Vitamin K Coagulopathy Overview: Manifestation, Diagnosis and Therapy
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Definition

Coagulopathy is a condition in which the blood's ability to coagulate (form clots) is impaired. This condition can cause a tendency toward prolonged or excessive bleeding, which may occur spontaneously or following an injury or medical and dental procedures.
Vitamin K Dependent Factors

<table>
<thead>
<tr>
<th>Assay</th>
<th>Pathway</th>
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<tbody>
<tr>
<td>ACT</td>
<td>Intrinsic and common</td>
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<tr>
<td>aPTT</td>
<td>Intrinsic and common</td>
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<tr>
<td>PT</td>
<td>Extrinsic and common</td>
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<tr>
<td>Fibrinogen</td>
<td>Fibrinogen only</td>
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Epidemiology

- Can occur in any age group
- In infants coagulopathy associated mostly with Vitamin K (VK) deficiency
- In adults – with VK antagonist overdose
- In United States, the prevalence of VK coagulopathies varies by geographic region
- In infants VK deficiency without bleeding may occur in as many as 50% of infants younger than 5 days
- The classic hemorrhagic disease occurs in 0.25-1.7% of infants
- The prevalence of late hemorrhagic disease in breastfed infants is about 20 cases per 100,000 live births with no prior VK prophylaxis.
Causes

Insufficient intake of VK with food

- Alcohol abuse
- Long-lasting parenteral nutrition without VK supplementation
- Exclusively breast-feeding (newborns)
Deficient bioavailability of VK due to impaired biosynthesis in IT

- Medicine induced intestinal dysbiosis (after AB treatment)
- Enteropathies accompanied by heavy diarrhea (infectious diarrhea, inflammatory bowel disease)
- Malabsorption (cystic fibrosis)
- Mechanical jaundice with acholia that leads to reduction or absence of bile secretion in the intestinal tract
- Prematurity of the newborns associated with subnormal synthesis of vitamin K in intestinal tract
Causes

- **Severe liver disease:**
  - Acute dystrophies
  - Hepatitis
  - Cirrhosis

- **Side effect of a series of different therapeutic regimens:**
  - Statins (bind bile acid, thus preventing the absorption of fat-soluble vitamins)
  - Salicylates
  - Rifampicin
  - Isoniazid
  - Barbiturates
  - Overdose of orally prescribed anticoagulants of indirect-action, (vitamin K antagonists/VKA)
The signs and symptoms VK coagulopathies

- Easy bruising
- Oozing from nose or gums
- Excessive bleeding from wounds, punctures, injection
- Heavy menstrual periods
- Bleeding from the gastrointestinal (GI) tract
- Blood in the urine and/or stool
- Increased prothrombin time (PT)
- Intracranial bleeding
Vitamin K deficiency bleeding (VKDB) in children

- Potentially life-threatening bleeding disorder of early infancy

- Classical VKDB occurs in the first week of life with incidence between 2.5 to 17.0 per thousand newborns not given vitamin K prophylactically

- Late VKDB is rarer, rates of 4.4-7.2/100,000 live births
## VKDB types and their characteristics

<table>
<thead>
<tr>
<th>Type of VKDB</th>
<th>Location</th>
<th>Causes and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early</strong></td>
<td>Cephalhematoma, umbilicus, intracranial, intraabdominal, intrathoracic, gastrointestinal</td>
<td>Drugs taken during pregnancy (anticonvulsants, oral anticoagulants, tuberculostatics and antibiotics)</td>
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<tr>
<td>0-24 hours after birth</td>
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<tr>
<td><strong>Classical</strong></td>
<td>Gastrointestinal tract, umbilical cord, nose, needle-prick sites, circumcision, intracranial</td>
<td>Marginal VK content in breast milk. Inadequate milk intake for any reason, include late onset of feeding</td>
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<td>1-7 days after birth (mostly 3-5)</td>
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<tr>
<td><strong>Late</strong></td>
<td>Intracranial (30-60%), skin, nose, needle-prick sites, gastrointestinal tract, umbilicus, urogenital tract, intrathoracic</td>
<td>Marginal VK content in breast milk (idiopathic). Malabsorption of VK (liver or bowel disease)</td>
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<td>Week 2 to 6 month (mostly weeks 2-8)</td>
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Vitamin K deficiency causes and risks factors in children

