Overview and Considerations

Introduction
A 4-week-old White male infant was brought to the emergency department (ED) by his parents because of lethargy, irritability, decreased interest in breastfeeding, and one episode of emesis 3 hours before arriving at the ED. Earlier in the day, the infant presented to his primary care provider (PCP) with parental concern for fussiness, increased sleepiness, and difficulty breastfeeding of a 2-day duration. Because he was afebrile at that time and had no focal concerns, he was sent home with planned follow-up for persistent or worsening symptoms.

The infant's mother reported that he had been breastfeeding well until 2 days prior to presentation when he seemed "less interested" in latching. He had been feeding at the breast every 4 hours, with only 5 to 10 minutes of latch. The parents denied arching or emesis with feedings. The patient was less interactive than in the past and sleeping more than usual (not waking to eat every 3 to 4 hours as he had been) and was difficult to console while awake. The parents reported no cough, congestion, rhinorrhea, diarrhea, or constipation. The patient had no change in his voiding pattern, and his last diaper change was 30 minutes before arrival at the ED. The family denied any contacts with sick people, day care attendance, traumatic events, or known injuries.

History
The patient was born at 41 weeks' gestational age to a gravida 2 para 1 32-year-old mother who delivered at home via spontaneous vaginal delivery (water birth) with a midwife. The infant was seen by his PCP at 2 days of life and again at 2 weeks of life, and no concerns were identified. According to his mother, results of his newborn screening were normal. The parents refused erythromycin ointment, vitamin K prophylaxis, and the hepatitis B vaccine at birth. The infant was circumcised at day 8 of life without prolonged bleeding or complications. He took no medications or supplements and had no known food, drug, or environmental allergies.

Social, Developmental, and Family History
The patient's biologic parents were married and in good health with no routine medication use. The patient's 3-year-old brother was in good health, with a history of mild eczema. He did not attend day care and the family had no concerns of recent illness. The family history included no bleeding disorders or stroke, and the parents did not express a concern about domestic violence. The patient was cared for by his mother during the day and by both parents in the evening and on weekends. According to his parents, the patient had been meeting developmental milestones, including turning his head to sounds, tracking, and cooing, and he had improving head control.

Physical Examination
Upon physical examination the infant was irritable and crying and was unable to be consoled by his mother. He weighed 5.2 kg (75th percentile) and had a head circumference of 38.0 cm (50th percentile) and a length of 55 cm (50th percentile). His vital signs were as follows: temperature, 38.1°C; heart rate, 112 beats per minute; respiratory rate, 49 breaths per minute; blood pressure, 100/38 mm Hg; and oxygen saturation, 99% on room air. His head was atraumatic and normocephalic, with anterior and posterior fontanels open and notably full. His pupils were equal, round, and briskly reactive to direct light, 2 to 3 mm bilaterally. The red reflex was present bilaterally, and no eye...
deviation was noted. The infant's nares were patent bilaterally, with no drainage, swelling, or lesions. His lungs were clear to auscultation bilaterally, and he had no retractions or nasal flaring. The patient's heart sounds were regular with no murmur, and his brachial and femoral pulses were 2+ bilaterally. His abdomen was soft, rounded, and nondistended, with no palpable masses or hepatosplenomegaly. The penis was circumcised and well healed with no discharge, swelling, or bleeding. The infant's testes were descended bilaterally, and he voided to an open diaper during the physical examination.

The infant had a 2 by 3 cm red, flat lesion at the base of the skull that the mother reported has been present since birth; however, no rash, petechiae, or purpura was noted. His skin was moist with good skin turgor. He had symmetric, spontaneous movement of all extremities. His tone was normal, and no arching, tremor, clonus, or seizures were appreciated. His palmar, plantar, moro, rooting, and stepping reflexes were intact. Although he was noted to have a weak suck, his cough and gag reflexes were intact.

