Current and Emerging Treatment Paradigms in the Management of Hemophilia

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Hemophilia: An Inherited Disorder

- X-linked recessive bleeding disorder
- Leads to spontaneous bleeding and bleeding following trauma or surgery
  - Typically expressed in males; female carriers may have symptoms
  - Characterized by a deficiency of Factor VIII (hemophilia A) or Factor IX (hemophilia B)
- Current prevalence in the United States: ~20,000 males
  - Occurs in ~1 of every 5,000 live male births
  - ~30% of cases are new mutations
  - Affects individuals from all racial and ethnic groups
- Hemophilia A is ~4X as common as hemophilia B


Clinical Manifestations

- Bleeding into joints (hemarthrosis), muscles, soft tissues, and other locations
- Life threatening bleeding: CNS, retroperitoneum, neck
- Interference with normal activities and ability to participate fully in school or work
- Long-term sequelae if bleeding not prevented
  - Flexion contractures
  - Arthritis/arthropathy
  - Chronic pain
  - Muscle atrophy
  - Loss of mobility
  - Neurologic impairment
- Neutralizing antibody (inhibitor) development to factor replacement therapy is major complication

Clinical Classification

<table>
<thead>
<tr>
<th>Classification (% of affected patients)</th>
<th>Severe (50%-70%)</th>
<th>Moderate (10%)</th>
<th>Mild (30%-40%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVIII or FIX activity</td>
<td>&lt;1%</td>
<td>1% – ≤5%</td>
<td>6% – 40%</td>
</tr>
<tr>
<td>Pattern of spontaneous bleeding episodes</td>
<td>~2 – 4 per month*</td>
<td>~4 – 6 per year**</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cause of bleeding episodes</td>
<td>Spontaneous</td>
<td>Minor trauma</td>
<td>Major trauma, Surgery</td>
</tr>
</tbody>
</table>

*If not on prophylactic therapy
**Patients with moderate disease may bleed like those with severe or mild disease

Detection/Diagnosis

**Prior Family History**
- Identify carriers
- Pre-conception counseling
- Cord blood testing of males
- Low-level carriers should be identified early to prevent bleeding with surgery or injury

**No Previous Family History**
- Bleeding with birth or post-natal, circumcision, immunizations
- Excessive bleeding following trauma/injury
- Joint bleeds and hematomas

Treatment of Hemophilia

- **Treatment goal**
  - Prevent bleeding through use of prophylactic factor therapy
  - If bleeding, rapid and effective replacement of missing coagulation factor

- **Treatment approach**
  - Comprehensive hemophilia treatment center (HTC) staffed by a multidisciplinary team of experts who care for patients with bleeding disorders

- **Treatment strategies**
  - Episodic or “on-demand” factor replacement
  - Prophylaxis

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Advances in Hemophilia Care:
The Past Six Decades

- Hospitalization
- Transfusion
- HIV, Hepatitis
- Factor concentrates
  - Home infusion
- Longer acting products
  - Gene therapy
- Increasing use of primary prophylaxis
- Recombinant factor concentrates
- High-purity factor concentrates
Prophylaxis

- Infused factor replacement before the occurrence of, and to prevent, bleeding\(^1,2\)
- Since the 1990s, prophylaxis supported by WHO, NHF, and WFH as first-line treatment for children with severe hemophilia\(^2,3\)
  - Use increasing for adult patients\(^4\)
- Demonstrated benefits include
  - Prevention of chronic arthropathy and sequelae\(^5\)
  - Prevention of intracranial and other serious bleeds\(^1\)
  - Prevention of pain\(^6\)
  - Improvement in quality of life\(^6\)
  - Reduction in long-term disability\(^1,6\)


\(=1591\)

Darby et al, Blood 2007

American Thrombosis and Hemostasis Network dataset, 6/2015
Randomized Trial of FVIII Prophylaxis in Adults (SPINART)


