CASES IN PRIMARY CARE

Best practice in clinical diagnosis, treatment, and management
CASES IN PRIMARY CARE

The presentation of interesting cases has a long tradition as an educational tool and contributes to lifelong learning. Discussing the clinical course and management of individual patients enhances our understanding of disease and provides a framework for learning about medical advances.

The *New England Journal of Medicine* publishes several case-based series including Case Records of the Massachusetts General Hospital, Clinical Problem-Solving, and Clinical Practice, plus our online Interactive Medical Cases. We have chosen the cases in this collection based on their clinical relevance to primary care. We hope you find this collection engaging and instructive.

Edward W. Campion, MD
Executive Editor and Online Editor
*The New England Journal of Medicine*
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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

The Journal has been publishing Case Records of the Massachusetts General Hospital since 1923. These reports of clinicopathological conferences are one of the most popular medical teaching tools in the world. They describe actual cases that expose the process of medical decision making, and range in focus from common conditions to medical mysteries, exploring advances in challenging differential diagnosis and treatment.
Presentation of Case

Dr. Akash Gupta (Medicine and Pediatrics): A 6-month-old boy was seen in the emergency department of this hospital because of gastrointestinal bleeding and abdominal pain.

The patient had been in his usual state of health until 2 days before presentation, when his parents noted that he began to have intermittent episodes of abdominal pain. During these episodes, some of which woke the patient from sleep, he cried and pulled his legs up toward his chest while lying on his back. His parents reported that they palpated his abdomen during some of the episodes and it felt rigid; they suspected that he might be having discomfort related to excessive intestinal gas. He continued to eat and drink normally without vomiting. The next day, the patient had two bowel movements, and the stools had reddish discoloration. With the first bowel movement, the redness seemed to be present in a small amount and only on the outside of the stool; with the second bowel movement, the amount of redness increased. The patient’s mother attributed the stool discoloration to beet consumption, since bowel movements with reddish stools had also occurred in the past after the patient had eaten beets. Intermittent episodes of apparent abdominal pain continued, and between the episodes, the patient behaved normally. On the morning of presentation, he had a third bowel movement with reddish stools. His parents took him to day care, where he continued to have occasional periods of crying and pain, followed by a bowel movement that appeared to consist almost entirely of blood, including a large clot. After this bowel movement, he was reportedly pale and diaphoretic. The day care provider called the patient’s mother, who picked him up and took him to the emergency department of another hospital.

On examination at the other hospital, the temperature was 36.5°C, the pulse 178 beats per minute, the blood pressure 95/52 mm Hg, the respiratory rate 24 breaths per minute, and the oxygen saturation 100% while the patient was breathing am-
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The weight was 9.1 kg. On palpation of the abdomen, there was diffuse tenderness, which was greater on the right side than on the left, and no masses. There were no external anal fissures, and the remainder of the physical examination was normal. Two hours after arrival at the other hospital, the patient passed a dark-red stool that was described as resembling currant jelly. Intravenous normal saline (5 ml per kilogram) was administered, and he was brought by ambulance to the emergency department of this hospital for further evaluation and treatment.

The patient had a history of infantile colic and gastroesophageal reflux, which had previously been treated with ranitidine. He received a low-lactose cow milk–based formula. Pureed fruits and vegetables had recently been introduced into his diet, after which constipation developed, his stools became more firm, and daily bowel movements were associated with straining. He received cholecalciferol, and he had begun using an unspecified over-the-counter teething gel and unspecified homeopathic teething tablets 1 week earlier. Immunizations were current through 4 months of age; vaccines (including the second dose of live, oral human–bovine reassortant pentavalent rotavirus vaccine) had been administered 6 weeks earlier. There were no known allergies. The patient lived with his parents, attended day care, and had no known sick contacts. His parents were from Brazil; he was born in the United States and had not traveled outside the country. There was no family history of bleeding disorders.

On examination, the temperature was 36.3°C, the pulse 160 beats per minute, the blood pressure 98/47 mm Hg, the respiratory rate 32 breaths per minute, and the oxygen saturation 99% while the patient was breathing ambient air. He appeared well. Bowel sounds were present; the abdominal examination was otherwise limited because the patient was crying. The diaper contained melena and a small amount of stool. The remainder of the examination was normal.

Dr. Ruth Lim: Thirty-five minutes after the patient’s arrival in the emergency department, an ultrasound examination of the abdomen was performed. There was no evidence of intussusception, appendicitis, a focal lesion, or abnormally dilated bowel loops. Bowel peristalsis was present.

Dr. Gupta: On examination after ultrasonography, the pulse was 168 beats per minute, and the blood pressure 98/47 mm Hg. The patient appeared pale. The abdomen was soft, without distention, tenderness, or masses, and bowel sounds were present. Results of the physical examination were otherwise unchanged. Blood levels of electrolytes, glucose, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, and C-reactive protein were normal, as were the anion gap, platelet count, red-cell indexes, and results of renal-function tests. The results of other laboratory tests are shown in Table 1. Packed red cells were transfused, and pantoprazole and famotidine were administered intravenously.

A diagnosis was made.

### Table 1. Laboratory Data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Age-Adjusted†</th>
<th>On Presentation, This Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>33.0–39.0</td>
<td>17.5</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.5–13.5</td>
<td>5.7</td>
</tr>
<tr>
<td>Reticulocyte count (%)</td>
<td>0.5–2.5</td>
<td>7.6</td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>6000–17,500</td>
<td>22,200</td>
</tr>
<tr>
<td>Differential count (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>17–49</td>
<td>38</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>67–77</td>
<td>59</td>
</tr>
<tr>
<td>Monocytes</td>
<td>4–11</td>
<td>3</td>
</tr>
<tr>
<td>Red-cell count (per mm³)</td>
<td>3,700,000–5,300,000</td>
<td>2,070,000</td>
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<tr>
<td>Prothrombin time (sec)</td>
<td>11.0–14.0</td>
<td>12.4</td>
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<tr>
<td>Prothrombin-time international normalized ratio</td>
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<tr>
<td>Activated partial thromboplastin time (sec)</td>
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<tr>
<td>Total protein (g/dl)</td>
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<td>Albumin (g/dl)</td>
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<tr>
<td>Iron (µg/dl)</td>
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<tr>
<td>Iron-binding capacity (µg/dl)</td>
<td>230–404</td>
<td>351</td>
</tr>
</tbody>
</table>

* To convert the values for iron and iron-binding capacity to micromoles per liter, multiply by 0.1791.
† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are age-adjusted, for patients 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. Lauren M. Allister: This 6-month-old boy presented with gastrointestinal bleeding manifested by hematochezia, along with intermittent abdominal pain and one episode of melena. He appeared ill and had tachycardia. Pertinent features of the history include gastroesophageal reflux, a possible milk-protein allergy (since he was receiving a low-lactose formula), and exposure to unspecified teething tablets and a homeopathic teething medication. It is important to note the absence of fever, forceful vomiting, and hematemesis. Because care in the emergency department is more process-driven than outcome-driven, the evaluation in this case can be condensed into the following steps: rapid assessment, stabilization, and diagnostic evaluation.*

**Rapid Assessment**

This ill patient had tachycardia, pallor, profound anemia with ongoing blood loss, and intermittently abnormal findings on abdominal examination. He presented with gastrointestinal bleeding manifested by hematochezia and melena. My initial diagnostic considerations include causes of lower gastrointestinal bleeding, although the description of melena gives me reason to think that this patient could have bleeding from both upper and lower gastrointestinal sources. Less likely is an isolated, massive upper gastrointestinal bleed with rapid transit time through the infant's gastrointestinal tract.

**Stabilization**

The patient's airway was intact, and his breathing was unlabored. However, his circulation was compromised; he was pale and had tachycardia, and the hematocrit was 17.5% with ongoing blood loss. He required volume resuscitation with the administration of isotonic fluids and the transfusion of packed red cells, which was performed in the emergency department.

The patient was neurologically intact. A bedside glucose measurement may have been useful in determining whether poor feeding with resultant hypoglycemia contributed to his unwell appearance. The reported use of homeopathic and unspecified teething medications raises concerns about an unintentional toxic exposure. Could the teething tablets or medications have contained acetaminophen, which can cause an overdose that leads to liver failure and gastrointestinal bleeding, or nonsteroidal antiinflammatory drugs, which can cause irritation of the gastric mucosa and subsequent gastrointestinal bleeding? Although these exposures are unlikely underlying causes of this patient's illness, they warrant further consideration and, possibly, toxicologic testing.

**Diagnostic Evaluation**

My diagnostic considerations fall into three broad categories: common, less common, and potentially life-threatening. Among the common diagnoses, ileocolic intussusception seems to be the most likely possibility; the patient presented at a typical age (since intussusception most commonly occurs during infancy or early childhood) and had colicky abdominal pain and worsening gastrointestinal bleeding, with stool described as resembling currant jelly. Meckel's diverticulum is the most common congenital malformation of the gastrointestinal tract, and if the diverticulum contains ectopic or heterotopic mucosa, it can cause gastrointestinal bleeding.\(^1,2\) Of the clinical findings associated with Meckel's diverticulum, bleeding is one of the most common in children.\(^1,3,4\) Since Meckel's diverticulum is classically associated with painless bleeding, this patient's apparent abdominal pain is difficult to reconcile with this diagnosis.\(^5,6\) However, if Meckel's diverticulum is associated with obstruction caused by intussusception, volvulus, or perforation, then pain can be a complicating feature.\(^7\) I would also consider an inflammatory or allergic gastritis or colitis, because these are common causes of lower gastrointestinal bleeding among children who present to the emergency department.\(^7\) The presence of mild gastritis plus colitis related to a milk-protein allergy could explain both the hematochezia and melena (mixed upper and lower gastrointestinal bleeding), as well as the associated pain. Infectious colitis seems unlikely, given the absence of fever, sick contacts, and travel. Other common causes of lower gastrointestinal bleeding, such as a fissure or polyp, are not typically associated with such a severe presentation, so these diagnoses are easily ruled out in this case.

In a 6-month-old infant, the less common diagnoses that cause lower gastrointestinal bleeding include vascular malformations of the gastrointestinal tract, atypical lymphonodular hyperpla-
sia, the hemolytic–uremic syndrome, inflammatory bowel disease, toxin-mediated processes, and underlying bleeding diatheses. I would give these causes careful consideration only after the common diagnoses have been ruled out.

In this case, several diagnoses must be considered because they are potentially life-threatening if missed. These diagnoses can be consequences of either the common or the less common conditions and include a perforated viscus, an acute abdomen, obstruction, hemorrhagic shock, septic shock, and the presence of associated upper gastrointestinal bleeding while the patient is being evaluated for lower gastrointestinal bleeding. Serial physical examinations and diagnostic testing are critical in identifying any of these potentially life-threatening processes.

**Diagnostic Testing**

The findings ascertained through diagnostic testing that are the most important in developing a differential diagnosis in this case are the hematocrit of 17.5%, the elevated white-cell count of 22,200 per cubic millimeter (which is nonspecific but worrisome), and the absence of intussusception and other notable findings on ultrasonography. The normal electrolyte levels, liver profile, and coagulation indexes are reassuring, and they argue against some systemic disease processes that would typically be associated with abnormalities in one or more of these measures. However, a few additional studies would help to narrow the differential diagnosis. Because of the possibility of a toxic exposure, I would perform a serum toxicology screen. In addition, I would perform blood and stool cultures to evaluate for infection, as well as abdominal radiography to assess for bowel perforation, given the multiple days of gastrointestinal symptoms and the worsening clinical appearance. To rule out upper gastrointestinal bleeding, I would consider performing gastric aspiration.

In view of the available test results, the absence of intussusception on abdominal ultrasonography, and the patient’s ongoing blood loss, two diagnoses from my list of common diagnoses remain most likely: Meckel’s diverticulum and gastritis plus allergic colitis. Many other diagnoses have been effectively ruled out through diagnostic testing, and several less common causes would not be seriously considered until these two common diagnoses are ruled out. In addition, I am worried about the possibility of potentially life-threatening hemorrhagic shock, given the patient’s continued blood loss and profound anemia.

In the emergency department, emphasis is placed on providing the best possible systematic care during the period leading up to the diagnosis rather than conclusively determining the diagnosis; nevertheless, I think the diagnosis in this case is Meckel’s diverticulum. In an infant who has massive lower gastrointestinal bleeding with resultant hemodynamic compromise and for whom intussusception has been ruled out on the basis of ultrasonographic findings, the most likely diagnosis is Meckel’s diverticulum, and this possibility needs to be investigated before other diagnoses can be considered. The abdominal pain is one aspect of this patient’s clinical presentation that does not totally fit with the diagnosis of Meckel’s diverticulum, although an obstruction or perforation could introduce pain into the clinical picture. The description of melena is not consistent with Meckel’s diverticulum but could be explained if the bleeding mucosa from the diverticulum was proximal enough for resultant blood to undergo partial digestion. It is also possible that the single stool described as melena was not truly melena but stool with darker or maroon blood that originated from a lower, rather than an upper, gastrointestinal source. Mixed gastritis and colitis is less likely than Meckel’s diverticulum overall, and bleeding related to allergic gastrointestinal disease is unlikely to be as acute and severe as the bleeding seen in this case.

In the emergency department, it is more straightforward to obtain a scan to assess for Meckel’s diverticulum than to perform upper and lower endoscopy; the scan mandates coordination of fewer hospital resources, does not require the administration of anesthesia, and is noninvasive. If a scan were nondiagnostic, I would consider other studies, such as endoscopy or abdominal computed tomography.

**Dr. Virginia M. Pierce** (Pathology): Dr. Baldwin, what was your impression when you evaluated this patient?

**Dr. Katherine R. Baldwin** (Pediatric Gastroenterology): Our first step was to localize the source of blood loss. Melena is classically thought to reflect upper gastrointestinal bleeding (proximal to the ligament of Treitz), but it can also be
caused by more distal lesions, such as lesions in the small bowel and right colon. We considered both upper gastrointestinal sources (including variceal bleeding, vascular malformations, and ulcer) and lower gastrointestinal sources (including colitis, Meckel's diverticulum, and vascular malformations). We thought that the subacute tempo of this patient's clinical presentation, the large volume of blood loss, and his age were most consistent with Meckel's diverticulum. Although Meckel's diverticulum is commonly thought to be a painless lesion, pain can result from intussusception (with the diverticulum serving as the lead point), intermittent volvulus around associated fibrous bands, or torsion.

We recommended that the patient undergo prompt evaluation by a pediatric surgeon and that a scan to assess for Meckel's diverticulum be obtained after the administration of a histamine H2-receptor antagonist to help retain radiotracer in the gastric mucosa. We did not think that endoscopy would be immediately useful; although the performance of upper gastrointestinal endoscopy is standard for a large volume of blood loss because of the potential for diagnostic and therapeutic intervention, most causes of lower gastrointestinal bleeding do not require colonoscopy. Furthermore, colonoscopy in a patient with acute severe bleeding may be technically challenging because of difficulty with visualization.

**Clinical Diagnosis**

Gastrointestinal bleeding due to Meckel's diverticulum.

**Dr. Lauren M. Allister's Diagnosis**

Gastrointestinal bleeding due to Meckel's diverticulum.

