



Teaching Children about Bleeding Disorders

Jocelyn Bessette Gorlin RN, MSN, CPNP

There have been several studies that have investigated a child's concept of illness. Generally, a child's understanding of illness correlates with his cognitive development, as outlined by Piaget. [1, 6, 13-14] Two studies directly assessed how preschoolers, school-age children, and adolescents with hemophilia understand their illness. [8-11, 15] Much of this education summary is based on the original data obtained from the study described in the book, "Teach Your Child about Hemophilia." [9]

Why is it important to understand a child's concept of illness? Theoretically, knowing what children comprehend at each age can assist healthcare providers to tailor healthcare education to the child's age. This, in turn, may result in better self-care, health prevention, and overall adherence to treatment regimens by both the child and the family.

GENERAL CONCEPTS TO REMEMBER WHEN TEACHING:

- 1. Healthcare providers often underestimate or overestimate knowledge:** Healthcare providers often overestimate what younger children understand and underestimate what older children understand. In essence, they often talk up to young children and talk down to older children. In general, try to tailor education to the child's level of understanding and don't teach more than one step above their present level of cognitive understanding.
- 2. Knowledge and education will vary from child to child:** Learning is complex and is dependent on a variety of factors including the child's cognitive level, learning style preference, life experiences, and emotional state, to name a few. In light of this, remember that each child is unique and utilize this education summary as a guide rather than a set of rules.
- 3. A combination of teaching modalities is often successful:** In general, learning is best accomplished when both visual and auditory educational tools are employed such as the combination of pictures/photos and explanations. Having the learner explain to the educator what was just taught also has been found to be beneficial.
- 4. Photographs and illustrations are powerful teaching tools:** Often, photographs or illustrations are the simple key to unlocking understanding of complex concepts such as the clotting cascade or the genetics of hemophilia. This is often the case for both young and older learners. Photos and illustrations also cross language barriers and are useful for those who cannot read or have reading challenges.
- 5. Children like to share what they know:** It is wise to begin any conversation with children by asking the child first about *his* experience. For example, you might ask, "Why do you think you come to the hospital?" or "What is hemophilia?" This will provide a springboard for conversation and help to alleviate any misconceptions that might exist. Allow the child to



explore his thoughts safely without judgment and gently interject guidance. KISS is a wonderful acronym, which stands for, "Keep it simple, silly." Try not to correct a misconception he has with an explanation he may not understand. Keeping the explanation simple and appropriate for his cognitive level should suffice.

6. A quiet environment promotes attention: Providing a quiet environment in clinic when teaching, free of distractions such as TV or cell phones, is optimal because it fosters attention. Try to schedule a clinic appointment that allows sufficient time for teaching or else schedule a home visit for education purposes. Occasionally, parents are rushed for time or the environment in the clinic room becomes chaotic. In this case, it is better to send education tools home rather than to be rushed in a distracting environment. Follow-up can occur by phone or at another meeting.

7. The effect of prophylaxis on learning is unclear: It is unclear what children who receive prophylaxis know about bleeding disorders. One theory is that they may know less about their bleeding disorder because they have less experience with bleeding episodes. They may, for example, not know how to recognize a joint bleed or what to do in the event of a bleed. Others suggest that they know more about their bleeding disorder because they have extensive experience with infusions. Probably both are true. They are more familiar with the infusion process, but may have less experience with actual bleeding episodes and therefore less experience with recognizing them. Both of these concepts are important to keep in mind when providing education to children on prophylaxis. [8-11]

8. Language/ethnicity/religion will impact understanding: If there is any question whether the child understands the language used in education, an interpreter should be used. Also consider that the child and family's ethnicity and spiritual practices will influence how they comprehend their illness. For example, in some cultures illness is seen as a curse or due to the spirits. What they believe will greatly affect their understanding of the bleeding episode, so it is worth exploring these issues.

9. Siblings are part of the team: Often siblings are not involved in the conversation during education. Usually, they want to talk with you, learn and help. It is important to acknowledge that they are an important member of the team.

10. Education should continue throughout the lifespan: Though it is assumed that children with a chronic condition may have more experience and therefore have a more advanced understanding of their illness process, this may not be the case. One study [6] found that only 1/3 of the adolescents with a chronic illness had a good understanding of their disease. This supports the concept of continuing education throughout the life span rather than education at one point in time.