- **Cause:** physiological low VK level at birth
- **Risk:** babies who do not receive a vitamin K shot at birth.
- **Cause:** physiological low concentrations of VK in human milk
- **Risk:** babies under exclusively breast-feeding and premature babies (gut is not yet colonized with bacteria)
- **Cause:** malabsorption of VK
- **Risk:** babies who have diarrhea, celiac disease, or cystic fibrosis
- **Cause:** Inability to use the VK stores in their body
- **Risk:** babies who have liver disease
- **Cause:** isoniazid or anticonvulsants which interfere with how the body uses VK
- **Risk:** babies whose mothers used isoniazid or anticonvulsants medications
Clinical Case #1

4 week old Caucasian male presents in hospital after his parents noted a streak of bright red blood in his stool as well as emesis with brown streaks. Few weeks earlier infant was diagnosed with Cystic Fibrosis (CF) when he was noted to be “gassy and colicky” with yellow-green, foul smelling stools, 10 times a day. Weight gain was appropriate. Routine CF care was prescribed (bronchodilator, pancreatic enzymes and fat soluble vitamins supplementation)
Boy was born at full term, had routine care, including vitamin K prophylaxis at birth.
Coagulopathy with markedly prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) was evident:

PT >100 s (normal range of 9.5–11.7 s)  
aPTT - 86.1 s (23–32 s)  
Complete blood count – N  
Metabolic panel - N  
Vitamin A level - N  
Vitamin E - 2.6 (3.8–18.4 mg/l)  
Factor VII < 5% (50–150%)  
Factor X < 5% (50–150%)  
Factor V (non-VK dependent clotting factor) - 91% (50-150%).

Cranial ultrasound: no hemorrhage.  
Stool hemeoccult test: positive.
Clinical Case #1 – Diagnosis and Management

Coagulopathy due to vitamin K deficiency.

Infant received 1 mg subcutaneous injection of vitamin K. Next laboratory evaluation, 7.5 h later, showed complete correction of his coagulopathy. He was discharged home on daily ADE vitamins and oral vitamin K supplementation three times a week. He had no further evidence of bleeding in the next few months. Repeat PT and PTT continued to be within normal limits.
Clinical Case #2

28-day-old male, presented in emergency department with ecchymosis of his left hemiscrotum. This exclusively breastfed infant, without significant family history, had been thriving at home when the parents noted acute discoloration of his right testicle at 26 days of age. In the 24 hours prior to admission, the discoloration of his right testicle migrated to the left testicle. His parents reported that he had become progressively fussy and appeared more pale. The infant did not receive vitamin K prophylaxis at birth, though his mother was taking oral vitamin K daily.
Clinical Case #2 – Examination Results

On medical examination:
Baby appeared lethargic, pale, and jaundiced and had evidence of oozing from peripheral IV attempts. His left hemiscrotum was purpuric.

Laboratory results reveals vitamin K-deficiency related coagulopathy:
- PT > 70 s (9.5–11.7 s)
- aPTT - 66.2 s (23–32 s)
- Factor VII < 10% (50–150%)
- Factor X < 10% (50–150%)
- Factor V (non-VK dependent clotting factor) - 91% (50-150%).
Clinical Case # 2 – Diagnosis and Management

Vitamin K deficiency coagulopathy.

