Prophylaxis

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INTRODUCTION

The word 'prophylaxis' comes from the Greek 'prophulaktikos' which means "to guard against". In today's health care it refers to a treatment that is intended to prevent or minimize a disease complication. In a person with a severe bleeding disorder, prophylaxis is the regularly scheduled infusion of factor concentrate to prevent bleeding episodes. If scheduled factor infusions are started prior to any or after only one or two bleeding episodes, it is referred to as primary prophylaxis. Once started, primary prophylaxis is continued indefinitely without interruption. When prophylaxis is started later in childhood or in an adult, it is called secondary prophylaxis. Secondary prophylaxis can be used on a long-term continuous basis or intermittently in response to a temporary situation (i.e. prophylaxis for several months after joint-replacement surgery). The alternative to prophylaxis is episodic treatment, that is, treatment that is given after a bleeding episode has started.

The use of scheduled infusions of factor, i.e. prophylaxis, was first pioneered in the late 1950's in Sweden. The use of this approach increased over time, and clinical studies allowed comparison of outcomes. The outcomes monitored are usually the number of bleeds, patient joint scores (objective medical evaluation of the status of a joint), and patient quality of life between people using a prophylactic approach to treatment versus those who are on an on-demand /episodic treatment regimen. The results support scheduled infusions of factor as the best way to avoid the serious complications of a severe bleeding disorder. In a US study, Manco-Johnson et al. (2007), studied 65 young boys with hemophilia A that were randomly assigned to prophylaxis (n=32) with a factor VIII dose of 25 units/kg every other day or on-demand treatment (n=33) consisting of 40 units/ kg of factor VIII at the time of the start of the bleeding episode, followed by a second and third treatment at 24 and 72 hours. Although the boys on prophylaxis used 3 times the amount of factor as those who were on-demand treatment, they experienced less bleeding episodes per year. In addition, children were evaluated with radiographic imaging during the study. At age of 6 years, joint damage was found in 7% (2/32) on prophylaxis and in 45% (13/33) of those who followed on-demand treatment. MRI changes were even found in children who had never reported a joint bleed, suggesting that sub-clinical joint hemorrhaging may occur. Many current national and international treatment guidelines, such as those of the World Health Organization, World Federation of Hemophilia, and National Hemophilia Foundation, recommend prophylaxis as "optimal" therapy. (Caraco, 2003).

Despite the fact that regularly scheduled factor infusions are thought to be optimal treatment, there is no universal agreement on what the schedule should be and the amount of factor to use for a prophylactic dose for a particular bleeding disorder. The goal is to administer enough factor concentrate at the appropriate intervals to keep a patient's trough factor levels great than 1%. For persons with Hemophilia A, this generally means a dose of 30-50 units/kg factor VIII concentrate 2-3 times a week; for Hemophilia B, the dose is generally 20-50 units/kg of factor IX

concentrate 2 times a week. However, many Hemophilia Treatment Centers (HTC's) determine the patient's half life of factor concentrate to determine dose and frequency of factor infusions. It is important that once a regimen is started, there is ongoing evaluation. Accurate record keeping of factor infusions and bleeding episodes provide crucial information for the HTC team to make any needed adjustments to a patient's plan.

IF PROPHYLAXIS IS CONSIDERED THE OPTIMAL TREATMENT, WHY ISN'T IT PRESCRIBED FOR EVERYONE?

Besides the expense of factor concentrates, there are hurdles to this treatment approach that have been identified and that need to be thoroughly reviewed with the patient and/or family prior to making a decision to begin prophylaxis. The period of time that the factor infusion is "protective" from bleeding is limited, so maintaining protection often requires infusions several times per week. This schedule is described by some as too labor intensive and difficult to maintain. Although the pharmaceutical industry has worked to make the infusions convenient and easy, they still require significant time and commitment. Another issue is venous access. Successfully completing venipuncture several times a week for those with challenging veins or certain physical disabilities is a difficult task that may, at least temporarily, prevent prophylaxis. However, venous access devices may be used to assist with infusions. They will be discussed later in this chapter.

