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CASES IN CLINICAL MEDICINE

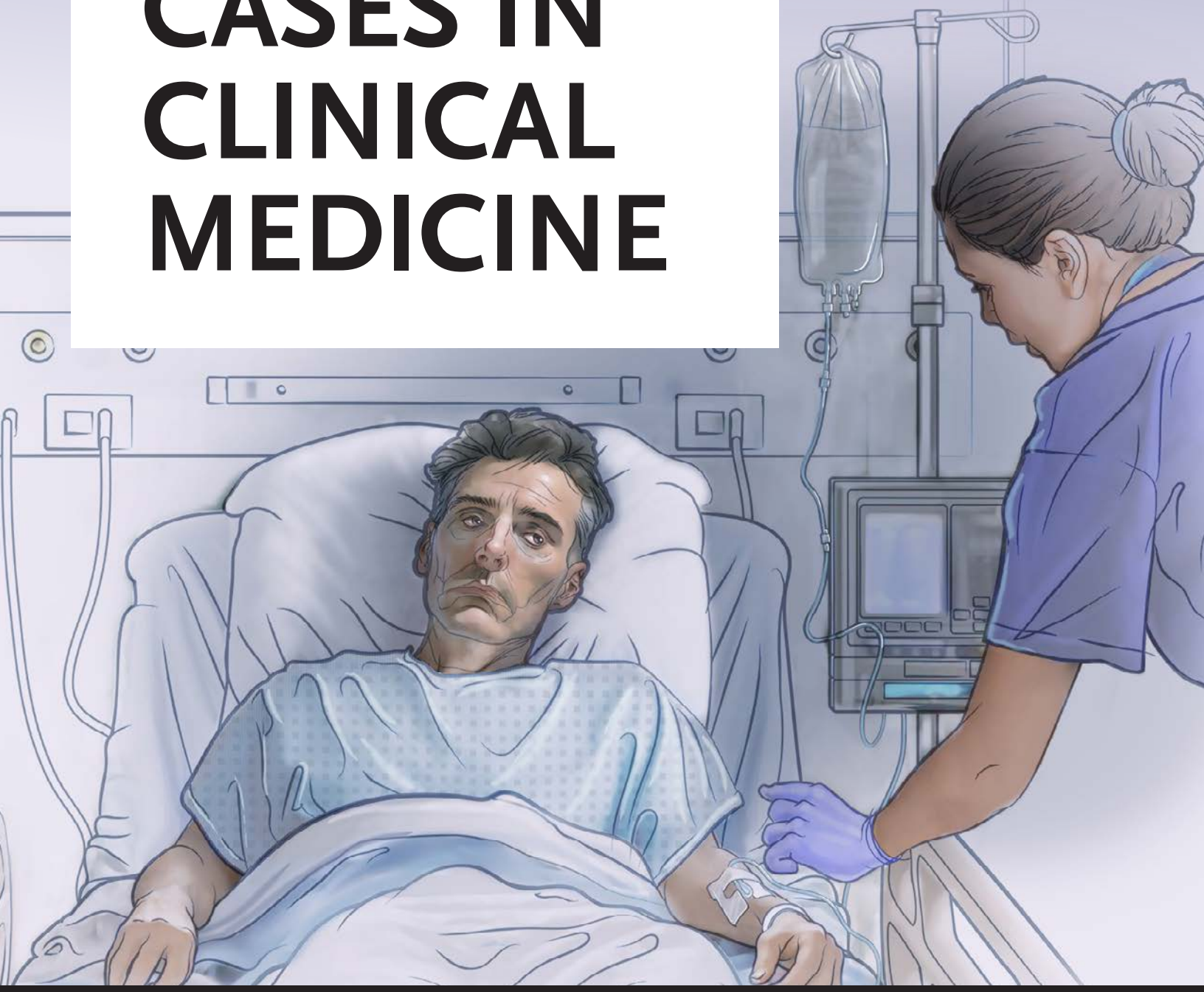

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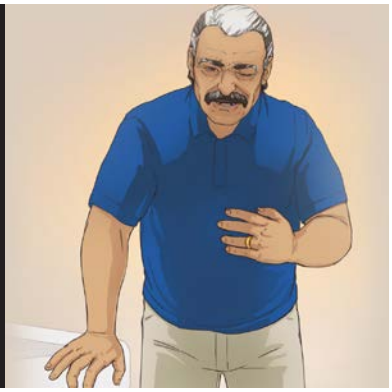
Table of Contents



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CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

The Syndrome of Inappropriate Antidiuresis

Horacio J. Adrogué, M.D., and Nicolaos E. Madias, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

An 85-year-old man is found to have a serum sodium level of 128 mmol per liter during his annual evaluation. He has noted some "mental slowing" and gait instability. The patient's history is notable for primary hypertension and prostatic hypertrophy. His medications include amlodipine, finasteride, and tamsulosin. His blood pressure is 136/68 mm Hg without orthostatic changes; the remainder of the examination is unremarkable. Repeat testing reveals a serum sodium level of 127 mmol per liter, osmolality of 260 mOsm per kilogram of water, creatinine level 0.8 mg per deciliter (70.7 μmol per liter), blood urea nitrogen level of 8 mg per deciliter (2.9 mmol per liter), and uric acid level of 4 mg per deciliter (0.24 mmol per liter). The urine osmolality is 645 mOsm per kilogram of water, and the sodium level is 95 mmol per liter. How should this patient be further evaluated and treated?

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THE CLINICAL PROBLEM

Hyponatremia (serum sodium level, <135 mmol per liter) is the most common electrolyte abnormality and affects approximately 5% of adults overall and 35% of hospitalized patients.[1,2] It is categorized as mild (130 to 134 mmol per liter), moderate (125 to 129 mmol per liter), or severe (<125 mmol per liter); about 70% of hyponatremia cases are mild, whether in outpatients or inpatients. Even mild hyponatremia is associated with adverse outcomes, including increased length of hospitalization, readmission, resource use, and death.[2-4]

The serum sodium level approximates the ratio of osmotically active sodium and potassium content to total body water. Hyponatremia typically reflects water excess relative to these body cations, most commonly resulting from disorders impairing electrolyte-free water excretion by the kidneys (aquaresis).[5] Impaired aquaresis largely depends on increased secretion of arginine vasopressin (AVP), the antidiuretic hormone, which activates the vasopressin 2 receptor in the collecting duct of the nephron, thus promoting water retention. AVP is triggered by osmotic and hemodynamic stimuli (hypertonicity and reduced effective arterial blood volume, respectively).[5,6] In hyponatremia that is associated with hypovolemia and certain hypervolemic disorders (e.g., heart failure), water retention is driven by AVP release caused by reduced effective arterial blood volume. In contrast, in the syndrome of inappropriate antidiuresis (SIAD), a euvolemic disorder, AVP secretion occurs in the absence of osmotic and hemodynamic stimuli (and the antidiuresis is therefore deemed "inappropriate").[5-7]

Hyponatremia can also reflect impaired aquaresis independent of AVP release, including low-solute intake, acute kidney injury, and chronic kidney disease

Back to Table of Contents

KEY CLINICAL POINTS

SYNDROME OF INAPPROPRIATE ANTIDIURESIS (SIAD)

- Hyponatremia is the most common electrolyte abnormality. The condition is usually caused by a water excess relative to sodium and potassium content.
- In SIAD, a frequent cause of hyponatremia, increased secretion of antidiuretic hormone in the absence of osmotic and hemodynamic stimuli leads to water retention by the kidneys and water excess.
- Manifestations of SIAD depend on the rapidity of development and the severity and duration of the condition. Symptoms range from mild and nonspecific (e.g., weakness and headache) to severe and life-threatening (e.g., seizures and coma).
- Causes of SIAD include cancer, medications, pulmonary conditions, disorders of the central nervous system, postoperative state, severe nausea, and stress; frequently the cause is undetermined.
- Severely symptomatic SIAD leads to emergency treatment with 3% sodium chloride to reverse cerebral edema. Consultation with a specialist is warranted.
- Management strategies for SIAD include reversal or amelioration of the underlying disorder when possible; fluid restriction; supplementation with sodium chloride, often with furosemide; and treatment with urea or tolvaptan.

(stages G3 through G5).[2] Infrequently, hyponatremia results from excessive water intake that overwhelms aquaresis. Regardless of pathogenesis, hyponatremia does not arise unless water intake outstrips water losses from the kidneys and through other routes.[5,6] This article focuses on hyponatremia caused by SIAD.

The prevalence of hyponatremia overall, and of SIAD specifically, increases with age; 40% of older (>65 years of age) inpatients have hyponatremia, with 25 to 40% of cases attributed to SIAD.[2,4,8] This increased prevalence is attributable to the frequent presence among older persons of coexisting conditions (e.g., cancer, pulmonary diseases, and disorders of the central nervous system [CNS]) and medications that predispose to SIAD.[2-4,9] In addition, aging impairs aquaresis by means of diminished glomerular filtration rate, decreased renal prostaglandins, and increased AVP response to osmotic and nonosmotic stimuli[10]; low salt and protein intake, common in older persons, also contributes to impaired aquaresis.[11] Even a modest increase in water intake compounds the risk of hyponatremia.[5,12]

Manifestations of SIAD depend on the rapidity of development and the severity and duration of hyponatremia.[2] Symptoms of acute SIAD (<48 hours from onset of hyponatremia) result from cerebral edema and range from mild and nonspecific (e.g., weakness and headache) to severe and life-threatening (e.g., seizures and coma). Because brain-volume regulation reverses cerebral edema, symptoms of chronic SIAD (≥48 hours from onset of hyponatremia) are commonly subtle, although severe chronic SIAD can be associated with nausea, vomiting, headache, confusion, delirium, and, rarely, seizures.[2,12] Other manifestations associated with chronic SIAD, such as cognitive deficits, gait abnormalities, falls, osteoporosis, and fragility fractures, may be misattributed to normal aging.[13-15]

STRATEGIES AND EVIDENCE

DIAGNOSIS

The diagnosis of SIAD requires clinical confirmation of euvolemic hypotonic hyponatremia (Fig. 1).[16] Given the low sensitivity and specificity of a physical examination in assessing volume status, European guidelines prioritize measurement of urine osmolality and sodium.[17] Urine studies showing natriuresis (sodium, >30 mmol per liter) and inappropriate concentration (osmolality, >100 mOsm per kilogram of water) are consistent with SIAD. However, diagnosing SIAD requires ruling out secondary adrenal insufficiency and severe hypothyroidism.[3,7,16-18] In practice, requisite serum and urine tests for diagnosis are often omitted; the Hyponatremia Registry showed that those tests were completed in only 21% of patients in whom SIAD was diagnosed.[19]

The causes of SIAD are numerous (Table 1).[2-4,7] Major categories of causes (and relative frequencies) of SIAD included in the Hyponatremia Registry are cancer (24%), certain drugs (18%), pulmonary conditions (11%), and CNS disorders (9%).[20] Additional causes are exercise, pain, stress, severe nausea, postoperative state, and, rarely,

Back to Table of Contents

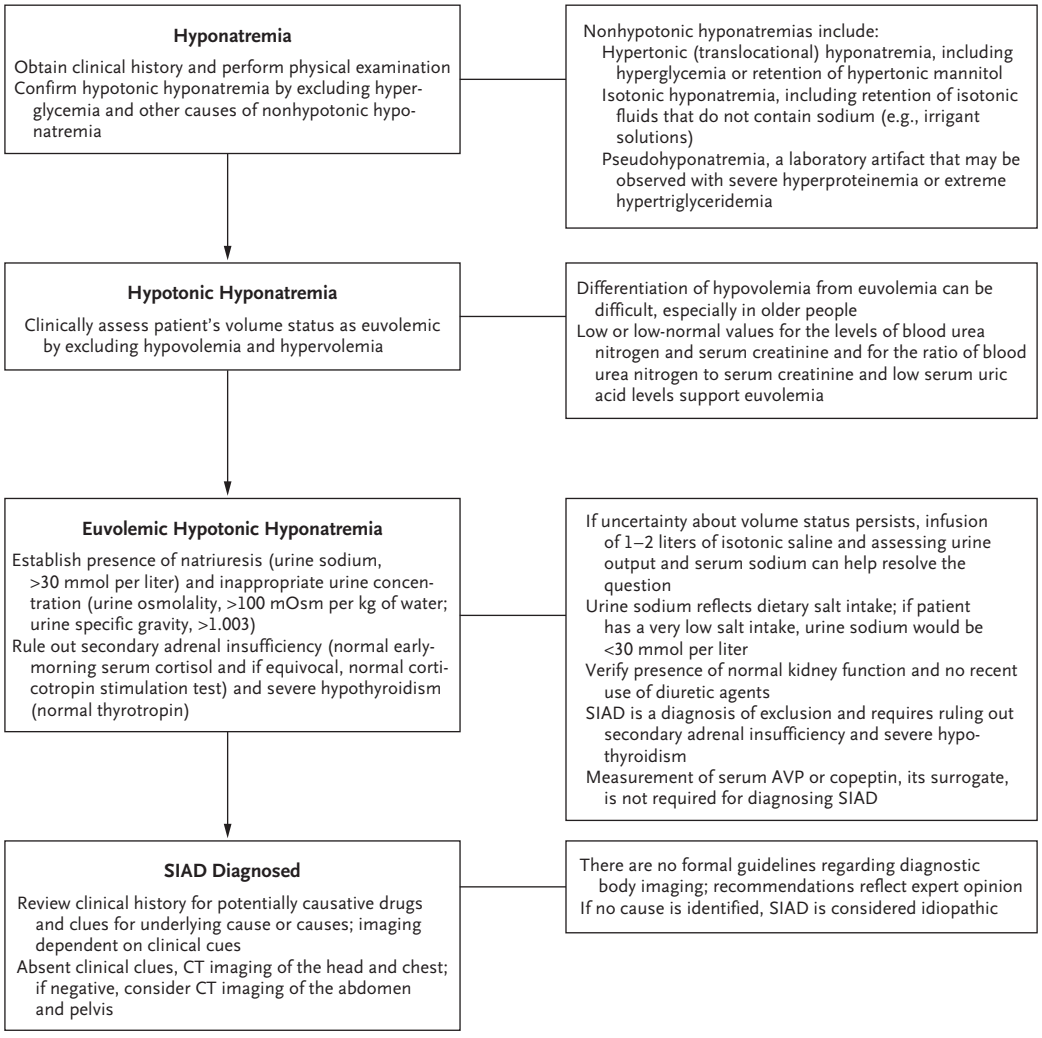


Figure 1. Diagnostic Algorithm for the Syndrome of Inappropriate Antidiuresis (SIAD).
AVP denotes arginine vasopressin, and CT computed tomography.

gain-of-function variants of gene encoding vasopressin 2 receptor (in nephrogenic SIAD).[2-4] More than one cause is frequently present.[12,21] Antidepressants are the most commonly implicated drugs, especially in underweight older women[22]; the risk relative to the use of antidepressants has been reported to be highest with the use of selective serotonin-reuptake inhibitors and lowest with mirtazapine. No cause is identified in 17 to 60% of patients with SIAD, depending on the extent of the evaluation and patient age (occurrence is highest among older persons).[21,23]

Reversal of hyponatremia upon discontinuation of a drug establishes the causal relationship. In the absence of clinical diagnostic clues, experts generally recommend computed tomography (CT) of the head and chest; if imaging results are negative, CT of the abdomen and pelvis may be considered.[4]

MANAGEMENT

Emergency Treatment

Urgent treatment is required for patients with SIAD who have severe symptoms of hyponatremia (e.g., somnolence, seizures, cardiorespiratory distress, or coma); moderately severe symp-

Back to Table of Contents

Table 1. Causes of the Syndrome of Inappropriate Antidiuresis (SIAD).*

Categories	Causes	Comments
Cancer	Pulmonary and mediastinal, nasopharyngeal, gastrointestinal, genitourinary	Most commonly observed in small-cell lung cancer (approximately 25% of the cases of SIAD that are caused by cancer), followed by head and neck cancer and olfactory neuroblastoma; ectopic production of AVP by some cancers has been documented (e.g., small-cell lung cancer and its metastases and olfactory neuroblastoma); tumor regression can reverse SIAD
Pulmonary conditions	Infections, asthma, acute respiratory failure	Most commonly seen in pneumonia of all causes; observed with positive-pressure ventilation
Central nervous system disorders	Mass lesions, infections, cerebrovascular accident, head trauma, pituitary surgery, acute psychosis	Develops in up to 56% of patients with subarachnoid hemorrhage and up to 35% of those with transsphenoidal pituitary surgery; a rare but treatable cause of rapidly progressive dementia, anti-LGI1 limbic encephalitis, leads to SIAD in 60 to 90% of patients
Drug-related	Stimulants of AVP release (e.g., opiates, ifosfamide, MDMA [also known as "ecstasy"], vincristine, and platinum compounds), enhancers of AVP effects (e.g., NSAIDs), AVP analogues (e.g., desmopressin and oxytocin), and stimulants of V2R (e.g., SSRIs, haloperidol, carbamazepine, cyclophosphamide, and chlorpropamide)	MDMA intoxication can result in severe hyponatremia because AVP stimulation is coupled with excessive ingestion of fluids on the users' belief that they can avoid the characteristic hyperthermia; desmopressin, prescribed for enuresis (nocturnal polyuria), can cause severe hyponatremia and occasionally osmotic demyelination syndrome; antidepressants are among the most common causes, especially in underweight older women (risk is highest with SSRIs and lowest with mirtazapine); high-dose intravenous cyclophosphamide can result in severe hyponatremia if large amounts of fluid are prescribed for prevention of hemorrhagic cystitis
Other	Exercise-associated, pain, stress, severe nausea, general anesthesia, postoperative state, gain-of-function variants in V2R gene (nephrogenic SIAD)	Prevention of exercise-associated hyponatremia requires that athletes drink only in response to thirst and avoid weight gain during exercise; in postoperative state, hyponatremia reflects combined effects of pain, stress, nausea, anesthesia, opiates, and hypotonic fluids; most cases of hereditary SIAD feature persistent activation of V2R (gene located on the X chromosome) that is unresponsive to vaptans
Idiopathic		Widely variable prevalence (17 to 60% of cases), most commonly reported in older patients; occasionally, an apparent idiopathic case has later been found to have been caused by occult tumor

* AVP denotes arginine vasopressin, LGI1 leucine-rich, glioma-inactivated 1 antibodies, MDMA 3,4-methylene-dioxymethamphetamine, NSAIDs nonsteroidal antiinflammatory drugs, SSRIs selective serotonin-reuptake inhibitors, and V2R vasopressin 2 receptor.

toms (e.g., vomiting or confusion) and a high risk for progression on the basis of the clinical presentation (e.g., postoperative state or exercise-associated); or any hyponatremia accompanying intracranial disease (e.g., subarachnoid hemorrhage or head trauma), in which case worsening of cerebral edema could be catastrophic. Typically, such patients have acute hyponatremia, but some have acute-on-chronic hyponatremia or extreme chronic hyponatremia.[2,12,16,17,24-26]

Traditional treatment has been the administration of 3% sodium chloride by means of slow, continuous infusion to raise serum sodium by 1 to 2 mmol per liter per hour for a few hours, with a correction limit of 8 to 10 mmol per liter over 24 hours and 18 to 25 mmol per liter over 48 hours.[7] The current rapid approach, supported by guidelines from a U.S.–Irish expert panel and by European guidelines, is the administration of 100 ml and 150 ml of 3% sodium chloride, respectively, administered as an intravenous bolus and repeated two or three times as needed.[16,17] The goal of this treatment approach is to increase serum sodium by 4 to 6 mmol per liter within 1 to 2 hours, an increase sufficient to reverse clinical manifestations of cerebral edema.[16,17] Guidelines set a correction limit of 10 mmol per liter within the first 24 hours and 18 mmol per liter within the first 48 hours. Correction limits are imposed because overly rapid correction of chronic hyponatremia increases the risk of osmotic demyelination, a rare but potentially devastating complication that involves the central pons or extrapontine structures and can cause hyperreflexia, pseudobulbar palsy, parkinsonism, locked-in syndrome, and death.[16,17,25]

For patients at high risk for osmotic demyelination (i.e., chronic hyponatremia of <110 mmol per liter, alcohol use disorder, liver disease or transplantation, potassium depletion, or malnutrition), the correction limit is 8 mmol per liter during any 24-hour period.[12,16,17] Other experts recommend stricter correction limits: in any 24-hour period, a correction limit of 8 mmol per liter for patients at low risk for osmotic demyelination and 6 mmol per liter for patients at high risk.[2,12,25] If hyponatremia is known to be acute (e.g., occurring during a postoperative state), adherence to correction limits is unnecessary. However, the duration of hyponatremia usually cannot be ascertained[12]; even in exercise-associated hyponatremia, preexisting chronic hypona-

Back to Table of Contents

tremia cannot be ruled out. Emergency treatment requires close monitoring, preferably in the intensive care unit, and consultation with a specialist (i.e., intensivist, nephrologist, or endocrinologist).[2]

A nonrandomized study involving patients with severe symptomatic SIAD who were treated with 100 ml of 3% sodium chloride administered as an intravenous bolus showed an increase in serum sodium levels that was greater than that observed in a historical comparison group in which patients received 3% sodium chloride in a continuous infusion (6 mmol per liter vs. 3 mmol per liter at 6 hours) and reported greater neurologic improvement in that time interval[27]; overcorrection occurred in 4.5% of the patients who received sodium chloride by intravenous bolus as compared with none of the patients who received continuous infusion, and sodium-relowering therapy was used in 23% and 0%, respectively. Two other small studies also showed high rates of overcorrection (17% and 28%) and sodium-relowering therapy (41% and 28%) with the bolus approach (150 ml per dose); however, these studies included many participants with hypovolemia in whom aquaresis probably developed after volume repletion.[28,29]

Overcorrection can occur because of excessive administration of 3% sodium chloride owing to repeated fixed-dose boluses.[2,12,30] The effects that a given dose has on the serum sodium level depend on the sodium level at baseline and the total body water (the latter affected by sex, weight, and body fat). An individualized approach to the administration of 3% sodium chloride can be applied with the use of a formula that effectively predicts the change in the serum sodium level after the infusion of 1 liter of any solution if there is no other input or output. The change from baseline in sodium level is calculated according to the following formula: (sodium+potassium) infusate−sodium level at baseline÷total body water+1.[2,5,12] The formula has been validated with regard to patients with SIAD who remain antidiuretic, with actual serum sodium levels at 24 hours that are very similar to predicted levels.[31,32]

Overcorrection can also occur because of transition to aquaresis (urine output, >100 ml per hour) after the discontinuation of causative drugs or reversal of transient SIAD (e.g., postoperative state). The effect of aquaresis on serum sodium can be quantitated by means of a simple fluid-loss formula.[12] To counter such risk, desmopressin can be used proactively (anticipating aquaresis) or reactively (responding to aquaresis).[25,32,33] However, randomized trials of desmopressin are lacking in these contexts; retrospective studies have shown no consistent benefit associated with its use and potential complications, including volume overload, longer hospitalization, more testing, and worsening hyponatremia.[34-36] If overcorrection develops, urgent treatment is required, including discontinuation of 3% sodium chloride, infusion of a 5% solution of dextrose in water, and administration of desmopressin as rescue therapy.[2,25] Because potassium retention increases serum sodium, special caution is required with potassium supplementation when treating hyponatremia to avoid overcorrection.[2,12]

Nonemergency Treatment

Fewer than 5% of patients with hyponatremia have sufficiently severe symptoms to need emergency treatment.[2,19] For the majority of patients, treatment focuses on addressing the underlying cause (or causes) and is typically administered on an outpatient basis; exceptions include treatment of patients who are hospitalized for management of an underlying cause of hyponatremia or whose serum sodium level is less than 120 mmol per liter. Among patients in the latter group, the absence of severe manifestations is evidence of substantial brain-volume adaptation, so close monitoring of serum sodium levels is indicated during treatment to minimize the risk of osmotic demyelination. If the underlying cause can be reversed (e.g., drug effects or pneumonia), hyponatremia resolves within several days.

Observational studies in patients with moderate or severe chronic SIAD have shown associations between correction of sodium levels and improvements in neurocognitive performance, motor function, and mood[13,37,38]; however, other aspects of patient care, including treatment of associated coexisting conditions, may confound these findings. Limited data from randomized, controlled trials bear out findings of improvement on the physical component score of the 12-item Short-Form Health Survey Questionnaire (a tool for evaluating quality of life) with increases in sodium levels.[39] In addition, increases in serum sodium levels in patients with chronic

SIAD and mild or moderate hyponatremia have been associated with increases in markers of osteoblast function,[40,41] although the effects on the incidence of fractures are not known. These observations support reasonable efforts to correct hyponatremia of any level in patients with SIAD.

Several therapies are available for patients with SIAD (Table 2). Fluid restriction, the first-line treatment, is inexpensive and safe but of limited efficacy; urine output of less than 1.5 liters per day or urine osmolality greater than 500 mOsm per kilogram of water predicts SIAD that is unresponsive to this approach.[2,16] A randomized, controlled trial that assessed fluid restriction (fluid intake limited to 1 liter per day) as compared with no hyponatremia treatment in 46 patients with chronic SIAD (in whom transient and reversible causes were ruled out) showed a modest rise in serum sodium levels with fluid restriction (3 mmol per liter vs. 1 mmol per liter at day 4; and 4 mmol per liter vs. 1 mmol per liter at day 30). Only 17% and 4% of patients, respectively, had a rise in serum sodium of at least 5 mmol per liter at day 4.[42]

Other therapies involve increasing salt, urea, or protein intake,[16,17,24,26] although data are lacking from randomized, blinded trials. In a retrospective study involving 83 patients with chronic SIAD, patients who took salt tablets (median dose, 5 g per day) had a mean increase in serum sodium levels of 5.2 mmol per liter, as compared with 3.1 mmol per liter in patients who did not receive salt tablets.[43] Salt tablets plus furosemide are widely used on the premise that replacement of salt lost in the urine promotes aquaresis, thus raising serum sodium levels. However, in an open-label, randomized, controlled trial involving 92 patients with SIAD, treatment with salt tablets plus furosemide and severe fluid restriction as compared with fluid restriction alone resulted in modestly higher sodium levels at day 7 but no difference at day 28; the addition of salt plus furosemide also increased the risk of acute kidney injury and hypokalemia.[44]

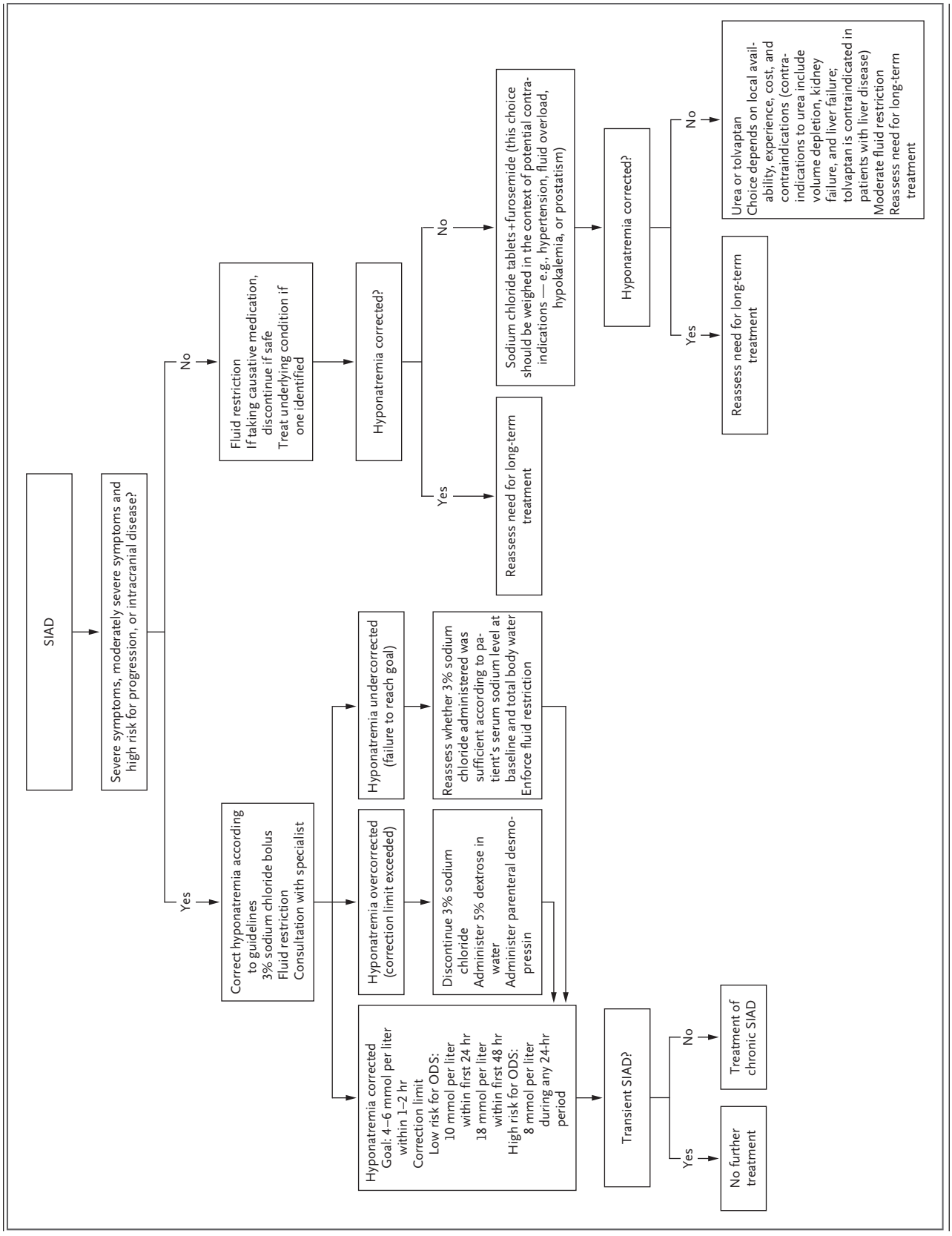
Small observational studies ranging in duration from 2 days to 1 year have shown improvements in sodium levels among outpatients and inpatients who received urea in addition to moderate fluid restriction (fluid intake limited to 1 to 1.5 liters per day).[24,45] A retrospective study showed that among 12 patients treated only with urea, serum sodium levels increased by 6 mmol per liter over 4 days without incidents of overcorrection or other serious adverse effects.[46] Urea has been used effectively in managing nephrogenic SIAD.[45] Patients with SIAD commonly have low protein intake[11]; increasing protein intake (to approximately 1 g per kilogram of body weight) may ameliorate hyponatremia by mimicking urea therapy, but data regarding this effect are lacking.

