Elective Orthopedic Surgery in Patients With Inhibitors:
The Hematologist/Orthopedic Surgeon Consult
Hemophilic Arthropathy and the Multidisciplinary Team Approach to Patient Management

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The Multidisciplinary Approach: Team Players

Core team members include:

- Hematologist
- Nurse coordinator
- Physical therapist
- Licensed social worker

Subspecialists on the team include:

- Orthopedic surgeon
- Occupational therapist
- Dentist
- Geneticist
- Hepatologist
- Infectious disease specialist
- Immunologist

The Multidisciplinary Approach: Goals

Utilizing a team approach in hemophilia care ensures the following:

• Accurate diagnosis
• Prompt and effective treatment
• Fewer hospitalizations
• Healthy joints and muscles
• Support for patients and their families

Musculoskeletal Complications of Hemophilia

• Intra-articular hemorrhage (hemarthrosis) is clinical hallmark of hemophilia¹,²

• Hemarthrosis typically occurs before 2 years of age in severe hemophilia (clotting factor level <1%)³

• If inadequately treated, repeat bleeding leads to progressive deterioration of the joint and muscles, resulting in⁴:
  - Severe loss of function
  - Loss of motion
  - Muscle atrophy
  - Contractures

Synovitis and the Cycle of Joint Damage

- Synovitis is recurring inflammation of the synovial membrane, resulting from repeat joint bleeds
- Single hemarthrosis may give rise to synovitis
- Synovitis predisposes target joint to recurrent hemarthrosis, initiating cycle of chronic synovitis, inflammatory arthritis, and progressive arthropathy

Late Hemophilic Arthropathy

- Natural history of hemophilic synovitis is progression to end-stage arthropathy
- Fibrous tissue
  - Contractures
  - Fibrous ankylosis
- Progressive muscle atrophy
- Joint subluxation
- Large periarticular synovial cysts in adjacent bone

Photo courtesy of Amy Shapiro, MD, and Medscape.com.

Effects of Arthropathy

- Joint bleeds profoundly increase the morbidity of patients with hemophilia:
  - Weight-bearing issues
  - Limited limb use
  - Impact on school/work attendance
- These outcomes result in a decrease in quality of life (QoL) for affected patients with hemophilia and their caregivers\(^1,2\)
- QoL is significantly impaired in children with hemophilia\(^3\)

Common Sites of Joint Bleeding

- Knee: 45%
- Elbow: 30%
- Ankle: 15%
- Shoulder: 3%
- Wrist: 3%
- Hip: 2%
- Other: 2%

Treatment Options for Hemophilic Arthropathy

- Management will depend on
  - Stage at identification
  - Patient’s symptoms
  - Available resources

- Physiotherapy is a vital component of any treatment program

- Control of arthropathic pain: analgesics or narcotics if absolutely necessary

- Conservative management: serial casting, bracing, orthotics (eg, shoe inserts, crutches)

- Elective orthopedic surgery
Patients With Hemophilia and Inhibitors: The Burden of Joint Disease

- Prolonged bleeding episodes
- Increased risk for synovitis
- Increased joint disease
- Increased risk for arthropathy
- Quality of life significantly associated with orthopedic status

Surgical Challenges in Patients With Hemophilia and Inhibitors

- Major orthopedic interventions present a challenge to the surgeon due to:
  - Contracted flexor muscles (decreased ROM)
  - Chronic synovitis (leads to extensive fibrosis)
  - Severe change in anatomic axis of the joint
  - Poor bone stock (osteopenia)

- Patients with inhibitors
  - Hemostasis may be more difficult to control

Successful orthopedic surgery can result in:

- Improved joint function
- Improved ROM
- Pain reduction or resolution
- Fewer bleeding episodes
- Improved mobility
- Improved quality of life

Successful reconstructive surgery in patients with hemophilia requires an experienced multidisciplinary team and should be performed at established hemophilia treatment centers (HTC)

- Thorough preoperative planning and patient counseling
- Vigorous postoperative rehabilitation regimen
- Attention to infection prevention recommendations

Mainstay of programs: education of patients and healthcare professionals

The Bypassing Agents
Products for Treating Hemophilia A With Inhibitors

- Prothrombin complex concentrates (PCCs), activated prothrombin complex concentrates (aPCCs/FEIBA)
  - Active form may be more effective (≈65%) than nonactive form
  - FEIBA shown to be beneficial ≈50%-90% of the time
  - For joint bleeds, FEIBA given by bolus infusion preoperatively; subsequent doses q6-8h at 50-75 IU/kg⁻¹ to maximum dose of 200 IU/kg⁻¹