Emergency Department Management

In the ED, the initial concern was for an occult infection. Peripheral intravenous (IV) access was obtained, the infant was connected to a cardiac-respiratory monitor, and laboratory samples were sent for evaluation. Initial laboratory tests revealed a white blood cell count of 13,780/mL (normal, 6200–17,000/mL); a red blood cell count of 3.64/mL (normal, 4–6/mL); a hemoglobin of 11.1 g/dL (normal, 10–17 g/dL); a hematocrit of 32.8% (normal, 39%–59%); and a platelet count of 330,000/mL (normal, 200,000–475,000/mL). The urinalysis was unremarkable. Peripheral anaerobic and aerobic blood cultures and a urine culture were sent for analysis. Because of focal neurologic findings and concern for increased intracranial pressure (ICP), a lumbar puncture (LP) was not performed. A computed tomography (CT) scan of the head was obtained, which revealed a large left frontal hemorrhage, large subdural and subarachnoid areas of bleeding, and an 11-cm midline shift with probable left uncal herniation and bilateral occipital infarcts. In light of the CT findings, additional laboratory tests were performed and revealed a prothrombin time (PT) greater than 140 seconds (normal, 11.0–12.5 seconds) and a partial thromboplastin time (PTT) of 117 seconds (normal, 60–70 seconds).

Given this infant's history of no vitamin K administration at birth and prolonged PT, he was given 1 mg of vitamin K intravenously and 10 mL/Kg fresh frozen plasma (FFP) to correct his coagulopathy. A basic metabolic panel, factor panel, and liver function panel studies were obtained; all were within normal range. His factor studies revealed the following: fibrinogen, 286 (normal, 125–300 mg/dL); d-dimer, 666 μg/L (normal, < 250 μg/L); factor II, 54% (normal, 80%–120%); factor V, 166% (normal, 50%–150%); factor VII, 114% (normal, 65%–140%); factor VIII, 162% (normal, 55%–145%); factor IX, 59% (normal, 60%–140%); and factor X, 57% (normal, 45%–155%). The infant was transported to the pediatric intensive care unit for further management.

Hospital Course

Shortly after arrival in the pediatric intensive care unit, the infant became difficult to arouse, and he began having apneic episodes lasting up to 30 seconds with associated oxygen desaturation. He was intubated and supported by invasive mechanical ventilation, along with continuous sedative infusions of morphine and midazolam. A femoral central venous catheter was placed, and dextrose 5% with 0.9% normal saline solution was administered to deliver maintenance fluids.

Although an ICP monitor was not yet in place, 3% hypertonic saline solution boluses were administered to maintain the infant's serum sodium at 145 to 150 mEq/L with the goal of decreasing any possible intracranial hypertension. The head of the infant's bed was kept at 30° elevation, his temperature was maintained 36° to 37°C with a cooling blanket, acetaminophen was scheduled every 6 hours, and he was kept on nothing by mouth status. Keppra was administered for seizure prophylaxis. Follow-up coagulation studies revealed a normalized PT of 14.5 seconds, a PTT of 32.6 seconds, and an international normalized ratio of 0.98 (normal, 1.0). In light of the infant's history, corrected coagulation studies, and normal platelet and fibrinogen levels, he was diagnosed with vitamin K deficiency bleeding.
On hospital day 2, the infant underwent an emergent craniotomy after an acute decompensation in which his left pupil became fixed and dilated and he experienced the onset of clinical seizure activity. The left frontal hemorrhage was evacuated in the operating room, an ICP bolt was placed, and Fosphenytoin was administered for seizure management. He received numerous blood products intraoperatively. A continuous electroencephalogram was placed, which revealed subclinical seizure activity. The child's midazolam drip was increased, and Topiramate and Phenobarbital were administered, which led to a cessation in seizure activity by hospital day 4. He briefly required inotropic support for hypotension. Magnetic resonance imaging and magnetic resonance angiography of the brain on hospital day 7 revealed no vascular abnormalities or new hemorrhage or injury, although he was noted to have decreased movement on his right side. The infant was extubated on hospital day 11 and subsequently was able to breastfeed. He was discharged home on hospital day 17.

