Management of Bleeding Episodes in Patients With Hemophilia and Inhibitors to Reduce Complications and Minimize Joint Damage

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Background Information:
Inhibitors in Hemophilia

- Inhibitors are antibodies against factor VIII (FVIII) developed after therapeutic FVIII administration¹
  - Neutralize hemostatic ability of FVIII²
  - Are the most serious complication of hemophilia A, rendering conventional factor-replacement therapy ineffective³
- Incidence
  - Hemophilia A: 20%-35%⁴
  - Hemophilia B: 4%-6%⁴
  - Most likely to develop in young children and those with severe hemophilia³

Impact of Hemophilia With Inhibitors on Quality of Life and Productivity⁵

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients 14-35 years old with hemophilia</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>With inhibitors</td>
</tr>
<tr>
<td>Mean days absent from school</td>
<td>35.5</td>
</tr>
<tr>
<td>Mobility-related problems</td>
<td>75%</td>
</tr>
<tr>
<td>Problems with “self-care”</td>
<td>22.2%</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>72%</td>
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</tbody>
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- Health-related quality of life study⁶
  - On SF-12v2, mean patient physical component summary score (39.9) substantially lower than that of general US population (49.6)
  - Most affected are “physical functioning” and “role physical,” with social and emotional functioning also impaired
The Multidisciplinary Approach: Importance for Inhibitor Patients

• Education and counseling\(^7\)
  ▪ Risks and problems of everyday living
• Management of serious bleeding events\(^7\)
• Long-term management of joint and muscle damage and other consequences of bleeding\(^7\)

The Multidisciplinary Approach: Team Members\(^7\)

Core team members include:

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

Subspecialists on the team may include:

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

Risk Factors for Inhibitor Development Are Multifactorial\(^8\)

• Patient related
  ▪ Family history of inhibitors
  ▪ Ethnicity
  ▪ FVIII gene mutation
  ▪ Major histocompatibility complex class
  ▪ Variation in immune response to foreign antigen
• Treatment related
  ▪ Number of FVIII exposure days
  ▪ Young age at first FVIII exposure
  ▪ Indication for FVIII concentrate use (surgery vs prophylaxis)
  ▪ Intense early exposure to FVIII concentrate
Factors That Increase or Reduce Risk of Inhibitor Development

Patient Case

- 6-year-old boy with hemophilia A presents with unexpected bleeding
- Patient has received no prophylactic treatment
- No prior evidence or suspicion of inhibitor development
- Acute bleeding episode is brought under control with administration of FVIII concentrate

Question 1:
How would you treat the patient once the acute bleed is controlled?

A. Continue on-demand treatment once bleeding is controlled
B. Initiate FVIII prophylaxis
C. Inject steroids
D. Perform surgery

Question 1 Clinical Discussion:
Once acute bleeding is controlled, patient should be started on prophylaxis, which has been shown to have superior efficacy to that of on-demand therapy in preventing hemorrhage.9,10
- No type of surgery should be performed until bleeding is under control.7
- Intra-articular steroid injections may provide transient reductions in pain and inflammation, but they are palliative only.11
Comparison of Bleeding Rates, On-demand vs Prophylactic Treatment

### All etiologies

<table>
<thead>
<tr>
<th></th>
<th>Intention-to-treat analysis set</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On-demand</strong></td>
<td>43.9 (21.9)</td>
</tr>
<tr>
<td><strong>Any prophylaxis</strong></td>
<td>1.1 (4.9)*</td>
</tr>
<tr>
<td><strong>% reduction</strong></td>
<td>99.4 (13.4)*</td>
</tr>
</tbody>
</table>

*P < .0001 for differences between on-demand and any prophylaxis treatments.

### Spontaneous etiologies

<table>
<thead>
<tr>
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<th>Intention-to-treat analysis set</th>
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<tbody>
<tr>
<td><strong>On-demand</strong></td>
<td>32.2 (23.6)</td>
</tr>
<tr>
<td><strong>Any prophylaxis</strong></td>
<td>0 (2.1)*</td>
</tr>
<tr>
<td><strong>% reduction</strong></td>
<td>100 (7.6)*</td>
</tr>
</tbody>
</table>

*P < .0001 for differences between on-demand and any prophylaxis treatments.

### Traumatic etiologies

<table>
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<th>Intention-to-treat analysis set</th>
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<tbody>
<tr>
<td><strong>On-demand</strong></td>
<td>11.5 (17.2)</td>
</tr>
<tr>
<td><strong>Any prophylaxis</strong></td>
<td>0 (2.0)*</td>
</tr>
<tr>
<td><strong>% reduction</strong></td>
<td>98.7 (17.6)*</td>
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*P < .0001 for differences between on-demand and any prophylaxis treatments.

Abbreviations: ABR, annualized bleeding rate

Frequency of Joint Hemorrhage Among Children With Severe Hemophilia Based on Type of rFVIII Treatment

Question 2:
The patient, now on prophylaxis, presents with bleeding that does not respond to his usual dose of factor, suggesting the presence of an inhibitor. What is the first thing you should do?

