Nutritional Dermatoses in the Hospitalized Patient

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PRACTICE **POINTS**

- Nutritional deficiencies are common in hospitalized patients and often go unrecognized.
- Awareness of the risk factors predisposing patients to nutritional deficiencies and the cutaneous manifestations associated with undernutrition can promote early diagnosis.
- When investigating cutaneous findings, undernutrition should be considered in patients with chronic infections, malabsorptive states, psychiatric illness, and strict dietary practices, as well as in those using certain medications.
- Prompt nutritional supplementation can prevent patient morbidity and mortality and reverse skin disease.

Cutaneous disease may be the first manifestation of an underlying nutritional deficiency, highlighting the importance of early recognition by dermatologists. Undernutrition occurs when there is an imbalance between nutrient intake and metabolic demand. Many hospitalized patients are in catabolic states due to chronic illness, infection, malabsorption, or medication. These patients are at an increased risk for undernutrition and therefore associated cutaneous disease. This review details the risk factors for nutritional deficiency, illustrates the presentations of cutaneous disease, reviews diagnostic workups, and provides suggestions for supplementation in the undernourished patient.

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The World Health Organization defines malnutrition as deficiencies, excesses, or imbalances in an individual's intake of energy and/or nutrients.[1] This review will focus on undernutrition, which may result from macronutrient or micronutrient deficiencies. Undernutrition in the hospitalized patient is a common yet underrecognized phenomenon, with an estimated prevalence of 20% to 50% worldwide.[2] Malnutrition is an independent risk factor for patient morbidity and mortality and has been associated with increased health care costs.[3] Nutritional deficiencies may arise from inadequate nutrient intake, abnormal nutrient absorption, or improper nutrient utilization.[4] Unfortunately, no standardized algorithm for screening and diagnosing patients with malnutrition exists, making early physical examination findings of utmost importance. Herein, we present a review of acquired nutritional deficiency dermatoses in the inpatient setting.

Protein-Energy Malnutrition

Protein-energy malnutrition (PEM) refers to a set of related disorders that include marasmus, kwashiorkor (KW), and marasmic KW. These conditions frequently are seen in developing countries but also have been reported in developed nations.[5] Marasmus occurs from a chronic deficiency of protein and calories. Decreased insulin production and unopposed catabolism result in sarcopenia and loss of bone and subcutaneous fat.[6] Affected patients include children who are less than 60% ideal body weight (IBW) without edema or hypoproteinemia.[7] Kwashiorkor is the edematous form of PEM that develops from isolated protein deficiency, resulting in edema, diarrhea, and immunosuppression.[6] Micronutrient deficiencies, oxidative stress, slow protein catabolism, and excess antidiuretic hormone have been proposed as potential drivers of KW.[8] Kwashiorkor affects children between 60% and 80% IBW. Marasmic KW has features of both diseases, including children who are less than 60% IBW but with associated edema and/or hypoproteinemia.[9]

Although PEM is uncommon in adults, hospitalized patients carry many predisposing risk factors, including infections, malabsorptive conditions, psychiatric disease, and chronic illness (eTable). Patients with chronic infections present with findings consistent with marasmic KW due to lean body mass loss.

The cutaneous findings in PEM are related to dysmaturation of epidermal keratinocytes and resultant epidermal atrophy.[10] Patients with marasmus exhibit dry, wrinkled, loose skin due to subcutaneous fat loss. Emaciated children often lose their buccal fat pads, and reduced perianal

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The eTable is available in the Appendix online at www.mdedge.com/dermatology.

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adipose may lead to rectal prolapse. Increased lanugo hair may be present on the face, and alopecia of the scalp may occur.[6] In KW, cutaneous disease progresses from confluent hyperkeratosis to a dry atrophic epidermis that erodes easily, leaving underlying pale erythema. The resultant pattern is one of hyperpigmented plaques with slightly raised borders, and hypopigmented patches and erosions described as flaky paint dermatitis (Figure 1).[5] Lesions appear first in areas of friction. The hair often is dry and brittle; curly hair may straighten and scale.[11] Red-yellow to gray-white hypopigmentation may develop, denoting periods of inadequate nutrition. The flag sign describes alternating horizontal bands of hypopigmentation interspersed with bands of pigmented hair. The nails usually are thin and soft and may exhibit the nail flag sign, characterized by horizontal bands of white and red.[12] Cheilitis, angular stomatitis, and vulvovaginitis may be present.[6]

In adults, weight loss and body mass index can be used to assess nutritional status, along with a focused history and physical examination. Complete blood cell count, electrolyte levels, and blood urea nitrogen should be assessed, as hypoglycemia and anemia often accompany PEM.[13] In KW, hypoalbuminemia and hypoproteinemia are invariably present. Although prealbumin may be a valid prognostic indicator of disease outcomes and mortality in patients at risk for malnutrition, checking other serum biomarkers remains controversial.[14] Focused testing may be warranted in patients with risk factors for chronic infectious processes, such as human immunodeficiency virus or tuberculosis.[6] Skin biopsy may solidify the diagnosis of PEM. Hypertrophy of the stratum corneum, atrophy of the stratum spinosum and stratum granulosum, and increased basal layer melanin have been reported.[15]

