HFGF CONNECTIONS

Hemophilia Foundation of Greater Florida

The Quarterly Newsletter of the HFGF

Summer 2016 vol. 20 issue 44

In This Issue

FOLLOW US ON SOCIAL MEDIA!

Register Now for the Gainesville Gator Clot Trot

Come and join us
Saturday
September 24th, 2016

for the 5th Annual
Gator Clot Trot 5K Run and Fun Walk!

Registration is only $25 for the run and is free for the walk. Our goal this year is to raise $35,000. Walk yourself or as part of a team. The 5K run begins at 8 A.M. with the one mile fun walk starting right after at 9:30 A.M.

Tioga Town Center
105 S.W 128th St.
Newberry, FL 32669

Register and get fundraising tips online at **http://www.hemophiliaflorida.org/gainesville.html**.

Hemophilia Foundation of Greater Florida

Help the HFGF's

Flight for Tomorrow Golf Tournament

Monday, October 24th, 2016
Avila Golf and Country Club Tampa, FL

Are you a golfer? Please join us for a fun-filled day of golf action to raise funds for the HFGF! Ready to play? Have a connection in the entertainment, sports or travel industries? We are looking for auction items for the golf tournament. Restaurant certificates, hotel stays, golf outings, other entertainment events, sports memorabilia, all types of donations are being sought for this event.

Sign up at
http://www.hemophiliaflorida.org/flight-for-tomorrow-golf-tournament.html

If you can provide a donation, please contact us at
the HFGF office at 800 293-6527.




Tampa Woodstock Walk Exceeds Fundraising Goal

This year's Tampa Walk, renamed the Woodstock Walk for Bleeding Disorders (formerly The Tampa Bay Clot Trot), raised $43,172. More than 200 walkers, some part of the 27 teams that participated, gathered to walk in Al Lopez Park on Saturday, May 14th. First place for most funds raised by individual walkers was Framk and Cheryl Vazquez; second place was Kristy Begerow; and third place was Paula Beersdorf. Team Devan won the Taveling Walk Trophy for most funds raised by a team; second place was Alyssa's Angels, and third place was Pedro's Peace Posse. The Team Spirit Award, for having the most walkers on a team, was captured by Team CSL Behring.

Special thanks to our sponsors for this event:

Accredo Specialty Pharmacy
Baxalta
Bayer Health Care
Biogen
Bio RX
bpl Plasma
Cottrill's Pharmacy Inc.
CSL Behring
CVS Caremark
emergent biosolutions
Johns Hopkins All Children's Hospital
Novo Nordisk
Octapharma
Pfizer Hemophilia
St. Joseph's Children's Hospital

In-Kind Sponsors:

CJ Photo & Design
Dunkin' Donuts
Jazzy Jewels
Matrix Health
Q-Zar Laser Tag
Sweet Tomatoes
Zumba

If you would like to help grow the fund, go to
http://www.hemophiliaflorida.org/donate.html

Executive Director's Column

Dear Friends,

It has been a whirlwind summer! The HFGF was honored to host the **National Hemophilia Foundation Annual Meeting** and the **World Hemophilia Federation Congress** in July. We had folks from all over the world attend both conferences—what an experience!

Have you seen our new video? Ed Bookbinder, one of our board members, was kind enough to create a short video for us that provides an overview of bleeding disorders. You can find in on youtube at

https://www.youtube.com/watch?v=2WCOOwa4uMU.

We invite you to use the video if you are a Team Captain raising money for the walks, or you need information to explain living with a bleeding disorder while visiting your child's school.

Sixty kids with bleeding disorders had a great time at **Camp Spirit** at Camp Boggy Creek—they got to swim, participate in theater, play games and make tons of friends. We love camp! Our next camping program is **The Family Retreat Weekend**, October 7-8, 2016 at Camp Boggy Creek. You can register online at **www.boggycreek.org.**

Hold on to your seats because we have educational programs and fundraising events throughout the summer and into the Fall for you. Check out our calendar of events (www.hemophiliaflorida.org) for the most updated information.

