Barriers and perceived limitations to early treatment of hemophilia

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Abstract: Early treatment of bleeds in hemophilia patients, both with and without inhibitors, has been shown to be of immense benefit in the overall clinical outcome. Despite the advantages of treating the bleeding episodes early, significant barriers and limitations remain. The aim of this review is to highlight the various barriers and perceived limitations to early therapy of bleeding episodes, especially in patients who have developed inhibitors to factor VIII. The peer-reviewed literature was searched for articles on hemophilia patients, with and without inhibitors, and early treatment, to identify the barriers to early treatment and potential impact on patient outcomes. The most important barrier is the educational barrier, which involves lack of awareness among patients regarding the signs of a bleed, as well as importance of early therapy. It is also common for parents or caregivers of school-age children to exhibit inconvenience and scheduling barriers. Distance to the treatment center can also play a role here. Some patients experience financial barriers related to cost of clotting factor products, insurance coverage, or insurance caps and out-of-pocket costs. Rarely, there can also be problems related to venous access or home infusion. Lastly, multiple psychosocial barriers can prevent adherence to treatment regimens. Identification and addressing these individual barriers will result in improved compliance rates, prevent joint damage, be more cost-effective, and lead to better overall health of these patients.

Keywords: hemophilia A, hemophilia B, inhibitors, outcomes, quality of life, cost of care

Introduction

Hemophilia is a rare, inherited, X-chromosome-linked bleeding disorder resulting from a deficiency of clotting factor VIII (hemophilia A) or factor IX (hemophilia B). Inhibitors to clotting factors VIII and IX develop in 20%–33% of patients with moderate to severe hemophilia A and in 1%–6% of patients with hemophilia B. Treatment options are typically more limited for hemophilic patients with inhibitors compared to those without inhibitors. In addition, a majority of hemophilic patients live in the developing world, where there is little or no access to factor-replacement therapy, leading to greater mortality and morbidity in the developing world.1 In these less developed nations, the greatest challenges include recognition and diagnosis of hemophilic patients, and the lack of trained health-care professionals with the knowledge to prescribe factor products properly and safely.1

Initiation of primary prophylaxis, with infusions of factor VIII before or soon after the first bleeding episode, has been shown to reduce joint bleeding and osteochondral changes, and leads to better musculoskeletal outcomes in patients without inhibitors.2,3 Several studies4–6 have reported on the benefits of early treatment with bypass agents for bleeds in hemophilic patients with inhibitors (Table 1). The efficacy of early
treatment of intramuscular hemorrhage with the bypass agent recombinant activated factor VII (rFVIIa [NovoSeven]; Novo Nordisk, Bagsvaerd, Denmark) was compared using outcomes of three open-label studies: a US home treatment study, a dose-escalation study, and a compassionate use study. The majority of patients had hemophilia A or B with high-titer inhibitors (a few in the compassionate use study had acquired hemophilia). The time interval from onset of bleeding to rFVIIa administration, the doses and number of injections required to achieve hemostasis, and global response to treatment were recorded for each bleeding episode. Patients in the home treatment study rapidly administered 90 mcg/kg rFVIIa (mean time to treatment, 1.1 hours), with a 92% efficacy after a mean number of 2.2 injections. By contrast, patients in the dose-escalation study were treated at the hemophilia treatment center (HTC; median time to treatment, 10 hours), with a 72% efficacy after a mean number of 3.6 injections for the high-dose (70 mcg/kg) group. In the compassionate use study, where patients were treated late in the course of the bleed (mean time to treatment, 5 days) after other forms of treatment failed, the efficacy was 62% after a mean number of 13.6 doses (mainly at 90 mcg/kg [range 60 to 120 mcg/kg]).

The HemoRec registry in the Czech Republic recorded demographic information along with information regarding primary diagnosis, symptoms, treatments, and adverse events. Overall, 60.2% (77/128) of rFVIIa-treated bleeds were treated within 2 hours of bleed onset. Early treatment (≤2 hours) with rFVIIa resulted in significantly fewer incidences of rebleeding than bleeds treated more than 2 hours after bleed onset. Despite the advantages of treating bleeding episodes early, significant barriers and perceived limitations remain for patients with hemophilia in seeking early treatment.