Bleeding in Patients in SPINART Trial

Treatment Options

- Replacement of missing clotting protein
  - Factor VIII and IX
- Desmopressin acetate (IV, intranasal) in mild FVIII deficiency
  - Need to test to see effectively increases FVIII levels
- Adjunctive therapies
  - Antifibrinolytic agents
    - Aminocaproic acid
    - Tranexamic acid
  - Supportive measures
    - Icing
    - Immobilization
    - Rest
  - Physical therapy


Factor VIII and IX Products

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Factor VIII</th>
<th>Factor IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous infusion</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>• IV push</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Continuous infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>20 - 50+ units / kg body weight</td>
<td>20 - 100+ units / kg body weight</td>
</tr>
<tr>
<td>Half-life</td>
<td>8 - 12 hours</td>
<td>18 - 24 hours</td>
</tr>
<tr>
<td>Expected change in Factor level with each unit infused</td>
<td>+2%</td>
<td>+1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Factor VIII</th>
<th>Factor IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy to store and prepare</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>May contain immuno-modulatory proteins</td>
<td>√/-*</td>
<td>√/-*</td>
</tr>
<tr>
<td>Increase dose up to 1.5 x vs. plasma-derived</td>
<td>√</td>
<td></td>
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Inhibitors

- Infusion of exogenous clotting factor can trigger an immune response
- IgG antibodies (inhibitors) directed against Factor VIII or IX protein that neutralizes the procoagulant effect of the infused factor\(^1\)
- Incidence highest in patients with severe disease (Hemophilia A is 20-30%; Hemophilia B, 1-4%)
- Typically develop early in life (median age 1.7 – 3.3 years)
- Greatest risk for inhibitor development occurs within the first 50 days of exposure to infused product\(^2\)
- But risk continues throughout lifetime and may increase in older age\(^3\)
- Regular laboratory monitoring needed


Management of Inhibitors

- Bypassing agents
  - Activated prothrombin complex concentrates
  - Recombinant factor VIIa
- Bypassing agents have unpredictable efficacy (50 – 90%)
  - Patients often need access to both products
  - Surgery historically difficult to perform
- Immune Tolerance Therapy (ITT)
  - Methods to eradicate inhibitor
  - ~ 70% effective overall
- Overall cost of treating inhibitors is significant
  - More bleeding, more joint damage
- New agents for treatment under study
Longer-Acting Hemophilia Therapeutics

- Half-life of standard hemophilia therapies results in frequent injections
  - Factor VIII – three times per week to every other day
  - Factor IX – two to three times per week
- Benefits of replacement product with a longer half-life could include
  - Reduced frequency of administration
  - Ability to achieve higher trough levels in certain clinical situations
  - Potentially improved adherence
- The first longer-acting rFVIII and rFIX have obtained FDA approval
  - Additional longer-acting agents are currently under study and in development


New Treatments for Bleeding Disorders

- Hemophilia A
  - Longer-lasting FVIII
    - Increases factor half-life ~ 1.5X
  - One product (rFVIIIIC) FDA approved
- Hemophilia B
  - Longer-lasting FIX
    - Increases factor half-life ~5X
  - One product (rFIXFc) FDA approved
  - Gene Therapy in late-phase clinical trials
Who should get long acting factor?
Who should get long acting factor?

Summary of Factor IX Activity and Liver Function after Vector Infusion in 10 Patients with Hemophilia B.

FIX-AAV Gene Therapy

Better Predict Those at Risk of Complications

- Better define genetic and clinical factors:
  - Predict those who will develop inhibitors
  - Predict those who will bleeding less (or more)

- Current Initiative: MyLifeOur Future:
  - A collaboration between the National Hemophilia Foundation, the American Thrombosis and Hemostasis Network, BloodworksNW and Biogen
  - Offers free or very low cost genotyping to people with hemophilia and their families
  - Improves hemophilia care by increasing understanding of the disorder today
  - Builds the scientific foundation for the breakthrough treatments of tomorrow

