pool and her associates discovered that when FFP was slowly thawed, a gelatinous material – which Pool coined *cryoprecipitate* (or "cryo") – formed at the bottom of the plasma bag. This cryo contained 50 times the amount of factor VIII as did an equal volume of plasma. Now, much more factor could be infused in a much smaller volume. Although administration of cryo still usually required a hospital visit, it was now possible to effectively stop a bleed faster, reducing some of the pain and joint damage caused by uncontrolled bleeding.[1] Like FFP, cryo was derived from human blood donations and stored frozen. It revolutionized hemophilia treatment, and within a year cryo became the standard of care.

Cryoprecipitate quickly led the way for another breakthrough in 1966: freeze-dried powdered factor VIII concentrate that could be refrigerated. People with hemophilia could now reconstitute powdered factor concentrate with water, and conveniently infuse at home in a few minutes. Bleeds could be stopped sooner, and pain and joint damage reduced or prevented.



Victims of Our Own Success?

Unfortunately, to meet demand for these new drugs, the process used to produce factor concentrates on a large scale directly led to the widespread distribution of HIV and HCV. To take advantage of economies of scale, plasma fractionators (companies that separate factor from blood plasma and produce factor concentrates) would combine large volumes of plasma – from 1,000 to even 60,000 donors – into one giant lot.[2] Just one infected donor could potentially contaminate the entire lot, which would then infect hundreds or thousands of factor users. No viral inactivation treatment processes were in place.

At that time, plasma collection practices further increased the risk of viral contamination. US fractionators paid donors for plasma, and often purchased plasma from groups considered at high risk of carrying viral diseases: prisoners and the homeless, including many drug addicts. As a result, an estimated 90% of people with severe hemophilia A born before 1985 became infected with HIV through clotting factor concentrates.

Since the 1940s, we had known that blood and plasma products could transmit pathogens causing hepatitis, a liver disease. But before 1977, only two types of hepatitis were recognized: hepatitis A (HAV), with a short incubation time of 15–40 days; and hepatitis B (HAB), with a longer incubation time of 60–160 days. Soon after clotting factor concentrates were introduced, we learned that these products also transmitted the pathogens, now known to be viruses, responsible for hepatitis. By the mid-1970s, we learned that factor concentrates were also infected with another, as yet unknown virus that

1. Cryo is still used to treat hemophilia in many developing countries where clotting factor concentrates are not readily available.
2. When other proteins added to the factor are taken into account (such as albumin, a blood protein used to stabilize factor concentrate and derived from other plasma pools), the final product in some cases contained material from as many as 400,000 donors.

slowly attacked the liver, often with no early symptoms. This unidentified virus was initially called *non-A, non-B hepatitis*. For more than a decade, extensive efforts to identify it were unsuccessful. In 1989 a virus that caused more than 90% of the non-A, non-B hepatitis was finally identified and renamed hepatitis C. Today we know of five hepatitis viruses: A, B, C, D, and E.

By the early 1980s, practically all Americans with severe hemophilia, and many with mild and moderate, were using factor concentrates – though the high risk of contracting hepatitis was well known, and the factor packaging and vials carried warnings. Most people with hemophilia and their physicians believed that the benefits of rapid treatment of bleeds, reduced joint damage, and increased quality of life overshadowed the risk of hepatitis. And a vaccine for HAB was scheduled for release in 1981, which would eliminate the risk of contracting HAB for those uninfected.[3]

But hepatitis viruses weren't the only pathogens in the plasma supply. Sometime in 1978 a virus, later identified and named HIV, entered the blood supply. Although at the time HIV was found in only a tiny percentage of Americans, our plasma collection practices greatly amplified the risk, spreading HIV to many users of fractionated plasma products, including people with hemophilia. Because the US paid plasma donors, collected plasma from donors at high risk for viral diseases, and pooled tens of thousands of donations into giant lots, the likelihood increased that a lot of factor concentrate would contain an infectious donation.

Not until 1981 did the Centers for Disease Control and Prevention (CDC) identify a new immunodeficiency syndrome – named AIDS the following year – that at the time mainly affected homosexual men. The disease was originally thought to be transmitted sexually, although the syndrome had been diagnosed in one person with hemophilia in 1981. But by 1982, when eight more people with hemophilia and no other known risk factors were diagnosed with the same syndrome, there was hard evidence that AIDS was also transmitted by blood products. As the number of people with hemophilia who developed AIDS increased, it became evident that the use of clotting factor concentrate carried a high risk for contracting HIV. Finally, in early 1984, HIV was discovered as the virus responsible for AIDS. Not until 1985 was an antibody test commercially available to detect the virus in blood or plasma.

