Inhibitor development poses a significant challenge in the management of hemophilia because once an inhibitor is present, bleeding episodes can no longer be treated with standard clotting factor replacement therapy. Consequently, patients with inhibitors are at increased risk for difficult-to-control bleeding and complications, particularly arthropathy and physical disability. Three clinical trials in patients with inhibitors have demonstrated that prophylaxis with a bypassing agent reduces joint and other types of bleeding and improves health-related quality of life compared with on-demand bypassing therapy. In hemophilia patients without inhibitors, the initiation of prophylaxis with factor (F) VIII or FIX prior to the onset of recurrent hemarthroses can prevent the development of joint disease. Whether this is also true for bypassing agent prophylaxis remains to be determined. (Blood. 2015;126(2):153-159)

Clinical case: part 1

R.D. is a 6-year-old boy who was diagnosed at birth with severe hemophilia A. At age 30 months, following 11 exposure days (EDs) to recombinant factor VIII (rFVIII) concentrate for soft tissue and joint bleeding, he developed an inhibitor (peak titer: 250 Bethesda units [BU]). Immune tolerance induction (ITI) was recommended to eradicate the inhibitor but was delayed to allow the inhibitor titer to drop to <10 BU. In the interval before ITI started, infrequent bleeding episodes were treated on-demand with recombinant activated factor VII (rFVIIa; Novo Seven, Novo Nordisk). rFVIIa was also used to provide perioperative hemostasis for placement of a subcutaneous port to facilitate regular factor (F) VIII infusions for ITI.

Eight months after inhibitor diagnosis, when the titer was 8 BU, ITI was initiated with rFVIII, continuing with the same product previously used to treat acute bleeding, at a dose of 200 IU/kg per day. During 30 months of treatment, the child experienced 2 episodes of port-related sepsis and occasional soft-tissue bleeding but no hemarthroses. His inhibitor titer peaked at 300 BU then gradually decreased, but it never fell below 20 BU. ITI was deemed a failure, and the port was removed.

Overview of inhibitor development and initial management

Follow-up exposure to clotting factor replacement therapy, up to 30% of patients with severe hemophilia A1 (baseline FVIII activity <1% of normal) develop immunoglobulin G alloantibodies that bind to functional domains on the FVIII molecule and inhibit or neutralize its clotting function.2 Most FVIII alloantibodies (ie, inhibitors) develop early in life, with risk highest during the first 50 EDs to clotting factor concentrate and the majority occurring between 10 to 20 EDs.3 Inhibitors to FIX are uncommon, occurring in <5% of patients with severe hemophilia B.4 Anti-FIX antibodies are difficult to manage and often require treatment strategies distinct from those used to treat FVIII inhibitors. This article will primarily focus on the management of patients with FIX inhibitors. FIX inhibitors pose unique challenges, with the majority of patients developing anaphylactic reactions to FIX replacement that complicate treatment decisions.

An inhibitor should be suspected whenever a bleeding event is not promptly controlled by a patient’s usual replacement dose of clotting factor.5 Alloantibodies may also be detected on laboratory screening done as part of a routine comprehensive assessment at a hemophilia clinic visit. Inhibitors are quantified by the Bethesda assay or a modification of this assay (ie, Nijmegen modification). One BU is defined as the amount of inhibitor needed to inactivate 50% of FVIII in an equal volume of pooled normal plasma.5

Inhibitors are classified as high titer (≥5 BU) or low titer (≤5 BU). Acute bleeding in the presence of a high-titer inhibitor cannot be controlled with FVIII, regardless of dose, and bypassing agents that circumvent the need for FVIII (ie, activated prothrombin complex concentrate [aPCC; factor eight inhibitor bypassing activity (FEIBA), Baxter] or rFVIIa) are used for hemostasis.6 Low-titer inhibitors can usually be overcome by supratherapeutic doses of clotting factor concentrate that sufficiently raise circulating FVIII levels and halt bleeding.6 Inhibitors are also classified as high or low responding on the basis of the Bethesda titer and the nature of the anamnestic response. High-responding inhibitors, which account for ~70% to 80% of all FVIII inhibitors,6 are defined by a peak titer >5 BU following exposure to FVIII (anamnesis).7 In many cases, the inhibitor titer will fall below 5 BU when a patient is not exposed to FVIII for a period of time, and FVIII concentrates may once again be used to control bleeding. However, such treatment is reserved for life- or limb-threatening hemorrhage, as the duration of hemostatic efficacy is limited by the anamnestic response, which generally occurs within 6 to 7 days after resuming FVIII replacement therapy.8 Low-responding inhibitors always measure ≤5 BU, are not anamnestic,9 and may be transient.6