Barriers and perceived limitations to early treatment

Educational barriers
Patients with hemophilia are not always knowledgeable about their disorder or how significantly their personal involvement in treatment can affect outcomes. Moreover, 30% of patients may have no familial history of hemophilia. Thus, long-term sequelae resulting from untreated bleeds are unknown to them and their families.

Lack of awareness concerning the importance of early treatment of bleeding episodes is a common barrier. Current World Federation of Hemophilia guidelines recommend the treatment of an acute bleed within 2 hours of its initiation. Young children are typically afraid of receiving injections. School-age children may also hide their bleeds for fear of being reprimanded or causing undue stress and financial liability to their family. Parents, in turn, may not wish to infuse an uncooperative child with clotting factor until they deem it absolutely necessary. Parents have reported feeling uneasy about injecting their child, a lack of confidence in their ability to carry out the injection correctly, and fear of causing harm or pain to their child as major challenges in home-based care. In regard to greater responsibility, parents reported difficulty in deciding the right form of treatment for their child, anxiety about contamination of blood products (often due to familial history), fear of the potential long-term side effects of prophylaxis, and a desire to avoid any unnecessary medications.

Lack of awareness of the early signs of bleeding is a serious deficiency related to the lack of patient education. In response to a questionnaire survey distributed between 2008 and 2009, 47 physicians from Europe, the US, Africa, Australia, and Central and South America reported that although they recommend bleeds be treated within 1 hour of onset, in practice only 64.6% of bleeds were treated within 1–2 hours. In a survey sponsored by the Centers for Disease Control and Prevention (CDC), only 31% of patients with hemophilia aged 13–21 years treated bleeding episodes within 1 hour, and 15% waited over 6 hours. When patients were queried, 29% replied that they did not recognize the bleeding episode, and 11% did not think the bleed was serious enough to warrant treatment. Similarly, a global survey of practice patterns in the management of hemophilia A (2003 Practice Patterns Survey [PPS]) cited “infrequency of bleeding” as the primary reason that respondents (80% of patients and 60% of nurses) chose not to administer prophylactic treatment. Although early treatment of muscle hematomas is critical, difficulty in recognizing whether symptoms are due to a bleed or other muscle conditions (ie, contusions, strains) may delay treatment. Patients and their families should be mindful of bleeding symptoms and seek immediate medical attention when they appear.

Instructional aids and programs dedicated to patients with hemophilia are invaluable, with the goal of empowering
patients to take responsibility for their own treatment (Table 2). Patients should understand the particulars of their diagnosis and carry information indicating the type and severity of their condition, inhibitor status, type of clotting agent used, and contact information of the treating physician.10

Parents of minors with hemophilia have additional responsibilities. Extra care should be taken in childproofing the surroundings, although experts warn against overcompensation and overprotection. Parents should be extra-vigilant concerning changes in the child’s actions and demeanor, such as an unusual gait, which may be symptomatic of a bleed. At the proper stage of the child’s development, parents should gradually transfer responsibility for home infusion to the child to enhance independence and self-confidence. Today, many school-age children are technologically savvy and can easily use electronic patient diaries and computerized data-management tools to track bleeds and infusions, which may also increase treatment adherence.18,19

Inconvenience and scheduling barriers
Lack of time and inconvenience have been cited in surveys as primary barriers for both prophylaxis and early episodic treatment.20,21 Many parents and school-age children find it challenging to incorporate a prophylactic regimen into a busy morning schedule. The storage and administration of clotting agents also present significant barriers to early treatment. In the aforementioned CDC-sponsored survey, 25% of patients who were not “early treaters” reported that they did not have clotting agent in their possession at the time of the bleed.14 Need for refrigeration is a further inconvenience and expense for patients, particularly those on prophylactic treatment, who must carry the clotting agents in a cooler during extended stays away from home. Moreover, administration of a single dose of clotting factor may be as brief as 2–5 minutes for some formulations or greater than 50 minutes for others. Finally, most clotting agents are not stable enough for room-temperature storage and require refrigeration, and must be reconstituted at room temperature immediately before use, resulting in further treatment delays.