INFANT: 0-1 YEARS OLD:

We do not have data to support how infants comprehend a bleeding disorder, but we do know that infants experience their world through their senses of hearing, seeing, and touching. Here are some suggestions based on infant cognitive development and nursing clinical experience that may be helpful when educating families of infants with a bleeding disorder.

Nursing Interventions for Teaching the Parent:

- **Comfort/educate the parent:** A parent's anxiety can be communicated to a child, so helping the parent feel comfortable will help the child. Speak respectfully and complement parents on the positive aspects of their child's condition and the care they give. Sit in a chair that is the same height or lower than the parent's chair. Talk to and play with the baby first before you begin any procedure such as an infusion. In infancy, most education will involve the parent and family. As soon as possible, involve the child in the learning process.
- **Provide books which may be helpful for this age** (See Recommended Reading):
 - Raising a Child with Hemophilia*
 - Teach Your Child about Hemophilia*
 - My First Factor Series*
 - Illustrated Hemophilia Guide*
- **Teach special techniques:** Show the parents how to comfort their child during an infusion or procedure by encouraging them to talk, sing, hold, cuddle or distract the child. Often infusions can be done while the child is sitting on the parent's lap cradling him. Special stuffed animals, blowing bubbles, and calm music can help to comfort and distract the child. Utilize the help of several team members such as the Child Life Specialist to assist in these efforts.
- **Encourage the use of emergency medical identification (EMI):** In a national study by the Nursing Working Group of the National Hemophilia Foundation, nurses reported poor adherence in wearing an EMI among all age groups of children with hemophilia. In the infant age group, EMI was often not worn on the body, but rather placed in external sites such as the parent's wallet or the car glove compartment. Anecdotal reports revealed that EMIs could be separated from the child in the event of a car accident. Encourage parents to use emergency medical identification and place it *on the child* at every age (see: National Hemophilia Foundation. Medical and Scientific Advisory Council Recommendation on the Use of Emergency Medical Identification Devices for Children). [5, 12]

TODDLER: 1-3 YEARS OLD:

We do not have data to know what the child under three understands about illness or bleeding disorders. Children at this age, however, continue to understand their world through their senses such as seeing, hearing and touching. We also know that preschoolers cannot yet understand cause and effect and what is occurring inside their body because they cannot see it. They also cannot take the perspective of another person. We assume, therefore, that the toddler cannot do



this as well. Based on normal cognitive development, here are some suggestions when working with a toddler.

Nursing Interventions for Teaching the Toddler:

- **Comfort/educate the parent:** Continue to provide as calm and reassuring an environment as possible. A room free of television and cell phones is important if parents are to be able to assimilate any information that is given to them. Give the parents positive reinforcement for the care and support they have given their child thus far. Although most education involves the parent, begin to involve the toddler in the education process.
- **Comfort/educate the child:** Older children are able to associate pain relief with the infusion, but toddlers may associate infusions *only* with pain. It is difficult to explain why they need an infusion because they cannot understand the inner workings of their bodies or blood nor understand sequences of events. Ask them questions such as “Why do you think you come to the clinic?” Parents can allay fears by treating infusions matter-of-factly and by telling the child that they are necessary to make his leg, etc., feel better. Another general way to explain it is, “When you have hemophilia you need to get factor. Factor helps you take care of your body”.
- **Provide Books which may be helpful for this age** (See Recommended Reading)
 - Raising a Child with Hemophilia*
 - Teach Your Child about Hemophilia*
 - My First Factor Series*
 - Illustrated Hemophilia Guide*
- **Clinic Setting: medical playbox and books:** Because toddlers are dependent on their senses to understand their world, you can provide items for the child to touch in order for him to learn about his bleeding disorder. Give him a medical playbox full of band-aids, butterfly needles with the needle removed, large plastic syringes, gauze, alcohol wipes, and medical gloves. Add two small plastic vials of normal saline to pretend they are factor bottles. Sit with the child as he touches the various items. Let him ask questions and answer them as simply as possible.
- **Home setting: encourage a “bag of tricks”:** Encourage parents to make a canvas “bag of tricks” for home use which includes three different ziplock bags easily transported to the hospital. One ziplock bag contains “play supplies” for the child to touch and feel like the medical playbox explained above. The second ziplock bag contains books for the child to touch and parents to read to him. Making a small photo book of “A Trip to the Hospital” or “Tommy Gets an Infusion” including photos of the child and siblings/parents may be helpful. The third bag contains comforts such as a beloved stuffed animal or a CD that he enjoys listening to.