Tolvaptan, which competitively inhibits the vasopressin 2 receptor in the collecting duct, is a highly effective therapeutic agent.[47] In a subset analysis involving 110 patients with SIAD who were included in two randomized, placebo-controlled trials of tolvaptan for the treatment of hyponatremia, patients who received tolvaptan had larger increases in serum sodium levels than patients who received placebo. The average daily area under the curve for the serum sodium level among patients who received tolvaptan was 5.3 mmol per liter from baseline to day 4 and 8.1 mmol per liter from baseline to day 30; among patients who received placebo, the average daily area under the curve for the serum sodium level was 0.5 mmol per liter from baseline to day 4 and 1.9 mmol per liter from baseline to day 30. Patients who received tolvaptan had less need for fluid restriction and a shorter duration of hospitalization than those who received placebo.[39] However, thirst and dry mouth were common, and overcorrection of hyponatremia occurred in 5.9% of patients treated with tolvaptan.[39] In an open-label extension of these trials, daily therapy with tolvaptan continued to be effective over 4 years.[48] Tolvaptan is contraindicated with concomitant use of hypertonic saline, and caution is recommended in patients with serum sodium levels of less than 120 mmol per liter because of limited safety information.[24,26,47] Tolvaptan is ineffective in the management of nephrogenic SIAD.[4] A treatment algorithm for SIAD is shown in Figure 2.

More recent data support a potential role for empagliflozin, a sodium glucose cotransporter 2 inhibitor that promotes osmotic diuresis by means of glucosuria, in the treatment of patients with SIAD. In a randomized, controlled trial involving 87 patients, fluid restriction to 1 liter per day plus treatment with empagliflozin was associated with a greater increase in serum sodium levels at day 5 than fluid restriction alone (10 mmol per liter vs. 7 mmol per liter). How-

Table 2. Treatment Approaches.

Treatment	Mechanism	Amount or Dose	Efficacy	Adverse Effects	Comments
Fluid restriction	Reduces electrolyte-free water intake and total body water; should include all fluids, not just water	Moderate, <1.5 liters per day; severe, <1 liter per day	First-line treatment; difficult to adhere to and thus often ineffective	Increases thirst; may result in low caloric intake	Inexpensive and safe; predictors of failure at baseline include urine output of <1.5 liters per day, urine osmolality >500 mOsm per kg of water, and the sum of urine sodium and urine potassium levels exceeding the serum sodium level; contraindicated in subarachnoid hemorrhage and other intracranial processes
Sodium chloride supplement	Increases body sodium content, reduces electrolyte-free water intake, and increases water excretion	2–5 g per day (500 mg per tablet); frequently combined with furosemide 20 mg twice daily or equivalent loop diuretic to increase aquaresis	Limited long-term efficacy	Increases body sodium content, risking sodium and fluid excess; combining with furosemide can cause potassium depletion	Inexpensive; addition of sodium chloride plus furosemide to severe fluid restriction has no persistent benefit with respect to correction of serum sodium levels; contraindicated in hypertension, heart failure, and other sodium-retentive states
Urea	Increases electrolyte-free water excretion (by means of osmotic diuresis); decreases sodium excretion	15–60 g per day orally or enterally combined with moderate fluid restriction; 30 g of urea (500 mOsm) increases water excretion by 1 liter (for urine osmolality of 500 mOsm per kg of water)	Short- and long-term efficacy reported in observational studies	Nausea, diarrhea, and bitter taste; rare overly rapid correction of serum sodium, but osmotic demyelination not reported	Palatability is improved by dissolving in fruit juice or syrup (European guideline provides a recipe); citrus-flavored U.S. formulation (ure-Na) is available; initially used in Europe but more recently prescribed worldwide; contraindicated in volume depletion, kidney failure, and liver failure
Tolvaptan	Sole therapy that addresses underlying pathophysiology; competitive vasopressin receptor 2 blocker	15–60 mg per day orally combined with moderate fluid restriction; initiated in hospital to allow close monitoring of serum sodium (every 6–8 hr or more frequently depending on risk of osmotic demyelination syndrome) and dose adjustment; fluid restriction should not be used during the initial dose-finding phase to decrease risk of overly rapid correction of serum sodium; 7.5 mg per day appears as effective as 15 mg per day as a starting dose	Highly effective both in short- and long-term use; aquaretic response and increase in serum sodium correlate directly with severity of hyponatremia	Polyuria and increased thirst; overly rapid correction of serum sodium occurs in 13 to 25% of patients in real-life experience (appears to be exclusive to baseline serum sodium of <125 mmol per liter); sporadic cases of osmotic demyelination syndrome; 7.5-mg dose not associated with overly rapid correction in chronic SIAD	Food and Drug Administration warns against use for >30 days (on the basis of duration of pivotal trials) and in patients with liver disease; not recommended by the European guideline owing to risks of overly rapid correction of serum sodium level and hepatotoxicity; hepatotoxicity not observed in tolvaptan trials for hyponatremia, but reversible hepatotoxicity was reported in trials that used high doses of tolvaptan to alter course of polycystic kidney disease; cost is a barrier to use in some countries



Back to Table of Contents

Figure 2 (facing page). Treatment Algorithm for SIAD.
ODS denotes osmotic demyelination syndrome.

ever, although the frequency of serious adverse events did not differ materially between the empagliflozin and placebo groups in that trial, empagliflozin was associated with transient kidney dysfunction in 4 patients and overcorrection of hyponatremia in 2 patients (as compared with no patients and 1 patient, respectively, in the placebo group).[49] In a subsequent randomized 4-week crossover trial involving 14 patients, treatment with empagliflozin resulted in an increase of 4.1 mmol per liter in the serum sodium level, as compared with no increase with placebo.[50]

AREAS OF UNCERTAINTY

Whether the observed associations between chronic hyponatremia and adverse outcomes (such as fractures and increased risk of death) are causal remains uncertain, although some evidence supports causal relationships. For example, the experimental induction of chronic SIAD in aged rats resulted in loss of bone density, sarcopenia, cardiomyopathy, and hypogonadism.[14,51]

Whether reversing hyponatremia results in improved long-term outcomes is also uncertain. A meta-analysis of observational studies showed substantially lower occurrences of in-hospital and postdischarge death among patients whose hyponatremia improved during hospitalization as compared with patients whose hyponatremia did not improve.[52] However, the possibility of confounding by coexisting conditions and other aspects of treatment cannot be excluded.

Prospective studies are needed to assess emergency management of hyponatremia with the use of guideline-directed fixed doses of hypertonic saline (administered as an intravenous bolus) as compared with an individualized formula-based approach. Encouraging reports regarding the efficacy and safety of smaller starting doses of tolvaptan warrant additional investigation.[53] Long-term randomized trials are needed to compare treatment with tolvaptan, urea, and empagliflozin (as well as other sodium glucose cotransporter 2 inhibitors) with respect to efficacy outcomes, safety, and costs.

GUIDELINES

Recommendations from a U.S.–Irish expert panel[16] and European guidelines[17] regarding the diagnosis and management of hyponatremia, including hyponatremia due to SIAD, have been published previously. Our recommendations align with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient who is described in the vignette has hyponatremia consistent with SIAD. To confirm the diagnosis, testing is needed to rule out secondary adrenal insufficiency and severe hypothyroidism. Because he is taking no medications associated with SIAD and no other cause is apparent, we would pursue CT imaging of the chest and head; if imaging is negative, we would consider the case idiopathic. His high urine osmolality level predicts a poor response to fluid restriction as monotherapy. Given the patient's hypertension and prostatism, we would avoid recommending salt tablets and furosemide. We would instead recommend urea at a dose of 15 g twice daily (delivered as an oral urea formulation) along with fluid restriction to 1500 ml per day, although data from randomized trials are not available to support this approach. Alternatively, we would consider long-term use of tolvaptan at a starting dose of 7.5 mg per day; however, the cost of this therapy may be a barrier for some patients. Sodium levels should be closely monitored during treatment.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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CLINICAL PRACTICE

Patrick G. O'Malley, M.D., M.P.H., *Editor*

Asthma in Adults

Giselle Mosnaim, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 47-year-old woman with a history of asthma, which has been treated with daily low-dose inhaled glucocorticoids and a short-acting β_2-agonist (SABA) as needed, presents for a follow-up visit. She reports having shortness of breath 4 days per week when she is outdoors watching her daughter's soccer matches. Over the past year, she has had asthma exacerbations resulting in treatment with oral glucocorticoids in the spring and fall. How should this patient be evaluated and her care managed?

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THE CLINICAL PROBLEM

The prevalence of asthma in adults in the United States is approximately 7.7%.[1] It is one of the most common chronic, noncommunicable diseases in the country and worldwide.[1,2] Among U.S. adults, asthma disproportionately affects women, persons who are Black or Puerto Rican, and persons with low household income.[1] Although overall asthma-related mortality in the United States has decreased from 15.1 per million in 2001 to 9.9 per million in 2017,[3] the incidence of death due to asthma in the United States remains consistently higher among Black and Puerto Rican persons than among White persons.[4] In addition, although severe asthma affects 5 to 10% of all patients with asthma, it accounts for over 50% of asthma-related costs.[5,6]

The National Asthma Education and Prevention Program Expert Panel-3 Report defines asthma as "a complex disorder characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation" and notes that "[t]he interaction of these features of asthma determines the clinical manifestations and severity of asthma and the response to treatment."[7] This article focuses on treatment advances for mild-to-moderate asthma.[7-10] The approach to treatment should be decided on the basis of a confirmed diagnosis of asthma that includes findings of variable airflow obstruction on spirometry.

The typical symptoms of asthma are also symptoms of other respiratory and nonrespiratory conditions.[7,8] Chronic cough, in the presence of normal lung function and a normal chest radiograph, should prompt consideration of allergic and nonallergic rhinitis, rhinosinusitis, nasal polyposis, gastroesophageal reflux disease, postviral tussive syndrome, chronic bronchitis, eosinophilic bronchitis, and cough induced by an angiotensin-converting enzyme inhibitor. If a patient presents with chronic wheeze, the differential diagnosis includes vocal-cord dysfunction, bronchiectasis, chronic obstructive pulmonary disease, bronchogenic carcinoma, and foreign-body aspiration. Common causes of shortness of breath that may be con-

Back to Table of Contents

KEY CLINICAL POINTS

ASTHMA IN ADULTS

- Asthma guidelines state that a definitive diagnosis of asthma should be based on the presence of characteristic respiratory symptoms such as wheeze, cough, chest tightness and shortness of breath, and variable expiratory airflow obstruction on spirometry.
- The three main goals of asthma management are control of symptoms, reduction in risk of exacerbations, and minimization of adverse effects of medications.
- Every visit should include a review of inhaler technique, medication adherence, coexisting conditions, ongoing exposures to environmental triggers, and confirmation of a correct diagnosis of asthma.
- In patients with mild asthma, the preferred treatment option is an inhaled glucocorticoid–formoterol combination as needed, and alternative options include the use of combination inhaled glucocorticoid–albuterol as needed or low-dose maintenance inhaled glucocorticoid plus a short-acting β_2-agonist reliever as needed.
- Combination inhaled glucocorticoid–formoterol maintenance and reliever therapy is the preferred treatment for moderate-to-severe asthma as compared with an inhaled glucocorticoid with long-acting β_2-agonist maintenance plus as-needed short-acting β_2-agonist reliever therapy.

fused with asthma are chronic obstructive pulmonary disease, heart failure, pulmonary embolism, and sarcoidosis.[7,8]

A personal history of atopy (e.g., atopic dermatitis or allergic rhinitis) or a strong family history of asthma is suggestive of asthma. Although asthma often presents in childhood, many children have a remission of symptoms in puberty and a recurrence in adulthood.[11] Approximately half of adults who present with what appears to be newly diagnosed asthma instead have had a recurrence of childhood asthma.[12,13]

Typical asthma triggers include exercise, cold air, and inhalant indoor and outdoor allergens.[7] Persons with asthma typically present with variable symptoms that may last from hours to days and resolve without intervention with avoidance of the trigger. Up to 10 to 25% of new-onset adult asthma cases are attributable to work-related exposures (e.g., wood dust, grain dust, and animal dander),[14,15] a correlation that emphasizes the importance of an occupational-history assessment and the identification of contact with known sensitizing agents to determine whether there is a temporal relationship between work exposures and symptoms.[16]

Approximately 7% of adults with asthma also have aspirin-exacerbated respiratory disease, which is characterized by cough, chest tightness, or wheeze within 30 to 120 minutes after ingestion of aspirin or any cyclooxygenase-1 inhibitor.[17] Obesity, anxiety, depression, and obstructive sleep apnea may also contribute to worsening asthma.

STRATEGIES AND EVIDENCE

GOALS OF ASTHMA THERAPY

The three main goals of asthma management are control of asthma symptoms, reduction in the risk of asthma exacerbations, and minimization of adverse effects of medications (e.g., side effects of oral glucocorticoid therapy).[7-10] Goals for asthma control are reduction in intensity and frequency of daytime and nighttime cough, chest tightness, wheezing, and shortness of breath; maintenance of normal daily activities without limitation caused by asthma symptoms, including symptoms related to school, work, and exercise; and lung function that is normal or nearly normal. Reduction of asthma risk focuses on prevention of severe exacerbations, which can be defined as deterioration that leads to treatment with oral glucocorticoids for 3 days or longer, an emergency department visit, or hospitalization.[7,8]

Treatment is focused on patient education, asthma trigger control, monitoring of symptoms and lung function, and pharmacologic therapy.[7-10] Empowerment of patients to be active participants in their asthma care is important. Such efforts include educating patients about strategies to identify and mitigate triggers, providing medications to be used for quick relief and those to be used for maintenance of control, encouraging adherence to daily controller therapy to reduce symptoms and minimize risk, and teaching the correct inhaler technique for each prescribed inhaler.[18] Some studies show that such patient education reduces the incidence of asthma exacerbations.[19-22]

A personalized, written asthma action plan is a tool that patients can use to assist in managing asthma at home. For patients whose symptoms occur after exposure to specific indoor allergens (confirmed by history and positive results on specific IgE blood or skin tests), multicomponent allergen-specific mitigation measures are recommended.[9] Symptom monitoring can be supported by the use of brief, patient-administered, validated instruments to assess asthma control, such as the five-item Asthma Control Test (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[23-25]

ASTHMA SEVERITY AND CONTROL

Asthma severity and control are categorized on the basis of consideration of daytime and nighttime symptoms that have occurred in the 4 weeks before presentation, the number of exacerbations leading to oral glucocorticoid use in the past year, and lung function.[7,8] Guidelines recommend a step up in therapy for patients with uncontrolled asthma and a step down in therapy after a patient's asthma has been controlled for 3 months with a stable treatment regimen.[7,8]

GUIDELINES FOR ASTHMA THERAPY

Figure 1 shows the most recent algorithm for asthma management in persons 12 years of age or older, according to the Global Initiative for Asthma (GINA) Science Committee, across categories of mild, moderate, and severe asthma.[8]

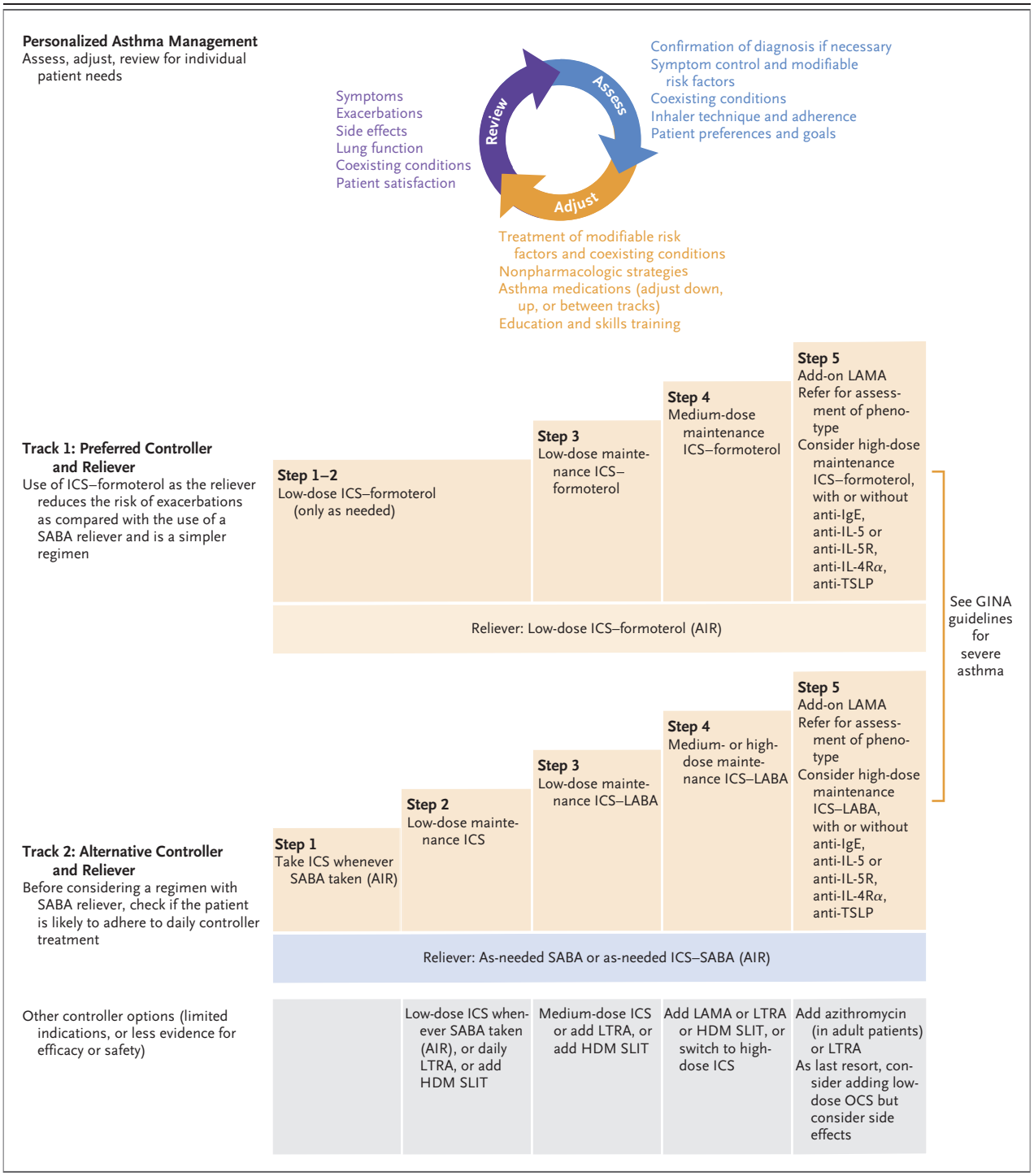
RELIEVER THERAPIES

In patients with occasional asthma symptoms, as-needed treatment with a combination of an inhaled glucocorticoid and a β_2-agonist is the current treatment of choice; the precise combination of inhaled glucocorticoid and β_2-agonist that is appropriate depends on availability and affordability. In a multinational, randomized, event-driven trial involving patients with moderate-to-severe asthma who were receiving inhaled glucocorticoid–containing maintenance therapy, the use of combination albuterol–budesonide therapy administered as needed at doses of 180 μg of albuterol and 160 μg of budesonide (two inhalations of 90 μg of albuterol and 80 μg of budesonide) reduced the occurrence of severe exacerbations by 27% as compared with as-needed albuterol alone.[26] In a pragmatic, open-label, randomized trial involving Black and Latinx adults with moderate-to-severe asthma, participants who were assigned to receive a dose of inhaled glucocorticoid whenever they used their SABA inhaler had 15% fewer severe exacerbations than participants who used the SABA inhaler alone.[27]

Data comparing combinations of an inhaled glucocorticoid and a long-acting β_2-agonist (LABA) or SABA as reliever therapies are limited. Formoterol is unique in that it is a fast-acting LABA and therefore works as a reliever medication, and its combination with an inhaled glucocorticoid has proven efficacy when used as a reliever therapy. However, data from direct comparisons between an inhaled glucocorticoid–formoterol combination reliever and an inhaled glucocorticoid–SABA combination reliever are lacking. In a study involving patients who were assigned to receive maintenance therapy with budesonide–formoterol, there were fewer occurrences of severe asthma exacerbations among patients assigned to receive budesonide–formoterol as the reliever than among those assigned to receive the SABA terbutaline alone as reliever therapy (relative risk, 0.78; confidence interval [CI], 0.67 to 0.91).[28] Inhaled glucocorticoid–formoterol combination therapy has received regulatory approval for use as a reliever therapy in the United Kingdom but not in the European Union or the United States. Overall, the regulatory approvals for combination inhalers as maintenance and reliever therapy are confusing and vary greatly among countries.[29,30]

Budesonide–formoterol and beclomethasone–formoterol are the only two inhaled glucocorticoid–formoterol formulations for which there is clinical evidence supporting their use as relievers in treating all levels of asthma severity.[31,32] Owing to safety concerns with the use of two different classes of LABAs, the use of inhaled glucocorticoid–formoterol combination reliever therapy is not recommended for use concurrently with inhaled glucocorticoid–LABA combination control therapy other than inhaled glucocorticoid–formoterol. Therefore, GINA describes different treatment tracks that are based on the type of LABA used (i.e., fast-onset formoterol or standard-onset LABA). GINA also recommends the use of inhaled glucocorticoid–formoterol as prophylaxis before exercise, given evidence that inhaled glucocorticoid–formoterol

Back to Table of Contents



is more protective than SABA against exercise-induced asthma.[8,32]

STEPS ONE AND TWO: THERAPY FOR MILD ASTHMA

At step one, the preferred treatment (GINA track one) for mild asthma is low-dose combination inhaled glucocorticoid–formoterol as needed for symptom relief; controller treatment is no longer recommended as part of step one (Table 1). Alternative treatments (track two) include the use of an inhaled glucocorticoid whenever SABA is taken (step one) and daily low-dose inhaled gluco-

Figure 1 (facing page). Global Initiative for Asthma 2023 (GINA) Personalized Asthma Management for Adolescents and Adults.

The cycle of assessment, adjustment, and review is recommended for each patient visit. First, confirm the diagnosis of asthma (if applicable) and assess symptom control, modifiable risk factors, coexisting conditions, adherence to and technique for inhaler use, and patient preferences and goals. Second, treat modifiable risk factors and coexisting conditions, use nonpharmacologic therapeutic strategies, adjust medications (up, down, and between tracks), and provide education and skills training. Third, review symptoms that occur during the day and at night, exacerbations, treatment side effects, lung function, coexisting conditions, and patient satisfaction. Treatment steps are grouped into tracks: track 1 (preferred) and track 2 (alternative) pharmacologic therapy for asthma that is mild (steps 1 and 2), moderate (steps 3 and 4), or severe (step 5). Orange shading denotes preferred treatment, and blue and gray denote alternative or nonpreferred treatment. AIR denotes antiinflammatory reliever, anti-IL5R anti–interleukin-5 receptor (monoclonal antibody), anti-IgE anti-immunoglobulin E (monoclonal antibody), anti-IL4Rα anti–interleukin-4 receptor alpha (monoclonal antibody), anti-IL5 anti–interleukin 5 (monoclonal antibody), anti-TSLP antithymic stromal lymphopoietin (monoclonal antibody), HDM SLIT house dust mite sublingual immunotherapy, ICS inhaled corticosteroid (i.e., glucocorticoid), LABA long-acting β_2-agonist, LAMA long-acting muscarinic antagonist, LTRA leukotriene receptor antagonist, OCS oral corticosteroid (i.e., glucocorticoid), and SABA short-acting β_2-agonist.

corticoid plus either as-needed SABA or as-needed inhaled glucocorticoid–SABA (step two). The evidence clearly shows a benefit of adding an inhaled glucocorticoid to a β_2-agonist for as-needed symptom relief, although comparative data are limited regarding which combinations are best.

Supporting this strategy are two Cochrane meta-analyses of as-needed inhaled glucocorticoid–formoterol combinations as compared with as-needed SABA, along with as-needed inhaled glucocorticoid–formoterol combinations as compared with a daily inhaled glucocorticoid plus SABA.[33,34] Two randomized, controlled trials involving 2997 participants showed with low-certainty evidence that, as compared with as-needed SABA, as-needed inhaled glucocorticoid–formoterol significantly reduced the odds of asthma exacerbations that led to the use of systemic glucocorticoids (odds ratio, 0.45; 95% CI, 0.34 to 0.60) and the odds of an asthma-related hospitalization or visit to an emergency department or urgent care center (odds ratio, 0.35; 95% CI, 0.20 to 0.60).[33] Four randomized, controlled trials involving 8065 participants showed with low-certainty evidence that, as compared with inhaled glucocorticoid for regular maintenance plus as-needed SABA, as-needed inhaled glucocorticoid–formoterol was not associated with lower odds of asthma exacerbations leading to treatment with systemic glucocorticoids (odds ratio, 0.79; 95% CI, 0.59 to 1.07) but did decrease the odds of an asthma-related hospitalization or visit to an emergency department or urgent care center (odds ratio, 0.63; 95% CI, 0.44 to 0.91).[34]

A separate network meta-analysis that included adult patients with mild asthma showed that the use of as-needed inhaled glucocorticoid–formoterol alone was associated with less risk of severe asthma exacerbations than either maintenance inhaled glucocorticoid plus as-needed SABA or as-needed SABA alone.[35] A pooled, post hoc analysis of the Symbicort Given as Needed in Mild Asthma (SYGMA) 1 and 2 trials showed that patients who received as-needed budesonide–formoterol had 26% fewer severe exacerbations than patients who received daily budesonide. In contrast, there was no difference in the occurrence of severe asthma exacerbation with as-needed inhaled glucocorticoid–formoterol as compared with daily inhaled glucocorticoids among patients whose asthma was well controlled with the use of a low-dose daily inhaled glucocorticoid or leukotriene receptor antagonist plus as-needed SABA.[36]

Patient behaviors and preferences, as well as treatment access and cost, should also be considered in the shared decision-making process of treatment selection. Clinical trials that involved the use of electronic medication monitors to track real-time inhaler actuation have shown that patient-reported inhaled glucocorticoid use was greater than the objectively measured use and that patients' use of inhaled glucocorticoids decreased over time.[36,37] In a survey of a subgroup of participants in a randomized, controlled trial that assessed the addition of as-needed budesonide–formoterol to daily budesonide plus as-needed SABA, as-needed budesonide–formoterol was preferred by 90% of the participants who received it, and daily budesonide plus as-needed SABA was preferred by 40% of the participants who received that combination.[38] Some asthma

Table 1. Medications and Doses for GINA Track 1: Antiinflammatory Reliever–based Therapy.*

Treatment Step and Age	Medication and Strength	Doses Administered with DPI†
1 and 2 (antiinflammatory reliever only)		
6 to 11 yr	No evidence to date	1 inhalation as needed
12 to 17 yr	Budesonide 200 μg (delivered dose, 160 μg) and formoterol 6 μg (delivered dose, 4.5 μg)	1 inhalation as needed
≥18 yr	Budesonide 200 μg (delivered dose, 160 μg) and formoterol 6 μg (delivered dose, 4.5 μg)	1 inhalation as needed
3 (maintenance-and-reliever therapy)		
6 to 11 yr	Budesonide 100.0 μg (delivered dose, 80.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg)	1 inhalation once daily, plus 1 inhalation as needed
12 to 17 yr	Budesonide 200.0 μg (delivered dose, 160.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg)	1 inhalation once or twice daily, plus 1 inhalation as needed
≥18 yr	One of the following regimens: Budesonide 200.0 μg (delivered dose, 160.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg) Beclomethasone 100.0 μg (delivered dose, 84.6 μg) and formoterol 6.0 μg (delivered dose, 5.0 μg)	1 inhalation once or twice daily, plus 1 inhalation as needed
4 (maintenance-and-reliever therapy)		
6 to 11 yr	Budesonide 100.0 μg (delivered dose, 80.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg)	1 inhalation twice daily, plus 1 inhalation as needed
12 to 17 yr	Budesonide 200.0 μg (delivered dose, 160.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg)	2 inhalations twice daily, plus 1 inhalation as needed
≥18 yr	One of the following regimens: Budesonide 200.0 μg (delivered dose, 160.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg) Beclomethasone 100.0 μg (delivered dose, 84.6 μg) and formoterol 6.0 μg (delivered dose, 5.0 μg)	2 inhalations twice daily, plus 1 inhalation as needed
5 (maintenance-and-reliever therapy)		
6 to 11 yr	Not recommended	
12 to 17 yr	Budesonide 200.0 μg (delivered dose, 160.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg)	2 inhalations twice daily, plus 1 inhalation as needed
≥18 yr	One of the following regimens: Budesonide 200.0 μg (delivered dose, 160.0 μg) and formoterol 6.0 μg (delivered dose, 4.5 μg) Beclomethasone 100.0 μg (delivered dose, 84.6 μg) and formoterol 6.0 μg (delivered dose, 5.0 μg)	2 inhalations twice daily, plus 1 inhalation as needed

* As recommended by the Global Initiative for Asthma 2023 (GINA) treatment track 1 (the preferred treatment track), the reliever is low-dose inhaled corticosteroid (i.e., glucocorticoid)–formoterol used as needed, with or without maintenance use of inhaled corticosteroid (i.e., glucocorticoid)–formoterol, depending on whether the patient has asthma that is mild (steps 1 and 2), moderate (steps 3 and 4), or severe (step 5). DPI denotes dry-powder inhaler and pMDI pressurized metered-dose inhaler.