Boy received 1 mg subcutaneous injection of vitamin K. He was discharged home on oral vitamin K supplementation three times a week. He had no further evidence of bleeding in the next few months.
VKDB Diagnostic Criteria

- Elevation of the prothrombin time (PT) $\geq$ 4 times the laboratory limit of normal
- Normal or elevated platelet count, normal fibrinogen, and absent fibrin degradation products (excludes disseminated intravascular coagulation)
- PT returning to normal after vitamin K administration
VKDB Treatment

- Infants with a non-life-threatening bleeding should receive a single 1-2mg intravenous dose of vitamin K1 (phylloquinone, phytonadione)

- For life-threatening bleeding presentations, additional treatment with fresh frozen plasma (at a dose of 10–15 mL/kg) may be necessary.
VK isolated from alfalfa by Dam and Doisy (Nobel Prize, 1942), and conducted clinical trials showing VK protects against hemorrhagic disease of the newborn

- Prophylactic use of VK recommended by the American Academy of Pediatrics (AAP), and by the American College of Obstetricians and Gynecologists since 1961

- But up until 1987, administration of VK at birth was mandatory in only five states in the US

- AAP recommendation renewed in 1993 and remains current:

  *Intramuscular administration within the first 6 hours after birth - preventing measure for both early and late hemorrhagic disease of the newborn.*
Other Countries

- Still not routine in Japan, Germany, United Kingdom
- Routine prophylactic Vitamin K for newborns adopted in:
  - Canada
  - Australia
  - New Zealand
  - Croatia
  - Russia
3.0% of infants born in hospitals did not receive injectable vitamin K due to parental refusal in 2013, a frequency higher than in 2011 and 2012.

The birthing centers have a higher refusal rate vs to the hospitals.

31% infants born at birthing centers from January through October 2013 did not receive injectable VK.
Interview/telephone survey results of families who refused injectable VK prophylaxis for their child

Participants characteristics:
Correctly identified bleeding as risk of refusal of VK 51%
Refused VK injection, erythromycin eye ointment and neonatal hepatitis B vaccine 49%

Reasons for refusal of VK injection (more than one per family):
• Not necessary 39%
• Desired natural birthing process 27%
• Concern about preservatives/ingredients 14%
• Adverse reactions 10%
• Avoid pain for infant 8%
• Concern about dose being too high 8%
• Concern that injection causes cancer 6%
• Did not want to overwhelm infant immune system 1%

VK Prophylaxis for the Different Forms of VKDB

**Early VKDB**
- stopping or replacing the offending medication during pregnancy if possible, or by VK prophylaxis to the mother during pregnancy.

**Classical VKDB**
- single postnatal dose of VK (oral or IM)

**Late VKDB**
- can also be prevented by VK prophylaxis.
Risk-benefit Analysis of VK Prophylaxis: International Surveys

- **Japan**
  Triple oral prophylaxis using doses of 2 mg VK reduced the incidence 15- to 30-fold.

- **Australia**
  Revert from triple oral to intramuscular (IM) VK prophylaxis demonstrates the efficacy of IM prophylaxis.
  *Intramuscular prophylaxis may form a depot of VK at the injection site and so protect for many weeks, increasing the chances of detecting underlying pathology before bleeding occurs.*

- **Sweden and the USA**
  Intramuscular VK prophylaxis has almost eliminated VKDB of infancy.

- **UK, Sweden, Germany, and Switzerland**
  Intramuscular VK protects more reliably than a single oral dose. Intravenous VK does not have the depot effect of IM VK and so may not give the same prolonged protection.
VK Coagulopathy due to Overdose of VKA

- VKA medicines overdose
- Rodenticides poisoning
VKA Poisoning Statistics

- Rodenticide (RD) poisoning is rare in comparison with other toxic substances but it continues to rise.
- 1988 in the USA - 5133 cases of superwarfarin poisonings.
- 1995 cases raised to 13423.
- 2004 more than 16000 cases of RD poisoning, among them 15000 in children.
- 2010-2015 – registered 315951 cases, nearly 90% of the subjects were children.
VKA Poisoning Routes

HOW?

