**ألجامعة المستنصرية /كلية الطب**

**ألمرحلة الرابعة /طب الأطفال**

**MALNUTRITION**

A pathological state due to a relative or absolute deficiency or excess of one or more essential nutrients; clinically manifested or detected only by biochemical, anthropometric, or physiological tests.

The greatest risk of undernutrition (underweight, stunting, wasting, and micronutrient deficiencies) occurs in the first 1000 days, from conception to 24 mo of age, and this early damage to growth and development can have adverse consequences in later life on health, intellectual ability, school achievement, work productivity, and earnings.

**Classification:**

1. Undernutrition: Marasmus

2. Over-nutrition: Obesity, Hypervitaminoses

3. Specific Deficiency: Kwashiorkor, Hypovitaminosis.

4. Mineral Deficiencies

5. Imbalance: Electrolyte Imbalance

**Etiology:**

1. child related:

Low birth wt.

Absence or early cessation of breastfeeding

Delay weaning

Incorrect dietary habit

Recurrent infection: diarrhea, measles

2. Maternal factor:

Maternal malnutrition

Ignorance about feeding

separation

3. socio-economical factor:

Poverty and unemployment

Large family size

Unhygienic living condition

Disadvantaged children (deprived of decent standard of living,education)

4. cultural factor: wrong believes

5. community factor:

Natural/man-made disaster

Generalized economic depression

Inadequate primary healthcare

**Severe Acute Malnutrition (SAM):**

It is defined as severe wasting and/or bilateral edema.

***Severe wasting***is extreme thinness diagnosed by a weight-for-length (or height) < −3 SD of the WHO Child Growth Standards.

In children ages 6-59 mo., a **m**id-**u**pper **a**rm **c**ircumference (MUAC)<115 mm also denotes extreme thinness: a color-banded tape is a convenient way of screening children in need of treatment.

***Bilateral edema***is diagnosed by grasping both feet, placing a thumb on top of each, and pressing gently but firmly for 10 sec. A pit (dent) remaining under each thumb indicates bilateral edema.

This definition of severe acute malnutrition distinguishes wasted/edematous children from those who are stunted since stunted children (although underweight) are not a priority for acute clinical care because their deficits in height and weight cannot be corrected in the short term.

The previous name *protein-energy malnutrition* is avoided because it oversimplifies the complex, multi-deficiency etiology. Other terms are *marasmus* (severe wasting), *kwashiorkor* (characterized by edema), and *marasmic-kwashiorkor* (severe wasting and edema).

**Marasmus**

Marasmus results from the body's physiologic response to inadequate calories and nutrients. Loss of muscle mass and subcutaneous fat stores can be confirmed by inspection or palpation and quantified by anthropometric measurements. Clinical finding: The head may appear large but generally is proportional to the body length. Edema usually is absent. The skin is dry and thin, and the hair may be thin, sparse, and easily pulled out. Marasmic children may be apathetic and weak and may be irritable when touched. Bradycardia and hypothermia signify severely and life-threatening malnutrition. Inappropriate or inadequate weaning practices and chronic diarrhea are common findings in developing countries. Stunting (impaired linear growth) results from a combination of malnutrition, especially micronutrients, and recurrent infections.

**Kwashiorkor**

Kwashiorkor results from inadequate protein intake in the presence of fair to good caloric intake. The hypoalbuminemia state results in pitting edema that starts in the lower extremities and ascends with increasing severity. Other factors, such as acute infection, toxins, and possibly specific micronutrient or amino acid imbalances, are likely to contribute to the etiology.

The major **clinical manifestation** of kwashiorkor is that the body weight is near normal for age; weight alone does not accurately reflect the nutritional status because of edema.

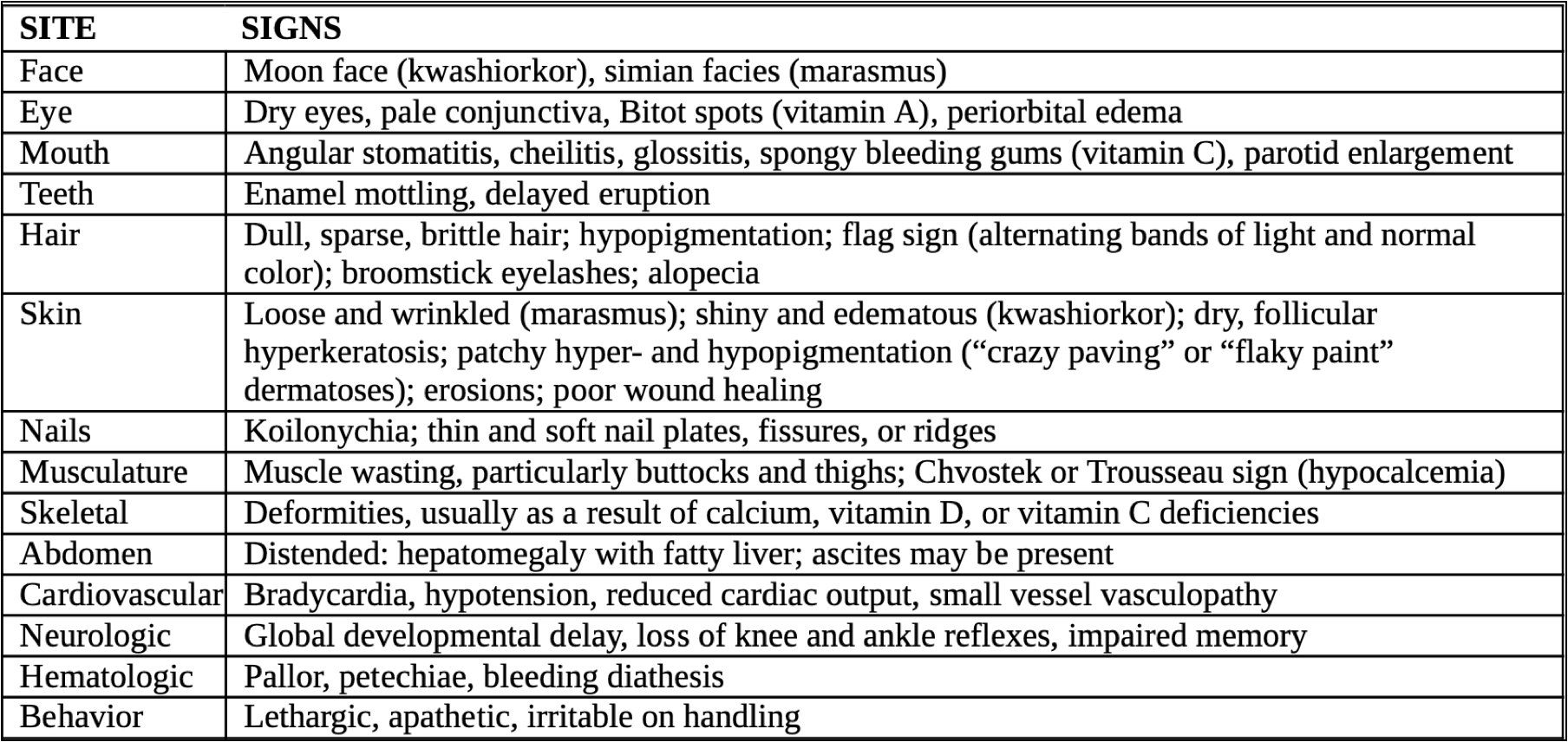
**Physical examination** reveals relative maintenance of subcutaneous adipose tissue and a marked atrophy of muscle mass. Edema varies from a minor pitting of the dorsum of the foot to generalized edema with involvement of the eyelids and scrotum. The hair is sparse, easily plucked, and appears dull brown, red, or yellow-white. Nutritional repletion restores hair color, leaving a band of hair with altered pigmentation followed by a band with normal pigmentation (flag sign). Skin changes are common and range from hyperpigmented hyperkeratosis to an erythematous macular rash (pellagroid) on the trunk and extremities. In the most severe form of kwashiorkor, superficial desquamation occurs over pressure surfaces (“flaky paint” rash).