† For delivery of antiinflammatory reliever only or maintenance-and-reliever therapy with budesonide–formoterol by means of a pMDI, patients should use an inhaler with half the strength of that used for the relevant DPI shown and should use double the number of doses shown. For example, at step 4 for a patient 12 years of age or older, budesonide–formoterol pMDI should be administered at a metered dose of 100 μg of budesonide and 3 μg of formoterol per inhalation in 4 inhalations twice daily plus 2 inhalations as needed.

experts have advocated changing the availability of inhaled glucocorticoid–formoterol from prescription to over-the-counter to increase patient access.[39]

STEPS THREE AND FOUR: THERAPY FOR MODERATE ASTHMA

Preferred step-three and -four treatment is single maintenance and reliever therapy (SMART) with

Back to Table of Contents

a low- or medium-dose inhaled glucocorticoid–formoterol combination (either budesonide–formoterol or beclomethasone–formoterol).[7,8] The SMART regimen may reduce cost and simplify treatment for patients, because only one inhaler is needed for both quick-relief and maintenance therapy. Alternative step-three and -four treatment includes either maintenance low- or medium-dose inhaled glucocorticoid–LABA plus as-needed SABA or as-needed combination inhaled glucocorticoid–SABA.[7,8] In a meta-analysis of randomized trials, switching patients with uncontrolled asthma at GINA step three to SMART at either step three or step four was associated with an increased time to the first severe asthma exacerbation, with a 29% reduction in risk as compared with stepping up to a step-four regimen of inhaled glucocorticoid–LABA maintenance plus a SABA reliever (hazard ratio, 0.71; 95% CI, 0.52 to 0.97). In addition, among patients at step three or step four with uncontrolled asthma, switching to SMART was associated with an increased time to the first severe asthma exacerbation and a 30% reduction in risk as compared to continuing therapy at the same treatment step (hazard ratio, 0.70; 95% CI, 0.58 to 0.85).[40]

STEP FIVE: THERAPY FOR SEVERE ASTHMA

Severe asthma is defined as a combination of symptoms and impairment in lung function that leads to treatment with a high-dose inhaled glucocorticoid plus a second controller medication (e.g., LABA) or nearly continuous oral glucocorticoid treatment.[41,42] Patients at step five (severe asthma) should be referred for expert evaluation (i.e., to an allergist–immunologist or pulmonologist), phenotyping, and add-on therapy. The severity of the asthma phenotype is determined on the basis of one or more of the following biomarkers: blood eosinophil level of at least 150 per microliter, fractional exhaled nitric oxide ($F_{E}NO$) of at least 20 parts per billion, sputum eosinophils of at least 2%, sensitization to a perennial aeroallergen on skin-prick testing or blood tests for specific IgE, and a total IgE level of 30 to 700 IU per milliliter. Each patient's unique biomarker profile guides the selection of biologic therapy (e.g., sensitization to a perennial aeroallergen and elevated total IgE levels vs. elevated levels of blood eosinophils may lead to selection of omalizumab vs. other asthma biologic therapies, respectively). A long-acting muscarinic antagonist (LAMA) may be considered as add-on therapy for patients with asthma that is persistently uncontrolled despite treatment with a medium- or high-dose inhaled glucocorticoid–LABA. A meta-analysis showed that the addition of a LAMA to a medium- or high-dose inhaled glucocorticoid–LABA led to a 17% reduction in the risk of severe asthma exacerbation.[43]

Biologic therapies are an additional option, especially with regard to avoiding or minimizing exposure to treatment with high-dose inhaled glucocorticoids and oral glucocorticoids. The six biologic agents for use in the treatment of severe asthma are omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, and tezepelumab, and the choice of biologic agent should include consideration of a variety of clinical and pragmatic factors, including biomarkers.[44] Although data from head-to-head clinical trials comparing biologics are lacking, each of these agents has shown efficacy as compared with placebo, with a 30 to 70% reduction in the relative risk of severe asthma exacerbations.[44-47]

AREAS OF UNCERTAINTY

Better strategies are needed for the objective evaluation of patient adherence and inhaler technique preceding a recommendation to step-up therapy. Clinical trials to evaluate the efficacy of digital inhalers and clinician dashboards (which provide the patient and health care professional with real-time data about medication-taking behavior and inhalation quality) regarding clinically important asthma outcomes are warranted. More studies to assess the role of biomarkers, such as blood and sputum eosinophil counts, $F_{E}NO$ levels, and serum total and allergen-specific IgE levels, are needed to better guide the selection of medications.[48,49]

GUIDELINES

The recommendations in this article are consistent with the guidelines of the National Asthma Education and Prevention Program Expert Panel-3 Report (and its 2020 focused update) as well as GINA (and its 2023 update).[7-9] GINA publishes an annual update to its guidelines, and the recommendations presented here are con-

cordant with the most recent GINA and National Asthma Education and Prevention Program reports and updates.

CONCLUSIONS AND RECOMMENDATIONS

With regard to the 47-year-old woman described in the vignette, her impairment (daytime symptoms) and risk (asthma exacerbations) warrant a step up in therapy. Because of the location of symptoms and timing of exacerbations, I suspect she has allergic asthma and concurrent allergic rhinitis due to pollens, and I would conduct skin testing for aeroallergens and provide education regarding relevant environmental-control measures and medical management. I would advise changing her treatment approach from GINA track 2 (alternative) to track 1 (preferred) therapy and increase treatment from step 2 to step 3 care, including a change to low-dose budesonide–formoterol as maintenance and reliever therapy. As compared with a SABA reliever alone, an inhaled glucocorticoid–formoterol reliever reduces severe exacerbations across treatment steps. The use of an inhaled glucocorticoid–formoterol combination for maintenance and reliever therapy simplifies the treatment regimen and allows for stepping up or stepping down without changing medication. I would also review inhaler technique, work with the patient to develop a written asthma action plan, and plan a follow-up visit in 3 months. (See inhaler technique video at https://www.nejm.org/doi/full/10.1056/NEJMra050380.)[50]

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

Peeling and Plummeting

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In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.*

A 20-year-old Guatemalan woman who had immigrated to Maryland 6 years earlier presented to an urgent care facility with a 6-month history of progressive joint pain and malaise.

Joint pain may result from an inflammatory or noninflammatory process. Inflammatory arthritis is characterized by morning stiffness that improves with activity, with articular swelling or synovitis. In contrast, noninflammatory arthritis, as from osteoarthritis or traumatic injury, typically manifests as joint pain that is exacerbated by activity. Pain near the joint may also arise from periarticular structures including tendons, ligaments, bursae, muscle, and bone.

The patient described symmetric joint pain and swelling affecting the small joints of the hands, wrists, and ankles. She reported 1 hour of morning stiffness accompanied by notable hair thinning, night sweats, and unintentional weight loss. Eating and dressing were compromised by impaired dexterity. She noted no recent interaction with children. She had last traveled to Guatemala 5 years previously. Given limited English proficiency, a qualified language interpreter was used.

The history of joint pain, swelling, and morning stiffness lasting more than 1 hour suggests an inflammatory arthritis. Her constitutional symptoms, together with the inflammatory arthritis, increase suspicion for a systemic rheumatic disease such as rheumatoid arthritis or systemic lupus erythematosus (SLE), but infection (e.g., parvovirus) or cancer also warrant consideration.

The white-cell count was 4750 per microliter, hemoglobin level 12.6 g per deciliter, and platelet count 273,000 per microliter. The serum creatinine level was 0.4 mg per deciliter (35 μmol per liter). Urinalysis did not show blood or protein. The thyrotropin level was 5.32 IU per milliliter (normal range, 0.30 to 4.00). A test for antinuclear antibodies was positive (1:80 titer); a test for rheumatoid factor was negative. At the urgent care facility, hydroxychloroquine and levothyroxine were prescribed, and the patient was referred to a rheumatology clinic for further evaluation and care management.

The presence of inflammatory arthritis and alopecia with positive antinuclear antibodies increases concern for SLE. However, antinuclear antibodies at such a low level are nonspecific and can be present in healthy persons and in those with

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other autoimmune diseases (autoimmune thyroid or liver disease), infection, or cancer. Rheumatoid arthritis also remains in the differential diagnosis. Hypothyroidism can cause arthralgias, although this condition is unlikely with minimally elevated thyrotropin levels. Although hydroxychloroquine serves as a cornerstone of treatment for SLE and can treat mild rheumatoid arthritis, it is advisable to administer this medication under specialty supervision and only after a definitive diagnosis has been established.

The patient lacked health insurance and had no primary care physician. With the onset of the coronavirus disease 2019 (Covid-19) pandemic, she found it difficult to obtain insurance coverage or to access care, and she ran out of the 2-month hydroxychloroquine supply that had been issued at the urgent care facility.

Ten months after initial symptom onset, she presented to the emergency department with a 30-lb (14-kg) unintentional weight loss (corresponding to 25% of her body weight), a diffuse hyperpigmented rash, and an inability to ambulate independently. She reported having had persistence of painful, swollen, and stiff joints since her initial urgent care evaluation, without abatement while she was taking hydroxychloroquine. She also noted continued fatigue and malaise, with subsequent development of generalized weakness. She attributed her difficulty walking to her fatigue and weakness and reported that it took her several minutes to walk as little as 8 ft (approximately 2.5 m). For the preceding 4 months, she had also been having early satiety, without abdominal pain or a change in bowel habits. In addition, she noted darkening of her skin over the trunk, arms, and legs and menstrual irregularity, as well as continued hair thinning.

The differential diagnosis for a diffuse rash is broad. An ulcerative or nodular skin process may suggest disseminated fungal or mycobacterial infection. Darkened skin, weight loss, and malaise also increase concern for adrenal insufficiency. A photosensitive skin eruption would be consistent with SLE or dermatomyositis; if the latter were present, it would increase concern for an underlying cancer. Proximal muscle weakness would increase suspicion for inflammatory myositis or paraneoplastic myopathy. Muscle-enzyme levels should be measured, and thyroid function should be reassessed.

The pronounced weight loss increases concern for cancer. Gastrointestinal disorders that may cause weight loss, such as inflammatory bowel disease or malabsorption syndromes (celiac disease or pancreatic insufficiency), are less likely in the absence of abdominal pain, diarrhea, or bloody stools. Early satiety suggests possible obstruction or gastroparesis; diabetes mellitus should be ruled out. Insufficient caloric intake owing to lack of money for food or an eating disorder should also be considered. Disseminated tuberculosis and histoplasmosis are endemic in Guatemala, and disseminated infection with one of these microbes could cause adrenal insufficiency, weight loss, and malaise.

On physical examination, the patient appeared chronically ill. The temperature was 38.4°C, heart rate 120 beats per minute, blood pressure 110/70 mm Hg, and respiratory rate 16 breaths per minute. The oxygen saturation was 95% while she was breathing ambient air. The weight was 79 lb (36 kg) and the height 59 in. (150 cm); the body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) was 16.0. She had a diffuse dry, fish scale–like rash, with hyperkeratosis over hands and feet, and hyperpigmented plaques on her face, chest, abdomen, arms, and legs (Fig. 1). There was thinning of scalp hair. The small joints of the hands, wrists, elbows, and knees were swollen and tender to palpation. Lymphadenopathy was absent; cardiovascular and pulmonary examinations were without abnormality. There was nontender hepatomegaly measuring 20 cm in the midclavicular line, without splenomegaly. She was profoundly weak, requiring assistance to change position in bed. Painless weakness in the proximal motor muscles was greater than that in the distal motor muscles, with 2/5 strength in neck flexors and hip flexors and 4/5 strength in other muscle groups.

Fever and tachycardia increase suspicion for infection. Computed tomography of the chest, abdomen, and pelvis should be considered to evaluate for an infectious focus, a mass lesion, or lymphadenopathy.

The ichthyotic rash suggests a systemic disease, such as Hodgkin's lymphoma, solid-organ cancer, human immunodeficiency virus (HIV)

infection, sarcoidosis, or nutritional deficiency. The prominent hepatomegaly increases concern for an infiltrative malignant or infectious process in the liver.

The white-cell count was 6.23 per microliter, with 73% neutrophils, 1% immature neutrophils, 15% lymphocytes, 7% monocytes, and 4% eosinophils; the hemoglobin level was 9 g per deciliter, mean corpuscular volume 94 fl, and platelet count 212,000 per microliter. The serum creatinine level was 0.3 mg per deciliter (27 μmol per liter). The ferritin level was 767 ng per milliliter (normal range, 13 to 150), and the erythrocyte sediment rate was 88 mm per hour (normal range, 4 to 25). The C-reactive protein level was 0.4 mg per deciliter (normal value, <0.5). The aspartate aminotransferase level was 650 U per liter (normal range, 0 to 31), alanine aminotransferase level 426 U per liter (normal range, 0 to 31), alkaline phosphatase level 443 U per liter (normal range, 30 to 120), total protein level 5.2 g per deciliter (normal range, 6.0 to 8.2), and albumin level 0.7 g per deciliter (normal range, 3.5 to 5.3); the total bilirubin level was normal. The thyrotropin level was 7.92 IU per milliliter, and the free thyroxine level was 1.0 ng per deciliter (12.9 pmol per liter) (normal range, 0.8 to 1.8 ng per deciliter [10.3 to 23.2 pmol per liter]). Urinalysis was negative for leukocytes, red cells, and bacteria but showed 2+ protein. Sputum, urine, and blood cultures were without growth.

Although the white-cell count is normal, volume resuscitation and antimicrobial therapy are appropriate pending culture data. Cachexia may contribute to tachycardia. A respiratory viral panel and tuberculosis testing with an interferon-γ release assay should be performed. Elevated aminotransferase levels, mild anemia, and lymphopenia could indicate a viral infection (e.g., with cytomegalovirus [CMV], Epstein–Barr virus [EBV], or HIV) but also could be consistent with SLE and associated autoimmune hepatitis.

The marked hypoalbuminemia suggests a profoundly malnourished state due to reduced caloric intake, protein-losing enteropathy, or nephropathy. The degree of proteinuria should be quantified; nephrotic syndrome can occur with SLE, cancer (paraneoplastic membranous nephropathy), or infection (e.g., hepatitis B or C virus). Painless proximal muscle weakness increases concern for inflammatory muscle disease, which can occur with active SLE.

A test for antinuclear antibodies was positive at a titer of 1:160, a test for anti–double-stranded DNA (dsDNA) antibodies was positive at a titer of 1:160, and the level of anti-Smith antibodies was 21 U (normal value, <20). The level of C3 was 71 mg per

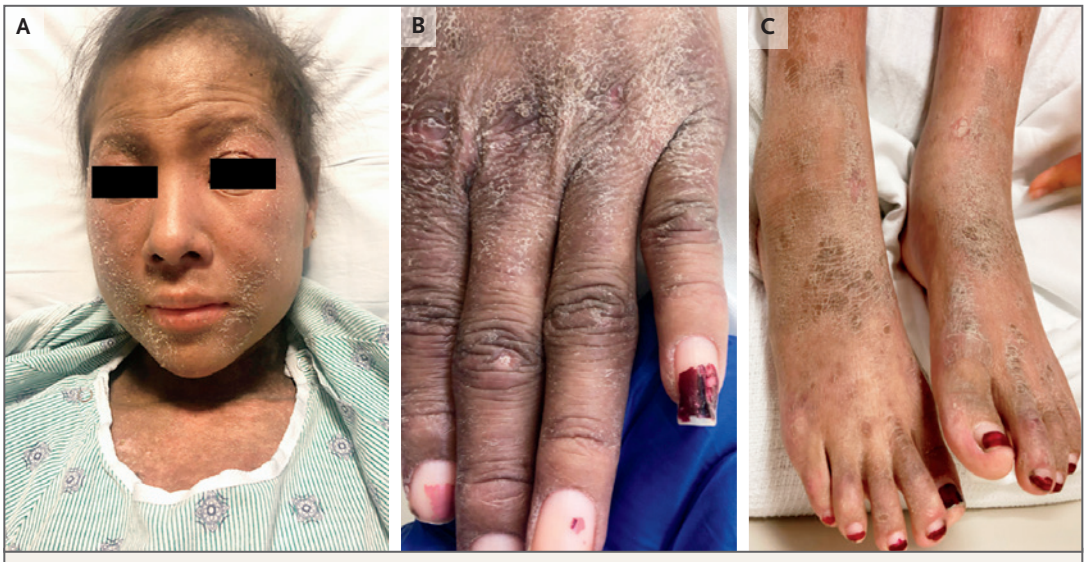

Figure 1. Photographs of the Patient.
Shown are diffuse ichthyosis and hyperkeratosis with hyperpigmented plaques affecting the face (Panel A), hand dorsal surface (Panel B), and distal legs and dorsal aspect of both feet (Panel C).

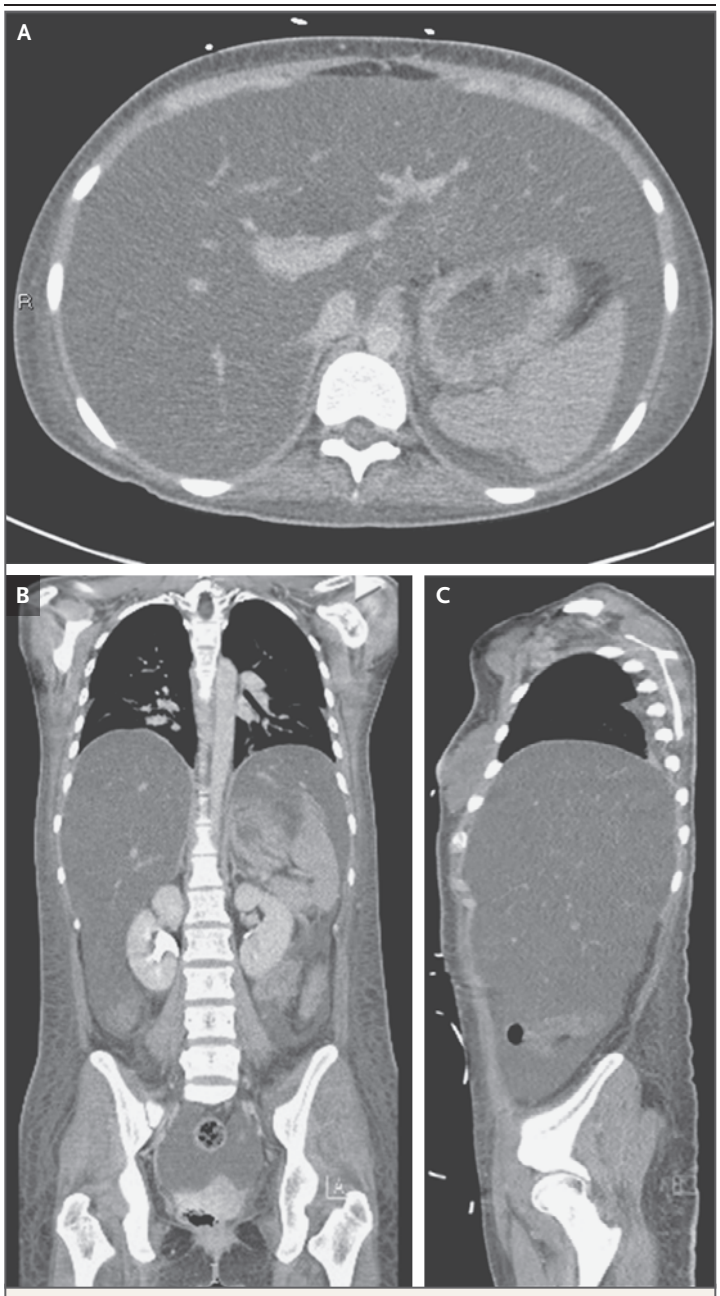

Figure 2. Computed Tomography of the Abdomen and Pelvis.
Computed tomography after the administration of intravenous contrast material showed marked hepatomegaly (measuring 25 cm in the craniocaudal dimension) with hepatic steatosis in the axial view (Panel A), coronal view (Panel B), and sagittal view (Part C).

deciliter (normal range, 82 to 167), and the C4 level was 18 mg per deciliter (normal range, 12 to 38); a Coombs' test was positive, without hemolysis on a peripheral smear. The creatine kinase level was 58 U per liter (normal range, 32 to 182), and the aldolase level was 16.4 U per liter (normal value, <8.1). The urinary protein:creatinine ratio was 2.27 (normal value, <0.19). Tests for IgA and IgG antibodies against tissue transglutaminase were negative. Measurement of 24-hour stool alpha$_1$-antitrypsin and fecal fat was normal.

The constellation of inflammatory arthritis, alopecia, lymphopenia, positive antinuclear antibody and dsDNA serologic tests, proteinuria, hypocomplementemia, and positive Coombs' test fulfills classification criteria for SLE. An elevated aldolase level and proximal muscle weakness suggest active myositis, even with the normal creatine kinase level, as can occur with profound weakness and muscle atrophy. However, aldolase levels can also be elevated with liver or lung pathologic processes. I would pursue renal and skin biopsy as well as muscle imaging. The presenting ichthyotic rash is atypical for SLE, which more often manifests with malar and discoid rashes and on occasion with panniculitis and bullous lesions. Similarly, although SLE may be associated with liver inflammation, the patient's profound hypoalbuminemia and marked transaminitis are uncommon for SLE and necessitate investigation for an alternative cause.

Additional history taking was negative for toxin exposure or alcohol use. Within 6 hours after the initiation of intravenous fluid repletion and antibiotic therapy, tachycardia and fever resolved. Hepatitis A, B, and C serologic tests were nonreactive. Tests for CMV, EBV, and HIV viral loads were negative. Computed tomography of the abdomen revealed hepatomegaly measuring 25 cm craniocaudally (upper limit of the normal range, <13 cm) with the appearance of diffuse fatty liver; there was no lymphadenopathy or splenomegaly (Fig. 2). Edema in the abdominal wall and paraspinal subcutaneous tissue was noted. Blood, sputum, and urine cultures remained negative for bacterial growth at 48 hours; antimicrobial therapy was stopped.

Acute infectious hepatitis is ruled out. Nontender hepatomegaly may be explained by hepatic steatosis (which can be associated with alcohol use or malnutrition), infection (e.g., mycobacterial), cancer, or other infiltrative diseases (e.g., amyloidosis, hemochromatosis, or sarcoidosis),

Back to Table of Contents

Kidney biopsy showed glomeruli with diffuse thickening of the capillary wall. On direct immunofluorescence assay, there was diffuse, fine granular capillary-wall and mesangial staining for IgG, IgA, and IgM antibodies and for kappa and lambda light chains in the capillary walls and mesangium. Electron microscopy identified numerous subepithelial and mesangial electron-dense deposits and endothelial tubuloreticular inclusions (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Together, these bright-field, immunofluorescence, and electron microscopy features supported a tissue diagnosis of class V (membranous) lupus nephritis, according to the the criteria of the International Society of Nephrology and the Renal Pathology Society.

Biopsy of the rash on the chest showed mild vacuolar dermatitis with a thick band of IgM and C3 along the epidermal basement membrane zone (interface dermatitis) compatible with lupus skin involvement. IgG, IgA, and fibrin deposition were absent on immunofluorescence studies.

Magnetic resonance imaging of thigh muscles identified proximal muscle and fascial edema in both thighs. Electromyography (EMG) showed fibrillations and positive sharp waves consistent with an inflammatory myopathy. On further questioning, the patient noted a 4-month history of difficulty with swallowing, initially limited to liquids but then also involving solid foods.

Although there is clinical evidence of active SLE with renal, articular, and muscle inflammation, the ichthyosis, profoundly low serum albumin level, and marked transaminitis have not been effectively explained. It is uncommon for lupus nephritis, even with related nephrotic syndrome, to result in a serum albumin level of 1.0 g per deciliter or less. Dysphagia increases concern for oropharyngeal and esophageal muscle involvement due to myositis and should be further evaluated. Liver biopsy should be performed to define the cause of the elevated liver-function values and prominent hepatomegaly. Muscle biopsy could be considered.

A videofluoroscopic swallowing study indicated impaired pharyngeal constriction, absent epiglottic inversion, and substantial pharyngeal retention of swallowed liquids, which did not clear with additional swallows. This retention resulted in laryngeal penetration and aspiration.

The patient underwent needle core liver biopsy, which revealed severe (large-droplet) macrovesicular steatosis, without evidence of hepatocellular injury, with mild portal chronic inflammation (Fig. 3 and Fig. S2). There was no stainable iron, no cytoplasmic globules within hepatocytes on periodic acid–Schiff staining with diastase, and no amyloid deposition. Histologic analysis showed no evidence of an active hepatocellular infiltrate,

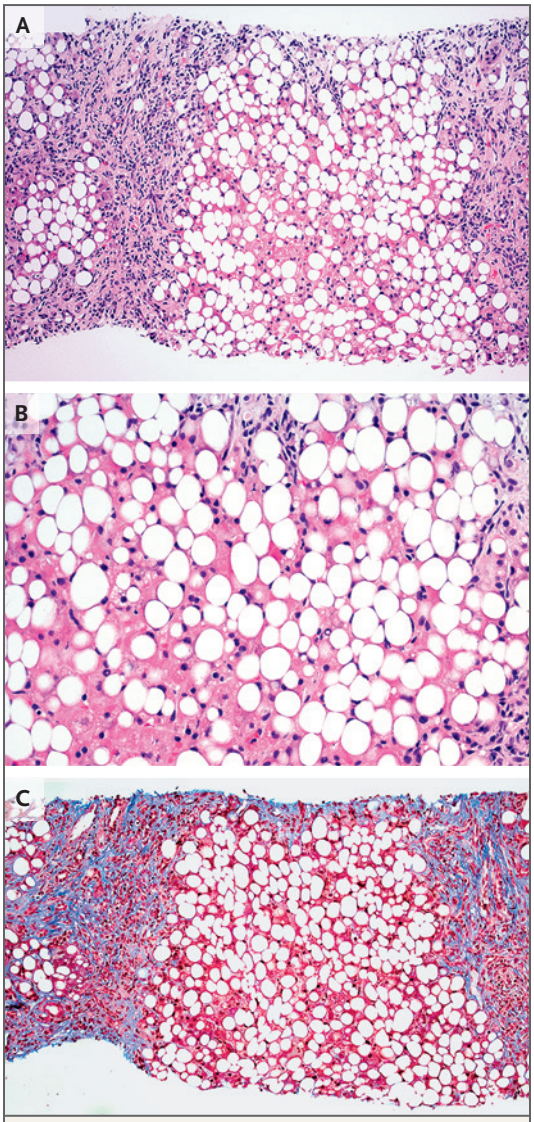

Figure 3. Liver-Biopsy Findings.
Hematoxylin and eosin staining showed severe large-droplet macrovesicular steatosis with bands of fibrosis and focal nodule formation, at a magnification of 100 (Panel A) and 200 (Panel B). The areas of fibrosis are highlighted by a trichrome stain at a magnification of 100 (Panel C).

as would be expected with SLE or autoimmune hepatitis. The hepatomegaly and observed histologic features, in concert with the skin findings, supported a diagnosis of kwashiorkor. Muscle biopsy was deferred given the clinical, radiographic and EMG evidence for active myositis.

"Peeling paint" or "flaky paint" dermatosis in a malnourished child or adult strongly suggests kwashiorkor. Evaluation for nutritional deficiencies is warranted, as is treatment of the underlying insult causing severe malnutrition — that is, dysphagia presumed to result from myositis associated with the patient's SLE.

The vitamin A level was 17 μg per deciliter (normal range, 38 to 98), 25-hydroxyvitamin D level 10 ng per milliliter (normal range, 30 to 100), and zinc level 16 μg per deciliter (normal range, 60 to 130). Levels of vitamins B_{12}, C, E, and K and selenium were normal. The patient was treated with pulse-dose glucocorticoids, mycophenolate mofetil, intravenous immune globulin, and intensive nutritional support, including intravenous vitamin repletion and caloric supplements. Electrolyte levels were monitored closely for potential refeeding syndrome. On the basis of consultation with a speech and language therapist, she was started on a pureed diet, which was advanced to regular consistency as her dysphagia abated with treatment. Physical and occupational therapy provided inpatient care and a home rehabilitation plan. She was discharged while receiving treatment with methylprednisolone, mycophenolate, hydroxychloroquine, a topical glucocorticoid, levothyroxine, ergocalciferol, and both multivitamin and nutritional supplements, with shakes thickened to improve safe swallowing.