**Imaging Studies**

Dr. Lim: After the patient received premedication with intravenous famotidine, a technetium-99m pertechnetate scan was obtained to assess for the presence of a Meckel's diverticulum. Immediately after the intravenous injection of 0.97 mCi of radiotracer, anterior planar imaging was performed continuously for 1 hour. Additional imaging was performed in a lateral view. An abnormal focus of radiotracer accumulation was seen in the right paramedian region of the abdomen that gradually increased in intensity over time (Fig. 1); this finding is consistent with ectopic gastric mucosa in a Meckel's diverticulum.

Technetium-99m pertechnetate normally accumulates in any gastric mucosa, including ectopic gastric mucosa; therefore, this radiotracer is useful in the evaluation of a suspected Meckel's diverticulum. False positive scans can occur. Technetium-99m pertechnetate is excreted by the urinary system, and activity is normally seen in the bladder and kidneys. Radiotracer activity in the stomach can pass distally into the duodenum and small bowel. Premedication with a histamine H2-receptor antagonist can reduce the release of radiotracer from the stomach. Bowel or urinary activity is suggested by movement of focal radiotracer activity over time, whereas focal accumulation in a Meckel's diverticulum should remain fixed in position. A lateral view of the abdomen can be helpful in distinguishing urinary activity in the ureters, which are located in a posterior position. A false positive scan can also result from inflammation, intussusception, bowel obstruction, or vascular lesions.

A false negative scan can result from the presence of too little or no gastric mucosa in a Meckel's diverticulum; approximately 20% of Meckel's diverticula do not contain gastric mucosa. Other causes of false negative scans include recent ingestion of barium or perchlorate, movement of the Meckel's diverticulum, and brisk gastrointestinal bleeding.

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**Discussion of Management**

Dr. Allan M. Goldstein: As a result of the clinical presentation and the findings on the scan, the infant was brought to the operating room. A short transverse incision was made in the right lower quadrant, and the diverticulum was identified (Fig. 2). Inflammation and scarring were present at its base; these findings are consistent with ulceration in the small intestine, at its junction with the diverticulum. A segmental small-bowel resection, which included the diverticulum and the presumed area of ulceration, was performed, followed by a hand-sewn end-to-end anastomosis.

A variety of operations can be performed to
treat a Meckel's diverticulum that causes gastrointestinal bleeding. These include simple diverticulectomy, wedge resection of the diverticulum and the small cuff of adjacent ileum at its base, and segmental small-bowel resection, which was done in this case. The primary cause of bleeding is the presence of acid-producing ectopic gastric mucosa in the diverticulum, which leads to the development of an ulcer in adjacent normal mucosa. The ulcer can be present in the diverticulum itself but is usually located at the junction of the diverticulum and the ileum, as appeared to be the case in this patient. Although removing both the ectopic mucosa and the ulcer would seem to be the best approach, removing the ectopic mucosa alone may be sufficient, since the ulcer would probably then heal. However, it is essential to remove all ectopic gastric mucosa, which cannot be reliably detected from the outside. Therefore, a reasonable approach is to perform a simple diverticulectomy for a diverticulum with a narrow base but to perform a wedge or segmental resection for a diverticulum with a broad base, since ectopic tissue may be left behind if the diverticular base is not fully excised. If the area of ulceration is apparent, as in this case, then resecting it with the diverticulum is also reasonable.

An important scenario to consider is whether this patient would have received different treatment if the scan had been negative, which could have easily occurred, given the imperfect sensitivity of the test. Meckel's diverticulum needs to be included in the differential diagnosis for any child being evaluated for hematochezia. If a technetium-99m pertechnetate scan is negative and other causes of bleeding have been ruled out, laparoscopy should be considered to assess for Meckel's diverticulum.

**PATHOLOGICAL DISCUSSION**

**Dr. Jochen K. Lennerz:** We received a segment of small bowel (1.7 cm by 1.5 cm by 1.5 cm) with an attached intact, blind-ending diverticulum (2.5 cm by 0.8 cm by 0.8 cm) for pathological examination. The serosa near the small intestine showed patchy fibrinous inflammation (Fig. 2) and was otherwise mildly hyperemic; the tip of the diverticulum had no attached bands. The sections showed an average wall thickness of 0.2 cm and normally folded mucosa with red discoloration toward the small bowel. In contrast to the mucosal herniation through the bowel wall that is present in diverticular disease, this diverticulum contained all three layers of bowel wall. Given the anatomical location of the diverticulum on the antimesenteric surface of the mid-ileum, these findings represent persistence of a proximal part of the vitelline duct (omphalomesenteric duct), or Meckel's diverticulum.

A histotopogram allowed us to perform a
Histologic examination in the spatial context of the entire diverticulum (Fig. 3A). There were two key mucosal findings. First, the intestinal mucosa at the opening of the diverticulum showed epithelial erosion and underlying granulation tissue, findings consistent with an ulceration (Fig. 3B). The gastric mucosa lines the entire diverticulum and is composed of surface foveolar cells, mucous neck cells, parietal cells, and basal chief cells (Panel C). The heterotopic gastric mucosa secretes hydrochloric acid, which causes peptic ulceration in the adjacent intestinal mucosa (Panel A, black arrow).

**Figure 3. Histotopogram.**
A histologic section of the diverticulum shows all three layers of bowel wall (Panel A); serosal fibrinous exudate is present (white arrow). The intestinal mucosa at the opening of the diverticulum shows mucosal erosion, acute inflammation, and underlying granulation tissue, findings consistent with an ulceration (Panel B). The gastric mucosa lines the entire diverticulum and is composed of surface foveolar cells, mucous neck cells, parietal cells, and basal chief cells (Panel C). The heterotopic gastric mucosa secretes hydrochloric acid, which causes peptic ulceration in the adjacent intestinal mucosa (Panel A, black arrow).

Histologic examination in the spatial context of the entire diverticulum (Fig. 3A). There were two key mucosal findings. First, the intestinal mucosa at the opening of the diverticulum showed epithelial erosion and underlying granulation tissue, findings consistent with an ulceration (Fig. 3B). The acute inflammation extended through the muscularis propria and was associated with fibrinous serositis. Second, this diverticulum was remarkable because the mucosa of the entire diverticulum was made up of at least four distinct cell types: surface foveolar cells, mucous neck cells, parietal cells, and basal chief cells (Fig. 3C). This composition is diagnostic of a Meckel's diverticulum containing a large amount of terminally differentiated, heterotopic gastric mucosa of the body (fundic type). There was no evidence of heterotopic pancreatic tissue, dysplasia, or cancer.

It is unusual for a Meckel's diverticulum in a 6-month-old patient to be completely lined by gastric mucosa that is most likely secreting a large amount of acid into the small intestine. The mucin-secreting surface foveolar epithelial cells in this Meckel's diverticulum protected the underlying diverticular mucosa from the acid secreted by the underlying parietal cells. Thus, the pathophysiological cascade in this patient can be described as follows: the secreted, non-neutralized acid produced by the heterotopic gastric mucosa and the secreted chief-cell–derived enzymes in the diverticulum led to peptic ulceration in the adjacent intestinal mucosa, which caused gastrointestinal bleeding. The conversion of the hemoglobin in the gastrointestinal bleed into melena was presumably related to the large load of digestive chemicals secreted by the Meckel's diverticulum. The serosal fibrinous adhesions may have caused the pain.

**Dr. Gupta:** After surgery, the patient's course was briefly complicated by ileus, but by the third postoperative day, his diet was regular and he was discharged home. Nine days later, he was seen for follow-up by the pediatric surgeon and was doing well; he had no pain, hematochezia, or melena, and the abdominal examination was normal.

**ANATOMICAL DIAGNOSIS**
Meckel's diverticulum with heterotopic gastric mucosa and associated peptic ulceration in the intestinal mucosa.

This case was presented at Pediatric Grand Rounds.
Dr. Allister reports receiving consulting fees from Medscape Consult. No other potential conflict of interest relevant to this article was reported.
Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.
We thank Dr. Rebecca Cook, Chief Resident in Pediatrics, for her assistance with organizing the conference.


Dr. Carolyn A. Boscia (Medicine and Pediatrics): An 18-year-old woman was seen in the emergency department of this hospital 11 weeks after the birth of her first child because of acute liver failure.

The patient had been well until 1 week before this presentation, when rhinorrhea, sore throat, and cough developed. On the fourth day of illness, she was seen in an urgent care clinic because of worsening cough, wheezing, and dyspnea. Bronchitis was diagnosed, and promethazine–dextromethorphan syrup and a 5-day course of oral azithromycin were prescribed. The patient returned home. Over the next 3 days, abdominal discomfort, nausea, vomiting, diarrhea, and vaginal bleeding developed. The patient also noted progressive yellowing of her skin and eyes. When she woke up on the morning of the current presentation, she felt light-headed. When she arose from bed, syncope occurred; the patient fell and had a laceration of the chin. Her boyfriend called emergency medical services (EMS), and a team was dispatched to the patient’s home.

On assessment by EMS personnel, the patient had jaundice and diaphoresis. She appeared fatigued. The pulse was 120 beats per minute, the blood pressure 82/56 mm Hg, the respiratory rate 22 breaths per minute, and the oxygen saturation 100% while she was breathing ambient air. Nystagmus occurred on right lateral gaze. The abdomen was distended, and tenderness was present in the right lower quadrant. The capillary blood glucose level was 121 mg per deciliter (6.7 mmol per liter), and an electrocardiogram showed sinus tachycardia. Intravenous fluids and supplemental oxygen (through a nasal cannula at a rate of 2 liters per minute) were administered, and the patient was transported to the emergency department of another hospital.

On arrival at the other hospital, the patient reported burning abdominal pain, which she rated at 10 on a scale of 0 to 10, with 10 indicating the most severe pain. The temperature was 37.0°C, the pulse 88 beats per minute, the blood pres-
sure 107/42 mm Hg, the respiratory rate 24 breaths per minute, and the oxygen saturation 100% while she was breathing ambient air. The abdomen was soft, with tenderness on the right side, and there was trace edema of the legs. The results of the examination were otherwise unchanged. The blood carbon dioxide level was 21 mmol per liter (reference range, 24 to 34), and the blood glucose level was 104 mg per deciliter (5.8 mmol per liter; reference range, 70 to 100 mg per deciliter [3.9 to 5.6 mmol per liter]). The anion gap and blood levels of sodium, potassium, and chloride were normal, as were the results of renal-function tests and a serum toxicology screen, which included a test for acetaminophen. Other laboratory test results are shown in Table 1.

On examination, the patient appeared tired and had marked jaundice. The temperature was 37.6°C, the pulse 90 beats per minute, the blood pressure 100/58 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% while she was breathing ambient air. Conjunctival icterus was present. The abdomen was soft, with mild epigastric tenderness; abdominal guarding, rebound tenderness, and Murphy's sign were absent. There was a 1.5-cm laceration on the chin. The remainder of the physical examination was normal. Examination of a peripheral-blood smear revealed smudge cells, burr cells, basophilic stippling, rouleaux formation, dysplastic neutrophils, and 1+ polychromasia. The anion gap, venous blood-gas measurements, and results of renal-function tests were normal, as were blood levels of sodium, potassium, chloride, carbon dioxide, magnesium, glucose, amylase, lipase, and fibrinogen; additional laboratory test results are shown in Table 1. Testing for urinary human chorionic gonadotropin was negative. A serum toxicology screen was negative, and a urine toxicology screen was positive for opiates and negative for all other analytes. Urinalysis revealed slightly cloudy, amber-colored urine with a specific gravity of 1.019, a pH of 6.0, 2+ bilirubin, 2+ urobilinogen, and 1+ occult blood by dipstick; there were 0 to 2 white cells and 0 to 2 red cells per high-power field. An electrocardiogram showed sinus tachycardia.

Doppler ultrasonography of the abdomen revealed persistent evidence of wall edema and intraluminal sludge in the gallbladder. Murphy's sign was absent, although this finding was not reliable because of the prior delivery because of unspecified abnormal laboratory test results. Her medications were albuterol as needed, azithromycin, and promethazine–dextromethorphan syrup; she did not take herbal remedies or supplements and had no known allergies. Immunizations were reportedly current.

Six weeks before this presentation, the patient had moved to an urban area of New England where she currently lived with her daughter, boyfriend, and boyfriend's parents. She was of Southeast Asian descent and had been born in the United States. She did not smoke tobacco, use illicit drugs, or drink alcohol. A grandmother had unspecified liver disease.

In the emergency department, the patient reported that the abdominal pain and light-headedness had resolved and the nausea had decreased. She recalled that during the past several days, her gums had bled easily when she brushed her teeth and her urine had been tea-colored. She had a history of mild asthma. Eleven weeks earlier, she had given birth to her first child; after an otherwise uncomplicated pregnancy, preterm labor developed and was complicated by placental abruption, and vaginal delivery occurred at 32 weeks of gestation. The patient reported that she had remained in the hospital for 1 week after delivery because of unspecified abnormal labor.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Other Hospital</th>
<th>On Presentation, Other Hospital</th>
<th>Reference Range, This Hospital†</th>
<th>On Presentation, This Hospital</th>
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</thead>
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<td>Hematocrit (%)</td>
<td>36–48</td>
<td>19.6</td>
<td>36.0–46.0</td>
<td>23.4</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.0–15.8</td>
<td>6.4</td>
<td>12.0–16.0</td>
<td>7.9</td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>4.8–11.2</td>
<td>10.1</td>
<td>4.5–13.0</td>
<td>11.1</td>
</tr>
<tr>
<td>Differential count (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>45–85</td>
<td>72</td>
<td>40–62</td>
<td>77</td>
</tr>
<tr>
<td>Band forms</td>
<td>0–8</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>15–45</td>
<td>10</td>
<td>27–40</td>
<td>9</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0–12</td>
<td>6</td>
<td>4–11</td>
<td>10</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0–7</td>
<td>1</td>
<td>0–8</td>
<td>1</td>
</tr>
<tr>
<td>Myelocytes</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count (per mm³)</td>
<td>150,000–400,000</td>
<td>140,000</td>
<td>150,000–400,000</td>
<td>175,000</td>
</tr>
<tr>
<td>Red-cell count (per mm³)</td>
<td>3,600,000–5,400,000</td>
<td>1,720,000</td>
<td>4,000,000–5,200,000</td>
<td>2,210,000</td>
</tr>
<tr>
<td>Nucleated red-cell count (per 100 white cells)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Mean corpuscular volume (fl)</td>
<td>82–98</td>
<td>113.8</td>
<td>80.0–100.0</td>
<td>105.9</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin (pg/red cell)</td>
<td>27.0–35.0</td>
<td>37.4</td>
<td>26.0–34.0</td>
<td>35.7</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration (g/dl)</td>
<td>32.0–37.0</td>
<td>32.9</td>
<td>31.0–37.0</td>
<td>33.8</td>
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<tr>
<td>Red-cell distribution width (%)</td>
<td>9.0–17.9</td>
<td>22.1</td>
<td>11.5–14.5</td>
<td>24.4</td>
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<tr>
<td>Direct antiglobulin test</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td></td>
<td>11.0–14.0</td>
<td>24.5</td>
<td></td>
</tr>
<tr>
<td>Prothrombin-time international normalized ratio</td>
<td>0.9–1.1</td>
<td>2.6</td>
<td>0.9–1.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Activated partial-thromboplastin time (sec)</td>
<td></td>
<td>22.0–35.0</td>
<td>43.4</td>
<td></td>
</tr>
<tr>
<td>D-Dimer (ng/ml)</td>
<td></td>
<td>&lt;500</td>
<td>591</td>
<td></td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.7–10.5</td>
<td>7.2</td>
<td>8.5–10.5</td>
<td>7.2</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td></td>
<td>2.6–4.5</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>6.4–8.6</td>
<td>5.5</td>
<td>6.0–8.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.4–4.8</td>
<td>2.1</td>
<td>3.3–5.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Globulin (g/dl)</td>
<td></td>
<td>1.9–4.1</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase (U/liter)</td>
<td>0–45</td>
<td>20</td>
<td>7–33</td>
<td>24</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/liter)</td>
<td>0–40</td>
<td>152</td>
<td>9–32</td>
<td>152</td>
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<tr>
<td>Alkaline phosphatase (U/liter)</td>
<td>40–150</td>
<td>22</td>
<td>15–350</td>
<td>14</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.2–1.2</td>
<td>19.7</td>
<td>0–1.0</td>
<td>26.3</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dl)</td>
<td>0–0.4</td>
<td></td>
<td>21.9</td>
<td></td>
</tr>
<tr>
<td>γ-Glutamyltransferase (U/liter)</td>
<td></td>
<td>5–36</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/liter)</td>
<td></td>
<td>110–210</td>
<td>344</td>
<td></td>
</tr>
<tr>
<td>Lactic acid (mmol/liter)</td>
<td>0.5–2.2</td>
<td>3.9</td>
<td>0.5–2.2</td>
<td>1.7</td>
</tr>
<tr>
<td>Ammonia (μmol/liter)</td>
<td></td>
<td>12–48</td>
<td>49</td>
<td></td>
</tr>
</tbody>
</table>

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*a* To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for lactic acid to milligrams per deciliter, divide by 0.1110. To convert the values for ammonia to micrograms per deciliter, divide by 0.5872.