Viral Inactivation Research Ramps Up

With the advent of AIDS, research into viral inactivation methods accelerated. The small German fractionator Behringwerke was first to successfully develop an effective heat-treatment (pasteurization) process; in 1981 it was granted a German license to sell a pasteurized factor VIII product. But not until 1983 was the first heat-treated factor VIII concentrate available in the US. Although a heat-treated factor VIII product from Baxter/Hyland was available in America in 1983, many Americans were still using untreated factor until as late as 1985, when all products included a viral inactivation step. Despite the accessibility of these products, the US Food and Drug Administration (FDA) inexplicably did not issue a recall of unused, untreated products until 1989.

The early success of the Behringwerke heat-treatment process galvanized efforts by other fractionators to develop their own heat-treatment viral inactivation methods. Unfortunately, the accelerated research into heat treatments derailed research into what some considered a superior viral inactivation process under development since the late 1970s: the solvent-detergent process. This process did not decrease the yield of the factor produced or the factor's activity, as did heat treatment. And because it did not denature the protein by changing its shape or configuration, as heat often did, the protein could properly perform its function in the clotting process. And the solvent-detergent process was effective at rapidly inactivating, or killing, lipid-enveloped (see box, p. 11) viruses such as HAB, HCV and HIV – the viruses that could be transmitted by plasma products and cause serious diseases.

Viruses weren't the only unwelcome components of factor concentrates. Early products also included a hodgepodge of unwanted proteins, which often triggered allergic reactions and changes in the immune system. A process was needed to purify the factor and filter out or separate the unwanted proteins. By the mid-1980s, fractionators were using *affinity chromatography* to purify factor VIII. Chromatography is a process used to separate a molecule, such as factor VIII, from a liquid, such as plasma. Chromatography is usually done in a cylindrical column, packed with many small beads coated with a chemical that attracts only factor. Plasma is poured through the column, and the factor sticks to the chemical on the beads while the unwanted proteins pass through the column. The factor is then removed by "washing" the column with a solution that releases it.

The purity of various factor concentrates differs. Currently, the greatest purity is achieved by a process called *immunoaffinity chromatography*, which uses antibodies instead of other chemicals to bind or attract the factor. Antibodies are proteins made by our immune system, custom-designed to attach themselves to specific targets, such as bacteria or viruses, inactivating them and marking them for removal from the body by white blood cells. By the mid-1980s, scientists learned how to clone large numbers of a single antibody (monoclonal) from a mouse; this antibody would target or bind with factor VIII. Highly specific, monoclonal antibodies will bind only to the factor, allowing other proteins to pass through. Attached to the beads in the column, the antibodies latch onto the factor as the plasma is poured through, removing factor

3. A vaccine for HAV was not licensed in the US until 1995, and there is still no vaccine and no cure for HCV.

from plasma. This type of chromatography is *monoclonal antibody purification*, and the resulting products are often called monoclonal purified. The first highly purified factor VIII concentrate using monoclonal antibody purification, Hemofil M, was licensed in the US in 1988.

Three-Legged Stool

To reduce the risk of viral transmission through plasma-derived products, not only must factor products be virally inactivated and pure, but changes in the plasma collection business have also been implemented. Safety depends on three equally important measures, or the *safety tripod*:

- ✦ Donor selection
- ✦ Testing for pathogens
- ✦ Inactivation and removal of pathogens

Following are some improvements in guidelines, standards, and procedures made since the late 1990s in the donor selection and testing processes:

- Limit plasma pools to 60,000 units, reducing the potential for viral exposure risk for those who use plasma products infrequently.
- Qualified Donor Standard: at plasma collection centers, each donor undergoes an initial physical exam and regular follow-up exams to create a comprehensive health history. The donor must return for a second donation and pass all health and blood tests again before his or her plasma can be used. Gone are the days when plasma was collected from prisoners or those practicing high-risk behaviors.
- 60-Day Inventory Hold Standard: source plasma (donated through plasmapheresis, where only plasma is taken and

How does the solvent-detergent process kill viruses?

Viruses are divided into two groups, based on whether they have a fatty (lipid) outer layer (envelope) or no envelope at all: **lipid-enveloped** and **non-enveloped** viruses. The blood-borne viruses that produce serious infections, such as HIV, HCV and HBV, are usually lipid-enveloped viruses. When bathed with a detergent and a solvent, the fats in the envelope covering the virus are dissolved or disrupted, destroying the ability of the virus to infect its host cells. Lipid-enveloped viruses are relatively easy to destroy or inactivate. Not so for non-enveloped viruses, which are unaffected by these solvent-detergent viral inactivation processes. Because they are also heat resistant, they are hard to destroy. HAV and Parvovirus B 19 are non-enveloped viruses.