The presence of an inhibitor does not generally change bleed site or frequency, but it makes bleeding more difficult to control because patients no longer respond to factor replacement therapy,7 thus increasing the risk for severe and/or protracted hemorrhage. Poorly controlled joint bleeding, the most common site of bleeding associated with severe hemophilia,10 can result in significant arthropathy.11 However, corrective orthopedic surgeries are less likely to be performed in
patients with inhibitors owing to higher operative bleeding risk. As a result, these individuals are more likely to have mobility impairment, permanent disability, and reduced health-related quality of life (HRQoL) compared with hemophilia patients without inhibitors. In persons with inhibitors are also at heightened risk for other types of poorly controlled bleeds, such as intracranial hemorrhage, soft tissue/muscle bleeds leading to compartment syndrome, and gastrointestinal hemorrhage, all of which are potentially life and/or limb threatening.

Bypassing agents are used to control bleeding in patients with high-titer or high-responding inhibitors. Both aPCC and rFVIIa achieve hemostasis by generating thrombin (in the absence of FVIII or FIX) at the site of bleeding. Although their precise mechanisms of action are not fully understood, a key target site of action of FEIBA is the prothrombinase complex, in which thrombin is converted into thrombin by FXa on a phospholipid surface, whereas rFVIIa activates sufficient FX on activated platelets to restore platelet surface thrombin generation. The 2 available agents differ with respect to their biochemical properties and pharmacokinetics, with rFVIIa having a shorter half-life of ~2 hours compared with 4 to 7 hours for aPCC (as measured by thrombin generation). Additionally, rFVIIa is a recombinant product, whereas aPCC is plasma derived and contains trace amounts of FVIII that may lead to an anamnestic rise in FVIII in ~20% of patients. Both agents can be thrombogenic when given in large, repetitive doses that exceed dosing recommendations or used in tandem (ie, sequential therapy). Dosing for these agents was empirically derived based on original efficacy studies performed during bleeding episodes, as no laboratory assay is available to monitor blood levels or guide dosing. A randomized crossover trial of aPCC and rFVIIa in patients with inhibitors demonstrated comparable efficacy in treating joint bleeding: 80.9% and 78.7%, respectively, at the primary end point 6 hours after the initial dose. However, substantial interpatient variability was observed, with 30% of patients reporting that 1 product was more effective than the other. These findings confirmed long-standing clinical observations that some patients respond better to 1 bypassing agent than the other and reinforce the importance of using an individual’s response to guide product selection.

Neither aPCC nor rFVIIa is as predictably effective in controlling bleeding in individuals with inhibitors as is clotting factor replacement therapy in hemophilia patients without inhibitors. Thus, an attempt at alloantibody eradication through ITI is undertaken in nearly all patients with hemophilia A who develop a high-responding inhibitor. The goal of ITI is to reestablish immunologic tolerance to FVIII, restore normal replacement FVIII pharmacokinetics, and allow the use of FVIII concentrates to treat and prevent bleeding.

According to data from large ITI registries published over the past 20 years and an international randomized trial evaluating optimal dosing, an estimated 50% to 80% of patients undergoing ITI using a wide variety of FVIII products and regimens ultimately achieve tolerance. Because an inhibitor titer measuring <10 BU before the start of ITI was identified as the most powerful predictor of successful outcome in the 2 largest registry studies, most treaters delay the start of ITI for up to 1 year to allow very high-titer inhibitors to fall below 10 BU (or to their lowest level). In a recently completed trial in patients at “good risk” for achieving tolerance, both high-dose (FVIII 200 IU/kg per day) and low-dose (FVIII 50 IU/kg thrice weekly) regimens had an overall success rate of 70%. However, time to achieving an undetectable inhibitor titer was significantly shorter and breakthrough bleeding less likely to occur with a high-dose regimen. Patients with peak inhibitor titers >200 BU are difficult to tolerate, and ITI is often unsuccessful in these individuals.