At 6-month follow-up, she had regained 35 lb (16 kg), with normalization of her albumin level and liver indexes and resolution of proteinuria, dysphagia, weakness, and generalized ichthyosis (Fig. 4). At 1-year follow-up, she had regained her independence in all activities of daily living and resumed working.

COMMENTARY

This 20-year-old woman presented with inflammatory arthritis, alopecia, and proteinuria, with subsequent serologic and pathological findings indicative of SLE[1,2]; however, this diagnosis did not account for all her phenotypic features. After an interruption in care in the context of the Covid-19 pandemic, she returned to the emergency department unable to walk or swallow, with substantial weight loss and malnutrition. Ultimately, her profound hypoalbuminemia, hepatomegaly, peeling-paint dermatosis, and liver histopathological findings led to a diagnosis of kwashiorkor.

Kwashiorkor is a consequence of severe protein malnutrition that results in marked muscle loss, hepatic enlargement, and hypoalbuminemia.[3] A hyperpigmented, ichthyotic, and peeling rash, as affected this patient's face, trunk, and limbs, is a characteristic finding.[4,5] Protein deficiency results in a reduction in plasma triglyceride and phospholipid levels, a rise in free fatty acid levels, and subsequent liver enlargement attributed to accumulation of triglycerides.[6,7] Her liver biopsy revealed severe large-droplet macrovesicular steatosis compatible with kwashiorkor.

The root cause of our patient's severe malnutrition was her inability to properly swallow. Her elevated aldolase levels and EMG findings supported an active myositis that was presumed to be caused by SLE. Myositis in SLE can lead to dysphagia, arm and leg weakness, and (less commonly) myocarditis.[8-10] Our patient's impaired oropharyngeal and esophageal swallowing mechanisms were identified at bedside by speech and language pathology evaluation and confirmed by a videofluoroscopic swallow study.[8-10]

Nutritional complications of systemic illnesses are often underrecognized and can substantially worsen patients' clinical course and prognosis. Nutritional deprivation compromises muscle and nerve function and probably compounded our patient's inflammatory myopathy and profound debility. Malnutrition diminishes autonomy and quality of life and may pose life-threatening risks because of infectious and visceral complications.[3] Timely and routine malnutrition screening has been recommended in all hospitalized patients as outlined by the Global Leadership Initiative on Malnutrition (incorporating variables of weight loss, low BMI, low skeletal muscle mass, low food intake, and disease burden or inflammation).[11]

In the present case, complications of undernutrition might have been avoided with earlier

recognition and treatment of the patient's myositis and weight loss; factors that contributed to her delayed evaluation included challenges to access the health care system posed by the Covid-19 pandemic and lack of health insurance. After treatment with immunosuppressive therapy and

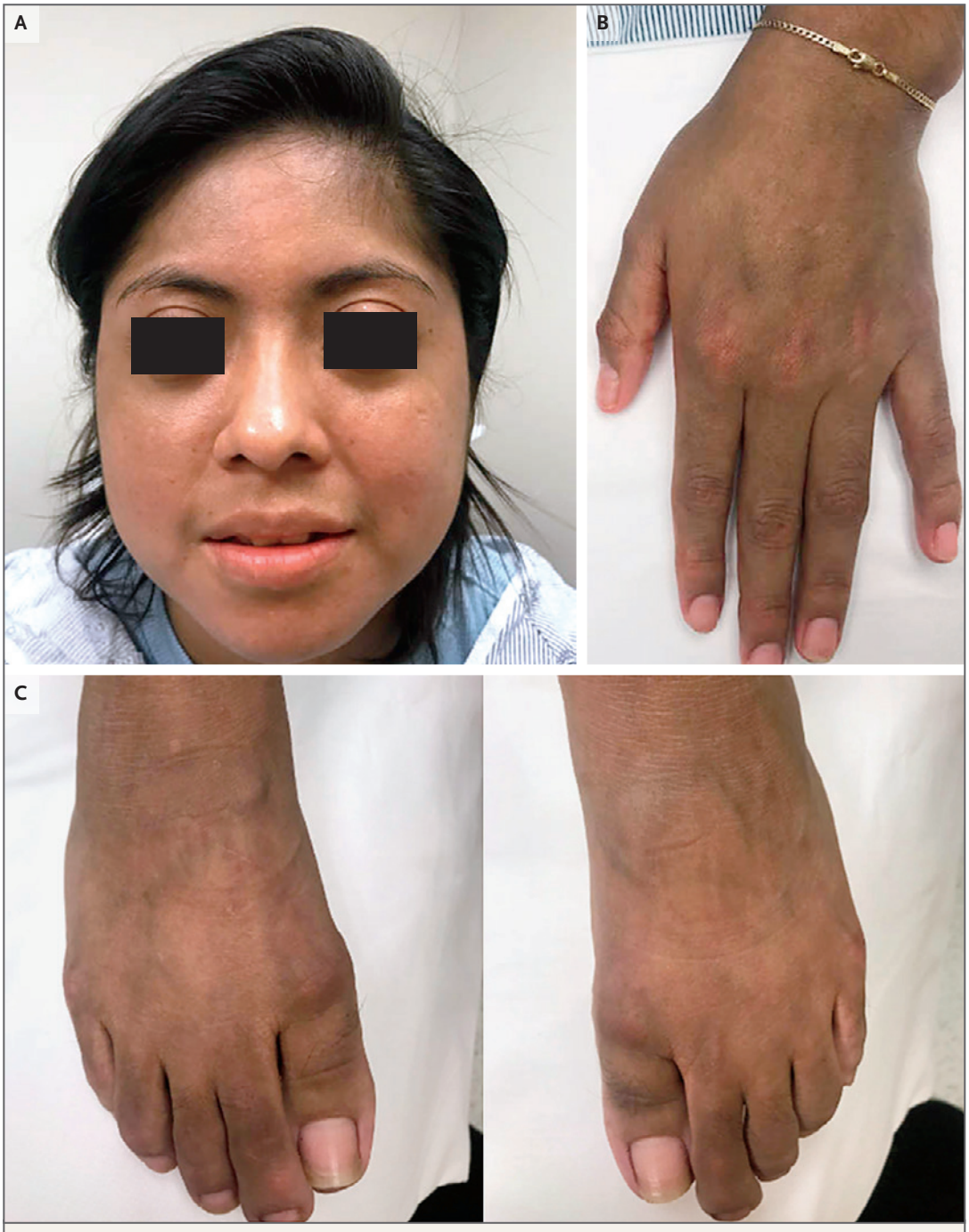

Figure 4. Patient Photographs after Treatment.
Shown are resolution of diffuse ichthyosis and hyperkeratotic rash of the face (Panel A), dorsum of the left hand (Panel B), and dorsum of both feet (Panel C) after treatment.

nutritional supplementation, she had a full recovery, with restoration of weight and resolution of weakness and laboratory abnormalities.

This case underscores the need to consider undernutrition exacerbating illness in patients with chronic conditions. It also highlights the importance of early screening for and treatment of root causes of malnutrition and its sequelae.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

It's All in the Timing

Alexander J. Beagle, M.D., Bernie Y. Sunwoo, M.B., B.S., Rebecca L. Olin, M.D., Brian S. Schwartz, M.D., and Brian L. Block, M.D.

In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.*

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A 55-year-old man with acute myeloid leukemia began to have shortness of breath, cough with blood-tinged sputum, and hypoxemia 17 days after receiving a myeloablative allogeneic stem-cell transplant from a haploidentical donor. His preparative regimen included fludarabine and total-body irradiation, and he received cyclophosphamide after transplantation. On the day his symptoms developed, 17 days after transplantation, he also began treatment with supplemental oxygen through a nasal cannula at a rate of 4 liters per minute. He had never smoked and had no history of heart or lung disease; his medical history was notable only for gastroesophageal reflux disease and hyperlipidemia. He had been hospitalized since transplantation.

The constellation of dyspnea, cough, and hypoxemia suggests the possibility of a pulmonary complication after hematopoietic stem-cell transplantation (HSCT). The differential diagnosis is broad in this immunocompromised patient. The list of diagnostic considerations includes infectious and noninfectious causes and can be narrowed by considering the type of HSCT (allogeneic or autologous), the intensity of conditioning chemotherapy, and the timing relative to transplantation.

Traditionally, pulmonary complications of HSCT are categorized temporally on the basis of reconstitution of the immune system as preengraftment (occurring days to weeks after transplantation), early postengraftment (weeks to months after transplantation), and late post-transplantation (months to years after transplantation). At post-transplantation day 17, this patient is most likely in the period of engraftment, when donor cells begin to produce normal blood cells. Before engraftment, neutropenia occurs, which increases the risk of infection with bacteria or angioinvasive fungi, particularly in patients who have prolonged neutropenia before HSCT. Because this patient underwent an allogeneic HSCT rather than an autologous HSCT, he has an even higher risk of such infections because of the level of immunosuppression required to prevent transplant rejection and graft-versus-host disease. Although there is no mention of fever, classic symptoms and signs of infection may be absent, given his immunocompromised state.

Possible noninfectious causes of his presentation include pulmonary toxic effects associated with the use of chemotherapy (particularly cyclophosphamide), aspiration, pulmonary edema, complications of transfusion, and idiopathic pneumonia syndrome. Idiopathic pneumonia syndrome is characterized by widespread alveolar injury in the absence of identifiable infection, cardiac dysfunction, kidney failure, and fluid overload.

Early engagement of a pulmonologist is essential because bronchoscopy is often indicated. However, the window for safe bronchoscopy may be narrow; many of these conditions may progress rapidly to hypoxemic respiratory failure.

The patient's post-transplantation hospital course had been notable for fevers (maximum oral temperature, 38.5°C), mucositis, and abdominal pain without vomiting in the context of neutropenia on post-transplantation day 14. At that time, blood cultures were negative, urinalysis was unremarkable, and computed tomography (CT) of the abdomen and pelvis revealed colitis. A serum polymerase-chain-reaction (PCR) test revealed an elevated level of cytomegalovirus (CMV) DNA (2500 IU per milliliter). The patient was treated with intravenous cefepime, metronidazole, and foscarnet in accordance with hospital protocol; treatment with ganciclovir was avoided, given its association with graft failure. Other medications included a proton-pump inhibitor, ursodiol, mycophenolate mofetil, tacrolimus, and the prophylactic use of posaconazole. Despite the use of antibiotic agents, he remained febrile.

On the day before hypoxemia developed, he received 1 unit of packed red cells after his hemoglobin level had decreased from 7.5 to 6.3 g per deciliter (normal range, 13.0 to 17.7), and he received platelets for thrombocytopenia (platelet count, 15,000 per cubic millimeter; normal range, 150,000 to 450,000). Both the hemoglobin level and the platelet count subsequently increased. His white-cell count was 500 per cubic millimeter (which had increased from a count of 100 per cubic millimeter that had been measured the previous day); 90% of the white cells were neutrophils.

At the time the patient began treatment with supplemental oxygen, his heart rate and blood pressure were normal. The serum creatinine level was also normal, but his fluid balance was positive and had increased by 11.6 liters since admission.

The additional history confirms that this patient is severely neutropenic; he is already having associated complications including typhlitis (also known as neutropenic enterocolitis). Typhlitis can cause fever, as can the antibiotics used to treat it, but this condition would not explain the new cough and hypoxemia.

Despite the administration of broad-spectrum antimicrobial agents, infection remains the leading concern in this immunocompromised patient. A thorough history, along with a review of his previous culture results and the prophylactic strategies used, may help determine his risk of unusual infections or antimicrobial resistance, and broadening the use of antibiotics should be considered. A history of vomiting in association with his typhlitis and mucositis would increase concern about aspiration, but this patient has no history of vomiting. The detection of CMV viremia suggests the possibility of CMV pneumonia, although this condition typically occurs later in the clinical course, after engraftment. Moreover, CMV-targeted therapy has (appropriately) already been initiated in this patient.

Although infection is the most likely cause of this patient's new cough and hypoxemia, noninfectious pulmonary complications of HSCT are also possible. Given his positive fluid balance, volume overload is likely, and diuresis should be considered. The development of hypoxemia after the receipt of packed red-cell and platelet transfusions suggests the possibility of transfusion-associated cardiac overload or transfusion-related acute lung injury. These reactions typically occur during or within 6 hours after transfusion, but delayed reactions are possible. This patient's transfusion requirements may also indicate transplantation-associated thrombotic microangiopathy, in which endothelial injury and complement activation lead to thrombus formation, hemolysis, and organ dysfunction and rarely lead to pulmonary hypertension or alveolar hemorrhage. However, this condition is usually associated with renal dysfunction and hypertension, neither of which is present in this patient.

The patient's increasing neutrophil count may signify engraftment. Periengraftment respiratory distress syndrome, a subtype of idiopathic pneumonia syndrome, typically occurs within 5 days after engraftment and is characterized by fever, noncardiogenic pulmonary edema, and sometimes rash. Anemia and blood-tinged sputum can suggest another subtype of idiopathic pneumonia syndrome, diffuse alveolar hemorrhage, which is characterized by bleeding into the alveolar spaces. The diagnosis of alveolar hemorrhage requires bronchoscopy with serial bronchoalveolar lavage (BAL) to differentiate true alveolar

bleeding from more proximal bleeding in the airways or the nasopharynx, which is common in the context of thrombocytopenia.

Several potential causes of this patient's presentation are life-threatening and have similar clinical manifestations but require vastly different treatments. Further diagnostic testing is urgently needed.

The infectious disease team was consulted, and additional tests were performed. A nasopharyngeal respiratory viral panel, serum 1,3-β-D-glucan and serum galactomannan antigen tests, PCR tests for human herpesviruses 6 and 8 DNA, and a test for strongyloides IgG were all negative. The serum lactate dehydrogenase level was 177 U per liter (normal range, 125 to 243). Bacterial culture of an expectorated sputum sample was insufficient for analysis, and testing of a nasopharyngeal swab obtained on admission had been negative for methicillin-resistant *Staphylococcus aureus*. He had been receiving prophylactic treatment with posaconazole since his transplantation.

Chest CT, performed without the administration of intravenous contrast material, revealed diffuse bilateral perihilar confluent consolidations and ground-glass opacities, which had developed during the 4 days since the patient's previous chest CT. The patient also had new interlobular septal thickening and small bilateral pleural effusions (Fig. 1). A transthoracic echocardiogram showed normal biventricular function, normal valves, and a normal estimated pulmonary-artery systolic pressure.

At this time, cefepime treatment was changed to empirical treatment with meropenem to cover a possible extended-spectrum beta-lactamase–producing bacterial infection. Metronidazole therapy was discontinued, and foscarnet therapy was continued.

The presence of diffuse ground-glass opacities and consolidation in a predominantly central distribution, interlobular septal thickening, and small bilateral effusions helps to narrow the differential diagnosis. Among the possible infectious causes of this patient's presentation, the radiologic appearance favors viral pneumonia, atypical bacterial pneumonia, and pneumocystis pneumonia. CMV pneumonia seems unlikely to develop 17 days after transplantation in a patient being treated with foscarnet. The normal serum lactate dehydrogenase level and the negative 1,3-β-D-glucan antigen test make a diagnosis of pneumocystis pneumonia unlikely. The diffuse distribution of ground-glass opacities makes typical bacterial and angioinvasive fungal infections unlikely because these infections tend to manifest with focal or multifocal consolidations or nodular opacities. Prophylactic treatment with posaconazole makes invasive aspergillosis unlikely.

I am increasingly concerned about a noninfectious cause of this patient's presentation. The perihilar distribution of ground-glass opacities, smooth interlobular septal thickening, and bilateral pleural effusions are consistent with pulmonary edema in the context of known fluid overload. A marked decrease in hypoxemia after undergoing diuresis would support fluid overload as the cause of the respiratory failure. However, even if there is fluid overload, this would not explain the patient's fevers. Periengraftment respiratory distress syndrome and diffuse alveolar hemorrhage could explain the hypoxemia, fevers, and radiologic findings, except that pleural effusions — which can occur with periengraftment respiratory distress syndrome — would not be expected to develop with alveolar hemorrhage alone. It is also possible that the lung parenchymal findings and pleural effusions reflect separate processes occurring simultaneously. Transplantation-associated thrombotic microangiopathy is essentially ruled out on the basis of the normal lactate dehydrogenase level.

Bronchoscopy with BAL is warranted promptly in this immunosuppressed patient with rapidly progressing hypoxemic respiratory failure and diffuse pulmonary infiltrates. Given the possibility of diffuse alveolar hemorrhage, serial BAL should be performed to look for progressively bloody return.

Despite treatment with diuresis (with a net negative fluid balance of 4.8 liters over a period of 24 hours), the patient's hypoxemia worsened, prompting transfer to the intensive care unit and initiation of 100% oxygen supplementation administered through a high-flow nasal cannula at a rate of 20 liters per minute.

Empirical treatment with methylprednisolone at a dose of 1 g daily was started for presumptive idiopathic pneumonia syndrome. The critical care

team discussed the risks and benefits of bronchoscopy with the patient and his family, including the safety of performing the procedure in the context of escalating oxygen requirements.

The questions about the safety of bronchoscopy are appropriate, given that bronchoscopy with sedation is associated with hypoxemia and hypoventilation. However, more information is needed to guide treatment for this patient, whose condition is progressively worsening despite appropriately broad antimicrobial coverage and effective diuresis. Bronchoscopy is the standard test for many of the infections that have been considered in this patient, and ruling out infection in this case would be diagnostic of idiopathic pneumonia syndrome. Given his clinical trajectory and degree of hypoxemia, I would rec-

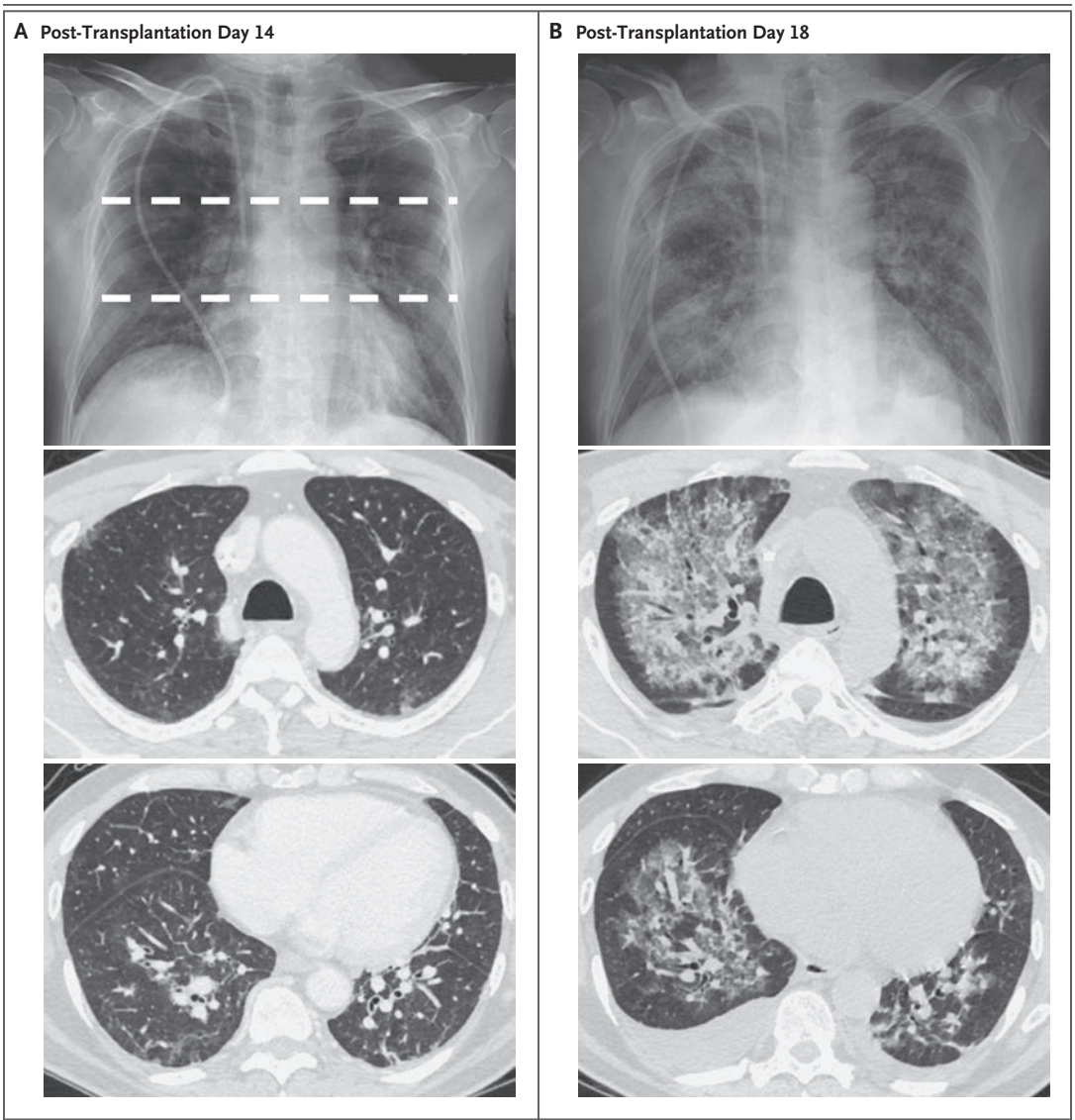

Figure 1. Chest Imaging Studies on Post-Transplantation Days 14 and 18.
Panel A shows a chest radiograph and axial CT images (obtained without the administration of intravenous contrast material) from post-transplantation day 14. Panel B shows images from anatomically similar locations 4 days later, on post-transplantation day 18. The dashed lines in Panel A indicate the approximate levels at which the CT images were obtained.

ommend intubation to permit bronchoscopy in this context.

The patient's trachea was intubated to permit diagnostic bronchoscopy with serial BAL. On visual inspection, the airways appeared normal. Examination of the BAL fluid revealed an increased percentage of neutrophils (34%; normal value in healthy nonsmokers, <3%) without lymphocytosis (lymphocytes, 4%; normal value, <15%) or eosinophilia (eosinophils, 0%; normal value, <1%). On serial BAL, the red-cell count increased from 36,500 per cubic millimeter in the first sample to 141,250 per cubic millimeter in the fourth sample. Gram's staining of the BAL fluid showed no leukocytes or organisms, and a potassium hydroxide preparation showed no fungal elements. A multiplex respiratory viral panel was negative for influenza virus, respiratory syncytial virus, human herpesvirus 6, human metapneumovirus, adenovirus, and rhinovirus. Staining for acid-fast bacilli and pneumocystis was negative. Bacterial and fungal cultures were negative. The level of CMV DNA in the BAL fluid was 1464 IU per milliliter.

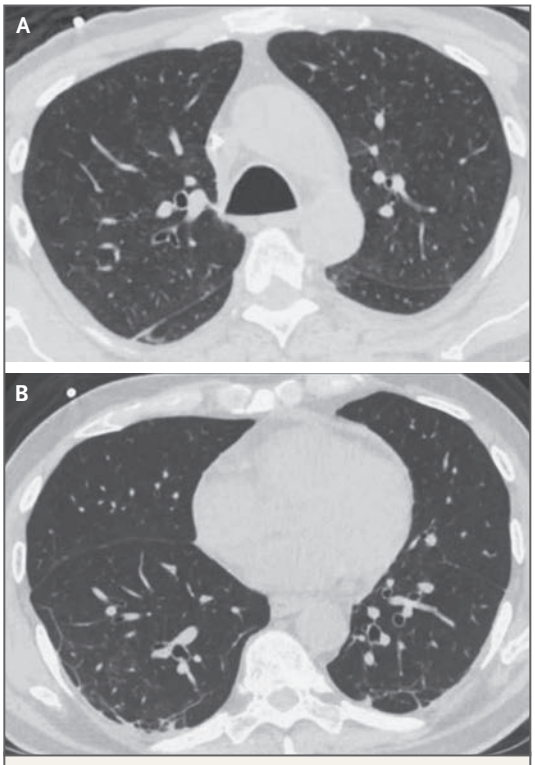

Figure 2. Chest CT after Initiation of Treatment.
Axial CT images (obtained without the administration of contrast material) from 3 weeks after the initiation of treatment with glucocorticoids show near-complete resolution of ground-glass and consolidative opacities.

Videos showing chest CT imaging are available at NEJM.org

BAL does not show evidence of bacterial or fungal infection, and pneumocystis staining is negative. Viral testing is also negative, except for CMV DNA. The presence of CMV DNA in BAL fluid does not distinguish between viral shedding and tissue-invasive disease, and CMV pneumonia remains an unlikely diagnosis so soon after transplantation in a patient whose condition has continued to decline despite treatment with foscarnet.

The progressively bloody return on serial BAL confirms a diagnosis of diffuse alveolar hemorrhage. Diffuse alveolar hemorrhage is an uncommon early pulmonary complication of HSCT that often coincides with marrow recovery and can be a component of periengraftment respiratory distress syndrome. Systemic glucocorticoid therapy, which has been started in this patient, is often used to treat patients such as this one with severe respiratory failure after HSCT when there is no evidence of infection or untreated volume overload, and it tends to be most helpful in those who have alveolar hemorrhage in the context of periengraftment respiratory distress syndrome.

Given the negative testing for infectious causes, the lack of improvement in the patient's condition after he underwent diuresis, and the timing of respiratory failure coincident with neutrophil engraftment, a diagnosis of periengraftment respiratory distress syndrome was made. His condition improved rapidly after the initiation of glucocorticoid therapy (Fig. 2 and Videos 1 through 3, available with the full text of this article at NEJM.org), and extubation was performed after 2 days. Administration of supplemental oxygen was stopped 2 days later. One year later, he was in complete remission of acute myeloid leukemia, and his transplant was durably engrafted, with 100% donor chimerism and no evidence of disease on flow cytometry.

COMMENTARY

In this case, a patient with acute myeloid leukemia began to have rapidly progressive hypoxemic respiratory failure with diffuse pulmonary

infiltrates 2.5 weeks after undergoing HSCT, at the time when his peripheral neutrophil count was beginning to recover. A thorough evaluation for infection, including bronchoscopy, was negative. Volume overload was considered, but his condition worsened despite the use of effective diuretics. His condition began to improve — and improved rapidly — only after the initiation of high-dose glucocorticoid therapy. Together, these factors supported a final diagnosis of periengraftment respiratory distress syndrome, a subtype of idiopathic pneumonia syndrome.

Approximately 15,000 patients undergo HSCT annually in the United States, and transplant recipients are increasingly encountered in both academic and community-based settings.[1] An estimated 30% of HSCT recipients have pulmonary complications in the year after transplantation, and these are associated with substantial morbidity and mortality.[2] In autopsy studies involving HSCT recipients, pulmonary complications were identified in 80 to 89% of decedents and implicated in 52 to 74% of deaths.[3,4] Infections account for approximately half of such complications,[2] and recipients of allogeneic transplantation and myeloablative conditioning regimens have the highest risk.[5,6]

As with other immunocompromised patients, the differential diagnosis of hypoxemic respiratory failure and fevers in HSCT recipients is broad. However, because pulmonary complications of HSCT occur in a somewhat predictable manner, mediated by the ablation and subsequent reconstitution of the immune system, it is important to consider the timing of the complication relative to the transplantation to help narrow the differential diagnosis.[7]

The earliest pulmonary complications (those that occur before neutrophil engraftment) are most often infections, but volume overload, aspiration, and transfusion-related reactions should also be considered. After engraftment (2 to 3 weeks after transplantation), neutrophil and lymphocyte counts recover, providing some protection against infection. During the early postengraftment period (3 to 12 weeks after transplantation), periengraftment respiratory distress syndrome and other forms of idiopathic pneumonia syndrome warrant particular consideration. During the late post-transplantation period (≥4 months after transplantation), pulmonary complications such as bronchiolitis obliterans (a form of chronic graft-versus-host disease) and infections related to maintenance immunosuppression should be considered.