Have a great summer,

Fran

Calendar of Events 2016

August 27	**Adventure Island**
September 1	**Exercise and Joints Program (Miami)**
September 10	**Gainesville Program**
September 24	**Gainesville 5k Run/ Fun Walk**
October 7-8	**Family Retreat Weekend**
October 22	**Jacksonville Creepy Crawl**
October 24	**Golf Tournament**
October 30	**Orlando Creepy Crawl**

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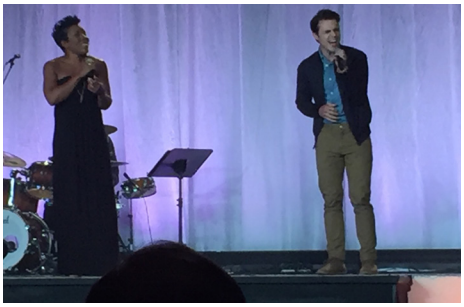
Mission
The mission of the Hemophilia Foundation of Greater Florida is dedicated to improving the quality of life for people with related bleeding disorders and their families through education, information, and referral services, advocacy, and research.

NHF Annual Meeting and WFH Congress in Orlando Are Successful

The two big events held this year in Orlando, and hosted by our own HFGF, were excellent. Special thanks go to the members of our local hemophilia health teams of doctors, nurses and social workers who volunteered their time to educate the community and staffed the treatment room. Here are pictures from the two meetings.



A big thank you to our medical and social work volunteer presenters and educators at the NHF:

Doctors
Dr. Gauger
Dr. Visweshwar
Dr. Ayala
Dr. Davis
Dr. Cockrell

Nurses
Mary Ann Cardenas
Maria Santaella

Social Workers
Sandra Davy
Margaret Rosa
Lourdes Arvelo
Lee Collopy

NHF Booth Volunteers
Patrick Solomon
Al Spinner
Shirley Spinner
Jimmy Solomon
William Solomon
Ellie Solomon
Gabriel Sanchez
Nick Vossburg
Frankie Vossburg
David Vossburg
Aiden Baidenmann
Fallon Baidenmann

Also volunteering at the World Federation of Hemophila Congress:

Dr. Sutphin
Dr. Eslin
Dr. Corrales
Dr. Davis
Dr. Naga
Dr. Ayala
Maya Bloomberg, ARNP
Maria Santaella RN-BC,
Treatment Room Coordinator
Samatha Grupa PT
Phillip Vangelakos PT

Dr. Wynn
Javier Aguilu
Maria Aguilu
Brett Palaschak
Melissa Duff
Jayden Duff
Emily Han
Missy Dolan
Daniel Moore
Tim Moore

Hemophilia Foundation of Greater Florida

Camp Spirit: A Good Time Was Had by All!

Sixty campers enjoyed a week at Camp Spirit, held at Camp Boggy Creek June 26-July 1 this year, thanks to your donations to the Hemophilia Foundation of Greater Florida!

SAVE THE DATE

15th Annual

Evening on Broadway Theatre Event

January 28, 2017 at 6:00 p.m.

*Featuring the **Broadway production** of*

Dr. Phillips Center for the Performing Arts
445 S. Magnolia Avenue
Orlando, FL 32801

This stellar event includes Orchestra Seating to Wicked and a Reception, Silent Auction, and Raffle

VOLUNTEER FOR THE HFGF

Contact us at
800-293-6527 or
info@hemophiliaflorida.org

SOCIAL WORK CORNER

by Sandra Davy, MSW

Greetings, everyone!

The National Hemophilia Foundation held its 68th Annual Meeting July 21, 2016 – July 23, 2016 at the beautiful Gaylord Palms Resort & Convention Center in Orlando, Florida. The session presentations for consumers were numerous and informative.
This year, three of the session speakers were Clinical Social Workers from Florida Hemophilia Treatment Centers.

