QUESTION 52
A 47-year-old man with severe haemophilia A and a high titre factor VIII inhibitor is scheduled for hip replacement surgery. The peri-operative replacement coagulation product of choice is:

A. recombinant activated factor VII.
B. recombinant factor VIII.
C. recombinant factor IX.
D. fresh frozen plasma.
E. cryoprecipitate.

Haemophilia
The hemophilias are a group of related bleeding disorders that most commonly are inherited. Inherited bleeding disorders include abnormalities of coagulation factors as well as platelet function; the most common of these disorders is von Willebrand disease. However, when the term "hemophilia" is used, it most often refers to one of the following two disorders:
- Factor VIII deficiency (hemophilia A)
- Factor IX deficiency (hemophilia B, Christmas disease)

Management

PREVENTIVE AND COMPREHENSIVE CARE —
- Circumcision — Approximately 50 percent of undiagnosed hemophilics bleed in association with circumcision. For this reason, male infants born to known or suspected carrier mothers should not be circumcised until hemophilia has been excluded.
- Routine immunizations — Routine immunizations, such as diphtheria-tetanus-pertussis or measles-mumps-rubella, may be given in the deep subcutaneous tissue or via the usual route. The smallest gauge needle should be used and pressure and ice applied to the site for three to five minutes post injection.
- Hepatitis B vaccine should be given to all infants with hemophilia as soon after birth as possible, while hepatitis A vaccine is given after the age of one year.
- Dental care — Dental care is essential for individuals with congenital bleeding diatheses.
- Counseling and education

REPLACEMENT THERAPY — Clotting factor concentrates are given to prevent bleeding and to limit existing hemorrhage. Dosing is reasonably standard, but the choice of product and the use of primary and secondary prophylaxis require expert intervention. Treatment of patients with inhibitors requires considerable expertise.

Patients with hemophilia, particularly those with severe disease, develop bleeding episodes that are treated with replacement of the missing factor (ie, factor VIII or factor IX concentrates). A complication of hemophilia is the development of an inhibitor which usually occurs shortly after replacement therapy has been initiated. The inhibitors are antibodies (primary IgG) directed against the specific deficient factor.

INHIBITORS IN HEMOPHILIA A — The development of inhibitors is more common in patients with hemophilia A than in those with hemophilia B.

Incidence — Factor VIII inhibitors have been reported in approximately 25 percent of patients with severe hemophilia A.

Predisposing factors
- Severe disease - the virtual complete lack of circulating factor VIII in patients with severe disease prevents the induction of tolerance and predisposes them to antibody formation after exposure to normal factor VIII. The concept that self factor VIII, even if altered, contributes to tolerance to factor VIII is supported by the lower frequency and often transient nature of inhibitors in patients with less severe hemophilia A.
• Product-related factors can lead to inhibitor formation with certain preparations. This possibility should be suspected when antibodies first form in multiply-transfused patients who have been switched to a new product.
• Patient age at the time of initial replacement treatment, as well as the early use of prophylaxis, may influence inhibitor formation.

Clinical manifestations — The clinical manifestations of factor VIII antibodies in patients with hemophilia A depend in part upon the severity of the disease. In general, the inhibitor does not lead to a marked increase in the frequency of bleeding events except when a moderate or mild deficient patient is converted to a more severe state. However, patients with inhibitors have more difficulty in controlling hemostasis and tend to have more musculoskeletal complications; in this setting, the bleeding frequency may increase due to the presence of acute and chronic synovitis.

Inhibitors make the treatment of bleeding episodes more difficult. Thus, an inhibitor should be suspected when any bleeding episode is refractory to usual therapy, particularly in patients with severe hemophilia.

Mechanism of action — The alloantibodies formed after exposure to factor VIII concentrates are directed against specific epitopes on the factor VIII molecule. Factor VIII consists of a heavy chain with A1 and A2 domains, a connecting region with a B1 domain that is not required for clotting, and a light chain with A3, C1, and C2 domains. Most antibodies are directed against the C2 [27,28], A2 [27,29,30], and other light chain epitopes that include the A3 domain [27,31]. In one series of 34 patients with hemophilia A, more than 80 percent had two or more inhibitor antibodies (A2, C2, and other light chain epitopes A3-A2-C1) whether treated with plasma or recombinant factor VIII [27]. The antibodies were directed against C2 in 82 percent, A2 in 70 percent, and both in 25 percent. This pattern is different from that in patients without hemophilia who form autoantibodies against factor VIII: these patients are more likely to have a single antibody, directed particularly against C2 [27].

Proteolysis — Some antibodies have direct catalytic (proteolytic) activity against factor VIII [39]. In one study, significant proteolytic activity against human factor VIII was detected in 13 of 24 patients with severe hemophilia A and factor VIII inhibitors [40]. The rate of hydrolysis of factor VIII by purified IgG from these patients correlated positively with its factor VIII neutralizing activity.