The patient described here had widespread alveolar injury without identifiable infection, heart disease, or kidney disease, and despite radiologic findings of possible volume overload, his condition did not improve after diuresis. He therefore met the criteria for idiopathic pneumonia syndrome (Table 1), a diagnosis of exclusion composed of several subtypes that are differentiated by clinical findings.[8] In this case, the timing of respiratory failure coincident with neutrophil engraftment supports a diagnosis of periengraftment respiratory distress syndrome. In contrast with older criteria, which required the presence

Table 1. Major Criteria for Idiopathic Pneumonia Syndrome.*

Widespread Alveolar Injury	Absence of Infection	Absence of Hydrostatic Pulmonary Edema
Multilobar infiltrates on chest radiography or, preferably, computed tomography Symptoms of pneumonia (cough, dyspnea, or rales) Abnormal physiological findings (hypoxemia or restrictive ventilatory defect)	Infection ruled out preferably on the basis of BAL Testing of the BAL fluid for typical causes of bacterial pneumonia, atypical infections (e.g., mycoplasma and legionella), unusual bacterial infections (e.g., nocardia), mycobacterial infections, viral infections (e.g., CMV, RSV, and HHV-6), and fungal infections (e.g., aspergillus and pneumocystis)	Pulmonary dysfunction not caused by cardiogenic pulmonary edema, acute kidney failure, or iatrogenic volume overload

* Adapted from Panoskaltsis-Mortari et al.[8] Patients with idiopathic pneumonia syndrome should meet all three major criteria. The infectious causes listed are not exhaustive and should be tailored to the individual patient. Patients who meet the criteria for idiopathic pneumonia syndrome can be considered to have the periengraftment respiratory distress syndrome subtype if they are within 4 or 5 days of engraftment, with engraftment defined as occurring on the day that the neutrophil count first exceeds 500 per cubic millimeter and remains at this level for at least 3 consecutive days.[9-11] BAL denotes bronchoalveolar lavage, CMV cytomegalovirus, HHV-6 human herpesvirus 6, and RSV respiratory syncytial virus.

of a rash for this diagnosis, newer criteria also take into account the potential for isolated fever and hypoxemia.[12] Alveolar hemorrhage, which was identified on this patient's BAL, is frequently associated with this syndrome.[3,4]

Although idiopathic pneumonia syndrome was initially thought to occur in up to 15% of HSCT recipients, more recent estimates in the era of reduced-intensity and nonmyeloablative chemotherapy suggest an incidence below 5%.[13,14] Among these patients, approximately one third have periengraftment respiratory distress syndrome.[8] Risk factors for idiopathic pneumonia syndrome include the use of myeloablative conditioning with total-body irradiation, an age older than 40 years, female sex, the use of cyclophosphamide or granulocyte colony-stimulating factors, and underlying acute leukemia or myelodysplastic syndrome.[8,15] Periengraftment respiratory distress syndrome is most common among recipients of autologous HSCT, those receiving platelet transfusions, and those with earlier neutrophil engraftment.[6,9]

Patients with idiopathic pneumonia syndrome typically receive invasive mechanical ventilation for respiratory failure. Ventilator management strategies for such patients are extrapolated from the approach to caring for patients with acute respiratory distress syndrome. Beyond supportive care, patients with periengraftment respiratory distress syndrome are treated with glucocorticoids on the basis of the presumed pathophysiological process of neutrophil proliferation and degranulation leading to capillary leak and nonhydrostatic pulmonary edema.[6] Case series support a rapid response to this therapy; in one series, 10 of 11 patients had a response within 24 hours after initiation of glucocorticoid therapy.[10]

In other subtypes of idiopathic pneumonia syndrome, animal models suggest etiologic roles for donor T cells and monocytes, including their possible association with cellular injury from oxidative stress, loss of pulmonary surfactant, and increases in inflammatory mediators, particularly tumor necrosis factor α.[8] The response to glucocorticoids in patients with these other forms of idiopathic pneumonia syndrome is variable.[8] Tumor necrosis factor α inhibitors have been studied as add-on therapy to glucocorticoids in patients with idiopathic pneumonia syndrome, but the benefit of such therapy remains uncertain.[8]

Pulmonary complications after HSCT are common, may progress rapidly, and are associated with substantial morbidity and mortality. Achieving diagnostic certainty in this immunocompromised population can be difficult, given the broad range of diagnostic possibilities that can manifest similarly. Moreover, the potential for severe disease often necessitates empirical treatment of the one or several conditions that are thought to be the most likely diagnoses. An organized approach to pulmonary complications of HSCT, informed by an understanding of immune deficits after transplantation, enables prioritization among the diagnostic possibilities and prompt initiation of appropriate treatment.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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CASE RECORDS *of the* MASSACHUSETTS GENERAL HOSPITAL

Case 10-2024: A 46-Year-Old Woman with Hyperglycemia Refractory to Insulin Therapy

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PRESENTATION OF CASE

Dr. Kaitlyn R. Shank (Medicine): A 46-year-old woman was admitted to this hospital because of hyperglycemia that was refractory to insulin therapy.

Five years before the current presentation, the patient received a diagnosis of type 2 diabetes mellitus after nausea, vomiting, polyuria, and polydipsia had developed. At that time, the weight was 113 kg, and the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) was 45.6. Treatment with metformin was started, along with subcutaneous insulin glargine at a dose of 10 units daily. The patient had adverse effects associated with metformin, so treatment with metformin was discontinued and glipizide was started. During the next 3.5 years, despite progressive weight loss, the patient's glycemic control worsened, which resulted in gradual intensification of her glucose-lowering regimen.

Two years before the current presentation, the patient moved to the Boston area and established care at a clinic affiliated with another hospital. The weight was 63 kg, and the BMI was 25.4. Medications for diabetes included subcutaneous insulin glargine (20 units daily) and glipizide, and the glycated hemoglobin level was 13.2% (reference range, 4.3 to 5.6). Treatment with empagliflozin was started but then stopped because of a urinary tract infection. The dose of subcutaneous insulin glargine was increased to 30 units daily, and treatment with subcutaneous insulin lispro, administered at a dose of 10 units three times a day with meals, was added. Treatment with glipizide was stopped, and treatment with glimepiride and pioglitazone was started.

One year before the current presentation, the weight was 48 kg, and the BMI was 19.4. Medications for diabetes included subcutaneous insulin glargine (34 units daily), subcutaneous insulin lispro (15 units three times a day with meals), glimepiride, and pioglitazone, and the glycated hemoglobin level was 14.0%. Anorexia had developed, along with fatigue. Although the patient reported eating very little, the blood glucose levels remained markedly elevated.

Nine months before the current presentation, the weight was 42 kg, and the BMI was 16.9. Medications for diabetes included subcutaneous insulin glargine (46 units

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daily), subcutaneous insulin lispro (20 units three times a day with meals), glimepiride, and pioglitazone, and the glycated hemoglobin level was 11.0%.

Six months before the current presentation, persistent abdominal pain developed, and the patient was admitted to the other hospital. Computed tomography (CT) of the abdomen and pelvis, performed after the administration of intravenous contrast material, reportedly did not show evidence of obstruction, perforation, or abscess. The abdominal pain was attributed to gastroparesis; treatment with gabapentin, metoclopramide, and oxycodone was started. During the hospitalization, the patient was found to have profound hyperglycemia without diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome. The glycated hemoglobin level was 15.5%. Testing was negative for antibodies to glutamic acid decarboxylase, islet antigen 2, and zinc transporter 8. A diagnosis of lipodystrophy was considered. Treatment with human regular U-500 insulin, given in daily doses of 250 units with breakfast and 200 units each with lunch and dinner, was started; treatment with subcutaneous insulin glargine and subcutaneous insulin lispro was stopped. The patient was discharged home. Subsequent to this hospitalization, a gastric-emptying study reportedly showed normal emptying at 1 hour.

Two months before the current presentation, the abdominal pain worsened, and the patient was again admitted to the other hospital. Her hyperglycemia was initially treated with continuous intravenous insulin at doses of up to 40 units per hour. When the blood glucose level improved, treatment with intravenous insulin was stopped. Treatment with human regular U-500 insulin was then resumed at an increased dose (550 units each with breakfast and lunch and 450 units with dinner); treatment with isophane insulin, also known as neutral protamine Hagedorn (NPH) insulin, was started at a dose of 80 units twice a day. The abdominal pain subsided with improved glycemic control, and the patient was discharged home.

Over the course of the 2 months between hospital discharge and the current presentation, the patient had five additional admissions to the other hospital because of abdominal pain and hyperglycemia. During each admission, the hyperglycemia was treated with high-dose intravenous insulin, the abdominal pain abated with improved blood glucose levels, and the patient was discharged home. During one admission, endoscopy was performed and reportedly revealed erosive gastritis and duodenitis due to infection with *Helicobacter pylori*, for which the patient was treated with amoxicillin, clarithromycin, bismuth subsalicylate, and pantoprazole.

Nine days before the current presentation, the abdominal pain worsened, and the patient was transported by ambulance to the emergency department of the other hospital. Treatment with intravenous insulin was initiated, and the patient was admitted to the hospital. On the second hospital day, treatment with intravenous insulin was stopped, and treatment with human regular U-500 insulin was resumed at an increased dose of 650 units each with breakfast and lunch and 600 units with dinner; treatment with NPH insulin was also restarted at a dose of 80 units twice a day. She was transferred to this hospital for further care.

On arrival at this hospital, the patient reported constant epigastric abdominal pain. She also reported that she had been administering her subcutaneous insulin medications at home without missed doses and confirmed that she had been rotating the injection sites on her abdomen. Other medical history included depression, as well as anemia and leukopenia; a bone marrow biopsy performed 7 months earlier revealed mild-to-moderate fibrosis with patchy myxoid degeneration. She had numbness and tingling in the hands and feet that had begun 9 months before the current presentation. Her menses had stopped 14 months before the current presentation. Other medications included acetaminophen, fluoxetine, gabapentin, glipizide, hydromorphone, lorazepam, mirtazapine, oxycodone, pancrelipase, pantoprazole, and pioglitazone. She had no known drug allergies. The patient was Black and lived in Boston with her husband and children; she had previously worked as a chef but was not working at the time of the current presentation. She rarely drank alcohol or smoked marijuana and had never smoked tobacco; she did not use illicit drugs. Her mother had rheumatoid arthritis and type 2 diabetes, and her father had liver disease.

On examination, the temporal temperature was 36.1°C, the blood pressure 108/78 mm Hg, the

Back to Table of Contents

pulse 98 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. The weight was 42 kg, and the BMI was 17.0. The patient appeared cachectic with a diffuse absence of body fat and muscle mass. Her face had acromegaly-like features, including broadening of the nose and thickening of the lips (Fig. 1). Acanthosis nigricans was present, most notably in the neck and axillae. She had skin tags on the face and neck, and vitiligo was present on the ears and on the fingers of the right hand. The abdomen was soft, nondistended, and diffusely tender on palpation, without rebound or guarding; there was no hepatosplenomegaly. There was skin breakdown in the legs. The remainder of the examination was normal.

Laboratory testing showed a fasting blood glucose level of 311 mg per deciliter (17.3 mmol per liter; reference range, 70 to 100 mg per deciliter [3.9 to 5.6 mmol per liter]) and a C-peptide level of 12.1 ng per milliliter (reference range, 1.1 to 4.4). Blood levels of cholesterol, triglycerides, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, total complement, C3, and C4 were normal. The blood level of leptin was undetectable, and the blood level of adiponectin was 24.5 μg per milliliter (reference range, 2.9 to 30.4). A screening test for human immunodeficiency virus was negative. Testing for antibodies to nuclear antigens was positive at a titer of 1:320 with a homogeneous pattern; testing for antibodies to double-stranded DNA was negative. Serum protein electrophoresis showed a normal pattern with a mild diffuse increase in the gamma globulin level. Other laboratory test results are shown in Table 1. Imaging studies were performed.

Dr. Leo L. Tsai: CT of the abdomen and pelvis, performed without the administration of intravenous contrast material, revealed a near-complete absence of both visceral and subcutaneous fat, with multiple skin folds reflecting a clinically significant lack of fat (Fig. 2). There was no bowel dilatation. The pancreas was atrophic, a finding commonly seen in patients with chronic insulin-dependent diabetes.[1] There were bilateral, nonobstructing renal stones measuring up to 3 mm in diameter. The attenuation level of the liver was 58 Hounsfield units (HU), which is not consistent with hepatic steatosis (which is usually defined by an attenuation level of <40 HU).[2] A nonspecific, round 3.3-cm hypodense lesion at the upper aspect of the spleen was noted.

A diagnostic test was performed.

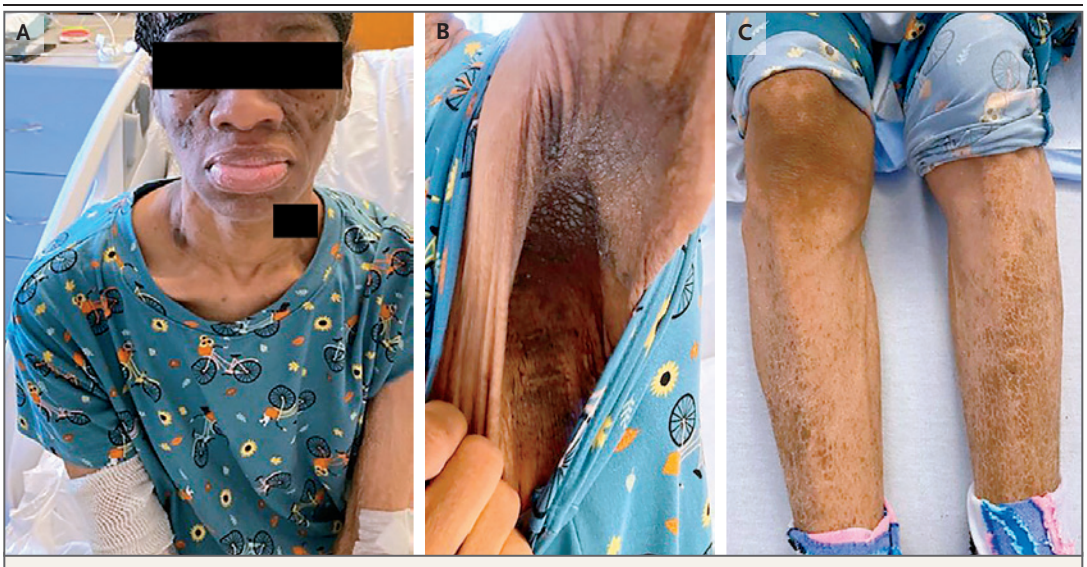


Figure 1. Clinical Photographs.
Clinical photographs obtained at the time of admission to this hospital show acromegaly-like features on the face, including broadening of the nose, thickening of the lips, and skin tags (Panel A); extensive acanthosis nigricans involving the neck and axillae (Panel B); and skin breakdown, muscle atrophy, and low fat mass in the legs (Panel C).

Back to Table of Contents

Table 1. Laboratory Data.*

Variable	Reference Range, Adults, This Hospital†	On Admission, This Hospital
Hematocrit (%)	36.0–46.0	20.7
Hemoglobin (g/dl)	12.0–16.0	6.8
White-cell count (per μl)	4500–11,000	1460
Differential count (per μl)		
Neutrophils	1800–7700	949
Lymphocytes	1000–4800	394
Monocytes	200–1200	103
Eosinophils	0–900	14
Basophils	0–300	0
Platelet count (per μl)	150,000–400,000	159,000
Mean corpuscular volume (fl)	80.0–100	91.4
Mean corpuscular hemoglobin (pg)	26.0–34.0	29.0
Mean corpuscular hemoglobin concentration (g/dl)	31.0–37.0	31.8
Red-cell distribution width (%)	11.5–14.5	15.5
Reticulocyte count (%)	0.7–2.5	1.5
Prothrombin time (sec)	11.5–14.5	13.3
Prothrombin-time international normalized ratio	0.9–1.1	1.0
Activated partial-thromboplastin time (sec)	22.0–36.0	27.9
Sodium (mmol/liter)	135–145	132
Potassium (mmol/liter)	3.4–5.0	3.7
Chloride (mmol/liter)	98–108	101
Carbon dioxide (mmol/liter)	23–32	23
Urea nitrogen (mg/dl)	8–25	24
Creatinine (mg/dl)	0.60–1.50	0.74
Glucose (mg/dl)	70–100	311
Calcium (mg/dl)	8.5–10.5	9.0
Albumin (g/dl)	3.3–5.0	3.3
Cholesterol (mg/dl)		
Total	<200	106
High-density lipoprotein	35–100	62
Low-density lipoprotein	50–129	21
Non–high-density lipoprotein	—	44
Triglycerides (mg/dl)	40–150	113
Glycated hemoglobin (%)	4.3–5.6	11.9
C peptide (ng/ml)	1.1–4.4	12.1
Glucagon (pg/ml)	<80	79
Proinsulin (pmol/liter)	3.6–22.0	8.8
Insulin-like growth factor 1 (ng/ml)	52–328	58
Thyrotropin (μIU/ml)	0.40–5.00	1.18
Testosterone (ng/dl)	<50	<12

Table 1. (Continued.)

Variable	Reference Range, Adults, This Hospital†	On Admission, This Hospital
Sex hormone–binding globulin (nmol/liter)	21–139	105

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for insulin-like growth factor 1 to nanomoles per liter, divide by 7.7.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

DIFFERENTIAL DIAGNOSIS

Dr. Lindsay T. Fourman: I participated in the care of this patient, and I am aware of the final diagnosis. The differential diagnosis presented here reflects my initial assessment of the patient at the time of her transfer to our hospital. This 46-year-old woman had received a diagnosis of type 2 diabetes 5 years before the current presentation. In the time between the diagnosis and the current presentation, the doses of exogenous insulin that were needed to lower her blood glucose level progressively increased. This impaired response to glucose-lowering medications is consistent with insulin resistance.

Physiologic insulin secretion approximates 0.4 to 1 unit per kilogram of body weight per day.[3] An exogenous insulin requirement greater than 2 or 3 units of insulin per kilogram per day is classified as severe insulin resistance.[4] On transfer to this hospital, this patient had a strikingly high insulin requirement, which exceeded 50 units per kilogram per day.

INSULIN PSEUDORESISTANCE

In patients with suspected insulin resistance, I first consider potential mimics. Poor adherence to insulin therapy or excessive carbohydrate consumption may masquerade as reduced insulin sensitivity. In addition, when insulin is administered subcutaneously, scar tissue or soft-tissue edema at injection sites may result in decreased insulin delivery to peripheral tissues.[5] Furthermore, the use of exogenous insulin that is expired or not stored properly (e.g., exposed to sunlight or not refrigerated) may reduce efficacy. This patient received high doses of insulin both intravenously and subcutaneously while in a monitored hospital setting, which made insulin pseudoresistance an unlikely diagnosis. In addition, she had classic signs and symptoms of insulin resistance that occur due to cross-reactivity of high circulating levels of insulin with the insulin-like growth factor 1 (IGF-1) receptor, including acanthosis nigricans, skin tags, and acromegaly-like features (Fig. 1).[4]

PHYSIOLOGIC AND PATHOPHYSIOLOGICAL CONDITIONS

Puberty, pregnancy, and older age are risk factors associated with insulin resistance, but none of these applied to this patient. Insulin resistance can also occur in association with pathophysiological conditions, such as acute stress (e.g., trauma or sepsis), end-organ damage (e.g., cirrhosis or uremia), weight gain, obesity, or starvation.[6] This patient had obesity when she received her initial diabetes diagnosis. However, obesity was an unlikely explanation for this patient's presentation because her insulin requirements continued to escalate despite profound weight loss and were highest when her BMI was in the underweight range.

MEDICATIONS

Specific medications may contribute to a reduced responsiveness to the glucose-lowering effect of insulin, including glucocorticoids, atypical antipsychotic agents, and antiretroviral therapy for human immunodeficiency virus infection.[7] However, this patient did not receive any of these medications.

ENDOCRINE DISORDERS

Glucagonoma, Cushing's syndrome, and acromegaly are endocrine disorders involving hormonal hypersecretion that can lead to insulin resistance.[6]

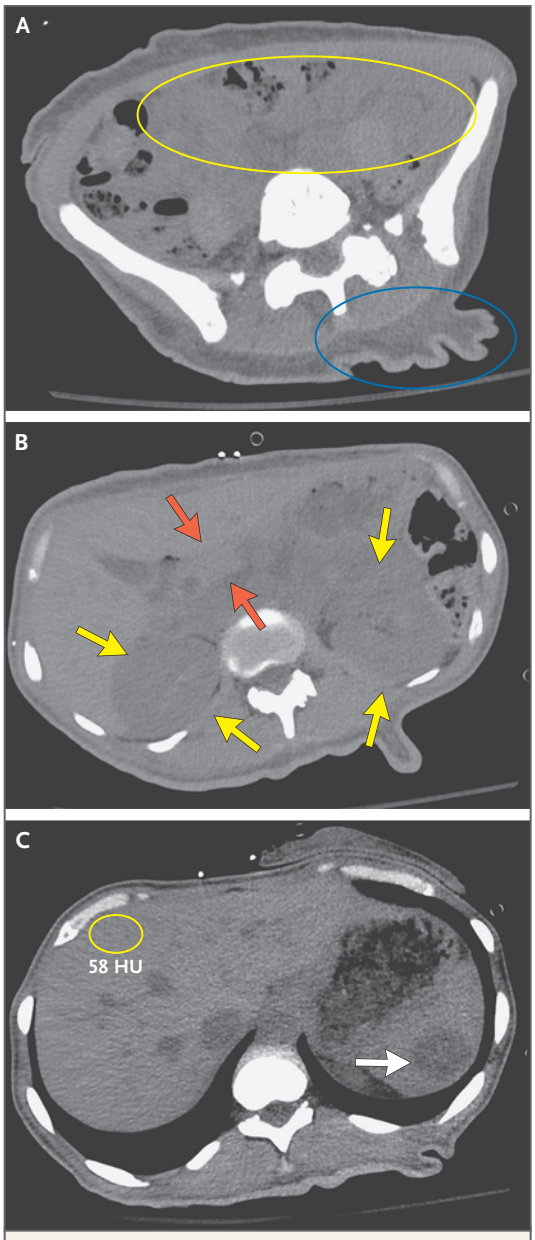


Figure 2. CT of the Abdomen and Pelvis.

CT was performed without the administration of contrast material. An axial image at the level of the mid-pelvis (Panel A) shows a near-complete absence of visceral fat between loops of nondilated bowel (yellow oval) and multiple skin folds with a near-complete absence of subcutaneous fat (blue oval). An axial image at the level of the mid-abdomen (Panel B) shows an absence of perinephric fat (yellow arrows) and pancreatic atrophy (red arrows). An axial image at the level of the upper abdomen (Panel C) shows a 3.3-cm hypodense lesion within the spleen (arrow) and a liver attenuation level of 58 Hounsfield units (HU) (oval).

Glucagonoma is a neuroendocrine tumor of the pancreatic islets that secretes glucagon. Hyperglycemia and weight loss are common findings in patients with glucagonoma. However, necrolytic migratory erythema, a characteristic rash present in more than half of patients with glucagonoma, was not seen in this case.[8] In addition, the plasma level of glucagon was normal.

Cushing's syndrome is characterized by a constellation of signs and symptoms associated with prolonged exposure to elevated levels of circulating cortisol, which may occur in patients who receive glucocorticoids or have pituitary or adrenal tumors. However, the typical findings associated with Cushing's syndrome — such as weight gain with central adiposity, rounded facies, fatigue, proximal muscle weakness, easy bruising, and violaceous striae — were not present in this case.

Acromegaly, a condition resulting from excessive secretion of growth hormone produced in the anterior pituitary gland, is most often caused by a pituitary tumor. Although this patient presented with some facial features consistent with acromegaly (i.e., broadening of the nose and thickening of the lips), there was no acral enlargement, joint pain, headache, or sweating, all of which are characteristic of this condition. In addition, the serum level of IGF-1 was not elevated in this patient.

Menstrual irregularities may develop in patients with Cushing's syndrome or acromegaly. However, I suspected that this patient's amenorrhea was most likely related to her low BMI. Thyrotoxicosis and pheochromocytoma are other endocrine disorders associated with insulin resistance, although this patient's clinical presentation was not suggestive of these diagnoses.

LIPODYSTROPHIC SYNDROMES

Lipodystrophy refers to a heterogeneous group of rare disorders characterized by a selective lack of subcutaneous adipose tissue accompanied by insulin resistance.[9,10] Lipodystrophic syndromes can be classified by the extent of deficient fat (generalized vs. partial) and the cause (genetic vs. acquired). In cases of partial lipodystrophy, areas of lipohypertrophy may also be present, involving sites such as the abdomen, neck, and chin. Insulin resistance develops in patients with lipodystrophy as a result of elevated circulating

Back to Table of Contents

free fatty acids and the accumulation of ectopic fat. Low fat stores also may lead to low circulating levels of the adipokine leptin, which further contributes to insulin resistance.[9]

When evaluating a patient with severe insulin resistance, it is important to differentiate lipodystrophy from cachexia due to poorly controlled diabetes.[9] Insulin is an anabolic hormone, and thus impaired insulin signaling in patients with insulin resistance may lead to catabolism of both muscle and fat. By contrast, patients with lipodystrophy have reduced body fat with preservation of muscle mass. On examination, this patient had muscle atrophy and low body fat, findings consistent with cachexia. However, a lack of subcutaneous fat accompanied by a low circulating level of leptin can occur in patients with either of these conditions. Thus, lipodystrophy remained a diagnostic possibility in my evaluation of this patient.

PRIMARY INSULIN-SIGNALING DEFECTS

Primary insulin-signaling defects are rare genetic or acquired disorders in which insulin signaling is directly impaired upstream, at the level, or downstream of the insulin receptor (Fig. 3).

Primary insulin-signaling defects that occur upstream of the insulin receptor (prereceptor insulin-signaling defects) are caused by insulin antibodies that bind to circulating insulin.[11] Insulin antibodies impair the ability of insulin to interact with its receptor, which leads to postprandial hyperglycemia. Fasting hypoglycemia may also occur owing to the gradual dissociation of insulin from its antibodies. Acanthosis nigricans does not typically develop in patients with insulin antibodies, since bound insulin does not cross-react with the IGF-1 receptor. This patient had severe acanthosis nigricans without fasting hypoglycemia, which made prereceptor insulin resistance an unlikely diagnosis.

Primary insulin-signaling defects that occur at the level of the insulin receptor (receptor-level insulin-signaling defects) are caused by mutations in the receptor or by antibodies that target the receptor.[4,10] Conditions that affect the insulin receptor may manifest at birth as autosomal recessive syndromes associated with growth and developmental disorders. Alternatively, heterozygous or homozygous mutations in the insulin receptor may result in type A insulin resistance syndrome, which often becomes clinically apparent during or after adolescence. Type B insulin resistance syndrome is a rare disorder characterized by the presence of antibodies to the insulin receptor. This disorder most commonly occurs in middle-aged Black women who have other autoimmune features or lymphoproliferative disorders.[12]

Primary insulin-signaling defects that occur downstream of the insulin receptor (postreceptor insulin-signaling defects) rarely arise from mutations involving the insulin-signaling cascade.[4] More commonly, postreceptor insulin resistance is caused by functional inhibition of intermediates within the insulin-signaling pathway (such as by posttranslational modification), which underlies the classic form of insulin resistance observed in patients with conditions such as obesity and lipodystrophy.[13,14]

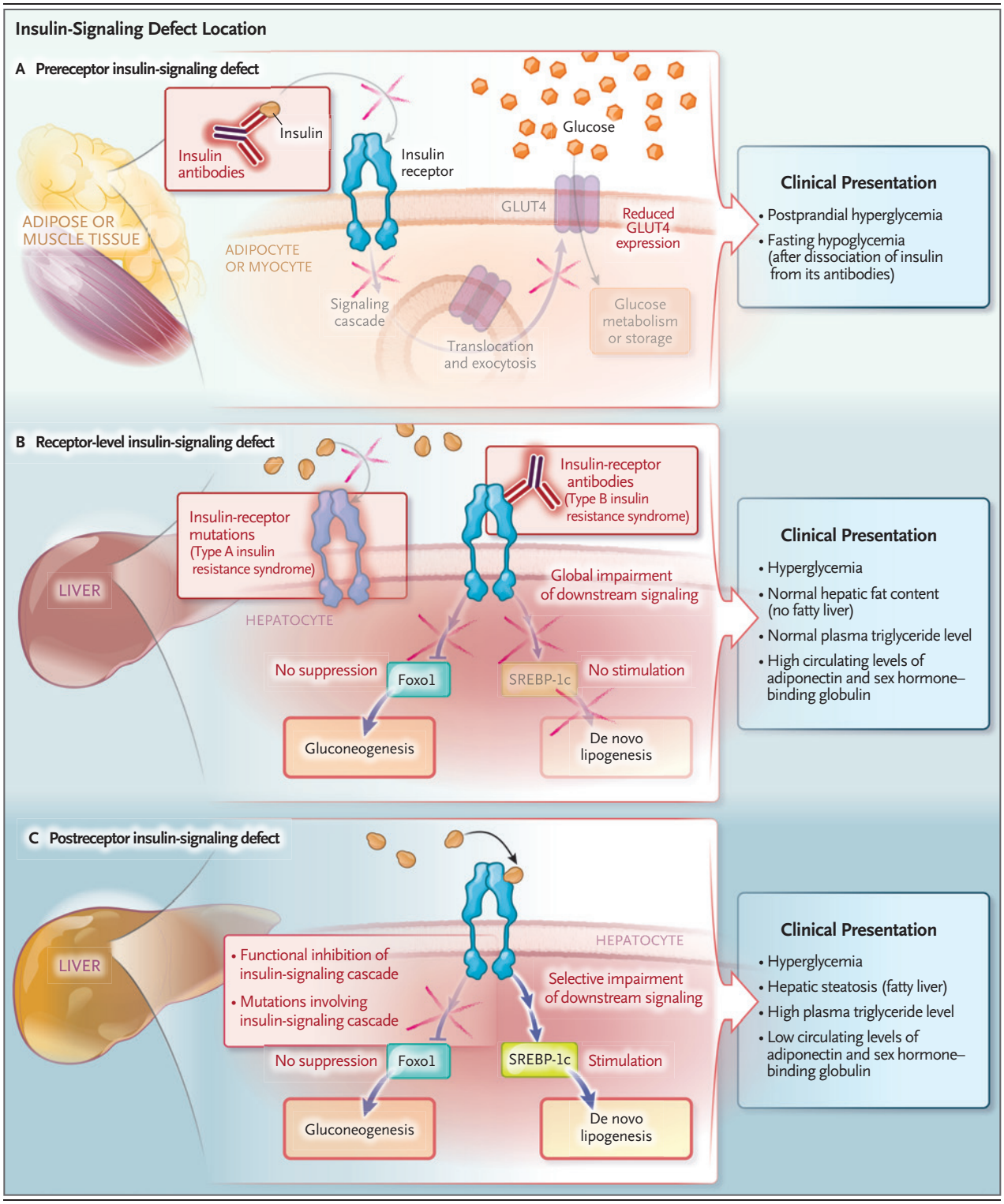
This patient's demographic characteristics and autoimmune profile were suggestive of a diagnosis of type B insulin resistance syndrome due to insulin-receptor antibodies. However, lipodystrophy remained a diagnostic consideration in this case.

