

World Federation of Hemophilia
XXVVIII International Congress – Istanbul

**Presentations made at an open meeting of the
VWD and Rare Bleeding Disorders Committee**
Wednesday, June 4, 2008

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1. Resource Room For Rare Plasma Protein Disorders

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On behalf of
Rare Plasma Protein Disorders; National Hemophilia Foundation; Medical & Scientific
Advisory Council

The Medical and Scientific Council (MASAC) of the National Hemophilia Foundation (U.S) created a sub-committee dedicated to the issues of patients with rare disorders in 2003. The members of the MASAC subcommittee include Amy Shapiro MD, Donna DiMichele MD, Diane Nugent MD, Marilyn Manco-Johnson MD, Marion Koerper MD, and Mark Skinner who also serves as the link to the WFH.

A project developed by this subcommittee was the development of a “Resource Room for Rare Bleeding & Coagulation Disorders”. The resource room was conceived as a readily accessible area with a compilation of current clinically relevant information targeted to rare disorders including their clinical manifestations, treatment as available, list of investigators in the United States holding pertinent INDs for studies related to each disorder, laboratories and investigators interested in genetic analysis of specific disorders, reference lists, and links to other pertinent websites.

Work on this project has been ongoing for approximately one year. The developed material will be easily accessible and available both as a special edition of the journal *Haemophilia* and as electronic postings on the websites of the National Hemophilia Foundation, WFH, and the National Alliance for Thrombosis and Thrombophilia (NATT) with a link from the American Thrombosis and Hemostasis Network website. The postings on NHF and WFH will include complete manuscripts while the posting on NATT will be partial to include only those pertinent manuscripts targeted to thrombotic disorders. The initial planned publication date is September 2008. We hope that the development of this resource room will prove to be an accessible and valuable source of information for rare disorders that will serve both the international medical and patient communities.

A listing of the topics and authors and their present status are as follows:

Topic	Authors	Status
Fibrinogen	Acharya & DiMichele	Resubmitted with revisions
Prothrombin	Meeks & Abshire	Resubmitted with revisions
Factor V	Huang & Koerper	Complete
Factor VII	Lapcorella & Mariani	Revisions in progress
Factor X	Brown & Kouides	Awaiting initial review

Factor XI	Gomez & Bolton-Maggs	Complete
Factor XIII	Hsieh & Nugent	Awaiting revision
Combined Factors V & VIII	Spreatico & Peyvandi	Resubmitted with revisions
Combined Factors II, VII, IX, X	Weston & Monahan	Revisions in progress
Platelet Defects	Kunicki & Nugent	Awaiting revision
Alpha-2 Antiplasmin	Carpenter & Matthew	Complete
PAI-1	Mehta & Shapiro	Resubmitted with revisions
Plasminogen	Mehta & Shapiro	Resubmitted with revisions
HHT	Sharathkumar & Shapiro	Complete
Protein C	Goldenberg & Manco-Johnson	Resubmitted with revisions

2. American Thrombosis and Hemostasis Network (ATHN)

Amy Shapiro
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On behalf of
American Thrombosis and Hemostasis Network (ATHN)

ATHN was formed in July 2006 in response to the need for organizational oversight for development of a national database for hemophilia treatment centres in the United States. A national data collection platform was adopted and is presently under conversion to a web-based system. The central server will be housed at the Center for Disease Control with each centre's data only visible to that centre. Data sharing may occur through either individual patient consent or HTC consent for aggregated and anonymized elements approved by the ATHN data oversight committee. ATHN therefore is the organization that provides stewardship of a secure U.S. national database. Examples of ATHN's roles and responsibilities in specific areas are as follows:

ATHN	Support Roles
Secure infrastructure & disaster plan	Emergency preparedness for RBD patients
Patient clinical characteristics	Patient recruitment / site selection for RBD treatment studies (e.g. HTRS)
Evidence of clinical practices & outcomes	Recommendations of best practices/standards for RBDs (e.g. MASAC)
Data on treatment economics & QOL	Fact-based advocacy and public health promotion (e.g., NHF, HFA, etc.)