- Recombinant activated factor VIIa (rVIIa)
  - For patients with inhibitors, the recommended dose is 90 µg/kg⁻¹ preoperatively by bolus infusion; subsequent doses q2h for at least 48h
  - Shown to control bleeding in 70%-100% of bleeding episodes
  - Larger doses may be required for serious bleeding or surgery

The Bypassing Agents: Comparative Efficacy

- Several studies have evaluated variations of efficacy\(^1,2\)
- Overall review comparing efficacy is lacking\(^2\)
- Individual studies have varying definitions and estimates of efficacy, making a direct comparison difficult\(^2\)
- FEIBA and rVIIa appear to exhibit similar effect on joint bleeds\(^1\)
- At recommended doses, both FEIBA and rVIIa effectively and safely control bleeding in patients with inhibitors undergoing surgical procedures\(^3\)

The Bypassing Agents: Benefits and Risks

- Bypassing agents are able to achieve hemostasis independent of factor VIII or factor IX activity\(^1\)
- aPCCs have potential for anamnestic response\(^2\)
- With rVIIa, no anamnestic response and no risk of human virus transmission\(^2\)
- With bypassing agents, thrombosis is a rare but well recognized potential complication\(^3-5\)
- Bypassing agents are not always effective and can have unpredictable hemostatic response\(^1,2\)

Elective Orthopedic Surgery in Patients With Hemophilia and Inhibitors

• Availability of bypassing agents (eg, FEIBA and rVIIa) has made it possible to perform various surgical procedures in hemophilia patients with inhibitors
  ▪ Further studies are warranted, however, to determine efficacy in major surgery
• In the absence of robust clinical data, personal experience and availability of bypassing agent may guide treatment choice

Role of the Hematologist

- Present the patient as hemostatically “normal” as possible for the surgery
- Maintain adequate hemostasis in the intraoperative period
- Maintain adequate hemostasis in the postoperative period without having the patient bleed at the surgical sites or develop a thrombosis because of excessive factor use and/or immobilization
- Maintain hemostasis during the time that physical therapy is initiated in the postoperative period
- Aid with pain control
- Help direct team efforts in the preoperative and postoperative periods
The Orthopedic Surgeon’s Perspective: Pathogenesis and Orthopedic Management of Hemophilic Arthropathy

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President, CEO & Medical Director
Orthopaedic Hospital
Professor and Vice Chairman
UCLA/Orthopaedic Hospital
Department of Orthopedic Surgery
Los Angeles, California
Hemophilia Treatment Center
Los Angeles Orthopaedic Hospital

- Founded 1962
- Federal treatment center grant 1964
- Patient base 400
- Clotting factor replacement 1966
- >800 procedures
Hemophilic Arthropathy

Target Joints
Treatment of Chronic Hemarthrosis

- Clotting factor replacement
- Physical therapy
- Synovectomy
  - Surgical
    - Open
    - Arthroscopic
  - Non-surgical
    - Radiosynovectomy
Chronic Hemarthrosis: Natural History

Cumulative No. of Joint Bleeds

Pettersson Score (max 78)

0  50  100  150  200

Pette

rsson Sc

50 100 150 200

Chronic Hemarthrosis
Treatment of Chronic Hemarthrosis: Synovectomy

**Radiosynovectomy**

- Reduces hemarthroses
- Minimally invasive
- Rare hospitalization
- Reduces clotting factor requirements
- Preserves ROM
- Minimal cost 1%-5% of surgical synovectomy
- Minimal discomfort
Treatment of Chronic Hemarthrosis: Radiosynovectomy

Ideal Candidate

- Frequent hemarthrosis: 2-3 bleeds/month
- Target joint
- Failed conservative treatment with clotting factor replacement and PT
- No radiologic evidence of joint damage

<table>
<thead>
<tr>
<th></th>
<th>$^{32}$P</th>
<th>$^{90}$Y</th>
<th>$^{198}$Au</th>
<th>$^{86}$Re</th>
<th>$^{165}$Dy</th>
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<tbody>
<tr>
<td>Radiation</td>
<td>$\beta$</td>
<td>$\beta$</td>
<td>$\beta, Y$</td>
<td>$\beta, Y$</td>
<td>$\beta$</td>
</tr>
<tr>
<td>Particle size ($\mu$)</td>
<td>6-20</td>
<td>10-20</td>
<td>3</td>
<td>0.1</td>
<td>3-5</td>
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<tr>
<td>Penetration (mm)</td>
<td>3-5</td>
<td>4-10</td>
<td>1-4</td>
<td>1-4</td>
<td>6</td>
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<tr>
<td>Half-life (days)</td>
<td>14</td>
<td>2.4</td>
<td>2.7</td>
<td>3.8</td>
<td>0.1</td>
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</table>
Radiosynovectomy: Procedure