Margaret Rosa, MSW, participated in the Career Coaching presentation with two other Social Workers and provided financial assistance information to individuals planning to attend college.

Lee Collopy, LCSW, also participated in the Career Coaching presentation and provided information that individuals with bleeding disorders need to know when choosing a college/university to attend; health insurance facts for college students; information on Federal laws that provide protection if emergencies arise; and key things to have in place for when emergencies may occur.

Lourdes Arvelo, LCSW, engaged session participants in an informative discussion topic entitled: "Yes, You Can: Reducing Stress from Infusion."

HFGF extends its thanks and appreciation for a job well done to Margaret Rosa, MSW, Saint Joseph's Children Hospital Tampa, FL; Lourdes Arvelo, LCSW, from All Children's Hospital, St Petersburg FL; and Lee Collopy, LCSW, from University of Florida at Shand's Hospital for Children.

Clinical Social Workers are not only an essential part of the Hemophilia Treatment Center team, they are also patient advocates, policy makers, mental health therapists, administrators, and educators.

New HFGF Web Site Feature

We are introducing a new feature available on our web site. Simply go to

http://www.hemophiliaflorida.org

and pull down the menu under **Resources** and select **Medical Product Information**. There you will find a list of factor product providers along with their contact information and web site links.

RESEARCH UPDATE

SIPPET Study Results Published in NEJM

The detailed findings of the much anticipated SIPPET (Survey of Inhibitors in Plasma-Products Exposed Toddlers) study were published today, May 26, 2016. The study, "A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A," appeared in The New England Journal of Medicine. The lead investigator was Flora Peyvandi, MD, University of Milan.

Peyvandi and fellow investigators found that previously-untreated patients (PUPs) had a significantly higher incidence of inhibitors when treated with recombinant factor VIII (rFVIII) than those treated with plasma-derived factor VIII (pdFVIII) containing von Willebrand factor (VWF). Developing an inhibitor to treatment remains the most prominent and challenging complication for clinicians, occurring in approximately 30% of hemophilia patients globally.

Back in December, a preview of the SIPPET findings presented during the American Society of Hematology's annual conference raised considerable interest among patients, providers and industry. While earlier studies have assessed the overall risk of inhibitor development in patients with hemophilia, the SIPPET study is the first large-scale international trial to randomize patients prospectively for the immunogenicity of pdFVIII vs. rFVIII usage.

SIPPET was a prospective randomized study which took place between January 2010 and December 2014 and collected data on 251 children (<6 years of age with severe hemophilia A) from 42 sites in 14 countries in Africa, North and South America, Asia and Europe. The authors reported that rFVIII was associated with an 87% higher incidence than pdFVIII. Half of the patients were randomly assigned to receive either pdFVIII or rFVIII. The authors reported an overall inhibitor incidence rate of 26.8%.

The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC) will be reviewing the full study, making a thorough assessment of these findings and best determine what changes may be needed to the current MASAC recommendations for PUPS.

Source: New England Journal of Medicine, original article, published May 26, 2016

MASAC Recommendation #243 on SIPPET (Survey of Inhibitors in Plasma-Product-Exposed Toddlers):

Results and Recommendations for Treatment Products for Previously Untreated Patients with Hemophilia A

The following recommendation was approved by the Medical and Scientific Advisory Council (MASAC) on June 17, 2016, and adopted by the NHF Board of Directors on June 28, 2016.

The development of inhibitors (neutralizing antibodies to factor VIII) is the most significant, current treatment-associated complication of hemophilia A, affecting up to 30% of previously untreated patients (PUPs) treated with factor VIII (FVIII).*(1)* Inhibitors to FVIII can occur with both plasma-derived and recombinant FVIII concentrates. The rate of inhibitors observed in PUPs is unacceptably high, therefore clinical trials in this patient population are critically important to efforts to reduce inhibitor formation.