DISTINGUISHING TYPE B INSULIN RESISTANCE SYNDROME FROM LIPODYSTROPHY

In the liver, the insulin-signaling cascade branches downstream of its receptor to form one pathway that suppresses gluconeogenesis and another pathway that activates de novo lipogenesis (Fig. 3). When insulin resistance is caused by a postreceptor insulin-signaling defect, as in the case of lipodystrophy, the suppression of gluconeogenesis is selectively impaired, whereas activation of de novo lipogenesis remains intact.[13] The inability of insulin to suppress gluconeogenesis results in hyperglycemia. Meanwhile, upregulation of de novo lipogenesis by high circulating levels of insulin leads to hepatic steatosis. Accordingly, hepatic steatosis and hypertriglyceridemia are common features of postreceptor insulin resistance in patients with lipodystrophy.[9,15] By contrast, receptor-level insulin resistance, as in the case of type B insulin resistance, results in global impairment of insulin signaling downstream of its receptor. Suppression of gluconeogenesis and activation of de novo lipogenesis both fail to occur in response to insulin, which leads to the

Back to Table of Contents

rare combination of insulin-resistant diabetes, normal hepatic fat content, and a normal plasma level of triglycerides.[13,15] Receptor-level insulin resistance also results in high or high-normal circulating levels of adiponectin and sex hormone–binding globulin, which are typically suppressed by partially intact insulin signaling in postreceptor insulin resistance.[16,17]



Back to Table of Contents

This patient had normal hepatic fat content and a normal triglyceride level, as well as high-normal levels of adiponectin and sex hormone–binding globulin. These findings made a diagnosis of lipodystrophy unlikely and instead favored a diagnosis of type B insulin resistance syndrome due to insulin-receptor antibodies.

DR. LINDSAY T. FOURMAN'S DIAGNOSIS

Type B insulin resistance syndrome.

Figure 3 (facing page). Localization of Insulin Resistance at the Cellular Level.

Insulin resistance may occur upstream, at the level, or downstream of the insulin receptor. The differential biologic characteristics of each form of insulin resistance underlie its unique clinical presentation. Although defective insulin signaling occurs across multiple organ systems, the tissue or tissues most salient to distinguishing each form of insulin resistance from other causes are featured here. Prereceptor insulin resistance (Panel A) arises from antibodies that bind to circulating insulin. These antibodies transiently block the ability of insulin to interact with its receptor, leading to impaired glucose uptake by adipose tissue and muscle with consequent postprandial hyperglycemia. Subsequently, the gradual dissociation of insulin from these antibodies leads to a delayed effect of insulin on glucose uptake, which results in fasting hypoglycemia. Receptor-level insulin resistance (Panel B) arises from mutations or antibodies to the insulin receptor. This form of insulin resistance is characterized by a global impairment of insulin signaling downstream of its receptor, such that insulin fails to suppress gluconeogenesis or to stimulate de novo lipogenesis in the liver. Accordingly, receptor-level insulin-signaling defects lead to insulin-resistant diabetes in conjunction with uniquely normal hepatic fat content and a normal plasma triglyceride level. Receptor-level insulin resistance also results in high or high-normal circulating levels of adiponectin and sex hormone–binding globulin, which are typically suppressed by partially intact insulin signaling in postreceptor insulin resistance. Postreceptor insulin resistance (Panel C), which underlies conditions such as obesity and lipodystrophy, most commonly arises from the functional inhibition of intermediates within the insulin-signaling cascade (e.g., by posttranslational modification). More rarely, mutations involving the insulin-signaling cascade can result in this condition. Postreceptor insulin resistance is characterized by a selective impairment of insulin signaling. In the liver, insulin fails to suppress gluconeogenesis, yet stimulation of de novo lipogenesis by high circulating levels of insulin remains intact. The partial nature of postreceptor insulin resistance gives rise to a constellation of features characteristic of the metabolic syndrome, including hyperglycemia, hypertriglyceridemia, and hepatic steatosis.

DIAGNOSTIC TESTING

Dr. Stephen O'Rahilly: Diagnostic testing for insulin-receptor antibodies can be performed by means of immunoprecipitation followed by Western blot analysis. In this case, at a serum dilution of 1:5, there was a strong positive signal for the presence of insulin-receptor antibodies (Fig. 4). This finding, in combination with this patient's clinical presentation, is consistent with a diagnosis of type B insulin resistance syndrome, a condition that was first reported in 1976.[18]

Until recently, there were no commercially available assays for the measurement of insulin-receptor antibodies. However, in 2023, a new assay was developed that was based on a bridge assay detection format, which captures insulin-receptor antibodies between an insulin receptor containing a C-terminal peptide tag bound in the solid phase and a soluble insulin receptor with luciferase encoded at its C-terminus.[19] The rarity of type B insulin resistance syndrome may present challenges for the widespread availability of such

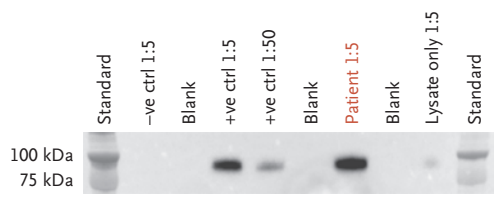


Figure 4. Western Blot Analysis.

Lysate from CL6 cells stably expressing the human insulin receptor was added to a sample of the patient's serum in addition to positive and negative controls. The Western blot image analysis confirmed the presence of insulin-receptor antibodies in the patient's serum. The insulin receptor β subunit was detected at 95kDa with the use of immunoprecipitation, shown as dark bands in the lanes for positive controls (+ve ctrl 1:5 and 1:50) and patient serum and as a faint band in the lysate-only lane. The standard lanes contained protein markers of a known size. The blank lanes contained diluent only. The positive control lanes contained serum from a patient who had had a diagnosis of type B insulin resistance syndrome; the serum was diluted at a ratio of 1:5 or 1:50 and incubated with recombinant human insulin receptors. The negative control (–ve ctrl) lane contained serum specimens from a patient who had not been found to have type B insulin resistance syndrome; the serum was diluted at a ratio of 1:5 and incubated with recombinant human insulin receptors. The lysate-only lane contained lysate from CL6 cells stably expressing the human insulin receptor.

Back to Table of Contents

an assay, but this assay represents a potentially substantial advance in facilitating the diagnosis of type B insulin resistance syndrome — a serious but treatable disorder.

LABORATORY DIAGNOSIS

Type B insulin resistance syndrome.

DISCUSSION OF MANAGEMENT

Dr. Rebecca J. Brown: The goal of treatment for type B insulin resistance syndrome is the complete remission of diabetes resulting from the elimination of the insulin-receptor antibody. Spontaneous remission can occur in some patients, but the time to remission may take many years. When left untreated, type B insulin resistance syndrome is associated with a mortality rate close to 50%.[12] Owing to the rarity of this condition, data from randomized, controlled trials of immunosuppressive or antibody-depletion therapies for the treatment of type B insulin resistance syndrome are lacking. A variety of treatment approaches have been tested in small numbers of patients, including plasmapheresis and plasma exchange,[20] intravenous immune globulin,[21] and immunosuppressive agents (e.g., rituximab, glucocorticoids, azathioprine, cyclophosphamide, and mycophenolate mofetil).[12,22-25] In 2010, Malek and colleagues reported on the successful treatment of type B insulin resistance syndrome in seven patients who received a combination of the following immunosuppressive agents: rituximab (an anti-CD20 monoclonal antibody that was used to target antibody-producing B lymphocytes), high-dose glucocorticoid pulse therapy (used to reduce the activity of antibody-containing plasma cells), and cyclophosphamide or cyclosporine (nonspecific B-cell and T-cell–suppressing drugs). The patients were switched to maintenance therapy with azathioprine once remission occurred.[26] In a follow-up report involving 22 patients, this combination regimen led to remission (defined as amelioration of the hyperglycemia with discontinuation of insulin treatment or normalization of hyperandrogenemia [or both]) in 19 of the patients after a mean duration of 5 months.[27] Toxic effects related to the use of this combination regimen of immunosuppressive agents vary depending on the individual agents used and include leukopenia, increased risk of infection, gonadal dysfunction, and temporary exacerbation of insulin resistance from glucocorticoids.

The induction of remission of diabetes in patients with type B insulin resistance syndrome usually takes months; therefore, effective management of diabetes while awaiting remission is a critical component of care. Owing to the extreme nature of type B insulin resistance syndrome, the standard inpatient or outpatient targets for blood glucose control are not feasible. Instead, the goals of diabetes management are to reverse the catabolic state observed in most patients and to allow patients to be safely treated with immunosuppressive therapy, while reducing the risk of both diabetic ketoacidosis and hypoglycemia.

The median dose of insulin used in the case series involving 22 patients with type B insulin resistance syndrome was 1775 units per day; doses as high as 18,000 units per day were reported.[27] In such cases, concentrated insulin products, including human regular U-500 insulin, can be used to reduce the injection burden. Antibodies block the insulin receptor in patients with type B insulin resistance syndrome, so insulin is not cleared normally through receptor-mediated degradation.[27] As a result, both endogenous and exogenous insulin have prolonged circulating half-lives, and it is not possible to replicate normal insulin physiology with the use of a basal–bolus insulin regimen. To reduce the risk of nocturnal hypoglycemia and fasting hypoglycemia due to a prolonged insulin half-life, most patients should receive the highest doses of insulin in the morning, followed by progressively lower doses over the course of the day. Hypoglycemia develops in some patients even in the absence of exogenous insulin due to the agonistic effects of low-titer antibodies at the insulin receptor. In these cases, the management of the hypoglycemia usually involves glucocorticoids or other treatments for ongoing immunosuppression,[28] and sometimes treatment is supplemented with slow-release carbohydrates (e.g., uncooked cornstarch).[29]

Dr. Shank: Additional testing was performed in this patient on the basis of the identification of insulin-receptor antibodies and the suspicion of an underlying autoimmune disease. Tests for antibodies to ribonucleoprotein were highly positive, and these findings were thought to be consistent with a diagnosis of systemic lupus erythematosus or mixed connective-tissue disease. A

biopsy of the splenic lesion was performed, which led to a diagnosis of lymphangioma.

Immunomodulatory therapy with rituximab, cyclophosphamide, pulse glucocorticoids, and hydroxychloroquine was initiated. Drug-induced liver injury developed and was attributed to cyclophosphamide, which was switched to intravenous immunoglobulin and azathioprine.

Unfortunately, after initial treatment at this hospital, the patient had recurrent hospitalizations for complications related to immunosuppression, including esophageal candidiasis, *Clostridium difficile* colitis, and reactivation of pulmonary blastomycosis. These infections led to multiple interruptions in her immunomodulatory therapy. Six months after the initial transfer to this hospital, she is still receiving high-dose human regular U-500 insulin, but her weight has increased by 18 kg, and the glycated hemoglobin level has decreased by 2.4%. The patient continues to undergo treatment with immunomodulatory agents and is being monitored for treatment-related toxic effects, with the goal of complete remission of type B insulin resistance syndrome.

FINAL DIAGNOSIS

Type B insulin resistance syndrome.

This case was presented at Medicine Grand Rounds.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Case 8-2024: A 55-Year-Old Man with Cardiac Arrest, Cardiogenic Shock, and Hypoxemia

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PRESENTATION OF CASE

Dr. Man Piu Wong: A 55-year-old man was evaluated at this hospital after a witnessed out-of-hospital cardiac arrest.

The patient had been eating at a restaurant late at night when he lost consciousness. A first responder used an automated external defibrillator to deliver a shock, and cardiopulmonary resuscitation (CPR) was initiated. Four minutes later, emergency medical services identified ventricular fibrillation, and defibrillation was performed. Intravenous amiodarone and epinephrine and intranasal naloxone were administered. Unstable ventricular tachycardia occurred, and the patient underwent cardioversion. He was transported to the emergency department of this hospital. The results of electrocardiography (ECG) performed before arrival at the hospital were suggestive of inferior ST-segment elevation myocardial infarction.

A review of systems could not be performed. The patient had no known medical history. He was not known to take any medications. He reportedly lived alone, worked in the service industry, and did not use tobacco or drink alcohol. His family history was unknown.

On the patient's arrival at the emergency department, the heart rate was 123 beats per minute, the blood pressure 188/107 mm Hg, the respiratory rate 26 breaths per minute, and the oxygen saturation 88% while he was receiving supplemental oxygen through a bag–valve–mask device at a rate of 15 liters per minute. The weight was 73 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) was 27.0. The patient was awake but not oriented. He did not spontaneously move the arms or legs or respond to tactile stimuli; he had increased work of breathing and posturing. The pupils were 3 mm in diameter and sluggishly reactive. Auscultation revealed sinus tachycardia and diffuse lung crackles. There was no leg edema. The remainder of the examination was normal.

Dr. Ada C. Stefanescu Schmidt: ECG showed sinus tachycardia, Q waves and 2-mm ST-segment elevations in the inferior leads, and upsloping ST-segment depressions in the lateral and precordial leads (Fig. 1A).

Dr. Wong: Laboratory test results are shown in Table 1. The white-cell count and differential count were normal, as were the levels of magnesium, bilirubin, and globulin. The high-sensitivity troponin T level was 3169 ng per liter (reference range, 0 to 14), and the N-terminal pro–B-type natriuretic peptide (NT-proBNP) level was 5679 pg per milliliter (reference value, <900). Urinalysis showed 3+ blood and 5 erythrocytes per high-power field. Blood was obtained for culture.

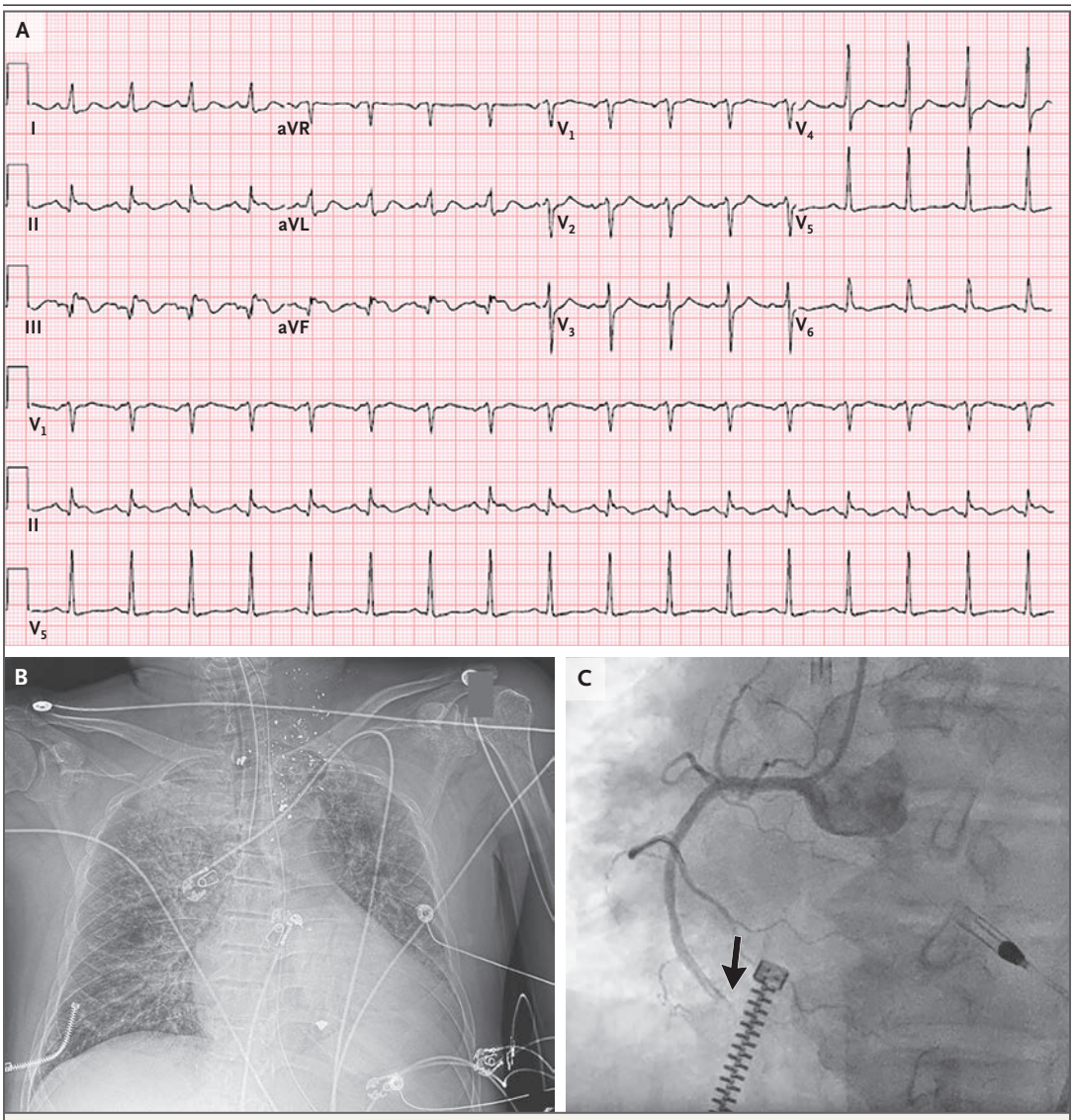


Figure 1. Initial Cardiopulmonary Diagnostic Studies.

An electrocardiogram (Panel A) shows sinus tachycardia, Q waves and 2-mm ST-segment elevations in the inferior leads, and reciprocal ST-segment depressions in the lateral and precordial leads. A chest radiograph (Panel B) shows an enlarged cardiac silhouette, as well as diffuse interstitial opacities in both lungs and an asymmetric consolidation in the right upper lobe; endotracheal and enteric tubes are in appropriate positions, and multiple metallic densities most likely related to a previous gunshot injury are projected over the left hemithorax. A coronary angiogram (Panel C) shows a thrombotic occlusion of the right coronary artery (arrow); a percutaneous left ventricular assist device is visible.

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Initial Evaluation, Hospital Day 1	During Cardiac Catheterization, Hospital Day 1	On CICU Admission, Hospital Day 2	6 Hr after CICU Admission, Hospital Day 2	14 Hr after CICU Admission, Hospital Day 2
Blood						
Hemoglobin (g/dl)	13.5–17.5	10.8	—	10.7	9.4	8.2
Hematocrit (%)	41.0–53.0	33.3	—	33.3	28.3	8.2
White-cell count (per μl)	4500–11,000	13,240	—	17,510	21,860	22,630
Platelet count (per μl)	150,000–400,000	330,000	—	447,000	371,000	257,000
Sodium (mmol/liter)	135–145	137	—	135	135	132
Potassium (mmol/liter)	3.4–5.0	3.2	—	3.5	3.6	5.1
Chloride (mmol/liter)	98–108	104	—	105	105	102
Carbon dioxide (mmol/liter)	23–32	15	—	20	14	12
Urea nitrogen (mg/dl)	8–25	12	—	17	25	24
Creatinine (mg/dl)	0.60–1.50	1.07	—	1.40	1.85	2.04
Glucose (mg/dl)	70–110	208	—	209	269	220
Calcium (mg/dl)	8.5–10.5	8.1	—	7.5	7.4	7.8
Ionized calcium (mmol/liter)	1.14–1.30	1.16	1.07	1.05	1.01	1.03
Albumin (g/dl)	3.3–5.0	3.0	—	2.5	2.4	2.4
Alanine aminotransferase (U/liter)	10–55	82	—	83	—	1018
Aspartate aminotransferase (U/liter)	10–40	88	—	98	—	1777
Alkaline phosphatase (U/liter)	45–115	132	—	121	—	102
Lactate (mmol/liter)	0.5–2.0	—	2.9	3.5	3.6	9.3
Glycated hemoglobin (%)	4.3–5.6	—	—	—	—	6.0
Prothrombin time (sec)	11.5–14.5	16.8	—	20.4	20.8	26.1
International normalized ratio	0.9–1.1	1.4	—	1.8	1.8	2.4
Partial-thromboplastin time (sec)	22.0–36.0	—	—	>150.0	47.4	87.0
Venous blood gas						
pH	7.30–7.40	7.17	—	—	—	—

Arterial blood gas						
Fraction of inspired oxygen	—	—	1.0	1.0	1.0	1.0‡
pH	7.35–7.45	—	7.24	7.22	7.28	7.14
Partial pressure of carbon dioxide (mm Hg)	35–42	—	42	49	40	35
Partial pressure of oxygen (mm Hg)	80–100	—	74	87	63	234
Urine						
Urine output (ml/hr)	—	—	140	150	40	0

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for lactate to milligrams per deciliter, divide by 0.1110. CICU denotes cardiac intensive care unit.
† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.
‡ In addition to mechanical ventilation, intravenous cisatracurium and inhaled nitric oxide (at a rate of 40 parts per million) were administered.

Intravenous norepinephrine and vasopressin were administered. Bedside ultrasonography revealed bilateral lung sliding and reduced left ventricular function. The trachea was intubated, and the oxygen saturation was 88% while the patient was receiving mechanical ventilation on a volume-controlled mode (tidal volume, 440 ml; respiratory rate, 20 breaths per minute; positive end-expiratory pressure [PEEP], 14 cm of water; fraction of inspired oxygen [FIO_2], 1.0).

Dr. Milena Petranovic: Portable chest radiography (Fig. 1B) revealed an enlarged cardiac silhouette, as well as diffuse interstitial opacities in both lungs and an asymmetric consolidation in the right upper lobe. Endotracheal and enteric tubes were in appropriate positions, and multiple metallic densities related to a previous gunshot injury were projected over the left hemithorax.

Dr. Stefanescu Schmidt: Unstable ventricular tachycardia recurred, and defibrillation was performed. Emergency cardiac catheterization was performed, and a percutaneous left ventricular assist device (LVAD) was placed through the right femoral artery. Coronary angiography (Fig. 1C) revealed a thrombotic occlusion of the right coronary artery, as well as 60 to 70% stenosis of the left anterior descending artery and a diagonal branch. The left ventricular end-diastolic pressure was 34 mm Hg. Intraprocedural transesophageal echocardiography (TEE) revealed a dilated, hypokinetic left ventricle with akinesis of the inferior and septal walls. Mild-to-moderate mitral regurgitation and tricuspid regurgitation were present, and there was no pericardial effusion.

The thrombosis of the right coronary artery was difficult to wire and cross. Percutaneous coronary intervention (PCI) was undertaken with the use of two drug-eluting stents in the middle and distal portions of the right coronary artery. Ventricular tachycardia recurred before reperfusion, and the patient underwent two cardioversions. Intravenous cangrelor, heparin, amiodarone, vancomycin, and cefepime were administered. Data from pulmonary artery catheterization, performed after PCI, are shown in Table 2. After the initiation of treatment with the percutaneous LVAD and reperfusion of the right coronary artery, the patient received low-dose norepinephrine.

Dr. Wong: The patient was admitted to the

Back to Table of Contents

Table 2. Data from Invasive Hemodynamic Monitoring and Pulse Oximetry.

Variable	Reference Range, Adults*	On Initial Evaluation, Hospital Day 1	During Cardiac Catheterization, Hospital Day 1	On CICU Admission, Hospital Day 2	6 Hr after CICU Admission, Hospital Day 2	14 Hr after CICU Admission, Hospital Day 2
Central venous pressure (mm Hg)	0–6	—	18	17	17	15
Right ventricular pressure (mm Hg)						
Systolic	20–30	—	68	—	—	—
End diastolic	0–6	—	15	—	—	—
Pulmonary artery pressure (mm Hg)						
Systolic	15–30	—	69	52	30	42
Diastolic	6–15	—	29	22	15	11
Mean	8–20	—	44	33	22	22
Pulmonary capillary wedge pressure (mm Hg)	6–14	—	20	—	—	—
Pulmonary artery pulsatility index	—	—	2.2	1.8	0.9	2.1
Central venous oxygen saturation (%)	70.0–80.0	—	56.6	—	—	—
Mixed venous oxygen saturation (%)	65.0–75.0	—	76.8	—	76.5	90.1
Arterial oxygen saturation (%)	94.0–99.0	91.5	93.0	94.2	96.9	99.1
Cardiac output by thermodilution (liters/min)	4.0–8.0	—	—	—	3.0	5.4
Cardiac index by thermodilution (liters/min/m^2)	2.4–4.0	—	—	—	1.7	3.0†

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

† The measurement was obtained while the patient was receiving intravenous epinephrine at a rate of 5 μg per minute.

cardiac intensive care unit early on the morning of the second hospital day. The temporal temperature was 36.7°C, the heart rate 98 beats per minute, and the blood pressure 81/72 mm Hg while he was receiving intravenous norepinephrine at a rate of 4 μg per minute and maximal support from the percutaneous LVAD. The oxygen saturation was 92% while he was receiving mechanical ventilation on a volume-controlled mode. The heart sounds were tachycardic and distant and were obscured by the mechanical hum of the LVAD. There was bleeding at the site of the right femoral arteriotomy. The arms and legs were cool. When sedation was temporarily discontinued, the pupils were sluggishly reactive, without corneal reflexes or blinking in response to threat; there was no response to noxious stimuli, and the plantar reflexes were mute.

A screening test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA was positive, and intravenous dexamethasone and remdesivir were administered. Aspirin was also administered. Results from laboratory testing and hemodynamic monitoring are shown in Table 1 and Table 2. The protocol for temperature management after cardiac arrest was initiated.

Dr. Petranovic: Chest radiography showed that the endotracheal tube, cardiac catheter, percutaneous LVAD, and enteric tube were in appropriate positions. There were diffuse alveolar opacities, which were greater on the left side than the right side, as well as a left pleural effusion.

Dr. Wong: During the 6 hours after admission to the cardiac intensive care unit, the blood pressure decreased to 74/72 mm Hg while the patient was receiving intravenous norepinephrine at a rate of 9 μg per minute and maximal support from the percutaneous LVAD. The urine output decreased, and the cardiac index measured by means of thermodilution was 1.7 liters per minute per square meter of body-surface area; other results are shown in Table 1 and Table 2. Treatment with intravenous epinephrine was initiated at a rate of 2 μg per minute. The oxygen saturation was 81% while he was receiving mechanical ventilation; intravenous cisatracurium and inhaled nitric oxide were administered.

By the afternoon, the patient was anuric. On examination, there was a systolic murmur, and the arms and legs remained cool and were mottled. He received doses of intravenous epinephrine at a rate of up to 5 μg per minute, and the blood pressure was 70/66 mm Hg. Laboratory test results are shown in Table 1 and Table 2.

Diagnostic test results were received, and management decisions were made.

DIFFERENTIAL DIAGNOSIS

Dr. Robert O. Roswell: The patient was a 55-year-old man who presented after a witnessed out-of-hospital cardiac arrest with ST-segment elevations in the inferior leads and reciprocal ST-segment depressions in the lateral leads on ECG. His syndrome included cardiogenic shock with acute hypoxemic respiratory failure, dysfunction of the left side of the heart, and elevated filling pressures. Despite stenting of a thrombosed right coronary artery, support from a percutaneous LVAD, and the administration of inotropes, the cardiogenic shock and hypoxemia worsened.

ACUTE RESPIRATORY FAILURE

Cardiologists who practice in the contemporary intensive care unit must be well versed in the management of respiratory failure and consider its effects on the heart and the differential diagnosis.[1,2] Clinicians must be mindful of the possibility that acute hypoxemic respiratory failure may have more than one cause, that new causes may develop during the course of acute illness, and that each cause may require attention, including appropriate treatments and approaches to ventilatory support.

The evaluation of patients with acute hypoxemic respiratory failure and bilateral opacities on chest radiography includes consideration of acute respiratory distress syndrome (ARDS) when an acute risk factor for its development, such as coronavirus disease 2019 (Covid-19) or aspiration pneumonitis after cardiac arrest, is present. The diagnosis of ARDS also requires the presence of severe hypoxemia, as determined by the ratio of partial pressure of arterial oxygen (PaO_2) to FIO_2. A recently proposed updated definition of ARDS allows for the ratio of oxygen saturation to FIO_2 to be used, as well, and does not require the presence of PEEP in the absence of invasive or noninvasive ventilation.[3]

It is important to note that the diagnosis of ARDS requires that pulmonary edema not be exclusively or primarily attributable to cardiogenic pulmonary edema.[3]

This patient had a positive test for SARS-CoV-2 infection, bilateral infiltrates, and an extremely low PaO_2:FIO_2 ratio (an initial ratio of 74 that worsened to 63 despite a PEEP of 14 cm of water). He also had clear evidence of prominent cardiogenic pulmonary edema, including an elevated NT-proBNP level (5679 pg per milliliter), a dilated, hypokinetic left ventricle on TEE, and a left ventricular end-diastolic pressure of 34 mm Hg — findings that preclude a confirmatory diagnosis of ARDS.