A. Give him a larger dose of factor and see if this controls the bleeding, and then perform laboratory studies to ascertain whether an inhibitor has developed
B. Start him on prophylaxis with plasma-derived activated prothrombin complex concentrate (pd-aPCC)
C. Start him on prophylaxis with activated recombinant FVII (rFVIIa)

Question 2 Clinical Discussion:
The first requirement is to prove the presence of an inhibitor, once the bleeding is under control

- Bleeding control can be accomplished with addition of more or higher-dose factor, but if patient has an inhibitor, it will neutralize the factor’s effect
- Secondary prophylaxis with a bypassing agent is appropriate for a patient with hemophilia and inhibitors and has been shown to prevent further joint hemorrhage, help prevent arthropathy, and improve functioning and quality of life
  - Prophylaxis results in fewer bleeding-related hospital days than does episodic treatment
  - If no resolution is achieved with more factor, testing should be performed to determine the presence of an inhibitor
  - Laboratory analysis is helpful in confirming presence of an inhibitor and indicating its severity but is too time consuming to be performed before hemorrhage is controlled
    - Bethesda inhibitor assay is used most commonly, with titer in Bethesda units (BU) used to quantify amount of antibody present.
• To date, only 2 head-to-head comparison trials of the 2 currently approved bypassing agents, pd-aPCC and rFVIIa
  ▪ One found little difference in overall efficacy but considerable interpatient discordance in early responses\textsuperscript{14}
  ▪ The other also showed no significant differences in global response, but patients given either of 2 doses of rFVIIa required less rescue medication than did those given pd-aPCC\textsuperscript{15}
• Each has advantages and disadvantages; eg, pd-aPCC can be administered less frequently, but rFVIIa can be administered more rapidly\textsuperscript{16}
• Cochrane review concluded that the 2 have similar hemostatic effects but that more randomized controlled trials are needed\textsuperscript{17}
• Both interpatient and intrapatient variations in response have been observed\textsuperscript{18}

**Question 3:**
It has been determined that the patient has an inhibitor. What is the next step?

A. Remove the antibody using plasmapheresis or immunoabsorption, then initiate treatment with FVIII concentrate
B. Initiate ITI plus prophylaxis with a bypassing agent immediately
C. Initiate prophylaxis with a bypassing agent until inhibitor titer is sufficiently low, then initiate ITI
D. Once inhibitor titer is sufficiently low, initiate ITI plus immunomodulation

**Question 3 Clinical Discussion:**
• Plasmapheresis or immunoabsorption yields temporary wipeout of inhibitor, but inhibitor returns with FVIII treatment\textsuperscript{2}
• Successful ITI results in normalized FVIII pharmacokinetics and improved patient quality of life\textsuperscript{19}
• ITI therapy should be initiated when the patient’s inhibitor titer is <10 BU\textsuperscript{20}
• Prophylaxis with bypassing agent can be used to control bleeding and prevent joint damage while waiting for titer to decrease and during ITI\textsuperscript{15}
  ▪ pd-aPCC not preferred for prophylaxis before ITI because of potential for anamnesis\textsuperscript{2,12,15}
• Addition of immunomodulator or immunosuppressant to ITI: some say no clear evidence for use, but may be useful (eg, rituximab); weigh risk vs benefit\textsuperscript{20,21}
• Monitor FVIII levels during ITI and consider discontinuing rFVIIa prophylaxis when FVIII levels can be measured\textsuperscript{15}
Suggested Algorithm for ITI Patient Selection and Timing

Most Common ITI Protocols

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Description</th>
<th>Success Rate</th>
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<tr>
<td>Bonn</td>
<td>High-dose regimen including bypassing agent</td>
<td>92%-100%</td>
</tr>
<tr>
<td>Malmö</td>
<td>High-dose FVIII + immunomodulation (adsorption and suppression)</td>
<td>59%-82%</td>
</tr>
<tr>
<td>van Crevelde</td>
<td>Lower-dose/adaptive FVIII dosing: neutralizing and tolerizing doses</td>
<td>61%-88%</td>
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Potential Algorithm for Bypassing Prophylaxis and ITI

ICH = intracranial hemorrhage; PK = pharmacokinetics.

**Question 4:**
What would be the optimal approach to patients with hemophilia and inhibitors to prevent or minimize joint damage?

A. ITI + prophylaxis with a bypassing agent + analgesia
B. Physical therapy + analgesic treatment
C. Bed rest + analgesia + prophylaxis with a bypassing agent
D. Prophylaxis with a bypassing agent + analgesia + physical activity

**Question 4 Clinical Discussion:**
- Risk of osteoporosis is high among patients with hemophilia largely because of decreased physical activity, especially weight-bearing exercise, resulting in insufficient peak bone mass that contributes to joint arthropathy\(^2\)^\(^2\)
- Rest may be important during bleeding episodes (along with application of ice and elevation of the joint to decrease inflammation), but this should be kept minimal, as long-term immobilization can lead to muscle atrophy and limitation of motion\(^2\)^\(^3\)
- Patient should be encouraged to adopt healthy lifestyle from childhood on, including regular, appropriate physical activity\(^1\)^\(^1\)
- Physical therapy is helpful in restoring and preserving mobility, balance, and muscle strength and preventing future injury\(^2\)^\(^3\)
  - Physical therapist should provide patient not only with therapy at sessions but also with an exercise program that patient can follow at home
- There is synergy between prophylaxis, which prevents bleeds and, thus, arthropathy; analgesia, which controls pain and thus facilitates activity; and physical activity, which builds strength and prevents falls and injury
Analgesia may be needed to relieve pain caused by bleeding, but selection should take into account that some analgesics can exacerbate bleeding. 

Examples of Instruments to Assess Pain in Hemophilia

- Prophylaxis with a bypassing agent has been shown to yield:
  - Fewer bleed-related hospital days
  - Improved mobility and functioning
  - Increased health-related quality of life
  - Less need for pain medication
- Factors affecting choice of agent include:
  - Frequency and volume of infusions
  - Cost
  - Patient age
  - Anamnestic response
  - Previous responses to ITI, if applicable, and/or prophylaxis

**Clinical Pearl**

“I think the key is probably identifying resources to help you manage the patient [with hemophilia and inhibitors]. If you are a hematologist who does not have a lot of experience managing inhibitor patients, it would be [advisable to] align yourself with somebody who has more experience.”