Treatment involves initial fluid resuscitation and correction of electrolyte imbalances, followed by nutritional replacement.[13] Oral or enteral tube feedings are preferred over total parenteral nutrition (TPN), as they enhance recovery of the gastrointestinal tract.[16] Refeeding should occur in small amounts and frequent intervals.[5] Skin-directed therapy is aimed at restoring epidermal function and hydration, with regular moisturization and application of barrier creams, such as zinc oxide ointment or petrolatum.[10]

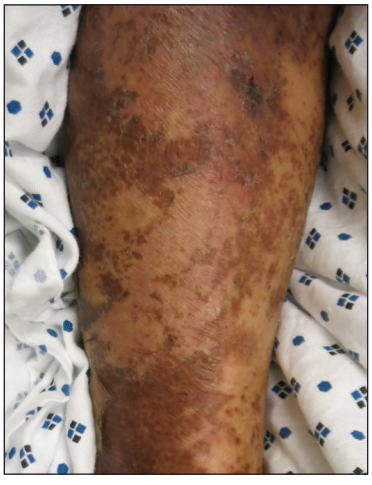

FIGURE 1. Dermatitis resembling flaky paint in a patient with protein-energy malnutrition (kwashiorkor).

Zinc Deficiency

Zinc is an essential trace element that provides regulatory, structural, and catalytic functions across multiple biochemical pathways[6] and serves as an enzymatic cofactor and key component for numerous transcription factors.[17] Zinc is derived from food sources, and its concentration correlates with protein content.[18] Zinc is found in both animal and plant-based proteins, albeit with a lower oral bioavailability in the latter. Zinc deficiency may be inherited or acquired. Primary acrodermatitis enteropathica is an autosomal-recessive disorder of the solute carrier family 39 member 4 gene, *SLC39A4* (encodes zinc transporter ZIP4 on enterocytes); the result is abnormal zinc absorption from the small intestine.[18]

Acquired zinc deficiency occurs from decreased dietary zinc intake, impaired intestinal zinc absorption, excessive zinc elimination, or systemic states of high catabolism or low albumin (eTable). Total parenteral nutrition–associated deficiency has arisen when nutritional formulations did not contain trace elements during national shortages or when prolonged TPN was not anticipated and trace elements were removed.[19] Zinc levels may already be low in patients with chronic illness or inflammation, so even a short period on TPN can precipitate deficiency.[18,19] Diets high in phytate may result in zinc deficiency, as phytate impairs intestinal zinc absorption.[20] Approximately 15% of patients with inflammatory bowel disease experienced zinc deficiency worldwide.[21] In Crohn disease, zinc deficiency has been associated with active intestinal inflammation, increased risk for hospitalization, surgeries, and disease-related complications.[22,23]

Medications such as antiepileptics, antimetabolites, or penicillamine may induce zinc deficiency, highlighting the importance of medication review for hospitalized patients (eTable). Catabolic states, frequently encountered in hospitalized patients, increase the risk for zinc deficiency.[24] Patients with necrolytic migratory erythema (associated with pancreatic glucagonomas) often experience low serum zinc levels.[25]

The skin is the third most zinc-abundant tissue in the human body. Within keratinocytes, zinc is critical to normal proliferation and suppression of inflammation.[17] Zinc also plays an important role in cutaneous immune function.[26] Zinc deficiency presents with sharply demarcated, flaccid pustules and bullae that erode into scaly, pink, eczematous or psoriasiform plaques. Lesions are found preferentially in acral and periorificial sites, often with crusting and exudate. The groin and flexural surfaces may be affected. Erosions often become secondarily impetiginized. Other cutaneous findings include angular cheilitis, stomatitis, glossitis, paronychia, onychodystrophy, generalized alopecia, and delayed wound healing.[26] Histopathology of skin lesions is characterized by

granular layer loss, epidermal pallor, confluent parakeratosis, spongiosis, dyskeratosis, and psoriasiform hyperplasia.[27] Acquired bullous acrodermatitis enteropathica has been reported as a histologic mimicker of pemphigus foliaceous in patients on TPN.[28]

Diagnosis of zinc deficiency is made by measuring plasma zinc levels. Fasting levels should be drawn in the morning, as they can fluctuate based on the time of day, stress levels, or inflammation.[6] Sample hemolysis and anticoagulants high in zinc may falsely elevate plasma zinc. A normal zinc level is greater than 70 µg/dL; however, normal levels do not rule out deficiency.[18] Measurement of zinc-dependent enzymes, such as alkaline phosphatase, can be a quick way to assess zinc status. Serum albumin also should be measured; because zinc is carried by albumin in the blood, hypoalbuminemia may result in secondary zinc deficiency.[18]