- Short
- Outpatient department
- Local anesthetic
- Joint access
- Drainage
- Injection of $^{32}\text{P}$
Radiosynovectomy: Efficacy

Effectively reduces frequency of bleeding

Outcomes:
- Excellent or good results: 80%
- Excellent + Good = >75% bleeding reduction
- Excellent = 100% bleeding reduction

Radiosynovectomy: Safety

- No growth plate disturbance
- Cartilage is resistant to radiation
- Minimal potential for radiation-induced neoplasia
  - More than 5000 RS for RA
- No premalignant chromosomal changes

Extra-articular radiation levels >1% in only 1 patient

Surgery for Advanced Arthropathy

Hemophilia Treatment Center at Orthopaedic Hospital
1970-2002
More than 500 surgeries

- Hip: 14%
- Ankle: 14%
- Elbow: 14%
- Shoulder: 4%
- Knee: 54%
Radiographic Progression
TKR in Hemophilia

Bone Stock Deficiency

Deformity

TKR = total knee replacement.
TKR in Hemophilia (cont)

Arthrofibrosis
TKR in Hemophilia (cont)
TKR—Demographics

- Mean age: 40 years (18-70)
- 93%: Severe hemophiliacs
- 67%: HIV (+)
- Mean CD4 count: 448 cells/mm$^3$ (33-1260)
## Range of Motion

<table>
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<tr>
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<th>Preop</th>
<th>Postop</th>
<th>Latest F/U</th>
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<tbody>
<tr>
<td>Range of Motion</td>
<td>57°</td>
<td>68°</td>
<td>72°</td>
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\[ P = .001 \quad P = .3 \]
Knee Society Functional Score

- Mean F/U: 8 years (2-22 y)
- Mean score: 89 points (15-100)

<table>
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<tr>
<th>KS-Functional Score</th>
<th>% of Knees</th>
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<tbody>
<tr>
<td>Excellent (85-100)</td>
<td>97</td>
</tr>
<tr>
<td>Good (70-84)</td>
<td>31</td>
</tr>
<tr>
<td>Fair (60-69)</td>
<td>0</td>
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<tr>
<td>Poor (&lt;60)</td>
<td>3</td>
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</table>
TKR–Infection

- 14 knees in 10 patients (16%)
- 10/46 bilateral TKR (22%)
- Mean: 5 years (6 m-25 y)

<table>
<thead>
<tr>
<th>Dx of Infection</th>
<th>No. of Knees</th>
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<tbody>
<tr>
<td>&lt;6 months</td>
<td>0</td>
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<tr>
<td>6 months - 1 year</td>
<td>3</td>
</tr>
<tr>
<td>1 - 5 years</td>
<td>7</td>
</tr>
<tr>
<td>5 - 10 years</td>
<td>2</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>2</td>
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</tbody>
</table>

- Irrigation + debridement + A/B: 7
  - Persistent infection: 2
- Component removal: 7
  - No recurrent infections
  - Two-stage revision: 5
  - Arthrodesis: 2
### Infection–HIV

<table>
<thead>
<tr>
<th>HIV</th>
<th>No Infection</th>
<th>Infection</th>
<th>Total</th>
<th>Incidence</th>
<th>$P$</th>
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<tbody>
<tr>
<td>Negative</td>
<td>26</td>
<td>4</td>
<td>30</td>
<td>13%</td>
<td>.6</td>
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<tr>
<td>Positive</td>
<td>50</td>
<td>10</td>
<td>60</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>14</td>
<td>90</td>
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Fisher exact test

<table>
<thead>
<tr>
<th>HIV</th>
<th>Infection</th>
<th>No Infection</th>
<th>$P$</th>
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<tbody>
<tr>
<td>CD4</td>
<td>458</td>
<td>446</td>
<td>.6</td>
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Rank sum test
Infection–Prophylaxis

- Meticulous antisepsis with self-infusion
- Regular medical checkups
- Immediate reporting of any type of infection
- Prophylactic antibiotic prior to dental work or any other contaminated procedure
Total Knee Replacement

- Long-lasting solution for end-stage arthropathy
- 96% mechanical survival at 10 to 20 years (non-inhibitor patients)
- Increased risk of late infection
- Attention to preventive measures
For more educational activities, please visit us at:

www.bloodcmecenter.org