Diagnosis — Factor VIII inhibitor activity generally is measured by the Bethesda assay, which both establishes the diagnosis of a factor VIII inhibitor and quantifies the antibody titer.

Treatment — Comprehensive Hemophilia Treatment Centers provide expertise for these specialized patients and should be consulted for the development of any treatment plan in a hemophilic patient with an inhibitor. The two components to therapy are
• treatment of active bleeding and
• inhibitor ablation via immune tolerance induction.

Active bleeding — The general approach to the treatment of bleeding episodes in patients with hemophilia A and inhibitors requires knowledge of the inhibitor type (high versus low responding): In patients with usual bleeding episodes involving the joints and muscle who are high responders, inhibitor bypassing products are generally employed regardless of the present inhibitor titer. Bypassing products include prothrombin complex concentrates (PCCs, or the original factor IX complex concentrates) and their activated counterparts (APCCs: FEIBA® and Autoplex®, and recombinant human factor VIIa (NovoSeven®)). PCCs and APCCs may be associated with reactions due to activation of the complement and bradykinin systems when infused rapidly, as well as other complications such as frank thromboembolic events, myocardial infarction, and disseminated intravascular coagulation. NovoSeven does not produce an anamnestic antibody response and markedly reduces the risk of disseminated intravascular coagulation and thrombosis due to its mechanism of action, which provides more localized hemostatic control at the site of injury or bleeding. In patients with life or limb threatening episodes, the present inhibitor titer is used to determine the appropriate infusion therapy regardless of inhibitor type (high versus low responding). In such patients, an immediate human and porcine factor VIII inhibitor titer should be established to determine if human or porcine factor VIII will provide hemostasis. These patients are best managed by a comprehensive hemophilia center experienced in the management of such patients.

High purity factor VIII concentrates — Although high purity factor VIII concentrates can be used in patients with low inhibitor levels (<10 Bethesda units), their main use is in the treatment of life-threatening hemorrhage or
emergency surgery in patients with low inhibitor levels or moderate inhibitor levels that have been reduced by plasmapheresis or immunoabsorption. In these settings, physiologic factor VIII levels can be attained before the anamnestic response occurs.

Porcine factor VIII concentrates — Porcine factor VIII is used primarily to treat patients who are high responders with high human factor VIII inhibitor titers and porcine factor VIII titers less than 10 Bethesda units who have life threatening episodes.

The administration of porcine factor VIII can be associated with hypersensitivity reactions in 1 to 2 percent of patients, mostly in those treated with higher doses.

Prothrombin complex concentrates and activated prothrombin complex concentrates — Manufacturers of the prothrombin complex concentrates (PCCs) increased the concentration of active proteases, resulting in production of activated prothrombin complex concentrates (APCCs); the latter preparations include FEIBA® and Autoplex®

Since the activated proteases that account for the procoagulant activity of APCCs are short-lived, initial hemostasis may be followed by breakthrough bleeding between doses that may create difficulty for maintenance of hemostasis. In addition, both PCCs and APCCs are associated with a risk of thrombosis, including myocardial infarction, which is most likely to occur when large doses are given. Other risk factors include crush injuries, surgery, and liver function abnormalities, leading to a decreased ability to clear activated products.

In summary, therapy with PCCs or APCCs is expensive, provides unpredictable hemostasis without the ability to monitor clinical efficacy with a laboratory test, and carries the risk of significant complications.

Recombinant human factor VIIa — Recombinant human factor VIIa (NovoSeven®, rFVIIA) produces an excellent or effective response in over 90 percent of patients. Because factor VIIa requires tissue factor to be active, it promotes coagulation only at the local level and should minimize the risk of systemic coagulation seen with PCCs and APCCs. The usual dose is 90 microg/kg at two to three hour intervals until hemostasis is achieved, with further dosing and lengthening of the interval based upon the patient's clinical circumstances.

A starting dose of 90 microg/kg is used in patients undergoing surgery.

Immune tolerance induction — Long-term management of hemophilic patients with factor VIII inhibitors is aimed at eliminating the inhibitors. The primary method used is the attempt at immune tolerance induction (ITI) via the administration of repetitive doses of factor VIII with or without immunosuppressive therapy. Many responders have an initial rise in antibody titers caused by the anamnestic response, followed by a progressive reduction to a low or undetectable titer [3,65]. Immune tolerance usually must be maintained by continued exposure to factor VIII.

INHIBITORS IN HEMOPHILIA B — The incidence of factor IX inhibitors in hemophilia B is much lower than that seen with factor VIII inhibitors in hemophilia A. The estimated incidence is 3 to 5 percent in patients with severe hemophilia B but is population-dependent.

In addition to diminished responsiveness to factor IX concentrates, patients with factor IX inhibitors also are at risk for anaphylaxis following factor IX infusion.