Zinc replacement therapy is largely through oral supplementation and should start at 0.5 to 2.0 mg/kg/d in adults with acquired disease.[29,30] Zinc sulfate is the most affordable and is the supplement of choice, with 50 mg of elemental zinc per 220 mg of zinc sulfate (~23% elemental zinc).[31] Alternative zinc salts, such as zinc gluconate (13% elemental zinc), may be used. Patients with malabsorptive disorders often require parenteral supplementation.[32] Clinical symptoms often will resolve within 1 to 2 weeks of supplementation.[29] In patients with primary acrodermatitis enteropathica, lifelong supplementation with 3 mg/kg/d elemental zinc should occur.[6] Calcium and folate may reduce zinc absorption, while zinc supplementation can interfere with copper and iron absorption.[33]

Iron Deficiency

Iron is an essential component of the hemoglobin molecule. Iron homeostasis and metabolism are tightly regulated processes that drive erythropoiesis. Only 5% to 10% of dietary iron is absorbed through nutrition, while the remainder is recycled from red cell breakdown. Both normal iron levels and iron deficiency (ID) are defined by age and gender.[34] Iron-deficiency anemia (IDA) is one of the most common cause-specific anemias worldwide.[35]

Fatigue is the most common and earliest symptom of ID. In a single study, pallor was predictive of anemia in hospitalized patients; however, absence of pallor did not rule out anemia.[34] Dyspnea on exertion, tachycardia, dysphagia, and pica also may be reported. Cutaneous manifestations include koilonychia (Figure 2), glossitis, pruritus, angular cheilitis, and telogen effluvium. Plummer-Vinson syndrome is characterized by microcytic anemia, glossitis, and dysphagia.

Risk factors for ID include insufficient dietary consumption,[36] blood loss, malabsorptive states,[37,38] and increased iron requirements (eTable). Patient fragility (eg, elderly, chronic disease) is a newly described risk factor where correction of ID may impact morbidity, mortality, and quality of life.[35]

Iron deficiency can be present despite a normal hemoglobin level. Serum ferritin and percentage transferrin saturation are key to early identification of IDA.[35] Ferritin levels lower than 30 µg/L confirm the diagnosis. Decreased transferrin saturation and increased total iron binding capacity aid in the diagnosis of IDA. Serum ferritin is an acute-phase reactant, and levels may be falsely elevated in the setting of inflammation or infection.

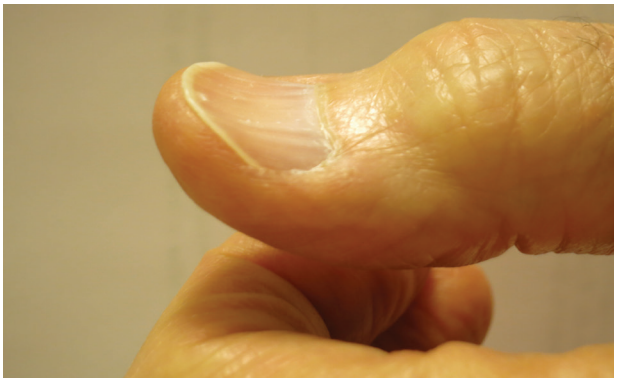

FIGURE 2. Koilonychia in a patient with iron-deficiency anemia.

Treatment includes reversing the cause of deficiency and supplementing iron. Calculation of the total iron deficit can help inform iron supplementation. First-line therapy for IDA is oral ferrous sulfate 325 mg (65 mg elemental iron) 3 times daily. Newer studies suggest 40 to 80 mg oral iron should be taken every other day to increase absorption.[39] Other iron salts, such as ferrous gluconate (325 mg is equivalent to 38 mg elemental iron), have been used. Iron absorption is enhanced by an acidic environment. Parenteral iron is utilized in patients with uncorrectable blood loss, malabsorption, renal failure, intolerance to oral iron, and nonadherence in those who are unable to receive transfusions. Iron infusions are favored in frail patients, such as the elderly and those with chronic kidney disease or heart failure.[35] Multiple parenteral iron formulations exist, and their use should be driven by underlying patient comorbidities and potential risks. Packed red blood cell transfusions should be considered in acute blood loss, hypoxia, or cardiac insufficiency.

Essential Fatty Acid Deficiency

Essential fatty acids (EFAs) including linoleic and α-linolenic acid cannot be synthesized by the human body and must be obtained through diet (mostly plant oils). Essential fatty acids have various functions, including maintaining phospholipid membrane integrity, forming prostaglandins and leukotrienes, and storing energy.[40] Essential fatty acids are important in the structure and function of the stratum corneum and are crucial in maintaining epidermal barrier function.[41] Increased epidermal permeability and transepidermal water loss may be the first signs of EFA deficiency (EFAD).[42]

The cutaneous manifestations of EFAD include xerosis, weeping eczematous plaques, and erosions in intertriginous sites. The lesions may progress to widespread desquamation and erythema. With time, the skin can become thick and leathery. Alopecia may occur, and hair

may depigment.[7] Additional findings include poor wound healing and increased susceptibility to infections.[43,44]