Angular cheilosis, atrophy of the filiform papillae of the tongue, and monilial stomatitis are common. Enlarged parotid glands and facial edema result in moon facies;

apathy and disinterest in eating are typical of kwashiorkor. Examination of the abdomen may reveal an enlarged, soft liver with an indefinite edge. Lymph nodes and tonsils are commonly atrophic. Chest examination may reveal basilar rales. The abdomen is distended, and bowel sounds tend to be hypoactive.

**Differences between Marasmus and Kwashiorkor**

**(Clinical signs of Malnutrition)**



**Assessment of nutritional status**

Malnutrition must be recognized and accurately defined for rational decisions to be made about refeeding. Evaluation is divided into the assessment of past and present dietary intake, anthropometry, and laboratory assessments.

**Dietary assessment**

Parents are asked to record the food the child eats for several days. This gives a guide to food intake.

**Anthropometry**

In addition to weight and height, the skinfold thickness of the triceps reflects subcutaneous fat stores and can be assessed by measuring it.

While it is difficult to measure skinfold thickness accurately in young children, mid­ upper arm circumference, which is related to skeletal muscle mass, can be measured easily and repeatedly and is independent of age in children 6 months to 6 years. It is especially useful for screening children for malnutrition in the community.

**Laboratory investigations**

These are useful in the detection of early physiological adaptation to malnutrition, but clinical history, examination, and anthropometry are of greater value than any single biochemical or immunological measurement.

**Investigations**

* CBC/CRP/GUE/GSE/RBS/RFT/TSP/S. albumin (low in both)

**Treatment**

**Rx. of PEM involves 3 phases:**

1-Stabilization phase (1st wk.)

2-Rehabilitation phase (2nd wk-6th wk.)

3-follow-up. (7th wk. till recovery)

**1. Stabilization phase (1st wk.):**

It involves Rx & Prevention of infection, hypoglycemia, anemia, dehydration & correction of

electrolyte disturbances, and vitamins & micronutrient deficiency (except iron).

feeding with F75 formula (75 kcal/100 ml)

**2. Rehabilitation phase (2nd wk-6th wk): -**

It involves feeding with the **F100 formula** (100 kcal/100 ml) to give 100 kcal/kg/day. If oral feeding is not tolerated, give it by NG tube. Or use ready-to-use therapeutic food **(RUTFs): a** mixture of powdered milk, peanuts, sugar, vitamins, and minerals it reduces mortality and is less susceptible to contamination than F100.

**3. Follow-up phase (7th wk. till recovery):** By feeding to cover catch-up growth and also the provision of emotional stimulation with the aid of family & the community.



The aim of the **stabilization** phase is to repair cellular function, correct fluid and electrolyte

imbalance, restore homeostasis, and prevent death from the interlinked triad of hypoglycemia, hypothermia, and infection. The aim of the **rehabilitation** phase is to restore wasted tissues (i.e., catch-up growth).

**Emergency Treatment**

In the following table shows that treatment of shock in these children is different (less rapid, smaller volume, different fluid) from treatment of shock in well-nourished children, because shock from dehydration and shock from sepsis often coexist and are difficult to differentiate on clinical grounds.Thus the physician must be guided by the response to treatment: children with dehydration respond to intravenous (IV) fluid, whereas those with septic shock will not respond. Since severely malnourished children can quickly succumb to fluid overload, they must be monitored closely.



**Treatment of hypoglycemia**….(not mentioned in the table above)

If conscious:

1. Give 10% glucose (50 mL), or a feed (Give 8-12 small feeds of F75 ) or1 tsp sugar under tongue, whichever is quickest.

2. Feed every 2 hr for at least 1st day. Initially give of feed every 30 min.

3. Keep warm.

4. Start broad-spectrum antibiotics.

If unconscious:

1. Immediately give sterile 10% glucose (5 mL/kg) rapidly by IV.

2. Feed every 2 hr for at least 1st day. Initially give of feed every 30 min. Use nasogastric (NG) tube if unable to drink.

3. Keep warm.

4. Start broad-spectrum antibiotics.

**Treatment of dehydration**….

Do *not* give IV fluids unless the child is in shock.

1. Give ReSoMal (see below)5 mL/kg every 30 min for 1st 2 hr orally or NG tube.

2. Then give 5-10 mL/kg in alternate hours for up to 10 hr. Amount depends on stool loss and eagerness to drink. Feed in the other alternate hour.

3. Monitor hourly and stop if signs of overload develop (pulse rate increases by 25 beats/min and

respiratory rate by 5 breaths/min; increasing edema; engorged jugular veins).

4. Stop when rehydrated (≥3 signs of hydration: less thirsty, passing urine, skin pinch less slow, eyes

less sunken, moist mouth, tears, less lethargic, improved pulse and respiratory rate).



**Re-feeding Syndrome**

It usually complicates the acute nutritional rehabilitation after aggressive enteral or parenteral alimentation due to the development of severe hypophosphatemia after the cellular uptake of phosphate during the 1st wk. of starting therapy. may occur if high-energy feeding is started too soon or too vigorously, and it may lead to sudden death with signs of heart failure. Other features of Refeeding syndrome include hypokalemia, hypomagnesemia, sodium retention, hyperglycemia, & vitamins deficiency (especially thiamin).. Onset is usually 24-48 hr after the start of high energy

feeding and is characterized by breathlessness, rapid pulse, increased venous pressure, rapid enlargement of the liver, and watery diarrhea The C.M. of hypophosphatemia especially when serum Pi is ≤ 0.5 mmol/L include

-weakness

-rhabdomyolysis

-neutrophil dysfunction, hemolysis, thrombocytopenia

-seizures, altered consciousness

-arrhythmias, cardiorespiratory failure, & sudden death

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| --- | --- | --- | --- | --- |
| **HYPOPHOSPHATEMIA** | **HYPOKALEMIA** | **HYPOMAGNESEMIA** | **VITAMIN/THIAMINE** | **SODIUM RETENTION** |
| ***Cardiac***  Hypotension  Decreased stroke volume  ***Respiratory***  Impaired diaphragm  contractility  Dyspnea  Respiratory failure  ***Neurologic***  Paresthesia  Weakness  Confusion  Disorientation  Lethargy  Areflexic paralysis  Seizures  Coma  ***Hematologic***  Leukocyte dysfunction  Hemolysis  Thrombocytopenia  ***Other*** | ***Cardiac***  Arrhythmias  ***Respiratory***  Failure  ***Neurologic***  Weakness  Paralysis  ***Gastrointestinal***  Nausea  Vomiting  Constipation  ***Muscular***  Rhabdomyolysis  Muscle necrosis  ***Other***  Death | ***Cardiac***  Arrhythmias  ***Neurologic***  Weakness  Tremor  Tetany  Seizures  Altered mental status  Coma  ***Gastrointestinal***  Nausea  Vomiting  Diarrhea  **Other**  Refractory hypokalemia  and hypocalcemia  Death | Encephalopathy  Lactic acidosis  Death | Fluid overload  Pulmonary  edema  Cardiac  compromise |

**Pathophysiology:**

An increase in the supply of energy (usually carbohydrates) is accompanied by an increase in sodium pump activity, and too sudden a supply risks causing a rapid release of accumulated sodium from cells, causing expansion of extracellular and plasma volumes. At the same time there is increased uptake by cells of glucose, potassium, magnesium, and phosphate. A sudden lowering of serum potassium, magnesium, and phosphate concentrations is an important

feature of the refeeding syndrome.

