COMMON TERMS FOR SEVERE VWD

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VON WILLEBRAND DISEASE A condition when a person does not have the normal amounts of von Willebrand factor (VWF) in the blood leading to excessive bleeding

VON WILLEBRAND TYPES Because there are different ways that VWF may be deficient, these are classified as different "Types"

- **Type 1** A quantitative lack of the VWF protein where it is still able to be produced in small amounts
- **Type 2** When the VWF protein is generally produced in normal amounts, but the protein is incorrect and lacks an essential function or ability
- **Type 3** The quantitative lack of VWF protein where it is not produced in any amount

WHAT IS SEVERE VWD? Typically, severe VWD is when a patient has an increased burden from bleeding symptoms, VWF activity levels <10 iu/dl and/or FVIII levels <20 iu/dl. Including:

- Type 3 VWD patients
- Most type 2B VWD patients
- Patients with type 2A and Type 1 Vicenza.

Certain bleeds are associated with severe VWD such as joint bleeding and bleeding of the bowels (GI bleeding)

WHAT IS A BLEED? The escape of blood from a blood vessel. Bleeding manifests in various ways depending upon location

- **Skin** bruising
- **Tissues under the skin** hematoma
- **Nose** epistaxis
- **Joints** Hemarthrosis
- **Vaginal bleeding or menstrual bleeding**
- **Profuse or uncontrolled bleeding** Hemorrhage

Bleeding is quantified in terms frequency, length, and flow of blood

JOINT BLEED A bleed that occurs into a joint space between the bones, also known as hemarthrosis

SPONTANEOUS BLEED A bleed that occurs without an obvious cause

ANNUAL BLEED RATE (ABR) The amount of bleeding over a specified time projected over an entire year (Example: 2 bleeding episodes in a month over 12 months is an ABR of 24)

INFUSION Introduction of a medicine or a solution into a vein

PROPHYLAXIS The use of a treatment in such a way as to prevent a disease from happening

- In the context of bleeding disorders, it is to provide regular factor, or a similar treatment, to prevent recurrent bleeding

ON DEMAND/PRN Pro Re Nata (as the situation demands); as needed

- The use of factor treatment when it is needed after a bleed or injury

INDICATION The advisable use of a drug for a particular disease

- An indication may be officially approved (as by the FDA) or off label

OFF LABEL The use of a drug for which it has not been officially approved

RECOMBINANT FACTOR Factors used to treat bleeding that is made in a lab using the ordered sequencing of DNA rather than collected from humans through plasma donation

PLASMA DERIVED FACTOR Factors derived and concentrated from human plasma donations

HEMOSTASIS The process of the stoppage of bleeding

PRIMARY HEMOSTASIS The portion of blood clotting occurring from the time of blood vessel injury to an initial loose platelet plug

SECONDARY HEMOSTASIS (the difference and why it matters to patients with VWD)
The portion of blood clotting started by the formation of a platelet plug that causes the sequence of clotting factor proteins to activate, ultimately stabilizing a clot with the formation of fibrin and cross-linking it

VWD PANEL TESTS

- **Von Willebrand Antigen Assay** measures the amount of the VW protein, regardless of how well it works
- **Von Willebrand Activity Assay** measures the ability of VW protein to help form a clot; this may be affected by how much VW protein there is
  - Ristocetin Cofactor
  - Collagen Binding Assay
  - GPIbM
- **Factor VIII Activity** measures the ability of Factor VIII protein to help form a clot; this is important for VWD patients because Factor VIII is needed to protect VWF in the blood stream

MULTIMER AND SIZES OF MULTIMERS

- The DNA sequence for von Willebrand makes only one protein piece
- 2 pieces join end to end and become a pair (dimer or a subunit)
- Dimers join with other subunits to make bigger and bigger multimers
- Large multimers (about 100 subunits) are the most effective to form clots

ENDOGENOUS vs EXOGENOUS (in reference to factors) Clotting factors are either made by the body (endogenous; plasma concentrate) or made outside the body (exogenous; recombinant)

HALF-LIFE The time required for a particular substance to be reduced in half

- It is the common way to communicate how long a drug lasts in the blood stream

PEAKS AND TROUGHS (as related to prophylaxis)

Peak The highest concentration level a drug or substance can be measured after it has been given; this usually is found within the time shortly after the drug has been given

- In factor administration, this is the level that is desired to be achieved to treat any certain bleeds
- Ex. Nosebleeds require factor levels of 40-60% and joint bleeds require levels to be 80-100%