Essential fatty acid deficiency may occur when dietary fat intake is severely restricted or in malabsorptive states.[45,46] It develops in patients on prolonged TPN, typically when receiving fat-restricted nutrition,[47,48] as occurs in hypertriglyceridemia.[47] Essential fatty acid deficiency has developed in patients on TPN containing EFAs,[47] as the introduction of novel intravenous lipid emulsions has resulted in varying proportions of EFA.[40] Premature neonates are particularly at risk for EFAD.[49]

The diagnosis of EFAD involves the measurement of the triene to tetraene ratio. A ratio of more than 0.2 suggests EFAD, but the clinical signs are not seen until the ratio is over 0.4.[40] Low plasma levels of linoleic, linolenic, and arachidonic acids also are seen. Elevated liver function tests are supportive of the diagnosis. Biochemical findings typically are seen before cutaneous manifestations.[40]

Treatment of EFAD includes topical, oral, or intravenous replacement of EFAs. Improvement of EFAD with the application of topical linoleic acid to the skin has been reported.[50] Patients receiving TPN should undergo assessment of parenteral lipid emulsion to ensure adequate fatty acid composition.

Vitamin A Deficiency

Vitamin A (retinol) is a fat-soluble vitamin that plays a critical role in keratinization, epithelial proliferation, and cellular differentiation.[6] Vitamin A is found in animal products as retinyl esters and in plants as beta-carotene. Vitamin A has 2 clinically important forms: all-trans retinoic acid and 11-*cis*-retinal. All-trans retinoic acid is involved in cellular differentiation and regulating gene transcription, while 11-*cis*-retinal is key to rhodopsin generation required for vision. Vitamin A deficiency presents with early ophthalmologic findings, specifically nyctalopia, or delayed adaptation to the dark.[51] Xerophthalmia, abnormal conjunctival keratinization, and Bitot spots subsequently develop and may progress to corneal ulceration and blindness.[6]

Vitamin A deficiency manifests in the skin as follicular hyperkeratosis, or phrynoderma. Notably, numerous other micronutrient deficiencies may result in phrynoderma. Clinically, multiple pigmented keratotic papules of various sizes, many with a central keratinous plug, are distributed symmetrically on the extensor elbows, knees, shoulders, buttocks, and extremities. The skin surrounding these lesions may be scaly and hyperpigmented.[52] Generalized xerosis without preceding nyctalopia has been reported.[53] Accompanying pityriasis alba may develop.[52] Lesions on the face may mimic acne, while lesions on the extremities may simulate a perforating disorder. Histopathology of phrynoderma reveals epidermal hyperkeratosis, follicular hyperkeratosis, and follicular plugging.[52]

Patients at risk for vitamin A deficiency include those with conditions that affect intestinal fat absorption, underlying psychiatric illness, or chronic disease (eTable). Chronic alcohol use predisposes patients to a multitude of micronutrient deficiencies, including vitamin A deficiency.[54] In chronic alcohol use, even mild cutaneous changes may be the first clue to low serum retinol.[55]

Vitamin A deficiency can be diagnosed by measuring serum retinol levels, with levels lower than 20 µg/dL being diagnostic of deficiency.[56] Decreased serum retinol in patients hospitalized with flaring irritable bowel disorder has been repeatedly reported.[57-59] Notably, serum retinol concentration does not decline until liver reserves of vitamin A are nearing exhaustion.[33]

The US Food and Drug Administration requires manufacturers to list retinol activity equivalents on labels. One international unit of retinol is equivalent to 0.3 µg of retinol activity equivalents.[60] The treatment of vitamin A deficiency involves high-dose oral supplementation when possible.[61] Although dependent on age, the treatment dose for most adults with vitamin A deficiency is 3000 µg (10,000 IU) once daily.

Phrynoderma has been specifically treated with salicylic acid ointment 3% and intramuscular vitamin A.[62] Topical urea cream also may treat phrynoderma.[63]

Vitamin B_2

Vitamin B_2 (riboflavin) is absorbed in the small intestine and converted into 2 biologically active forms—flavin adenine dinucleotide and flavin mononucleotide—which serve as cofactors in metabolic and oxidation-reduction reactions. Malabsorptive disorders and bowel resection can lead to riboflavin deficiency.[64] Other at-risk populations include those with restrictive diets,[65] psychiatric illness, or systemic illness (eTable). Riboflavin can be degraded by light (deficiency has been reported after phototherapy for neonatal jaundice[66]) and following boric acid ingestion.[67] Medications, including long-term treatment with antiepileptics, may lead to riboflavin deficiency.[68]

Riboflavin is critical to maintaining collagen production. Riboflavin deficiency may manifest clinically with extensive seborrheiclike dermatitis,[44] intertrigolike dermatitis,[69] or oral-ocular-genital syndrome.[70] Angular cheilitis may accompany an atrophic tongue that is deep red in color. The scrotum is characteristically involved in men, with confluent dermatitis extending onto the thighs and sparing the midline. Red papules and painful fissures may develop. Balanitis and phimosis have been reported. Testing for riboflavin deficiency should be considered in patients with refractory seborrheic dermatitis.