Inv: Monitor serum Pi, K, Mg & Ca frequently in the 1st 2 wk. after Rx.

Rx**:**  **to minimize the risk of the syndrome is the initial stabilization phase , which includes providing maintenance amounts of energy and protein and correcting electrolyte**

**imbalances and micronutrient deficiencies, followed by a controlled transition to**

**high-energy feeding. Milk-based diets are desirable because milk is a good**

**source of phosphate. No or minimal edema and return of appetite are signs of**

**readiness for the transition. Monitoring for sudden increases in pulse and**

**respiration rates during the transition to high-energy feeding is advisable to**

**detect these early warning signs. Should refeeding syndrome occur, prompt**

**treatment with a single parenteral dose of digoxin and furosemide has been useful.**

**Complications of Malnutrition**

Malnourished children are more susceptible to **infection,** especially sepsis, pneumonia, and gastroenteritis. **Hypoglycemia** is common after periods of severe fasting but may also be a sign of sepsis. **Hypothermia** may signify infection, with bradycardia, may signify a decreased metabolic rate to conserve energy. Bradycardia and poor cardiac output predispose the malnourished child to heart failure, which is exacerbated by acute fluid or solute loads. **Micronutrient deficiencies** also can complicate malnutrition. Vitamin A and zinc deficiencies are common in the developing world and are an important cause of altered immune response and increased morbidity and mortality. Depending on the age at onset and the duration of the malnutrition, malnourished children may have **permanent growth stunting** (from malnutrition in utero, infancy, or adolescence) and **delayed development** (from malnutrition in infancy or adolescence). Environmental (social) deprivation may interact with the effects of malnutrition to **impair further development and cognitive function**.

**Vitamin and Mineral Deficiencies**

**Water-Soluble Vitamins**

Water-soluble vitamins are not *stored* in the body except for vitamin B12; intake, therefore, alters tissue levels.

**Ascorbic Acid**

1.Vitamin C is important for synthesis of collagen at the level of hydroxylation of

lysine and proline in precollagen.

2. It is also involved in neurotransmitter metabolism (conversion of dopamine to norepinephrine and tryptophan to serotonin),

3.cholesterol metabolism (conversion of cholesterol to steroid hormones and bile acids), and the

4. biosynthesis of carnitine.

5.Vitamin C is an important antioxidant (electron donor) in the aqueous milieu of the body.

6. Vitamin C enhances nonheme iron absorption, the transfer of iron from transferrin to ferritin, and the formation of tetrahydrofolic acid and thus can affect the cellular and immunologic functions

of the hematopoietic system.

**Dietary Needs and Sources of Vitamin C**

Humans depend on dietary sources for vitamin C. An adequate intake is 40 mg

for ages 0-6 mo and 50 mg for 6-12 mo.

The best food sources of vitamin C are citrus fruits and fruit juices, peppers, berries, melons, guava, kiwifruit,tomatoes, cauliflower, and green leafy vegetables. Vitamin C is easily destroyed by prolonged storage, overcooking, and processing of foods.

Absorption of vitamin C occurs in the upper small intestine by an active process or by simple diffusion when large amounts are ingested. Vitamin C is not stored in the body but is taken up by all tissues; the highest levels are found in the pituitary and adrenal glands. The brain ascorbate content in the fetus and neonate is markedly higher than the content in the adult brain, a finding probably related to its function in neurotransmitter synthesis.

Breast milk contains sufficient vitamin C to prevent deficiency throughout infancy. Infants consuming pasteurized or boiled animal milk are at significant risk of developing deficiency if the other sources of vitamin C are also lacking in the diet. Neonates whose feeding has been delayed because of a clinical condition can also have ascorbic acid deficiency.

Parents and children who choose a limited (selective) diet or those on fad diets( diet used for rapid weight loss like ketogenic diet) are at risk for vitamin C deficiency.

**Vitamin C Deficiency**

A deficiency of vitamin C results in the clinical presentation of **scurvy** . Children

fed predominantly heat-treated (ultrahigh-temperature or pasteurized) milk or

unfortified formulas and not receiving fruits and fruit juices are at significant

risk for symptomatic disease. Infants and children on highly restrictive diets,devoid of most fruits and vegetables, are at risk of acquiring severe vitamin C deficiency.

In scurvy, there is defective formation of connective tissues and collagen in skin, cartilage, dentine, bone, and blood vessels, leading to their fragility. In the long bones, osteoid is not deposited by osteoblasts, cortex is thin, and the trabeculae become brittle and fracture easily.

**Clinical Features**

The early manifestations of vitamin C deficiency are irritability, loss of appetite, low-grade fever, musculoskeletal pain, and tenderness in the legs. These signs and symptoms are followed by leg swelling—most marked at the knees and the ankles—and **pseudoparalysis** . The infant might lie with the hips and knees semiflexed and the feet rotated outward. Subperiosteal hemorrhages in the

lower-limb bones sometimes acutely increase the swelling and pain, and the condition might mimic acute osteomyelitis or arthritis. A “rosary” at the costochondral junctions and depression of the sternum are other typical features.

The angulation of scorbutic beads is usually sharper than that of a rachitic rosary. Gum changes are seen in older children after teeth have erupted,manifested as bluish purple, spongy swellings of the mucous membrane, especially over the upper incisors . **Anemia,** a common finding in infants and young children with scurvy, is related to impaired iron absorption and coexistent hematopoietic nutrient deficiencies, including iron, vitamin B12 ,and folate. Hemorrhagic manifestations of scurvy include petechiae, purpura, and ecchymoses at pressure points; epistaxis; gum bleeding; and the

characteristic perifollicular hemorrhages . Other manifestations are poor wound and fracture healing, hyperkeratosis of hair follicles, arthralgia, and muscle weakness.



Scorbutic rosary



Gingival bleeding



Perifollicular petechiae in scurvy

**Laboratory Findings and Diagnosis**

The diagnosis of vitamin C deficiency is usually based on the characteristic clinical picture, the radiographic appearance of the long bones, and a history of poor vitamin C intake. A high index of suspicion is required in children on restrictive diets, particularly those with autism and other developmental disorders, and they should be evaluated for scurvy whenever they present with

difficulty in walking or bone pains.

The typical radiographic changes occur at the distal ends of the long bones and are particularly common at the knees. The shafts of the long bones have a ground-glass appearance because of trabecular atrophy. The cortex is thin and dense, giving the appearance of *pencil outlining*

of the diaphysis and epiphysis. The *white line of Fränkel,* an irregular but thickened white line at the metaphysis, represents the zone of well-calcified cartilage. The epiphyseal centers of ossification also have a ground-glass appearance and are surrounded by a sclerotic ring .

The more specific but late radiologic feature of scurvy is a zone of rarefaction under the white line

at the metaphysis. This zone of rarefaction *(Trümmerfeld zone),* a linear break in the bone that is proximal and parallel to the white line, represents area of debris of broken-down bone trabeculae and connective tissue.

A *Pelkan spur* is a lateral prolongation of the white line and may be present at cortical ends.

Subperiosteal hemorrhages are not visible using plain radiographs during the active phase of scurvy. However, during healing the elevated periosteum becomes calcified and radiopaque , sometimes giving a dumbbell or club shape to the affected bone. MRI can demonstrate acute as well as healing

subperiosteal hematomas along with periostitis, metaphyseal changes, and heterogeneous bone marrow signal intensity, even in absence of changes in plain radiographs. Gelatinous transformation of bone marrow, on aspiration, has been reported in children with suspected malignancy.