- Patients had psychiatric disorders: including depressive disorders, dementia and cognitive deterioration
- Took medications which can potentiate the VK antagonist, including counterdepressants; non-steroid anti-inflammatory drugs; disaggregants and antacids (ranitidine)
- Patients accidentally suffered from rodenticide impact
- Patients used rodenticides in suicidal attempts
- Rodenticides poisoning in a state of alcoholic intoxication

Being in an alcoholic condition the moment of intoxication intensifies coagulopathy and influences the genetic susceptibility to warfarin
Clinical Case Presentation #3

A 80-year-old male patient with severe visual impairment, was transferred to hospital with a diagnosis of mediastinal mass found during chest X-ray.
Clinical Case Presentation #3 – Examination Results

All clinical and laboratory signs of VK-dependent coagulopathy were diagnosed:

- **Albumin**: 3.26 (3.3-5.5 g/dL)
- **PT (sec)/INR**: 136/10
- **Factor:**
  - II: 28% (50–150%)
  - VII: 24% (50–150%)
  - XI: 16% (50–150%)
  - X: 19% (50–150%)
  - V: N
Clinical Case #3 – Clinical Interview Conclusion

Patient accidently (by mistake) was taking VKA tablets (Neodicumarinum - VKA from the group of coumarins). The tablets were prescribed to his wife for thrombophlebitis. He had confused these tablets with the nitrates prescribed to him.
Clinical Case #3 – Treatment and Management

The hemorrhagic coagulopathy was stopped by the administration of Prothrombin Complex Concentrate and vitamin K. The mediastinal “mass” entirely resolved.
Clinical Case Presentation #4

A female patient, aged 60, was repeatedly admitted to different hematology units, with severe hemorrhagic syndrome for several years. The huge bruises were noticed on the upper body skin, except from the area of the vertebral spine. The round, smooth, painful lesions were palpated in the abdominal cavity (subserosal haematomas of the intestine) and hematuria was present.
Clinical Case #4 – Examination Results

All laboratory results of Vitamin K-dependent coagulopathy were present:

- Albumin – 3.46
- PT (sec)/INR – 140/8
- Factor II – 7% (50–150%)
- VII – 2% (50–150%)
- XI – 6% (50–150%)
- X – 3% (50–150%)
Clinical Case #4 – Clinical Conclusion and Management

The calm behavior of the patient, in spite of emergency of the situation as depicted by the medical personnel, made the doctor suspicious. When the patient’s clothes were examined, a unit package of neo-dicoumarin was discovered. 

*Patient was found having psychiatric disorder.*

The therapy with fresh frozen plasma and Vitamin K preparation led to clinical recovery and normalization of the laboratory results. 

*Psychiatrist assistance was recommended.*
VKA – associated intracerebral hemorrhage

Intracerebral hemorrhage (ICH), defined as “bleeding into the parenchyma of the brain that may extend into the ventricles and, in rare cases, the subarachnoid space. It is a devastating disease that must be recognized immediately in the emergency department.

- 12–20% of ICH cases are related to VKA use
- The annual rate of VKA related ICH ranges from 0.3% to 0.6%
- ICH accounts for the vast majority (90%) of all VKA-related deaths. ICH has a much higher mortality than ischemic stroke.
- Most ICH related to VKA use occur with international normalizing ratios (INRs) in the recommended therapeutic range, although the risk of hemorrhage is further increased with progressive elevations of the INR
VKA – associated intracerebral hemorrhage

INR > 3.5 nearly doubles the risk of a fatal ICH in patients who are on warfarin when adjusted for age, sex, cardiovascular disease, diabetes, heart failure, hypertension, and type of ICH.
Death and Disability from Warfarin-Associated Intracranial and Extracranial Hemorrhages

- Among anticoagulated patients with atrial fibrillation, intracranial hemorrhages caused approximately 90% of the deaths from warfarin-associated hemorrhage and the majority of disability among survivors.

