



Failure to thrive

A 13-month-old girl is anemic and not gaining enough weight. How would you proceed with her care?

13-month-old girl arrives at your clinic, referred by the staff at the Women, Infants, and Children (WIC) nutritional center where her parents—recent immigrants from Africa—go for food supplements. The baby is bundled up in layers of clothing, even though it's a relatively mild winter day. The father carries her into the examining room and undresses her. The child is tiny and darkskinned, with curly hair painstakingly divided into little bunches. The parents seem caring, loving, and not particularly worried. They tell you the nurse at the WIC center thought their baby was not gaining enough weight and advised them to bring the baby to you. The referral note from WIC says hemoglobin levels found on routine blood test were low. You list the presenting complaint as anemia.

What are some of the etiologies for anemia in a child this age? What strategies would you use to narrow down the cause?



Additional medical history

- The birth history is unremarkable, with neither antepartum nor postpartum complications.
- At her 6-month well-child checkup, neither the child's physician nor her parents expressed any concerns about her development. Her parents received the routine anticipatory guidance at that visit, including advice on breastfeeding, vitamin

- supplementation, vaccination, and care of minor illnesses.
- She hasn't been in for a well-child visit since then, but she has been seen for an upper respiratory infection and a bout of gastroenteritis. Her parents have not been worried about her health.
- The parents tell you the baby doesn't sleep soundly, scratches her skin in her sleep, and cries a lot.

Family and social history

- The parents speak very little English.
- The patient is an only child, and no extended family live in the area.
- Her mother works nights and her father works days, with the parent who is not working caring for her at home.
- Her parents tell you she takes small sips of juice or water, and an occasional bite of noodles. She won't drink milk at all and refuses any other foods they offer.

Physical examination

- The child is in no acute distress. She is afebrile, and her vital signs are appropriate for her age.
- Height is 27½ inches, weight 15 lb, 15 oz, placing her at less than the 5th percentile for height and weight for her age—a regression from the 50th percentile she showed at earlier visits.
- Head and neck exam reveals mild frontal bossing and prominent sternoclavicular joints. There is no adenopathy or thyromegaly.
- · Heart and lung exam are normal.
- Abdomen is soft, nontender, nondistended, with bowel sounds present.

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When you see

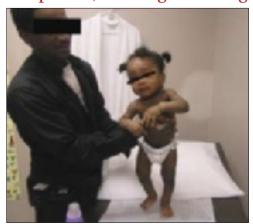
baby, consider

rickets.

failure to thrive

in a dark-skinned

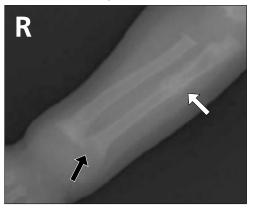
The patient, not weight-bearing



The 13-month-old patient has slight bowing of the lower extremities and puffiness around the wrists and ankles. She needs support to stand.

FIGURE 2

Forearm x-ray



The patient's x-ray shows a widening of the epiphyses (black arrow) and pseudofracture (white arrow).

• There is slight bowing of the lower extremities and puffiness around the wrists and ankles. When you ask her father to have her stand on the examining table, you see that she needs support to do so (FIGURE 1).



What is your clinical diagnosis, and what tests will you order?



Laboratory results

- Hemoglobin, 9.9 mg/dL (normal: 10.4-12.4 mg/dL)
- Mean corpuscular volume (MCV), 74 fL (normal: 70-86 fL)
- Alkaline phosphatase, 3417 U/L (normal: 115-460 U/L)
- Vitamin D (calcidiol), <7 nmol/L (normal: 60-108 nmol/L)
- Calcium, 9.1 mg/dL (normal: 8.8-10.8 mg/dL)
- Comprehensive metabolic panel, liver transaminases, and thyroid-stimulating hormone levels are all normal
- Parathyroid hormone level, 101 pg/mL (normal: 10-55 pg/mL).

Radiologic findings

• X-ray shows slight saber deformity of the femurs and broadening of the epiphyses of the forearm (FIGURE 2).

Can this be rickets?

Here is a child with a history of poor growth and peculiar eating habits. Her legs are bowed and her wrists seem swollen. She does not stand or walk, and refuses to bear weight on her legs. She is anemic, and the lab tests you've ordered show abnormal vitamin D, alkaline phosphatase, and parathyroid hormone levels. All of this suggests a diagnosis of rickets.