Biochemical tests are not very useful in the diagnosis of scurvy, because they do not reflect the tissue status. A plasma ascorbate concentration of <0.2 mg/dL usually is considered deficient. Leukocyte concentration of vitamin C is a better indicator of body stores, but this measurement is technically more difficult to perform.

Generalized nonspecific aminoaciduria is common in scurvy, whereas plasma amino acid levels remain normal.



**Radiographs of a leg. A, An early scurvy “white line” is visible on the ends of the shafts of the tibia and fibula; sclerotic rings (Wimberger sign) are shown around the epiphyses of the femur and tibia. B, More advanced scorbutic changes; zones of**

**destruction (ZD) are evident in the femur and tibia. Pelkan spur is also seen at the cortical end.**

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**Large subperiosteal hematoma (SH) with areas of calcification (CAL) is seen along the shaft of right femur of a child with advanced scurvy. Epiphyseal separation is seen in both knees, with linear displacement (LD)in left knee and compression (CE) against the shaft in right knee.**

**Differential Diagnosis**

Scurvy is often misdiagnosed as arthritis, osteomyelitis, nonaccidental trauma (child abuse), malignancy, or acrodynia. The early irritability and bone pain are sometimes attributed to nonspecific pains or other nutritional deficiencies.

Copper deficiency results in a radiographic picture similar to that of scurvy.

Henoch-Schönlein purpura, thrombocytopenic purpura, or leukemia is sometimes suspected in children presenting with hemorrhagic manifestations.

**Treatment**

Vitamin C supplements of 100-200 mg/day orally or parenterally ensure rapid and complete cure. The clinical improvement is seen within 1 week in most cases, but the treatment should be continued for up to 3 mo for complete recovery.

**Prevention**

Breastfeeding protects against vitamin C deficiency throughout infancy. In children consuming milk formula, fortification with vitamin C must be ensured. Children consuming heat-treated milk or plant-based beverages (e.g., almond milk, soy milk) should consume adequate vitamin C–rich foods in infancy.

Dietary or medicinal supplements are required in children on restrictive diets deficient in vitamin C, severely malnourished children, and those with chronic debilitating conditions (e.g., malignancies, neurologic disorders). Providing antenatal supplements of vitamin C to smoking mothers may mitigate some of the harmful effects of smoking on fetal and infant lung development and

function.

**B Vitamins**

**Vitamin B complex includes a number of water-soluble nutrients, includingthiamine (vitamin B1 ), riboflavin (B2 ), niacin (B3 ), pyridoxine (B6 ), folate,cobalamin (B12 ), biotin, and pantothenic acid. *Choline* and *inositol* are also considered part of the B complex and are important for normal body functions, but specific deficiency syndromes have not been attributed to a lack of these factors in the diet.**

**Because diets deficient in any one of the B-complex vitamins are often poor sources of other B vitamins, manifestations of several vitamin B deficiencies usually can be observed in the same person. It is therefore a general practice in a patient who has evidence of deficiency of a specific B vitamin to treat with the entire B-complex group of vitamins.**

**Thiamine**

Thiamine is absorbed efficiently in the gastrointestinal (GI) tract and may be deficient in persons with GI or liver disease. The requirement of thiamine is increased when carbohydrates are taken in large amounts and during periods of increased metabolism, such as fever, muscular activity, hyperthyroidism, pregnancy, and lactation.

fish, and poultry are good nonvegetarian **dietary sources** of thiamine. Main sources of thiamine for vegetarians are rice, oat,wheat, and legumes. Most ready-to-eat breakfast cereals are enriched withthiamine. Thiamine is water soluble and heat labile; most of the vitamin is lost

when the rice is repeatedly washed and the cooking water is discarded. The breast milk of a well-nourished mother provides adequate thiamine; breastfed infants of thiamine-deficient mothers are at risk for deficiency.

Thiamine deficiency occurs in alcoholics and has been reported in adolescents who have undergone bariatric surgery for severe obesity. Thiamine deficiency can develop within 2-3 mo of a deficient intake. Early symptoms of thiamine deficiency are nonspecific, such as fatigue, apathy, irritability, depression, drowsiness, poor mental concentration, anorexia, nausea,

and abdominal discomfort. As the condition progresses, more-specific manifestations of **beriberi** develop, such as peripheral neuritis (manifesting as tingling, burning, paresthesias of the toes and feet), decreased deep tendon reflexes, loss of vibration sense, tenderness and cramping of the leg muscles, heart failure, and psychologic disturbances. Patients can have ptosis of the

eyelids and atrophy of the optic nerve. Hoarseness or aphonia caused by paralysis of the laryngeal nerve is a characteristic sign (aphonic cry). Muscle atrophy and tenderness of the nerve trunks are followed by ataxia, loss of coordination, and loss of deep sensation. Later signs include increased intracranial pressure, meningismus, and coma. The clinical picture of thiamine deficiency is usually divided into a dry (**neuritic** ) type and a wet (**cardiac** ) type. The disease is wet or dry depending on the amount of fluid that accumulates in the body because of cardiac and renal dysfunction, even though the exact cause for this edema is unknown. Many cases of thiamine deficiency show a mixture of both features and are more properly termed **thiamine deficiency with cardiopathy and** **peripheral neuropathy**.

Diagnosis:

The biochemical diagnostic criteria of thiamine deficiency consist of low erythrocyte transketolase activity and high thiamine pyrophosphate effect (normal range: 0–14%).

A high index of suspicion in children presenting with unexplained cardiac failure may sometimes be lifesaving.

MRI changes of thiamine deficiency in infants are characterized by bilateral symmetric hyperintensities of the basal ganglia and frontal lobe, in addition to the lesions in the mammillary bodies, periaqueductal region, and thalami described in adults.

**Treatment**

In the absence of GI disturbances, oral administration of thiamine is effective.Children with cardiac failure, convulsions, or coma should be given 10 mg of

thiamine intramuscularly (IM) or intravenously (IV) daily for the 1st wk. This

treatment should then be followed by 3-5 mg/day of thiamine orally (PO) for at

least 6 wk.

**Riboflavin**

Riboflavin is part of the structure of the coenzymes flavin adenine dinucleotide (FAD) and flavin mononucleotide, which participate in oxidation-reduction (redox) reactions in numerous metabolic pathways and in energy production via the mitochondrial respiratory chain. Riboflavin is stable to heat but is destroyed by light.

Milk, eggs, organ meats, legumes, and mushrooms are rich dietary sources of riboflavin. Most commercial cereals, flours, and breads are enriched with riboflavin.

The causes of riboflavin deficiency (**ariboflavinosis** ) are mainly related to malnourished and malabsorptive states, including GI infections. Treatment with some drugs, such as probenecid, phenothiazine, or oral contraceptives (OCs), can also cause the deficiency. The side chain of the vitamin is photochemically destroyed during phototherapy for hyperbilirubinemia, since it is involved in the photosensitized oxidation of bilirubin to more polar excretable compounds.

**Clinical Manifestations**

Clinical features of nutritional riboflavin deficiency ( Ariboflavinosis) include cheilosis, glossitis, keratitis, conjunctivitis, photophobia, lacrimation, corneal vascularization, and seborrheic dermatitis. Cheilosis begins with pallor at the angles of the mouth and progresses to thinning and maceration of the epithelium, leading to fissures extending radially into the skin . In glossitis the tongue becomes smooth, with loss of papillary structure . Normochromic, normocytic anemia may also be seen because of the impaired erythropoiesis. A low riboflavin content of the maternal diet has been linked to congenital heart defects, but the evidence is weak.

Subclinical riboflavin deficiencies have been found in diabetic subjects, children in families with low socioeconomic status, children with chronic cardiac disease, and infants undergoing prolonged phototherapy for hyperbilirubinemia.