In addition ATHN is interested in rare disorders and has activities in these areas, including development of a web-based registry for physicians caring for patients with plasminogen deficiency, and development of a data collection module for the national database specifically geared towards rare disorders. ATHN is interested in assuring potential international data harmonization and is in the process of exploring consistent data collection between the U.S. and international efforts headed by Dr. Flora Peyvandi (EN_RBD). ATHN supports collaboration and continued discussion with international efforts targeted towards data collection on bleeding and thrombotic disorders.

3. CDC Data Collection

Mike Soucie

Center for Disease Control and Prevention, Division of Hereditary Blood Disorders

CDC has helped the U.S. hemophilia treatment centers (HTCs) develop a public health surveillance system that monitors product safety with annual centralized infectious disease testing, a blood specimen repository for use in blood safety investigations, and collection of standardized data on treatment and outcomes. Data from the system is useful for identification of population subsets for special study and for clinical trials of new products, post-market surveillance of new products, and facilitating communication and networking between providers.

Data collection tools were originally designed with a focus on the issues most pertinent to patients with hemophilia, and participation rates in the surveillance for these patients have been high (i.e., 80-90%). Rates of participation have been somewhat lower for patients with rare disorders. The working group that assists CDC with this surveillance project has taken steps to make modifications in the data collection tools designed to collect data more appropriate for these populations.

In addition, a multi-disciplinary subgroup was formed in July 2007 whose task is to focus on patients with RBDs and to help develop data collection elements to better characterize this population and their issues. Additional areas of focus for this group include:

- Encourage national data collection for these disorders
- International harmonization for data collection
- Improve access to therapies for rare disorder populations
- Create a national communication network of potential new products under development or in study

4. Women with Bleeding Disorders: Cross-National Collaboration

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In the last decade, there has been an increased international interest in women with inherited bleeding disorders. This has led to considerable progress in the identification of obstetric and gynecological problems in these women, and raising clinical awareness amongst their care providers. However most of the data in the literature are based on small case series from single centres, especially for women with rare bleeding disorders. The data is also limited in relation to obstetric and gynecological problems other than menorrhagia. International collaboration and multicentre studies are essential to gather good quality and unified data in a larger population of women to address many unanswered questions in this field. This has been recognized by the international societies and the following initiatives represent early steps towards an international network for collaboration across the world.

Advisory board on menorrhagia and other gynecological problems

An international working group of clinicians interested and involved in the management of women with bleeding disorders met in Milan on April 15th 2008 to establish an International collaborative network of their treatment centres. A 3-year multi-centre project is planned to collect retrospective-prospective follow-up data on women affected by severe bleeding disorders (including von Willebrand disease, rare bleeding disorders, and platelet function disorders) from centres in Egypt, France, Iran, Italy, Netherland, Serbia, Sweden, the U.K., and the U.S. The goals for the project are:

- To evaluate the prevalence of obstetric and gynecological problems
- To evaluate the association between menstrual loss and clinical severity (other bleeding symptoms)
- To evaluate the association between laboratory phenotype and clinical presentation and severity
- To determine the best treatment options to reduce the complications of menorrhagia and others gynecological problems and to evaluate the proportion of affected women requiring regular prophylactic treatment
- To collect and analyse data on concomitant gynecological abnormalities, complications of menorrhagia (anaemia), requirement for gynecological interventions
- To evaluate pregnancy complications in each disorder including the risk of miscarriage and ante-partum and post-partum hemorrhage

It is hoped that during the three years, 200 women with severe bleeding disorders will be recruited to the study. For comparison, their affected and unaffected siblings will be recruited as a control group.

The basic data is collected using a standardized questionnaire with the following sections:

- Demographic data/referral information
- Diagnosis information

- Bleeding symptoms/score – Bleeding score (BS) (Tosetto *et al.*, JTH 2006) will be used to allow a quantitative evaluation of the severity of the bleeding history
- Obstetric and Gynecological section – this includes detailed information on menstrual problems and other gynecological problems as well as information in relation to previous pregnancies.

Menstrual loss will also be assessed semi-objectively using PBAC during two subsequent menstruations after recruitment. Hemoglobin and ferritin levels will also be assessed prior to and after each period.