In 1988 Hemofil M, the first factor VIII concentrate to use a solvent-detergent viral inactivation process, was licensed for sale in the US. The **SD** appearing in some factor concentrate names indicates that the product uses a solvent-detergent viral inactivation process.

red blood cells are returned to the donor) is frozen and held in inventory by fractionators for a minimum of 60 days. Any suspect donations can be retrieved before being considered for use in fractionated blood products.

- Implement new and more sensitive viral blood tests, such as Nucleic Acid Tests (NAT; see p. 13). Since the late 1990s, this has allowed contaminated donations to be detected earlier and removed from the plasma pool.

The implementation of these voluntary guidelines, standards, and procedures has resulted in exceptionally safe plasma-derived products. Remember: no transmission of HIV or HCV in America has been seen since March 1985, and no instance of HAV transmission from factor concentrates since 1995. Since 2001, for companies that adhere to these voluntary safety recommendations, the Plasma Protein Therapeutics Association (PPTA)[4] offers the Quality Standards of Excellence, Assurance and Leadership (QSEAL) certification.

Developing Recombinant Factor

Although the monoclonal purified, virally inactivated plasma-derived factor concentrates introduced in the late 1980s were considered safe, pure and effective, the HIV epidemic left an indelible scar on the hemophilia community. Never again did we want to be the canary in the coalmine for the nation's blood supply. By the late 1980s, a goal of both the hemophilia community and the pharmaceutical industry was to develop a factor concentrate that was not derived from human blood. It would contain no blood products, so would carry no risk of transmitting blood-borne viruses or other pathogens.

This advancement occurred through genetic engineering. Between 1982 and 1984, the human gene for factor VIII was identified. By the late 1980s, researchers developed techniques to clone the gene and to insert copies of it into non-human *host cells*, such as baby hamster kidney cells or Chinese hamster ovary cells. These host cells could now produce human factor VIII. Then these modified cells were cloned to increase their numbers, and grown in large stainless steel vats containing a culture medium, usually calf serum or human plasma protein solution. The culture medium contained nutrients the cells needed to survive and grow. The cells, now containing the human recombinant DNA for factor VIII, could then produce human factor and release it into the culture medium. Factor VIII was separated from the culture medium and purified.

The resulting factor VIII is called *recombinant* because it is produced not from human plasma, but by cells whose DNA has been "recombined" with the human gene for factor VIII. The first recombinant factor VIII product was Recombinate, approved by the FDA in December 1992. In February 1993 a second recombinant product, Kogenate, was approved.

Recombinant Factor Generations

Although the first recombinant factor VIII concentrates didn't use blood plasma as the source of factor VIII, they required the addition of *albumin*, a blood protein, to stabilize the fragile factor VIII protein and prevent it from degrading while in the vial. In fact, these *first-generation* recombinant factor concentrates, like their plasma-derived cousins, contained mostly albumin. Although albumin has an excellent safety record, and is treated to destroy or inactivate viruses, to many in our community the idea of adding a blood protein to a recombinant product was a step backward, reintroducing the risk of viral contamination.

The first recombinant factor concentrate produced without albumin was Kogenate® FS, released in 1999, and others soon followed. These *second-generation* recombinant products still used human or animal proteins in the culture medium, but used sugars and traces of other compounds (instead of albumin) as stabilizers in the final product. Only trace amounts of proteins from the culture medium remain after the purification process, leaving the final product virtually free of extraneous animal or human proteins. Without albumin, second-generation recombinant factor concentrates were considered a significant advance in removing factor's potential to transmit blood-borne viruses and other pathogens.

In the quest for a recombinant factor concentrate with no known viral risk, the final step was to produce a factor with no human or animal proteins used in the culture medium *or* added to the final product. The first such *third-generation* recombinant factor VIII product, Advate, was licensed in the US in 2003; a second, Xyntha™, was licensed in 2008. Both Advate and Xyntha include a viral inactivation step in the manufacturing process, while Recombinate, a first-generation recombinant product still on the market, does not.

Plasma-Derived or Recombinant: Which Product to Use?

About 70% to 75% of American hemophilia patients use recombinant products. For those without inhibitors who currently use recombinant factor, there's no question – they intend to remain on recombinant factor, which they perceive as safer. But it's not so simple. Plasma-derived and recombinant products deserve a closer look in three areas: (1) pathogen transmission, (2) inhibitor incidence, and (3) ITI.

continued on page 14

4. The Plasma Protein Therapeutics Association (PPTA) is the primary industry trade group representing source plasma collectors and producers of plasma-derived and recombinant biological therapeutics.

What is NAT?
Nucleic Acid Testing

When a virus infects a person, it enters cells and begins to replicate, or make copies of itself. As the virus replicates, virus particles called **antigens** start to appear in the blood. In response to these viral antigens, the body's immune system begins making **antibodies** that are specific to the virus. The job of antibodies is to circulate in the blood, seek out the specific virus and attach themselves to it, and then generate an immune response to combat the infection.