Results were recently published from SIPPET, a study which analyzed data from 251 PUPs with severe hemophilia A who might have received transfusions of blood or blood products but not clotting factor concentrates. *(2)* The study aim was to assess the frequency of FVIII inhibitor formation in patients treated with plasma-derived FVIII concentrate containing von Willebrand Factor (pdFVIII/VWF) compared to patients treated with recombinant FVIII (rFVIII). In this prospective, randomized, controlled study, 125 PUPs were treated with either first, second, or third generation rFVIII, and 126 PUPs were treated with pdFVIII/VWF.

- The results showed a significant increase in inhibitor development in the rFVIII-treated patients compared to pdFVIII/VWF-treated patients.
- The cumulative incidence of all inhibitors was 26.8% with pdFVIII/VWF and 44.5% with rFVIII; the cumulative incidence of high-titer inhibitors was 18.6% with pdFVIII/VWF and 28.4% with rFVIII.
- The follow-up period was planned to be 3 years or 50 exposure days (EDs: days on which one or more

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infusions of factor concentrate were received). Not all patients achieved one of these endpoints because of early termination of the study due to publication of another study that implicated one of the rFVIII products used in SIPPET with increased inhibitor development. *(3)*

Historical Background

Inhibitor development in hemophilia

The development of inhibitors is a complex interplay of host and environmental factors. About half of all inhibitors that form are low titer and clinically insignificant and usually disappear spontaneously; thus FVIII therapy may be continued. However, the remaining inhibitors are high titer and persistent, rendering treatment with FVIII products ineffective at preventing or stopping bleeding. These inhibitors require intensive therapy, known as immune tolerance induction (ITI), to eliminate them. About 70% of the patients with high titer inhibitors can be successfully treated with ITI.

The widespread use of rFVIII beginning in 1992 suggested an increased incidence of inhibitors due, at least in part, to more frequent measurements than what had occurred historically, more intensive treatment frequency and dosing, and the development of more sensitive assays that detected inhibitors below 1.0 Bethesda unit (BU). *(1)* Focusing on high titer inhibitors of 5.0 BU and greater, which tend to be clinically relevant and persistent, mitigates these problems and provides a more accurate assessment of inhibitor incidence.

PUP studies and inhibitor development

PUP studies have been published for each new FVIII product introduced to the market in the past 25 years. Taken together, all of these studies have shown rFVIII inhibitor rates to be either similar to or greater than inhibitor rates for pdFVIII products. These studies have all suffered from using highly selected populations and have never included a pdFVIII concurrent comparator arm. Two large Western European prospective observational studies have been performed (RODIN and PedNet), in which a total of 883 PUPs were followed for over 10 years. More than 98% of patients in these studies reached 50 exposure days. 658 PUPs were treated with rFVIII and 225 with pdFVIII. No differences in inhibitor rates were found, even when comparing all pdFVIII/VWF products to all rFVIII products. *(3, 4)*

MASAC Observations on the SIPPET Study

With this background of conflicting study results on the relative risks of inhibitor development between pdFVIII and rFVIII, the SIPPET study was initiated. The SIPPET study is the only prospective, randomized, controlled trial to date that has attempted to study the risk of inhibitor formation between two classes of FVIII products. As such, this study provides compelling data showing an increased risk for inhibitor development in PUPs treated with rFVIII compared to pdFVIII/VWF.

However, there are clear differences between the SIPPET study and most of the previous studies that showed no or a minimal increase in inhibitor formation with rFVIII.