Distance to an HTC remains a difficult barrier to overcome, particularly for patients who live in rural areas, those with no means of transportation, and those with crippling physical disabilities. In the Hemophilia Utilization Group Study part Va (HUGS-Va) that examined the cost and burden of illness in people with hemophilia in the US, three of the most frequently cited barriers for patients in seeking treatment at an HTC were “distance to the center” (30.0%–43.8%), “clinic hours were not convenient” (26.7%–37.5%), and “transportation to center” (20.0%–31.3%).22 In the HUGS-Va study, the average distance from home to the HTC was 45.2 ± 63.6 miles (72.7 ± 102.4 km). Additional options to encourage HTC utilization are listed in Table 3.

Financial barriers
An estimated 30% of patients with hemophilia in the US are uninsured or underinsured.23 Many private insurance companies have existing lifetime caps on coverage, which patients often quickly surpass.24 Consequently, patients may incur significant out-of-pocket costs, and thus in some instances forgo necessary treatment.25 In the aforementioned HUGS-Va study, 28.3% of patients reported that the primary barrier to their seeking care in an HTC was “insurance does not pay for comprehensive care at HTCs.”22 Recently, there has been a rise in the amount of copayments for families for the clinic visits and factor prescriptions.

Hemophilic patients without inhibitors
The annual cost of episodic treatment of an adult with mild-to-moderate hemophilia (without comorbid conditions or arthropathy) in the US is estimated at $18,980.26 For patients with severe hemophilia and hemarthroses, the annual treatment cost may increase to $60,000–$200,000.24,25

Table 3 Options to encourage home infusion and hemophilia treatment center (HTC) utilization

<table>
<thead>
<tr>
<th>Home</th>
<th>HTC</th>
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<tr>
<td>• Involve children in the treatment plan from an early age so that they can assist their busy parents and begin to take responsibility for managing their own condition</td>
<td>• Greater attention to maintain contact with patient during transition periods, especially adolescent-to-adult phase</td>
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<td>• Develop regional adult clinics in cooperation with local hospitals</td>
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<td>• Reimburse patients for transportation costs</td>
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<td></td>
<td>• Encourage HTC hematologists to travel to hospitals within the state to present seminars and grand rounds to educate local medical personnel on hemophilia management</td>
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</table>

### Table 2 Instructional aids and programs to help address educational needs

- Educational and instructional CDs and DVDs
- More interactive video games, such as Nintendo Wii, which allow moderate amounts of physical activity
  - Children with hemophilia who are restricted from playing contact sports often spend much free time playing video games in lieu of participating in physical activities outdoors
- Summer camps for children with hemophilia
- Peer and mentor counseling services, where adults with hemophilia can mentor young children on coping with their condition over time
A retrospective study of US health insurance claims between 2002 and 2008 in patients with hemophilia with employer-sponsored insurance showed mean annual cost was higher for patients with hemophilia A than those with hemophilia B ($162,054 versus $127,194, P = 0.06).\textsuperscript{25} In patients with Medicaid, the mean annual cost for patients with hemophilia A was $148,215 and $113,223 for those with hemophilia B.\textsuperscript{27} Annual costs were similar for children and adults, overall.

