Vitamin K Deficiency: Pathophysiology, Clinical Manifestations, Diagnosis and Management — A Narrative Review

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***Abstract*—Vitamin K is a fat-soluble micronutrient essential for the post-translational gamma-carboxylation of clotting factors II, VII, IX and X, as well as several non-coagulation proteins such as osteocalcin and matrix Gla-protein. Although classic vitamin K deficiency bleeding has become uncommon because of routine neonatal prophylaxis, clinically significant deficiency continues to occur in newborns who do not receive prophylaxis, in patients with fat malabsorption, hepatobiliary disease, or prolonged antibiotic use and in individuals on vitamin K antagonist therapy. This narrative review summarizes the physiology, etiology, clinical presentation, diagnostic approach and management of vitamin K deficiency, with emphasis on recognizing at-risk populations and instituting timely phytonadione therapy. Early identification of risk factors, judicious laboratory testing including prothrombin time and protein induced by vitamin K absence-II and prompt vitamin K1 administration remain the cornerstones of preventing morbidity and mortality associated with this largely preventable condition.**

***Index Terms*—vitamin K; phytonadione; coagulopathy; vitamin K deficiency bleeding; phylloquinone; menaquinone**

I. INTRODUCTION

Vitamin K was first identified in the 1930s for its role in the "Koagulation" of blood and it remains indispensable for normal hemostasis nearly a century later (Shearer & Newman, 2008). Unlike most fat-soluble vitamins, vitamin K is poorly stored in the body, has a short biological half-life and must be continuously supplied from dietary phylloquinone, bacterially synthesized menaquinones and intestinal microbial production (Booth, 2009). Because of this limited reserve, even brief interruptions in intake or absorption can precipitate deficiency. Clinically, vitamin K deficiency is best known for its hemorrhagic consequences, ranging from minor bruising to life-threatening intracranial bleeding in neonates, but emerging evidence also implicates the vitamin in bone mineralization and vascular health through its non-coagulation dependent proteins (Beulens et al., 2013). Despite the success of neonatal prophylaxis programs in reducing classic hemorrhagic disease of the newborn, vitamin K deficiency continues to be encountered in clinical practice, particularly among exclusively breastfed infants who miss prophylaxis, patients with malabsorptive disorders and those receiving long-term antibiotic or anticoagulant therapy (Lippi & Franchini, 2011). This review consolidates current understanding of the physiology, causes, clinical features, diagnostic strategy and treatment of vitamin K deficiency for clinical reference.

II. VITAMIN K: FORMS, SOURCES AND PHYSIOLOGICAL FUNCTIONS

Vitamin K exists naturally in two principal forms: phylloquinone (vitamin K1), derived predominantly from green leafy vegetables and plant oils and the menaquinones (vitamin K2), a family of compounds produced by gut bacteria and present in fermented foods and animal products (Booth, 2009). A synthetic precursor, menadione (vitamin K3), is no longer used therapeutically because of its hepatotoxic potential. Because robust biomarkers of vitamin K nutritional status remain limited, current dietary reference intakes are based on an adequate intake level rather than an estimated average requirement, reflecting an incomplete understanding of population-level requirements (Shearer et al., 2012). Functionally,

vitamin K acts as an essential cofactor for the hepatic microsomal enzyme gamma-glutamyl carboxylase, which converts specific glutamate residues on precursor proteins into gamma-carboxyglutamate (Gla) residues (Shearer & Newman, 2008). This carboxylation step is indispensable for the calcium-binding activity of the vitamin K-dependent clotting factors II (prothrombin), VII, IX and X, as well as the natural anticoagulant proteins C and S.

During carboxylation, vitamin K is oxidized to its epoxide form and must be recycled back to its active hydroquinone form by vitamin K epoxide reductase, a cycle that is the pharmacological target of warfarin and related anticoagulants (Shearer & Newman, 2008). Beyond hemostasis, vitamin K-dependent gamma-carboxylation also activates osteocalcin, a bone matrix protein involved in mineralization and matrix Gla-protein, which inhibits vascular and soft-tissue calcification, linking the vitamin to skeletal and cardiovascular health (Beulens et al., 2013; Ferland, 2012). These extra-hepatic roles, although less acutely life-threatening than coagulopathy, underscore why vitamin K deficiency can have consequences that extend beyond bleeding alone.