Case Study Questions

1. What are the differential diagnoses for this infant?

2. What is the function of Vitamin K in the body?

3. What is VKDB? What populations are at greatest risk?

4. What is the appropriate management for persons with VKDB?

5. What are the current recommendations for Vitamin K prophylaxis? What are the concerns?

Case Study Answers

1. What are the differential diagnoses for this infant?

This 4-week old infant presented with a history of irritability, increased sleepiness, decreased oral intake, fever, and projectile emesis. Without a clinically apparent source of infection on initial examination, the initial concern in this neonate is occult infection, with bacteremia, sepsis, bacterial meningitis, urinary tract infection, and pneumonia as the differential diagnoses (Baraff, 2008). Physical examination findings were not suggestive of septic shock. Urinary tract infections are the most common serious bacterial infection in children younger than 2 years, and laboratory analysis is crucial to rule out this diagnosis (American Academy of Pediatrics [AAP], 2011). In this case, the infant's urinalysis and urine culture findings were negative. An LP is an appropriate diagnostic tool in the setting of an infant with fever; however, contraindications for LP include concern for increased ICP and uncorrected coagulopathies. This infant's history and neurologic examination required the deferral of the LP while an intracranial mass, hemorrhage, or midline shift were ruled out to prevent possible uncal herniation (Mann & Jackson, 2008).

Given his irritability, emesis, and full fontanels, an expanded differential that includes neurologic processes such as elevated ICP is appropriate. Increased ICP is commonly the result of traumatic brain injury, hydrocephalus, masses or tumors, hypoxic/ischemic brain injury, or intracranial hemorrhage (Singhi & Tiwari, 2009). Although assessment can be challenging in infants, it is important to be alert for the early signs and symptoms of increased ICP, including irritability, emesis, and pupillary sluggishness. Later signs include bulging of fontanels, sun-setting eyes, seizures, cranial nerve dysfunction, decreased spontaneous movement, posturing, pupillary inequality or dilation, hypertension, bradycardia, and irregular respirations (Keefe & LeFlore, 2005; Holleman et al, 2012, Lam, 2012). In an infant, the presence of intracranial hemorrhage is likely due to a traumatic process, a coagulation disorder, or a vascular abnormality (Hubbard & Tobias, 2006). Given this infant's age, elevated PT and PTT, and lack of vitamin K prophylaxis at birth, the concern for VKDB is high. In the setting of vitamin K deficiency, an abnormal form of coagulation factor II, also referred to as "protein induced by vitamin K absence" (PIVKA-II), is released into the bloodstream and can be directly measured (Gopakumar, Sivii, & Rajiv, 2010). PIVKA-II is unique in that it can help identify early or subclinical
vitamin K deficiency, and because of its long half-life, it can be used to identify VKDB on retrospective analysis (Clarke & Shearer, 2007a). Given the severity of this infant's presentation, PIVKA-II levels were not assessed in this situation. In retrospect, they could have been obtained to further support the child's diagnosis.

The presence of an intracranial hemorrhage in an infant raises the concern for nonaccidental trauma. Victims of severe head trauma are more likely to present with subdural and subarachnoid hemorrhages than are victims of accidents, along with multiple subdural hematomas in various stages of healing, skull fractures, retinal hemorrhages, or associated skin and skeletal injuries (Kellogg, 2007). Any infant or child with an unexplained brain injury or skull fracture should be evaluated for the possibility of nonaccidental trauma. It is reassuring that in this case the infant did not have any obvious injury, no skull fracture was seen on the CT scan, and the diagnosis of VKDB corresponded with the patient's age, presentation, and history. Nevertheless, it is important to keep the possibility of nonaccidental trauma in the differential diagnosis, because abusive head trauma and VKDB often present with similar, nonspecific symptoms (Kellogg, 2007).

2. What is the function of vitamin K in the body?

Vitamin K is a fat-soluble vitamin that is a critical part of the clotting cascade. It is necessary for synthesis in the liver of four clotting factors (II, VII, IX, and X), as well as the anticoagulation proteins C and S (Ardell, Offringa, & Soll, 2010). Two types of natural vitamin K exist: K1 (phyloquinone), which is plant based and typically is found in green leafy vegetables and oils, and K2 (menaquinone), which is produced through endogenous synthesis from intestinal flora (Ardell et al., 2010). Vitamin K works to facilitate binding of the procoagulation clotting factors II, VII, XI, and X with surface phospholipids through calcium ion channels, which initiates the thrombotic process (Sarnaik, Kamat, & Kannikeswaran, 2010). Deficits of vitamin K affect both the intrinsic and extrinsic clotting cascade and can result in prolonged clotting times and hemorrhage. Deficiency can occur relatively quickly because of the short half-life of the vitamin K–dependent coagulation factors. Deficiency is seen not only in newborns but also in persons with malabsorption syndromes, decreased production of bile salts, insufficient intake, or decreased intestinal flora related to antibiotic use (Ardell et al., 2010).