Riboflavin stores are assessed by the erythrocyte glutathione reductase activity coefficient.[44] A level of 1.4 or higher is consistent with deficiency. Serum riboflavin levels, performed after a 12-hour fast, may support the diagnosis but are less sensitive. Patients with glucose-6-phosphate deficiency cannot be assessed via the erythrocyte glutathione reductase activity coefficient and may instead require evaluation of 24-hour urine riboflavin level.[44]

Vitamin B_3

Vitamin B_3 (niacin, nicotinamide, nicotinic acid) is found in plant and animal products or can be derived from its

amino acid precursor tryptophan. Niacin deficiency results in pellagra, characterized by dermatitis, dementia, and diarrhea.[71] The most prominent feature is a symmetrically distributed photosensitive dermatitis of the face, neck (called Casal necklace)(Figure 3), chest, dorsal hands, and extensor arms. The eruption may begin with erythema, vesicles, or bullae (wet pellagra) and evolve into thick, hyperpigmented, scaling plaques.[71] The skin may take on a copper tone and become atrophic.[72] Dull erythema with overlying yellow powdery scale (called sulfur flakes) at follicular orifices has been described on the nasal bridge.[73]

Causes of niacin deficiency include malabsorptive conditions, malignancy (including carcinoid tumors), parenteral nutrition, psychiatric disease,[74,75] and restrictive diets (eTable).[76] Carcinoid tumors divert tryptophan to serotonin resulting in niacin deficiency.[77]

The diagnosis of niacin deficiency is based on clinical findings and response to supplementation.[75] Low niacin urinary metabolites (*N*-methylnicotinamide and 2-pyridone) may aid in diagnosis.[6] Treatment generally includes oral nicotinamide 100 mg every 6 hours; the dose can then be tapered to 50 mg every 8 to 12 hours until symptoms resolve. Severe deficiency may require parenteral nicotinamide 1 g 3 to 4 times daily.[75]

Vitamin B_6

Vitamin B_6 (pyridoxine, pyridoxamine, pyridoxal) is found in whole grains and plant and animal products. Vitamin B_6 functions as a coenzyme in many metabolic pathways and is involved in the conversion of tryptophan to niacin.[44] Absorption requires hydrolysis by intestinal phosphates and transport to the liver for rephosphorylation prior to release in active form.[6]

Cutaneous findings associated with vitamin B_6 deficiency include periorificial and perineal seborrheic dermatitis,[78] angular stomatitis, and cheilitis, with associated burning, redness, and tongue edema.[6] Vitamin B_6 deficiency is a rarely reported cause of burning mouth syndrome.[79] Because vitamin B_6 is involved in the conversion of tryptophan to niacin, deficiency also may present with pellagralike findings.[70] Other clinical symptoms are outlined in the eTable.[80,81]

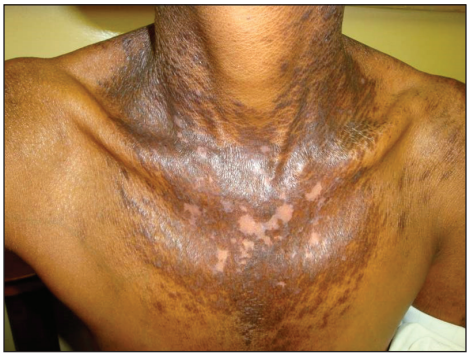

FIGURE 3. Photosensitive dermatitis of the neck and upper chest (Casal necklace) seen in vitamin B_3 deficiency (pellagra).

Conditions that increase risk for vitamin B_6 deficiency are highlighted in the eTable and include malabsorptive disorders; psychiatric illness[82]; and chronic disease, especially end-stage renal disease.[83] Vitamin B_6 deficiency associated with chronic alcohol use is due to both inadequate vitamin B_6 intake as well as reduced hepatic storage.[78] Medications such as isoniazid, hydralazine, and oral contraceptives may decrease vitamin B_6 levels (eTable).[82]

Vitamin B_6 can be measured in the plasma as pyridoxal 5′-phosphate. Plasma concentrations of less than 20 nmol/L are suggestive of deficiency.[82] Indirect tests include tryptophan and methionine loading.[6] The treatment of vitamin B_6 deficiency is determined by symptom severity. Recommendations for oral supplementation range from 25 to 600 mg daily.[82] Symptoms typically improve on 100 mg daily.[6]

Vitamins B_9 and B_{12}

Deficiencies of vitamins B_9 (folic acid, folate) and B_{12} (cobalamin) have similar clinical presentations. Folate is essential in the metabolism of amino acids, purines, and pyrimidines.[6] Cobalamin, found in animal products, is a cofactor for methionine synthase and methylmalonyl-CoA mutase.[84] Megaloblastic anemia is the main finding in folate or cobalamin deficiency. Neurologic findings only accompany cobalamin deficiency. Risk factors for folate deficiency include malabsorptive conditions,[6] chronic alcohol use,[85] and antifolate medication use (eTable).[6]