The goal of viral testing is to detect the presence of virus in the blood or plasma. The sooner this can be done, the better. When someone is first infected, the DNA and RNA of the virus are present, but the virus hasn't yet made enough antigen for testing to work. Over time, as the virus makes more antigen, the infected person begins to make antibodies to fight the antigens. But this also takes time, resulting in a **window period** — when a patient can be infected with the virus, but not have enough antibody or antigen in his system for detection methods to be fully effective.

Most viral blood tests check for the presence of either antibodies or antigens in the blood or plasma, indicating that the person has been exposed to a specific virus. But these tests don't look for viral genetic material, such as DNA or RNA. **NAT**, or **nucleic acid testing**, does not rely on the presence of antibodies or antigens. Instead, it directly detects segments of the viral DNA or RNA. NAT can detect very small amounts of viral genetic material: it works by amplifying a small part of such material over a billion times. Using this amplification, NAT can pick a needle out of a haystack. Because NAT looks for the presence of the amplified gene, it can detect minute amounts of viruses — like HCV and HIV — that would escape detection by less sensitive antibody and antigen tests. Plus, it can detect recent infections far more effectively than can other tests.

Detecting a virus early is key: suspect donations can be removed before they are used to manufacture plasma products. Antibody and antigen tests are very effective if a person has been infected long enough for the amount of antigen or antibodies to reach detectable levels, but they're not as effective during early stages of infection. For HCV, it takes about 82 days for antibodies to reach detectable levels; for HIV, about 22 days. Antigen tests have a shorter window period, providing earlier detection than antibody tests alone. Current testing procedures for HIV use both antibody and antigen tests.

NAT can dramatically cut the window period. When using NAT to detect HCV in blood or plasma, for example, the window period drops from about 82 days to about 25 days. NAT can detect viral infections earlier than antibody or antigen tests, making our blood supply safer.

NAT can be performed on individual donations or on small pools (minipools) of plasma. To reduce costs, source plasma (the plasma collected through plasmapheresis) is commonly pooled in lots of 96 to 1,200 units of plasma, and tested using NAT. After NAT testing, pools that test positive for HIV or HCV are traced backward to determine which donor was infective. The infected minipool is then discarded.

Today, the American Red Cross (ARC) estimates that only a tiny percentage of infected donors donate during the window period and test negative on antibody and antigen screening tests. These donors would be detected by the currently licensed NAT. Right now, the overall risk of contracting HIV through a single unit of blood, without using NAT, is one in 675,000. The same risk for HCV is one in 100,000. Data from ARC clinical trials of NAT indicate that each year in America, NAT could possibly identify about 100 additional HCV-infected units of donated blood, and two to six additional HIV-infected units during the window period.

Plasma-Derived and Recombinant... from page 12

Pathogen Transmission

Despite the excellent safety record of factor concentrates, concentrates derived from plasma or containing plasma proteins such as albumin (including first-generation recombinant products) still have the potential to transmit viruses and other pathogens. Every year, new or emergent viruses are identified: West Nile Virus, Monkeypox, SARS, avian flu (H5N1), and most recently, swine flu (H1N1). Each new emergent virus causes a wave of concern about the safety of the blood supply and plasma products. Fortunately, all the viruses in the headlines are lipid-enveloped viruses, inactivated by current viral inactivation methods. But what if a dangerous, emergent non-enveloped virus, resistant to viral inactivation processes, slipped into the plasma supply?

Other novel infectious agents, such as abnormal *prions*, the malformed proteins that cause the brain-wasting sickness Creutzfeldt-Jacob Disease (CJD), might potentially be transmitted through blood products. The hemophilia community was jolted in February 2009, when an elderly man with hemophilia died in Great Britain and was later confirmed to have variant CJD (vCJD), though he died of other causes and showed no symptoms. Variant CJD is the human form of "mad cow disease" or Bovine Spongiform Encephalopathy (BSE), a fatal neurological disease that affects cattle; eating beef infected with BSE can, in rare cases, cause vCJD in humans. In 1998 this man had infused plasma-derived, British-made clotting factor concentrate that was later found to be contaminated with plasma from a donor who eventually developed vCJD.[5] Whether this man contracted vCJD from his clotting factor or from eating contaminated beef is unknown, but the story serves as a reminder that we must remain vigilant for potential pathogens in plasma products.

Inhibitor Incidence

Recombinants aren't without concerns. When they were first introduced, some doctors and researchers worried that the new manufacturing process might make recombinants slightly different from the natural factor in PD products, and might lead to increased inhibitor formation among patients.[6] In fact, some studies using recombinant products seem to demonstrate a higher incidence of inhibitor formation than did earlier studies using PD factor. But recent studies suggest the apparent higher rate of inhibitors of those on recombinant products may be due to more frequent, stringent testing for inhibitors during more recent clinical trials of these products, compared to the infrequent testing for inhibitors in clinical trials of the older PD products.