- **Encourage child participation:** As soon as the child is able, parents and medical personnel should encourage the child to participate in treatment. This is one of the best ways for the child to learn about his bleeding disorder. Participation increases a sense of control and decreases feelings of helplessness and fear. The older toddler can participate by holding the band-aid until it is needed. Siblings can also participate by assisting in the infusion process.
- **Involve many care providers:** The hematology team, especially the Child Life Specialist, can be helpful in this respect. Finding a balance between education, comfort and distraction is an art, and when it is done well it is a beautiful art. Child Life Specialists are very creative with distraction techniques such as blowing bubbles and videos as well as comforting techniques such as calming music.
- **Emergency medical identification (EMI):** Continue to encourage parents to place an EMI directly on the child. Parents should not offer their child a choice of wearing or not wearing an EMI because children at this age have no understanding of health prevention. [5, 12]

PRESCHOOL CHILD: AGE 3-7 YEARS:

1. Magical Thinking:

Children who are preschoolers draw from their own direct experiences rather than from reality. This is called magical thinking. They do not understand bleeding as a step-by-step process. If you ask, "What is hemophilia?" The child may answer, "When I get hurt and need a needle" or "You have to wear a bracelet and get factor when you get hurt." It may seem like they understand the connection, but they are not related by cause and effect. During this age they may also think having a bleeding disorder is caught from something or someone. This is called "contagion".

Preschoolers cannot clearly understand the inside of their body because they cannot see it. So, for example, they do not understand that hemophilia is caused by a problem in the clotting cascade (they typically do not understand that hemophilia has any relation to blood), but rather think that it may be associated with something that just "happened to them." It may not be possible for them to ever understand the connection between their bleeding disorder and blood at this age or what it looks like inside a bleeding joint. Prevention or prophylaxis is generally too complex an issue for them to understand at this age.

2. Egocentric: Preschoolers are egocentric, meaning that they cannot experience the world from another's viewpoint. They experience it only from their own viewpoint. Because of this, you probably cannot use a doll or picture to teach them what will happen to *them*. They may be able to use a doll to act out their feelings, but the idea that what happens to the doll may happen to them is probably not understood at this age.

3. Perception: Preschool children perceive their world through their senses rather than through logical thinking. Because of this, the best way to teach them about their bleeding disorder may simply be to have simple, colorful picture books or a basket filled with medical supplies that they can touch and use in play.



Some examples of understanding at this age:

Blood: They do not associate hemophilia with blood. They do not understand the clotting cascade or proteins. Blood is red liquid.

Hemophilia: What is hemophilia? "It is when I get hurt and need a needle" but the two items are not causal.

Genetics: You are born with hemophilia. They may also think hemophilia is caught from someone or something.

Factor: Factor is a white powder or "My bottle of medicine." They do not understand the actual mechanism of clotting.

Nursing Interventions for Teaching the Preschool Child:

- **Comfort/educate the parent:** Continue to provide a relatively quiet environment free of distractions. Photos and illustrations continue to be useful tools.
- **Comfort/educate the child:** Though education was geared more to the parent before this time, the preschooler should be more directly involved in education at this age. Nurses should set the stage to include the child in as much age-appropriate education as possible. Encourage the child to tell you what he knows about his bleeding disorder. At this age he may not understand what type and severity of hemophilia he has, but he should memorize it for safety reasons.
- **Provide books which may be helpful for this age** (See Recommended Reading)
 - My First Factor Series*
 - Illustrated Hemophilia Guide*
 - Just a Boy*
 - What is Hemophilia? Series Level 1*
 - Must you always be a Boy?*Note: Educational websites and interactive games about hemophilia are presently being developed for children, which may be another good avenue for education.
- **Clinic Setting: medical playbox and books:** You can provide items for the child to touch to learn about his bleeding disorder in clinic. Provide the same box for medical play (See above). Sit with the child as he touches the various items. Let him ask questions and answer them as simply as possible. Dolls, puppets or stuffed animals can be used as teaching tools, but the child cannot put himself "in another person's shoes." Puppet-play may help him to express his feelings rather than helping him to understand what it might be like for *him* to receive an infusion.
- **Home setting: encourage a "bag of tricks":** As with the toddler, encourage parents to make a canvas "bag of tricks" for home use which includes three different ziplock bags easily transported to the hospital if necessary (See above).