**Diagnosis**

Most often, the diagnosis is based on the clinical features of angular cheilosis in a malnourished child, who responds promptly to riboflavin supplementation. A functional test of riboflavin status is done by measuring the activity of erythrocyte glutathione reductase (EGR), with and without the addition of FAD.

**Treatment**

Treatment includes oral administration of 3-10 mg/day of riboflavin, often as an

ingredient of a vitamin B–complex mix. The child should also be given a well balanced

diet, including milk and milk products.

**Niacin(Vitamin B3)**

Niacin (nicotinamide or nicotinic acid) forms part of two cofactors, nicotinamide adenine dinucleotide (NAD) and NADP, which are important in several biologic reactions, including the respiratory chain, fatty acid and steroid synthesis, cell differentiation, and DNA processing. Niacin is rapidly absorbed from the stomach and the intestines and can also be synthesized from tryptophan in the diet . Major dietary sources of niacin are meat, fish, and poultry for non vegetarians and cereals, legumes, and green leafy vegetables for vegetarians.

**Clinical Manifestations**

The early symptoms of pellagra are vague: anorexia, lassitude, weakness, burning sensation, numbness, and dizziness. After a long period of deficiency,the classic triad of dermatitis, diarrhea, and dementia appears. **Dermatitis** , the most characteristic manifestation of pellagra, can develop suddenly or insidiously and may be initiated by irritants, including intense sunlight. The lesions first appear as symmetric areas of erythema on exposed surfaces, resembling sunburn, and might go unrecognized. The lesions are usually sharply demarcated from the surrounding healthy skin, and their distribution can change frequently. The lesions on the hands and feet often have the appearance of a glove or stocking Similar demarcations can also occur around the neck (**Casal necklace** ).

In some cases, vesicles and bullae develop (wet type). In others there may be suppuration beneath the scaly, crusted epidermis; in still others the swelling can disappear after a short time, followed

by desquamation .The healed parts of the skin might remain pigmented. The cutaneous lesions may be preceded by or accompanied by stomatitis, glossitis, vomiting, and diarrhea. Swelling and redness of the tip of the tongue and its lateral margins is often followed by intense redness, even

ulceration, of the entire tongue and the papillae. Nervous symptoms include depression, disorientation, insomnia, and delirium.

The classic symptoms of pellagra usually are not well developed in infants and young children, but anorexia, irritability, anxiety, and apathy are common.

Young patients might also have sore tongues and lips and usually have dry scaly skin. Diarrhea and constipation can alternate, and anemia can occur.

**Diagnosis**

Because of lack of a good functional test to evaluate niacin status, the diagnosis of deficiency is usually made from the physical signs of glossitis, GI symptoms, and a symmetric dermatitis. Rapid clinical response to niacin is an important confirmatory test.

**Treatment**

Children usually respond rapidly to treatment. A liberal and varied diet should be supplemented with 50-300 mg/day of niacin; in severe cases or in patients with poor intestinal absorption, 100 mg may be given IV. The diet should also be supplemented with other vitamins, especially other B-complex vitamins. Sun exposure should be avoided during the active phase of pellagra, and the skin lesions may be covered with soothing applications. Other coexisting nutrient deficiencies such as iron-deficiency anemia should be treated. Even after successful treatment, the diet should continue to be monitored to prevent recurrence.

**Vitamin B6( pyrodoixine)**

Vitamin B6 includes a group of closely related compounds: pyridoxine ,pyridoxal, pyridoxamine, and their phosphorylated derivatives. It function as coenzymes for many enzymes involved in amino acid metabolism, neurotransmitter synthesis, glycogen metabolism, and steroid action. If vitamin

B6 is lacking, glycine metabolism can lead to oxaluria.

The vitamin B6 content of human milk and infant formulas is adequate. Good food sources of the vitamin include fortified ready-to-eat cereals, meat, fish, poultry, liver, bananas, rice, and certain vegetables.

**Vitamin B6 Deficiency**

Because of the importance of vitamin B6 in amino acid metabolism, high protein

intakes can increase the requirement for the vitamin; The risk of deficiency is increased in persons taking medications that inhibit the activity of vitamin B6 (e.g., isoniazid, penicillamine, corticosteroids, phenytoin, carbamazepine), in young women taking oral progesterone-estrogen

OCs, and in patients receiving maintenance dialysis.

The pyridoxal and pyridoxamine forms of the vitamin are destroyed by heat; heat treatment was responsible for vitamin B6 deficiency and seizures in infants fed improperly processed formulas. Goat's milk is deficient in vitamin B6.

**Clinical Manifestations**

The vitamin B6 deficiency symptoms seen in infants are listlessness, irritability,seizures, vomiting, and failure to thrive. Peripheral neuritis is a feature of deficiency in adults but is not usually seen in children. Electroencephalogram (EEG) abnormalities have been reported in infants as well as in young adults in controlled depletion studies. Skin lesions include cheilosis, glossitis, and seborrheic dermatitis around the eyes, nose, and mouth. Microcytic anemia can occur in infants but is not common. Oxaluria, oxalic acid bladder stones, hyperglycinemia, lymphopenia, decreased antibody formation, and infections also are associated with vitamin B6 deficiency.

**Diagnosis**

The activity of aspartate (glutamic-oxaloacetic) transaminase (AST) and alanine (glutamic-pyruvic) transaminase (ALT) is low in vitamin B6 deficiency; tests measuring the activity of these enzymes before and after the addition of PLP (pyridoxal 5 phosphate) may be useful as indicators of vitamin B6 status.

Vitamin B6 deficiency or dependence should be suspected in all infants with **seizures** . If more common causes of infantile seizures have been eliminated, 100 mg of pyridoxine can be injected, with EEG monitoring if possible. If the seizure stops, vitamin B6 deficiency should be suspected. In older children, 100 mg of pyridoxine may be injected IM while the EEG is being recorded; a

favorable response of the EEG suggests pyridoxine deficiency.

**Treatment**

Intramuscular or intravenous administration of 100 mg of pyridoxine is used to treat convulsions caused by vitamin B6 deficiency. One dose should be sufficient if adequate dietary intake follows. For pyridoxine-dependent children, daily doses of 2-10 mg IM or 10-100 mg PO may be necessary.

**Vitamin B6 Toxicity**

**Adverse effects have not been associated with high intakes of vitamin B6 from food sources. However, ataxia and sensory neuropathy have been reported with dosages as low as 100 mg/day in adults taking vitamin B6 supplements for several months.**

**Biotin**

Biotin (vitamin B7 or vitamin H) functions as a cofactor for enzymes involved in carboxylation reactions within and outside mitochondria. These biotin-dependent carboxylases catalyze key reactions in gluconeogenesis, fatty acid metabolism, and amino acid catabolism.

There is limited information on the biotin content of foods; biotin is believed to be widely distributed, making a deficiency unlikely. *Avidin* found in raw egg whites acts as a biotin antagonist. Signs of biotin deficiency have been demonstrated in persons who consume large amounts of raw egg whites over long periods. Deficiency also has been described in infants and children receiving enteral and parenteral nutrition formula that lack biotin. Treatment with valproic acid may result in a low biotinidase activity and/or biotin deficiency.

The clinical findings of biotin deficiency include scaly periorificial dermatitis, conjunctivitis, thinning of hair, and alopecia . Central nervous system (CNS) abnormalities seen with biotin deficiency are lethargy, hypotonia, seizures, ataxia, and withdrawn behavior. Biotin deficiency can be successfully

treated using 1-10 mg of biotin orally daily.

No toxic effects have been reported with very high doses

**Folate**

Folate exists in a number of different chemical forms. Folic acid (pteroylglutamic acid) is the synthetic form used in fortified foods and supplements.

