Von Willebrand Disease

Thomas M. McLoughlin Jr.

Risk

- Most common inherited bleeding disorder.
- >1 million people within USA; 1% carry the gene (severe disease 1:10,000-1,000,000).
- No race/gender with highest prevalence.

Perioperative Risks

- Significant risk of bleeding if untreated
- Increased risk if hepatic dysfunction present

Worry About

- Excessive periop hemorrhage
- Concurrent antiplatelet agents or NSAIDs contributing to bleeding
- Adverse reactions to desmopressin therapy (seizures due to hyponatremia, hypotension, anaphylaxis)

Overview

- Coagulopathy is characterized by quantitative/qualitative alterations in vWF. vWF acts as a bridge between plts and vascular subendothelium and stabilizes Factor VIII to prolong its circulating half-life.
- Presents as defect in primary hemostasis—mucocutaneous hemorrhage.
- Marked by highly variable severity; family Hx is very helpful in predicting severity.
- Diagnosed by prolonged aPTT, Factor VIII antigen and activity levels, vWF antigen, and Ristocetin aggregation studies. Many disease subtypes can be further classified by band pattern of radiolabeled vWF after gel electrophoresis (multimeric analysis).
- Type I: Quantitative decrease in vWF of all sizes (most common, 70–80% of cases). Type II: Quantitative/qualitative alterations primarily in largest molecular weight vWF multimers; many subtypes exist (20–30% of cases). Type IIB: May be accompanied by thrombocytopenia. Type III: Marked by severe quantitative reductions or absence of vWF (rare, secondary to homozygous inheritance).

Etiology

- Autosomal dominant trait; variable penetrance and expression lead to unpredictable clinical severity; most severe disease occurs in homozygotes.
- Acquired disorder (von Willebrand syndrome) can be associated with autoimmune disease, neoplasm, myeloproliferative or lymphoproliferative disorders, hypothyroidism, or circulatory destruction of large vWF multimers through shear stress (valvular or vascular stenoses, extracorporeal circulatory devices).

Usual Treatment

- Disease subtype must be determined prior to therapy.
- DDAVP, 0.3 μg/kg IV, stimulates release of endothelial vWF; variably effective in types I and II disease; first-line treatment in acquired von Willebrand syndrome (possible accelerated clearance in these pts, however).
- Intranasal desmopressin is used, but response is more variable.
- Desmopressin contraindicated in type IIB.
- Pasteurized pooled factor VIII concentrates that preserve vWF (Humate-P) and solvent detergent heat-treated pooled concentrates (Alphanate) are mainstays of therapy.
- Recombinant vWFs are not currently available in USA; agents are in Phase III trial in 2015.
- Cryoprecipitate is best alternative if concentrates are unavailable.
- Antifibrinolytics often useful adjuncts.

Assessment Points

System	Effect	Assessment by Hx	Test
HEENT	Mucocutaneous bleeding	Epistaxis	
GI	GI bleeding	Melena, hematochezia	Stool guaiac
HEPAT	Requirement for transfusion therapy	Random donor exposures	LFTs, hepatitis panel
HEME	Coagulopathy, principal defect in primary hemostasis	Easy bruising, menorrhagia, epistaxis, patient or family experience during prior surgery or hemostatic challenge (e.g., dental extraction) vital to assessing periop risk, given variable severity of disease among individuals	PT, PTT, plt count often normal; plt function assay; quantitative vWF antigen; ristocetin cofactor activity; multimeric analysis

Key References: Mensah PK, Gooding R: Surgery in patients with inherited bleeding disorders, *Anaesthesia* 70(Suppl 1):S112–S120, 2015; Stone ME, Mazzeffi M, Derham J, Korshin A: Current management of von Willebrand disease and von Willebrand syndrome, *Curr Opin Anesthesiol* 27(3):353–358, 2014.

Perioperative Implications

Preoperative Preparation

- Collaborate with consultant hematologist and blood bank.
- Desmopressin 1 h preop in all but IIB subtype.
- Antifibrinolytics for dental procedures.

