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Cardiovascular Disorders, Acquired von Willebrand Syndrome and Bleeding

Von Willebrand Factor (vWF) plays a key role in both platelet plug and fibrin clot formation. When endothelial damage occurs, vWF multimers bind to exposed subendothelial collagen and to platelets, promoting platelet adhesion and aggregation at the site of injury. Activated platelets initiate the coagulation cascade resulting in the formation of a fibrin clot.

During the past 55 years, many publications have documented the association of aortic stenosis and bleeding from gastrointestinal angiodysplasia. Bleeding associated with aortic stenosis was found to be caused by excessive proteolysis of high molecular weight vWF multimers under conditions of increased shear stress. Aortic valve replacement usually cures GI bleeding due to replenishment of the largest vWF multimers within a few hours.

Bleeding due to defects in vWF structure or function that are not inherited, but are consequences of other medical disorders, has been classified as acquired von Willebrand syndrome (AVWS) to distinguish it from congenital von Willebrand disease (vWD). More recently, excessive bleeding associated with other cardiovascular disorders such as ventricular septal defect, hypertrophic obstructive cardiomyopathy, and placement of left ventricular assist device (LVAD) has also been attributed to development of AVWS.

Development of AVWS and mucosal bleeding may be an additional indication for surgical correction of the underlying cardiovascular disorder. Laboratory detection of AVWS may be helpful in evaluating the efficacy of surgical management. Unfortunately, the panel of tests recommended to diagnose congenital vWD (vWF antigen, vWF activity and FVIIIc) are

usually normal in AVWS. Laboratory confirmation of AVWS requires VWF multimer analysis to detect the loss of high molecular weight multimers. This analysis involves a labor-intensive assay involving separation of vWF multimers by protein electrophoresis and detection of all molecular weight forms by Western Blot. Multimer analysis is only available at a few reference laboratories and has a long turnaround time. Results may not be available in time for clinical decision making.

Another sensitive indicator of impaired vWF function is the whole blood Platelet Function Screen performed on the PFA-100 analyzer. This assay is very sensitive for detection of vWD and AVWS. Prolonged closure times with both COL/EPI and COL/ADP are typical of either vWD or AVWS. Platelet function screen is available at Saint Luke's Hospital on the Plaza during day and evening shifts. One 5.0 mL sodium citrate (light blue top) tube is required. Sample must be received by the laboratory within 3 hours of collection.

Various transfusion therapies have been tried to treat excessive bleeding associated with these cardiovascular disorders including plasma, desmopressin (DDAVP), aprotinin, tranexamic acid, aminocaproic acid and recombinant FVIIa (Novoseven). However, none of these products specifically addresses the underlying problem. Replacement of loss of high molecular weight vWF is best achieved by transfusion of cryoprecipitate or a factor concentrate that contains Factor VIII and vWF multimers, such as Humate P.

No Return Rule for Unused Blood Components

For many years, hospital transfusion services have had a policy that allows the return of a blood component within thirty minutes if it is not

transfused. The original concern about allowing blood to sit at room temperature for more than thirty minutes was diminished cell viability. More recently, the primary concern has become the risk of bacterial contamination and rapid growth at room temperature. The origin of this 30-minute rule can be traced to an article by Pick and Fabijanic published more than forty years ago (Transfusion. 1971;11:213-5). This paper showed that when bags of blood were removed from a refrigerator and allowed to stand at room temperature, the average surface temperature of a blood bag reached 10.5 degrees C by 30 minutes.

During a recent AABB inspection of the blood bank we were reminded that once a unit of blood, platelets, or plasma leaves the hospital transfusion service it cannot be returned and re-issued to another patient unless there is a process in place to verify the safety, potency, and purity of the product. Given the large number of different locations that blood components are transfused, there is really no efficient or economical means to assure these parameters. The easiest way to comply with this standard is no longer allow blood to be returned for reuse after it is issued.

With this new rule, it is increasingly important to make certain that everything is in order, including signed informed consent, to start the transfusion immediately after a blood component is picked up from the transfusion service. If a unit is not transfused it should be returned to the blood bank for proper disposal.

Reticulocyte Count Reference Range Change

Reticulocytes are non-nucleated immature red cells in peripheral blood, containing residual RNA. After erythroid precursors lose their nuclei, another 4 days is required for the resulting reticulocytes to mature and lose their RNA.

Normally the first 3 days are spent in the marrow, and the last day in peripheral blood. Early reticulocytes continue to synthesize hemoglobin; approximately 25% of total red cell hemoglobin content is produced during this stage of development.

The reticulocyte count is useful as an index of effective red cell production. It is usually expressed as a percentage of total red cells and as an absolute count (# of reticulocytes per uL). The percentage value is falsely elevated in patients with anemia. This bias is overcome by correcting reticulocyte percentage according to the patient's red cell count using the following formula.

$\text{Corrected Reticulocyte Count} = \frac{\text{Reticulocyte \%} \times \text{Patient's red cell count}}{5 \text{ million per uL}}$
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The percentage value reported by Saint Luke's Regional Laboratories has already been corrected in this way. Absolute reticulocyte count does not require correction.

Recently, the reference range for reticulocyte count was changed. Separate ranges are now listed for male and female. The new ranges for percent and absolute reticulocyte counts are shown in the following table.

Gender	Percent	Absolute
Female	0.6 – 1.6	24 – 80
Male	0.6 – 1.8	26 – 105