Clinical case: part 2

Shortly after discontinuing high-intensity ITI, R.D. began to experience repeated right knee bleeds (43 hemarthroses in 2 months) that were treated on-demand with rFVIIa. Upon resolution of each hemorrhage, he had normal range of motion but persistent mild joint swelling suggestive of early synovitis. Because the child was at high risk for progressive, irreversible joint disease, his parents agreed to a trial of bypassing agent prophylaxis (BAP). To avoid the potential infectious complications associated with an in-dwelling line, they were taught peripheral infusion techniques. aPCC was selected for prophylaxis because it can be initiated thrice weekly, rather than daily for rFVIIa, thus reducing the likelihood that a central venous access device (CVAD) will be needed. Physical therapy was recommended 3 times weekly, with each session to follow an infusion of aPCC.

Prevention of bleeding with bypassing therapy

Inhibitor eradication ultimately proves unsuccessful in up to 50% of patients, and some individuals are not candidates for or refuse ITI. Thus, high-responding inhibitors are permanent for a substantial number of patients, and bypassing therapy is needed to manage bleeding. In hemophilia patients without inhibitors, prophylaxis, defined as the regular, ongoing (≥45 week/year) replacement of the deficient clotting factor, is considered optimal care for patients with severe hemophilia without inhibitors, particularly for children who have not yet developed repeated joint bleeding or joint disease. Prospective clinical trials have demonstrated the ability of FVIII prophylaxis to reduce joint and other bleeding, including limb-threatening soft tissue bleed and life-threatening central nervous system hemorrhage. By decreasing bleeding risk, prophylaxis allows children with hemophilia to participate in most normal childhood activities and appreciably lowers the incidence of joint disease in adulthood. Prophylaxis also reduces absences from school or work; improves academic performance and productivity; decreases the need for emergency room visits, hospitalization, and orthopedic interventions and other surgeries; and improves HRQoL.

Compared with hemophilia patients without inhibitors, those with inhibitors are at even greater risk for the development of target joint bleeding, end-stage arthropathy, and life- and limb-threatening hemorrhage. The ability to prevent bleeding in these individuals could, therefore, result in even greater gains in clinical outcomes and HRQoL. Beginning in the mid-1970s, anecdotal reports began to appear describing decreased joint bleeding and improved mobility in a small number of inhibitor patients treated every other day with early prothrombin complex concentrate products. In 1993, a large HRQoL study conducted in the European Union was published and showed that 15% of patients with inhibitors were using some form of BAP. Subsequently, a growing number of small case series and retrospective reports suggested that rFVIIa or aPCC given at regular intervals reduced bleeding frequency. The treatment strategies detailed in these reports varied widely, however, making it difficult to assess the true prophylactic potential of these agents.

Over the past decade, 3 prospective trials of BAP have been completed and showed that prophylaxis with rFVIIa or aPCC reduced joint and other types of bleeding and improved HRQoL, as compared with on-demand bypassing therapy, in hemophilia patients with inhibitors (Table 1). In the study of rFVIIa prophylaxis, adult and pediatric patients were treated on-demand during a 3-month pre-prophylaxis period. Those with ≥12 bleeds were randomized to receive daily rFVIIa prophylaxis for 3 months at 1 of 2 doses: 90 μg/kg
or 270 μg/kg.55 Bleeding frequency was reduced by 45% with the 90 mcg/kg dose vs 59% for the 270 μg/kg dose, a nonsignificant difference. At the end of the prophylaxis period, patients reported significantly fewer hospital admissions and days absent from school/work as well as reduced pain and increased mobility. Based on the results from this trial, prophylaxis with rFVIIa is generally initiated at a daily dose of 90 mcg/kg.

Two randomized controlled trials have evaluated aPCC prophylaxis in inhibitor patients.56,57 The first of these, the crossover PROFEIBA study, was conducted in adult and pediatric patients with ≥6 bleeds in the 6 months prior to study enrollment, most of whom had a history of significant joint damage and target joint bleeding.56 As compared with 6 months of on-demand therapy, 6 months of aPCC prophylaxis at a dose of 85 U/kg thrice weekly significantly reduced all bleeding events by 62% and joint bleeding by 61%. More than 60% of patients were good responders, experiencing >50% reduction in bleeding, and 24% had no bleeding during the 6-month prophylaxis period. Furthermore, joint function stabilized or improved during prophylaxis in all of the good responders, and they missed significantly fewer days from work or school (P = .01). In the second aPCC trial (the PROOF [Peripherally inserted central catheter Related Obstruction Of Flow] study), adult and pediatric patients were randomized to receive 12 months of aPCC 85 U/kg every other day or on-demand therapy. Bleeding was reduced in the prophylaxis arm by 72% (P = .0003). On the basis of the findings from these 2 randomized controlled trials, aPCC prophylaxis is typically initiated at a dose of 85 U/kg 3 times weekly. This regimen is effective for many patients, but some may benefit from increasing dose intensity to every other day.