Potential advantages of prophylaxis

- Decreased number of bleeds
- Fewer trips to hospital or clinic
- Prevention or stabilization of joint damage
- Decrease in time missed from work/school
- Potential increased participation in leisure/recreational activities

Hurdles to Prophylaxis

- Venous access issues
- Significant commitment of time and focus
- Insurance/cost barriers

VENOUS ACCESS

Although venipuncture is the preferred method of delivering factor concentrates, not all patients can tolerate the frequent needle sticks necessary to follow a prophylactic regimen. The advantages and disadvantages, including complications, associated with various types of venous access devices are considerations that should be addressed before an alternative to venipuncture is considered.

CENTRAL VENOUS ACCESS DEVICES (CVADS)

1. **Non-tunneled catheter:** The peripherally inserted central catheter (PICC) is a long catheter (18-24" long) that extends from an arm vein into the superior vena cava and typically provides central IV access for several weeks, but may remain in place for several months. PICC lines may have one or two lumens, and some may be able to be used for CT contrast injections (manufactured for forceful contrast injections). The catheter is secured in place by a special device called a StatLock® PICC Plus. This device locks the catheter in place to prevent the catheter from coming out. Around the

catheter insertion site (where it enters the skin), an antimicrobial disc called a BioPatch® is placed that helps to prevent the line from getting infected.
Because this catheter is temporary, it is used primarily to administer factor concentrate after a surgical procedure or a bleeding episode that will require frequent dosing for a short period of time (i.e. secondary prophylaxis). Because it is an external catheter, care must be taken to avoid infections. Dressings must be kept dry and changed weekly.

2. **Tunneled catheter:** Similar to the PICC, the tip of the catheter is in the superior vena cava. The catheter is then tunneled under the skin to an incision on the chest wall, where the distal end of the catheter exits the body. A Dacron cuff made of material that stimulates granulation tissue holds the catheter in place on the chest and helps reduce the risk of infection. Examples of the tunneled catheter include HICKMAN® catheters, BROVIAC® catheters, and GROSHONG® catheters. The tunneled catheter is preferred when venous access is needed for long period of time, as in an inhibitor immune tolerance regimen (see chapter 10). It is secure and easy to access, and there are no needle sticks to the skin. However, there is a risk of infection at the catheter entrance site and along the 'tunneled' track through the skin. The patient or caregiver must be willing to clean the access site, flush the catheter, change the dressing, and change the needleless connector, and must be able to recognize and report problems or complications. Body image and patient lifestyle may be deterrents because the catheter exits through the chest wall. For example, some practitioners may allow patients with tunneled catheters to swim in chlorinated pools, but swimming in other bodies of water is not recommended.
3. **Tunneled, fully implanted port:** An implanted catheter (also called a port) is completely housed under the skin and is made of plastic, titanium, or stainless steel with a self-sealing silicon septum designed to withstand 1000-2000 punctures if used with a beveled needle. Ports can be single- or double-chambered. They are surgically placed over a bony prominence, often below the clavicle on the chest wall. With a port, a raised disk about the size of a quarter is felt underneath the skin. Blood is drawn or medication is delivered by placing a small needle through the overlying skin into the port reservoir. An offset beveled needle is specifically made for ports that prevents coring of the septum. Once a port is accessed, the beveled needle can be left in place for several days, although most patients prefer that the port be de-accessed after each infusion to avoid the discomfort of the needle and adherent dressing. The 'Consensus Recommendations for Use of Central Venous Access Devices in Hemophilia' (2004) suggest that for individuals without inhibitors, a port is the preferable CVAD choice. For those patients with an inhibitor, a port may be the best choice for venous access, but under some circumstances, an external tunneled catheter may be a better option.

COMPLICATIONS OF CVADs

The benefit derived from a CVAD may be offset by potential complications including infections, local hemorrhage, mechanical failure, and venous thrombosis. The most frequent complications of CVAD's occur during extended use (Ewenstein et al, 2003).

1. **Infection:** Infection can be classified as local (exit site), regional (tunnel or pocket) or systemic (sepsis) (Ewenstein et al, 2003). Potential routes of catheter-associated infection include the skin, due either to organisms on the patient's skin or on the hands of the person accessing the port, the catheter hub/needleless connector, contaminated infusate, and hematogenous seeding of the CVAD from another source (Gorski, 2010). Once