3. What is VKDB? What populations are at greatest risk?

VKDB, formerly known as hemorrhagic disease of the newborn, is a bleeding disorder caused by low levels of vitamin K–dependent clotting factors. Although vitamin K deficiency can occur in older children and adults, it is most common in newborns who have limited stores of vitamin K and immature gastrointestinal tracts. Placental transfer of vitamin K is low, and the serum levels of vitamin K–dependent factors have been found to be as low as 50% those of adults (Ardell et al., 2010). Diagnosis of VKDB can be made in infants younger than 6 months who have spontaneous bleeding, bruising, or intracranial hemorrhage with a prolonged clotting time but with a normal or elevated platelet count. The exception to this scenario is infants with an inherited coagulopathy or disseminated intravascular coagulation (Gopakumar et al., 2010).

VKDB can be classified into three distinct groups. Early VKDB typically occurs within the first 24 hours of life and is not affected by vitamin K prophylaxis at birth. This early-onset bleeding is related to medications taken by women in the intrapartum period that affect vitamin K storage and function in the newborn, including Warfarin, anticonvulsants, Rifampin, and Isoniazid (Hubbard & Tobias, 2006). Women taking these medications should be given 5 mg of oral vitamin K daily during their third trimester of pregnancy to prevent the onset of early VKDB. Classic VKDB presents between day 2 and 7 of life and typically involves gastrointestinal, nasal, skin, or circumcision site bleeding. This classic form is related to the low placental transfer of vitamin K, low concentration in breast milk, lack of gastrointestinal flora in the newborn gut, and the poor oral intake that commonly occurs in the newborn period as breastfeeding is initiated (Hubbard & Tobias, 2006). Classic VKDB has been reported to occur in as many as 0.25% to 1.7% of infants without prophylaxis (AAP, 2003). Late onset of VKDB occurs between 7 days and 6 months and is seen primarily in infants who are exclusively breastfed and who have not received prophylaxis, although it may be related to other complications that interfere with synthesis or storage of clotting factors. Although few data are
available on the incidence of late VKDB in the United States, studies from Europe and Asia have reported a prevalence of 4.4 to 7.2 infants per 100,000 births (AAP, 2003). Common symptoms of late VKDB in infants include vomiting (44%), bulging fontanelles (40%), pallor (40%), decreased appetite (32%), seizures (40%), and "warning bleeding" occurring at other sites such as the nares, mucosa, or umbilicus (36%; Misirlioglu et al., 2009). Up to 50% of infants with late VKDB present with intracranial hemorrhage (Van Hasselt, et al., 2008), and up to 69% of these infants have multifocal hemorrhaging. As such, late VKDB carries a significant morbidity and mortality rate, with mortality as high as 20% to 50% in various studies (Cekinmez, Cemil, Cekinmez, & Altmors, 2008). Follow-up from a 2009 study of 29 infants with VKDB-associated intracranial hemorrhaging found that 57.1% were developmentally normal and 42.8% had neurologic defects including hydrocephalus, cerebral atrophy, encephalopathy, epilepsy, and developmental delay (Misirlioglu et al., 2009).

Breastfeeding has been implicated as a risk factor for the development of VKDB, because breast milk has very low levels of vitamin K (< 5–15 μg/L) when compared with formula (50–60 μg/L; Van Hasselt et al., 2008). Children with hepatic or intestinal disease that interferes with absorption of vitamin K also are at increased risk of developing VKDB (Van Hasselt et al., 2008). For some persons, VKDB is the first indicator of an underlying disorder such as malabsorption, infectious diarrhea, cystic fibrosis, alpha1-antitrypsin deficiency, hepatic dysfunction, or celiac disease (Van Hasselt et al., 2008).