Causes of rickets

Rickets is the result of abnormal mineralization of bone and cartilage in growing children. The analogous condition in adults whose epiphyseal plates have closed is osteomalacia. Clinical rickets typically presents with the constellation of signs and symptoms listed in the box on page 543 and depicted in **FIGURES 1.2.** and **3.**

Not enough vitamin D

The most common cause of rickets is a deficiency of vitamin D, a substance physiologically necessary to produce concentrations of calcium and phosphate adequate for proper bone mineralization. Vitamin D is produced in the skin in the presence of sunlight and can also be ingested in supplements and certain foods.

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Vitamin D deficiency may result from reduced sunlight exposure, inadequate dietary intake, malabsorption, or a combination of these factors. Rickets may also be caused by medications that alter absorption or secretion of phosphate and calcium, including antacids, anticonvulsants, corticosteroids, and loop diuretics. Various disease states, such as Crohn's disease, pancreatic disease, biliary disease, gastrointestinal loops and fistulae, cirrhosis, chronic renal disease, and mesenchymal tumors, may also alter absorption and metabolism of these ions.

How much sunshine does a baby need?

It doesn't take a great deal of sunlight exposure to provide adequate supplies of vitamin D. An infant wearing only a diaper will get enough vitamin D from half an hour per week of sun exposure. A fully clothed infant needs 3 hours. But children with dark skin, like this African baby, need more time in the sun. And if parents follow current anticipatory guidance about protecting children from overexposure to the sun and slather on the sunscreen, vitamin D synthesis decreases by more than 95%.²

Vitamin D in the diet

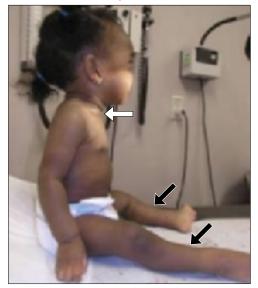
Consuming adequate quantities of vitamin D is difficult, unless the diet includes fortified foods or vitamin supplements. Current recommendations for daily intake are 400 IU per day for all infants, children, and adolescents.³ But the average daily intake by adults in North America from sources such as fish, eggs, and butter or margarine is only 50 to 100 IU.³

Infants born to vitamin-D replete women have an 8- to 12-week store of vitamin D at birth, but breastfeeding does not ensure the baby is getting adequate amounts of vitamin D, even if the mother's vitamin D status is adequate. Human milk from vitamin D-replete women has a vitamin D concentration of only 25 IU per liter, far below the recommended daily intake of 400 IU.³

How deficient is this baby?

Vitamin D deficiency may be categorized as mild, moderate, or severe. Calcidiol is the next-to-last step in the metabolism of vitamin D and is used as a marker because it is easier

FIGURE 3 Rachitic rosary



The patient had a developing rosary, most pronounced at the sternoclavicular joint (white arrow) and early saber deformity of the shin (black arrows). Frontal bossing and swollen wrists and ankles may also be seen in patients with rickets.

to measure than the concentration of calcitriol, the final step. Mild vitamin D deficiency is defined as serum calcidiol concentration of 25 to 50 nmol/L. A serum calcidiol concentration of 12.5 to 25 nmol/L indicates a moderate vitamin D deficiency, and at those levels the incidence of hypocalcemia and rickets increases. Serum calcidiol concentration of less than 12.5 nmol/L, as in the case of the patient presented here, indicates a severe deficiency.⁴

Not enough calcium

In addition to calcium malabsorption due to inadequate vitamin D levels, hypocalcemia may result from inadequate intake of calcium or from vitamin D-dependent metabolic disorders, of which there are 2 types.

- **Type I,** sometimes known as pseudovitamin D-deficiency rickets, is due to defective production of $25(OH)D_3$ -1-α-hydroxylase, an enzyme necessary for the conversion of calcidiol to calcitriol in the kidneys.
- Type II, also called hereditary rickets, is rare. It is caused by mutations in vitamin D receptors and the inability of the ligand to bind or stimulate the proper physiologic response.

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Breastfed infants need supplementation.



In this condition, laboratory tests may show high levels of calcitriol.

Not enough phosphorus

Vitamin D-resistant rickets, or familial hypophosphatemic rickets, refers to a clinical presentation of rickets that is caused by a hereditary renal wasting of phosphorus at the proximal tubule level. Laboratory evaluation of a child with this condition will show low phosphate levels, normal calcitriol levels, and hypercalciuria. The specific defect that causes this condition is not known. A family history of short stature, orthopedic abnormalities, poor dentition, alopecia, or parental consanguinity may be suggestive of vitamin D-dependent or vitamin D-resistant forms of inherited rickets.