III. ETIOLOGY AND RISK FACTORS

Vitamin K deficiency arises whenever intake, absorption, or hepatic utilization of the vitamin is insufficient to meet ongoing carboxylation demands. Neonates are uniquely vulnerable because of poor placental transfer of phylloquinone, immature hepatic synthetic function, sterile or immature gut flora and the low vitamin K content of human breast milk; without prophylaxis, these factors combine to produce a transient but potentially dangerous physiological deficiency in the first weeks of life (Shearer, 2009). Beyond infancy, fat malabsorption is the most common cause in older children and adults, since vitamin K absorption depends on adequate bile and pancreatic exocrine function; conditions such as celiac disease, cystic fibrosis, cholestatic liver disease, inflammatory bowel disease and short bowel syndrome all impair micellar solubilization of this fat-soluble vitamin (National Institutes of Health [NIH], Office of Dietary Supplements, 2021). Pharmacologic causes are also clinically important: vitamin K antagonists such as warfarin directly inhibit the vitamin K cycle, broad-spectrum and cephalosporin antibiotics can deplete vitamin K-producing intestinal flora and bile acid sequestrants or the anti-obesity drug orlistat reduce intestinal absorption of fat-soluble vitamins (Holmes et al., 2012; NIH, Office of Dietary Supplements, 2021). Severe hepatocellular dysfunction can mimic deficiency by impairing synthesis of clotting factors even when vitamin K stores are adequate, a distinction that is clinically relevant because such coagulopathy does not correct with vitamin K administration (Eden et al., 2023). Table 1 summarizes the principal categories of risk for vitamin K deficiency encountered in clinical practice.

Table 1. Major Causes and Risk Factors for Vitamin K Deficiency

Category	Specific Causes / Risk Factors	Underlying Mechanism
Neonatal	No prophylaxis at birth; exclusive breastfeeding; prematurity	Poor placental transfer, low hepatic stores, low vitamin K in breast milk, immature gut flora
Malabsorptive / GI disease	Celiac disease, cystic fibrosis, cholestasis, inflammatory bowel disease, short bowel syndrome	Impaired bile/pancreatic function reduces micellar absorption of fat-soluble vitamin K
Drug-induced	Warfarin/vitamin K antagonists; broad-spectrum or cephalosporin antibiotics; bile acid sequestrants; orlistat	Direct antagonism of the vitamin K cycle, depletion of gut flora, or reduced intestinal absorption
Hepatic disease	Cirrhosis; acute hepatocellular failure	Reduced hepatic synthesis of clotting factors despite adequate vitamin K
Dietary / Other	Prolonged parenteral nutrition without supplementation; restrictive diets; chronic alcohol use	Inadequate intake of phylloquinone and menaquinones

Note. Compiled from Shearer (2009), Holmes et al. (2012), NIH, Office of Dietary Supplements (2021) and Eden et al. (2023).

IV. CLINICAL MANIFESTATIONS

The hallmark clinical feature of vitamin K deficiency is a bleeding tendency resulting from impaired activity of clotting factors II, VII, IX and X. In neonates, this presents as vitamin K deficiency bleeding (VKDB), traditionally classified by timing of onset into early, classic and late forms, each with characteristic bleeding sites and underlying causes (Shearer, 2009; Araki & Shirahata, 2020). Late VKDB is of particular concern because it frequently manifests as sudden intracranial hemorrhage in an apparently healthy, exclusively breastfed infant, often without preceding minor bleeding and carries substantial mortality and neurological morbidity if not promptly recognized (Araki & Shirahata, 2020). In older children and adults, deficiency more commonly presents with easy bruising, mucosal bleeding such as epistaxis or gingival bleeding, hematuria, gastrointestinal bleeding and excessive bleeding after minor trauma or surgical procedures. Laboratory abnormalities precede overt bleeding and include a prolonged prothrombin time (PT) and international normalized ratio (INR), with a typically normal or only mildly prolonged activated partial thromboplastin time and normal platelet count, distinguishing it from disorders of platelet function or fibrinogen deficiency. Beyond hemostasis, chronic subclinical vitamin K insufficiency has been associated in observational studies with lower bone mineral density and increased fracture risk, attributable to under-carboxylation of osteocalcin and with greater vascular calcification, related to under-carboxylated matrix Gla-protein, although causal supplementation trials remain inconclusive (Booth, 2009; Beulens et al., 2013). Table 2 outlines the classification of VKDB in infancy.

Table 2. Classification of Vitamin K Deficiency Bleeding (VKDB) in Infancy

Type	Onset	Common Bleeding Sites	Typical Cause
Early VKDB	Within 24 hours	Cephalhematoma, intracranial, intra-abdominal	Maternal drugs affecting vitamin K (e.g., anticonvulsants, warfarin)
Classic VKDB	Day 1–7	Umbilical stump, GI tract, skin, post-circumcision	Delayed feeding; no vitamin K prophylaxis
Late VKDB	2–12 weeks	Intracranial (high mortality), GI tract, skin	Exclusive breastfeeding without prophylaxis; undiagnosed cholestasis or malabsorption

Note. Adapted from Shearer (2009) and Araki and Shirahata (2020).

V. DIAGNOSIS

The diagnosis of vitamin K deficiency is largely clinical, supported by coagulation studies and confirmed by therapeutic response. A history of inadequate neonatal prophylaxis, exclusive breastfeeding, malabsorptive illness, prolonged antibiotic use, anticoagulant therapy, or restricted dietary intake should heighten clinical suspicion in a patient presenting with unexplained bleeding or an incidentally prolonged PT/INR (Eden et al., 2023).