Cobalamin absorption requires gastric acid and intrinsic factor binding in the duodenum. Deficiency may occur from strict diets, psychiatric illness, old age,[86] decreased gastric acid secretion,[87] abnormal intrinsic factor function, or intestinal infections.[6]

Generalized cutaneous hyperpigmentation may be the first manifestation of vitamins B_9 and B_{12} deficiency.[88] Typically accentuated in acral creases and the oral cavity, pigmentation may mimic Addison disease. Hair depigmentation and linear streaking of the nails are reported.[84] The tongue becomes painful and red with atrophy of the filiform papillae (Hunter glossitis).[78] Linear lesions on the tongue and hard palate may serve as an early sign of cobalamin deficiency.[89]

Folate deficiency is diagnosed by measuring the plasma folate level; coincidental cobalamin deficiency should be excluded. Deficiency is managed with oral supplementation (when possible) with 1 to 5 mg of folate daily.[6] Cobalamin deficiency is based on low serum levels (<150 pg/mL is diagnostic).[86] Cobalamin deficiency may take years to develop, as vitamin B_{12} exists in large body stores.[6] Serum methylmalonic acid may be elevated in patients with clinical features but normal-low serum vitamin B_{12} level.[86] Treatment of vitamin B_{12} deficiency is with oral (2 mg once daily) or parenteral (1 mg every 4 weeks then maintained at once monthly) cyanocobalamin. For patients with neurologic symptoms, intramuscular injection should be given.[86] The underlying cause of deficiency must be elucidated and treated.

Vitamin C Deficiency

Vitamin C (ascorbic acid) is an essential cofactor for the hydroxylation of proline and lysine residues in collagen synthesis. Plant-based foods are the main dietary source of vitamin C, and deficiency presents clinically as scurvy. Cutaneous findings include follicular hyperkeratosis, perifollicular petechiae, and curled hair shafts (corkscrew hairs)(Figure 4). Ecchymoses of the lower extremities, forearms, and abdomen may be seen. Nodules representing intramuscular and subcutaneous hemorrhage can be present.[90] Woody edema may mimic cellulitis, while lower extremity hemorrhage may mimic vasculitis. Gingival hyperplasia, hemorrhage, and edema may occur,[90] along with linear splinter hemorrhages.[91]

Hypovitaminosis C has been routinely demonstrated in hospitalized patients.[92] Scurvy may occur in patients on strict diets,[93] chronic alcohol use,[94] psychiatric illness,[95] or gastrointestinal tract disease (eTable).[96-99] Those with low socioeconomic status[70] or dementia[100] as well as the elderly also are at risk.[101] Scurvy has developed in patients with iron overload and those who are on hemodialysis[44] as well as in association with nilotinib use.[102] Patients with chronic mucous membrane graft-vs-host disease may exhibit vitamin C deficiency.[103]

Scurvy is a clinical diagnosis. Vitamin C levels normalize quickly with supplementation. Cutaneous biopsy will exhibit follicular hyperkeratosis, perifollicular hemorrhage, and fibrosis.[91]

Oral ascorbic acid supplementation should be initiated at 500 to 1000 mg daily in adults.[104] The cause of deficiency should be identified, and further supplementation should be decided based on patient risk factors. Lifestyle modifications, such as cessation of smoking and chronic alcohol use, is recommended. The diagnosis of scurvy should prompt workup for additional nutrient deficiencies.

Final Thoughts

Dermatologists play an important role in the early recognition of nutritional deficiencies, as cutaneous manifestations often are the first clue to diagnosis. Nutritional deficiencies are common yet underrecognized in the hospitalized patient and serve as an independent risk factor for patient morbidity and mortality.[3] Awareness of the cutaneous manifestations of undernutrition as well as the risk factors for nutritional deficiency may expedite diagnosis and supplementation, thereby improving outcomes for hospitalized patients.

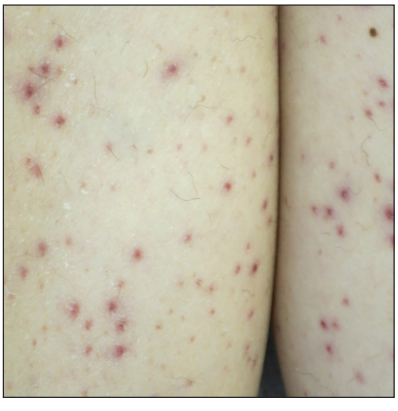

FIGURE 4. Perifollicular hemorrhage and corkscrew hairs in a patient with vitamin C deficiency (scurvy).