The overall numbers suggest that recombinant products do not significantly increase the risk of eliciting inhibitors. Yet some researchers still believe that because PD factor concentrates containing high levels of VWF mimic how factor VIII appears naturally in the body, they may be less likely to draw the attention of vigilant inhibitory antibodies.

Because inhibitor formation is not well understood, until we have more data it's hard to say for sure whether any new product is more or less likely to cause inhibitors. Patients should consult their treatment providers to determine if anything in their health history might make inhibitor concerns important in product selection. For example, if two older siblings developed inhibitors to recombinant factor, a newborn might be treated with a PD product in the hope of reducing risk.

ITI

Why did Sal's hematologist recommend a PD product for Eshaan, her son with inhibitors? ITI requires high doses of factor to desensitize the body to factor; eventually the inhibitor tires of fighting factor VIII, and tolerates it. When the inhibitor titer decreases to low levels or disappears, a patient is said to be "tolerized." ITI is usually started using the same factor concentrate the patient was using before developing inhibitors: typically a recombinant. Yet 20% to 30% of people on ITI do not become tolerized, and ITI fails. Some of these patients may be enrolled in another round of ITI using a PD factor VIII product with VWF. Might some have become tolerized initially if they'd used such a product?

Three studies, two in Germany and one in France, demonstrated higher rates of success in achieving immune tolerance when using PD factor concentrates containing high levels of VWF than when using products without VWF. But other studies find no difference between products in the success rate of ITI. Is one kind of factor better than another for ITI? Two new studies just got underway to answer this question.[7] In light of the German and French studies, some hematologists are considering using PD factor VIII with VWF, such as Alphanate®, for ITI in patients like Eshaan, who are at high risk of failing ITI.

5. British-made factor products no longer use British plasma; plasma has been imported from the US since 1996 for use in UK products.
6. "Natural" factor in PD products may also undergo changes when a heat-treatment viral inactivation process is used.
7. These studies may take up to ten years to complete, but in the end we should have a reliable answer about whether products with VWF are more likely to result in successful ITI for inhibitor patients. For information on these inhibitor studies: www.itistudy-resist.com/ and www.itistudy.com/default.asp

US Bleeding Disorder Products

Manufacturer	Recombinant			Plasma-Derived		
	Factor VIII	Factor IX	Other*	Factor VIII	Factor IX	Other*
Baxter	Advate Recombinate			Hemofil M	Bebulin VH	FEIBA VH
Bayer	Kogenate®FS					
CSL Behring	Helixate®FS			Monoclate-P®	Mononine®	Humate-P®
Grifols				Alphanate®	AlphaNine® SD	
Novo Nordisk			NovoSeven®RT			
Talecris				Koate®-DVI		
Wyeth®	Xyntha™	BeneFIX®				

*Includes products indicated for inhibitors (NovoSevenRT, FEIBA VH) or VWD products (Humate-P). Humate-P is also indicated for factor VIII deficiency. *Note:* Recombinate is a first-generation product. Kogenate FS and Helixate FS are second-generation products. Advate, BeneFIX and Xyntha are third-generation products.

To Make Better Choices, Stay Informed

Your choice of clotting factor product, recombinant or plasma-derived, depends on many factors. Ask your hematologist these questions:

- **Do I have a choice of products? What are my choices? Which do you recommend, and why?** American patients with VWD don't have a choice: they must use a plasma-derived product.
- **Which product is most efficacious (effective in controlling bleeds) for** *me?* Not all factor concentrates work well in all people. For people with inhibitors, the recombinant bypassing agent NovoSevenRT may be the answer. But it doesn't work for everyone, and some patients with inhibitors use the only other bypassing agent available, plasma-derived FEIBA VH.
- **What is my risk of developing inhibitors? Do I have any known risk factors?**
- **What is the risk of the transmission of pathogens in PD products versus recombinant products?**
- **To what types of products have I previously been exposed?** Many hematologists avoid prescribing a PD product for a newborn, yet have no qualms about prescribing a PD product for someone older who was previously on a PD product.
- **Am I HIV positive?** If yes, then it's generally recommended that you use only the purest products – recombinants or monoclonally purified PD products. Plasma-derived products of low and intermediate purity contain much extraneous protein, producing negative changes in the immune system. Such changes have been shown to cause people with HIV to progress to AIDS more rapidly and have a higher mortality rate.

You should also know if you have a lifetime insurance maximum (cap) and how much of it you have used so far. Generally, PD products are less expensive than recombinants and may allow you more time before you reach your cap.