Other causes of hypophosphatemia include inadequate nutritional intake, X-linked hypophosphatemia, generalized tubular disorders such as renal tubular acidosis, Fanconi syndrome, and Dent disease. These disorders may also lead to rickets.



What are the available treatments for rickets? What about prevention?



Replenishing vitamin D

Vitamin D deficiency may be remedied by supplementing anywhere along the metabolic pathway. Dihydrotachysterol (DHT, or D₁), the substance in the skin that responds to sunlight, is given as 60,000 IU once, then 6000 IU daily until the rickets are clinically and radiologically resolved. Further downstream, ergocalciferol (D₂) may be given as 1000 to 5000 IU daily for 6 to 12 weeks. The dosage is calibrated by age: 1000 IU/d if age <1 month, 3000 IU/d for ages 1 to 12 months, and 5000 IU/d for children older than 12 months. The final form of vitamin D is cholecalciferol (D₂). This is typically administered as either 5000 to 10,000 IU daily for 2 to 3 months, or as 600,000 IU in 1 day, divided into 4 to 6 doses.^{5,6} All of these supplements taste bad and children are often resistant to swallowing them.

When follow-up and multiple dosing are impractical—because the family finds repeated clinic visits too difficult, or because the child will not comply with the regimen—you can use stosstherapy. This is a bolus of cholecalciferol (D_3) or ergocalciferol (D_2), 150,000 to 600,000 IU, given as a single dose or divided over several days. For example, you would give 300,000 IU over 1 to 7 days in children 1 to 12 months of age. With this therapy, onset of action is less than a day and maximal effects are seen in 4 weeks. Some preparations contain propylene glycol, which is limited in food additives to <25 mg/kg of body weight because of potential toxicity.

• When supplementation doesn't work. Vitamin D is not effective in treatment of familial hypophosphatemic rickets, Type II vitamin D-dependent rickets, or disorders of phosphate metabolism.

Monitoring therapeutic success

When possible, treatment should be monitored by checking serum calcium and alkaline phosphatase at 1 month, and calcium, magnesium, phosphate, alkaline phosphatase, calcidiol, parathyroid hormone, and wrist x-ray at 3 months from initiation of treatment, to ensure that they are normalizing.

Preventing rickets

In the developed world, public health efforts to prevent rickets have been largely successful. Rickets was prevalent worldwide in the early decades of the 20th century, but after milk began to be routinely fortified with vitamin D in the 1920s, cases of nutritional rickets almost disappeared in industrialized nations.

In 1963, the American Academy of Pediatrics (AAP) began recommending vitamin D supplementation to prevent rickets. Although the recommendation remains controversial because of concerns about the possibility of hypervitaminosis and the resultant hypercalcemia and hypercalciuria, there has been renewed emphasis on this recommendation in light of a rise in the number of cases of rickets in the United States in recent years. Belau Current AAP recommendations for vitamin D supplementation are daily supplementation of 400 IU vitamin D for the following groups:



Properly applied sunscreen reduces vitamin D synthesis by 95%.

- Breastfed infants, beginning with the first few days of life and continued until they are weaned to at least 1000 mL per day of vitamin D-fortified formula or milk.
- Nonbreastfed infants who are ingesting less than 1000 mL per day of vitamin D-fortified formula or milk. Most commercial baby formulas contain 400 IU/L, which means that an intake of 500 mL of formula per day provides 200 IU.¹⁵ Additionally, special milk supplemented with vitamin D₃ up to 200 IU per 250 mL has recently become available in Europe.¹⁶
- Children and adolescents who do not get regular sunlight exposure, do not ingest at least 32 ounces per day of vitamin Dfortified milk, or do not take a daily multivitamin supplement containing at least 400 IU of vitamin D.

Others have suggested a bolus dosing 150,000 IU each autumn for those in northern climates.¹⁷

Most over-the-counter vitamin formulations now contain D_3 (cholecalciferol), as recent studies show this form is more potent than D_2 (ergocalciferol). Calcium supplements are available in combination with vitamin D. Calcitriol, the most active form of vitamin D, is available only by prescription. Because it does not require activation in the kidneys, it is the drug of choice for renally impaired patients.