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APPENDIX

eTABLE. Risk Factors and Manifestations of Nutritional Deficiency

Condition	Risk Factors	Cutaneous Manifestations	Systemic Manifestations
Protein-energy malnutrition	• Decreased intake: severe dietary restriction[1] • Infection: HIV/AIDS,[2,3] *Mycobacterium tuberculosis* infection[4] • Malabsorption: cystic fibrosis,[5] IBD,[6] celiac disease,[7] diverticulitis,[8] intestinal bypass surgery[9] • Psychiatric illness: chronic alcohol use,[10,11] substance abuse,[12] eating disorders[13] • Chronic illness: CKD,[14] dialysis[15]	• Marasmus: dry, wrinkled, loose skin; loss of buccal fat pads; increased lanugo hair; alopecia; petechiae and purpura; impaired nail growth[16] • Kwashiorkor: flaky paint dermatitis, confluent hyperkeratosis, hyperpigmented plaques, hypopigmented patches, cutaneous atrophy and erosions at frictional sites,[17] pale erythema, flag sign of the hair and nails,[8] cheilitis, angular stomatitis, vulvovaginitis	Marasmus: failure to thrive; chronic diarrhea,[18] shrunken wasted appearance[18] Kwashiorkor: symmetric edema, anasarca, secondary infections[17]
Zinc deficiency	• Inherited: *SLC39A4* gene mutation[19] • Decreased intake: strict diets (vegan, vegetarian),[20] zinc-deficient TPN,[21-23] zinc-deficient breast milk,[24,25] premature infants[26] • Malabsorption: high-phytate diets,[27] IBD,[28,29] intestinal bypass surgery,[30] short bowel syndrome,[31] cystic fibrosis,[32] celiac disease,[33] pancreatic insufficiency,[34] chronic granulomatous disease[35] • Medication induced: EDTA, penicillamine,[36,37] antimetabolites, antiepileptics[38] • Excessive elimination: thiazides, loop diuretics, ACE inhibitors, and angiotensin receptor blockers[39]; chronic alcohol use[40]; chronic diarrhea[41] • Psychiatric illness: eating disorders,[42,43] chronic alcohol use[44] • Chronic illness: hepatic disease,[45] renal disease, sickle cell disease,[46] diabetes,[47] malignancy, chronic infection, burns, trauma, surgery[41]	Periorificial, perianal, and acral dermatitis; sharply demarcated, flaccid pustules and bullae; scaly, pink, eczematous and psoriasiform plaques; erosions[16]; angular cheilitis[19]; stomatitis; glossitis; paronychia; onychodystrophy; Beau lines[48]; alopecia[49]; delayed wound healing[50]	Diarrhea, photosensitivity, anorexia, irritability, depression, hypogeusia, growth failure, increased infections, pubertal delay, pica[19]
Iron deficiency	• Decreased intake: strict diets (vegan/vegetarian)[51,52] • Malabsorption: celiac disease[53], atrophic gastritis,[53] IBD,[54,55] intestinal bypass procedures,[56] *Helicobacter pylori* infection,[57] esophagitis,[52] gastric antral vascular ectasia, Cameron ulcer, epistaxis[52] • Medication-induced: long-term use of aspirin or nonsteroidal anti-inflammatories,[52] long-term use of proton pump inhibitors[58] • Psychiatric illness: mood disorders, autism spectrum disorder, attention deficit hyperactivity disorder, developmental disorders[59] • Blood loss: blood donation,[53,52] peptic ulcer disease,[52] surgery,[53] menstruation[53] • Chronic illness: CKD, heart failure,[54] malignancy,[52] connective tissue disease[60] • Other: elderly,[54] obesity,[52,56] extracorporeal photopheresis,[61] pregnancy,[62] chronic intravascular or traumatic hemolysis,[63] hookworm infection[64]	Pallor, koilonychia, glossitis,[52] pruritus, angular cheilitis,[65] telogen effluvium[66]	Fatigue,[66] dyspnea on exertion, tachycardia,[66] dizziness, dysphagia, palpitations, headache, pica[65]
Essential fatty acid deficiency	• Decreased intake: TPN[67,68] • Malabsorption: intestinal bypass surgery, IBD, celiac disease,[69] cystic fibrosis[70] • Psychiatric illness: eating disorders,[71] chronic alcohol use[72] • Chronic illness: nephrotic syndrome, chronic kidney disease[73]	Diffuse cutaneous xerosis,[74] weeping eczematous plaques, intertriginous erosions,[74] desquamation and erythema,[75] alopecia, hair depigmentation,[74] scaling scalp dermatitis, petechiae, purpura	Poor wound healing, increased infections, growth restriction, fatty liver, anemia, thrombocytopenia[74]
Vitamin A deficiency	• Malabsorption: cystic fibrosis, pancreatic insufficiency, IBD, biliary disease, hepatic disease, intestinal bypass surgery,[76] short bowel syndrome,[77] celiac disease,[33] Whipple disease,[78] chronic intestinal giardiasis[79] • Medication induced: antiepileptics[38] • Psychiatric illness: chronic alcohol use[80] • Chronic illness: nephrotic syndrome[81]	Symmetric phrynoderma, pigmented keratotic papules,[82] diffuse cutaneous xerosis,[77] hyperpigmentation, scaling plaques, pityriasis alba[82]	Nyctalopia,[18] xeropthalmia, keratomalacia, Bitot spots, corneal ulceration, blindness,[16] increased infections (severe measles if unvaccinated),[83] impaired growth, altered bony development[18]