- The SIPPET study included ethnicities which differ from those for which we have the most data (i.e., Caucasian), as the majority of its patients came from Egypt, India, and Iran. The risk of inhibitor development in these populations relative to European and North American populations is unknown.
- A large proportion of patients had gene mutations known to be associated with increased inhibitor risk (e.g., null mutations).
- Not all patients achieved 50 ED, the historical benchmark by which time the majority of inhibitors are seen to form.
- About half of the patients were on on-demand therapy (episodic), and some received as few as 1-4 treatments per year, which is quite different than the prophylactic treatment regimens used in the U.S.
- A cutoff of 0.4 BU was used for inhibitor detection; most other recent studies use 0.6 BU, while older studies used 1.0 BU. A lower BU cutoff will result in a greater number of inhibitors being detected.
- Third-generation and extended half-life products are currently used by the majority of patients in the U.S. Since only 16% of SIPPET patients in the rFVIII arm were treated with a third-generation product, SIPPET results using predominantly first and second generation products should not be extrapolated to these newer products.
- SIPPET does not address what to do after 50 EDs. Inhibitors may still occur beyond 50 EDs, and it would be difficult to determine if they were the result of any treatment changes or part of the natural history of inhibitors.

Plasma-derived products continue to carry the theoretical risk of viral

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transmission. HIV and hepatitis viruses are no longer risks due to extensive viral screening, inactivation, and elimination procedures. However, many new pathogens have emerged in the three decades since HIV and hepatitis viruses contaminated plasma-derived clotting factors. Zika, bird flu, SARS, and numerous other emerging viruses are eliminated by current pathogen removal and inactivation methods. However, some pathogens such as parvovirus B19 are less susceptible to heat and solvent-detergent inactivation methods, are small enough to pass through nanofiltration devices *(5)*, and therefore are surrogate markers for future viruses of very small size. Thus, there remains a small risk that a new pathogen will emerge that is transmissible by blood, that will not be detected quickly by testing and screening, and that will not be cleared in the manufacturing process of plasma-derived clotting factors to eliminate the risk of transmission.

Thus there are many differences between the SIPPET study, previous inhibitor detection studies in PUPs, and clinical practice in the U.S. We do not yet fully understand the applicability of the SIPPET findings to the U.S. population. Also, the risk of inhibitor development must be weighed against the risk of a pathogenic infectious agent being transmitted by pdFVIII/VWF. PdFVIII/VWF products are, by definition, intermediate, not high, purity plasma products, meaning that they contain many other proteins in addition to FVIII and VWF. The three pdFVIII/VWF products licensed in the U.S. are Alphanate (used by only 7% of pdFVIII/VWF group in SIPPET) and Humate P and Koate DVI (not utilized in SIPPET). Thus it is difficult to make a blanket recommendation about which product to use in a given patient. Patients and families must discuss these issues with their treating provider.

MASAC Recommendations

Based on currently available evidence, MASAC makes the following recommendations:

1. Individuals with greater than 50 exposure days to any recombinant product (i.e., Previously Treated Patients or PTPs) should consider remaining on their current product, since multiple clinical studies have shown that their risk for inhibitor development with any FVIII product is markedly diminished after 50 EDs.
2. Individuals with more than zero and less than 50 exposure days should consider staying on their current recombinant FVIII product, since the differences between SIPPET and numerous other studies may not warrant switching patients who have already initiated a treatment regimen.
3. Newly diagnosed individuals and their caregivers should consider the new data from the SIPPET study in the context of all the accumulated data on inhibitor formation in PUPs and the pathogen safety risk/benefit of the two product classes and consider the following options:
   a. Initiate therapy with a pdFVIII/VWF product in all PUPs.
   b. Initiate therapy with a rFVIII product as previously recommended by MASAC *(6)*.
   c. Initiate therapy with a newer rFVIII product.
4. Regardless of which option is chosen, all PUPs should be enrolled in the ATHN data collection system or a clinical trial to assess outcomes.
5. For all classes of treatment products, the risk for inhibitor formation in PUPs is unacceptably high. All efforts by government, HTCs, patient advocates, and industry should be directed at reducing the risk of inhibitor formation.

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