Folate is important for CNS development during embryogenesis. Rice and cereals are rich dietary sources of folate, especially if enriched. Beans, leafy vegetables, and fruits such as oranges and papaya are good sources as well. The vitamin is readily absorbed from the small intestine and also synthesized by colonic bacteria, and its half-life is prolonged by enterohepatic recirculation.

**Folate Deficiency**

Folate deficiency can result from

poor nutrient content in diet, inadequate absorption (celiac disease, inflammatory bowel disease), increased requirement (sickle cell anemia, psoriasis, malignancies, periods of rapid growth

as in infancy and adolescence), or inadequate utilization (long-term treatment with high-dose nonsteroidal antiinflammatory drugs; anticonvulsants such as phenytoin and phenobarbital; methotrexate).

Rare causes of deficiency are

hereditary folate malabsorption, inborn errors of folate metabolism (methylene tetrahydrofolate reductase).

**Clinical Manifestations**

Folic acid deficiency results in megaloblastic anemia and hypersegmentation of neutrophils. Non hematologic manifestations include glossitis, listlessness, and growth retardation not related to anemia. An association exists between low maternal folic acid status and **neural tube defects** , primarily spina bifida and anencephaly, and the role of periconceptional folic acid in their prevention is well established

**Hereditary folate malabsorption** manifests at 1-3 mo of age with recurrent or chronic diarrhea, failure to thrive (malnutrition), oral ulcerations, neurologic deterioration, megaloblastic anemia, and opportunistic infections.

**Diagnosis**

The diagnosis of folic acid deficiency anemia is made in the presence of macrocytosis along with low folate levels in serum or RBCs. Normal serum folic acid levels are 5-20 ng/mL; with deficiency, levels are <3 ng/mL. Levels of RBC folate are a better indicator of chronic deficiency. The bone marrow is hypercellular because of erythroid hyperplasia, and megaloblastic changes are prominent. Large, abnormal neutrophilic forms (giant metamyelocytes) with cytoplasmic vacuolation also are seen.

**Prevention**

Breastfed infants have better folate nutrition than non breastfed infants throughout infancy. Consumption of folate-rich foods and food fortification programs are important to ensure adequate intake in children and in women of childbearing age.

All women desirous of becoming pregnant should consume 400-800 μg folic acid daily; the dose is 4

mg/day in those having delivered a child with neural tube defect. To be effective, supplementation should be started at least 1 mo before conception and continued through the 1st 2-3 mo of pregnancy. The benefit of periconceptional folate supplementation in prevention of congenital heart defects, orofacial clefts, and autistic spectrum disorders is unclear. Preconceptional folate supplementation

continued throughout pregnancy may marginally reduce the risk of delivering a small-for-gestational-age infant. Providing iron and folic acid tablets for prevention of anemia in children and pregnant women is a routine strategy in at risk populations.

**Treatment**

When the diagnosis of folate deficiency is established, folic acid may be administered orally or parenterally at 0.5-1.0 mg/day. Folic acid therapy should be continued for 3-4 wk or until a definite hematologic response has occurred.

Maintenance therapy with 0.2 mg of folate is adequate.

Treatment of hereditary folate malabsorption may be possible with intramuscular folinic acid; some patients may respond to high-dose oral folinic acid therapy.

**Vitamin B12**

*Vitamin B12 ,* a generic term encompassing all biologically active **cobalamins** , is a water-soluble vitamin. Methylcobalamin and adenosylcobalamin are the metabolically active derivatives, serving as cofactors in 2 essential metabolic reactions, the products and by-products of these enzymatic reactions are critical to DNA, RNA, and protein synthesis.

**Cobalamin** (Cbl) is synthesized *exclusively* by microorganisms, and humans must rely on dietary sources (animal products, including meat, eggs, fish, and milk) for their needs .Unlike folate, older children and adults have sufficient vitamin B12 stores to last 3-5 yr. In young infants born to mothers

with low vitamin B12 stores, clinical signs of Cbl deficiency can become apparent in the 1st 6-18 mo of life.

Dietary sources of vitamin B12 are almost exclusively from animal foods. Organ meats, muscle meats, seafood ( oysters, fish), poultry, and egg yolk are rich sources. Fortified ready-to-eat cereals and milk and their products are the important sources of the vitamin for vegetarians. Human milk is an adequate source for breastfeeding infants if the maternal serum B12 levels are

adequate. Vitamin B12 is absorbed from ileum at alkaline pH after binding with intrinsic factor. Enterohepatic circulation, direct absorption, and synthesis by intestinal bacteria are additional mechanisms helping to maintain the vitamin B12 nutriture.

**Vitamin B12 Deficiency**

Deficiency of vitamin B12 caused by inadequate dietary intake occurs primarily in persons consuming strict vegetarian or vegan diets.

Breastfeeding infants of B12 -deficient mothers are also at risk for significant deficiency. Malabsorption of B12 occurs in celiac disease, ileal resections, Crohn disease, *Helicobacter pylori* infection, and autoimmune atrophic gastritis (pernicious anemia). Use of metformin, proton pump inhibitors, and histamine(H2 ) receptor antagonists may increase the risk of deficiency. Hereditary

intrinsic factor deficiency (Mutations in the hereditary intrinsic factor gene) is an inborn error of metabolism leading to vitamin B12 malabsorption.

**Clinical Manifestations**

The hematologic manifestations of vitamin B12 deficiency are similar to manifestations of folate deficiency.

Irritability, hypotonia, developmental delay, developmental regression, and involuntary movements (predominantly coarse tremors) are the common neurologic symptoms in infants. Older children with vitamin B12 deficiency may show poor growth and poor school performance, whereas sensory deficits, paresthesias, peripheral neuritis, and psychosis are seen in adults.

Hyperpigmentation of the knuckles and palms is another common observation with B12 deficiency in children .Maternal B12 deficiency may also be an independent risk factor for fetal neural tube defects.



Hyperpigmentation of knuckles in an infant with vitamin B12

deficiency and megaloblastic anemia.

**Laboratory Findings**

The hematologic manifestations of folate and Cbl deficiency are identical. The

anemia resulting from Cbl deficiency is macrocytic, with prominent macroovalocytosis of the RBCs. The neutrophils may be large and hypersegmented. In advanced cases, neutropenia and thrombocytopenia can occur, simulating aplastic anemia or leukemia. Serum vitamin B12 levels are low, and the serum concentrations of methylmalonic acid and homocysteine (because B12 help for conversion of homocysteine to methionine) are usually elevated. Concentrations of serum iron and serum folic acid are normal or elevated. Serum lactate dehydrogenase activity is markedly increased, a reflection of ineffective erythropoiesis.

Moderate elevations of serum bilirubin levels (2-3 mg/dL) also may be found. Excessive excretion of methylmalonic acid in the urine (normal: 0-3.5 mg/24 hr) is a reliable and sensitive index of vitamin B12 deficiency.

**Diagnosis:**

Information regarding clinical symptoms, dietary history, diseases, surgeries, or medications is likely to provide important clues.

The physical examination may reveal relevant findings such as irritability, pallor, or specific neurologic symptoms. Screening laboratory findings offer important information, but more focused testing will be required to confirm a diagnosis of vitamin B12 deficiency and its cause. Cbl deficiency is usually identified by measuring total or TC(transcobalmine) bound vitamin B12 in the blood.. In untreated patients, methylmalonic acid and total homocysteine levels are often helpful because they are greatly elevated in the majority of those with clinical signs of B12 deficiency. Again, excessive urinary methylmalonic acid excretion is also a sensitive test of B12 deficiency.