Ongoing/Emerging Questions and Issues

- Prophylaxis
  - Target trough levels: Is 1% the best level?
  - Cost : benefit ratio of targeted higher levels
    - Impact on patient outcomes and QoL
  - Applicable age groups – not just for pediatrics

- Treatment of bleeding
  - What is the best target peak level?
  - Optimal length of hemostatic coverage

- Individualized Treatment
  - PK parameters (needed to inform dosing of new factor products)
  - Tools for prediction of levels
  - Activity related

- Management of Comorbidities of Aging
  - Opportunity to cure hemophilia C
    - Less expensive to treat hepatitis C than to pay for clotting factor use in liver failure
  - Probably some decreased in CVD risk, but still very common
The HTC/Comprehensive Care Model

- A hemophilia treatment center (HTC) is a federally recognized comprehensive care facility featuring a multidisciplinary team expert in the care of patients with bleeding disorders and whose staff spends a majority of their time caring specifically for these patients
- Key features:
  - Expertise in coagulation disorders
  - Development and provision of individual treatment plans
  - Preventive medicine
  - Access to multiple health care disciplines
  - Optimization of care
- May have an associated 340B factor program
  - Lower cost and/or better factor management


Assessment and Management of Adverse Outcomes/Adherence

- Routine joint assessment
  - PE: Hemophilia-experienced provider and PT
    - At least yearly visits for patients on home infusion therapy
  - Old scoring used X-ray: More advanced disease
  - MRI can detect earlier pathology
  - Increasing use of joint ultrasound
    - Helpful to define acute bleed versus other pathology (such as arthritis)
    - A growing resource at many HTCs
- Effective treatment of bleeds with appropriate rehabilitation
- Close collaboration with patient/family
  - Logging of bleeding episodes and treatment
  - Monitoring of coagulation factor use
Treatment via the HTC Model Results in More Comprehensive Care with Efficiencies that Drive Improved Outcomes

Outcome Data from 31 HTCs

<table>
<thead>
<tr>
<th>Outcome Data</th>
<th>Year Before Program 1975</th>
<th>10th Year of Program 1985</th>
<th>% Increased (+)</th>
<th>% Decreased (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number patients receiving regular comp care</td>
<td>1,333</td>
<td>5,683</td>
<td>+ 326%</td>
<td></td>
</tr>
<tr>
<td>Number patients on homecare</td>
<td>514</td>
<td>2,517</td>
<td>+ 390%</td>
<td></td>
</tr>
<tr>
<td>Average days/year lost from work/school</td>
<td>14.5</td>
<td>3.9</td>
<td>- 73%</td>
<td></td>
</tr>
</tbody>
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Benefits of Care Delivered Through an HTC

For Patients Receiving Care Outside of an HTC:
Mortality Rate Increases by 70% and Hospitalization Rate Rises by 40%

New Data to Measure Outcomes

- Hemophilia Care Guidelines
  - Developed independently by McMaster led group
  - To be published next year – and placed in National Guidelines Clearinghouse
- American Thrombosis and Hemostasis Network (ATHN)
  - Non-profit organization to maintain a secure database
    - >130 Hemophilia Treatment Center Affiliates
  - National Hemophilia Program Coordinating Center for HHS program
    - Evaluative programs underway to establish best practices
  - CDC Public Health Surveillance
  - >27,000 patients in HIPAA compliant database (A: >9000; B:>2700, 10/15)

Summary

- Hemophilia - an X-linked recessive bleeding disorder
- Leads to spontaneous and trauma-induced bleeding
- Common symptom is bleeding into joints and muscles
- Long-term complications include joint destruction, muscle atrophy, and decreased quality-of-life
- Inhibitor development is the most severe complication
- Prophylactic factor replacement may avoid or reduce musculoskeletal impairment, decreases death from bleeding, and enhances quality-of-life
- Longer-acting factor replacement products and gene therapy will change treatment models
- The HTC model offers improved clinical and economic outcomes via multidisciplinary, comprehensive care