Monitoring

- Bleeding time/vWF activity periodically in prolonged procedures; $T_{1/2}$ of administered vWF is about 8–12 h.
- Target vWF factor levels:
  - Major surgery: 100 IU/dL vWF preop, trough levels 50 IU/dL through POD 7–10
  - Minor surgery: 50 IU/dL vWF preop, trough levels 30 IU/dL through POD 3–5
  - Dental extractions: 60 IU/dL pre-procedure (single level)
  - Peripartum: 50–80 IU/dL predelivery, trough levels 30 IU/dL through postdelivery d 3–5
  - Avoid levels of 200 IU/dL or greater to reduce periop thrombosis risk

Airway

- Laryngoscopy can lead to tissue trauma.
- Nasotracheal route best avoided.

Induction

- No specific recommendations

Maintenance

- Meticulous surgical hemostasis.

Extubation

- Avoid coughing if possible; gentle orotracheal suction best performed under direct vision.

Adjuvants

- Consider RA with caution; no epidural hematoma from neuraxial technique has been reported when diagnosis of vWD known in advance.
- Repeat desmopressin doses likely to be less effective than initial; reaccumulation of endothelial stores takes time.

Anticipated Problems/Concerns

- Excessive intraop and postop blood loss
- Increased likelihood of infectious bloodborne disease

Waldenström Macroglobulinemia

Amy C. Robertson

Risk

- Rare hematologic neoplasm (accounts for 1–2% of hematologic malignancies).
- In USA, age-adjusted incidence of 5.7 per million among males and 2.7 per million among females. Median age at diagnosis is 73 y.
- Racial preponderance: Whites >African Americans (4.1 vs. 1.8 million).
- 10-y survival rate is 66%.
- Factors associated with worse prognosis: age >65 y, hemoglobin <11.5 g/dL, platelet count <100,000, B_2-microglobulin >3 mg/L, and monoclonal IgM >7 g/dL.

Perioperative Risks

- Consequences of hyperviscosity
- Anemia and coagulopathy

Worry About

- Anemia
- Coagulopathy
- Hyperviscosity
- Hypervolemia
- Hepatomegaly (20%)
- Splenomegaly (15%)
- Lymphadenopathy (15%)
- Peripheral neuropathy: Most common neurologic complication; may be seen in up to half of all pts.
- Primary systemic amyloidosis is a rare complication.

Overview

- Uncommon lymphoplasmacytic lymphoma associated with monoclonal IgM protein.
- Diagnosis: Presence of IgM monoclonal protein is associated with >10% clonal lymphoplasmacytic cells in bone marrow.
- Symptoms attributable to tumor infiltration and/or excessive IgM production.

- Most common presenting symptom is fatigue related to anemia.
- Anemia can be caused by combination of factors: Decrease in red cell survival, impaired erythropoiesis, hemolysis, plasma volume expansion, and blood loss from GI tract.
- Potentially severe adverse neurologic, hematologic, and CV problems periop.
- Anesthetic concerns similar to those in multiple myeloma, except that hypercalcemia and bone lesions are rare; renal failure and proteinuria less common.

Etiology

- Familial clustering: First-degree relatives of pts with WM have a 20-fold increased risk of WM.
- L265P mutation in myeloid differentiation primary response 88 gene (*MYD88*) is detectable in more than 90% of pts.
- Role of environmental factors remains to be clarified.