**Hemophilic patients with inhibitors**

The cost of treating patients with inhibitors relative to patients without inhibitors varies widely in the literature, from a 1.3-fold to a tenfold higher cost, including increased clotting agent use, hospitalization, and surgery.\textsuperscript{25,28,29} The cost of care in these patients is typically more than $100,000 annually, excluding the cost of elective orthopedic surgery and immune-tolerance therapy (ITT). In the aforementioned retrospective claims study, for patients with inhibitors with employer-sponsored insurance, mean annual cost of treatment was 4.8 times higher compared to those without inhibitors ($696,279, P < 0.01);\textsuperscript{26} and for those with Medicaid, mean annual cost was 3.6 times higher ($446,945, P < 0.01).\textsuperscript{27}

**Comorbid conditions**

Comorbid conditions, such as obesity, synovitis, liver disease, HIV infection, and hepatitis C virus (HCV) infection, add substantial direct and indirect costs to the treatment of patients with hemophilia. A retrospective claims analysis of the PharMetrics database over a 7-year period determined that treatment of hemophilic patients without inhibitors coinfected with HIV and HCV was 59% more costly than uninfected patients ($696,279, P < 0.01);\textsuperscript{26} and for those with Medicaid, mean annual cost was 3.6 times higher ($446,945, P < 0.01).\textsuperscript{27}

**Prophylaxis**

In the US, approximately one-half of children with severe hemophilia A and one-third of those with severe hemophilia B are on prophylaxis, although there is considerable regional variability.\textsuperscript{33} The estimated annual cost ranges from $300,000 to $440,000,\textsuperscript{24,34} but varies depending on disease severity and inhibitor status.

Despite the demonstrated clinical benefits of prophylaxis in early childhood,\textsuperscript{34,36} compliance is markedly lower for patients on high-intensity treatment regimens, such as prophylaxis compared with episodic treatment.\textsuperscript{37} In the 2003 PPS, “high cost” was the third most frequently cited reason that respondents (45%) chose not to administer prophylaxis.\textsuperscript{15}

Despite the high cost, the use of prophylactic agents may ultimately be cost-saving, especially when compared with the combined use of ITT and episodically administered clotting agents in hemophiliac patients with inhibitors.\textsuperscript{38} One study estimated savings of $8,312–$17,675 per bleeding episode in a patient with severe hemophilia without inhibitors.\textsuperscript{39} Additional adjustments in dosing and frequency of administration have resulted in savings of more than $58,000 per patient with severe hemophilia.\textsuperscript{40}

**Immune tolerance therapy**

ITT is the primary treatment used to eliminate inhibitors in hemophilic patients. The average cost of ITT may approach or even exceed $1 million in patients with good prognostic indicators (ie, pre-ITT titers less than 10 Bethesda units and less than 5 years since inhibitor diagnosis), but can be fivefold higher in patients with poor prognostic indicators.\textsuperscript{41}

**Elective orthopedic surgery**

The most common sequela following a lifetime of bleeding episodes, especially in patients with inhibitors, is severe arthropathy. Use of walking aids and wheelchairs was more than 20% higher in patients with severe hemophilia and inhibitors aged 14–35 years (50% and 24%, respectively) compared to those without inhibitors (29% and 4%, respectively).\textsuperscript{42}

The costs of any given orthopedic procedure are related to the duration of hospitalization and replacement clotting factor consumption; for example, surgical synovectomy ($61,000) is far more costly than outpatient radiosynovectomy ($2,850).\textsuperscript{43} The average knee surgery in hemophilic patients with inhibitors, including perioperative rFVIIa coverage, costs between $694,000 for knee arthrodesis to $855,000 for total knee replacement, with proximal tibial osteotomy and distal femoral osteotomy intermediate in cost.\textsuperscript{44} Consistent with these studies, the cost of elective orthopedic surgery for patients with inhibitors (range $5000–$500,000) can be...
Quality of life
Quality of life (QoL) assessment tools are being used with increasing regularity in both clinical trials and pharmacoeconomic modeling studies to unravel the potential long-term benefits of expensive procedures, such as prophylaxis, ITT, and elective orthopedic surgery. The high cost of prophylactic therapy, for example, is weighed against improvements in QoL, days gained at work and school, reduced hospitalizations, and reduced need for surgery.46–48 The European Haemophilia Economic Study Group compared the outcomes of 1033 hemophilic patients from 16 European HTCs using prophylaxis with episodic treatment.49 The patients on prophylactic therapy reported less pain and improved health, and performed better on three of the eight measured QoL indices (mental health and physical and social functioning). In a Dutch study of 49 patients with severe hemophilia, the cohort on prophylaxis had fewer joint bleeds per year (median 2.8 versus 11.5), improved clinical scores (median 2.0 versus 8.0), and less arthropathy (median 7 points versus 16 points by Pettersson scoring) than the cohort being treated episodically, but with comparable clotting factor usage.36