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Condition	Risk Factors	Cutaneous Manifestations	Systemic Manifestations
Vitamin B_2 deficiency	• Decreased intake: strict diets (vegan/vegetarian),[84] • Malabsorption: intestinal surgery, intestinal bypass surgery[85] • Chronic illness: hypothyroidism[86] • Psychiatric illness: chronic alcohol use, eating disorders[76] • Medications: antiepileptics[38] • Other: elderly,[87] pregnant or lactating women,[88] phototherapy,[89] boric acid ingestion[90]	Seborrheiclike dermatitis,[75] intertrigolike dermatitis,[91] oral-ocular-genital syndrome (cheilitis; angular stomatitis; glossitis; deep red, atrophic tongue; scrotal dermatitis extending onto the thighs),[18,76] red papules and fissures, balanitis, phimosis	Rare, predominantly mucocutaneous symptoms seen
Vitamin B_3 deficiency	• Decreased intake: strict diets,[92] TPN[93] • Malabsorption: carcinoid tumors,[94] Hartnup disease,[95] intestinal bypass surgery,[96] IBD[97] • Psychiatric illness: eating disorders,[98] chronic alcohol use[99]	Pellagra (photosensitive dermatitis of the face, neck [Casal necklace], chest, dorsal hands, and extensor arms; vesicles or bullae (wet pellagra); thick, hyperpigmented, scaling plaques),[18] copper tone to skin,[100] dull erythema with yellow powdery scale over follicular orifices (sulfur flakes),[101] cheilitis, glossitis, perineal eruption[102]	Psychiatric symptoms, dementia, diarrhea[102]
Vitamin B_6 deficiency	• Malabsorption: celiac disease[103] • Psychiatric illness: chronic alcohol use,[104] eating disorders[103] • Medication induced: isoniazid, hydralazine, theophylline, cycloserine, penicillamine, oral contraceptives[103] • Chronic illness: hepatic disease, hepatocellular carcinoma,[105] dialysis[106] • Other: elderly[107]	Angular stomatitis, cheilitis, glossitis, burning tongue, pellagralike dermatitis, intertrigo,[18] seborrheiclike dermatitis[104]	Sideroblastic microcytic anemia, peripheral neuropathy,[108] neurologic symptoms,[109] depression, irritability, increased infections[108]
Vitamin B_9 deficiency	• Decreased intake: strict vegan diet[110] • Malabsorption: IBD,[111] intestinal bypass surgery, celiac disease, chronic diarrhea[16] • Psychiatric illness: chronic alcohol use[112] • Medications: trimethoprim, methotrexate, oral contraceptives, antiepileptics, pyrimethamine[16]	Generalized cutaneous hyperpigmentation (accentuated in acral creases, intertriginous sites, oral cavity),[16] glossitis, angular cheilitis, depigmented hair, linear streaking of nails,[113] linear lesions on the tongue and hard palate[114]	Megaloblastic anemia, pallor, irritability, fatigue
Vitamin B_{12} deficiency	• Decreased intake: strict diets (vegan/vegetarian)[115] • Malabsorption: decreased gastric acid secretion (proton pump inhibitors, H2 antihistamines),[116] decreased intrinsic factor (pernicious anemia), intestinal infection (bacterial overgrowth, giardiasis, *Diphyllobothrium latum*),[16] IBD, celiac disease, Whipple disease, Zollinger-Ellison syndrome[117] • Psychiatric illness: chronic alcohol use,[118] obsessive-compulsive disorder[119] • Medication induced: metformin[120] • Other: elderly,[110] inborn errors of metabolism[110]	Generalized cutaneous hyperpigmentation (accentuated in acral creases, intertriginous sites, oral cavity),[16] glossitis, angular cheilitis, depigmented hair, linear streaking of nails,[113] linear lesions on the tongue and hard palate[114]	Megaloblastic anemia, pallor irritability, fatigue, neurologic sequelae[110]
Vitamin C deficiency	• Decreased intake: strict diets[121] • Malabsorption: Whipple disease,[122] IBD,[123] celiac disease,[124] intestinal bypass surgery[125] • Psychiatric illness: chronic alcohol use,[126] anorexia nervosa,[127] psychiatric disorders[128] • Medication induced: vemurafenib,[129] nilotinib[130] • Chronic illness: iron overload,[131] dialysis,[132] chronic GVHD,[133] hospitalization[134] • Other: autism,[135] low socioeconomic status,[136] dementia,[137] elderly[138]	Follicular hyperkeratosis, perifollicular petechiae, curled hair shafts (corkscrew hairs), ecchymoses, nodules (intramuscular and subcutaneous hemorrhage), woody edema, gingival hyperplasia, linear splinter hemorrhages[139]	Fatigue, epistaxis, loose teeth, mood changes, bony changes, depression[76]

Abbreviations: HIV, human immunodeficiency virus; IBD, irritable bowel disease; CKD, chronic kidney disease; *SLC39A4*, solute carrier family 39 member 4; TPN, total parenteral nutrition; EDTA, ethylenediaminetetraacetic acid; ACE, angiotensin-converting enzyme; GVHD, graft-vs-host disease.

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