4. What is the appropriate management for persons with VKDB?

Once the diagnosis of VKDB is established, the priority is to rapidly correct the coagulopathy to prevent ongoing hemorrhage and minimize complications. Administration of vitamin K is the most appropriate means to correct a vitamin K deficiency and has been shown to normalize PT and PTT in as little as 4 to 6 hours (Cekinmez et al., 2007). One study showed a 30% to 50% correction of PT within 1 hour (Clarke & Shearer, 2007b). Doses of 1 to 3 mg of vitamin K have been administered in the setting of VKDB via intramuscular, IV, or subcutaneous injection (Clarke & Shearer, 2007b). Studies have shown that parenteral administration of a single dose of vitamin K in the setting of VKDB is sufficient to correct coagulation disturbance (Ardell et al., 2010). Intramuscular vitamin K has been shown to be effective in correcting the PT and reversing the coagulopathy, but the concern exists for hematoma associated with intramuscular injection in a person with coagulopathy. IV vitamin K administration carries less risk of hematoma formation, but reports have been made of allergic and anaphylactic reactions to this form of administration. Less risk of hematoma or anaphylaxis occurs with subcutaneous administration; however, the drug absorption with subcutaneous administration been shown to be inconsistent (Gopakumar et al., 2010).

FFP also is used frequently to urgently correct coagulopathies in infants with VKDB (Sarnaik et al., 2010). FFP is plasma taken from a unit of whole blood, which contains all coagulation factors in their normal concentrations and can correct the PT. Transfusion is indicated in patients presenting with a coagulation deficiency who are actively bleeding or undergoing invasive procedures (Gopakumar et al., 2010). Dosed at 10 to 20 mL/kg, FFP ideally requires cross-matching before administration, although AB plasma can be administered in emergent situations (Helfaer & Nichols, 2009). Although Hubbard and Tobias (2006) expressed a concern regarding the possibility for delay in administration because of the necessity for thawing FFP before administration and the concern for volume overload in the pediatric population, a review of the literature reveals that administration of FFP remains standard practice in the setting of severe VKDB (Gopakumar et al., 2010; Hubbard & Tobias, 2006; Samaik et al., 2010). The use of recombinant factor Vlla, a newer clotting agent currently approved by the Food and Drug Administration for use in patients with hemophilia and factor deficiencies, was discussed in one case study. Results showed reversal of coagulopathy after administration of recombinant factor Vlla. Further analysis of its use in the pediatric population continues (Hubbard & Tobias, 2006).

After correction of the underlying coagulopathy, the priority is the management of hemorrhage-associated sequelae, which are largely dependent on the location and severity of the bleeding. In an infant or child with a complicated intracranial hemorrhage, management includes hospitalization with intensive care monitoring, management of ICP, neurosurgical evaluation with surgical decompression and evacuation of clots once coagulopathy has resolved, and a
neurology evaluation for seizure management.

5. What are the current recommendations for vitamin K prophylaxis? What are the concerns?

After the identification of an association between vitamin K and spontaneous hemorrhage in newborns, the AAP began recommending in 1961 that all newborns receive vitamin K prophylaxis to prevent hemorrhage, either as a one-time intramuscular dose or as a series of 3 oral doses (AAP, 1961). In the 1950s and 1960s, concern was raised regarding the increased incidence of hemolytic anemia and kernicterus associated with the use of menadione, or VK3, a water-soluble form of vitamin K used at the time (Hubbard & Tobias, 2006). In 1990, a British study linked administration of intramuscular vitamin K at birth with an increased risk of childhood cancers (Golding, Paterson, & Kinlen, 1990). A follow-up study in 1992 showed no increased risk with oral vitamin K but supported the association between intramuscular prophylaxis and the development of childhood cancer. This study showed an increased rate of leukemia in children who had received intramuscular vitamin K, and the authors subsequently recommended prophylaxis exclusively with oral vitamin K to eliminate the increased risk of leukemia (Golding, Greenwood, Birmingham, & Mott, 1992). An early preparation of intramuscular vitamin K (Synkavit) included the emulsifier polyethoxylated castor oil, as well as the preservatives propylene glycol and phenol, which was shown to cause tumors in mice (Clarke & Shearer, 2007a) and was cited as being administered to infants in the 1992 Golding study (Golding et al., 1992). Newer formulations of vitamin K, Konakion and AquaMEPHYTON, contain more natural emulsifiers and have an "improved safety profile" with less risk of jaundice and anaphylaxis and no known carcinogenic properties (Clarke & Shearer, 2007a).