CARDIOGENIC SHOCK

Chest pain is the most common presenting symptom of acute coronary syndrome.[4] The patient's history from the time before the cardiac arrest could not be obtained to assess for antecedent chest pain. However, the presence of Q waves on the initial ECG suggests a subacute process. The presence of difficult-to-cross thrombosis in the right coronary artery lends credence to the hypothesis that he may have had a late-presenting ST-segment elevation myocardial infarction with cardiogenic shock. Acute myocardial infarction complicated by cardiogenic shock is defined by a systolic blood pressure of less than 90 mm Hg, end-organ hypoperfusion, and a cardiac index of less than 2.2 liters per minute per square meter; cardiogenic shock can occur hours to days after the myocardial infarction.[5,6]

Use of the Society for Cardiovascular Angiography and Interventions (SCAI) shock stage classification can help in discerning the risk of death from cardiogenic shock, with the stages ranging from A (least severe) to E (most severe).[7] This patient had refractory stage E shock on the basis of the minimal intrinsic cardiac pulsatility and hypotension despite intervention with mechanical and pharmacologic therapy, persistent severe lactic acidosis, and evolving hepatic and renal dysfunction. Stage E shock is associated with in-hospital mortality of at least 60% and 30-day mortality of at least 77%.[7,8]

Features of cardiogenic shock in this patient included a narrow pulse pressure, cool arms and legs, lactic acidemia, anuria, and a cardiac index measured by means of thermodilution of 1.7 liters per minute per square meter. In such a scenario, the mixed venous oxygen saturation would typically be low, perhaps approximately 40%. Yet, the concurrent mixed venous oxygen saturation in this patient was 76.5%. This finding corresponds to a cardiac index calculated according to Fick's principle of 4.9 liters per minute per square meter, which is discordant with the clinical picture. However, a cardiac index calculated according to Fick's principle can be erroneous because the calculation relies on an assumed oxygen consumption value, which is likely to be aberrant in a critically ill patient.[9]

Nevertheless, the higher-than-expected mixed venous oxygen saturation must be investigated, in part because it may help to explain the cause of acute myocardial infarction complicated by cardiogenic shock. With the pulmonary artery catheter in the appropriate position, the possible causes for a higher-than-expected mixed venous oxygen saturation in the context of acute myocardial infarction complicated by cardiogenic shock are extracardiac arteriovenous shunting, cardiogenic shock with concurrent distributive shock, acute severe mitral regurgitation from papillary muscle rupture, or ventricular septal rupture.

This patient had a history of a gunshot wound, which can cause the formation of arteriovenous fistulae from trauma. Arteriovenous fistulae can lead to a high mixed venous oxygen saturation but can also cause high-output heart failure. He had SARS-CoV-2 infection, which can cause distributive shock. Distributive shock can increase the mixed venous oxygen saturation owing to dysfunctional oxygen extraction.[10]

The patient might have had a late-presenting ST-segment elevation myocardial infarction with the development of a systolic murmur after presentation. Both ischemic papillary muscle rupture and ventricular septal rupture are mechanical complications of myocardial infarction. Intraprocedural TEE showed mild-to-moderate mitral regurgitation; it is possible that the severity of the mitral regurgitation was underestimated, given that the jet may be directed eccentrically. However, a ruptured papillary muscle is typically evident on TEE. A decrease in the pulmonary artery pulsatility index from 2.2 to 0.9

reflects right ventricular dysfunction, which could be due to ventricular septal rupture but could also be caused by new, severe, acute mitral regurgitation.

It is important to note that the central venous oxygen saturation was 56.6% while the mixed venous oxygen saturation was 76.8%. This combination of findings could indicate a "step-up" in oxygen saturation from the right atrium to the right ventricle due to extant left-to-right interventricular shunting, which would be suggestive of ventricular septal rupture. The administration of inhaled nitric oxide would lead to vasodilation of the pulmonary beds and offloading of the right ventricle, thereby increasing the flow across the left-to-right interventricular shunt and increasing the mixed venous oxygen saturation. In this patient, the mixed venous oxygen saturation was 90.1% after the administration of inhaled nitric oxide.

Given the patient's clinical history, echocardiography focused on the ventricular septum would be indicated. Because he had severe concurrent respiratory failure and SCAI stage E cardiogenic shock, venoarterial extracorporeal membrane oxygenation (ECMO) would be the next intervention to stabilize his condition, and additional treatment would be directed toward possible mechanical complications of myocardial infection as well as SARS-CoV-2 infection.

DR. ROBERT O. ROSWELL'S DIAGNOSIS

Ventricular septal rupture in the context of acute myocardial infarction complicated by cardiogenic shock.

ECHOCARDIOGRAPHIC STUDY

Dr. Emily K. Zern: Transthoracic echocardiography (TTE) revealed aneurysmal deformity of the inferoposterior aspect of the left ventricle. There was a 16-mm serpiginous defect in the inferoseptum with left-to-right interventricular shunting (Fig. 2A and 2B; and Videos 1 and 2, available with the full text of this article at NEJM.org). This finding is diagnostic of ventricular septal rupture. The peak interventricular flow velocity was at least 2.7 m per second. The right ventricle was dilated and hypokinetic, and the tip of the percutaneous LVAD was visible 39 mm from the aortic valve. Mild mitral regurgitation, moderate tricuspid regurgitation, mildly elevated right ventricular systolic pressure, and a small anterior pericardial effusion were detected.

ECHOCARDIOGRAPHIC DIAGNOSIS

Ventricular septal rupture.

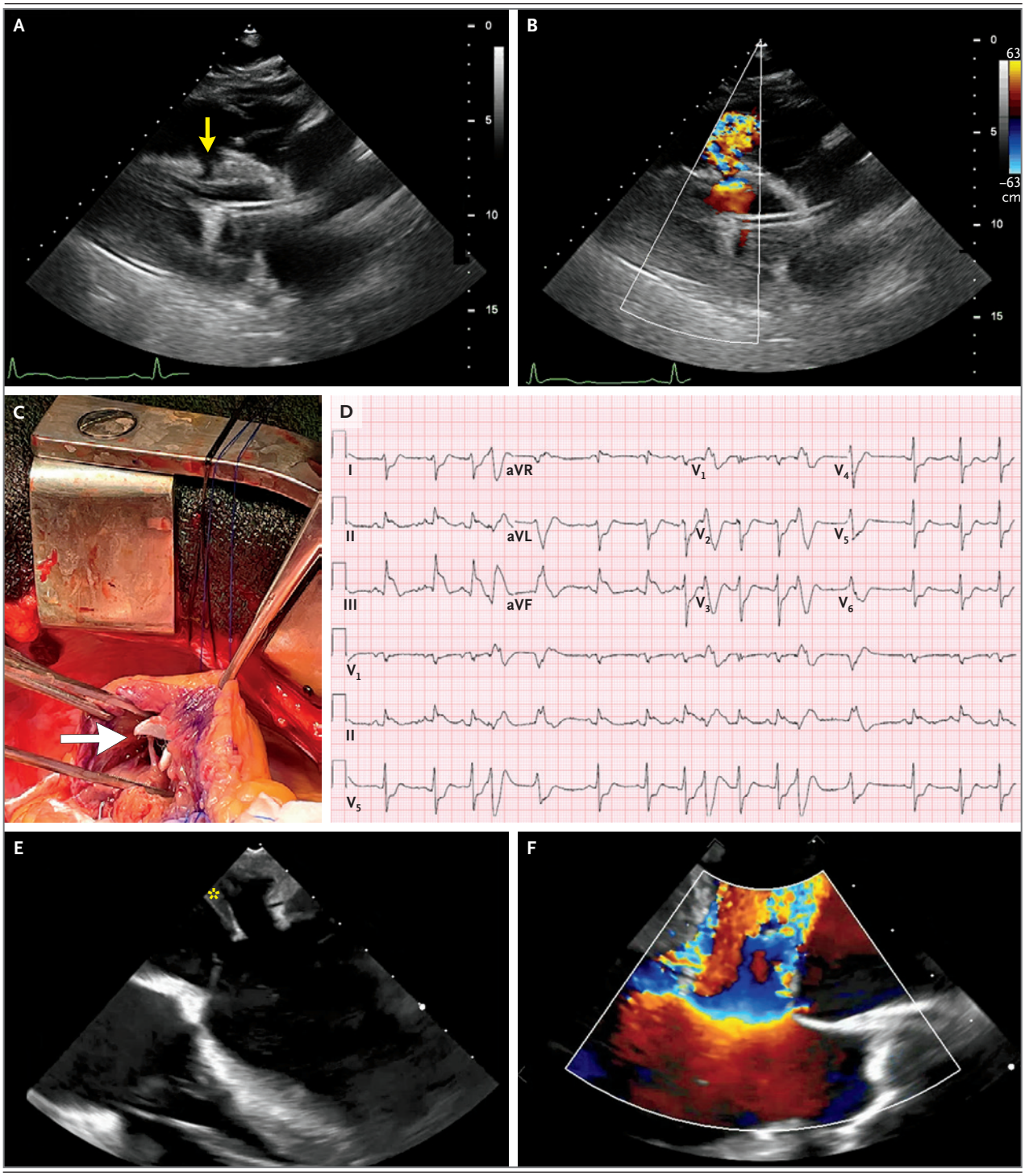
DISCUSSION OF MANAGEMENT

Dr. Daniel Burkhoff: Preoperative stabilization before the definitive surgical treatment of ventricular septal rupture typically involves medical therapy or temporary mechanical circulatory support. Hemodynamic goals for such therapies include normalizing the blood pressure and forward cardiac output, maintaining the pulmonary artery pressure and central venous pressure within the normal ranges, and reducing the flow through the pulmonary vasculature. In patients with acute ventricular septal rupture with left-to-right shunting, the flow through the pulmonary vasculature can reach 2 to 3 times the normal rate (e.g., 8 to 10 liters per minute), with the ratio of pulmonary to systemic flow typically ranging from 3 to 4. However, patients with ventricular septal rupture have a wide range of hemodynamic profiles, depending on the size of the ventricular septal rupture and the degree to which ventricular contractility is compromised by the infarction. This variability necessitates a customized approach to therapeutic decision making that can be guided, in part, by hemodynamic data obtained on pulmonary artery catheterization when feasible.

Treatment with vasopressors can unfavorably decrease forward systemic blood flow; the increased vascular resistance disproportionally increases the flow through the ventricular septal rupture into the lower-pressure right ventricle and through the pulmonary vasculature. In contrast, treatment with vasodilators can favorably decrease pulmonary flow and increase forward flow through the aorta, such that the blood pressure may not decrease despite the reduction of systemic vascular resistance. However, this approach may not be feasible if the patient has clinically significant hypotension. The administration of inotropes may be of limited

Videos showing echocardiographic studies are available at NEJM.org

Back to Table of Contents



value in overcoming the marked decrease in right and left ventricular function due to the infarction. The left ventricular ejection fraction may be misleading as an index of left ventricular contractility because the left ventricle is ejecting against a markedly reduced effective afterload and is receiving a higher preload from recirculated blood.

Because medical therapies are typically insufficient in patients with acute myocardial infarction

Back to Table of Contents

Figure 2 (facing page). Additional Cardiac Diagnostic Studies.

One day after the out-of-hospital cardiac arrest, a transthoracic echocardiographic (TTE) image obtained from a parasternal long-axis window (Panel A) shows a ventricular septal rupture (arrow); a percutaneous left ventricular assist device is in place. A TTE image obtained with color Doppler (Panel B) shows extensive left-to-right shunting across the ventricular septal rupture during ventricular systole. In a photograph obtained during surgical repair (Panel C), the apex of the heart is reflected cephalad, and a ventriculotomy established to the left of the posterior descending coronary artery provides access to the infarct zone; the ventricular septal rupture is visible through a left ventriculotomy (arrow). After resuscitation was performed for a subsequent in-hospital cardiac arrest, an electrocardiogram (Panel D) shows sinus rhythm with ventricular ectopic beats, ST-segment elevations of up to 6 mm in the inferior leads, and 5-mm ST-segment depressions in the lateral and precordial leads. A transesophageal echocardiographic (TEE) image obtained from the midesophageal four-chamber view (Panel E) shows a ruptured papillary muscle of the mitral valve, as evidenced by the presence of papillary muscle tissue in the left atrium (asterisk) during systole. A TEE image obtained with color Doppler from the midesophageal long-axis view, at a different omniplane angle (Panel F), shows severe mitral regurgitation due to the papillary muscle rupture.

complicated by cardiogenic shock and ventricular septal rupture, temporary mechanical circulatory support is often considered. Case reports and small case series of mechanical circulatory support[11] include the use of an intraaortic balloon pump,[12,13] a percutaneous transaortic ventricular assist device,[14] a transeptal bypass system from the left atrium to the femoral artery (e.g., TandemHeart),[15] or ECMO.[11] Owing to a lack of data, there is no agreed-upon approach to the treatment of ventricular septal rupture as a complication of myocardial infarction. The choice therefore largely depends on device availability, local expertise, the severity of hemodynamic compromise, and whether supplemental oxygenation of the blood is needed. The following sequence of therapies may be a reasonable approach: initial medical therapy, followed by the use of an intraaortic balloon pump, and then followed by the use of either a ventricular assist device or ECMO. Given the multiorgan failure and severity of hypotension in this patient, and despite the presence of a percutaneous LVAD, the next step was ECMO.

Dr. Wong: Peripheral venoarterial ECMO and continuous venovenous hemodialysis were initiated. Second and third tests for SARS-CoV-2 RNA were negative. The patient's family members confirmed that he had received two vaccines against Covid-19 in previous months. Treatment with dexamethasone and remdesivir was stopped after 3 days, and the patient underwent surgical repair of the ventricular septal rupture. Intraoperative TEE again showed the ventricular septal rupture with left-to-right shunting (Video 3).

Dr. Thoralf M. Sundt: Repair of the inferoposterior ventricular septal rupture (Fig. 2C) was conducted with the patch technique with infarct exclusion.[16] A large bovine pericardial patch was sewn to the inside of the left ventricle, eliminating the need for débridement of the myocardium. The flexible patch simply bridges the defect, leaving intact any viable myocardium that may still be able to contract and maintain ventricular geometry. The patch also serves to exteriorize the ventricular septal rupture, such that with a simple linear closure of the myocardium, hemostasis can be established with only right ventricular pressure on the suture line.

The left anterior descending artery was bypassed. The posterior descending artery was oversewn because the subtended myocardium had been infarcted and was patched. The ECMO equipment and percutaneous LVAD were removed.

Dr. Wong: The trachea was extubated and mechanical ventilation was discontinued on postoperative day 1. Treatment with inotropes and vasopressors was stopped on postoperative day 2, and continuous venovenous hemodialysis was discontinued on postoperative day 3 with recovery of renal function. Once the patient was able to provide his medical history, he recalled having had new chest pressure for approximately 3 days before the cardiac arrest.

After the repair, aspirin, clopidogrel, atorvastatin, and metoprolol were administered. On postoperative day 7, TTE showed no evidence of residual interventricular shunting. A dilated left ventricle (left ventricular ejection fraction, 35%) with regional inferior dysfunction, a dilated right ventricle with dysfunction, mild-to-moderate mitral regurgitation and tricuspid regurgitation with biatrial dilatation, and a pleural effusion were detected.

On postoperative day 13, the patient had dyspnea and became unresponsive after urinating. The initial cardiac rhythm was consistent with pulseless electrical activity with sinus bradycardia. CPR was initiated, and intravenous atropine and epinephrine were administered. The subsequent cardiac rhythm was consistent with ventricular tachycardia, and three shocks and intravenous epinephrine, lidocaine, amiodarone, and sodium bicarbonate were administered. The trachea was intubated for mechanical ventilation, and venoarterial ECMO was initiated with right femorofemoral cannulation. Subsequent ECG showed sinus rhythm with ventricular ectopic beats, ST-segment elevations of up to 6 mm in the inferior leads, and ST-segment depressions in the lateral and precordial leads (Fig. 2D).

TEE, performed during ECMO cannulation, revealed a ruptured papillary muscle of the mitral valve with severe mitral regurgitation (Fig. 2E and 2F and Videos 4 and 5). Serial ECGs showed resolution of the ST-segment elevations.

Dr. Sundt: The patient underwent surgical exploration, and the posteromedial head of the papillary muscle that supplies chordae tendineae to the anterior leaflet was ruptured. The affected segment of the anterior leaflet and associated papillary muscle head were excised. The remainder of the anterior leaflet was detached at its base from the aortomitral continuity and reflected posteriorly, such that it was included with the intact posterior leaflet in the valve sutures. A 29-mm porcine bioprosthetic mitral valve was implanted with preservation of the remaining chordal attachments.

PATHOLOGICAL DISCUSSION

Dr. Cynthia K. Harris: On microscopic examination of the surgical specimen (Fig. 3), the cardiomyocytes of the papillary muscle were devoid of nuclei, a finding consistent with coagulative necrosis. There was abundant neutrophilic inflammation, with no histologically significant histiocytic inflammation. Acute hemorrhage and surface fibrin deposition were also seen.

This patient's case shows a well-characterized progression of histologic findings that develop after acute myocardial infarction. Coagulative necrosis begins within 4 hours after the infarction

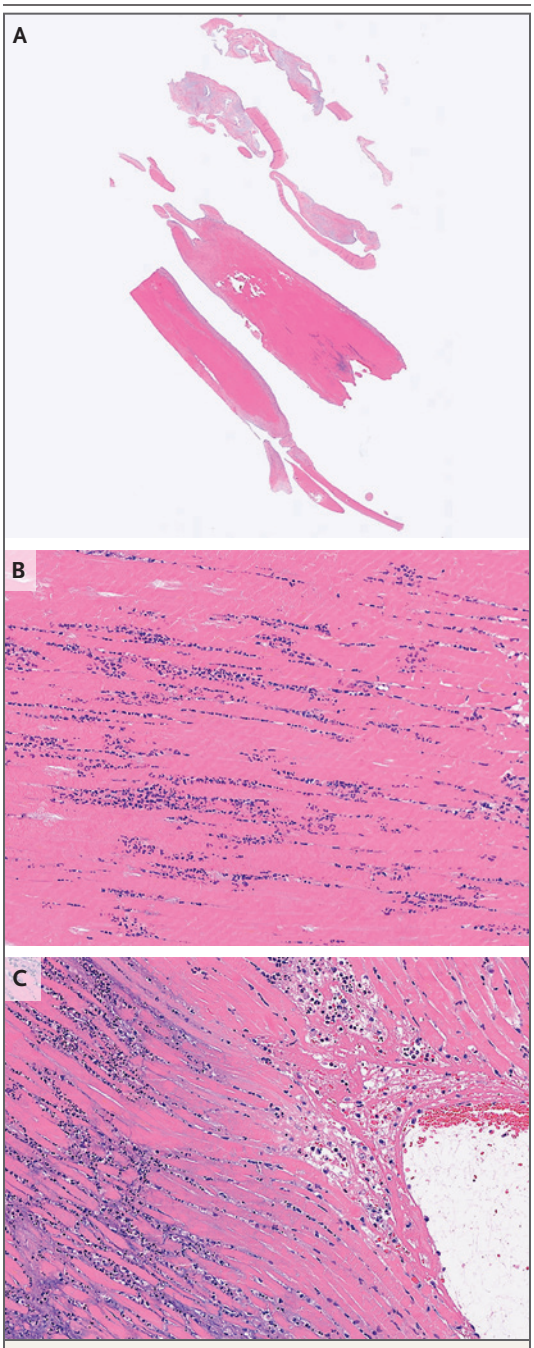


Figure 3. Histologic Examination of the Surgical Specimen.

Hematoxylin and eosin staining shows fragments of papillary muscle with attached chordae tendineae and valve tissue (Panel A). The cardiomyocytes of the papillary muscle are devoid of nuclei, a finding consistent with coagulative necrosis (Panel B). Abundant neutrophilic inflammation, acute surface hemorrhage, and surface fibrin deposition are shown (Panel C).

Back to Table of Contents

and peaks 2 to 5 days after the infarction.[17,18] Neutrophilic infiltration begins 1 day after the infarction. By day 3 to 7, the myofibers begin to disintegrate, the neutrophils break down, and macrophages infiltrate the tissue to phagocytose the dying cells. The histologic changes present in the papillary muscle in this patient indicate that the infarct had occurred 1 to 3 days earlier.

PATHOLOGICAL DIAGNOSIS

Papillary muscle and chordae tendineae with acute infarction, neutrophilic inflammation, and surface fibrin.

MECHANICAL COMPLICATIONS OF MYOCARDIAL INFARCTION

Dr. Patrick T. O'Gara: Pump failure due to severe left ventricular systolic dysfunction is the leading cause of acute myocardial infarction complicated by cardiogenic shock, accounting for nearly 80% of cases. Mechanical complications of myocardial infarction — such as rupture of the ventricular septum, papillary muscle, or left ventricular free wall — account for approximately 12% of cases.[19] The incidence of mechanical complications has decreased considerably over the past four decades, in temporal association with the increasing use of early reperfusion therapy, particularly primary PCI.[20,21]

The time course of myocardial rupture is bimodal, with one peak occurring within the first 24 hours and the other peak occurring 3 to 5 days after myocardial infarction.[22] Shared risk factors for the various types of myocardial rupture include older age, female sex, hypertension, a first infarction, the absence of a collateral blood supply, and the use of medications that may interfere with wound healing, such as glucocorticoids or nonsteroidal antiinflammatory drugs.

Mechanical complications of myocardial infarction can be distinguished from each other on the basis of the findings on physical examination, echocardiography, and cardiac catheterization. Ventricular septal rupture with shock can complicate the course of both anterior and inferior myocardial infarction. With anterior myocardial infarction, the rupture typically involves the anterior apical septum, whereas with inferior myocardial infarction, the rupture involves the inferior basal septum and has a worse prognosis. Ventricular septal rupture can be accompanied by a harsh systolic murmur at the middle or lower left sternal border, left-to-right shunting detected on echocardiography or contrast ventriculography, and a step-up in oxygen saturation from the right atrium to the right ventricle — findings that were all present in this patient. In patients with acute myocardial infarction complicated by cardiogenic shock and ventricular septal rupture, hemodynamic stabilization is usually established with mechanical circulatory support before definitive surgical repair, the timing of which is individualized. Transcatheter repair can be considered in selected patients with ventricular septal rupture who are considered to be poor candidates for surgical repair.

Thirteen days after this patient had undergone surgical repair of the ventricular septal rupture and concomitant coronary artery bypass, he had posteromedial papillary muscle rupture with severe acute mitral regurgitation, electrical instability, and cardiogenic shock. The systolic murmur associated with papillary muscle rupture is usually soft or absent owing to equalization of the pressures between the left atrium and the left ventricle. Rupture of the posteromedial papillary muscle is more common than rupture of the anterolateral papillary muscle; the posteromedial muscle has a singular coronary blood supply, whereas the anterolateral muscle has a dual coronary blood supply. The infarct that causes posteromedial papillary muscle rupture may therefore be relatively small, involving an isolated obtuse marginal branch or posterolateral ventricular branch, and may be accompanied by only modest ST-segment depressions in the precordial or lateral leads. Large V waves may be inscribed on the tracing of the pulmonary capillary wedge pressure. The diagnosis can be established by means of echocardiography or contrast ventriculography. In this patient, mechanical circulatory support was reinitiated after the papillary muscle rupture, and bioprosthetic mitral valve replacement was performed.

The occurrence of two sequential mechanical complications of myocardial infarction in the same patient is exceedingly rare. The late papillary

muscle rupture could have resulted from impaired wound healing after the initial injury associated with his inferior myocardial infarction. Alternatively, it could have been an unintended consequence of further compromise of blood flow in the distal right coronary artery during surgical repair of the ventricular septal rupture.

FOLLOW-UP

Dr. Wong: Two days after the patient underwent mitral valve replacement, ECMO was discontinued. A tracheostomy was maintained, and mechanical ventilation was continued for 6 weeks after the procedure, in the context of ventilator-associated pneumonia due to carbapenem-resistant enterobacteriaceae. Renal replacement therapy was administered for 3 months, until renal recovery was achieved. After 1 month of rehabilitation, the patient was discharged home with prescriptions for aspirin, ticagrelor, atorvastatin, bumetanide, metoprolol, sacubitril–valsartan, empagliflozin, and spironolactone. Discharge occurred 145 days after his initial presentation.

At an outpatient follow-up visit 12 months after the initial presentation, the patient reported that he walked 45 minutes daily, which resulted in mild fatigue but no orthopnea or edema. Echocardiography showed a left ventricular ejection fraction of 27% and a hypokinetic right ventricle. The prosthetic mitral valve was functioning well, and there was no evidence of residual interventricular shunting.

FINAL DIAGNOSIS

Inferior myocardial infarction with ventricular septal rupture and acute papillary muscle rupture.

This case was presented at the Harvard Medical School postgraduate course "5C: Concepts in Contemporary Critical Care Cardiology," directed by Dr. David M. Dudzinski.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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UNCOVERING A HIDDEN THREAT

N Engl J Med 2023;389: e55
DOI: 10.1056/NEJMimc2306268

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Victor Kovac, M.D., Wilfredo R. Matias, M.D., Alexander Pyden, M.D., Anand Vaidya, M.D., and Jacob Johnson, M.D.

CASE PRESENTATION

A 36-year-old man with human immunodeficiency virus (HIV) infection presented to the hospital with fever and a mass on the left side of the neck.

Three weeks before the current presentation, the patient presented to the same hospital. The CD4 count was 13 cells per cubic milliliter and the HIV viral load 88,000 copies per milliliter. The patient reported inconsistent adherence to bictegravir–emtricitabine–tenofovir alafenamide, owing to pain with swallowing and nightmares associated with oral candidiasis. The patient was treated for oral candidiasis and advised to take his daily antiretroviral therapy (ART) as prescribed.

One week before the current presentation, daily fevers with temperatures of up to 40.0°C, chills, night sweats, and an enlarging mass on the left side of his neck developed, prompting him to present to the hospital.

He reported no headaches, vision changes, focal weakness or numbness, dysphagia, sore throat, chest pain, shortness of breath, cough, abdominal pain, nausea, vomiting, diarrhea, dysuria, or rash.

Back to Table of Contents

FROM THE HEART

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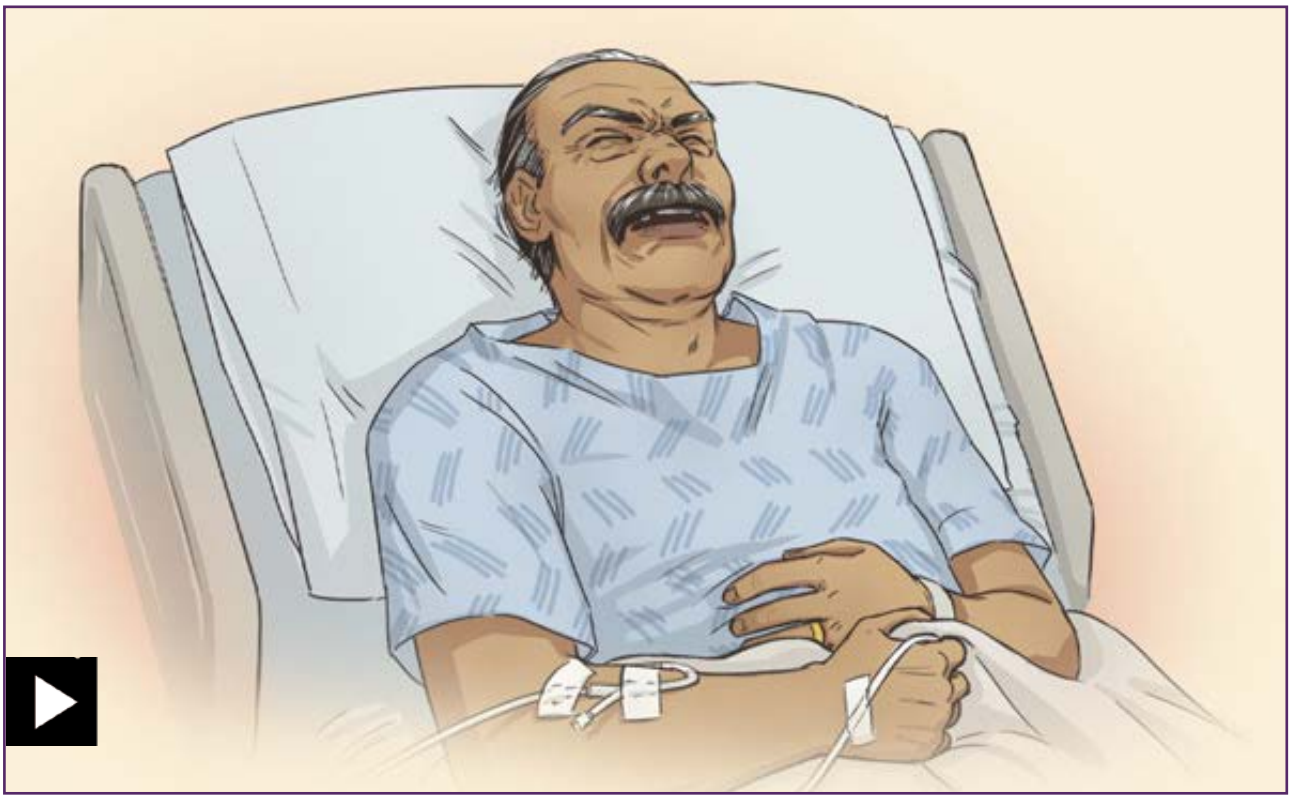
DOI: 10.1056/NEJMimc2214471



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Amanda C. Garfinkel, M.D., Anand Vaidya, M.D., Judith Strymish, M.D., Stephen M. Brecher, Ph.D., and Jussi Saukkonen, M.D.

CASE PRESENTATION

A 59-year-old man presented to the hospital with crampy abdominal pain on the left side, irritability, and confusion that began 2 days before presentation.

He reported no nausea, vomiting, diarrhea, or constipation.

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CLINICAL DECISIONS
INTERACTIVE AT NEJM.ORG

Anticoagulation for Secondary Atrial Fibrillation

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options as assigned. Readers can participate in forming community opinion by choosing one of the options.

CASE VIGNETTE

A Woman with Atrial Fibrillation Triggered by Sepsis

Suellen Li, M.D.