microorganisms contaminate a catheter, they form colonies that secrete a polysaccharide or biofilm matrix. Under stressful conditions, these organisms can detach into the bloodstream, producing bacteremia. In these circumstances, systemic antibiotics are able to eliminate the organisms that are released from the biofilm. However, antibiotics are not usually effective in eliminating the organisms that are imbedded in the biofilm. Biofilm eradication is difficult, and thus, most biofilm-related infections require prompt removal of the device (Aslam, 2008). The rate of infection of PICC lines in patients with hemophilia has not been reported. A meta-analysis of CVAD infection in patients with hemophilia indicated a pooled infection rate of 0.66 per 1000 CVAD days. In the meta-analysis, 44% of patients were affected by an infectious episode (Valentino 2004). The risk of infection was increased in children < 6 years of age and those using the devices on a frequent basis as in an immune tolerance regimen (Izzi, 2010). To help avoid infections, patients or their caregivers must be instructed in strict aseptic technique. In addition, patients with CVADs require the use of prophylactic antibiotics 1 hour before dental work or other invasive procedures.

2. **Thrombosis:** Blood clots within the catheter and surrounding vein have been reported in hemophilia patients with CVADs. Clots can form in the lumen of the catheter from inadequate flushing. Clots can also form at the site at which the catheter enters the vein, at the tip of the catheter, and in other areas where the catheter can irritate the intima of the vein. In the previously reported studies, many CVADs were placed in children at a very young age. As they grow older, the tip of the catheter, which normally sits in the superior vena cava, can migrate to smaller vessels, increasing the risk of thrombosis. In addition, the frequent administration of clotting factor may contribute to the development of a thrombus. In patients with hemophilia, prospective studies screening for infection at regular intervals are not available. In a meta-analysis of CVADs in hemophilia, the pooled incidence of thrombosis was 0.056 per 1000 CVAD days (Valentino et al. 2004). However, most agree that the incidence of thrombotic events is vastly underreported due to the proportion of events that are clinically silent. The consensus of hemophilia providers is to remove CVADs as soon as peripheral venipuncture becomes possible.

ARTERIO-VENOUS FISTULAS (AVF)

Internal AV fistulas may be an option for venous access in patients with hemophilia who have experienced repeated problems with surgically inserted or implanted devices. AVFs are surgically constructed by creating an anastamosis from end to end or side to side between the brachial artery and an adjacent vein (McCarthy 2007). After the procedure, it takes 6-8 weeks for the fistula to mature into a functioning vessel. Manusco et. al. (2008) reported on their experience with AVFs over an 8-year period. Forty-three procedures were performed in 38 children (median age: 2.7 years). Thirty-five AVFs (81%) achieved maturation after a median of 58 days and were used for a median of five years (range: 0.4–8.5). A brachial artery caliber larger than 1.2 mm was associated with successful maturation ($p<0.05$). Complications with some impact on arteriovenous fistula use or duration were observed in 14/43 procedures (32%) and in 13/38 children (34%). Mild forearm hematomas and failure of the AVF to mature were the most common adverse outcomes. There was one thrombotic event and 2 reports of patients with distal ischemia that resolved without intervention. Long-term complications due to aneurysms or limb hypertrophy were rare and never occurred before three years of use. In 2007, RUSH Hemophilia and Thrombophilia Center reported

their experience with AV fistula placement. From 2000-2006, 10 AV fistulas were created for 9 patients. One AV fistula failed to mature, and a new one was created in the other arm that occluded in 13 months. Of the mature fistulas, patency was 100% at 1 year, 80% (4/5) at 3 years, and 75% (3/4) at 4 years, with mean follow-up of 22 months. (McCarthy, 2007). Patients and families reported a high degree of satisfaction with these devices despite the complications.

CONCLUSION

If prophylaxis, primary or secondary, is a chosen treatment regimen for a person with a bleeding disorder, HTC staff must ensure that the patient and family have a thorough understanding of potential benefits and risks prior to initiation. Some children on continuous prophylaxis who have had little or no break-through bleeding may not recognize early joint bleeding. The patient and family should be aware of the need for ongoing assessment and education regarding factor dosing and timing intervals to achieve the best outcome and how to recognize a bleed.

The best route of factor administration must be individualized and depends on the length of treatment and the patient's overall risk of complications. Children and occasionally adults with hemophilia may require central venous access lines to facilitate administration of factor concentrate infusions long-term. These devices have enabled prompt treatment of bleeding episodes and have allowed prophylaxis and immune tolerance to begin or continue. A thorough central device management education program should be ongoing to reduce the risk of complications. Nurses and providers are obliged to remind families that these devices are not permanent and that the expected transition to venipuncture should be made as soon as possible to avoid long-term complications from these devices.

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