Multiple studies subsequent to the 1990 and 1992 studies by Golding and colleagues found no correlation between intramuscular vitamin K administration and an increased incidence of childhood cancers (AAP, 2003; Draper & Stiller, 1992; Hubbard & Tobias, 2006; Ross & Davies, 2000). In 2003, the AAP Vitamin K Ad Hoc Task Force concluded that no evidence exists to support an increased risk of cancer with the administration of parenteral vitamin K, and the AAP continues to recommend the administration of intramuscular vitamin K at a dose of 0.5 to 1 mg for all newborns (AAP, 2003).

Historically, much debate has ensued about the best route and effectiveness of oral versus intramuscular vitamin K prophylaxis. The benefits of prophylaxis for prevention of VKDB are well established, and studies have shown that prophylactic administration, regardless of route, is more cost-effective than management of VKDB sequelae (Ross & Davies, 2000). Practice has varied during the past 50 years and continues to vary from country to country. Oral vitamin K prophylaxis has the benefit of being minimally invasive and less expensive than the intramuscular version. Because oral administration generates lower peak levels and lower sustained levels than parenteral administration, an oral regimen requires repeated dosing and includes the risk of missed doses. In the 1990s, the Netherlands and Denmark both offered examples of oral prophylaxis models. Infants in the Netherlands received 1 mg of vitamin K orally at birth and 25-μg daily doses for 3 months. In 2005, a study showed a discouraging 3.2/100,000 incidence of late VKDB (Ijland, Pereira, & Cornelissen, 2008). Danish infants were given 2 mg orally at birth and weekly 1-mg doses for 3 months. From 1992 to 2000, no VKDB cases were reported in a population in which 71% of mothers reported breastfeeding (Clarke & Shearer, 2007a). Intramuscular vitamin K administration is more invasive than oral administration, but it is a one-time dose with no concerns for ongoing compliance. Although early concerns were expressed regarding jaundice risk and more recent concerns have regarded the carcinogenicity of the intramuscular preparation, no evidence has supported this concern since 1992, and the modern formulation has been shown to be safer than the one previously used. The AAP at this time recommends only intramuscular administration, but it does cite a need for continued research regarding the optimal dosing and safety of oral prophylaxis (2003).

Equally if not more pressing is the need for promotion of the risks of VKDB related to missed prophylaxis. Although parents have a right to make medical choices for their children, parental refusal of vitamin K administration has been associated with 31% to 70% of cases of VKDB (Clarke & Shearer, 2007b). The AAP recommends administration of prophylactic vitamin K to all newborns, regardless of the location of their birth (2003). Although midwifery regulations vary from state to state, formal state regulations and standards of practice typically include a recommendation for
vitamin K administration (Department of Regulatory Agencies, 2012; New York State Department of Health, 2010). Although no concrete data exists regarding the incidence of vitamin K administration for infants born at home, it is clear that the frequency of home births is increasing. In 2010 in the United States, 0.8% of births took place in the home (U.S. Department of Health & Human Services, 2012), an increase from 0.73% in 2009 (U.S. Department of Health & Human Services, 2011) and 0.6% in 2007 (U.S. Department of Health & Human Services, 2010). No direct evidence exists to link home birth to an increased rate of vaccination and vitamin K refusal. However, one qualitative study of women who chose home birth found that women choosing to give birth at home tended to do so in an attempt to "redefine authoritative knowledge," enhance their control of the birthing process, and create a greater sense of intimacy (Cheyney, 2008, p. 265). Although this finding does not directly indicate an increased likelihood to refuse vaccinations, it does reflect an overall questioning of the "validity of mainstream metanarratives" regarding the birth experience as a whole (Cheyney, 2008, p. 265).

Refusal of vaccinations and prophylactic medications such as vitamin K has continued associated risks that create challenges for the provider and health system. Discussions that include the risk and benefits of safe vitamin K administration may correct any misconceptions and misinformation that would allow parents to make a fully informed decision (AAP, 2005).

**Patient Outcome**

At 4 months of age, the infant was residing at home. He was alert, active, breastfeeding, and sleeping well according to his family. He continued to take oral Topiramate and Phenobarbital and had been seizure-free since hospital discharge. He had no recurrent bleeding, and follow-up coagulation studies had been normal. He displayed a degree of visual impairment, decreased head control, delayed milestones, and decreased right-sided movement, for which he is being followed up by neurology and physical therapy. His vaccinations remain delayed. The infant's family has expressed a concern about giving multiple vaccinations simultaneously, and by 4 months of age he had not received any vaccinations.

**References**