The data will be collected online via the web-site www.wrbd.org. The website also reports the progress of the project and other activities of the working group.

International registry for Levonorgestrel intrauterine system (LNG-IUS, Mirena)

The levonorgestrel intrauterine system is well established as an effective, long-acting and reversible contraceptive. It is associated with a significant reduction in menstrual blood loss as early as the first period after insertion. It therefore provides an effective treatment modality for menorrhagia.

The National Institute for Clinical Excellence in the UK recommends its use as a first line treatment for menorrhagia in women seeking contraception. In women with bleeding disorders, the data is very limited. Small case series have reported promising results. Therefore, it can be an attractive option for women with long-standing menorrhagia to obviate the need for surgical interventions. However, prospective data is required to assess long-term effectiveness, effect on quality of life, bleeding pattern and tolerability of side effects in these women.

As bleeding disorders are relatively uncommon, especially severe types, multicentre studies are required to obtain significant data. This has been recognized by the Women Board of the International Society of Thrombosis and Haemostasis and the establishment of an international registry is under development. The registry will soon be available on the ISTH website. All clinicians involved in the management of women with bleeding disorders and menorrhagia are invited to include their patients in the registry. It is aimed to collect prospective follow-up data for 3 years for women for whom LNG-IUS is considered as a treatment option. The data collection is focused to achieve the following:

- Establish risk of bleeding and the need for prophylaxis during insertion
- Establish the expulsion, discontinuation rate, and failure rate as a contraceptive
- Effectiveness (short- and long-term) as a treatment for menorrhagia; its effect on menstrual loss, iron status, and quality of life
- Establish the bleeding pattern, in particular to assess whether the rate of persistent/recurrent menorrhagia and irregular bleeding/spotting are different in women with bleeding disorders.

VWD and other bleeding disorders in women experiencing menorrhagia or postpartum hemorrhage - consensus meeting and statement

Menorrhagia and postpartum hemorrhage are common bleeding symptoms in women with inherited bleeding disorders. Menorrhagia can be the presenting symptom in many women affected by these disorders. However, there has historically been a lack of awareness and under-diagnosis of these disorders. To increase the awareness of bleeding disorders such as

von Willebrand disease, an international group of expert obstetrician-gynecologists and hematologists came together to discuss the diagnosis and management of menorrhagia and postpartum hemorrhage in affected women. The discussion focused on the following questions:

- What is menorrhagia?
- When should a gynecologist suspect a bleeding disorder and pursue a diagnosis?
- What haematological evaluations should be ordered and when should they be repeated?
- How should menorrhagia be managed in women with bleeding disorders?
- How can postpartum hemorrhage be prevented in women with bleeding disorders?
- What is known about menorrhagia in women with rare bleeding disorders (RBDs)?

This discussion and consensus are intended to allow physicians to better recognize bleeding disorders as a cause of menorrhagia and postpartum hemorrhage and to provide guidance for management. The consensus reached at the meeting has been reported and submitted for publication in the *Journal of Reproductive Medicine*.

5. 5. Harmonization of the EN-RBD Project and CNS Bleeding Study

Flora Peyvandi, MD, PhD

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Rare bleeding disorders database and European Network of Rare Bleeding Disorders

Since its inception in 2004 within the FVIII/IX subcommittee, the SSC working group on Rare Bleeding Disorders has attempted to improve our understanding of prevalence, diagnosis, and treatments of RBDs by developing the rare bleeding disorders database (RBDD, www.rbdd.org), with the collaboration of clinicians, biologists, and computer scientists who have pooled their expertise and resources. Actually, the RBDD contains clinical, phenotype, genotype, and treatment data of more than 350 patients from 21 countries and collected in the last 10 years at our Institute, an international reference centre for diagnosis and treatment of RBDs.

The aims and the background of the RBDD project are well explained on the dedicated website, www.rbdd.org. The RBDD project has already obtained the adhesion of 66 Centres scattered all over the world (see the “join” section of the RBDD website), demonstrating the willingness of the international community to build a network on RBDs and allowing the collection of epidemiological information on 3,230 RBD patients. An update of the results derived from this global survey is published on the www.rbdd.org website.