- At hospital discharge, 76% of patients with intracranial hemorrhage had severe disability or died.

- Of the 40 deaths from warfarin-associated hemorrhage that occurred within 30 days, 88% were from intracranial hemorrhage.

- Compared with extracranial hemorrhages, intracranial events were strongly associated with 30-day mortality (odds ratio 20.8) even after adjusting for age, sex, anticoagulation intensity on admission, and other coexisting illnesses.

http://dx.doi.org/10.1016/j.amjmed.2006.07.034
Subdural Hematoma on CT

Figure 1: The CT of one 81 years old women patient with atrial fibrillation taking warfarin for 30 years after falling down. (A) CT of 3 hours after falling down; (B) Postoperative CT of 3 days; (C) Postoperative CT change of two week; (➔) Postoperative CT change of chronic subdural hematoma 4 years ago.
Clinical Case # 5

A 27 y.o. pregnant woman (31 week), undergoing US examination. US revealed mild enlargement of the left lateral ventricle of the fetus which enlarged on the fifth day of the 33 weeks. MRI performed on the first day of the 35 week of gestation revealed bilateral intracranial subdural hematoma in the fetus, and the left ventricle was found to have enlarged due to compression by the hematoma.

Woman had undergone aortic valve replacement (mechanical) for aortic regurgitation at the age of 10 years. Since then, she had been receiving AC with warfarin, 5 mg/day. Oral administration of warfarin was switched to continuous IV infusion of heparin in the fifth week of gestation. In the 12 weeks of gestation, oral administration of warfarin was resumed at a dose of 3 mg/day, and then, the dose was increased to 4.5 mg/day. The APTT was maintained between 50-60 sec during heparin use, and PT by international normalized ratio (PT/INR) was maintained between 1.5-2.0 during oral administration of warfarin.

Guidelines for vitamin K antagonists (VKAs) reversal

(1) Discontinue VKAs when ICH is present or suspected (good practice statement)

(2) Urgent reversal of VKAs in patients with ICH with the following exceptions:
   a. High suspicion of ICH due to cerebral venous thrombosis
   b. In patients with concurrent symptomatic or life-threatening thrombosis, ischemia, heparin-induced thrombocytopenia, or DIC (good practice statement)

(3) Administration of vitamin K as soon as possible or concomitantly with other reversal agents (strong recommendation, moderate quality evidence).
   The following dosing is recommended:
   a. One dose of vitamin K 10 mg IV
   b. Subsequent treatment should be guided by follow-up international normalizing ratios (INRs) (good practice statement)
   c. If repeat INR is still elevated within the first 24–48 h after reversal agent administration, redose with vitamin K 10 mg IV (good practice statement)
Guidelines for vitamin K antagonists (VKAs) reversal

(4) Administer 3-factor or 4-factor prothrombin complex concentrates (PCCs) rather than fresh frozen plasma (FFP) to patients with INR >1.4 (strong recommendation)

- 4-factor PCC is preferred over 3-factor PCC (conditional recommendation)
- Suggest initial reversal with PCC alone rather than combined with FFP or recombinant FVIIa (rFVIIa) (conditional recommendation)
- PCC dosing should be weight-based and vary according to admission INR and type of PCC used (strong recommendation, moderate quality evidence)
- INR testing should be repeated soon after PCC administration (15–60 min), and serially every 6–8 h for the next 24–48 h.
- Subsequent treatment should be guided by follow-up INR.
- Repeat PCC dosing may lead to increased thrombotic complications and risk of DIC.
- If repeat INR is still elevated >1.4 within the first 24–48 h after initial PCC dosing, suggest further correction with FFP.
Guidelines for vitamin K antagonists (VKAs) reversal

(5) Recommend against administration of rFVIIa for the reversal of VKA (strong recommendation, low quality evidence)