† 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.
administration of analgesic agents. Pulsed-wave Doppler ultrasonography revealed normal arterial flow in the main hepatic artery (Fig. 1D). There was also normal hepatopetal flow in the portal veins (Fig. 1E) and hepatofugal flow in the hepatic veins (Fig. 1F).

Dr. Boscia: The administration of N-acetylcysteine was continued, and the chin laceration was
sutured. Additional laboratory tests were performed, and a diagnosis was made.

**DIFFERENTIAL DIAGNOSIS**

Dr. Kristian R. Olson: This previously healthy 18-year-old woman presented 11 weeks after the birth of her first child with evidence of worsening liver failure after a nonspecific 7-day illness. To develop a differential diagnosis, it is important to determine whether the patient’s liver dysfunction is consistent with a diagnosis of acute liver failure.

**ACUTE LIVER FAILURE**

Acute liver failure in adults is characterized by a sudden loss of hepatic function without evidence of preexisting liver disease. Criteria for the diagnosis include the presence of coagulopathy (international normalized ratio (INR), >1.5), hepatic encephalopathy, and an illness of less than 24 weeks’ duration. This patient has evidence of liver injury and an INR well above 1.5. She does not have features of encephalopathy, such as altered consciousness, compromised intellectual functioning, tremors, or asterixis, and thus she may meet only the criteria for acute liver injury. However, in the pediatric population (which can be considered to include patients who are up to 21 years of age), up to 50% of patients who present with acute liver failure do not present with encephalopathy. Modified criteria for the diagnosis of acute liver failure in children include evidence of acute liver injury and severe coagulopathy (INR, >2.0) in the absence of encephalopathy. Given this patient’s age, I would argue that she meets the criteria for acute liver failure.

A specific diagnosis is important in determining prognosis, guiding treatment, and counseling the patient’s relatives. Using data derived from several large, multicenter series involving the Pediatric Acute Liver Failure Study Group and the Acute Liver Failure Study Group, we can construct lists of recognized causes of acute liver failure in children older than 10 years of age and in adults. Because this patient is at the threshold of adulthood, we need to consider the causes in each population (Fig. 2).

This patient has nonspecific symptoms and findings on physical examination, and so it might seem futile to arrive at a specific diagnosis. However, the presence or absence of relatively elevated values on routine laboratory tests can help immensely. She has an aspartate aminotransferase level that is nearly 5 times the upper limit of the normal range, whereas the alanine aminotransferase level is not elevated at all. The direct bilirubin level is more than 26 times the

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**Figure 2. Causes of Acute Liver Failure in Children and Adults.**

Data are adapted from Lee et al.1 and Squires and Alonso. The numbers shown are percentages. Among children older than 10 years of age, Wilson’s disease accounted for 90% of metabolic disease.
upper limit of the normal range, with the majority being conjugated bilirubin (22 mg per deciliter [374.5 μmol per liter]). Cholestasis, which represents a decrease in bile flow caused by either impaired secretion of hepatocytes or obstruction, is heralded by prominent elevations in the bilirubin level and in the alkaline phosphatase or \(\gamma\)-glutamyltransferase level. Despite the direct hyperbilirubinemia in this patient, the alkaline phosphatase level is below the normal range. However, with a \(\gamma\)-glutamyltransferase level of more than 3 times the upper limit of the normal range, evidence of a cholestatic pattern remains.

**ACETAMINOPHEN EXPOSURE**

Although a serum acetaminophen level was undetectable in this patient on presentation, it is important to maintain suspicion for either inadvertent chronic ingestion or an acute one-time ingestion several days before presentation. The Rumack–Matthew nomogram, which is used to assess for potential hepatotoxicity after an acetaminophen exposure, is developed to assess only for acute, single ingestions. The prevalence of postpartum depression is approximately 10%,\(^4\) and young age and unplanned pregnancy have been identified as risk factors. Although this patient could have ingested acetaminophen 48 to 72 hours before presentation and had an undetectable level on presentation, there is no history of a psychiatric illness, which might suggest the possibility of an intentional overdose. In addition, the mechanism of acetaminophen hepatotoxicity is centrilobular necrosis, which is caused by the accumulation of \(N\)-acetyl-p-benzoquinone imine. The hallmark of liver injury is markedly elevated aminotransferase levels, which are usually in the thousands and frequently 400 times the upper limit of the normal range. This biochemical feature is not consistent with this patient’s laboratory test results. However, she received treatment with \(N\)-acetylcysteine, which results in increased survival even among patients with acute liver failure that is unrelated to acetaminophen exposure.\(^5\)

**DRUG-INDUCED LIVER INJURY**

Idiosyncratic hepatic reactions to medications other than acetaminophen and to complementary or alternative therapies are referred to as drug-induced liver injury. In adults, 11% of cases of acute liver failure are caused by drug-induced liver injury. This patient did not report use of over-the-counter medication; however, it is important to confirm that she includes dietary and nutritional supplements as over-the-counter medications. She began taking azithromycin and promethazine–dextromethorphan 3 days before the current presentation. Antimicrobial therapy is the most frequent cause of drug-induced liver injury, and in particular, the incidence of azithromycin-associated hepatic injury is increasing. Drug-induced liver injury affects women in 72% of cases and results in hepatocellular injury in 61% of cases.\(^6\) A cholestatic pattern can arise but typically does so 1 to 3 weeks after the patient has started a new medication. In addition, eosinophilia and fever are typical features of drug-induced liver injury that are not present in this patient. Furthermore, the time between the initiation of azithromycin therapy and the development of acute liver failure in this patient was only a few days, which makes the diagnosis of drug-induced liver injury unlikely.

**PREGNANCY**

During pregnancy, dilutional hypoalbuminemia and elevation of the placental-derived alkaline phosphatase level can lead providers to falsely assume that the patient has liver disease. However, the elevations of the aspartate aminotransferase level, INR, and \(\gamma\)-glutamyltransferase level in this patient are uniformly abnormal. Eclampsia affects 2 to 8% of pregnant women and can occur up to 6 weeks post partum, but this patient’s symptoms developed later. Furthermore, in pregnant women, the aminotransferase levels are typically 10 to 20 times the upper limit of the normal range and the bilirubin level is typically less than 5 mg per deciliter (85.5 μmol per liter); also, the alkaline phosphatase level in this patient is higher than would be expected during pregnancy. The HELLP syndrome (hemolysis, elevated liver enzyme levels, and a low platelet count) occurs in less than 1% of pregnant women, and a low platelet count occurs in less than 1% of pregnant women, and only one third of cases occur after delivery.\(^7\) In this case, examination of a peripheral-blood smear did not reveal typical features of hemolysis, although the presence of indirect hyperbilirubinemia may suggest a hemolytic process. However, the patient’s platelet count was normal, and thus
the diagnosis of the HELLP syndrome is unlikely.

**ISCHEMIC HEPATOPATHY**

Although the patient had hypotension when the EMS team arrived, the hemodynamic insult in ischemic hepatopathy is normally present well before evidence of liver injury. In addition, the typical biochemical profile of ischemic hepatopathy includes a dramatic rise in aminotransferase and lactate dehydrogenase levels and normal or only mildly abnormal hepatic synthetic function. The Budd–Chiari syndrome, or hepatic venous outflow obstruction, is another consideration because the pooled prevalence during pregnancy and the puerperium is approximately 6.8%. However, acute liver failure develops in less than 5% of patients with the Budd–Chiari syndrome. In addition, although the aminotransferase levels may be only moderately elevated (as in this patient), the bilirubin level is seldom higher than 7 mg per deciliter (119.7 μmol per liter), whereas the bilirubin level in this patient is higher than 20 mg per deciliter (342.0 μmol per liter). This patient also had a normal vascular Doppler ultrasound evaluation, which rules out the diagnosis of the Budd–Chiari syndrome.

**VIRAL INFECTION**

Viral hepatitis is the cause of acute liver failure in 10% of cases in developed countries. It is interesting to note that this patient’s grandmother had “unspecified liver disease” and that the patient is of Southeast Asian descent. In the United States, the rate of chronic hepatitis B virus infection is 6% among pregnant women of Asian descent versus only 0.6% among pregnant white women. An exacerbation of hepatopathy can occur as the result of the relative immunosuppression associated with pregnancy. However, if this patient received prenatal care, she would have been screened for hepatitis B virus. In addition, she had no fever and few risk factors for acute hepatitis B virus infection, and viral hepatitis typically results in aminotransferase levels that are more than 25 times the upper limit of the normal range.

**AUTOIMMUNE HEPATITIS**

Autoimmune hepatitis is a chronic, progressive disorder, but it can also cause acute liver failure. Patients with autoimmune hepatitis typically present with nonspecific symptoms, including fatigue, lethargy, malaise, anorexia, nausea, abdominal pain, and itching. Symptoms may first become evident during pregnancy, and postpartum exacerbations do occur. However, some features of autoimmune hepatitis are absent in this patient, including coexisting autoimmune conditions, associated small-joint arthralgias, and the typical pattern of markedly elevated aminotransferase levels. In addition, she does not have elevated globulin levels (which typically correlate with IgG levels, even in the setting of acute liver failure). Given that the patient is female and her ratio of alkaline phosphatase (IU per liter) to aspartate aminotransferase (IU per liter) is lower than 1.5, her globulin level is not elevated, and there is no evidence of illicit-drug or excessive alcohol use, we can calculate that she has a score on the scoring system of the International Autoimmune Hepatitis Group of 7 (on a scale ranging from –20 to 31, with a score of 10 to 15 indicating probable autoimmune hepatitis and a score higher than 15 indicating definite autoimmune hepatitis). Although the information we are given at this point is inadequate to allow us to completely calculate the score and definitively rule out the possibility of autoimmune hepatitis, it makes this diagnosis unlikely.

**WILSON’S DISEASE**

Wilson’s disease, also known as hepatolenticular degeneration, is an autosomal recessive disease characterized by impaired copper metabolism due to a defective ATPase. The mean age at onset ranges from 12 to 23 years, and this patient’s age falls within that range. Patients with Wilson’s disease may present with chronic liver disease, acute liver failure, hemolysis, and psychiatric or neurologic manifestations. The Leipzig criteria for Wilson’s disease might be helpful in determining the diagnosis in this patient, but we are not given the results of biochemical tests for copper or genetic testing.

Fortunately, rapid diagnostic criteria for Wilson’s disease can be used in patients who present with acute liver failure. A screen that shows a ratio of alkaline phosphatase (IU per liter) to total bilirubin (mg per deciliter) of lower than 4.0 and then subsequently shows a ratio of aspartate aminotransferase (IU per liter) to alanine
aminotransferase (IU per liter) of higher than 2.2 has been described as 100% sensitive and specific for the diagnosis of Wilson's disease. According to these criteria, this patient has a presumptive diagnosis of Wilson's disease. Furthermore, patients with acute liver failure who have Wilson's disease have a median alkaline phosphatase level of 20.5 U per liter, as compared with a median level of 146.5 U per liter among patients with acute liver failure who do not have Wilson's disease. This patient's alkaline phosphatase level was 22.0 U per liter.

In Wilson's disease, acute liver failure develops in the setting of subclinical chronic liver disease. If liver transplantation is not performed, acute liver failure due to Wilson's disease is fatal. I believe that serum copper and 24-hour urinary copper levels were most likely obtained to confirm the diagnosis of Wilson's disease in this patient and that, if she survived, she underwent liver transplantation.

Dr. Virginia M. Pierce (Pathology): Dr. Schaefer, what was your impression when you evaluated this patient?

Dr. Esperance A. Schaefer: The hepatology service was consulted after the patient's arrival at the emergency department. The pattern of liver injury — including minimal elevation of aminotransferase levels, marked hyperbilirubinemia, and a low-to-normal alkaline phosphatase level — did not fit neatly into a hepatocellular or cholestatic pattern. These biochemical findings, combined with the parenchymal changes observed on ultrasonography, suggested preexisting chronic liver disease with superimposed acute liver injury.

Given that this patient was taking azithromycin, we considered the diagnosis of drug-induced liver injury. However, several clinical features in this case strongly suggested an alternative diagnosis. The patient's age, sex, possible hemo-lytic anemia, and low alkaline phosphatase level raised strong clinical suspicion for Wilson's disease. We used the rapid diagnostic criteria for Wilson's disease, and the ratio of alkaline phosphatase to total bilirubin was 0.5 and the ratio of aspartate aminotransferase to alanine aminotransferase was 6.3; these findings suggest that a diagnosis of Wilson's disease could be made with 100% sensitivity and specificity. It has been previously noted that viral infection or drug toxicity may serve as a trigger for fulminating Wilson's disease. In this patient, therefore, either the antecedent illness or treatment with azithromycin may have played a role.

The revised Wilson's disease prognostic index is highly accurate in predicting death due to fulminant Wilson's disease in both children and adults. A score higher than 11 portends death if the patient does not undergo transplantation, and in this patient, the score was 14. Given the patient's vanishingly low likelihood of survival, we recommended admission to the intensive care unit (ICU) and immediate evaluation for orthotopic liver transplantation.

After the patient was admitted to the ICU, the 24-hour urinary copper level was obtained. She underwent a slit-lamp examination, and there was no evidence of Kayser–Fleischer rings. Because she had intact renal function, chelation therapy with penicillamine was initiated to promote urinary copper excretion as a bridging measure while she awaited transplantation.