Diagnosis — As in factor VIII deficiency, an inhibitor is suspected in patients with factor IX deficiency when they fail to respond to infusion therapy or when an anaphylactic reaction occurs. The diagnosis should be confirmed in the laboratory with a Bethesda assay for factor IX.

Treatment — A family history of inhibitors in factor IX deficient patients should lead to the utmost caution when treating any newly diagnosed patient. It has been recommended that the first 20 infusions of factor IX be administered where facilities for resuscitation are immediately available in patients with severe disease and a known high-risk mutation or when the mutation is unknown.
Active bleeding — The optimal therapy of active bleeding should be determined by the treatment center. In patients without anaphylaxis, PCCs or APCCs can be given, although they will lead to continued stimulation of antibody production. There is also a risk of thrombosis, including myocardial infarction.

Immune tolerance induction — Immune tolerance induction (ITI), similar to that described above for patients with factor VIII, can be attempted.

FRESH FROZEN PLASMA — Fresh frozen plasma (FFP) is prepared from single units of whole blood or from plasma collected by apheresis techniques. It is frozen at -18 to -30°C within eight hours of collection and, when appropriately stored, is usable for one year from the date of collection. Standard FFP units derived from a single unit of whole blood have a volume of about 250 mL; "jumbo" units prepared by hemapheresis may be as large as 800 mL.

FFP contains all of the coagulation factors and other proteins present in the original unit of blood, slightly diluted by the citrate-containing anticoagulant solution used to collect the blood. FFP is not a concentrate of any of the circulating plasma proteins, and, in general, should not be used to treat coagulation defects caused by known deficiencies of a single factor, or for replacing factors better provided in concentrated form (eg, factor VIII concentrates for hemophilia A). FFP should not be used as a source of albumin or other nutrients, or as a volume expander.

Dose and indications — As a general rule, hemostasis can be achieved when the activity of coagulation factors is at least 25 to 30 percent of normal, in the absence of an inhibitor such as heparin, and when the level of fibrinogen is at least 75 to 100 mg/dL.

Indications for the use of FFP must be carefully followed: FFP may be needed
- For inherited factor XI deficiency
- as a source of factor V in severe cases of disseminated intravascular coagulation (DIC) when platelet concentrates and cryoprecipitate do not correct the factor V, VIII, and fibrinogen consumption defects.
- to correct a bleeding condition caused by a deficiency of multiple coagulation factors, such as is seen in warfarin overdose, vitamin K deficiency, liver failure, or dilutional coagulopathy following massive transfusion
- FFP should not be used as primary therapy for a specific coagulation defect (eg, hemophilia A, hemophilia B, factor VII or XIII deficiency) when specific coagulation factor concentrates are available.

Limitations — Given that the INR of FFP units can be as high as 1.3, transfusion of FFP will have little effect on minimally elevated INRs.

Side effects —
- Infections
- TRALI
- Allergic reaction, rigors
- Anaphylactic reactions following transfusion of plasma may occur in patients with IgA deficiency and antibodies to IgA

CRYOPRECIPITATE — When FFP is thawed at 4°C, a precipitate remains, which can be separated by centrifugation; this material is termed cryoprecipitate (cryo). It is a concentrated preparation which contains virtually all of the factor VIII, fibrinogen, fibronectin, factor XIII, and von Willebrand factor (vWF) in fresh frozen plasma, reduced from an initial volume of 250 mL to a final volume of 10 to 15 mL. The remaining material can be refrozen and used as cryo-poor FFP. Cryo contains about 200 mg of fibrinogen and 100 units of Factor VIII (80 to 110 IU) per bag and carries the same infectious risk as a unit of red cells, or of FFP. Cryo is used in the treatment of congenital and acquired deficiencies of fibrinogen and Factor XIII. Ten bags of cryo (obtained from 10 units of plasma) contain about 2 gm of fibrinogen and will raise the fibrinogen level about 70 mg/dL in a 70 kg recipient. Because of past experience with viral transmission, cryo should no longer be used for the treatment of hemophilia A; pasteurized factor VIII concentrates derived from plasma or from recombinant DNA techniques are preferred sources of factor VIII for replacement therapy, as well as for vWF in many circumstances. However, cryo does contain the large multimers of vWF and may be needed for the treatment of von Willebrand disease when there is no other recourse.
A. recombinant activated factor VII. ' 
Correct
B. recombinant factor VIII.
Not appropriate – he has developed an inhibitor to his required factor VIII
C. recombinant factor IX.
Used in haemophilia B not A
D. fresh frozen plasma.

**FFP is not a concentrate of any of the circulating plasma proteins, and, in general, should not be used to treat coagulation defects caused by known deficiencies of a single factor, or for replacing factors better provided in concentrated form (eg, factor VIII concentrates for hemophilia A).**
E. cryoprecipitate.
Can be used in treatment of von Willebrand disease