Once BAP is initiated, patients are monitored clinically every 3 to 6 months, with the treatment regimen modified as appropriate. If breakthrough bleeds occur, we generally treat with the same bypassing agent used for prophylaxis, although in some cases, the alternative agent may work better. When switching between bypassing agents, we recommend waiting a minimum of 6 hours after aPCC administration before infusing rFVIIa and a delay of at least 2 hours after rFVIIa administration before infusing aPCC.19

Figure 1 presents an algorithm for implementing BAP.

### Clinical case: part 3

Three months after starting aPCC prophylaxis (85 U/kg thrice weekly), R.D. and his family returned to the hemophilia clinic for a follow-up visit. Although bleeding frequency has decreased, he has had 2 hemarthroses in the previous 3 months, indicating a need to modify the prophylactic regimen. The recommendation was to continue aPCC prophylaxis but shorten the dose interval to every other day and continue with peripheral infusions to avoid placement of an indwelling line.

Following 3 months of every-other-day aPCC prophylaxis at 85 U/kg, the child has experienced no further breakthrough bleeding and has completed a course of physical therapy. Physical examination of his right knee is normal. The immediate plan is to continue with this prophylactic regimen for an additional 3 months. If breakthrough bleeding persists, consideration will be given to advancing to daily prophylaxis with rFVIIa. If no joint bleeding occurs, the resumption of thrice-weekly dosing will be considered.

### Implementing BAP

#### Early BAP before the onset of joint disease

In young children with normal or near-normal joints who have failed ITI and are likely to have a permanent inhibitor, the goal of prophylaxis is to prevent joint bleeding and preserve joint health. Treatment should be pursued aggressively; at the same time, it must be balanced against the need for frequent infusions and placement of an indwelling line. As is true for FVIII and FIX prophylaxis, BAP that is successful should be continued indefinitely.

Although BAP has been shown to reduce hemarthroses and other bleeding episodes, clinical trials to date have been of relatively short duration and enrolled many patients with preexisting joint disease, meaning that the impact of BAP on patients with normal joints is unclear.55-57 However, case series of children with inhibitors who started BAP at a young age and were followed for a median duration...
of >6 years demonstrated a very low annual joint bleed rate of 1.5. These findings suggest that when BAP is started prior to the development of arthropathy, treatment may prevent or mitigate progressive joint damage.

**BAP before and during ITI.** BAP should be considered for very young, newly diagnosed inhibitor patients experiencing joint bleeding in the interval before ITI is initiated. In this setting, rFVIIa is often the preferred agent for both prophylaxis and acute bleed management, as aPCC has the potential to induce anamnesis in some patients, causing inhibitor titers to rise and possibly delay the onset of ITI. Although an indwelling line will likely be needed, because rFVIIa is administered daily, young children may require a CVAD with any regimen requiring frequent infusions, including ITI.

High intensity ITI regimens using daily FVIII are associated with reduced bleeding and may be effective in preventing hemarthroses without the addition of BAP. For patients who continue to experience joint bleeding on ITI, consideration should be given to adding BAP, with the choice of product based on previous efficacy in that individual, if known. To reduce thrombotic risk, the bypassing agent is typically infused several hours before or after FVIII administration. When the sequential administration of BAP and FVIII is unavoidable, the usual preference is to begin with FVIII, which will be rapidly cleared by circulating alloantibodies, followed by the bypassing agent. In between infusions, the line should be thoroughly flushed. Once the inhibitor titer falls below 5 BU and/or FVIII recovery is demonstrated, BAP should be discontinued to avoid the excess thrombogenicity associated with the administration of bypassing therapy to a patient with circulating FVIII.

**Prophylaxis after the onset of repeated joint bleeding or joint disease.** For patients like R.D. who fail ITI and experience joint bleeding, a trial of BAP is warranted. Key issues to consider when selecting a bypassing agent include the desire to avoid an indwelling line (a choice that favors the less frequently administered aPCC) balanced against which agent has demonstrated greatest efficacy in treating bleeds in a given patient. A reasonable strategy is to start with the regimen that allows peripheral administration and modify it based on the patient’s clinical response.