During hospital days 2 through 4, additional testing was performed. The patient's serum copper level was normal (0.96 μg per milliliter [15.1 μmol per liter]; reference range, 0.75 to 1.45 [11.8 to 22.8 μmol per liter]), her ceruloplasmin level was low (8 mg per milliliter; reference range, 20 to 60), and her 24-hour urinary copper level was markedly elevated (1419 μg per specimen; reference range, 15 to 60). Her coagulopathy worsened, and confusion and hyperammonemia developed. Shortly after the patient was placed on the liver transplantation list, a donor was identified, and the patient underwent orthotopic liver transplantation that day.

Clinical Diagnosis
Fulminant hepatic failure due to Wilson's disease.

Dr. Kristian R. Olson's Diagnosis
Wilson's disease (hepatolenticular degeneration).

Pathological Discussion
On examination of the explanted liver, the cut surface was mottled and had a subtle nodular appearance, with scattered regenerative nodules that varied in color from...
Figure 3. Explanted Liver.

A photograph of the cut surface of the liver shows a mottled appearance, with several regenerative nodules that vary in color from tannish-brown to yellow (Panel A). Hematoxylin and eosin staining shows that the parenchyma has a nodular appearance and widespread inflammation (Panel B). At higher magnification, the hepatocytes have relatively abundant eosinophilic cytoplasm and cytoplasmic vacuolization at the periphery of the cell (Panel C). Several central veins have endophlebitis, with mononuclear infiltrates in the endothelium of the veins (Panel D). A trichrome stain for collagen highlights a portal tract with pale, bluish-gray septa that are indicative of collapse and fibrosis (Panel E). A rhodanine stain for copper shows copper deposition (reddish granules) in hepatocytes in a nodule (Panel F).
tannish-brown to yellow (Fig. 3A). On microscopic examination, the parenchyma was nodular and had moderate inflammation, and some nodules were steatotic (Fig. 3B). At higher magnification, the hepatocytes had abundant eosinophilic cytoplasm, and many of them showed vacuolization of the cytoplasm (Fig. 3C). Portal tracts showed mononuclear inflammation and occasional plasma cells. Several hepatic veins showed endophlebitis, with mononuclear cells infiltrating the endothelium (Fig. 3D); this particular feature has been described only rarely in Wilson’s disease.18 A trichrome stain highlighted septa, which did not have the dense, blue staining typical of established cirrhosis but rather had pale, bluish-gray staining, which is suggestive of fibrosis and collapse (Fig. 3E). A rhodanine stain for copper was performed, and copper was identified in hepatocytes in a few nodules (Fig. 3F). The pathological diagnosis of Wilson’s disease is generally based on the presence of compatible histomorphologic features and results of staining for copper, including a rhodanine stain. However, staining for copper in tissue is unreliable, since the presence of copper in the cytoplasm of hepatocytes might not be detected on a rhodanine stain.19 Therefore, in patients with suspected Wilson’s disease, copper quantification performed on either a dedicated core-biopsy specimen or a paraffin-embedded tissue sample is considered to be the best available diagnostic test.20 A value of 30 μg per gram of dry weight is normal, and a diagnosis of Wilson’s disease is highly likely when the value exceeds 250 μg per gram. In this case, copper quantification was performed on a formalin-fixed, paraffin-embedded tissue sample from the explanted liver, and a value of 978 μg per gram was obtained, confirming the diagnosis of Wilson’s disease.

MANAGEMENT AND FOLLOW-UP

Dr. Nahel Elias: Identifying the cause of acute liver failure in this patient was critical in determining her place on the liver transplantation list.21 In this country, the highest priority (United Network for Organ Sharing status 1A) is reserved for patients with liver failure who have a life expectancy of less than 7 days if they do not undergo transplantation.22 Wilson’s disease is the only cause of acute liver failure that allows a patient with preexisting liver disease to be listed as status 1A. Therefore, making this diagnosis is essential, as was shown in this case.

This patient received a good-quality liver donated from a deceased 23-year-old man who had been declared brain dead because of penetrating head trauma and hemorrhagic shock. We performed liver transplantation with the use of the “piggyback” technique, in which the surgeon performs hepatectomy with preservation of the inferior vena cava and then performs anastomosis to attach the donor’s suprahepatic inferior vena cava to the recipient’s inferior vena cava at the level of the hepatic veins. The graft cold ischemic time was 5 hours, and the graft warm ischemic time was 27 minutes. Total blood loss was 800 ml. The patient was extubated on day 1 after transplantation and transferred to the inpatient transplant unit the following day. She received maintenance therapy with a triple immunosuppression regimen (tacrolimus, mycophenolate mofetil, and prednisone) and was discharged home on day 9 after transplantation.

Since the transplantation, the patient has done well, with the exception of three episodes of allograft dysfunction; the first was relatively minor and occurred during an upper respiratory tract infection, and the second and third were due to acute rejection during the administration of subtherapeutic tacrolimus levels 11 and 15 months after transplantation. The two episodes of rejection resolved after treatment with intravenous methylprednisolone and an increase in immunosuppression maintenance therapy. The outcomes associated with liver transplantation for acute liver failure induced by Wilson’s disease are excellent, if transplantation is performed prior to neurologic deterioration.23-25

ANATOMICAL DIAGNOSIS

Fulminant hepatic failure due to Wilson’s disease.

This case was presented at the Internal Medicine Case Conference.

No potential conflict of interest relevant to this article was reported.

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


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CLINICAL PROBLEM-SOLVING

Appearing in the first issue of each month, this Journal feature presents particulars about real patients in stages to experts, who respond to the information, sharing their clinical reasoning with the reader.
A 41-year-old man with a weight of 159 kg and a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 49.1 presented for consideration of bariatric surgery. He had been morbidly obese since childhood; he had tried several commercial weight-loss programs in addition to dieting on his own but had had little long-term success.

Bariatric surgical procedures are a well-established approach to the treatment of morbid obesity, offering sustainable weight loss and a reduction in the risk of conditions related to obesity. Candidacy is stratified according to BMI. Adults with a BMI of 40 or higher are potential candidates for the procedure. Patients with a BMI of 35.0 to 39.9 are generally considered to be eligible if they have at least one serious coexisting condition, such as obstructive sleep apnea, type 2 diabetes, or hypertension.

The patient had a history of hyperlipidemia and had undergone cholecystectomy. His medications included rosuvastatin and ezetimibe. He had no known drug allergies. He lived with his wife and three children and worked in information technology. He was a current smoker, with a 30-year history of one to three packs per day. He had a remote history of excessive alcohol use and had been abstinent for the past 15 years. He reported no illicit drug use. He had no known family history of gastrointestinal disorders. After consultation, he decided to undergo Roux-en-Y gastric bypass.

Roux-en-Y gastric bypass is one of the most common bariatric surgical treatments for obesity. The procedure involves the creation of a small upper gastric pouch (with a capacity of approximately 30 ml), stapling of the stomach, and division of the small intestine at the proximal jejunum, with anastomosis of the distal portion (the alimentary, or Roux, limb) to the gastric pouch. The proximal end of the divided jejunum (the biliopancreatic limb) is anastomosed farther down the jejunum (Fig. 1). Pancreatic and biliary secretions come into contact with food below this anastomosis, in the “common channel” of the small intestine. Although the initial theory was that Roux-en-Y gastric bypass led to weight loss through mechanical restriction of the upper gastric pouch and a reduction in the surface area for nutrient absorption, it is now known that the surgery also causes neurohormonal changes that may influence metabolism and weight.
The patient quit smoking several months before surgery. He underwent an uncomplicated laparoscopic Roux-en-Y gastric bypass that included the creation of an 80-cm Roux limb. In the first year after surgery, he lost more than 80% of his excess weight, with his total weight declining to 83.9 kg. After that first postoperative year, the patient had some weight gain, which prompted him to resume smoking. His weight eventually stabilized at 95.3 kg (BMI, 29.4).

Some weight regain after Roux-en-Y gastric bypass is not uncommon and may result from progressive nonadherence to the prescribed diet or from anatomical changes, including dilation of the gastrojejunual anastomosis or enlargement of the gastric pouch. Gastrogastric fistula, a complication seen more commonly after open Roux-en-Y gastric bypass than after laparoscopic procedures, is another potential cause of weight regain. In this case, weight gain may occur because the channel between the gastric pouch and the excluded remnant stomach facilitates the passage of food through the previously bypassed foregut. Excessive weight regain in patients with altered anatomy may require consideration of another intervention, after appropriate steps are taken to re-educate the patient with regard to appropriate dietary choices.

Eight years after undergoing Roux-en-Y gastric bypass, the patient presented to his primary care physician with pain in the epigastric region and the left upper quadrant of the abdomen. The patient rated the pain as 5 on a scale of 1 to 10 (with higher scores indicating more severe pain), and he said that the pain was exacerbated by eating. He had no melena or hematochezia. The physical examination was notable for abdominal tenderness, without rebound or guarding. The results of a basic metabolic panel, blood count, and liver-function tests were unremarkable.

There are several potential causes of abdominal pain in patients who have undergone Roux-en-Y gastric bypass. These include internal hernias, which often occur at defects in the mesentery created at the time of bypass surgery; ulceration of the gastrojejunal anastomosis, which can result when acid injures the jejunum; cholelithiasis, which can be triggered by rapid weight loss after Roux-en-Y gastric bypass; and disorders of the remnant stomach.

Computed tomography of the abdomen revealed no evidence of an internal hernia but did show inflammation of the gastrojejunal anastomosis. An ulceration on the jejunal side of the surgical

Figure 1. Schematic Representation of Procedure for Roux-en-Y Gastric Bypass.
During Roux-en-Y gastric bypass, the gastric pouch is restricted and is anastomosed to the distal jejunum (Roux limb). The distal stomach and biliopancreatic limb of the jejunum are also anastomosed, thereby creating a common channel.
The gastrojejunal anastomosis was identified on esophagogastroduodenoscopy (Fig. 2). Suture material was removed from the site to prevent further irritation of the mucosa.

High-dose proton-pump inhibitors are the mainstay of therapy and should be initiated, and the patient’s nutrition status should also be reviewed to make sure that it will allow for adequate tissue healing. Discontinuation of smoking, avoidance of nonsteroidal antiinflammatory drugs (NSAIDs), and the removal of endoscopic sutures or staples at or near the site of marginal ulceration are associated with an increased likelihood of successful healing. With appropriate treatment, these ulcers heal in the majority of patients.

The patient was treated with 40 mg of omeprazole twice daily, but despite excellent adherence to the regimen, his abdominal pain did not abate. Sucralfate, 1 g per 10 ml administered four times per day, was added as adjunctive therapy, but serial repeat endoscopies conducted at 2-month intervals revealed that the ulcer was persistent. Within 6 months after the diagnosis of marginal ulceration, the patient suddenly began to have foul-smelling, watery diarrhea six to seven times a day, without nocturnal diarrhea. These episodes were most voluminous after meals and often had visible particulate matter that was consistent with what he had recently eaten. There were no specific dietary triggers. Episodes were associated with mild urgency but no tenesmus or fecal incontinence. The stool was pale, without melena or hematochezia, often floated, and left a residue after flushing. The patient also noted an increase in flatus and daily feculent eructation.

The symptoms are suggestive of a malabsorptive process, which is typically manifested in pale, greasy, voluminous, foul-smelling stools that float and are difficult to flush, in addition to weight loss despite adequate food intake. In this specific case a secondary osmotic diarrhea is likely, with the poorly absorbed solutes causing water retention in the bowel. Osmotic diarrhea resolves with fasting and thus does not typically occur overnight. Disorders that may cause malabsorption after Roux-en-Y gastric bypass include bacterial overgrowth in the small intestine and enteroenteric fistula; the latter limits the surface area for intestinal absorption and is also known to cause feculent eructation.

Although enteroenteric fistulas are rare and are most commonly associated with inflammatory bowel disease, ulceration causes a predisposition to their formation. Other causes of malabsorption in the general population (which can also be present after bariatric surgery) include new lactose intolerance, chronic pancreatitis, celiac disease, bile-salt deficiency, and chronic infections.

The patient did not initially pursue further evaluation, but after 4 months of persistent symptoms, including progressive generalized weakness, myalgias, and muscle cramps, he presented to the emergency department for evaluation. His weight had decreased from 95.3 kg to 72.6 kg.

This patient has chronic diarrhea, as defined by persistently loose stools for more than 4 weeks, occurring at an average of more than three times per day. His associated symptoms suggest clinically significant electrolyte abnormalities, which should be addressed expeditiously.

Biopsy of the colonic mucosa should be pursued. Normal-appearing mucosa will be observed in many processes that cause chronic diarrhea, which makes histologic examination an essential component of the evaluation. Although this examination could be accomplished by means of
flexible sigmoidoscopy, the fecal eructation is suggestive of an enteroenteric fistula, which makes colonoscopy a better choice, since it allows visualization of the entire colon. In general, upper endoscopic evaluation should be considered in patients with chronic diarrhea if the lower endoscopic evaluation is unrevealing. This recommendation is particularly appropriate in this case given the possibility of an enteroenteric fistula; if the fistula involves the upper gastrointestinal tract, it may be more easily visualized through upper endoscopy. Breath testing for small intestinal bacterial overgrowth should also be considered.

The patient's temperature was 37.0°C, pulse 97 beats per minute, blood pressure 113/69 mm Hg, respiratory rate 16 breaths per minute, and oxygen saturation 99% while he was breathing ambient air. He appeared to be chronically ill and cachectic but was not in acute distress. The oropharynx was clear, with dry mucous membranes and feculent breath. His thyroid was not palpable. The cardiac and pulmonary examinations were normal. His abdomen was nondistended, with minimal tenderness to deep palpation in the epigastrum and left upper quadrant. Excessive loose, sagging skin was noted around his midabdomen. The skin turgor in his legs was diminished. The results of neurologic and rectal examinations were unremarkable, and a stool test for guaiac was negative. The potassium level was 2.2 mmol per liter, magnesium 1.6 mg per deciliter (0.7 mmol per liter; reference range, 1.7 to 2.6 mg per deciliter [0.7 to 1.1 mmol per liter]), and phosphorus 1.5 mg per deciliter (0.5 mmol per liter; reference range, 2.4 to 4.3 mg per deciliter [0.8 to 1.4 mmol per liter]). Sodium and chloride levels were normal. The blood urea nitrogen level was 5 mg per deciliter (1.8 mmol per liter) and creatinine 0.85 mg per deciliter (75 μmol per liter). The hematocrit was 35.4%. The white-cell count and platelet count were normal. The thyrotropin level was 2.96 mIU per liter. The level of albumin was 1.5 g per deciliter, and prealbumin 9.3 mg per deciliter (reference range, 20 to 40). The erythrocyte sedimentation rate was 16 mm per hour (reference range, 0 to 13), and the C-reactive protein level 13.4 mg per liter (reference range, 0 to 5). The prothrombin time was elevated at 15.9 seconds (reference range, 12.0 to 14.4). Liver-function tests were normal. Tests for antibodies to tissue transglutaminase IgA and the human immunodeficiency virus were negative; the total IgA level was normal. Stool studies were negative for bacterial infection and for ova and parasites. The fecal fat level was elevated, and fecal leukocytes were rare.