- **Encourage child participation:** Because they like to feel a sense of initiative, preschool children should be encouraged to participate more in the infusion process and make more choices than when they were younger. Children may be asked to choose one of two venipuncture sites, help dissolve the factor, and assist in taking out the needle or applying pressure to the venipuncture site. During infusions, preschool children and their siblings can assist with the infusion by preparing the area and helping with infusion supplies. They can help apply topical anesthetic cream if used and hold the band-aid after the infusions.
- **Involve many care providers:** The hematology team, especially the Child Life Specialist, can be helpful in this respect. Finding a balance between education, comfort and distraction is the key.
- **Emergency medical identification (EMI):** Continue to encourage parents to place an EMI directly on the child. Parents should not offer their child a choice of wearing or not wearing an EMI because children at this age have no understanding of health prevention. [5, 12]

SCHOOL-AGE CHILD: 7-11 YEARS OLD:

1. Logical Thinking: At this age children can think in a more step-to-step progression and therefore understand causality. If you ask, "What is hemophilia?" they may respond, "When you get hurt, you bleed a lot." They may know that it is associated with blood and that factor helps the bleeding stop. They may still believe contagion is the etiology of their disease. They still cannot fully understand what is happening inside their body because they cannot see it, but they begin to understand it if explained in a simple, concrete manner.

2. Less Egocentric: This is a turning point for children. School-age children are generally less egocentric and can view the world through another person's eyes, so they can understand others' feelings. Because of this, you can use a doll or model to describe the illness or an impending procedure. For the most part, they may be able to extrapolate that what the doll is experiencing (i.e. an infusion) may actually happen to them.

3. Perception: School-age children can understand more logically and need to touch less. Books become increasingly important in educating the school-age child about his condition.

Some examples of cognitive understanding at this age:

Blood: Children 9-11 years old may be able to understand cells, but they may not understand the particulars of the clotting process.

Hemophilia: They know it is a blood disorder but are nonspecific. They understand causality so they may understand that after an injury they may need factor. They should be able to understand their type of bleeding disorder. The severity will not be understood in terms of percentages, but can be understood as "a lot or a little."



Genetics: Usually they can understand that hemophilia is more than just a condition from birth. The younger children know that hemophilia comes from the mother; the older school age child may start to understand chromosomes.

Factor: School-age children know that factor is more than just white powder. They may think that it is like a cork that stops the bleeding. They understand that they get factor *because* they bleed instead of *when* they bleed.

Nursing Interventions for Teaching the School-age Child

- **Comfort/Educate the child:** Nurses should talk directly with the child using age-appropriate education materials. Explanations should be simple: “Hemophilia is a clotting disorder. Clots stop bleeding. Factor VIII makes the blood clot.” and “A bleeding joint is like a balloon.” Because he understands causality, you can discuss why he needs to tell someone if he hits his head, why factor is needed quickly, and why prophylaxis is used. Medical personnel or the child's parents should review signs and symptoms of bleeding episodes. At this age, the child is capable of learning the relationship between certain activities and subsequent bleeding.
- **Provide Books which may be helpful for this age** (See Recommended Reading)
 - Illustrated Hemophilia Guide*
 - Just a Boy*
 - What is Hemophilia? Series Level 2*
 - Must you always be a Boy?*Note: Educational websites and interactive games about hemophilia are presently being developed for children, which may be another good avenue for education.
- **Clinic setting: medical playbox:** The younger school-age child will still probably enjoy playing with medical supplies in a medical playbox (see above). Three-dimensional models of a bleeding joint can be used in clinic to explain what occurs inside the joint in hemophilia. The child can understand what another person is experiencing, so using a doll or puppet in the clinic setting can help him express feelings *and* might help him understand what it might be like for *him* to have an infusion.
- **Home setting: encourage a "bag of tricks":** Although the child is older, he can still use “props” in a bag that can be brought from home (see above). School-age children are less dependent on touch and more dependent on books.
- **Encourage child participation** At this time children begin to self-infuse. This is a pinnacle time for learning about their bleeding disorder and self-care. Even if they cannot fully self-infuse, they can participate by organizing, mixing and documenting the infusions. They can also begin to order medication and speak directly with the hematology staff when needed. Children may be asked to choose one of two venipuncture sites, help dissolve the factor, assist in taking out the needle or applying pressure to the venipuncture site. Siblings can



assist with the infusion as well by helping with infusion supplies and preparing the area. They can help apply anesthetic cream to the skin if used and hold the band-aid after the infusion.