Usual Treatment

- Alkylating agents (chlorambucil, cyclophosphamide), purine analogues (cladribine, fludarabine), monoclonal antibody (rituximab), and dexamethasone
- Stem cell transplantation
- Plasma exchange to treat hyperviscosity symptoms

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Hyperviscosity (high output cardiac failure, valvular dysfunction, MI)	Angina Dyspnea Fatigue	Venous thrombosis Fluid overload	Serum viscosity >4 g/dL
RESP	Pulm involvement	Dyspnea	Hypoxia	CXR (pleural effusion, diffuse pulm infiltrates)
HEME	Coagulopathy (multifactorial)	Episodic epistaxis, mucosal and gum bleeding		Coagulation studies
	Anemia (multifactorial)	Fatigue	Pallor	CBC (normocytic, normochromic anemia)
	Cryoglobulinemia	Cold intolerance Raynaud syndrome Arthralgia	Purpura	Cryoglobulin assay
	Lymph node involvement		Lymphadenopathy	
RENAL	Glomerulonephritis	Dehydration Uremic symptoms		BUN/Cr UA (proteinuria)
CNS	Leukoencephalopathy Abn cerebrovascular permeability (hyperviscosity)	Headaches Blurred vision	Mental status changes Retinal hemorrhage, papilledema	
PNS	Demyelinating peripheral neuropathy		Symmetric, distal sensorimotor neuropathy, ataxic gait	
GI	Organomegaly secondary to IgM infiltration		Hepatomegaly Splenomegaly	

Key References: Gertz MA: Waldenström macroglobulinemia: 2015 update on diagnosis, risk stratification, and management, *Am J Hematol* 90(4):347–354, 2015; Leff J, Shore-Lesserson L, Fischer GW: Hematologic diseases. In Fleisher LA, editor: *Anesthesia and uncommon diseases,* ed 6, Philadelphia, PA, 2012, Elsevier, pp 350–358.

Perioperative Implications

Preinduction/Induction/Maintenance

- Consider plasmapheresis and transfusion.
- All drugs: Theoretical unpredictable pharmacokinetics due to alterations of relative proportions of globulins in blood and expanded plasma volume.
- Judicious fluid management.

Monitoring

- Normothermia to prevent cryoglobulin precipitation.

General Anesthesia

- Macroglossia if amyloidosis (rare).

Regional Anesthesia

- Relative contraindication in presence of peripheral neuropathy.

Postoperative Period

- Transient postop paresis due to disease rather than anesthetic management.

Anticipated Problems/Concerns

- Hyperviscosity symptoms (<15% of pts; rare in pts with IgM concentration <4 g/dL):
  - Symptoms are due primarily to shear forces of excessive IgM that rupture venous channels.
  - Capillary blood flow impaired, leading to decreased O_2 delivery through microcirculation and tissue ischemia.
  - Epistaxis, gingival bleeding, and visual changes due to retinal hemorrhage are common presenting manifestations.
  - Severe cases of hyperviscosity syndrome may be associated with confusion, dementia, stroke, and coma.
  - CV manifestations secondary to expanded plasma volume include angina, high output cardiac failure, valvular dysfunction, or MI.
  - Plasma exchange is the fastest, most effective method to reduce plasma viscosity. Should be considered a temporizing measure until systemic therapy reduces IgM protein concentration.
- Anemia:
  - Hgb value may be artificially reduced by 2 g/dL secondary to increased plasma volume.
  - Transfusion may precipitate CHF or hyperviscosity syndrome (by increasing serum viscosity) and potentially decrease O_2 delivery.
  - Consider plasmapheresis before transfusion.
- Coagulopathy
- Cryoglobulinemia (5% risk):
  - Precipitation of cryoglobulins at cold blood temp triggers complement activation, which results in immune complex vasculitis and ischemia.
  - Raynaud syndrome, arthralgia, purpura, peripheral neuropathy, hepatic dysfunction, and renal failure may develop.

Wegener Granulomatosis (Granulomatosis With Polyangiitis)

Christopher J. Cullom | Alan David Kaye

Risk

- Prevalence of 3:100,000 persons affected
- More common in the white race; however, no gender affinity
- Respiratory failure
- Upper airway compromise
- Cardiovascular instability
- Acute renal failure
- Peripheral neuropathy
- Bleeding disorder

Perioperative Risks

- Medication toxicity, side effects, and interactions
- Systemic involvement, primarily respiratory, cardiovascular, and renal systems
- Airway compromise