Whereas excessive loose, sagging skin can be seen after substantial weight loss, the diminished skin turgor and dry mucous membranes in the patient indicate interstitial volume depletion. The severe hypokalemia and hypomagnesemia are consequences of his profound diarrhea. The low levels of albumin and prealbumin suggest that he is severely malnourished. His anemia may reflect poor iron absorption or could be due to gastrointestinal blood loss that was not detected on a single guaiac test. The prolongation of prothrombin time is probably due to the depletion of vitamin K–dependent coagulation factors, and the elevated level of C-reactive protein, although nonspecific, suggests inflammation. Although tissue levels of antibodies to transglutaminase IgA have high sensitivity and specificity for celiac disease in the presence of normal total IgA levels, normal findings do not definitively rule out celiac disease. However, celiac disease would not account for the feculent eructation in this patient. Fecal fat excretion can be increased in diarrheal illnesses even in the absence of fat malabsorption. The standard for the diagnosis of increased fecal fat excretion in patients with malabsorption is quantitative measurement with a biochemical assay. Normal excretion is less than 6 g per day, assuming that the patient is consuming 70 to 120 g per day of dietary fat. Collection periods of 3 days or longer increase the sensitivity of detection.

The patient was admitted to the hospital for hydration and electrolyte supplementation, diagnostic testing, and monitoring. After hydration and electrolyte repletion, a colonoscopy revealed a small area of erythema near the hepatic flexure; no other abnormalities were noted. Biopsy specimens of the colon and terminal ileum were normal. Upper endoscopy revealed normal esophageal mucosa, with marginal ulceration and severe inflammation at the gastrojejunal anastomosis; when pressure was exerted on one of the areas of inflamma-
tion, the endoscope passed through a fistulous tract, terminating in the transverse colon.

The endoscopy revealed an enteroenteric fistula. Symptoms vary depending on the location of the fistula and the extent of the bowel that is bypassed. Enteric fistulas in which only a short segment of the bowel is circumvented may be asymptomatic. Conversely, fistulas that bypass a larger segment of the bowel typically cause diarrhea but may also be associated with weight loss or abdominal pain. Gastrocolic fistula is a well-recognized but rare complication of peptic ulcer disease, stomach and colon cancer, Crohn’s disease, and surgical procedures. The combination of feculent eructation and vomiting, diarrhea, and malnutrition is the classic symptom complex.

An upper gastrointestinal series showed contrast material traversing the gastric pouch into a fistulous tract that terminated in the transverse colon. The contrast material did not pass into the small bowel or the proximal large bowel (Fig. 3).

These findings confirm the diagnosis of a gastrocolic fistula and also help to delineate the anatomy of the gastrointestinal tract. Although surgical repair is indicated, the patient’s poor nutritional status makes him a poor candidate for such a procedure.

Total parenteral nutrition was provided for 8 weeks before the endoscopic removal of the gastrocolic fistula and the revision of the gastrojejunal anastomosis and gastric pouch. After surgery, the patient began to have normal formed bowel movements and transitioned back to oral nutrition. Complete resolution of the fistulous connection was confirmed on a repeat upper gastrointestinal series. At follow-up 5 months after surgery, the patient had returned to a weight of 95.3 kg.

Commentary
This patient initially presented with abdominal pain, for which the differential diagnosis was broad given his history of gastric bypass surgery. The marginal ulceration identified at that time failed to heal and was eventually complicated by a profound malabsorptive diarrhea, with resultant dehydration. Although dumping syndrome and bacterial overgrowth in the small intestine are common causes of diarrhea after gastric by-
pass, other causes, including enterocentric fistula, must be considered in this patient population, especially when fecal eructation is present. These patients should therefore undergo anatomic evaluation before their symptoms are attributed to the more common causes. In this case, a full diagnostic workup ultimately led to the diagnosis of gastrocolic fistula.

The increasing prevalence of severe obesity and associated conditions has resulted in a substantial increase in the number of bariatric procedures performed. Roux-en-Y gastric bypass is one of the most commonly performed weight-loss surgeries. Outcomes of bariatric procedures have improved substantially in the past decade, but complications can occur; vigilance and thorough assessment of patients presenting with symptoms is required.

The cause of marginal ulceration is usually multifactorial. Poor perfusion of local tissue is believed to contribute to the occurrence of ulcers, which can also be caused by excessive acid exposure in the gastric pouch; analysis of a consecutive series of patients suggests that foreign materials (e.g., sutures or staples), a history of smoking, and the use of NSAIDs are associated with an increased incidence of marginal ulceration. The potential role of Helicobacter pylori infection as a predisposing factor remains controversial.

Retrospective data support the view that the majority of patients with marginal ulcerations have a response to medical therapy with high doses of proton-pump inhibitors and sucralfate; the addition of sucralfate has been recommended in patients who are already taking a proton-pump inhibitor at the time of diagnosis. In addition, smoking cessation and indefinite discontinuation of NSAIDs are recommended. The removal of foreign material and testing for H. pylori (as well as treatment, if test results are positive) should also be considered. The use of endoscopic suturing to oversew the ulceration has been proposed in the treatment of recalcitrant marginal ulceration, but more information regarding efficacy and durability is needed.

Fistulous complications have also been reported after Roux-en-Y gastric bypass and are often associated with a chronic leak from the surgical anastomosis or with a marginal ulcer that does not heal. Gastrogastric fistulas—which occur when a channel develops between the gastric pouch and the excluded stomach remnant and allows ingested food to enter the bypassed foregut—are most commonly associated with Roux-en-Y gastric bypass procedures that are performed with an open approach, although fistulas may also occur after laparoscopic procedures. Gastrocolic fistulas are a rare complication of the formation of a gastrojejunostomy and are typically initiated by ulceration at the site of the anastomosis. This type of fistula formation has been reported as late as 20 years after the surgical Roux-en-Y gastric bypass has been performed. Depending on the size and location of the fistula, consideration of endoscopic closure (including endoscopic suturing or over-the-scope clips) or surgical closure should be considered. In rare instances, other types of fistulas have been reported after gastric bypass surgery, including gastrobronchial, gastropericardial, and jejunal fistulas.

The current case underscores the importance of considering late complications of bariatric surgery as causes of new symptoms in patients who have had this surgery. Although gastrocolic fistula is an uncommon complication of Roux-en-Y gastric bypass, the combination of malabsorptive diarrhea, fecal eructation, and previous marginal ulceration provided important clues that pointed to this complication.

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

Back to the History

Mary W. Montgomery, M.D., Sigal Yawetz, M.D., Bruce D. Levy, M.D., and Joseph Loscalzo, M.D., Ph.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, sharing his or her reasoning with the reader (regular type). The authors’ commentary follows.

An 82-year-old man presented to the emergency department with a 6-month history of worsening back and left hip pain. He had been well until 6 months earlier, when acute fever and cough developed. Pneumonia was diagnosed, and a 10-day course of levofloxacin was prescribed. His respiratory symptoms resolved. At about the same time that the respiratory symptoms resolved, low back pain began to develop. The patient did not recall any antecedent trauma, fall, or heavy lifting. Over the course of the ensuing months, his back pain continued to worsen, and left hip pain developed; he presented to the emergency department after walking became painful. The pain did not radiate down his legs, but it occasionally woke him from sleep and was worse after activity. He reported no relief from bending forward. He reported no morning stiffness, fever, chills, or night sweats. He noted that he had lost 9 kg (20 lb) of weight over the course of the preceding few months. He had no bowel or bladder incontinence.

This patient has chronic (duration of >12 weeks) back pain. Demographic and clinical features, including age, the presence of constitutional symptoms, pain awakening him from sleep, and persistence and worsening of the pain, indicate the need for imaging. This history arouses concern for an underlying systemic illness, such as metastatic cancer, a systemic infection, or an autoimmune process. Polymyalgia rheumatica can cause hip pain and systemic symptoms such as weight loss, but it is associated with morning stiffness, particularly in the shoulders and hips.

The patient’s medical history included the sick sinus syndrome for which a pacemaker had been placed years earlier, diastolic heart failure, pulmonary fibrosis, hyperlipidemia, hypertension, gout, herpes zoster with postherpetic neuralgia, and basal-cell carcinoma for which the patient underwent Mohs micrographic surgery. His medications included allopurinol, aspirin, metoprolol, simvastatin, gabapentin, and recently, oxycodone and acetaminophen for the low back pain. He had no known drug allergies. He was retired but had worked previously as a university professor. He lived with his wife and had grown children. He had smoked cigars for many years but had quit 28 years before the current presentation. He reported drinking one glass of alcohol per night until 6 months before this presentation, when his current illness began. He reported no history of illicit-drug use. He had traveled internationally in the distant past, including trips to Asia and South America, and had traveled throughout the United States. His family history was notable for congestive heart failure in his mother, coronary heart disease in his father, and non-Hodgkin’s lymphoma in his brother.
The most important risk factor for metastatic cancer to the spine is a personal history of cancer. The patient has a history of basal-cell carcinoma, but this type of cancer rarely causes distant metastases and is unlikely to be related to his current presentation. He has a remote smoking history, which puts him at risk for lung cancer. His age is a risk factor for prostate cancer, which can metastasize to the vertebrae. He has had no recent device implantation, surgery, or trauma that could have introduced infection. His previous travel to Asia and South America could put him at risk for tuberculous spondylitis.

On physical examination, he appeared to be in no acute distress. His temperature was 37.1°C (98.7°F), the blood pressure 110/60 mm Hg, the pulse 60 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 98% while he was breathing ambient air. The oropharynx was clear, without thrush or oral ulcerations. The lungs were clear to auscultation. A cardiovascular examination revealed a regular rate and rhythm without murmurs, rubs, or gallops. A pacemaker generator was palpated over the left pectoralis muscle, and no erythema, fluctuance, or tenderness was noted. The abdomen was soft and nontender, with normal bowel sounds and without hepatosplenomegaly. There was no palpable cervical, axillary, or inguinal lymphadenopathy. A neurologic examination revealed that the patient was oriented to person, place, and time. Cranial nerves II to XII were normal. He had no muscle wasting in his legs, and the muscle strength in his legs was 5/5 both proximally and distally. The patellar reflexes were slightly diminished in both knees. A sensory examination showed that sensations to light touch and vibration were intact. No saddle anesthesia was present, and the rectal tone was normal. He had no point tenderness over any portion of his spine or his sacroiliac joints. The straight-leg raising maneuver revealed no radicular symptoms in either leg. A bilateral hip examination, including flexion, internal rotation, and external rotation, was normal. No Janeway lesions or Osler nodes were present.

The patient has no neurologic deficits to suggest spinal cord compression or the cauda equina syndrome. The negative results of the straight-leg raising test make lumbar sacral radiculopathy unlikely. The absence of focal spinal tenderness does not rule out vertebral osteomyelitis since only one quarter of patients with vertebral osteomyelitis present with this finding. Focal tenderness on examination can also be absent in early metastatic spinal disease. Spondyloarthropathy is unlikely, given his age, the normal hip examination, and his history of worsening pain with activity (rather than with rest).

The white-cell count was 8000 per cubic millimeter, with 87% neutrophils, 8% lymphocytes, 2% monocytes, and 0% eosinophils. The hematocrit level was 39.1%, and the platelet count was 231,000 per cubic millimeter. A comprehensive metabolic panel and coagulation studies were normal. The erythrocyte sedimentation rate was 64 mm per hour, and the C-reactive protein level was 47.9 mg per liter (normal range, 1 to 3).

The elevations in erythrocyte sedimentation rate and C-reactive protein are of concern and suggest an inflammatory, infectious, or neoplastic cause of the back pain. These tests have high sensitivity in vertebral osteomyelitis and spinal metastatic disease but are nonspecific. The normal white-cell count does not rule out vertebral osteomyelitis, since more than one third of patients with this condition present without leukocytosis. When systemic disease is suspected, as in this case, the preferred imaging method is magnetic resonance imaging (MRI), unless a contraindication exists. Pacemakers are a relative contraindication to MRI, although some devices are MRI-compatible.

Because the patient had a pacemaker, MRI was not performed. Computed tomography (CT) of the lumbar spine with contrast enhancement revealed end-plate irregularity and destruction of the L4 and L5 vertebrae, with a surrounding left paravertebral and ventral epidural soft-tissue collection extending into the right foramen. There was no evidence of nerve-root compression (Fig. 1).

The imaging findings aroused suspicion for vertebral osteomyelitis. Involvement of two contiguous vertebrae is more consistent with osteomyelitis than with cancer. Vertebral osteomyelitis is primarily the result of hematogenous seeding, direct infection after spinal surgery, or extension from an infected adjacent tissue. The most common isolated organism is Staphylococcus aureus,
followed by gram-negative bacilli and streptococcus. Coagulase-negative staphylococci and Propionibacterium acnes are often causes of osteomyelitis after spinal surgery with fixation devices. This patient has had no recent spinal surgery; however, the history of pacemaker placement could be relevant. Persistent bacteremia from pacemaker lead infections with nonvirulent organisms, such as coagulase-negative staphylococci, can lead to vertebral osteomyelitis that manifests subacutely.

Given the CT findings, more thorough travel and dietary histories were obtained to assess the patient’s epidemiologic risk for atypical causes of vertebral osteomyelitis. The patient’s travel history included trips to Thailand, Malaysia, Venezuela, Belize, Nicaragua, Australia, and New Zealand, as well as locations throughout the United States. He resided in Boston during the summer and spent the winters in Arizona, which is where he was residing when the back pain first developed 6 months earlier. He had never worked or lived on a farm and did not consume unpasteurized dairy products.

His extensive travel history broadens the differential diagnosis to include infection with Mycobacterium tuberculosis and infection with brucella species, both of which may manifest subacutely. This patient reports no exposure to livestock or to unpasteurized dairy products, which makes the diagnosis of brucellosis unlikely. Other possibilities include infection with endemic fungi, such as Cryptococcus neoformans, Histoplasma capsulatum, Blastomyces dermatitidis, or Coccidioides immitis. Rare cases of vertebral osteomyelitis have also been reported with Burkholderia pseudomallei, the causative agent of melioidosis, which is endemic to parts of Australia and Southeast Asia.

Overall, the patient appears well, without any neurologic deficits, so there is no immediate need for surgical intervention or empirical antibiotics. A definitive diagnosis determined by laboratory evaluation, including blood cultures, followed by aspiration biopsy if the blood cultures are negative, should be pursued before therapy is initiated.

Testing for human immunodeficiency virus (HIV) antibody was negative. The prostate-specific antigen level was 0.7 ng per milliliter (reference range, 0 to 4). The blood level of angiotensin-converting enzyme was normal. Three sets of blood cultures were negative. Chest radiography showed multiple calcified mediastinal and hilar lymph nodes. CT of the chest confirmed this finding and also showed parenchymal scarring in the right upper lobe and a trace pleural effusion on the right side (Fig. 2).

The patient has extensive calcified mediastinal lymph nodes, a finding that is suggestive of previous granulomatous disease. Disease processes that can lead to calcification include tuberculosis, histoplasmosis, coccidioidomycosis, and sarcoid-
Sarcoidosis and histoplasmosis are rare causes of vertebral osteomyelitis; therefore, tuberculosis and coccidioidomycosis are the more likely diagnoses.