Trough The lowest concentration level that a drug or substance is allowed to decrease; in general the trough level occurs immediately before the next dose of drug is given

- The trough level is the level that is desired at all times which may effectively reduce or eliminate recurrent bleeding in prophylaxis therapy

INHIBITOR

- Any protein not found in the body can cause the immune system to reject it, like bee venom proteins
- If you do not make clotting factor on your own, infused factor can look like a foreign protein
- An **inhibitor** is an antibody that is produced by your immune system to reject clotting factor and prevent it from working to raise clotting factor levels
- If a person has an inhibitor to a clotting factor, it is likely to impact the effectiveness of all brands of factor, and an alternative to treatment has to be used if bleeding starts

TITER (HIGH AND LOW)

- The amount or level of inhibitor is its titer and is stated in "Bethesda Units"
- It is a logarithmic scale meaning that 1 additional "Bethesda Unit" is 10X the amount of the previous
- A low titer is consider to be a titer less than 5 BU

TRANSIENT INHIBITOR An inhibitor that is felt to be temporary and will eventually go away

- Generally the lower the levels of an inhibitor, the more likely it will be transient

PERSISTENT INHIBITOR An inhibitor that is unlikely to go away on its own

- Generally a high titer inhibitor is more likely to be persistent

STUDY TERMS

PATIENT REGISTRY An organized system that uses observational methods to collect information to evaluate specified outcomes for a group defined by a particular disease or condition to serve one or more scientific purpose.

NATURAL HISTORY STUDY A study that follows a group of people over time who have a specific medical condition or disease. It collects information in order to understand how the medical condition or disease develops and how to treat it best.

CLINICAL TRIAL A scientific research study of the safety and effectiveness of a therapeutic agent or approach using consenting human subjects. As a drug is developed, it will move through specific phases of clinical trials with an expressed purpose and intent for each phase.

Phases of a clinical trial:

- **Pre-clinical trials** cell line and animal experiment to determine if a drug is likely to work in humans.
- **Phase 1: Safety Trials** Generally the first human trials of a drug. Goal is to find safe and tolerable dose for a drug in a limited number of subjects. Groups of subjects are started with a low dose of drug and each new subject group gets an increased dose as the previous group is able to show it is tolerated, before a maximum dose is reached in the last subject group. Safety of use of the drug is the main concern.
- **Phase 2: Efficacy Trials** The goal is to use the drug at the maximal dose and show that it is effective for specific indications or diseases. Effectiveness of a drug is the main concern.
- **Phase 3: Pivotal Trials** Even if a drug is effective, it has to show that it is comparable to or better than what is currently available to patients. These are larger trials that last longer and are pivotal for approval by regulatory bodies such as the FDA. The goal is to compare effectiveness against current treatments and drugs.

LONGITUDINAL STUDY DESIGN A study that follows individuals enrolled on it over a prolonged period of time

PROSPECTIVE AND RETROSPECTIVE STUDY DESIGN

- In **prospective studies**, individuals at risk for a disease or condition are followed over time and data about them is collected as their characteristics or circumstances change.
- In **retrospective studies**, individuals are sampled and information is collected about their past. This might be through interviews in which participants are asked to recall important events, or by identifying relevant administrative data to fill in information on past events and circumstances.

ELIGIBILITY CRITERIA The list of conditions that potential subjects have to meet in order to be able to be included in a study

RANDOMIZATION (rare in bleeding disorders) When there a comparison between 2 or more treatments and/or a placebo, and the placement into any of the groups is allowed to occur by chance

BLIND A study that is designed to prevent subjects enrolled in it from knowing the treatment group that they are assigned to

DOUBLE BLIND A study that is designed to prevent subjects *and* researchers from knowing the treatment group that a subject is assigned to

END POINT An event or outcome that can be measured objectively to determine whether the treatment being studied is beneficial

DISCONTINUED Stopped

CONTINUATION In the context of a study, it is the approval for a study to continue to be conducted by an independent reviewing body of the conduct of a study. Most studies are reviewed annually and allowed for continuation by an Independent Review Board (IRB).

NUMBER NEEDED TO TREAT (NNT) The number of subjects that need to receive a drug in order to prevent one specified outcome from occurring.

STATISTICAL SIGNIFICANCE The determination of the likelihood that a result occurred because of random chance or as a result of a studied intervention or treatment. This is most commonly stated as a P-value.