Many hemophilia patients without inhibitors benefit from prophylactic treatment started after the onset of repeated joint bleeds or even early joint disease. In these individuals, secondary prophylaxis can reduce joint and other bleeding episodes; slow the progression of, although not reverse, existing joint damage; allow physical therapy; permit participation in sports and other activities; and improve HRQoL. These benefits of secondary prophylaxis also appear to extend to BAP.

Secondary BAP is typically initiated with a 3-month trial using the bypassing agent that has historically been most effective in treating hemarthroses in a particular individual. If this trial is successful at reducing or eliminating joint and other bleeding, synovitis, and pain and improving quality of life, consideration should be given to continuing BAP long term.

**Considerations in the application of BAP**

Although accumulating evidence suggests that BAP effectively prevents bleeding in hemophilia patients with inhibitors, several issues deserve consideration before embarking on this treatment strategy.

**Central venous access.** Peripheral venipuncture is preferred for the administration of replacement clotting factor. However, a CVAD (either a tunneled, fully implantable, subcutaneous port or a tunneled, external catheter) may be needed as a bridge to venipuncture in infants and children, whose small peripheral veins are difficult to access, and occasionally in older children or adults requiring very frequent (ie, daily) peripheral venous access to administer clotting factor. CVADs make regular infusion of clotting factor feasible for some patients but are not without risks.

Infection is the most common complication associated with CVADs. The presence of an inhibitor increases this risk, possibly attributable to the heightened propensity for subcutaneous bleeding around ports that facilitates entrance of bacteria through the skin. A meta-analysis of 48 studies that included 2704 hemophilia patients and 2973 CVADs showed that 44% of patients and 40% of CVADs were affected by an infectious episode, and that infection was the most common cause for device removal.

Thrombosis is the second most common complication linked to CVADs. In the previously described meta-analysis, the risk for this adverse event did not differ among inhibitor and noninhibitor patients. However, our personal experience indicates that thrombosis may be of greater concern in some inhibitor patients treated with BAP. Thorough catheter flushing following prophylactic infusions and leaving CVADs in place for the shortest possible time reduce the risk for thrombosis.

**Cost.** The cost of FVIII prophylaxis in hemophilia patients without inhibitors is 2.4 to 3.1 times that of on-demand therapy. Similarly, in the randomized crossover study of aPCC prophylaxis, the cost of 6 months of treatment was 2.4 times greater when aPCC was used prophylactically thrice weekly, as compared with on-demand treatment. The cost of every-other-day aPCC dosing or daily rFVIIa prophylaxis has not been reported but is expected to be higher. It is important to recognize, however, that these costs do not reflect the potential benefits of avoiding hospitalizations and days lost from school or work and preventing long-term complications, such as arthropathy and disability, nor do they take into account the enhanced HRQoL reported by patients receiving prophylaxis.

**Adherence.** Poor adherence to treatment is a major impediment to optimizing FVIII or FIX prophylaxis in hemophilia patients without inhibitors. A global survey of practice patterns identified disease denial; lack of parental or family commitment; failure to understand the potential benefits of prophylaxis; and the time-consuming nature of regular infusions, which can interfere with
other family needs and social obligations, as challenges to full adherence.71 Although no similar surveys have been conducted with respect to BAP, we believe these same issues adversely impact adherence in patients with inhibitors. Ongoing education and support provided by the hemophilia treatment team are key to encouraging patients and families to make the long-term commitment to a demanding treatment regimen.

Discussion

Prior to the widespread use of FVIII and FIX prophylaxis, most patients with severe hemophilia experienced an average of 1 to 2 hemarthroses per month and had ≥1 end-stage joints by adulthood.30 For patients with inhibitors, joint disease has been an even greater problem. In a study of 2378 children with hemophilia aged 2 to 19 years, loss of joint range of motion was more than twofold greater among the 186 children with inhibitors ≥0.5 BU at the time of joint measurement.72 Although the average loss of function in this group of young patients was a modest 5%,72 in a study of slightly older inhibitor patients, joint function was significantly more impaired.73 Only 2.3% of 122 patients (mean age: 22.4 years) with severe hemophilia A without inhibitors had measurable abnormalities in all 6 joints (ie, ankles, knees, and elbows) evaluated, as compared with 22.7% of 22 patients (mean age: 21.2 years) with persistent inhibitors. Finally, a study of 52 older adults with inhibitors (mean age: 36 years) found that 80% were physically disabled, and more than 70% had impaired mobility resulting from end-stage joint disease.74 These studies clearly demonstrate that among patients with inhibitors, predictable and progressive joint disease begins in childhood and worsens with age, with older adults experiencing significant orthopedic disabilities. Optimal interventions to prevent joint bleeding should primarily be aimed at children who have not yet developed irreversible joint changes.

