

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

## Evaluation and Management of Bleeding Risks With Athletic Activities in Children With Hemophilia



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### H&O How does hemophilia manifest in children?

**CB** Hemophilia is a bleeding disorder that results from either an absence or a deficiency of clotting factors. In the case of hemophilia A, it is a deficiency or absence of clotting factor 8, and in the case of hemophilia B, it is a deficiency or absence of clotting factor 9. There are degrees of the disease. It can be classified as either mild, moderate, or severe depending on the level of endogenous clotting factor in the blood. Hemophilia is the most common X-linked recessive disorder, so it predominantly affects males. Females tend to be asymptomatic carriers.

There is no racial predilection for hemophilia, so the incidence is the same throughout the world: approximately 1 in 5,000 live male births. The reported prevalence, however, is higher in the developed world compared to the developing world, which reflects differences in survival rates and stringency of reporting mechanisms or tools.

In children, hemophilia results mostly in bleeds into the soft tissues, muscles, and, predominantly, into the joints, which is the main cause of morbidity. Recurrent bleeding episodes into the same joints result in joint destruction, a condition known as *hemophilic arthropathy*. It is the main cause of morbidity in children with hemophilia, who can have pain, stiffness, and swelling in the joints that can occur early in life depending on the treatment that has been administered. Children who do not have access to prophylactic clotting factor have higher rates of joint bleeding and are more likely to develop irreversible joint damage in the childhood years.

A child born today with hemophilia, particularly in the developed world, can expect to have a similar life expectancy to his healthy peers. This has not always been the case. In the 1800s, when there was very little treatment for hemophilia, the

median life expectancy was only 11 years. It increased, peaking in the late 1970s at approximately 67 years, but then fell to about 49 years in the late 1980s largely due to widespread human immunodeficiency virus (HIV) infection. Currently, with the advent of viral-safe clotting factor, a hemophilia patient's life expectancy is similar to that of his healthy peers.

### H&O How are these patients managed?

**CB** The management of children with hemophilia differs greatly, depending on where they live. Treatment is very expensive, so it is out of the reach of much of the world's hemophilia population. Only about 25% of the world's hemophilia population has access to best care, which is the use of prophylactic clotting factor. These patients are in Western Europe, Scandinavia, the United Kingdom, the United States, Canada, Australia, and New Zealand. The treatment involves prophylactic injections of clotting factor administered by the patient's family or at hemophilia care centers, particularly for severe hemophilia. For hemophilia A, the injection usually is given approximately 3 times a week, and in the case of hemophilia B, it is usually given approximately twice a week. The aim of prophylactic clotting factor is to prevent joint bleeds to avoid joint damage.

An issue concerning prophylactic clotting factor is the expense. For example, in Australia, for a child who weighs about 66 pounds, the annual cost of treatment can range from \$150,000–\$200,000. Current research aims to determine whether lower doses of clotting factor can be clinically effective in order to expand treatment to the developing world. In developing countries, children experience many more bleeding episodes, and so irreversible joint damage occurs often in the first decade of life.

## H&O Are patients usually instructed to limit certain types of physical activity?

**CB** In the past, children with hemophilia were discouraged from playing sports because of the risk of bleeding episodes. They were directed towards non-impact-loading activities, such as swimming and walking. More recently, particularly in countries with access to prophylactic clotting factor, children have been encouraged to be more physically active because we are starting to see the effects of inactivity, namely overweight, low bone density, and poor fitness and strength. The general advice has been to increase levels of physical activity but still to avoid contact sports. Although the benefits of sports participation in childhood are well known, in children with hemophilia, it is necessary to balance those benefits against the possible risk of increasing bleeding episodes, particularly bleeding into the joints.

## H&O What prompted your recent study on physical activity and risk of bleeding in children with hemophilia?

**CB** Hemophilia in children predominantly affects boys and adolescent males, among whom physical activity and sport is a very important part of not just physical development but psychosocial development as well. Parents of children with hemophilia did not know whether sport was a safe activity for them. The study was undertaken to quantify the magnitude of the risk involved in vigorous physical activity so that families would be able to make informed decisions about sports participation.

## H&O What was the study design?

**CB** It was a case crossover study nested in a prospective cohort study. An advantage of a case crossover design is that it enables the study of transient risks, which is what exercise is. Another advantage of a case crossover design is that participants act as their own control, so it eliminates intersubject bias. We followed 104 boys with hemophilia who were between the ages of 4 and 18 years. They came from the 3 eastern states of Australia. We recorded all of their bleeding episodes for 1 year. Once a week, we sent them a text message to ask if they had experienced a bleeding episode in the previous week. If they answered “yes,” we would contact them by telephone to find out more information about the bleeding episode, namely, exposure to physical activity for the 3-day period preceding the bleed. We considered the case period to be the 8-hour window before the bleed, and the control periods to be the 8-hour window, 24 hours and 48 hours before the bleed.

We then compared exposure to the trigger—in this case, physical activity—in the case and control periods, whilst accounting for the level of clotting factor in the blood.

We divided the sports into 3 categories. Category 1 included activities in which no collisions or injuries would be expected, such as walking and swimming. We were not concerned about Category 1 sports because these are activities of daily living that children with hemophilia do without fear of bleeding. Category 2 activities were those that involved limited contact, such as soccer and basketball. Category 3 activities included contact and collision sports, such as rugby, wrestling, skateboarding, and snowboarding.

## H&O What were the study findings?

**CB** Vigorous physical activity was associated with a moderate increase in the risk of bleeding compared to inactivity. For Category 2 activities, the bleeding risk was approximately 3 times greater as compared with inactivity (30.6% of bleed windows vs 24.8% of first control windows; odds ratio, 2.7; 95% CI, 1.7–4.8;  $P < .001$ ). For Category 3 activities, the bleeding risk was approximately 4 times greater as compared with inactivity (7.0% of bleed windows vs 3.4% of first control windows; odds ratio, 3.7; 95% CI, 2.3–7.3;  $P < .001$ ). Despite these findings, however, the absolute increase in bleeds risk was small because the overall amount of time spent by children in vigorous sporting activity was small compared to the total number of hours in a week. We also found that administering clotting factor before activities reduced risk. For every 1% increase of clotting factor in the blood, the bleed risk was reduced by 2%.

We think that many families will be reassured by the finding of a low absolute risk of bleeding associated with physical activity. Parents can encourage their children to engage in sports, particularly where there is the opportunity to administer prophylactic clotting factor before a high-risk activity.

The data from this study will be used to create a freely available online bleeds calculator that will help parents of children with hemophilia determine the effects of changes in physical activity patterns on bleeding rates. Parents can use this information to make decisions about their child's participation in sports.

## Suggested Readings

- Broderick CR, Herbert RD, Latimer J, et al. Association between physical activity and risk of bleeding in children with hemophilia. *JAMA*. 2012;308:1452-1459.
- Manco-Johnson MJ. Collision sports and risk of bleeding in children with hemophilia. *JAMA*. 2012;308:1480-1481.
- Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med*. 2007;357:535-544.