- **Involve the child in making decisions:** Involving the child in decisions about his activities decreases the tendency to engage in forbidden activities without the parents' knowledge. Learning how to solve problems around the bleeding disorder will encourage the child to start making healthy choices early, rather than engaging in self-pity and blaming the bleeding disorder for not being able to participate in some activities. This is particularly important in the school-age years.
- **Involve many care providers:** Members of the hematology team, especially the Child Life Specialist, continue to be important in providing comfort and distraction. Music, videos, and electronic games are some tools that can be used to comfort or distract the child in clinic if a procedure is needed.
- **Encourage use of emergency medical identification (EMI):** As in the previous ages, EMI should be worn on the child's body. Encourage parents to make this a non-negotiable option with their child. [5, 12]

ADOLESCENT AGE: 11 YEARS AND OLDER:

Like the previous age, adolescents have the ability to think step-by-step logically and to understand causality. They continue to be less egocentric and can imagine what it is like to experience what someone else is experiencing or feeling.

In adolescence, however, they begin to think abstractly, so they begin to fully understand and visualize the inner workings of their body. Now they should be able to understand the steps of the clotting cascade, genetics, and degrees of hemophilia. At this time, dominoes can represent the clotting cascade, and the flip of a coin can explain genetics. It is only in adolescence that they can expect to associate different symptoms of an illness, understand progression of an illness, and verbalize prevention steps. Despite this, one study found significant deficits in children's knowledge of their illness even at age 13. [6]

Blood: They should be able to understand that blood is comprised of plasma, red and white blood cells, platelets, and the proteins that clot the blood.

Hemophilia: At this time they should be able to grasp the clotting process. They should understand the type and severity of their illness.

Genetics: They should be able to understand genetic terms and concepts and explain the genetic transmission possibilities of hemophilia from a carrier mother.

Factor: Factor is seen as a medicine that replaces the protein missing in their blood in order to allow their blood to clot.

Nursing Interventions for Teaching the Adolescent:



- **Support/educate the adolescent:** Education should be directly with the adolescent. An environment free from distractions of television and cell phone continues to be important. Ask questions assessing what he knows about his bleeding disorder. Ask him to name his type of bleeding disorder and explain its treatment. It is best not to assume that he has a full understanding of his condition. Remain non-judgmental if he has misconceptions. Encourage him to talk about how the bleeding disorder affects his life. At this age, young adolescents should understand more advanced analogies. You might say for example, “An injury is like a dam that bursts. The rocks used to plug the hole are the platelets. The cement is the missing factor.” Dominoes can be used to simulate the clotting cascade and coin tosses to teach chance in genetics. Simple illustrations and three-dimensional models of a bleeding joint can be used to portray your message.
- **Provide Books which may be helpful for this age** (See Recommended Reading)
 - Illustrated Hemophilia Guide*
 - What is Hemophilia? Series Level 3*Other books that deal with adolescents facing and overcoming adversity can be educational and provide comfort. Additionally, educational websites and interactive games about bleeding disorders are presently being developed for children and adolescents.
- **Home setting: a new "bag of tricks":** Does an adolescent still need a bag of items to bring to clinic to help him with distraction and comfort? It might be helpful for young adolescents to continue to bring a beloved item for comfort. Additionally, music in any portable device might be relaxing. Relaxation techniques such as yoga and deep breathing techniques may be especially useful when infusions in clinic and/or hospitalizations are needed.
- **Encourage participation:** Self-infusion is one of the best ways to educate adolescents about their bleeding disorder and self-care. Self-infusion should be well under way by this time. Teens can organize supplies, mix factor, and document the infusions. They can also order medication and speak directly with the hematology staff when needed. Siblings can continue to assist with the infusions as well by helping with infusion supplies and preparing the area. By late adolescence, most teens should take full responsibility for determining activity decisions, need for treatment, self-infusion, and documenting infusions.
- **Encourage use of emergency medical identification (EMI):** It has been reported by nurses nationally that about half of adolescents who have hemophilia do not wear an EMI. The most frequent reason for not wearing it is that the adolescent does not want to be different from his peers. At this age, the need to have identification on the body is paramount because the adolescent will begin driving with his peers more than his parents. It might be effective to describe examples of outcomes of when people did not wear EMI and to find an EMI that is acceptable to the adolescent such as a necklace. Having an ID card is acceptable but should not be a substitute for jewelry-type identification worn on the body. [5, 12]