NHF's Medical and Scientific Advisory Council (MASAC) recommends using recombinant clotting factor concentrates for their "potentially improved safety profile over plasma-derived products with respect to pathogen transmission."[8] Your choice of clotting factor concentrate should be a joint decision between you and your hematologist, based on carefully considering the pros, cons, and latest scientific research. You may even need to suspend some of your preconceived notions about products and safety.

Whichever product you choose, be assured that all of today's factor products have excellent safety records. We're lucky to live in a country with a variety of products, both plasma-derived and recombinant, that are safe, efficacious, and abundantly available.

8. See MASAC Recommendation #169: www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=57&contentid=581 (accessed June 24, 2009).

organizations

Deadline for Grants to Support Advocacy Initiatives!

The PACT grant program provides financial assistance to support state advocacy initiatives by hemophilia organizations. Eligible grantees are selected by an independent committee chosen for experience in hemophilia advocacy and healthcare policy. Grants may support partial staff salaries required to execute grant proposals; consultant services, such as a lobbyist, health insurance consultant or attorney; travel and lodging, including mileage/airfare to cover legislative and agency visits; printing and production costs, including creating background materials or newsletters providing information and guidance about policy initiatives; conference and workshop fees, including funding to attend workshops/meetings associated with advocacy. Supported by Baxter BioScience.

Deadline: August 28

For information:
Hemophilia Association of New Jersey
www.hanj.org/services_pact.html

home care

Tag! You're It

Coram Specialty Infusion Services will provide all hemophilia camps in 2009 with Buddy Tags. Designed to help campers meet new friends and keep in touch with them after the camp season is over, Buddy Tags facilitate new and lasting connections.

For information:
www.factorforward.com/Patients/resources/camps.aspx

BioRx

Jeff Salantai

BioRx Employees Climb Mt. Rainier

On August 5, two BioRx employees – Jeff Salantai, a person with hemophilia, and Eric Hill, president – climbed Mt. Rainier as part of a national fundraiser, Summit For Someone. The fundraiser benefits at-risk inner-city youth who are unable to experience life outside the city. All BioRx proceeds exceeding $8,000 have been donated to Save One Life, an international child sponsorship program for impoverished people with hemophilia in developing countries. The 14,410' summit was achieved by a technical, physically demanding three-day hike and ice climb.

For information: www.summitforsomeone.org

independent resources

New Book on Infusion Empowers Kids!

Just A Boy by Ziva Mann

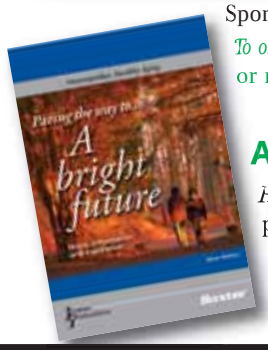
Whimsical storybook for ages 3–6 about an imaginative child with hemophilia who learns to control his pain as he transitions to needlesticks. Guided by loving suggestions from his mother, the boy tries different pain control techniques, while using his imagination, until he conquers his fears. Sponsored by Baxter BioScience.

To order: 800-249-7977, www.kelleycom.com or request a copy from your HTC

Premier Issue: PEN's Insurance Pulse

We're excited to announce this special publication sponsored by Baxter BioScience. PEN'S INSURANCE PULSE keeps you up-to-date on the many changes in the insurance industry that directly impact our bleeding disorder community, and inspires you to be a better advocate. Filled with practical advice on the latest insurance topics: how to prepare for insurance transitions at different ages; Ask the Expert; Community Forum; Real Life family report; Tracks & Trends.

Information and orders: 800-249-7977, www.kelleycom.com or www.thereforyou.com



Appreciating the Senior Experience

Healthy Aging–Silver Edition is the fourth volume in Inalex Productions' A Bright Future™ DVD series portraying the lives of three men living with hemophilia. Examines the early challenges they face and celebrates the joys of personal accomplishment, family, and living life to the fullest. Emphasizes the importance of healthy aging, both physically and emotionally. Sponsored by Baxter BioScience.

To order: www.inalex.com or contact your Baxter sales representative

Bill Aims to Subsidize Healthcare after Layoffs

A bill working its way through Congress may provide subsidies to help people recently laid off afford to continue their job-based health insurance through COBRA. In 1986 the COBRA budget bill created a way for people who lost or left their jobs to keep their employer-provided health coverage for up to 18 additional months by paying the monthly premium themselves. But few families can afford the high premiums. The House version of the new bill would provide a 65% subsidy to purchase COBRA coverage for workers laid off since last September. The subsidy would last for up to 12 months or whenever workers obtain employment with health coverage. The Senate version also includes a 65% subsidy for nine months, retroactive to last September. The number of uninsured Americans is approximately 46 million and growing with higher unemployment rates.

advocacy

Lifetime Caps Legislation

NHF has been working diligently to get the provisions of HR 1085/S 442 included in the broader health reform bills being considered by Congress this summer. In the Senate, the HELP Committee has released its first-draft bill, and the Finance Committee has released a report outlining policy options. Both the HELP and Finance proposals eliminate lifetime caps. In the House, the chairs of the three committees of jurisdiction over health reform released their draft bill, which also includes eliminating lifetime caps.