(6) If PCCs are not available or contraindicated, alternative treatment is recommended over no treatment (strong recommendation)

- Treatment with FFP and vitamin K is recommended over no treatment (strong recommendation)
- Suggest dosing FFP at 10–15 ml/kg IV along with one dose of vitamin K 10 mg IV (conditional recommendation, low-quality evidence)
Clinical Case Presentation #6

The patient K., 45 year old, was admitted to the hematology department because of progressive multiple hematomas on the limbs and body, bleeding gums and nasal bleeding. The patient reported that he had originally noticed skin hematomas and nasal and dermal bleedings 2 weeks ago.

During the examination massive subdermal and endermic hematomas were found. The patient categorically denied being beaten (taking into account the location of the hematomas) as well as administration of indirect anticoagulants. Pathology of liver, gall-bladder, gastro-intestinal tract and kidneys were excluded.
Factors

- II – 11% (50–150%)
- X – 11% (50–150%)
- VII – 18% (50–150%)
- IX – 21% (50–150%)
- V, VII, XI – N
- Antithrombin III - N
- Plasminogen – N
- Hemoglobin – 103 g/dl
- Protein C - low
Clinical Case #6 – Diagnosis and Management

Deficiency of Vitamin K-dependent factors of coagulation and of the inhibitor of coagulation protein C.

Treatment start with fresh frozen plasma and 1% Vikasolum solution 1 ml 3 times a day intravenously was started. The hemorrhagic syndrome recessed in 3 days.
Clinical Case # 6 – Clinical Interview Conclusion

The patient was further interviewed with the purpose of diagnosing the possible reasons (including criminal reasons) of the severe deficiency of K-dependent factors. To the question about rat-poison use, the patient’s answer was affirmative. From March to June 2011 and from July to September 2011, the patient, a greengrocer, without any professional help and with bare hands used rat-poison in large quantities. The active agent in rat-poison was brodifacoum (AC). The patient reported that he had worked in food store and he consumed himself fruit and vegetables kept in this location.
VKA poisoning was diagnosed.
Therapy of VKA poisoning

- Hospitalization to the intensive therapy unit for more than 24 h
- Transfusion of fresh-frozen plasma or administration of concentrated prothrombin complex
- For emergency correction of anticoagulation, use the three-factor prothrombin complex concentration (PCC)
- In patients with INR 4 and in patients with higher INR levels – four factor PCC
Therapy of VKA poisoning

- Vitamin K prescription:
  - Preferable to use preparations of Vitamin K1 and not vitamin K3
  - If the patient does not present active bleeding use oral prescription of Vitamin K1 (1–2 mg) or in case of high INR an oral dose of 5 mg
  - For the treatment of the massive life threatening bleeding, Vitamin K1 should be injected slowly in doses of 10–20 mg (not less than 30 min)
  - After the intravenous administration the effect occurs in 2–4 h, the maximum effect occurs in 24 h independently of the way of administration
  - The coagulogram indexes should be followed up to its complete normalization.
Takeaway Messages

- VK Coagulopathy can occur in any age group
- In infants coagulopathy associated mostly with deficiency of VK
- Intramuscular administration within the first 6 hours after birth - preventing measure for both early and late hemorrhagic disease of the newborn
- In adults coagulopathy associated mostly with VKA overdose
- When considering anticoagulation, patients and clinicians need to weigh the risk of intracranial hemorrhage far more than the risk of all major hemorrhages
- VK Coagulopathy diagnostic criteria: elevation of the PT ≥ 4 times of N limit; N or elevated platelet count, N fibrinogen, and absent fibrin degradation products
- VK coagulopathy usually is not life threatening condition, a single dose of parenteral VK is sufficient to stop the bleeding and return PT values to the reference range
THANKS FOR YOUR ATTENTION

QUESTIONS?
PLEASE CLAP AND DON'T ASK TOUGH QUESTIONS.