However, thanks to our long experience in this field and considering all available information on RBDs, we realized that:

- the epidemiological data on RBDs does not give a real picture of their distribution in the world, as about 50% of this data refers to patients in Europe;
- specific data collected so far in the RBDD and other national registries are not as yet sufficient to indicate which course of action is needed to improve both diagnosis and treatment of RBDs;
- data are not homogenous and hardly suitable for any statistical analysis or to provide evidence-based diagnostic and therapeutic guidelines.

To fill the gap between knowledge and clinical practice, cross-sectional studies among different Centres are warranted and require the creation of a network link to provide relevant exchange and extension of findings. Hence, thanks to a recently funded European project (EN-RBD: http://ec.europa.eu/phea/documents/2006_Health_Information.pdf), we set up a network, comprising 10 European Treatment Centres, in order to develop a new and homogeneous communication tool, based on the existing RBDD, for inserting, managing, editing, and viewing information on RBD patients (www.rbdd.eu). In November 2007, the first workshop of the EN-RBD working group was held in Milan, where involved partners presented the structure of their databases, the content on coagulation disorders (phenotype, genotype, treatment, complication of treatment, surveillance), how their database is linked to their own National Database, and the compatibility with the EN-RBD questionnaire, which should represent the tool for homogeneous data collection.

The testing phase, where partners started to insert specific data about their severely affected patients, is ongoing. By the end of May 2008, 39 patient records from 37 unrelated families (18 males and 21 females) were inserted. Inserted patients were affected by afibrinogenemia, FV, FV+FVIII, FVII, FX, FXI and FXIII deficiencies. Queries and reports allowed to derive preliminary results about clinical manifestations, treatment, and identified mutations (www.rbdd.eu). In conclusion, the online database proved to be a powerful tool to improve the quality of data collection. Preliminary results showed that a homogeneous and harmonized data collection using a unique model will help to have more accurate data for statistical analysis even if, to derive evidenced conclusions on bleeding manifestations and best therapeutic decisions, larger amounts of homogeneous data are required. Some improvements on the EN-RBD database will be performed according to suggestions derived from the partners, in order to ameliorate data collection.

CNS bleeding study

Recently, in the RBDD website, links to specific projects, designed to address particular issues of RBDs were published (<http://www.rbdd.org/studyonline.htm>): a study on menorrhagia and other gynecological problems in women affected by bleeding disorders and a study to investigate central nervous system (CNS) bleeding in patients affected by RBDs. CNS bleeds are generally rare, but there are several reports of the frequent occurrence of these manifestations in patients with RBDs. Unfortunately, treatment and prophylaxis of CNS is often a challenge because of a generalized lack of experience, paucity of data on these disorders, non-availability of factor concentrates for some deficiency states, and possible occurrence of severe complications. Moreover, triggering agents and risk factors associated with the onset of spontaneous CNS bleeding episodes are not well established. As a consequence, guidelines to assist clinicians in the management of patients are needed. To solve this problem, a retrospectively multi-centre study on RBDs patients that experienced CNS bleeding was designed, in collaboration with Dr. Zanon, Italy, from the Associazione Italiana Centri Emofilia (AICE).

The main goals are:

- To establish incidence, mortality rate, and incidence of invalidating sequences of cerebral hemorrhage
- To characterize risk factors related to CNS bleeds and their importance
- To establish the most frequent location of bleeds
- To verify the treatment used during the acute phase of bleeding episodes and the most frequent prophylaxis used for prevention (their failure and success)

The study will involve at least 10 cases for each deficiency. For each enrolled patient a specific questionnaire will be compiled according to his/her age (one for children of < 2 years of age, one for patients of > 2 years of age). Specific information about inclusion criteria, protocol of the study, and informed consent can be downloaded from the www.rbdd.org website. Considering the rarity of both RBDs and of CNS symptoms, to involve interested clinicians and promote the study, an e-mail was already sent to all the 66 Treatment Centres that joined the RBDs project. The website will facilitate networking of Hemophilia Centres around the world and we hope that it will allow us to recruit a large cohort of affected patients to analyse CNS bleeding symptoms.