RECOMMENDED READING FOR PARENTS AND CHILDREN

- Brush S. (2008). *My First Factor Words Series*. Georgetown, Massachusetts: LA Kelly Communications.
- Kelley LA. (2007). *Raising a Child with Hemophilia*. Georgetown, Massachusetts. LA Kelley Communications.
- Kelley LA. (2007). *Teach Your Child about Hemophilia*. Georgetown, Massachusetts: LA Kelley Communications.
- Kelley LA. (2007). *What is Hemophilia? Series*. Georgetown, Massachusetts. LA Kelley Communications.
- Kelley LA. (2007). *Must you Always be a Boy?* Georgetown, Massachusetts. LA Kelley Communications.
- Mann Z. (2009). *Just a Boy*. Georgetown Massachusetts: LA Kelley Communications.
- National Hemophilia Foundation. (2003) *Medical and Scientific Advisory Council Transition Guidelines for People with a Bleeding Disorder*. MASAC Document #147.
- National Hemophilia Foundation. (2010) *Medical and Scientific Advisory Council Recommendation on the Use of Emergency Medical Identification Devices for Children*. MASAC Document #201.
- World Federation of Hemophilia. (1983) *Illustrated Hemophilia Guide*. Munich, Germany: World Federation of Hemophilia.

REFERENCES

1. Bibace R, Walsh ME. Development of Children's Concepts of Illness. *Pediatrics* 1980; 66(6): 912-917.
2. Brazelton TB. (1994) *Touchpoints: The Essential Reference: Your Child's Emotional and Behavioral Development*. Massachusetts: Addison-Wesley.
3. Brush S. (2008) *My First Factor Words Series*. Georgetown, Massachusetts: LA Kelly Communications.
4. Erikson EH. (1993) *Childhood and Society* (3rd ed.). New York: W.W. Norton & Company.
5. Gorlin JB, Hooke MC, Leonard N. Use of Emergency Medical Identification in the Pediatric Hemophilia Population: A National Study. *Haemophilia* 2011; 17(2): 215-222.
6. Greenley RN, Coakley RM, Holmbeck GN, Jandasek B, Wills K. Condition-Related Knowledge Among Children with Spina Bifida: Longitudinal Changes and Predictors. *Journal of Pediatric Psychology* 2006; 31(8): 828-2006.
7. Kagan J. (1984) *The Nature of the Child*. New York: Basic Books.
8. Kelley LA. (2007) *Raising a Child with Hemophilia*. Georgetown, Massachusetts. LA Kelley Communications.
9. Kelley LA. (2007) *Teach Your Child about Hemophilia*. Georgetown, Massachusetts: LA Kelley Communications.
10. Kelley LA. (2007) *What is Hemophilia? Series*. Georgetown, Massachusetts. LA Kelley Communications.
11. Kelley LA. (2007) *Must You always be a Boy?* Georgetown, Massachusetts. LA Kelley Communications.
12. National Hemophilia Foundation. (2010) *Medical and Scientific Advisory Council Recommendation on the Use of Emergency Medical Identification Devices for Children*. MASAC Document #201.
13. Perrin E, Gerrity PS. There's a Demon in Your Belly: Children's Understanding of Illness. *Pediatrics*. 1981; 67(6): 841-849.
14. Piaget J, Inhelder B. (2000). *The Psychology of the Child*. New York: Basic Books.
15. Spitzer A. Children's Knowledge of Illness and Treatment Experience in Hemophilia. *Journal of Pediatric Nursing* 1992; 7(1): 43-51.

I would like to thank Laureen A. Kelley for her invaluable research about children's understanding of hemophilia and her editing of this manuscript. I would also like to thank my husband, Jed Gorlin, MD, for editing the manuscript.