A modeling analysis using a standard ITT regimen (ie, 100 IU/kg/day of FVIII for 420 days) for a prototypical 5-year-old boy with severe hemophilia and high-titer inhibitors was projected to increase his life expectancy by 4.6 years and result in a lifetime reduction in the cost of clotting agent of $1.7 million.41 Knee surgery is expected to reduce mean annual bleeding episodes at the target joint from 9.13 to 1.64 (based on efficacy studies), such that the cost of elective orthopedic surgery is offset at 8–10 years after surgery.48 Another analysis predicted that total hip replacement in a 75 kg patient experiencing one bleed per month in the target joint could result in net savings of $448,000 over 5 years when a reduction in future bleeds was considered.50

In general, findings from these studies support QoL benefits for positive outcomes in hemophilic patients undergoing prophylaxis, ITT, and elective orthopedic surgery. Patients with limited financial means should seek state, federal, and corporate financial support51,52 to take full advantage of these high-intensity, costly treatments (Table 4).

Technical barriers
The self-management of bleeds via home infusion of clotting agent requires significant commitment by patients and experienced health-care practitioners.53 Issues include finding a vein, using a nondominant hand, and dealing with fear of needles. In the 2003 PPS, difficulties with venous access was the second most frequently (60%) cited reason for respondents who chose not to administer prophylactic treatment.15

Insertion of a central venous access device alleviates many of the problems associated with home infusion of clotting agent, and is convenient for both medical personnel and patients who self-inject. A Dutch study demonstrated that hemophilic patients with a central venous access device begin prophylaxis and home treatment at an earlier age.54 Significant drawbacks to the use of many of these types of devices are increased risks of infections and thrombotic complications.54,55 Technical complications may also occur, such as a catheter that is blocked, damaged, buckled, poorly positioned, or disconnected from the port or skin erosion over the port.55,56 Suggestions to minimize infections and other complications50,55 are provided in Table 5.

Psychosocial barriers
With the recent interest in psychometric assessments of the well-being of patients with hemophilia, the psychological and social barriers to patient and parental compliance with treatment have been examined. These include denial;
fear of pain, hospitals, and needles; the parental burden of providing care along with a balance of caution and control for the child; risky behavior in teenagers; and the adolescent-to-adult transition. In some countries, viral transmission of HCV and HIV through the national blood supply has left a legacy of fear and distrust between patients and the health authorities.\textsuperscript{15,57} Parents may have a difficult time adjusting to the child’s diagnosis. In multiple surveys, “denial” and “lack of parental/family commitment” consistently ranked among the most frequent responses to why patients do not adhere to treatment regimens.\textsuperscript{15}

Every stage in a child’s development is characterized by unique life challenges that have a dramatic impact on treatment for hemophilia. The time at which a child begins school coincides with increased socialization and cognitive development. They may begin to take excessive risks to fit in with their peers and hide their bleeds, with potentially serious consequences.\textsuperscript{11} Adolescents have a reduced compliance with prophylaxis compared with younger age-groups.\textsuperscript{15,58} Even in Scandinavia, where patients with hemophilia are highly compliant, 41% of patients aged 13–25 years were noncompliant at some point during the prescribed prophylactic regimen.\textsuperscript{11} Reduced compliance with early and preventive treatment in adolescence is especially disconcerting, because learning to self-infuse is a big step toward independence and self-confidence for a patient with hemophilia.