**Treatment**

The hematologic symptoms respond promptly to parenteral administration of 250-1,000 μg vitamin B12 . Children with severe deficiency and those with neurologic symptoms need repeated doses, daily or on alternate days in first week, followed by weekly for the 1st 1-2 mo and then monthly. Children having only hematologic presentation recover fully within 2-3 mo, whereas those with

neurologic disease need at least 6 mo of therapy. Children with a continuing malabsorptive state and those with inborn errors of vitamin B12 malabsorption need lifelong treatment. Prolonged daily treatment with high-dose (1,000-2,000 μg) oral vitamin B12 preparations is also equally effective in achieving hematologic and neurologic responses in elderly patients, but the data are inadequate in children and young adults.

**Prevention**

Pregnant and breastfeeding women should ensure an adequate consumption of animal

products to prevent cobalamin deficiency in infants. Strict vegetarians, especially vegans, should ensure regular consumption of vitamin B12 . Food fortification with the vitamin helps to prevent deficiency in predominantly vegetarian populations.

**Fat-Soluble Vitamins**

Fat-soluble vitamins generally have stores in the body, and dietary deficiencies generally develop more slowly than for water-soluble vitamins.

Absorption of fat-soluble vitamins depends on normal fat intake, digestion, and absorption. The complexity of normal fat absorption and the potential for perturbation in many disease states explains the more common occurrence of deficiencies of these vitamins.

**Vitamin A**

As a fat-soluble micronutrient, vitamin A is recognized as being essential for all vertebrates for normal vision, reproduction, cell and tissue differentiation, and functions of the immune system. Vitamin A plays critical roles in neonatal development. It is required for normal embryonic

development, hematopoiesis, immune response, metabolism, and growth and differentiation of many types of cells.

Vitamin A can be obtained from the diet from preformed vitamin A (retinyl esters, such as retinyl palmitate) primarily in foods of animal origin. Organ meats (especially liver, kidney) are very rich in vitamin A, whereas other meats, milk, and cheese contain moderate levels. Other sources of vitamin A include several provitamin A carotenoids, which are found naturally in many fruits and vegetables, especially yellow-orange vegetables (pumpkin, sweet potato), and leafy green vegetables ( spinach, broccoli). One of the most abundant carotenoids is β-carotene.

In the body, these precursors are used for the synthesis of 2 essential metabolites of vitamin A. **All-*trans* retinoic acid** is the form required for cell differentiation and regulation of gene transcription and is the most bioactive form of vitamin A; **11-*cis* retinal** is the form required for

vision as the light-absorbing chromophore of the visual pigments rhodopsin and iodopsin.

clinical manifestation:

The most characteristic and specific signs of vitamin A deficiency are *eye lesions,*ons of vitamin A deficiency in humans appear as a group of ocular signs termed **xerophthalmia**. An earlier

symptom of vitamin A deficiency is delayed dark adaptation, as a result of reduced resynthesis of rhodopsin; this may progress to **night blindness.**

**Photophobia is a common symptom,** **Stages in vitamin A deficiency include corneal keratinization and opacity, susceptibility to infection, and formation of dry, scaly layers of cells (xerophthalmia ) ,The conjunctival membrane undergoes keratinization and may develop foamy appearing plaques (Bitôt spots). When lymphocytes infiltrate the cornea in later stages of infection, it degenerates irreversibly (keratomalacia and corneal ulceration ), resulting in irreversible blindness.**

Clinical and subclinical vitamin A deficiencies are associated with **immunodeficiency**; increased risk of infection, especially measles; and increased risk of mortality, especially in developing nations. Xerophthalmia and vitamin A deficiency should be urgently treated.

Other clinical signs of vitamin A deficiency include poor overall growth, diarrhea, susceptibility to infections, anemia, apathy, intellectual impairment, and increased intracranial pressure, with wide separation of the cranial bones at the sutures. There may be vision problems as a consequence of bone overgrowth causing pressure on the optic nerve.

Hypervitaminosis A also has serious sequelae, including headaches, pseudotumor cerebri, hepatotoxicity, and teratogenicity.

A status based on serum retinol. In children, plasma retinol <0.35 μmol/L is considered *very deficient,* 0.35-0.7 μmol/L *deficient.*

A daily supplement of 1,500 μg of vitamin A is sufficient for treating latent vitamin A deficiency, after which intake at the RDA level should be the goal. Xerophthalmia is treated by giving 1,500 μg/kg body weight orally for 5 days, followed by intramuscular injection of 7,500 μg of vitamin A in oil, until recovery

**Vitamin E**

Vitamin E is a fat-soluble vitamin and functions as an antioxidant, but its precise biochemical functions are not known. Vitamin E deficiency can cause hemolysis or neurologic manifestations and occurs in premature infants, in patients with malabsorption, and in an autosomal recessive disorder affecting vitamin E transport.

**Pathogenesis**

The term *vitamin E* denotes a group of 8 compounds with similar structures and antioxidant activity. The most potent member of these compounds is **α-** **tocopherol** , which is also the main form in humans. The best dietary sources of vitamin E are vegetable oils, seeds, nuts, green leafy vegetables, and margarine.

The majority of vitamin E is located within cell membranes, where it prevents lipid peroxidation and the formation of free radicals.

Premature infants are particularly susceptible to vitamin E deficiency, because there is significant transfer of vitamin E during the last trimester of pregnancy.Vitamin E deficiency in premature infants causes thrombocytosis, edema, and hemolysis, potentially causing anemia. The risk of symptomatic vitamin E deficiency was increased by the use of formulas for premature infants that had a high content of polyunsaturated fatty acids (PUFAs). These formulas led to a high content of PUFAs in red blood cell membranes, making them more susceptible to oxidative stress, which could be ameliorated by vitamin E.

Oxidative stress was augmented by aggressive use of iron supplementation; iron increases the production of oxygen radicals. The incidence of hemolysis as a result of vitamin E deficiency in premature infants decreased secondary to the use of formulas with a lower content of PUFAs, less-aggressive use of iron, and provision of adequate vitamin E.

**Clinical Manifestations**

Clinical manifestations do not appear until after 1 yr of age, even in children with cholestasis since birth. Patients may have cerebellar disease, posterior column dysfunction, and retinal disease. Loss of deep tendon reflexes is usually the initial finding. Subsequent manifestations include limb ataxia (intention tremor, dysdiadochokinesia), truncal ataxia (wide-based,unsteady gait), dysarthria, ophthalmoplegia (limited upward gaze), nystagmus, decreased proprioception (positive Romberg test), decreased vibratory sensation, and dysarthria. Some patients have pigmentary retinopathy. Visual field constriction can progress to blindness. Cognition and behavior can also be affected. Myopathy and cardiac arrhythmias are less common findings.

In premature infants, hemolysis as a result of vitamin E deficiency typically develops during the 2nd mo of life. Edema may also be present.

**Laboratory Findings**

Serum vitamin E levels increase in the presence of high serum lipid levels, even when vitamin E deficiency is present. Therefore, vitamin E status is best determined by measuring the ratio of vitamin E to serum lipids; a ratio <0.8 mg/g is abnormal in older children and adults; <0.6 mg/g is abnormal in infants <1 yr. Premature infants with hemolysis caused by vitamin E deficiency also often have elevated platelet counts.

**Treatment**

For correction of deficiency in neonates, the dose of vitamin E is 25-50 units/day for 1 wk, followed by adequate dietary intake. Children with deficiency as a result of malabsorption should receive 1 unit/kg/day, with the dose adjusted based on levels; ongoing treatment is necessary.

**Prognosis**

The hemolytic anemia in infants resolves with correction of the vitamin E deficiency. Some neurologic manifestations of vitamin E deficiency may be reversible with early treatment, but many patients have little or no improvement. Importantly, treatment prevents progression.

**Vitamin K**

Vitamin K is necessary for the synthesis of clotting factors II, VII, IX, and X; deficiency of vitamin K can result in clinically significant bleeding. Vitamin K deficiency typically affects infants, who experience a transient deficiency related to inadequate intake, or patients of any age who have decreased vitamin K absorption. Mild vitamin K deficiency can affect long-term bone and vascular

Health.