Illinois Hemophilia Assistance in Trouble

On May 31, Illinois passed only a partial budget after failing to support an income tax increase proposed by the governor. The resulting $8 billion budget gap will mean massive cuts to essential state programs vital to people with hemophilia and other bleeding disorders: Medicaid; Illinois Hemophilia Program, which helps pay for factor products and other medical expenses not covered by insurance; All Kids, which provides free or low-cost health insurance coverage for uninsured children and youth; and Illinois Cares Rx, which helps pay prescription drug costs.

Source: NHF eNewsletter, June 19, 2009

New Resources for VWD Patients

Grifols has created two new free resources for patients with von Willebrand Disease. *What is von Willebrand Disease?* is a simple Q&A booklet with bright colors and diagrams for ages 7–11. Grifols' excellent *von Willebrand Disease: Information for Patients*, a large booklet covering many aspects of the disorder, is now available in Spanish: *Enfermedad de von Willebrand: Información Para Los Pacientes*.

To order: 888-GRIFOLS (888-474-3657)
www.grifolsusa.com
Or contact professional services:
ps@grifols.com

manufacturer

CSL Takeover of Talecris Ends

After the Federal Trade Commission announced it would oppose the proposed merger through the US courts, Talecris management decided to withdraw from the $3.1 billion takeover deal by CSL Behring. The FTC alleged that the US plasma market is a tightly controlled oligopoly, and that the merger would violate antitrust laws. CSL Behring has rejected these claims.

Better Connected to Your HTC

CSL Behring has launched new enhancements to HeliTrax™, a wireless electronic therapy management system for Helixate® FS. HeliTrax lets you track and record treatment progress in real time with Internet access and stay connected to your HTC by recording infusion data.

For information: 888-508-6978
www.ConnectwithHeliTrax.com

Inbox... from page 2

Cerri family

Joshua Cerri

My son Joshua is only three-and-a-half, so he is unable to do infusions on his own, but I found a great way to get him learning! Our factor manufacturer gave us practice vials of factor, so we let him practice reconstituting them. He does every step except putting in the needle. It keeps him interested in learning and being part of his infusions.

Kelly Cerri
CALIFORNIA

Your books are very informative. That's where I learned most everything I know about hemophilia and what to expect. Thank you so much!

Dawn Christman
CALIFORNIA

Thank you for *A Guide to Living With von Willebrand Disease*. It helped me, more than I can say, to understand VWD when I was diagnosed two years ago. I had never heard of VWD. I read your book cover to cover twice. I was saddened to hear of Renée Paper's passing. Thanks for all you do for the bleeding disorder community.

Anonymous

Project SHARE

Thank you very much for helping with nine vials of factor VIII shipment to such a distant country. Each child was treated once the donation arrived.

Tadesse Belay
ETHIOPIA

God bless you all. I am so happy to inform you that I am feeling better every day since I had my transplant. I am recovering fast, thanks to your support. Thank you for the second batch of factor VIII that we received through Dr. Parayno. Thank you for your help, your support, and your prayers. I am so grateful to God and to all of you who helped and are still helping me during this trying time. I will not forget that I owe you my new lease on life. Without your support, I may not make it. Kindly extend my gratitude to all the donors and all who make this donation possible. My congratulations to all of us for the success of my transplantation.

Viany Manuel
PHILIPPINES

On behalf of my team and the entire Ghanaian hemophilia community, thank you for your immeasurable help and support. You made all the difference by your visit! We assure you that we shall do our best to help the society you have started stand the test of time and grow to fulfill its mission and vision. Thank you!

Martin Boakye
President, Ghana Hemophilia Society

Your visit to Kenya was a great source of inspiration to all of us with relatives living with this devastating condition. Maureen Miruka, president of the Jose Memorial Haemophilia Society–Kenya, is simply a wonderful and courageous lady who turned her misfortune into a great window of opportunity that has immensely benefited us. I am the father of Franklin and the late Victor Munene Nyagah, age 15, who was our first born. May God bless all of our joint efforts.

Nicholas Nyagah
KENYA

Today I received the factor you sent to help take care of my stomach bleed. We don't have enough factor available in my country, and it's wonderful that someone from the United States is helping children so far away as Romania. I hope others will benefit from your generosity. May God bless you.