A purified protein derivative skin test was negative. A test for urinary *Histoplasma capsulatum* antigen was negative. Antibiotics were not initiated, and the patient underwent CT-guided L4–L5 disc aspiration and core-needle biopsy. Fluid could not be aspirated on the initial attempt; 2 to 3 cc of sterile saline were injected and reaspirated. This sample and two core bone-biopsy specimens were sent for culture and histopathological examination. The results of initial staining for bacteria, fungi, and acid-fast bacilli were negative. The core bone-biopsy specimens were sent to the state laboratory to test for *M. tuberculosis* by means of a polymerase-chain-reaction assay; the results were negative.

Pathological analysis of the vertebral disk-biopsy specimens revealed chronic granulomatous inflammation with giant cells, plasma cells, and necrotic bone, as well as round, thick-walled, nonbudding fungal forms that were 15 to 25 μm in diameter, as best seen on fungal stain (Fig. 3). A fungal culture grew mold, which was identified as *C. immitis*. Serologic testing for coccidioidal antibodies was positive. The complement-fixing antibody titer was 1:64. The patient was offered initial treatment with amphotericin, but he declined this intravenous therapy and was instead started on oral itraconazole. Because he had side effects with itraconazole, he was switched to high-dose fluconazole. Six months later, he had progression of his coexisting conditions and chose to discontinue the antifungal therapy; he died after transitioning to hospice care.

**COMMENTARY**

Coccidioidomycosis, which is caused by the fungi *C. immitis* and *C. posadasii*, is endemic to the southwestern United States. Infections occur after the inhalation of spores. The majority of infections are acquired in southern Arizona (as was probably the case with this patient), central California, New Mexico, and Texas.

Up to two thirds of persons with coccidioidomycosis have an asymptomatic or mild illness and do not present for medical care. Of persons who seek care, the majority present with a self-limited subacute pulmonary process or flulike illness, often referred to as valley fever. Many patients have evidence of infiltrates on chest imaging, which makes it difficult to differentiate valley fever from community-acquired pneumonia. In endemic regions, coccidioidomycosis accounts for up to one quarter of the cases of community-acquired pneumonia. This patient had a history of pneumonia that antedated the development of back pain; in retrospect, his respiratory symptoms were probably caused by coccidioidomycosis.

Most respiratory infections resolve without treatment, and extrapulmonary dissemination from the hematogenous spread of coccidioidomycosis develops in less than 0.5% of immunocompetent patients. The most common sites of
dissemination are the skin, meninges, joints, and vertebrae. Factors that increase the risk of dissemination include HIV, lymphoma, diabetes, solid-organ transplantation, pregnancy, and treatment with high-dose glucocorticoids or tumor necrosis factor inhibitors.3,4 The risk of dissemination also appears to be higher among men than among women and higher among persons of African or Filipino descent than among persons of other ethnic groups.5 Other than being male, this patient had no apparent risk factors. Older age, when adjusted for coexisting conditions, has not been associated with an increased risk of dissemination.3

Coccidioidal vertebral osteomyelitis can involve multiple vertebrae, as was the case with this patient, in whom the L4 and L5 vertebrae were affected.5 The intervertebral disk is often spared early in the course of coccidioidal vertebral osteomyelitis, as it is in the course of tuberculous osteomyelitis, and the absence of intervertebral disk involvement can help differentiate this disease from bacterial causes.6 Unlike tuberculosis, coccidioides does not cause a gibbus deformity (a form of structural kyphosis that may result from vertebral compression).5 As the disease progresses, paraspinal soft-tissue abscesses or epidural abscesses can develop and may lead to neurologic complications. Disseminated spinal coccidioidomycosis is important to recognize since it is associated with a high risk of complications and death if it remains untreated.7

Most patients present with subacute or chronic back pain and often do not have systemic signs of infection, such as fevers or night sweats.5 As a result of the indolent nature of this infection, the diagnosis is often delayed by weeks or months, as was the case with this patient. The diagnosis of disseminated coccidioidomycosis is made by the isolation of coccidioides species through culture or direct microscopy or by serologic detection of coccidioidal antibodies. Laboratory personnel should be alerted that the differential diagnosis includes coccidioidomycosis, because the inhalation of spores can lead to infection.8

Coccidioidal antibodies can be detected with the use of several techniques. In most patients, antibodies develop within 3 weeks after the onset of symptoms. Immunodiffusion kits that detect antibodies have the highest specificity (100%), and enzyme-linked immunoassays have the highest sensitivity (range, 68.5 to 100%, depending on test kit and laboratory performance).9 The IgM and IgG antibodies in most patients with coccidioidomycosis revert to negative as the illness resolves; therefore, a positive antibody test usually signifies a recent infection.9 The concentration of complement-fixing antibodies is associated with the extent of disease and can be checked during treatment to monitor the response to treatment. A titer higher than 1:16 often correlates with extrapulmonary dissemination; this
patient had a titer of 1:64. A urine coccidioides antigen enzyme immunoassay was found to have a sensitivity of 71% in patients with profound immunosuppression, although more data are needed to assess its performance in immunocompetent patients.

On the basis of limited data from case series, treatment of severe coccidioidal osteomyelitis, defined as extensive vertebral involvement, spine instability, or risk of spinal cord impingement, often consists of initial administration of amphotericin B, followed by administration of itraconazole, fluconazole, posaconazole, or voriconazole. Liposomal amphotericin B can be used as an alternative to amphotericin B in patients who are at risk for drug-induced renal toxic effects. Moderate-to-severe disease is often treated with an oral azole alone. A randomized, controlled trial that compared fluconazole with itraconazole for nonmeningeal coccidioidomycosis showed no significant difference in response rates between the two treatments; however, a subgroup analysis suggested that patients who have skeletal infections are more likely to have a response to therapy with itraconazole than to therapy with fluconazole. Adjunctive surgical débridement or stabilization is often indicated in these cases and is crucial if there is cord impingement or spine instability. The combination of medical and surgical treatment has been associated with better outcomes, including symptom relief and control of the disease, than medical therapy alone. Most cases of coccidioidal vertebral osteomyelitis require more than 1 year of antifungal treatment, and some require indefinite treatment.

This case highlights an uncommon cause of vertebral osteomyelitis that manifested as chronic low back pain in an elderly man. It is important to consider the possible presence of C. immitis in the differential diagnosis of vertebral osteomyelitis, even in areas in which coccidioidomycosis is not endemic, since patients may have previously lived in, or even briefly visited, endemic areas.

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CLINICAL PRACTICE

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.
A 79-year-old woman visits your office for routine health maintenance. She has normal daily bowel movements without rectal bleeding. Her medical history is notable for osteoarthritis but no other medical conditions. She takes nonsteroidal anti-inflammatory medication and multivitamins. Her maternal uncle received a diagnosis of colorectal cancer at 65 years of age, but she has never undergone screening for colorectal cancer. Would you advise this patient to undergo screening for colorectal cancer, and if so, which screening strategy would you recommend?

**THE CLINICAL PROBLEM**

Colorectal cancer is the third most commonly diagnosed cancer and cause of death from cancer in the United States; however, it can be detected in asymptomatic patients at a curable stage, and several randomized, controlled trials have shown lower mortality among patients who undergo screening than among those who do not. Screening can also detect precancerous polyps that can be removed during colonoscopy, thereby reducing the incidence of cancer. This review focuses on screening patients at average risk for the development of colorectal cancer.

**STRATEGIES AND EVIDENCE**

Multiple strategies are available to screen patients who are at average risk for the development of colorectal cancer, including fecal occult blood testing (with the use of guaiac-based or immunochemical tests) alone or in combination with stool DNA examination, endoscopy (flexible sigmoidoscopy or colonoscopy), radiologic examination (computed tomographic [CT] colonography), and testing for blood-based molecular markers, such as circulating methylated septin 9 gene (SEPT9) DNA. Each strategy has differing characteristics with respect to accuracy, invasiveness, interval, costs, and quality of evidence supporting its use. The advantages and disadvantages associated with each screening strategy are summarized in Table 1. Colorectal cancer screening involves not only the one-time use of a screening test, but also repeated testing over a person's lifetime (programmatic screening). In addition, if colonoscopy is not performed as the primary screening test, all other screening strategies require colonoscopy as follow-up to a positive test.
Fecal Screening Tests
Fecal screening can be divided into two broad categories: those that detect blood from ulcerated colonic mucosa resulting from cancer or large polyps and those that detect molecular markers that are shed from cancerous epithelial cells. Fecal occult blood tests include guaiac-based tests and immunochemical tests that use antibodies to detect human blood. The fecal immunochemical test (FIT) has the advantage of not requiring dietary restrictions; such restrictions are necessary with guaiac-based tests because they may be falsely positive in the presence of blood from red meat or food that reacts with the guaiac (e.g., raw horseradish, turnips, or broccoli). FIT should be performed at home on successive bowel movements; digital rectal examination in the clinic does not provide an adequate stool sample for testing. One-time FIT has been reported to have a sensitivity of 79% (95% confidence interval [CI], 69 to 86) and a specificity of 94% (95% CI, 92 to 95) for detection of cancer, and two or three samples do not significantly increase the accuracy over a single sample. However, many types of immunochemical tests are available, and their test characteristics vary widely.

High-quality evidence supports a strategy of fecal occult blood testing every year or every 2 years to screen for colorectal cancer, with colonoscopy used as follow-up to a positive test. Several randomized, controlled trials have shown up to 32% lower mortality from colorectal cancer with this strategy than with no screening, with up to 30 years of follow-up (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Although these studies used guaiac-based testing, almost all current population-based screening programs use immunochemical tests because their accuracy is greater and dietary restrictions are not required. Molecular markers including abnormal DNA from cancerous cells can be detected in stool. FIT combined with a stool DNA test (FIT-DNA) has been approved by the Food and Drug Administration (FDA) for colorectal cancer screening. One study showed that one-time FIT-DNA had a higher sensitivity for detection of colorectal cancer than one-time FIT alone (92.3% vs. 73.8%), but specificity was lower (86.6% vs. 94.9%). The screening interval differs between FIT (annual) and FIT-DNA (interval unknown, although the U.S. Preventive Services Task Force recommends 1 or 3 years), which makes a comparison of the effectiveness of programmatic screening difficult. Data from studies evaluating the colorectal cancer mortality benefit of screening FIT-DNA are lacking.

Endoscopic Screening
Flexible Sigmoidoscopy
Randomized trials have shown that screening with flexible sigmoidoscopy, followed by colonoscopy if precancerous polyps are detected, reduces colorectal cancer mortality. Although not all trials have shown a significant benefit with respect to reducing mortality (mortality benefit), the intention-to-treat analyses in several large, randomized, controlled trials have confirmed the effectiveness of one-time and periodic (every 3 to 5 years) sigmoidoscopy, with a 26 to 31% lower mortality from colorectal cancer among patients who underwent flexible sigmoidoscopy screening than among those who underwent no screening.
<table>
<thead>
<tr>
<th>Strategy and Effect on Cancer Mortality*</th>
<th>Quality of Evidence</th>
<th>Interval</th>
<th>Cost-Effectiveness‡</th>
<th>Convenience and Requirements</th>
<th>Detection of Precancerous Neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guaiac FOBT and FIT: 32% lower mortality</td>
<td>Multiple RCTs have shown a mortality benefit (reduction in mortality) for guaiac FOBT; although FIT is more accurate than guaiac FOBT, RCTs evaluating FIT are lacking</td>
<td>Annual</td>
<td>May be more effective and less expensive than no screening; total costs lower than no screening, because of the high expense of late-stage cancer treatment with biologic agents</td>
<td>Performed at home</td>
<td>Does not reliably detect precancerous neoplasia</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy: 27% lower mortality</td>
<td>RCTs have shown a mortality benefit</td>
<td>Every 5 yr</td>
<td>Cost-effective as compared with no screening and other strategies</td>
<td>Limited bowel preparation as compared with colonoscopy</td>
<td>Can detect precancerous neoplasia</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy plus FIT: 38% lower mortality</td>
<td>A single RCT showed that flexible sigmoidoscopy plus FIT reduces cancer mortality more than sigmoidoscopy alone</td>
<td>Annual (FIT) and every 10 yr (sigmoidoscopy)</td>
<td>Cost-effective as compared with no screening and other strategies</td>
<td>Strategy that combines endoscopic and stool testing</td>
<td>Can detect precancerous neoplasia</td>
</tr>
<tr>
<td>FIT-DNA: unknown effect on mortality</td>
<td>Data from studies showing a mortality benefit are lacking; studies were limited to the detection of cancer and precancerous polyps by FIT-DNA as compared with colonoscopy</td>
<td>Every 1 or 3 yr</td>
<td>Less effective and more costly than FOBT, FIT, or colonoscopy</td>
<td>Performed at home</td>
<td>Does not reliably detect precancerous neoplasia</td>
</tr>
<tr>
<td>Colonoscopy: 68% lower mortality</td>
<td>A prospective cohort study showed a mortality benefit</td>
<td>Every 10 yr</td>
<td>Cost-effective as compared with no screening and other strategies</td>
<td>Requires full bowel preparation; usually requires sedation and an escort</td>
<td>Can detect precancerous neoplasia</td>
</tr>
<tr>
<td>CT colonography: unknown effect on mortality</td>
<td>Data from studies showing a mortality benefit are lacking; studies were limited to the detection of cancer by CT colonography as compared with colonoscopy</td>
<td>Every 5 yr</td>
<td>Less effective and more costly than FOBT, FIT, or colonoscopy</td>
<td>No sedation required but requires bowel preparation</td>
<td>Can detect precancerous neoplasia</td>
</tr>
<tr>
<td>Circulating methylated SEPT9 DNA: unknown effect on mortality</td>
<td>Data from studies showing a mortality benefit are lacking; studies were limited to the detection of cancer by circulating methylated SEPT9 DNA as compared with colonoscopy</td>
<td>Unknown</td>
<td>A blood test may be associated with greater adherence than that with other screening tests</td>
<td>Unknown</td>
<td>Does not reliably detect precancerous neoplasia</td>
</tr>
</tbody>
</table>

*CT denotes computed tomography, FIT fecal immunochemical test, FIT-DNA fecal immunochemical test combined with stool DNA test, FOBT fecal occult blood test, and RCT randomized, controlled trial.
†The effect on mortality represents a comparison of the strategy with either no screening or other strategies.
‡Cost-effectiveness was determined as the cost per quality-adjusted life-year gained.
(Table S1 in the Supplementary Appendix).8-10,13,17 However, the benefit of sigmoidoscopy is limited to cancer in the distal colon (rectum, sigmoid, and descending colon), for which the reduction in mortality was reported to be 46%.17

Colonoscopy
Case-control and prospective cohort studies have estimated cancer mortality to be 68 to 88% lower among persons who undergo screening colonoscopy than among those who do not.12,17-19 A meta-analysis of observational studies showed that despite a 68% lower mortality overall, no significant mortality benefit from colonoscopy was seen compared to cancer in the proximal colon.17 This discrepancy may be explained by the quality of colonoscopy (i.e., incomplete colonoscopy, poorer bowel preparation, or more difficult polyp removal in the proximal colon) or differences in the biologic characteristics of proximal and distal colorectal cancer. The mechanism underlying the majority of colorectal cancers is chromosomal instability with early mutations in \( \text{APC} \) followed by \( \text{KRAS} \) and late mutations in \( \text{P53} \).20 Sessile serrated polyps are more commonly associated with early \( \text{KRAS} \) or \( \text{BRAF} \) mutations that may lead to chromosomal or microsatellite instability than are adenomatous polyps.21 Sessile serrated polyps are often flat or minimally raised, making them more difficult to detect than other polyps to detect by colonoscopy, and are more common in the proximal colon, which may contribute to the higher risk of proximal cancer than distal cancer after colonoscopy.22

Radiographic Tests
Published data from studies evaluating the effect of CT colonography on colorectal cancer incidence and mortality are lacking. The reported sensitivity and specificity of CT colonography to detect adenomas 1 cm in diameter or larger have ranged from 66.7 to 93.5% and from 86.0 to 97.9%, respectively.13 Because sessile serrated polyps are flat, CT colonography is inferior to colonoscopy for detection of these polyps.22 A polyp 6 mm in diameter or larger typically prompts a referral for optical colonoscopy, although the most useful size cutoff is controversial. Disadvantages of CT colonography include exposure to radiation and associated concerns regarding radiation-induced cancers and the potential need for additional testing and care for lesions outside the colon that were discovered incidentally.