Standard coagulation testing typically reveals a prolonged PT and INR with a normal or near-normal activated partial thromboplastin time and platelet count; in more severe or prolonged deficiency, the aPTT may also become mildly elevated because factor IX is vitamin K-dependent. Where available, measurement of protein induced by vitamin K absence or antagonism-II (PIVKA-II), an under-carboxylated form of prothrombin, offers a more sensitive marker of subclinical deficiency than PT alone (Shearer, 2009).

The most pragmatic confirmatory test remains the therapeutic trial: correction of the PT/INR within 24 to 48 hours of parenteral vitamin K1 administration strongly supports a diagnosis of vitamin K deficiency, whereas failure to correct should prompt evaluation for hepatocellular disease, disseminated intravascular coagulation, or an inherited coagulation factor deficiency. Figure 1 presents a stepwise diagnostic and management algorithm for a patient with suspected vitamin K deficiency.

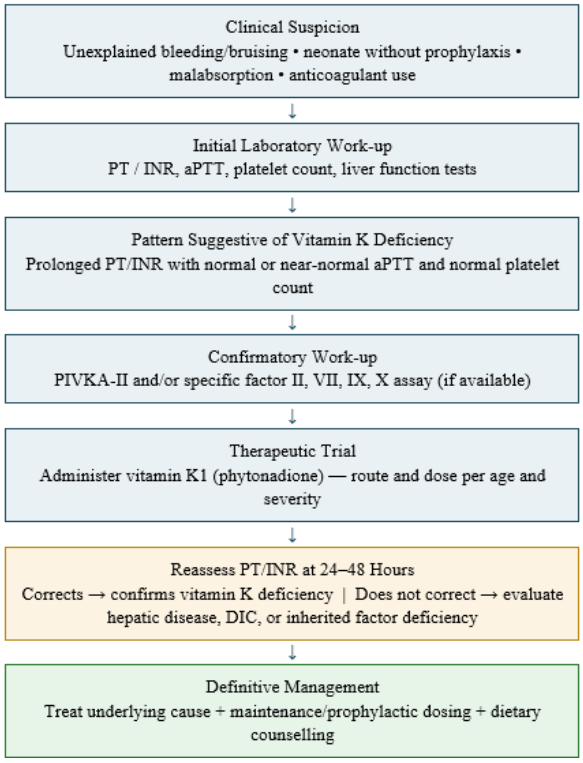

Figure 1. Diagnostic and Management Algorithm for Suspected Vitamin K Deficiency

VI. TREATMENT AND PREVENTION

Management of vitamin K deficiency centers on prompt repletion with vitamin K1 (phytonadione) and correction of the underlying cause. For neonates, the American Academy of Pediatrics and most national guidelines recommend a single intramuscular dose of 0.5 to 1 mg phytonadione at birth, which has proven highly effective in preventing classic VKDB and in reducing late VKDB; oral regimens are used in some countries but require multiple doses and stricter compliance to achieve comparable protection (Lippi & Franchini, 2011). In older children and adults with confirmed deficiency, oral or intravenous phytonadione is administered according to the severity of bleeding and the magnitude of INR elevation, with intravenous dosing reserved for active or severe hemorrhage because of the small but recognized risk of anaphylactoid reactions with rapid infusion. Patients on warfarin therapy with an elevated INR are managed with individualized low-dose vitamin K1, balanced against the desired degree of anticoagulation, rather than full repletion, to avoid abrupt reversal of therapeutic anticoagulation (Holmes et al., 2012). Underlying causes must be addressed concurrently: malabsorptive disorders warrant treatment of the primary gastrointestinal or hepatobiliary disease together with ongoing vitamin K supplementation, while prolonged antibiotic courses in at-risk patients may justify prophylactic supplementation. Dietary counseling emphasizing consistent intake of green leafy vegetables and other vitamin K-rich foods is appropriate for most patients, except where intake must be kept stable rather than increased, as in those stabilized on vitamin K antagonists (NIH, Office of Dietary Supplements, 2021). Universal neonatal prophylaxis remains the single most effective public health measure for preventing vitamin K deficiency-related morbidity and mortality (Suttie, 2009).

VII. CONCLUSION

Vitamin K deficiency, though largely preventable, remains a clinically significant cause of bleeding across the lifespan, from neonatal intracranial hemorrhage to coagulopathy in adults with malabsorption, hepatic disease, or drug-induced depletion. A sound understanding of vitamin K physiology, recognition of at-risk groups and timely use of coagulation testing and phytonadione therapy allow most cases to be diagnosed and treated effectively. Continued emphasis on universal neonatal prophylaxis, vigilance in malabsorptive and pharmacologically at-risk populations and further research into the vitamin's non-coagulation roles in bone and vascular health will help refine future preventive and therapeutic strategies.

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