A 68-year-old woman with a history of hypertension and diabetes presents to the emergency department with a 3-day history of progressive shortness of breath, cough, and fever. She has no history of ischemic stroke, cardiac arrhythmias, congestive heart failure, coronary artery disease, or gastrointestinal bleeding. Her medications are lisinopril and metformin.

On initial examination, her temperature is 38.5°C, blood pressure 105/53 mm Hg, heart rate 105 beats per minute and regular, respiratory rate 24 breaths per minute, and oxygen saturation 86% while she is breathing ambient air. She has crackles in the base of the left lung and she appears confused. There are no focal neurologic deficits. Laboratory studies show an elevated creatinine level of 1.8 mg per deciliter (159 μmol per liter), an anion gap of 16 mmol per liter, an elevated white-cell count of 18,500 per cubic millimeter with a predominance of neutrophils, and an elevated lactate level of 2.8 mmol per liter. An electrocardiogram shows sinus tachycardia. Chest radiography shows opacity in the left lower lobe that is suggestive of pneumonia. Community-acquired pneumonia and sepsis are diagnosed. Appropriate antibiotics are initiated and the patient receives supplemental oxygen; she is admitted to the general medical floor for continued care.

On day 1 of the hospital stay, the patient is found to have atrial fibrillation with an irregularly irregular cardiac rhythm (heart rate, 133 beats per minute). She reports no symptoms. Intravenous heparin infusion is initiated, and after 16 hours, the heart rhythm spontaneously converts to normal sinus rhythm at a rate of 86 beats per minute.

You are the provider caring for this patient when she is ready for discharge from the hospital 3 days later. She has had no recurrence of atrial fibrillation since the initial episode. You believe that secondary atrial fibrillation has a high risk of recurrence and may confer an increased risk of ischemic stroke. Anticoagulant agents may mitigate these risks; however, anticoagulation can have serious adverse side effects. You must decide whether or not to recommend anticoagulant therapy for this patient after discharge.

TREATMENT OPTIONS

Which one of the following approaches would you recommend for this patient? Base your choice on the published literature, your own experience, guidelines, and other sources of information, as appropriate.

1. **Recommend anticoagulant therapy.**
2. **Do not recommend anticoagulant therapy.**

To aid in your decision making, we asked two experts in the field to summarize the evidence in favor of approaches assigned by the editors. Given your knowledge of the issue and the points made by the experts, which approach would you choose?

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OPTION 1

Recommend Anticoagulant Therapy

Gregory Y.H. Lip, M.D.

Patients in whom new atrial fibrillation develops from a secondary cause are at high risk for future cardiovascular events, including stroke, if they do not receive anticoagulant therapy.[1,2] The community-acquired pneumonia may have unmasked in this patient a predisposition to atrial fibrillation. Furthermore, she may have had undetected and asymptomatic episodes of atrial fibrillation before her hospital admission and before the atrial fibrillation was diagnosed by electrocardiography.

Although she has had no apparent recurrence of atrial fibrillation in the 3 days since diagnosis, she may continue to have episodes that are undiagnosed. In the Framingham Heart Study, when first-detected episodes of atrial fibrillation with a secondary precipitant were assessed, the 5-year incidence of recurrence was 42%, the 10-year incidence was 56%, and the 15-year incidence was 62%, as compared with 59%, 69%, and 71%, respectively, in patients without secondary precipitants.[3] The presence of symptoms is not a good way to indicate whether episodes of atrial fibrillation occur, and this patient was asymptomatic during her episode. In many patients with atrial fibrillation, searching for the arrhythmia requires that we look harder, longer, and in more sophisticated ways. With the increasing use of digital technologies and wearables (e.g., smartphones or smartwatches), such monitoring may facilitate the detection of atrial fibrillation recurrences.

Nevertheless, this woman is older than 65 years of age and has multiple risk factors for stroke, including hypertension and diabetes. Her CHA_2DS_2-VASc score is 4 (scores range from 0 to 9, with higher scores indicating a higher risk of stroke), which puts her at high risk for stroke if atrial fibrillation recurs, even if she is asymptomatic. The risk associated with asymptomatic episodes of atrial fibrillation is similar to that with symptomatic episodes when the patient has risk factors for stroke. Given that arrhythmia burden can change over time, her risk of stroke is not static and would potentially increase if her atrial fibrillation were to progress from paroxysmal to sustained.

Although oral anticoagulation for stroke prevention is needed in this patient, patients who receive anticoagulant therapy still have a residual risk of major adverse cardiovascular events and death. The management strategy for this patient — similar to that for patients who present with primary atrial fibrillation — should be a holistic management approach and adherence to the guideline-recommended Atrial fibrillation Better Care (ABC) pathway: avoidance of stroke with the use of anticoagulation unless the patient is at low risk (CHA_2DS_2-VASc score of 0 in males or 1 in females); better management of symptoms with patient-centered, symptom-directed decisions on rate or rhythm control (early rhythm control may be beneficial in selected patients); and management of cardiovascular risk factors and coexisting conditions, including attention to lifestyle and psychological factors.[4,5] Adherence to the ABC pathway has been associated with a reduction in all-cause mortality, cardiovascular mortality, stroke, and bleeding,[5] regardless of whether the atrial fibrillation is primary or is attributed to secondary causes.

In short, this patient should be offered oral anticoagulant therapy as part of the overall holistic management of atrial fibrillation. Stroke prevention necessitates oral anticoagulation, with the preferred option being a direct oral anticoagulant. Aspirin is not the solution because it hardly reduces atrial-fibrillation–related stroke and does not appear to differ from direct oral anticoagulants in terms of the risk of major bleeding or intracranial hemorrhage.

Disclosure forms provided by the author are available at NEJM.org.

From the Liverpool Centre for Cardiovascular Science at the University of Liverpool, Liverpool John Moores University, and Liverpool Heart and Chest Hospital — all in Liverpool, United Kingdom, and the Danish Center for Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

OPTION 2

Do Not Recommend Anticoagulant Therapy

Darae Ko, M.D., and Allan Walkey, M.D.

The clinical vignette describes a patient with no history of atrial fibrillation in whom atrial fibrillation was diagnosed for the first time during a hospitalization for sepsis. She does not have a known history of cardiomyopathy or ischemic stroke. We are asked to decide whether long-term oral anticoagulation should be prescribed for this patient when she is discharged from the hospital.

New-onset atrial fibrillation is present in 8 to 10% of patients hospitalized with sepsis and up to 44% with septic shock.[6] According to the American Heart Association Scientific Statement on Atrial Fibrillation Occurring during Acute Hospitalization,[6] in the absence of contraindications to oral anticoagulation, long-term oral anticoagulation according to stroke risk "may be reasonable" on the basis of the high risk of recurrence for patients with newly-diagnosed atrial fibrillation in the context of acute triggers.

However, it is important to consider not only the risk of recurrence of atrial fibrillation, but also the evidence regarding the effectiveness of long-term oral anticoagulation initiated after new-onset atrial fibrillation in the context of acute triggers. First, patients with atrial fibrillation with "reversible" triggers have been routinely excluded from clinical trials of oral anticoagulants,[7,8] which has resulted in a lack of direct evidence from randomized, controlled trials to inform a risk–benefit profile of long-term oral anticoagulation in patients such as this woman with new-onset atrial fibrillation during sepsis. Therefore, physicians are left to use either indirect evidence from randomized, controlled trials that excluded patients such as the woman in our case or more-direct evidence from observational studies in patients with new-onset atrial fibrillation during sepsis. Although the incidence of recurrence after new-onset atrial fibrillation in patients with sepsis is high (approximately 40% at 1 year), it is lower than that in community-dwelling patients with newly-diagnosed atrial fibrillation.[3,6] In addition to lower risks of atrial fibrillation recurrence, risks of stroke after new-onset atrial fibrillation during sepsis are lower than predicted stroke risks for community-dwelling patients with atrial fibrillation and similar CHA_2DS_2-VASc scores.[3,6] Furthermore, an observational study showed that initiation of oral anticoagulant therapy within 30 days after discharge in a patient who had been hospitalized with new-onset atrial fibrillation during sepsis was not associated with a reduced risk of ischemic stroke.[9] Despite the potential for residual confounding as a limitation in this nonrandomized study, the combined lower risk of recurrence of atrial fibrillation and lack of predictive validity of CHA_2DS_2-VASc score after new-onset atrial fibrillation during sepsis make it additionally unlikely that oral anticoagulant therapy in this case would confer a degree of benefit similar to that seen among community-dwelling patients with atrial fibrillation.

Given the lack of observed benefit of oral anticoagulant therapy after new-onset atrial fibrillation during sepsis and the potential increased risk of bleeding, we do not recommend routine oral anticoagulation for the patient in the vignette. Instead, we would recommend further assessment of the risk of thromboembolism by performing echocardiography before hospital discharge to rule out underlying structural heart disease, which might suggest that the presumably newly-diagnosed atrial fibrillation was more likely to have been preexisting; if such structural heart disease is identified, long-term oral anticoagulation would be more likely to be beneficial. In the absence of substantial structural heart disease, we would recommend long-term rhythm monitoring (i.e., beyond 30 days) with commercially available noninvasive devices or an implantable loop recorder to monitor for atrial fibrillation recurrence, with shared decision making regarding initiation of oral anticoagulation if atrial fibrillation recurs.

Disclosure forms provided by the authors are available at NEJM.org.

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Dietary Protein Restriction in Patients with Chronic Kidney Disease

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options as assigned. Readers can participate in forming community opinion by choosing one of the options.

CASE VIGNETTE

A Man with Chronic Kidney Disease

Leslie L. Chang, M.D.

A 63-year-old Black man with well-controlled hypertension, coronary artery disease, and stage 3B chronic kidney disease (CKD) presents to you, his primary care provider, for routine follow-up. His estimated glomerular filtration rate (eGFR) is 35 ml per minute per 1.73 m^2, calculated with an equation that incorporates both creatinine and cystatin C measurements and omits race. He has a history of CKD with non–nephrotic-range proteinuria that is thought to be due to long-standing hypertension, although he has not had an extensive evaluation. To the patient's knowledge, there have been no family members with kidney disease. The patient was seen in consultation by a nephrologist several years ago. The nephrologist noted at that time that the patient's eGFR had steadily declined by approximately 1 ml per minute per 1.73 m^2 per year. The patient's body-mass index (the weight in kilograms divided by the square of the height in meters) is 25. He has no history of acute kidney injury and has never received a diagnosis of diabetes. He notes that he formerly smoked cigarettes but quit many years ago. He reports good adherence to his medications, which consist of daily aspirin, lisinopril, and amlodipine.

The patient expresses concern today about the gradual decline in his kidney function and states that he would like to avoid dialysis, if possible. He asks whether there is anything he can change in his diet to slow the progression of CKD. He says he has read that a strict low-protein diet might be of benefit. He is motivated to pursue any dietary modification you recommend. You must decide whether to advise your patient to adhere to a low-protein diet of less than 0.8 g per kilogram of body weight per day or to recommend against such a diet.

TREATMENT OPTIONS

Which one of the following approaches would you take for this patient? Base your choice on the published literature, your own experience, published guidelines, and other information sources.

1. **Recommend a low-protein diet.**
2. **Do not recommend a low-protein diet.**

To aid in your decision making, each of these approaches is defended in a short essay by an expert in the field. Given your knowledge of the patient and the points made by the experts, which approach would you choose?

OPTION 1

Recommend a Low-Protein Diet

Connie M. Rhee, M.D., and
Kamyar Kalantar-Zadeh, M.D., Ph.D., M.P.H.

Interventions that slow progression of CKD and delay the need for kidney-replacement therapy include nonpharmacologic strategies. Conservative and preservative CKD management should be at the forefront of clinical practice, and dietary interventions are considered to be a cornerstone in delaying or averting the need for dialysis.

On the basis of high-quality evidence, guidelines for adults with stage 3 to stage 5 non–dialysis-dependent CKD who do not have diabetes recommend a low-protein diet of 0.55 to 0.60 g

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Back to Table of Contents

per kilogram per day or a very-low-protein diet of 0.28 to 0.43 g per kilogram per day supplemented with essential or ketogenic amino acids to meet dietary protein intake requirements and reduce the risk of kidney failure, impaired quality of life, and death.[1] Although precise thresholds vary across guidelines, most guidelines recommend dietary protein intake of less than 0.8 g per kilogram per day, yet population-based data have shown that persons with CKD generally exceed recommendations.[2]

Both animal models and clinical studies have suggested that lower dietary protein intake leads to vasoconstriction of glomerular afferent arterioles, thereby reducing intraglomerular pressure and damage, whereas high-protein diets cause dilation of afferent arterioles, which leads to glomerular hyperfiltration and progression of CKD.[2] Dietary interventions are synergistic with pharmacotherapies that reduce glomerular hyperfiltration, such as renin–angiotensin–aldosterone system inhibitors and sodium–glucose cotransporter 2 (SGLT2) inhibitors. Such physiological observations are corroborated by findings from trials and meta-analyses indicating that lower dietary protein intake in patients with non–dialysis-dependent CKD decreases the risk of metabolic complications, progression of kidney failure, and death.[3]

In the Modification of Diet in Renal Disease trial, which examined the effects of low-protein diets on CKD progression, participants were assigned to study 1 (a comparison of a low-protein diet with usual protein intake [0.58 vs. 1.3 g per kilogram per day]) if their glomerular filtration rate (GFR) was 22 to 55 ml per minute per 1.73 m^2 or to study 2 (a comparison of a supplemented very-low-protein diet with a low-protein diet [0.28 vs. 0.58 g per kilogram per day]) if their GFR was 13 to 24 ml per minute per 1.73 m^2.[4] Although the trial concluded that low-protein diets did not reduce the incidence of CKD progression, it should be noted that a reanalysis of study 1 showed a slower decline in kidney function with low-protein diets from month 3 onward. In addition, study 2 showed that very-low-protein diets marginally attenuated the decline in kidney function; furthermore, the trial had a high prevalence of patients with polycystic kidney disease and almost no patients with diabetes, which limits its generalizability. In contrast, pooled data from three international trials showed benefits of a low-protein diet in reducing the risk of end-stage kidney disease, death, or both.[1] In a more contemporary trial of non–dialysis-dependent CKD in which patients were randomly assigned to supplemented vegetarian very-low-protein diets or to low-protein diets, those in the very-low-protein diet group were less likely to reach the primary end point of initiation of kidney-replacement therapy or a reduction by greater than 50% in the GFR; an increasingly greater benefit with respect to CKD outcomes was seen with incrementally lower levels of dietary protein intake.[5]

Despite concerns about consequences of inadequate dietary protein intake and protein-energy wasting, we note that dietary protein intake of 0.6 to 0.8 g per kilogram per day is nutritionally adequate, since the recommended dietary allowance for protein is 0.8 g per kilogram per day, and 0.66 g per kilogram per day is the average requirement for persons with non–dialysis-dependent CKD. Clinical studies support the safety of low-protein diets. In an open-label trial involving older adults with very advanced non–dialysis-dependent CKD (GFRs of 5 to 7 ml per minute per 1.73 m^2) who were randomly assigned to supplemented vegan low-protein diets or to initiation of dialysis without dietary interventions, those in the low-protein diet group were able to delay the time to dialysis initiation (by approximately 1 year) and had fewer hospitalizations than those in the dialysis group; mortality was similar in the two groups.[6] Pooled trial data also showed no differences in malnutrition between the low-protein diet group and the usual-protein-intake group.[3] Collaboration with kidney dietitians further enhances safety and adherence to low-protein diets. Thus, given evidence showing the efficacy and safety of low-protein diets in persons with non–dialysis-dependent CKD who do not have diabetes, a dietary protein intake of 0.6 to 0.8 g per kilogram per day should be advised for this patient to slow progression of CKD.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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OPTION 2

Do Not Recommend a Low-Protein Diet

Graham Woodrow, M.B., Ch.B., M.D., F.R.C.P.

This patient has CKD and may progress to needing kidney-replacement therapy — but potentially not for more than 20 years at the current rate of decline. Strategies to slow the decline that have a robust evidence basis are tight blood-pressure control, blockade of the renin–angiotensin system by angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers, and use of SGLT2 inhibitors.

Historically, before the wide availability of dialysis and kidney transplantation, protein restriction was used to reduce production of protein-derived uremic toxins, with hopes of alleviating symptoms of kidney failure and extending survival in the absence of other treatment options for advanced CKD. Some clinicians suggest that protein restriction reduces hyperfiltration and slows loss of kidney function in CKD, but this approach is controversial. Concerns have been raised regarding the level of evidence supporting the effectiveness of protein restriction in slowing progression of CKD, whether such evidence applies given current clinical management, and whether protein restriction is practical and safe.

Evidence for a benefit of protein restriction is inconclusive. There have been a few randomized, controlled trials of protein restriction and several meta-analyses, with differing conclusions. Methodologic concerns about trials with positive results include small sample sizes; the validity of end points, with protein restriction affecting biochemical markers of kidney function and with the decision to start dialysis being at the discretion of the clinician; and publication bias toward positive studies.[7] The largest and most robust randomized trial is the Modification of Diet in Renal Disease trial, in which the intention-to-treat primary-outcome analysis showed no benefit from dietary protein restriction.[4]

A Cochrane review by Hahn et al. that focused on patients with advanced CKD and without diabetes showed that a low-protein diet, as compared with a normal diet, had little or no effect on the number of patients who reached end-stage kidney failure. The discussion suggested that very low protein intake in comparison with lesser protein restriction or a nonrestricted diet "probably slows the progress to kidney failure" but that further research is required to assess the side effects and the effect on quality of life because of difficulties in adhering to such a diet.[8]

It is important to note that studies that suggested a benefit of protein restriction were often conducted in the context of less-stringent blood-pressure control and low use of renin–angiotensin system inhibitors and before the introduction of SGLT2 inhibitors for CKD. For example, in the Modification of Diet in Renal Disease trial, only 27 to 54% of participants received an ACE inhibitor at some time during the trial.[4] Thus, positive findings of older studies might not apply if protein restriction were added to current standard-of-care medication regimens.

Studies have shown difficulties with regard to adherence to protein-restricted diets and with the requirement for intensive expert input from dietitians and nutritionists.[7] One author estimates that only approximately 15% of patients in a standard clinical setting (i.e., not as participants in a trial) can comfortably follow protein-restricted diets.[9] Safety concerns are important, with the World Health Organization recommending a required median daily protein intake for healthy adults of 0.66 g of protein per kilogram, with 0.83 g per kilogram per day considered to be the "safe" level of protein intake.[10]

The patient described in the vignette should receive drug therapies for management of his CKD, but no additional benefit can be gained from adherence to a standard low-protein diet. Indeed, uncertainty about benefits and concern about adverse effects of very-low-protein diets and about the ability to sustain such diets on a long-term basis preclude recommendation of these diets for this patient.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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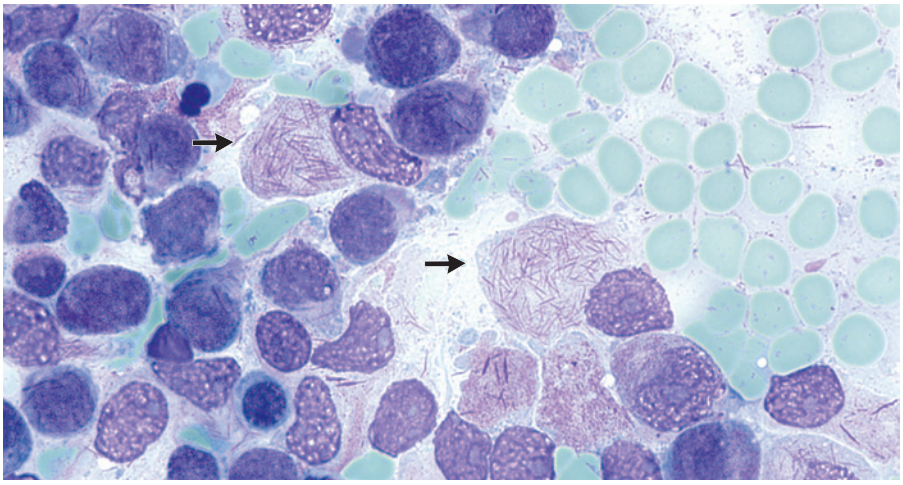
IMAGES IN CLINICAL MEDICINE

Stephanie V. Sherman, M.D., *Editor*

Acute Promyelocytic Leukemia



A 47-year-old man presented to the hospital with a 2-day history of weakness and fever. His blood pressure was 64/47 mm Hg, heart rate 110 beats per minute, and temperature 39.0°C. On physical examination, the patient had swelling and redness of the left thigh, which aroused concern about the presence of an abscess. Laboratory studies showed pancytopenia and extreme elevation of the D-dimer level. Promyelocytic blast cells with intracellular Auer rods — needle-shaped cytoplasmic structures specific for myeloid neoplasms — were seen on a peripheral-blood smear. Owing to concern about acute promyelocytic leukemia and sepsis, the patient was admitted to the intensive care unit. Induction chemotherapy with all-*trans* retinoic acid and prednisolone was initiated. A bone marrow biopsy showed promyelocytes with abundant intracellular Auer rods in formations that resembled bundles of sticks (arrows). Genetic analysis for chromosomal translocation identified a *PML–RARA* fusion gene. A diagnosis of acute promyelocytic leukemia was confirmed. Two days after the start of treatment, differentiation syndrome developed. The hospital course was further complicated by the presence of disseminated intravascular coagulation and *Staphylococcus aureus* bacteremia with leg abscesses. After molecular complete remission had been attained, consolidation chemotherapy that included arsenic trioxide was administered. On hospital day 72, the patient was discharged.

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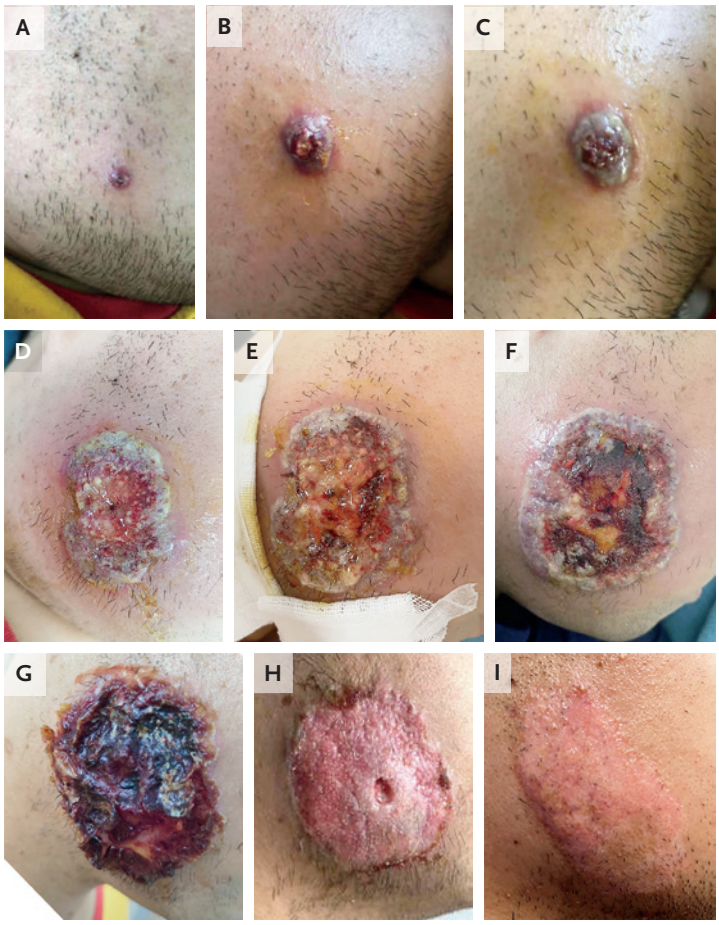
Evolution of Pyoderma Gangrenosum



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A 32-year-old man presented to the rheumatology clinic with a 4-month history of recurrent abscesses and a 3-day history of a skin lesion on his face. The abscesses had developed in his kidney, spleen, liver, lung, and skin. During previous evaluations of the abscesses, cultures had been negative, and antimicrobial therapy had been ineffective. Tests for rheumatologic conditions and immunodeficiency had been negative. At the current presentation, the physical examination was notable for a skin ulcer with a violaceous border on the right lower portion of the face that had started as an umbilicated, tender papule (Panels A, B, and C are photographs from days 1, 2, and 3, respectively, taken by the patient; Panel D is a photograph from day 4, taken during the current presentation). The next day, the ulcer had enlarged (Panel E, day 5). Histopathological analysis of a skin-biopsy specimen obtained from the border of the lesion showed a diffuse neutrophilic infiltrate with no organisms. A colonoscopy showed no evidence of inflammatory bowel disease. A diagnosis of pyoderma gangrenosum associated with aseptic abscess syndrome — an autoinflammatory disorder — was made. Treatment with colchicine and a tapering course of an oral glucocorticoid was initiated. The skin lesion started to subside 1 day after the start of treatment (Panel F, day 6; Panel G, day 8; and Panel H, day 14). At the 3-month follow-up, the ulceration (Panel I) and abscesses had abated.

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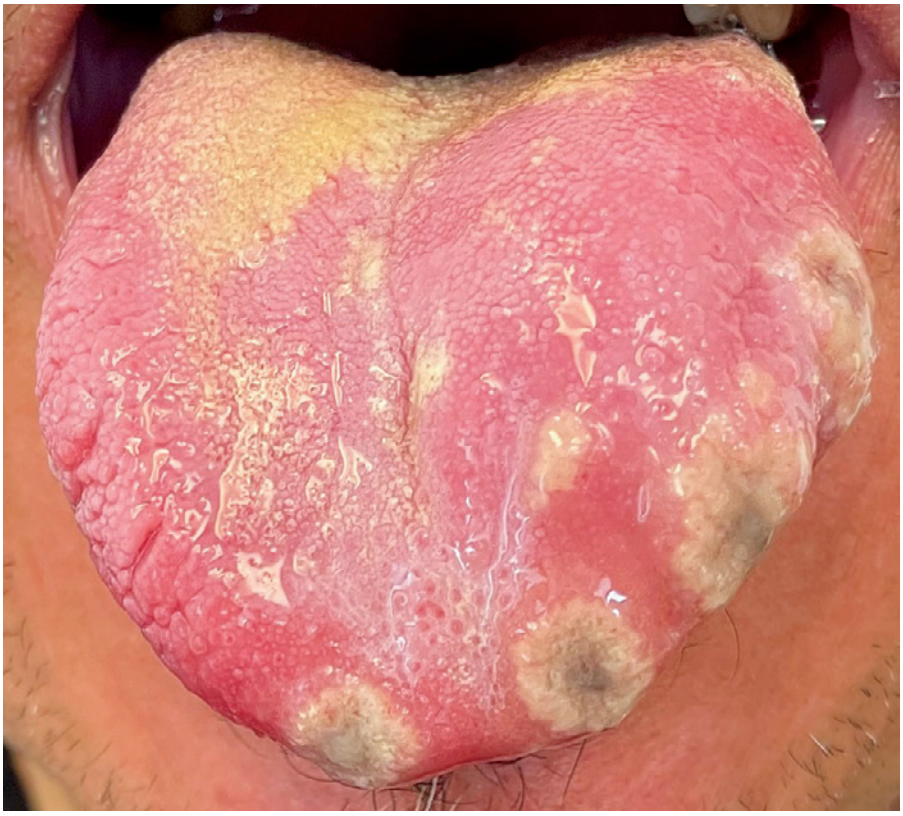
Mpox Tongue Lesions



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A 49-year-old man with human immunodeficiency virus (HIV) infection presented to a primary care clinic with an 11-day history of painful tongue lesions and a 1-week history of sore throat and fevers. He had last been sexually active with his male partner 9 days before the onset of symptoms; his partner was asymptomatic. Five months before presentation, the patient's CD4 cell count had been 519 per microliter (reference range, 297 to 1551), and 1 month before presentation, the HIV viral load had been undetectable. On physical examination, four ulcers with central darkening and raised borders were seen on the tip and left lateral aspect of the tongue. Tender submandibular lymphadenopathy was also present on the left side. No other lesions were seen in the mouth or throat or on the skin. Testing of a tongue lesion with a polymerase-chain-reaction assay for the virus that causes mpox (formerly known as monkeypox) was positive. A diagnosis of mpox was made. During the eruptive phase of mpox, a rash is very common, but isolated oral mucosal lesions may be the only mucocutaneous manifestation — as occurred in this case. The patient was lost to follow-up with primary care after the diagnosis was made, so no antiviral treatment was given. During a telephone appointment with a different clinic 2 weeks later, he reported feeling in his usual health.

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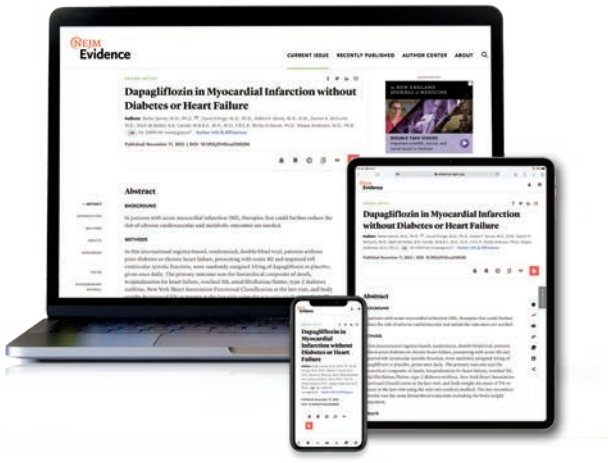

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