Blood-Based Tests
The FDA has approved a blood-based colorectal cancer screening test that detects circulating methylated \( \text{SEPT9} \) DNA. Data from studies evaluating the colorectal cancer mortality benefit of blood-based screening are lacking. In a prospective study conducted in a screening population, in which colonoscopy was used as the reference standard, the presence of circulating methylated \( \text{SEPT9} \) DNA was shown to have a sensitivity of 48.2% (95% CI, 32.4 to 63.6), a specificity of 91.5% (95% CI, 89.7 to 93.1), a positive predictive value of 5.2% (95% CI, 3.5 to 7.5), and a negative predictive value of 99.5% (95% CI, 99.2 to 99.6) for detection of colorectal cancer.14

When to Start and Stop Screening
The U.S. Preventive Services Task Force used comparative effectiveness modeling to examine different ages at which to initiate screening. Starting screening at 45 years of age instead of 50 years could increase life-years and reduce cancer mortality but could also increase the potential harms due to the increased burden of colonoscopy; for this reason, the recommendations are to begin screening at 50 years of age in patients at average risk for colorectal cancer.23 Although the risk of colorectal cancer increases with age, the competing risk of death from other diseases and the risk of serious complications from colonoscopy also increase with age.24,25 Several national organizations recommend that screening for patients between 76 and 85 years of age should be tailored on the basis of the presence of coexisting illnesses and that screening should be stopped after patients reach 85 years of age.23,26 A microsimulation model suggested that the intensity of prior screening and the individual risk of colorectal cancer should also be considered in determining the age at which to stop screening. Patients without a notable coexisting illness who are at average or higher risk for colorectal cancer and have had no prior screening would be expected to benefit from screening into their 80s.27

Adherence
The percentage of U.S. residents with up-to-date screening for colorectal cancer has not increased
appreciably since 2010 and remains at approximately 60%.\textsuperscript{28} Currently, the percentage of U.S. adults undergoing colonoscopy screening greatly exceeds the percentage screened by fecal occult blood testing, and less than 1% undergo flexible sigmoidoscopy.\textsuperscript{27} Barriers to screening include costs, lack of knowledge of colorectal cancer and screening, underappreciation of the effect or severity of colorectal cancer, fatalism, and a perceived lack of importance or fear of screening tests.\textsuperscript{30} Costs remain a barrier despite the mandate in the Affordable Care Act that health plans cover colorectal cancer screening with no patient cost-sharing, because Medicare and other insurers impose a cost-sharing requirement when a colonoscopy is performed to evaluate a positive screening test or when a screening colonoscopy becomes a therapeutic procedure with the inclusion of polypectomy.\textsuperscript{31}

Various interventions used in randomized, controlled trials have been shown to increase patient participation in screening; such interventions include sending patients invitations from their primary care provider, sending reminder letters and making telephone calls, and mailing fecal occult blood test kits to patients’ homes. The most successful programs use patient navigators to reduce logistic barriers, address cultural issues, and encourage participants to undergo screening; the use of patient navigators is especially important in underserved populations.\textsuperscript{32,33}

The National Colorectal Cancer Roundtable has established a goal of 80% adherence to colorectal cancer screening by the year 2018. Kaiser Permanente has implemented a comprehensive strategy focused on FIT screening, with colonoscopy performed as follow-up to a positive test, and has reached and maintained the goal of 80% adherence through four rounds of screening.\textsuperscript{34} Adherence to screening tests varies among strategies, and preference of strategy varies by race and ethnic group; white participants more commonly prefer colonoscopy, and nonwhite participants tend to prefer fecal testing.\textsuperscript{30,35} To achieve the highest level of adherence to colorectal cancer screening, it may be best to provide participants a choice, because the “best” strategy is the one that they will adhere to consistently.

QUALITY OF SCREENING
Maximizing the benefit of colorectal cancer screening requires a programmatic approach to implementing screening strategies. The quality of a screening program should be measured by its ability to identify patients who are due for screening, provide access to screening, assess adherence to the screening test and to follow-up colonoscopy if a noncolonoscopy screening test is positive, document test outcomes and disseminate accurate follow-up recommendations, identify patients with a negative test to follow them for repeat screening at the appropriate intervals, and provide timely surgery for cancers. The rate of adenoma detection (the percentage of patients in whom precancerous polyps are detected during screening colonoscopy) differs substantially among endoscopists and may be used as a measure of the ability of screening to prevent colorectal cancer.\textsuperscript{36} A retrospective study showed that for every 1% increase in the rate of adenoma detection, there is a 3% decrease in the rate of cancer developing after colonoscopy.\textsuperscript{37}

HARMs AND COST-EFFECTIVENESS
The harms of noncolonoscopy screening tests are low; however, all strategies require colonoscopy as follow-up to a positive test. As a result, the programmatic harms of screening are proportional to the number of colonoscopies and in particular polypectomies that are performed over the lifetime of the screened population. The technical report from the Cancer Intervention and Surveillance Modeling Network (CISNET) Colorectal Cancer Working Group estimated the number of complications (perforations, gastrointestinal bleeding, nausea and vomiting, ileus, dehydration, abdominal pain, myocardial infarction, angina, arrhythmias, congestive heart failure, respiratory arrest, syncope, hypotension, or shock) in a population of 1000 persons screened between 50 and 75 years of age to be 14 to 15 with colonoscopy at 10-year intervals, 9 to 12 with flexible sigmoidoscopy at 5-year intervals, 9 to 10 with FIT-DNA at 3-year intervals, and 10 to 11 with annual FIT.\textsuperscript{38}

Cost-effectiveness models more than a decade ago suggested that programmatic screening with fecal occult blood testing, flexible sigmoidoscopy, or colonoscopy reduced colorectal cancer mortality at a cost society was willing to pay.\textsuperscript{39} Findings from a more recent analysis suggest that given the high expense of late-stage cancer treatment with biologic agents, FIT screening may be cost-saving, with reductions in both cancer mor-
tality and overall costs — even if one includes program support costs to increase screening uptake. Moreover, screening with colonoscopy or FIT is more effective in reducing cancer mortality and less expensive than screening with FIT-DNA or CT colonography. From an economic perspective, FIT-DNA or CT colonography should not be recommended unless screening with FIT, sigmoidoscopy, or colonoscopy has been declined.

**Patients at Elevated Risk for Colorectal Cancer**

Earlier and more frequent screening is recommended for patients at higher risk (Table S2 in the Supplementary Appendix). Patients with a first-degree relative in whom colorectal cancer developed before 60 years of age should undergo colonoscopy at 40 years of age or an age 10 years younger than the relative’s age when cancer developed, whichever is earlier.
Additional factors that might influence colorectal screening strategies include race, lifestyle factors, or aspirin use. For example, among black men and women, the rates of death from colorectal cancer are 28.4 and 18.9 per 100,000 population, respectively; among white men and women, the corresponding rates are 18.7 and 13.2 per 100,000 population.6 Obesity, tobacco smoking, low physical activity, high intake of alcohol, high intake of red or processed meat, and low intake of fruits and vegetables are associated with increased risk of colorectal cancer, and regular use of aspirin has been associated with reduced risk. However, none of these factors are currently used to differentiate screening strategy, age of screening initiation, or surveillance intervals.49

**GUIDELINES**

Several national organizations have published guidelines on strategies to reduce colorectal cancer mortality, including the National Comprehensive Cancer Network,43 the U.S. Multi-Society Task Force,50 and the American College of Gastroenterology.51 Whereas these organizations recommend certain screening strategies over others (Table 2), the 2016 U.S. Preventive Services Task Force recommendations do not support any specific testing strategy or strategies over others, but rather highlight the importance of screening patients at average risk for colorectal cancer between 50 and 75 years of age, with tailored screening for those between 76 and 85 years of age.23

**CONCLUSIONS AND RECOMMENDATIONS**

Although the patient described in the vignette is 79 years of age, she has not previously undergone screening for colorectal cancer. Because of her limited coexisting illnesses, she is expected to derive an overall benefit from a first screening for colorectal cancer, and thus I would recommend screening for this patient. I would explore her reasons for not previously pursuing screening and review with her the benefits and harms of different strategies. Because it is not feasible to summarize the entire menu of options during the span of a routine health maintenance visit, I would initially focus the discussion on colonoscopy or on annual FIT, followed by colonoscopy if the test was positive, and engage the patient in shared decision making. If she declined colonoscopy and FIT, I would discuss additional screening options, with the understanding that insurance coverage, cost-sharing, and other barriers may affect the feasibility of some options.

Dr. Inadomi reports receiving consulting fees from ChemImage. No other potential conflict of interest relevant to this article was reported.

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

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A 73-year-old woman with a history of dyspnea on exertion presents for a follow-up visit after hospitalization for acute worsening of dyspnea and orthopnea. On admission to the hospital, the patient had atrial fibrillation with a ventricular rate of 120 beats per minute, and chest radiography revealed pulmonary venous hypertension. Despite anticoagulation, rate control with a beta-blocker, and administration of loop diuretics during the hospitalization, she continues to have fatigue and exertional dyspnea. On physical examination, the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) is 39, pulse 76 beats per minute, and blood pressure 160/70 mm Hg. There is jugular venous distention and lower-extremity edema but no third heart sound, murmurs, or rales. The serum creatinine level is 1.4 mg per deciliter (124 μmol per liter), estimated glomerular filtration rate (GFR) 37 ml per minute per 1.73 m² of body-surface area, and N-terminal pro–brain natriuretic peptide (NT-proBNP) level 300 pg per milliliter (age-specific and sex-specific normal range, 10 to 218 pg per milliliter). Echocardiography reveals an ejection fraction of 70%, a normal left ventricular cavity dimension and wall thickness, and left atrial enlargement. Doppler echocardiography shows elevated left atrial pressure (E/e′ ratio, 22) and an estimated pulmonary-artery systolic pressure of 52 mm Hg. How should this patient’s condition be managed?

THE CLINICAL PROBLEM

Epidemiologic studies indicate that up to 50% of patients with heart failure have a preserved ejection fraction, and this proportion has increased over time.¹ In observational studies, rates of hospitalization and death among patients who have heart failure with a preserved ejection fraction approach those among patients who have heart failure with a reduced ejection fraction,¹ but in clinical-trial populations, outcomes are better in patients who have heart failure with a preserved ejection fraction.² Death from noncardiovascular causes is more common in patients who have heart failure with a preserved ejection fraction than in those with a reduced ejection fraction.³,⁴

Ventricular diastolic dysfunction (impaired relaxation and increased diastolic stiffness) that is present at rest or induced by stress (from exercise, tachycardia, or hypertension) is a central perturbation in heart failure with a preserved ejection fraction.⁵,⁶ Although the ejection fraction is normal at rest, the ejection fraction does not increase appropriately with stress,¹ and other measures of systolic function are abnormal.⁷ Endothelial dysfunction, arterial stiffening, and increased ventricular systolic
stiffness are also common and may result in heightened sensitivity to changes in load; this sensitivity manifests as rapid-onset pulmonary edema with increases in load and excessive hypotension with decreases in load.1 Exercise performance is impaired owing to impaired chronotropic, vasodilatory, and ventricular diastolic and systolic reserve functions and impaired oxygen uptake and utilization in the peripheral muscles.5,11,12

The fundamental pathophysiological perturbation leading to heart failure with a preserved ejection fraction remains incompletely defined, but traditionally it has been attributed to hypertensive left ventricular remodeling2 (Fig. 1). Systemic microvascular endothelial inflammation related to coexisting conditions has been proposed as an additional mechanism leading to myocardial inflammation and fibrosis, increases in oxidative stress, and alterations in cardiomyocyte signaling pathways. These alterations promote cardiomyocyte remodeling and dysfunction (Fig. 1)13,14 as well as microvascular dysfunction and rarefaction in cardiac15,16 and skeletal11,12 muscle (Fig. 1).

<table>
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<tr>
<th>KEY CLINICAL POINTS</th>
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<tr>
<td><strong>HEART FAILURE WITH PRESERVED EJECTION FRACTION</strong></td>
</tr>
<tr>
<td>- In patients who have signs and symptoms of heart failure but a preserved ejection fraction, objective evidence of abnormal cardiac structure and function should be confirmed by means of echocardiography, electrocardiography, chest radiography, and measurement of natriuretic peptide levels.</td>
</tr>
<tr>
<td>- Natriuretic peptide levels may be normal in patients who have heart failure with a preserved ejection fraction, particularly in obese patients or those with symptoms only on exertion.</td>
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<tr>
<td>- Right heart catheterization may be required in patients in whom there is indeterminate noninvasive testing or evidence of pulmonary hypertension.</td>
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<tr>
<td>- Medications that improve outcomes in patients who have heart failure with a reduced ejection fraction have not been shown to be of benefit in those who have heart failure with a preserved ejection fraction.</td>
</tr>
<tr>
<td>- Treatment of heart failure with a preserved ejection fraction should include diuretics for volume overload, treatment for cardiovascular and noncardiovascular coexisting conditions, aerobic exercise training to increase exercise tolerance, education regarding self-care, and disease management programs for patients with refractory symptoms or frequent hospitalizations for heart failure.</td>
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</table>

**ECHOCARDIOGRAPHIC FINDINGS AND NATRIURETIC PEPTIDE LEVELS**

In observational studies and clinical trials, the value used to define a “preserved” ejection fraction has ranged from 40 to 55%, but current guidelines recommend a partition value of 50%.17,18 An ejection fraction of 40 to 49% is a gray area.17 Patients who previously had an ejection fraction of less than 40% but in whom the ejection fraction increased with therapy for heart failure are considered to have “recovered” heart failure with a reduced ejection fraction. In these patients, medications for heart failure that have a proven benefit in patients with a reduced ejection fraction should be continued.

If the ejection fraction is preserved, evidence of altered cardiac structure and function should be sought to provide further objective evidence of heart failure (Fig. 2). The size of the left ventricular cavity is usually normal. Evidence of left ventricular hypertrophy (Fig. 2) is common but absent in many patients.8,19 Doppler echocardiographic evidence of diastolic dysfunction (slowed ventricular relaxation and increased diastolic stiffness or elevated left atrial pressure) is common.