How would you treat this child?



Bad taste is a big hurdle

The child in this case was prescribed 150,000 U oral cholecalciferol. She spit it out at the clinic, and the dose was sent home for her parents to administer. She was also started on a multivitamin (Poly-Vi-Sol). On the return visit a few days later, the parents reported that she only took three-quarters of the vitamin D dose, spitting out the remainder.

When that didn't work...

The child was then admitted to the hospital for

Clinical features of rickets

Clinical findings

- Apathy, listlessness, and poor growth
- Muscle cramps, weakness, hypotonia, numbness, paresthesias, tetany, and seizures
- Pot belly and waddling gait
- Soft, misshapen head with widened sutures and frontal bossing
- Delayed eruption of teeth
- Rachitic rosary (see below)
- Harrison's groove (indentation at point of insertion of diaphragm, due to the pull of the diaphragm against the softened lower ribs)
- Bowed limbs and swollen joints

Radiologic findings

- Epiphyses widened and flared with irregular, "cupped" epiphyseal-metaphyseal junctions; involvement of the costrochondral junctions produces a row of beadlike prominences often called the "rachitic rosary"
- Long bones bowed ("saber shaped"), with indistinct cortices
- Pseudofractures (also called Looser's zone or Milkman's fractures), often found on the concave side of femoral neck, pubic rami, ribs, clavicles, and lateral aspect of scapulae
- Pathologic fractures

Laboratory findings

- **Creatinine**: Normal value excludes renal insufficiency as etiology
- Liver enzymes: Normal value excludes liver disease as etiology
- Phosphorus: Normal phosphorus and parathyroid hormone make a diagnosis of rickets unlikely
- Parathyroid hormone: Elevated in hypocalcemic rickets (>55 pg/mL)
- Calcium, total and ionized with albumin:
 May be normal in rickets
- Alkaline phosphatase: Usually markedly increased over the age-specific reference range in rickets
- Urinary calcium level: Usually decreased in rickets (<50 mg/d, depending on calcium content of diet)
- Calcidiol level: May be low in rickets (<50 nmol/L [20 ng/mL])
- Calcitriol level: Usually normal in rickets, because of its short-half life (60-108 nmol/L [25-45 pg/mL])

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The child was prescribed 150,000 U oral cholecalciferol, but she spit it out.



administration of vitamin D and to allow for dietary and social work evaluations of factors contributing to her malnutrition.

Social services evaluation ruled out an economic etiology for the child's failure to thrive. The family was able to afford a nutritionally adequate diet for the child. They were enrolled in Medicaid and WIC. Willful neglect was not an issue: A very loving and appropriate relationship was evident between the child and her parents. Child care was shared equally by the young parents, but they simply didn't know what foods were appropriate for a child of her age.

Turning things around

The hospital dietician observed one of the child's meals. The child ate some of everything on the plate: mashed potatoes and gravy, chicken strips, vegetables, bananas, yogurt, and milk. She was willing to try a variety of foods, and ate most of them. Both the physician and the dietician spent a lot of time with the parents reviewing feeding techniques and healthy food choices. Language was a problem, solved for the most part with the assistance of a dial-up language translation service to ensure clear understanding of the instructions. The health care professionals prepared a list of healthy foods to buy at the grocery store, with pictures illustrating healthy food items. In addition, appropriate exposure to sunlight was explained and encouraged.

Parent education is the key

The child's father expressed gratitude several times for the instruction on healthy food choices for the daughter, while the mother smiled in shy agreement. He said they did not know what to feed her, and when she refused most things they offered, they fed her the noodles and juice she seemed to prefer. He was grateful to the nutritionist, social worker, nursing staff, and physicians for taking care of his daughter. He was eager to go to the grocery store and to start feeding her the "right foods."

Ready to go home

By discharge, the child had received the full dose of vitamin D and was eating a variety of foods, including 1 to 4 ounces of milk daily, supplemented with Poly-Vi-Sol, 1 mL orally twice daily, and calcium carbonate (OsCal) with vitamin D, 1 crushed tablet orally twice daily. Home health nursing provided follow-up twice a week, and weekly appointments in the clinic with the physician were also scheduled. Compliance with the discharge plan was impeccable. Both laboratory and clinical signs of rickets resolved over the subsequent weeks.

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They hadn't known what to feed her. When she refused most things they offered, they fed her the noodles and juice she seemed to prefer.