**Pathogenesis**

Vitamin K is a group of compounds that have a common naphthoquinone ring structure. Phylloquinone , called vitamin K1 , is present in a variety of dietary sources, with green leafy vegetables, liver, and certain legumes and plant oils having the highest content. Vitamin K1 is the form used to fortify foods. Vitamin K2 is a group of compounds called menaquinones , which are produced by intestinal bacteria.

There is uncertainty regarding the relative importance of intestinally produced vitamin K2 . Menaquinones are also present in meat, especially liver, and cheese.

The classic **γ-carboxyglutamate (Gla)** -containing proteins involved in blood coagulation that are decreased in vitamin K deficiency are factors II (prothrombin), VII, IX, and X.

Vitamin K deficiency causes a decrease in proteins C and S, which inhibit blood coagulation, and protein Z, which also has a role in coagulation. All these proteins are made only in the liver, except for protein S, a product of various tissues.

Gla-containing proteins are also involved in bone biology (osteocalcin and protein S) and vascular biology (matrix Gla protein and protein S).

There are 3 forms of **vitamin K deficiency bleeding (VKDB)or previously reffered as hemorrhagic disease of newborn** :

***classic*** *hemorrhagic disease of the newborn*  occurs at 1-14 days of age. Early VKDB issecondary to low stores of vitamin K at birth as a result of the poor transfer of

vitamin K across the placenta and inadequate intake during the 1st few days of life. In addition, there is no intestinal synthesis of vitamin K2 because the newborn gut is sterile. Early VKDB occurs mostly in breastfed infants as a consequence of the low vitamin K content of breast milk (formula is fortified). Delayed feeding is an additional risk factor.

***Late***VKDB most often occurs at 2-12 wk of age, although cases can occur up to 6 mo after birth. Almost all cases are in breastfed infants because of the low vitamin K content of breast milk. An additional risk factor is occult malabsorption of vitamin K, as occurs in children with undiagnosed cystic fibrosis or cholestatic liver disease (e.g., biliary atresia, α1 –antitrypsin deficiency). Without vitamin K prophylaxis, the incidence is 4-10 per 100,000 newborns.

The third form of VKDB of the newborn is the **early** form occurs *at birth* or shortly thereafter (0-24 hr),It is secondary to maternal intake of medications (warfarin, phenobarbital,phenytoin) that cross the placenta and interfere with vitamin K function.

Other predisposing factors for VKDB include:

1.fat malabsorption can occur in children of any age.Potential etiologies include cholestatic liver disease, pancreatic disease, and intestinal disorders (celiac sprue, inflammatory bowel disease, short bowel syndrome).

2.Prolonged diarrhea can cause vitamin K deficiency, especially in breastfed infants.

3.Children with cystic fibrosis are most likely to have vitamin K deficiency if they have pancreatic insufficiency and liver disease.

4. beyond infancy low dietary intake by itself never causes vitamin K deficiency. However, the combination of poor intake and the use of broadspectrum antibiotics that eliminate the intestine's vitamin K2 –producing bacteria can cause vitamin K deficiency. This scenario is especially common in the intensive care unit.

5.Vitamin K deficiency can also occur in patients who receive total parenteral nutrition (TPN) without vitamin K supplementation.

**Clinical Manifestations**

In early VKDB, the most common sites of bleeding are the gastrointestinal (GI) tract, mucosal and cutaneous tissue, umbilical stump, and postcircumcision site; intracranial bleeding is less common. GI blood loss can be severe enough to require a transfusion. In contrast, the most common site of bleeding in late VKDB is intracranial, although cutaneous and GI bleeding may be the initial

manifestation. Intracranial bleeding can cause convulsions, permanent neurologic sequelae, or death. In some patients with late VKDB, the presence of an underlying disorder may be suggested by jaundice or failure to thrive (malnutrition). Older children with vitamin K deficiency can present with

bruising, mucocutaneous bleeding, or more serious bleeding.

**Laboratory Findings**

1.In patients with bleeding as a result of vitamin K deficiency, the prothrombin

time (PT) is prolonged. The PT must be interpreted based on the patient's age,

because it is normally prolonged in newborns .

2. The partial thromboplastin time (PTT) is usually prolonged but may be normal in

early deficiency.

3.Factor VII has the shortest half-life of the coagulation factors and is the first to be affected by vitamin K deficiency, but isolated factor VII deficiency does not affect PTT.

4.The platelet count and fibrinogen level are normal.

5. Measurement of undercarboxylated factor II (PIVKA-II)( *proteins induced by vitamin K absence)* can be used to detect mild vitamin K deficiency, when the PT will be normal in the mild deficiency. Determination of blood vitamin K levels is less useful because of significant variation based on recent dietary intake; levels do not always reflect tissue stores.

**Diagnosis and Differential Diagnosis**

Other possible causes of bleeding and a prolonged PT include:

1.DIC, which is usually secondary to sepsis, is associated with thrombocytopenia, low fibrinogen, and elevated D-dimers.

2. Severe liver disease results in decreased production of clotting factors; the PT does not fully correct with administration of vitamin K.

3.Children with a hereditary disorder have a deficiency in a specific clotting factor (I, II, V, VII, X).

**4.Coumarin** derivatives inhibit the action of vitamin K by preventing its recycling to an active form after it functions as a cofactor for γ-glutamyl carboxylase. Bleeding can occur with overdosage of the common anticoagulant **warfarin** or with ingestion of rodent poison, which contains a coumarin

derivative.

5. High doses of salicylates also inhibit vitamin K regeneration, potentially leading to a prolonged PT and clinical bleeding.

**Treatment**

Infants with VKDB should receive 1 mg of parenteral vitamin K. The PT should decrease within 6 hr and normalize within 24 hr. For rapid correction in adolescents, the parenteral dose is 2.5-10 mg. In addition to vitamin K, a patient with severe, life-threatening bleeding should receive an infusion of fresh-frozen plasma (FFP), which corrects the coagulopathy rapidly. Children with vitamin K

deficiency caused by malabsorption require chronic administration of high doses of oral vitamin K (2.5 mg twice/wk to 5 mg/day). Parenteral vitamin K may be necessary if oral vitamin K is ineffective.

**Prevention**

Administration of either oral vitamin K (1-2 mg at birth, again at discharge, and again at 3-4 wk of

life) or parenteral vitamin K (single dose) soon after birth prevents classical VKDB of the newborn. In contrast, oral vitamin K does not prevent a substantial number of cases of late VKDB. However, a single intramuscular (IM) injection of vitamin K (1 mg), is almost universally effective, except in children with severe malabsorption. This increased efficacy of the IM form is thought to be the result of a depot effect. Concerns about an association between parenteral vitamin K at birth and the later development of malignancy are unsubstantiated.

Discontinuing the offending medications before delivery can prevent VKDB attributable to maternal medications. If this is not possible, administration of vitamin K to the mother may be helpful. In addition, the neonate should receive parenteral vitamin K immediately after birth. If parenteral vitamin K does not correct the coagulopathy rapidly, the child should receive FFP.

Children who are at high risk for malabsorption of vitamin K should receivsupplemental vitamin K and periodic measurement of the PT.

**Vitamin D**

Vitamin D deficiency appears as **rickets** in children and as **osteomalacia** in post pubertal adolescents.Inadequate direct sun exposure and vitamin D intake are sufficient causes, but other factors, such as various drugs (phenobarbital, phenytoin) and malabsorption, may increase the risk of development of vitamin- deficiency rickets. Breast fed infants, especially those with dark-pigmented skin, are at risk for vitamin D deficiency.