<table>
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<tr>
<th>STRATEGIES AND EVIDENCE</th>
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<tbody>
<tr>
<td><strong>DIAGNOSIS AND EVALUATION</strong></td>
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<tr>
<td>Since signs and symptoms of heart failure are nonspecific, clinicians should maintain a high index of suspicion for heart failure in patients with risk factors, but they also should consider alternative or contributing diagnoses (Fig. 2). The clinical history should include ascertainment of reduced symptoms in response to diuretic therapy and previous hospitalizations for or complicated by heart failure. In some patients, heart failure manifests as “unexplained” exertional dyspnea. In such patients, differentiating heart failure from noncardiac dyspnea or deconditioning can be challenging. In patients with suspected heart failure, comprehensive Doppler echocardiography should be performed.</td>
</tr>
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</table>
However, diastolic dysfunction also may be present in patients who do not have heart failure and absent in patients who have received aggressive treatment for heart failure or those with predominantly exertional symptoms. The left atrium is usually enlarged. Pulmonary-artery systolic pressure, estimated by means of Doppler echocardiography, is often elevated (>35 mm Hg). Right ventricular systolic dysfunction is present in 20 to 30% of patients, often in association with atrial fibrillation. Atrial remodeling can lead to annular dilatation and functional mitral and tricuspid regurgitation, but primary valvular disease should be ruled out.

Atrial fibrillation is very common and may precede, present concurrently with, or occur subsequent to the onset of heart failure with a preserved ejection fraction. Radiographic evidence of heart failure is common in patients who present with acute heart failure, but radiographic evidence of heart failure is not necessarily present in patients who are in stable condition. Ventricular wall stress and thus circulating levels of natriuretic peptides are lower in patients who have heart failure with a preserved ejection fraction than in patients who have heart failure with a reduced ejection fraction. Levels of natriuretic peptides may be normal in up to 30%
of patients who have heart failure with a preserved ejection fraction, particularly in those who are obese or have purely exertional symptoms. The higher the natriuretic peptide level, the more likely it is that the patient has heart failure (Fig. 2). However, some elderly patients or patients who have atrial fibrillation without heart failure may have natriuretic peptide levels...
that are similar to those of patients with heart failure.

**SPECIALIZED TESTING IN SELECTED PATIENTS**

Specific cardiac conditions that can cause heart failure when a preserved ejection fraction is present (e.g., pericardial disease and hypertrophic or infiltrative cardiomyopathies) must be considered in the differential diagnosis in patients who have heart failure with a preserved ejection fraction (Fig. 2). Epicardial coronary atherosclerosis can account for symptoms of heart failure with exertional dyspnea or angina, but angina is also common in patients who do not have coronary disease. In most patients with coronary disease, the coronary disease is of insufficient severity to account for the severity of heart failure, but it is a risk factor for future coronary events and death.

Stress testing, coronary angiography, or both should be performed if the patient has symptoms of or risk factors for coronary artery disease and is a candidate for anti-ischemic medications or revascularization. Standard exercise stress testing provides information about functional limitation and about the possibility of chronotropic incompetence or exaggerated hypertensive response to exercise. Cardiopulmonary exercise testing can be useful to rule out noncardiac limitations to exercise such as poor effort, deconditioning, and pulmonary disease. Pulmonary-artery catheterization with or without exercise may be needed to establish the diagnosis in patients in whom the findings of noninvasive studies are indeterminate or to document the severity and mechanism of pulmonary hypertension when pulmonary-artery systolic pressure estimated with Doppler echocardiography is significantly elevated (>50 mm Hg).

Pulmonary hypertension in heart failure is due to pulmonary venous hypertension and sometimes modest increases (2 to 4 Wood units) in pulmonary vascular resistance; higher values should spur evaluation of other causes contributing to pulmonary hypertension. Large “V waves” (twice the mean pulmonary arterial wedge pressure value and >25 mm Hg) in the pulmonary arterial wedge pressure wave forms at rest or with stress (in the absence of marked mitral regurgitation) indicate reduced left atrial compliance, a hemodynamic hallmark of this condition.

Cardiac magnetic resonance imaging may be useful if infiltrative cardiomyopathy (amyloidosis) or inflammatory cardiomyopathy (sarcoidosis) is suspected. Scintigraphy with specific radioactive tracers can also assist in the recognition of transthyretin cardiac amyloidosis and should be considered in older patients with increased ventricular-wall thickness (≥12 mm) on echocardiography.

Renal artery stenosis should be considered in patients with risk factors for this condition (e.g., renal dysfunction or peripheral vascular disease) and a history of recurrent acute episodes of heart failure with a preserved ejection fraction. In patients who have a normal or only mildly elevated creatinine level, the requirement for a high dose of a diuretic should prompt further evaluation of renal function (e.g., measurement of the cystatin C level).

**TREATMENT**

Since no therapy has been shown to improve outcomes in patients who have heart failure with a preserved ejection fraction, current therapy (Fig. 3) includes the relief of volume overload (when present), treatment of coexisting conditions, additional strategies that may increase exercise tolerance or reduce symptoms, and strategies to manage chronic disease and prevent hospitalizations.

**Trials of Therapies to Improve Outcomes**

Individually or in a meta-analysis, three randomized trials of angiotensin antagonists (angiotensin-converting–enzyme [ACE] inhibitors or angiotensin-receptor antagonists) involving patients who had heart failure with a preserved ejection fraction did not show significant effects of these agents on composite end points of all-cause or cardiovascular mortality and hospitalizations for heart failure. The mineralocorticoid-receptor antagonist spironolactone did not reduce rates of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure in these patients.

Spironolactone reduced the rate of hospitalization for heart failure but not the rate of death from any cause or hospitalization for any cause, and it increased the rate of renal dysfunction and hyperkalemia. Analyses that were limited to patients who were enrolled in centers in the Americas (which had higher event rates) showed beneficial effects of spironolactone on the composite primary end point, but these post hoc analyses must be interpreted with caution. The effect of beta-blockers in patients with heart failure and a pre-
served ejection fraction has not been evaluated in an adequately powered study, and the limited available data are conflicting.40-43

Thus, the use of angiotensin antagonists and beta-blockers in the treatment of patients who have heart failure with a preserved ejection fraction should be limited to patients who have alternative indications for their use. The use of

Figure 3. Treatment Algorithm for Heart Failure with Preserved Ejection Fraction.

ACE denotes angiotensin-converting–enzyme inhibitor, and ARB angiotensin-receptor blocker.
spironolactone in patients who have heart failure with a preserved ejection fraction remains controversial.

Treatment of Volume Overload
Diuretics, which should be used for relief of symptoms in patients with volume overload, should be adjusted according to the patient’s body weight, symptoms, and electrolyte status. Intermittent use of a thiazide-like diuretic such as metolazone, administered before the dose of a loop diuretic, may be helpful in outpatients with volume overload that is refractory to higher doses of loop diuretics. However, the use of this agent calls for careful monitoring because of the risk of hypokalemia, hyponatremia, and worsening renal function. Persistent diuretic resistance may result from impaired diuretic absorption, necessitating intravenous administration of loop diuretics.

Although the evidence base is limited, sodium restriction (to 2 g per day) may be helpful in patients who are prone to volume overload. At a minimum, high-sodium diets (>6 g per day) and rapid fluctuations in sodium intake should be avoided.

Treatment of Coexisting Conditions
Data to guide treatment of coexisting conditions and risk factors specifically in patients with heart failure and a preserved ejection fraction are very limited. Hypertension can exacerbate heart failure and predispose patients to other adverse outcomes. The Eighth Joint National Committee guidelines do not include a specific blood-pressure target for persons with heart failure.44 However, they recommend target blood pressures of less than 150/90 mm Hg in persons who are 60 years of age or older in the general population44 and of less than 140/90 mm Hg in persons with kidney disease (estimated GFR, <60 ml per minute per 1.73 m² of body-surface area or >30 mg of albumin per gram of creatinine, regardless of diabetic status) and for persons with diabetes, regardless of age. A recent trial showed that lower rates of cardiovascular events and death were associated with blood-pressure targets lower than those recommended by current guidelines, but the trial did not enroll patients with heart failure.45

Atrial fibrillation should be managed according to current guidelines, which recommend rate control and anticoagulation initially, and a trial of rhythm control should be considered if symptoms persist despite adequate rate control.17,48 Patients may be most likely to benefit from rhythm control if the symptoms of heart failure started or worsened after the onset of atrial fibrillation.

Most patients with heart failure and hypertension and concomitant kidney disease should receive an angiotensin antagonist, regardless of their race or diabetic status44 (Fig. 3). In patients who do not have concomitant kidney disease, a thiazide-like diuretic, angiotensin antagonist, or calcium-channel blocker for non-blacks and a thiazide-like diuretic or calcium-channel blocker for blacks are appropriate for initial management.44 Aggressive use of vasodilators may lead to unacceptable side effects in patients with heart failure with a preserved ejection fraction. The choice of additional agents to achieve blood-pressure control should be guided by the presence of coexisting conditions, the patient’s ability to receive the agent without adverse effects, and the effect of the agent on blood pressure.

Patients should be treated with statins according to the usual criteria. Observational studies, including a propensity-score–matched analysis,46 have shown lower mortality among patients with heart failure with a preserved ejection fraction who have received statins than among those who have not received statins, but it remains unclear whether this association is causal.

Patients with coronary artery disease should receive medical therapies according to current guidelines.47 Limited (and potentially confounded) observational data in patients who have heart failure with a preserved ejection fraction and coronary disease have suggested better outcomes among those who have undergone complete revascularization than among those who have not.31 Revascularization can be considered for symptom relief in patients who are otherwise eligible for this procedure and who have clinically significant angina or in whom clinically significant ischemia is evident and thought to contribute to dyspnea as an angina equivalent.18

Atrial fibrillation should be managed according to current guidelines, which recommend rate control and anticoagulation initially, and a trial of rhythm control should be considered if symptoms persist despite adequate rate control.17,48 Patients may be most likely to benefit from rhythm control if the symptoms of heart failure started or worsened after the onset of atrial fibrillation.

Obesity may contribute to exercise intolerance. In a small randomized trial, intentional weight loss significantly increased exercise toler-
ance but did not increase a heart failure–specific quality-of-life score in obese patients who had heart failure with a preserved ejection fraction.49 To increase exercise tolerance, weight loss in obese patients (BMI, ≥35) with heart failure should be considered.17

Lung disease and disordered breathing during sleep are common comorbid conditions in patients with heart failure, provoke symptoms (dyspnea and fatigue) that are similar to those of heart failure, and may exacerbate hypertension and heart failure. Thus, aggressive treatment of concomitant lung disease and sleep apnea according to current guidelines is reasonable.

**Other Therapies to Reduce Symptoms or Increase Exercise Tolerance**

Nitrates are often prescribed for patients who have heart failure and a preserved ejection fraction. However, a randomized, placebo-controlled trial of isosorbide mononitrate did not show increases in submaximal exercise capacity or quality-of-life scores in these patients.50

In small studies, exercise training has consistently been shown to produce clinically meaningful increases in exercise capacity and a reduction in symptoms.49,51 Cardiac rehabilitation programs are reimbursed by U.S. government payers for patients who have heart failure with a reduced ejection fraction but not for those with a preserved ejection fraction. Clinicians should recommend a daily target of 30 minutes of aerobic exercise tailored to the abilities and resources particular to each patient and should monitor compliance and address barriers to exercise training in ongoing follow-up.17,18

**Disease Management**

All patients with heart failure should receive education regarding self-care. Self-care includes monitoring of weight and symptoms, adjustment of doses of diuretics, compliance with dietary restrictions, use of medications, exercise, and regular follow-up.

In patients with refractory symptoms or frequent hospitalizations for heart failure, referral to a disease management program should be considered. In patients who do not have a response to aggressive management, a palliative care program for symptom management and assistance in end-of-life planning should be considered.18

The effect of remote-monitoring strategies is unclear. However, a randomized trial of pulmonary-artery pressure–guided management in patients with heart failure showed that this strategy reduced hospitalizations for heart failure in patients with a reduced or a preserved ejection fraction.52

**Areas of Uncertainty**

Owing to positive findings in a phase 2 study,53 a large outcomes trial of a neprilysin–angiotensin-receptor inhibitor (sacubitril–valsartan) in patients with heart failure and a preserved ejection fraction is ongoing (ClinicalTrials.gov number, NCT01920711). Information from ongoing phase 2, randomized trials of a variety of other drugs and medical devices in patients with heart failure and a preserved ejection fraction is needed.54

The incidence of ventricular arrhythmias and the role of implantable defibrillators are unknown. The most appropriate strategies for the treatment of hypertension, obesity, diabetes, atrial fibrillation, iron deficiency, anemia, and coronary disease in patients with heart failure and a preserved ejection fraction have not been defined.

**Guidelines**

Recently updated guidelines for the management of heart failure with a preserved ejection fraction are available.17,18 The recommendations in this article are largely consistent with those guidelines.

**Conclusions and Recommendations**

The patient in the vignette has heart failure with a preserved ejection fraction, exacerbated by, but probably predating, the onset of atrial fibrillation. The dose of diuretics should be increased to reduce the patient’s clinical congestion. Given her hypertension and renal dysfunction, an angiotensin antagonist should be added and other agents used as needed to achieve a blood pressure of less than 140/90 mm Hg. She should receive education regarding self-care for heart failure. Anticoagulation should be continued. If symptoms persist, a trial of rhythm control should be considered.

The patient’s atherosclerotic risk and the
presence of coronary disease should be assessed to guide the use of statins and other treatments for coronary disease. Evaluation for sleep apnea may also be reasonable, given her obesity, fatigue, hypertension, and atrial fibrillation. Once her condition is stable, exercise and weight-loss programs should be commenced. Persistent symptoms or recurrent hospitalizations should prompt referral to a disease management program for patients with heart failure. She should be informed about clinical trials of therapeutic strategies for heart failure with a preserved ejection fraction.

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

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CASE PRESENTATION

A 61-year-old man presented to the emergency department with cough and shortness of breath. Earlier that morning, he had had sudden onset of severe shortness of breath and tightness in his chest. The chest tightness had resolved, but he continued to feel short of breath. He reported no fevers but did have a productive cough.

The patient also reported increasing shortness of breath when he was lying flat and waking from sleep, with the sudden need to sit upright in order to breathe. To breathe comfortably, he had to sleep on two or three pillows.

The patient also described a 2-month history of worsening fatigue, along with swelling of the legs and an unintentional weight loss of 6.5 kg. He used to walk about 5 km per day without difficulty, but now had chest tightness and shortness of breath when climbing a few stairs or walking a few steps.
CASE PRESENTATION

A 43-year-old man with no notable medical history presented to the emergency department within 1 hour after the abrupt onset of abdominal pain. The patient stated that he had been dressing for work when severe, “crampy” abdominal pain occurred in the left upper quadrant. On a scale of 0 to 10, with 0 indicating no pain and 10 the worst imaginable pain, the patient rated the pain at 10. After the onset of pain, the patient had nausea, several episodes of nonbilious, nonbloody emesis, and flatus.