Adults with hemophilia whose bleeds were aggressively treated when living in their parents’ home then become responsible for their own treatment. Some adult patients who had stable joints while under prophylaxis from childhood, later neglect treatment, and physicians may be treating patients with worsening arthropathy as a result.\textsuperscript{59,60} Suggestions to minimize psychosocial barriers in patients with hemophilia\textsuperscript{10,21,61} are provided in Table 6.

### Conclusion

Two of the most critical yet tractable parameters affecting the degree of arthropathy in patients with hemophilia are physical activity and the timing of treatment. Early treatment of bleeding episodes in hemophilic patients both with and without inhibitors:

1. likely delays arthropathic progression and disability\textsuperscript{2,62}
2. improves efficacy at stopping bleeds\textsuperscript{5,9}
3. results in the use of less product and is more cost-effective\textsuperscript{5}
4. delays or prevents the need for more expensive interventions later.\textsuperscript{5,6}

Understanding what prevents patients with hemophilia from seeking early treatment and determining their attitudes and preferences with respect to treatment may lead to improved compliance rates and better overall health for these patients.

Barriers and perceived limitations to early treatment in patients with hemophilia can be broadly classified

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**Table 6 Options to help overcome psychosocial barriers**

<table>
<thead>
<tr>
<th>Infants and toddlers</th>
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<tbody>
<tr>
<td>1. Coming to terms with the diagnosis of hemophilia as soon as possible</td>
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<td>2. Developing coping strategies for their new reality because hemophilia is a lifelong, chronic condition</td>
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<td>3. Developing lasting relationships with a hemophilia care team</td>
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<td>4. Finding the right hemophilia support groups</td>
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<tr>
<td>5. Distinguishing between caution and overprotection, and guiding the child’s confidence in daily activities</td>
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<tr>
<th>School-age children</th>
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<td>1. Educating the child on the basics of hemophilia at his level of comprehension</td>
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<tr>
<td>2. Stressing to the child how important it is to treat a bleed, and that he will neither get into trouble for disclosing a bleed nor be kept from his favorite risk-appropriate activity once the bleeding has stopped</td>
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<tr>
<td>3. Facilitating discussions with school officials concerning the child’s condition, the future likelihood of missed school days, the school nurse’s ability to safely inject replacement clotting factor during a bleeding episode, and systems in place in case of an emergency</td>
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<tr>
<td>4. Creating occasions for social interactions with family and friends to promote the child’s positive social development</td>
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<tr>
<td>5. Sharing any psychological and emotional strains that the condition is having on the parents and siblings, and referring them to counselors and/or support groups</td>
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<th>Preadolescent and adolescent children</th>
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<tbody>
<tr>
<td>1. Encouraging the child to actively participate in the management of their bleeds at preadolescence, leading to more autonomy and self-management at adolescence</td>
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<tr>
<td>2. Encouraging the child to avoid unnecessary risks, and setting boundaries without becoming overprotective</td>
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<td>3. Familiarizing the child with an infusion of clotting factor in the morning of any day when extra exertion will be required (eg, sporting events or field trips), whether or not they are on a prophylactic regimen\textsuperscript{10,21,61}</td>
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<tr>
<td>4. Helping the child deal with physical changes and health issues common to this age-group</td>
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<tr>
<td>5. Guiding the child through psychosocial issues such as self-esteem and social peer interactions</td>
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<tr>
<th>Adolescent-to-adult transition</th>
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<tbody>
<tr>
<td>1. Ensuring that the young adult with hemophilia who moves out of his parents’ home transitions to a new health-care provider or hemophilia treatment center, if necessary</td>
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<tr>
<td>2. Encouraging continued compliance with early treatment or prophylaxis to avoid any worsening orthopedic condition</td>
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<tr>
<td>3. Guiding the young adult to a smooth and safe transition into the workforce</td>
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<tr>
<td>4. Encouraging continued social interaction or hemophilia support groups</td>
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as educational barriers, inconvenience and scheduling barriers, financial barriers, and psychosocial barriers. While hematologists have often focused on the treatment regimens of patients with hemophilia, health-care providers need to address nontreatment concerns that affect patient compliance, particularly in the psychosocial arena.

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