Tcaciuc Tiberiu
ROMANIA

We enjoyed the visit by Laureen Kelley, and injecting our patients with the factor she brought. We injected a nine-year-old boy with bleeding in his elbow, and the bleeding stopped. Thank you again for taking care of the poor and those in need. The factor is helping our patients a lot, and we look forward to the coming donations. Thanks!

Dr. Stella Rwezaula
TANZANIA

HemaBlog

I have been reading your blog every day with amazement. I am certain many people read the blog but hesitate to make comments, which is unfortunate. I want to see other people's comments and encourage them to leave a note. I want to know the community out there is watching together.

Your ability to provide awareness about hemophilia and the challenges in developing countries is exactly like the first person on a rope team climbing a mountain. The leader has to kick steps in deep, heavy snow. The teammates, roped up to the leader, follow by placing their boots into precisely those steps the leader has made. That is how a rope team works together. But it's the first person on the rope team who must have the stamina and strength to punch the toe of their boot into the deep, heavy snow, gain their balance, and lift their body weight (and heavy pack) up each step. One at a time. Slog. Slog. Slog. And as part of good rope management, when one leader tires of the strain, the others on the team trade off to continue the long, slow journey up the mountain.

Interestingly, you seem to gain more strength with each step you kick, and never fatigue. What a champion and role model for the rest of us. More of us need to ask how we can help, and then, do it. Thank you for not only slogging up the mountain, but for letting us join the journey as part of your rope team via your blogs.

Cheryl D'Ambrosio
WASHINGTON

Insights... from page 4

decision for us at the time. I felt the choice wasn't really in my hands, but that it had to be done. I was worried. I was, and will continue to be, afraid of the possibilities that a plasma-derived product could bring on."

Concerns over plasma-derived factor date back to the early 1980s, when the production of clotting factor concentrates included no viral inactivation steps, so products were contaminated with HIV and hepatitis. The screening process for plasma donors is much more stringent now, and today's plasma-derived products undergo steps to inactivate most viruses. These improved procedures have resulted in safer plasma-derived factor concentrates: there has been no transmission of HIV or hepatitis C (HCV) in America since March 1985, and no instance of hepatitis A (HAV) transmission from factor concentrates since 1995. Although there is still some risk of HAV transmission for people who use plasma-derived products (HAV is resistant to viral inactivation methods), HAV may be prevented by immunization with a vaccine.[2]

Moving Forward with the Best Information

Dr. Young notes, "Any conversation about switching from recombinant to plasma-derived must weigh the risks and benefits of the approach. Eradicating an inhibitor in a patient who is having a lot of bleeding problems on a daily or weekly basis is extremely important in achieving long-term health. If this can be achieved with a plasma-derived product, my opinion is that with the current knowledge regarding the infectious risk of the products, it's worth the risk – which is likely exceedingly small."

Rachel addressed her concerns by contacting other families with hemophilia and inhibitors, her home care nurse, and her HTC staff. She also attended an Inhibitor Education Summit.[3] These summits, sponsored by Novo Nordisk twice a year, draw families and physicians from around the country.

Other sources to help you stay informed:

- National Hemophilia Foundation (NHF)
  www.hemophilia.org
- Hemophilia Federation of American (HFA)
  www.hemophiliafed.org
- Committee of Ten Thousand (COTT)
  www.cott1.org
- Patient Notification System
  www.patientnotificationsystem.org
  (sign up for free periodic updates on blood safety issues and product recalls)

Parents must continually make decisions about their child's inhibitor treatment. This may mean setting aside deeply emotional concerns in light of the most current scientific information available. As Rachel can attest, "I am thankful every day that at least we are lucky enough to have something that works. My goal is to find a way to knock the inhibitor out of Blake's system. I hope that the future will show us that we made the right choice. So far it looks like we may have."

In the end, being a parent is about making the best decision for today, while being aware of what history has taught us, and keeping informed about what the future may hold.

Special thanks to Paul Clement, PEN science editor, for his contribution to this column.

2. For more information on hepatitis and vaccines, see the NHF website: www.hemophilia.org

3. Inhibitor Education Summits are sponsored by Novo Nordisk. Upcoming summits: Hollywood, CA, August 27–30, 2009; Washington, DC, September 17–20, 2009.

Visit Your HTC Annually!

Parenting Moment

Never do a task or assignment for your child that he could do for himself.

When a problem crops up at school, think the best instead of the worst of your child, and hear his side of the situation before forming any conclusion.

365 Ways to Build Your Child's Self-Esteem
Cheri Fuller © 1994 Piñon Press

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the hemophilia newsletter by families & for families

Inside: PLASMA-DERIVED AND RECOMBINANT FACTOR: HISTORICAL PERSPECTIVE, MATTER OF CHOICE