Because inhibitor patients constitute a small subset of persons with hemophilia, itself a relatively rare disorder, adequately powered clinical trials are difficult to accomplish. Nevertheless, 3 trials of BAP have been completed to date in this patient population, and all showed that bypassing agents given on a regular basis using a variety of regimens can reduce joint and other bleeding events by up to 70% and improve HRQoL.55-60 Most of the subjects were older and had a history of frequent hemarthroses and/or evidence of arthropathy at the time of study entry. To truly assess the magnitude of the protective effects of BAP, it is necessary to evaluate each bypassing agent in young inhibitor patients with normal joints and a negative history of joint bleeding. Such clinical trials will require major resources and, as was true for other prospective trials in inhibitor patients, will almost certainly necessitate international recruitment. In the absence of specific clinical trial data on joint outcomes, most treaters assume that patients on BAP who achieve significant bleed reduction are likely to experience long-term benefits.

In selecting a bypassing agent for prophylaxis, rFVIIa is generally preferred before ITI and may also be used in patients whose bleeds respond well to this agent and who are likely to manage the risks of an indwelling line. In addition, some parents/patients express a strong preference for a recombinant product, although reassurance can be given about the effectiveness of current methodologies used to ensure pathogen safety of aPCC.75 For most other patients, prophylaxis is initiated with aPCC because of the convenience of less frequent dosing and the potential for avoiding CVAD placement. Regardless of product choice, once BAP is initiated, patients should be monitored after 3 months to ensure that they are achieving optimal benefits and are adhering to the dosing schedule. Reviewing treatment logs can be helpful in elucidating the cause(s) of breakthrough bleeding. If, for example, bleeds typically occur after a scheduled dose is missed or on the third day of a thrice-weekly regimen, adjusting the dosing schedule may be appropriate. Nontraumatic bleeding developing within 12 hours of a prophylactic dose may indicate the need to switch to the other bypassing agent. Although the initiation of BAP is based on evidence gained from clinical trials, appropriate adjustments must be predicated on clinical judgment and careful follow-up.

In conclusion, patients with hemophilia A and inhibitors experiencing recurrent joint bleeds or limb- or life-threatening bleeding may be candidates for BAP with rFVIIa or aPCC. Response to prophylaxis is monitored clinically, and breakthrough joint bleeding is managed by increasing dosing frequency or switching to the alternate bypassing agent. Because of its potential to reduce joint and other bleeding episodes, BAP should be continued indefinitely and halted only when treatment is ineffective, problems develop with an indwelling line, or adverse drug reactions occur.

Acknowledgment

Michele Grygotis, an independent consultant, provided medical writing services that were funded by Tulane University School of Medicine.

Authorship

Contribution: All authors contributed to writing, reviewing, and editing the manuscript.

Conflict-of-interest disclosure: C.A.L. has received research funding from Baxter, Bayer, Biogen, CSL Behring, and Novo Nordisk and has received honoraria for advisory board participation from Baxter, Bayer, Biogen Idec, CSL Behring, Kedrion, Novo Nordisk, Pfizer, and Roche. T.S. has received research funding from Baxter and Biogen and consulting fees from Baxter, CSL Behring, and Novo Nordisk. R.K.-J. has received research support from Baxter Bioscience and Biogen Idec and has received honoraria for advisory board participation and consulting fees from Baxter Bioscience, Bayer Healthcare, Biogen Idec, Grifols, and Novo Nordisk.

Correspondence: Cindy A. Leissinger, Tulane University School of Medicine, 1430 Tulane Ave, New Orleans, LA 70112; e-mail: cleissi@tulane.edu.
References


18. Harwood CA, Buxton DL, Ewing NP, Valentin LA. Prophylaxis with activated prothrombin complex concentrate (FEIBA) reduces the frequency of bleeding episodes in...


How I use bypassing therapy for prophylaxis in patients with hemophilia A and inhibitors

Cindy A. Leissinger, Tammuella Singleton and Rebecca Kruse-Jarres

Updated information and services can be found at:
http://www.bloodjournal.org/content/126/2/153.full.html

Articles on similar topics can be found in the following Blood collections
  Clinical Trials and Observations (4514 articles)
  Free Research Articles (4439 articles)
  How I Treat (194 articles)
  Thrombosis and Hemostasis (1059 articles)

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml