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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

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A 39-year-old man with a 2-year history of type 2 diabetes mellitus presents for care. He has no microvascular or macrovascular complications. His family history is positive for type 2 diabetes and cardiovascular disease in his mother and older brother. On examination, his weight is 99.8 kg (220 lb), with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 37, and his blood pressure is 125/85 mm Hg. His glycated hemoglobin level is 8.9%, serum creatinine level 1.0 mg per deciliter (88.4 μmol per liter), low-density lipoprotein (LDL) cholesterol 88 mg per deciliter (2.3 mmol per liter), high-density lipoprotein (HDL) cholesterol 45 mg per deciliter (1.2 mmol per liter), and triglyceride level 130 mg per deciliter (1.5 mmol per liter); he does not have microalbuminuria. His medications include metformin (500 mg twice daily), glipizide (5 mg twice daily), simvastatin (20 mg daily), and lisinopril (10 mg daily). What would you recommend to improve his glycemic control?
postprandial suppression of glucagon secretion also occurs. Beta-cell failure is mediated by genetic factors and exposure to chronically elevated levels of blood glucose (glucotoxicity) and free fatty acids (lipotoxicity). Older age, amyloid fibrils in islets, and chronically high rates of insulin secretion also play mechanistic roles. The majority of genetic abnormalities that have been identified in patients with type 2 diabetes are related to beta-cell function.¹¹

According to the American Diabetes Association, the diagnosis of type 2 diabetes is based on a glycated hemoglobin level of 6.5% or more, a fasting plasma glucose level of 126 mg per deciliter (7.0 mmol per liter) or more, or a 2-hour plasma glucose level of 200 mg per deciliter (11.1 mmol per liter) or more, or during an oral glucose-tolerance test.⁶ The diagnosis can also be established by classic symptoms of hyperglycemia and a random plasma glucose level of 200 mg per deciliter or more. Test results require confirmation with the use of the above criteria, unless the diagnosis is obvious on the basis of the symptoms.⁶

This article focuses on glycemic management in type 2 diabetes. However, glycemic control is only one facet of the multifactorial approach required for attempted control of all known risk factors for the development of cardiovascular and microvascular disease.¹²

GOALS OF GLYCEMIC CONTROL AND TARGET RANGE FOR GLYCATED HEMOGLOBIN

The overall aim of glycemic management is to minimize long-term complications while avoiding severe hypoglycemic events. Results of large randomized trials involving patients with type 1 diabetes or newly recognized or established type 2 diabetes show that control of glycemia delays the onset and slows the progression of microvascular complications, including nephropathy, retinopathy, and neuropathy.¹³⁻¹⁸ Long-term follow-up of patients with newly diagnosed type 2 diabetes enrolled in the U.K. Prospective Diabetes Study (Current Controlled Trials number, ISRCTN75451837) showed a reduced risk of cardiovascular disease events 10 years after the end of the trial among patients who were initially randomly assigned to intensive glycemic management, as compared with conventional therapy (average glycated hemoglobin level, 7.0% vs. 7.9%).¹⁹ Results of three trials involving older patients with established type 2 diabetes and a history of or risk factors for cardiovascular disease showed no reduction in total mortality or cardiovascular disease–related mortality associated with intensive lowering of glucose levels to near-normal levels with the use of multiple agents, as compared with standard glycemic control¹⁵,¹⁶,²⁰; one of the studies showed increased mortality.²⁰ Moreover, intensive glycemic control was associated with higher rates of hypoglycemia and weight gain. Thus, the microvascular benefits that are derived from intensive glycemic control must be balanced against the risks.

KEY CLINICAL POINTS

- Intensive glycemic control reduces the risk of microvascular complications of type 2 diabetes, but the effect of strict glycemic control on the risk of macrovascular disease (especially in well-established type 2 diabetes) is less certain.
- Psychosocial factors (e.g., motivation and capacity for self-care) and clinical factors (e.g., age, presence or absence of coexisting conditions, and presence or absence of a tendency toward hypoglycemia) should be considered in setting a target range of glycated hemoglobin for an individual patient.
- A near-normal glycemic target range (6.0 to 6.5%), if implemented safely, could be considered for otherwise healthy patients with recently diagnosed type 2 diabetes and a long life expectancy; more relaxed goals for the glycated hemoglobin level may be preferable in older patients with long-standing type 2 diabetes and cardiovascular disease.
- Lifestyle modification and metformin are recommended as initial therapies for most patients with type 2 diabetes.
- Several therapeutic agents are available when therapy in addition to metformin is needed to control glycemia, but evidence is lacking to support the choice of any one agent over another. Decisions should take into account cost, side effects, and long-term safety and effects on complications of diabetes.

STRAtegies and evidence

The new engl land jour na l of me dicine

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The first step in glycemic management is setting an appropriate glycemic target in each individual patient. Current guidelines specify glycated hemoglobin targets of less than 7.0% or less than 6.5%. However, the appropriateness of these goals varies according to clinical characteristics and psychosocial factors, including the patient’s capacity for self-care and home support systems. Intensive glycemic control often requires a greater number and larger dosages of medications, resulting in an increase in adverse events and costs.

Figure 1 shows the influence of various patient-specific features on the selection of glycated hemoglobin targets. In general, in patients with recently recognized type 2 diabetes and few or no complications (especially younger patients), a near-normal glycemic target aimed at prevention of complications over many years of life can be suggested. In contrast, in older persons with cardiovascular disease or multiple risk factors for cardiovascular diseases, higher targets are often appropriate.

**GENERAL TREATMENT CONSIDERATIONS**

Whenever possible, patients should be involved in decision making regarding glycemic targets and should be informed that the targets may require adjustment over time with changes in clinical or personal factors, such as the patient’s experience with and acceptance of frequent self-monitoring of blood glucose levels and his or her ability to identify and prevent hypoglycemic events. In general, the glycated hemoglobin level should be checked at least twice yearly.

Long-term maintenance of glycemic control ideally should involve a multidisciplinary approach, including nutrition counseling and visits with a diabetes nurse, certified diabetes educator, or both. Educational programs that empower patients to become involved in their day-to-day glycemic management and education of health care providers are helpful. Successful glycemic control at a reasonable cost has been reported with the use of telecommunication and computer-based information-transfer systems.

**LIFESTYLE APPROACHES**

Weight loss and exercise are important nonpharmacologic approaches to improving glycemic control (Fig. 1). The American Diabetes Association recommends a balanced diet that is rich in fiber, whole grains, and legumes; contains less than 7% saturated fat and reduced trans fats; and is limited in calories and foods with a high glycemic index. Exercise has an additive effect when combined with caloric restriction for glycemic control.

Figure 1. Pathophysiological Alterations Leading to Hyperglycemia in Type 2 Diabetes and Specific Types of Treatment. Increased insulin resistance and decreased insulin secretion for the given metabolic state of the individual patient constitute major underlying causes of the hyperglycemic state in type 2 diabetes. However, several pathophysiological derangements contribute to hyperglycemia. Various treatment approaches that counteract the underlying disturbances are listed under each alteration. A specific agent or treatment approach may exert a beneficial effect in more than one category. DPP-IV denotes dipeptidyl peptidase IV, and GLP-1 glucagon-like peptide 1.
such episodes may increase the risk of dementia. With impaired cognitive function are prone to severe hypoglycemia, and hyperosmolar coma. Adapted from Ismail-Beigi.

Water and electrolyte loss, infections, and the development of nonketotic comas may be caused by the atherosclerotic process and microvascular derangements, which usually occur for several weeks after an unexplained severe hypoglycemic episode. More prolonged relaxation of glycemic goals should be considered after two or more episodes. Glycemic targets in patients with “hypoglycemia unawareness” should be relaxed for prolonged periods, pending the potential reversal of the condition. Older patients with impaired cognitive function are prone to severe hypoglycemia, and such episodes may increase the risk of dementia. In general, the older the patient and the longer the duration of the disease, the more established the atherosclerotic process and microvascular derangements, which usually signify less benefit from intensive glycemic treatment. In patients with severe coexisting conditions that could interfere with implementation of the management strategy, the goal is prevention of clinically significant glycosuria, water and electrolyte loss, infections, and the development of nonketotic hyperosmolar coma. Adapted from Ismail-Beigi.

Figure 2. Suggested Goals for Glycemic Treatment in Patients with Type 2 Diabetes.
Factors that should be considered in determining glycemic goals, including psychosocial limitations (e.g., depression, which is common in patients with type 2 diabetes) and clinical factors, are shown. Characteristics listed in the column at the right warrant the most attention. Despite the strong positive correlation between glycated hemoglobin levels and mean blood glucose levels in populations, blood glucose levels vary at any given level of glycated hemoglobin and glycated hemoglobin values vary at any given blood glucose level. Severe hypoglycemia in patients with type 2 diabetes and cardiovascular disease may lead to myocardial ischemia and may increase the risk of myocardial infarction, cardiac arrhythmias, or sudden death. The intensity of glucose control should be immediately relaxed by approximately 1.5 to 2.0% for several weeks after an unexplained severe hypoglycemic episode. More prolonged relaxation of glycemic goals should be considered after two or more episodes. Glycemic targets in patients with “hypoglycemia unawareness” should be relaxed for prolonged periods, pending the potential reversal of the condition. Older patients with impaired cognitive function are prone to severe hypoglycemia, and such episodes may increase the risk of dementia. In general, the older the patient and the longer the duration of the disease, the more established the atherosclerotic process and microvascular derangements, which usually signify less benefit from intensive glycemic treatment. In patients with severe coexisting conditions that could interfere with implementation of the management strategy, the goal is prevention of clinically significant glycosuria, water and electrolyte loss, infections, and the development of nonketotic hyperosmolar coma. Adapted from Ismail-Beigi.

**Agents That Improve Insulin Sensitivity**
Metformin is the cornerstone of type 2 diabetes treatment. By stimulating AMP-activated protein kinase, metformin reduces hepatic glucose production. It does not cause weight gain and may result in a slight weight loss, and it rarely causes hypoglycemia; gastrointestinal side effects may occur, especially if therapy is initiated at higher doses.

Thiazolidinediones (pioglitazone and rosiglitazone) are peroxisome proliferator-activated receptor γ activators that enhance insulin sensitivity in peripheral tissues and reduce hepatic glucose production. Although a randomized trial showed that rosiglitazone, as compared with metformin or a sulfonylurea as the only initial therapy, maintained glycemic control for a longer period, the use of rosiglitazone is highly restricted in the United States (and was discontinued in Europe) owing to concern about an increased risk of myocardial infarction. This concern was based mostly on a meta-analysis of observational studies. In a randomized study, pioglitazone was associated with a reduction in the secondary composite cardiovascular disease outcome but also with increased risks of edema and heart failure.

**Agents That Increase Circulating Insulin Levels**
Insulin is the most potent agent for reducing glycemia. By activating plasma-membrane receptors, it stimulates glucose uptake by responsive tissues and decreases hepatic glucose production. The use of insulin causes weight gain and may cause severe hypoglycemia. Long-acting (basal) and short- and rapid-acting insulin formulations and combined formulations are available.

Sulfonylureas (e.g., glipizide) stimulate insulin release by closure of specific potassium channels on beta cells. Their use is associated with modest weight gain and hypoglycemia. Meglitinides (e.g., repaglinide) have actions similar to those of sulfonylureas but have a short duration of action (hours) and are most effective preprandially.

The Food and Drug Administration (FDA) has approved agents that increase blood glucagon-like peptide 1 (GLP-1) activity or levels and stimulate insulin secretion (in a glucose-dependent manner)
while inhibiting glucagon secretion. GLP-1–receptor agonists (e.g., exenatide and liraglutide) are injectable agents that are structurally similar to endogenous GLP-1 and activate GLP-1 receptors in many tissues. Other effects include delayed gastric emptying and appetite suppression, typically resulting in a weight loss of approximately 2 to 4 kg (4.4 to 8.8 lb).\textsuperscript{21} Dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g., sitagliptin) are oral agents that inhibit the degradation of GLP-1 and result in modest elevations of circulating GLP-1 levels; they do not affect weight. Either class of agent may cause hypoglycemia if used with insulin or sulfonylureas. The long-term safety of these agents (including their potential for causing pancreatitis), as well as their effects on the risk of cardiovascular disease, are unknown.

Other Agents
Other FDA-approved agents are used less frequently because of the smaller reductions in glycated hemoglobin levels (typically, approximately 0.6%) and, in some cases, side effects (Table 1).\textsuperscript{21} Alpha-glucosidase inhibitors (e.g., acarbose) interfere with the digestion of glucose polymers, thereby decreasing carbohydrate absorption; a high frequency of gastrointestinal side effects limits their use. The bile acid sequestrant colesevelam reduces hepatic glucose production and increases incretin levels by unknown mechanisms; it also reduces LDL cholesterol levels. The dopamine agonist bromocriptine activates D2 dopamine receptors and increases insulin sensitivity by unknown mechanisms; a rapid-release form was approved by the FDA for this indication. Pramlintide, an amylin mimetic, is an injectable agent that stimulates receptors for amylin. It suppresses glucagon secretion, delays gastric emptying, and decreases appetite.

**STRATEGIES FOR IMPLEMENTATION**

Of the various strategies for glycemic control, lifestyle modification and metformin are preferred and are cost-effective.\textsuperscript{21,34,38,40} Patients with chronically high levels of glycated hemoglobin (approximately 9.0%) are unlikely to have adequate glycemic control with metformin alone, and in patients with clinically significant hyperglycemia (blood glucose level, \(>300\) mg per deciliter [\(>16.7\) mmol per liter]; glycated hemoglobin level, \(>10\)%), initial insulin therapy should be considered. If metformin monotherapy cannot be used, other oral agents (e.g., a sulfonylurea, a DPP-IV inhibitor, or pioglitazone) or a GLP-1–receptor agonist can be administered. Over time, additional medications become necessary for glycemic control. A logical strategy is to consider agents with complementary mechanisms of action (Fig. 1).\textsuperscript{5,21} Combinations that are effective in reducing glycemia include metformin plus another oral agent, a GLP-1–receptor agonist, or long-acting insulin.\textsuperscript{21,34,38,46} However, strong evidence is lacking to support any one particular second agent over another.

Perhaps because of the reluctance of patients and providers, insulin is generally added much later than medically indicated.\textsuperscript{21} The recent introduction of disposable pen devices may make insulin therapy more acceptable to patients.\textsuperscript{42} Initiation of insulin therapy with the use of a single dose of basal (long-acting) insulin, preferably at bedtime (starting with approximately 10 units and increasing by 2 to 3 units every several days) can reduce the glycated hemoglobin level by 1.5 to 2.0% or more.\textsuperscript{21,36} If glycemia is not controlled, a dose of rapid-acting insulin can be added at the largest meal. Premixed “biphasic insulin” preparations, typically administered before breakfast and dinner, or basal insulin plus rapid-acting insulin (“basal-bolus”) therapy before a meal can also be considered. Lower glycated hemoglobin levels are obtained with the use of biphasic or basal-bolus regimens but at the expense of a greater likelihood of hypoglycemia and weight gain.\textsuperscript{36,39}

**SURGICAL APPROACHES TO GLYCEMIC CONTROL**

Long-term observational studies have shown considerable improvements in glycemic control, as well as improvements in associated cardiovascular risk factors and a reduced risk of cardiovascular disease,\textsuperscript{47} among patients who have undergone bariatric surgery (laparoscopic adjustable gastric banding or Roux-en-Y gastric bypass), as compared with obese patients who have not undergone surgery. Benefits have been noted particularly among very obese persons with a shorter duration of type 2 diabetes and in association with procedures that limit the absorptive surface (by-pass surgery).\textsuperscript{48} Bariatric surgery is increasingly used in patients with type 2 diabetes who are obese but not morbidly obese. The results of two recently published randomized trials of bariatric surgery involving patients with type 2 diabetes (one of which included patients with a BMI of <35) showed significant improvement in glycemic control.
Table 1. Pharmacologic Agents for Glycemic Control in Patients with Type 2 Diabetes.

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<th>Class</th>
<th>Agent (Brand Name)</th>
<th>Expected Reduction in Glycated Hemoglobin Level %</th>
<th>Advantages</th>
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<th>Cost</th>
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<td>Oral</td>
<td></td>
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<tr>
<td>Biguanide</td>
<td>Metformin (Glucophage)</td>
<td>1.0–2.0</td>
<td>Extensive clinical experience; hypoglycemia rare; improved lipid profile; decreased cardiovascular disease events; some weight loss in most patients</td>
<td>Gastrointestinal intolerance; lactic acidosis rare (avoid in patients at increased risk, such as men with a serum creatinine level of ≥1.5 mg/dl and women with a serum creatinine level of ≥1.4 mg/dl); vitamin B&lt;sub&gt;12&lt;/sub&gt; deficiency</td>
<td>Low (generic)</td>
</tr>
<tr>
<td>Sulfonylurea‡</td>
<td>Glyburide (Diabeta), glipizide (Glucoeset), gliclazide (Diamicron), glimepiride (Amaryl)</td>
<td>1.0–1.5</td>
<td>Extensive clinical experience</td>
<td>Hypoglycemia; less durability; weight gain</td>
<td>Low (generic)</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>Nateglinide (Starlix), repaglinide (Prandin)</td>
<td>0.5–1.0</td>
<td>Short duration of action, hepatic clearance, glucose-dependent postprandial action</td>
<td>Low efficacy, hypoglycemia in some patients, weight gain</td>
<td>High</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>Rosiglitazone (Avandia), pioglitazone (Actos)</td>
<td>0.5–1.4</td>
<td>Hypoglycemia rare, more durable effect than that of metformin or sulfonylurea, improved lipid profile, some evidence of beneficial effect on coronary atherosclerosis (with pioglitazone)¶</td>
<td>Edema, heart failure, weight gain, increased risk of long-bone fractures and potential risk of bladder cancer and cardiovascular events (with rosiglitazone); use of rosiglitazone highly restricted</td>
<td>High</td>
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<td>DPP-IV inhibitor</td>
<td>Saxagliptin (Onglyza), linagliptin (Tradjenta), vildagliptin (Galvus), sitagliptin (Januvia)</td>
<td>0.5–0.8</td>
<td>Hypoglycemia rare, infrequent side effects</td>
<td>Less efficacy than GLP-1–receptor agonists, angioedema, unknown long-term safety, risk of pancreatitis</td>
<td>High</td>
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<tr>
<td>Alpha-glucosidase inhibitor</td>
<td>Miglitol (Glyset), voglibose (Volia), acarbose (Precose)</td>
<td>0.5–0.9</td>
<td>Decreased level of postprandial glucose, hypoglycemia rare, possible decrease in risk of cardiovascular disease events**</td>
<td>Flatulence, diarrhea</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>Colesevelam (Welchol)</td>
<td>0.5</td>
<td>Lowering of LDL cholesterol level; hypoglycemia rare</td>
<td>Gastrointestinal side effects, including constipation; low efficacy; only approved agent in class</td>
<td>High</td>
</tr>
<tr>
<td>D2 dopamine–receptor agonist</td>
<td>Bromocriptine, rapid release (Cycloset)</td>
<td>0.5</td>
<td>Hypoglycemia rare</td>
<td>Low efficacy; gastrointestinal side effects, including nausea; fatigue; dizziness; rhinitis; only rapid-release agent approved</td>
<td>High</td>
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<tr>
<td>Injectable</td>
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<tr>
<td>GLP-1–receptor agonist</td>
<td>Exenatide (Byetta), exenatide once weekly (Bydureon), liraglutide (Victoza)</td>
<td>0.5–1.5</td>
<td>Hypoglycemia rare, weight loss in most patients; possible protective cardiovascular effects</td>
<td>Nausea and vomiting; risks of pancreatitis, thyroid C-cell hyperplasia, and tumors (with liraglutide and weekly exenatide); unknown long-term safety</td>
<td>High</td>
</tr>
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mia at follow-up 1 to 2 years postoperatively. Weight loss in some patients is minimal and may not be sustained; data on the long-term effects of these procedures are lacking.

**Areas of Uncertainty**

The underlying cause or causes of accelerated cardiovascular disease in type 2 diabetes and the effects of glycemic control on this process remain incompletely understood. Whereas intensive glycemic control clearly reduces the risk of microvascular complications, its effect (measured as the glycated hemoglobin level, a surrogate marker) on outcomes of cardiovascular disease is less certain. A better understanding of the factors underlying the large variations in insulin resistance and beta-cell number and function in healthy persons is needed for the development of strategies to prevent and treat type 2 diabetes; data are lacking on treatments that preserve beta-cell function. Although there is general agreement on the first-line use of metformin in most patients with type 2 diabetes, evidence is lacking to inform the most appropriate choice of second-line agents. Devices such as continuous glucose-monitoring systems (to ascertain glycemic patterns over a period of a few days) and insulin pumps are increasingly used in patients with type 2 diabetes who require insulin, but data on the benefits and risks of these devices are lacking. Mechanisms underlying the impressive effects of bariatric surgery on glycemic control warrant further exploration. Finally, the long-term safety of GLP-1–receptor agonists, DPP-IV inhibitors, and other newer agents and their effects on diabetic complications, including cardiovascular disease, need to be determined.

**Guidelines**

The American Diabetes Association, the European Association for the Study of Diabetes, and other organizations have published guidelines for glycemic control in patients with type 2 diabetes, and all advocate lifestyle modifications and metformin as first-line therapy, though they differ in their subsequent recommendations. A joint statement by the American Diabetes Association and the European Association...
for the Study of Diabetes recommends that for patients with glycemia that is not adequately controlled with lifestyle changes and metformin, “well-validated” therapies, including sulfonylureas or basal insulin, should be used, followed by more intensive insulin therapy, as needed\(^1\); pioglitazone, GLP-1 agonists, and other medications discussed above are considered “less-well-validated” options. The recommendations in this article are generally concordant with these guidelines.

**CONCLUSIONS AND RECOMMENDATIONS**

The patient in the vignette is relatively young and has a recent diagnosis of type 2 diabetes with inadequately controlled glycemia and a family history of type 2 diabetes and cardiovascular disease. The major goals of treatment should be to prevent microvascular and macrovascular complications over a period of many years, given his long life expectancy. His blood pressure and lipid levels are well controlled. I would discuss with him the risks associated with hyperglycemia and the benefits of glycemic control, and I would assess his capacity and willingness to self-monitor his blood glucose levels. In the absence of any apparent contraindications to targeting a normal or near-normal glycemic range, I would recommend a target glycated hemoglobin level of 6.0 to 6.5% (if it can be implemented safely). I would also recommend an exercise program (preferably at least 150 minutes per week) and encourage him to follow a diet that is low in fat, carbohydrates, and salt and high in grains and fiber, with the aim of gradual weight loss (perhaps 4.5 to 6.8 kg [10 to 15 lb] over the next year). I would increase the dose of metformin to 2000 mg daily while diet and exercise are actively pursued.

If these approaches are effective, it may be possible to decrease or discontinue glipizide. If the glycated hemoglobin level remains high, it is unlikely that the addition of another oral agent would reduce the glycated hemoglobin level from approximately 9% to near-normal levels. Although data are currently insufficient to guide the most appropriate choice among additional therapies, I would recommend adding long-acting insulin at bedtime or a GLP-1–receptor agonist to his regimen. Although some clinicians would consider the discontinuation of glipizide, I favor its continuation, at least initially. Basal insulin is effective and less expensive, but it is associated with hypoglycemia and weight gain. GLP-1–receptor agonists have the advantage of causing weight loss in most patients. They rarely cause hypoglycemia but are more costly than basal insulin, and data are lacking on their long-term safety.

Dr. Ismail-Beigi reports receiving consulting fees from Eli Lilly and owning stock in Thermalin Diabetes. 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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...
Presentation of Case

Dr. Ian J. Barbash (Medicine): A 37-year-old man was admitted to this hospital because of muscle pain and weakness.

The patient had been well until the evening before admission, when mild diffuse myalgias developed. He awoke in the morning with diffuse muscle cramps and intense pain in his legs (he rated the pain at 10 on a scale of 1 to 10, with 10 indicating the most severe pain). On arising to go to the bathroom, he felt unsteady and had difficulty walking. After he returned to bed, diffuse muscle pain persisted, with weakness in his arms and legs and numbness in his legs; he was unable to arise again. He called family members and was brought to the emergency department at this hospital.

The patient reported that he had had similar but much less severe pain intermittently for the past month, not associated with weakness and primarily in his upper thighs, after prolonged periods of rest. The pain occurred several times a week, most often at night, occasionally awakened him, and resolved spontaneously after a few minutes. He reported weight loss of 3.2 kg during the previous month, occasional blurred vision during the previous year, intermittent left wrist pain, and a slight tremor. Six weeks before admission, he had fever, sore throat, and decreased appetite; a chest radiograph revealed patchy opacities in the upper lobe of the right lung, features consistent with possible pneumonia; his symptoms improved after azithromycin was administered. A diagnosis of gynecomastia had been made approximately 3 months earlier, when he presented with left breast tenderness and a palpable mass (4 cm by 3.5 cm) under the areola; mammography subsequently revealed bilateral subareolar densities (greater on the left breast than on the right breast) that were consistent with gynecomastia. The patient also had androgenetic alopecia and seborrheic dermatitis. He reportedly had been treated for tuberculosis 17 years earlier. His diet was high in carbohydrates; he reported eating 10 slices of pizza for dinner the night before admission. Medications included finasteride and clobetasol shampoo. He had no known allergies. He was born in Colombia, had lived in the United States for about 17 years, and had visited Colombia 6 months before admission. He drank alcohol infrequently, did not smoke or use illicit drugs, and reported no paint sniffing or exposure to toluene. He lived with his brother, worked in a restaurant, was single, and had been sexually active in the past, with women.
only. His mother had had diabetes mellitus and hypercholesterolemia and died of bladder cancer; his father had hypertension, and a cousin and a niece had thyroid disease; the patient was not sure of the exact diagnoses. There was no history of autoimmune disease.

On examination, the blood pressure was 166/72 mm Hg, the pulse 100 beats per minute, the temperature 37.3°C, the respiratory rate 16 breaths per minute, the oxygen saturation 99% while the patient was breathing ambient air, and the weight 66.2 kg. The patient was unable to stand; strength in the muscles of flexion and extension measured 3 out of 5 at the hips and knees and 4 out of 5 at the ankles and elbows. Hand grip measured 4+ out of 5. Ankle, knee, and brachioradialis reflexes were absent. The remainder of the examination was normal.

Results of a complete blood count were normal, as were blood levels of urea nitrogen, calcium, magnesium, total protein, albumin, globulin, total and direct bilirubin, creatine kinase, and aspartate aminotransferase. Serum toxicologic screening was negative; other test results are shown in Table 1. An electrocardiogram showed sinus rhythm at a rate of 96 beats per minute, with nonspecific ST-segment and T-wave changes. A urinalysis was normal.

Potassium chloride (120 mmol, total) was administered orally and intravenously, with resolution of weakness. An intravenous catheter was placed in the internal jugular vein. A chest radiograph was normal. Test results of urine solutes and osmolality, from a specimen obtained 3.5 hours after presentation, are shown in Table 1. The patient was admitted to the hospital.

Additional diagnostic tests were performed.

### Differential Diagnosis

**Dr. Eugene P. Rhee:** This 37-year-old man presented with a 1-month history of intermittent leg pain, culminating in an episode of profound weakness. The predominantly proximal deficits in muscle power and the lack of deep-tendon reflexes are consistent with a severe myopathy. Although a variety of inflammatory, infectious, toxic metabolic, and autoimmune processes can result in acute myopathy, this patient’s symptoms are readily attributable to his marked hypokalemia, which was

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Adults†</th>
<th>On Admission</th>
<th>14.5 Hr after Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/liter)</td>
<td>135–145</td>
<td>141</td>
<td>137</td>
</tr>
<tr>
<td>Potassium (mmol/liter)</td>
<td>3.4–4.8</td>
<td>1.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Chloride (mmol/liter)</td>
<td>100–108</td>
<td>107</td>
<td>104</td>
</tr>
<tr>
<td>Carbon dioxide (mmol/liter)</td>
<td>23.0–31.9</td>
<td>23.2</td>
<td>26.2</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.60–1.50</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>70–110</td>
<td>113</td>
<td>111</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>2.6–4.5</td>
<td>1.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/liter)</td>
<td>45–115</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase (U/liter)</td>
<td>10–55</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/liter)</td>
<td>Not defined</td>
<td>96</td>
<td>180</td>
</tr>
<tr>
<td>Potassium (mmol/liter)</td>
<td>Not defined</td>
<td>9.5</td>
<td>39.1</td>
</tr>
<tr>
<td>Osmolality (mOsm/kg of water)</td>
<td>Not defined</td>
<td>726</td>
<td>210</td>
</tr>
</tbody>
</table>

* To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229.
† 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.
confirmed by the rapid resolution of weakness after supplementation with potassium chloride. Thus, I will focus my discussion on the possible causes of hypokalemia. Ideally, the correct diagnosis will also explain other distinctive features of the case, including the patient’s weight loss and bilateral gynecomastia.

**CAUSES OF HYPOKALEMIA**

Potassium is the most abundant cation in the body. 1,2 Because of active potassium uptake by the sodium–potassium pump (Na+/K+–ATPase) across cell membranes, approximately 98% of total-body potassium is intracellular. The remaining 2%, approximately 60 mmol of potassium, constitutes the extracellular pool. Typical potassium intake on a Western diet is 50 to 100 mmol per day; therefore, robust mechanisms are needed to prevent dangerous increases in the potassium level in the extracellular fluid, in the short term and over time. Sudden increases can be prevented by increased cellular uptake by means of the Na+/K+–ATPase, a process that is stimulated by insulin and catecholamines. This transcellular shift does not result in the net removal of potassium from the body. Instead, the kidneys maintain long-term potassium balance, excreting approximately 90% of ingested potassium; the rest is secreted through the gastrointestinal tract and skin. Although potassium is freely filtered at the glomerulus, it undergoes extensive reabsorption in the proximal tubule and loop of Henle. Thus, net urinary excretion of potassium relies on secretion in the distal nephron, a process that is augmented by aldosterone.

Because the kidneys are able to reduce urinary potassium excretion to less than 20 mmol per day, hypokalemia due solely to inadequate intake is uncommon. Instead, the major causes of chronic hypokalemia are related to excessive potassium loss. In such cases, the clinician’s challenge is to differentiate renal from nonrenal potassium wasting. When hypokalemia is sudden in onset, the clinician must also consider whether transcellular potassium shift, and not total-body potassium depletion, is responsible for the patient’s presentation. Since 98% of total-body potassium is intracellular, relatively small changes in its distribution can cause clinically significant changes in the potassium level in the extracellular fluid.

**RENAL POTASSIUM LOSS**

This patient was hypertensive at presentation, albeit in the context of acute stress. Persistent arterial hypertension can be an important clue when distinguishing aldosterone-mediated from non–aldosterone-mediated renal potassium wasting.

**Aldosterone-Mediated Renal Potassium Wasting**

Primary aldosteronism, as with an aldosterone-producing adenoma (Conn’s syndrome) or adrenal hyperplasia, can cause hypokalemia and hypertension. An aldosterone-producing adrenocortical carcinoma could further explain the patient’s weight loss and gynecomastia (if the tumor also secreted estradiol). 3 If the patient were found to have an elevated renin level in addition to an elevated aldosterone level, secondary causes of hyperaldosteronism would need to be considered (e.g., a renin-secreting tumor or renal-artery stenosis). The absence of a concomitant metabolic alkalosis does not rule out a diagnosis of hyperaldosteronism.

Hypercortisolism can also present with hypokalemia and hypertension. Cortisol has a high affinity for the mineralocorticoid receptor but is normally prevented from binding because of rapid metabolism by 11β-hydroxysteroid dehydrogenase (11β-HSD). 4 Chronic licorice intoxication can mimic hyperaldosteronism, because glycyrhetinic acid, a component of licorice, inhibits 11β-HSD, allowing endogenous cortisol to activate mineralocorticoid receptors. 5 Alternatively, very high cortisol levels can exceed the metabolic capacity of 11β-HSD, allowing cortisol to exert aldosterone-like effects on potassium balance and blood pressure. This patient’s weight loss would seem to argue against Cushing’s syndrome but could be consistent with an ectopic corticotropin-producing lung tumor (perhaps misinterpreted as pneumonia on his recent chest images). The patient’s medications include clobetasol shampoo, a topical glucocorticoid. Cushing’s syndrome resulting from topical glucocorticoids has been reported in adults, although typically in those with inflammatory skin conditions such as psoriasis. 6 Finally, several genetic disorders, including glucocorticoid-remediable aldosteronism, congenital adrenal hyperplasia, 11β-HSD deficiency, and Liddle’s syndrome, can cause hypokalemia and hypertension by increasing the levels of aldosterone or by mimicking its activity; however, these
diagnoses are all unlikely given the patient’s age and family history.

Non–Aldosterone-Mediated Renal Potassium Wasting
If the patient is not persistently hypertensive, non–aldosterone-mediated causes of renal potassium wasting would need to be considered. Diuretic agents, for example, are the most common cause of hypokalemia. Intrinsic disorders that cause potassium wasting (e.g., Bartter’s syndrome and Gitelman’s syndrome) mimic the effects of diuretics but are manifested in childhood or adolescence. Some causes of renal tubular acidosis are associated with hypokalemia, but this patient’s bicarbonate level is normal. This also argues against surreptitious glue-sniffing or toluene intoxication, which the case history explicitly excludes; toluene is metabolized to hippuric acid, leading to acidaemia, and the rapid renal excretion of hippurate anions can result in obligate potassium wasting.

Urine Studies
In the absence of known diuretic use, assessment of urine potassium excretion is critical for establishing renal potassium wasting. Urine potassium loss of 20 mmol or more over a 24-hour period in a patient with hypokalemia indicates ongoing, excessive renal potassium secretion. When a 24-hour urine collection is impractical, a spot urine sample that reveals a potassium level of 15 mmol or more per liter is suggestive of an excessive renal potassium loss. Conversely, a urinary potassium loss of less than 20 mmol in 24 hours or a spot urine potassium level of less than 15 mmol per liter indicates previous renal potassium loss (e.g., prior use of diuretics), nonrenal potassium loss, or transcellular potassium shift (Fig. 1). This patient’s spot urine potassium level was 9.5 mmol per liter, mandating consideration of nonrenal causes of hypokalemia. It is important to recognize, however, that relatively low spot levels of urinary potassium can be consistent with renal potassium wasting if urine volumes are high; this is an important caveat, because hypokalemia can cause polyuria.

Nonrenal Potassium Loss
There is no history of heat exposure or prolonged exertion to support cutaneous losses as the cause of this patient’s hypokalemia. Diarrhea severe enough to cause this degree of hypokalemia would be associated with a metabolic acidosis due to concomitant bicarbonate loss. In contrast, excessive vomiting can cause hypokalemia and a metabolic alkalosis. Much of the potassium loss in patients with excessive vomiting, however, is through urination, as a result of potassium excretion alongside bicarbonate and because of the secondary hyperaldosteronism that results from volume contraction. This patient’s case history does not support either diarrhea or vomiting as the cause of his hypokalemia.

Transcellular Shift
Although any cause of severe hypokalemia can result in marked muscle weakness, most cases associated with acute paralysis are due to transcellular shift, rather than net potassium loss. This patient’s history of recurrent, transient episodes of muscle weakness, ranging from mild weakness to complete paralysis, is highly suggestive of acute swings in the transcellular distribution of potassium. On rare occasions, transcellular shift resulting from exogenous stimuli can result in severe hypokalemia. For example, abuse of an adrenergic agent such as pseudoephedrine could have caused the patient’s hypokalemia through catecholamine-induced stimulation of the transmembrane Na+/K+–ATPase; such abuse could also have caused the hypertension, tachycardia, and tremor. Barium intoxication is another rare cause of hypokalemic paralysis resulting from the transcellular shift of potassium. More commonly, however, a transcellular shift that results in hypokalemic paralysis represents a diagnosis of either familial hypokalemic periodic paralysis or thyrotoxic periodic paralysis (TPP).

Clinically, attacks of familial hypokalemic periodic paralysis and TPP are indistinguishable and are characterized by aches in the proximal muscles, cramping, and weakness that can progress to paralysis; hypokalemia is a hallmark of both presentations (Table 2). In both cases, attacks can be precipitated by carbohydrate-heavy meals (e.g., multiple slices of pizza) because of insulin’s stimulatory effects on the Na+/K+–ATPase. Attacks also occur during periods of rest, particularly after strenuous exercise, as potassium released during activity is reabsorbed by skeletal muscle. Other overlapping characteristics, all features of the current case, include a male predominance, normal acid–base status, and a low phosphorus level (also due to transcellular shift).

Familial hypokalemic periodic paralysis is an autosomal dominant genetic disorder due to mutations in ion channels of the skeletal-muscle sar-
colemma, including the α1 subunit of the dihydropyridine-sensitive calcium channel\textsuperscript{19} and the sodium channel SCN4A.\textsuperscript{20} TPP is generally viewed as an acquired disorder, defined by the presence of hyperthyroidism (of any cause), although signs and symptoms of excess thyroid hormone may be subtle or even absent at presentation. The pathogenesis of TPP remains unclear, but thyroid hormone is known to increase the expression and activity of the Na\textsuperscript{+}/K\textsuperscript{+}–ATPase, perhaps unmasking an underlying predisposition for an increased transcellular shift of potassium in selected persons.\textsuperscript{21,22} Recently, some patients with TPP have been shown to harbor a mutation in the inwardly rectifying potassium channel Kir2.6 that alters muscle-membrane excitability but is not sufficient to produce symptoms in the euthyroid state.\textsuperscript{16}

Since familial hypokalemic periodic paralysis is usually manifested in patients who are less than 20 years of age, this patient’s presentation is more characteristic of TPP, with disease onset between the ages of 20 and 50 years. More important, this patient has several cardinal features of hyperthyroidism. These are systolic hypertension with a wide pulse pressure, tachycardia, tremor, and weight loss. Furthermore, gynecomastia is a well-recognized complication of hyperthyroidism attributable to a relative increase in circulating free estradiol\textsuperscript{23}; the antiandrogenic effects of the finasteride that the patient was taking may have amplified this hormonal perturbation. Because hypokalemic paralysis rarely affects bulbar muscles, the patient’s blurred vision raises the possibility of Graves’ ophthalmopathy. The pneumonia 6 weeks before admission is not so neatly accounted for by the diagnosis of TPP. Perhaps the patient received an iodinated contrast agent during his evaluation, thus triggering the release of

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**Figure 1. Algorithm for the Differential Diagnosis of Hypokalemia.**
thyroid hormone from an underlying multinodular goiter. Alternatively, oropharyngeal dysmotility caused by hyperthyroidism may have resulted in aspiration.24

**Summary**

Numerous features of this case are consistent with a diagnosis of TPP, including episodic weakness with acute paralysis, hypokalemia with low levels of urinary potassium, and evidence of hyperthyroidism. Although the incidence of TPP is highest among Asians, it has been reported in other ethnic groups, including Hispanics.25-29 Early diagnosis is critical because definitive treatment of hyperthyroidism is curative. In the short term, potassium chloride supplementation is warranted to prevent life-threatening cardiac arrhythmias or respiratory failure. However, because patients with TPP do not have a net deficit in total-body potassium, overly aggressive repletion can be complicated by rebound hyperkalemia.30 This patient had a normal potassium level 14.5 hours after presentation. I suspect that a diagnosis of TPP was confirmed soon thereafter by biochemical evidence of hyperthyroidism.

**Dr. Eric S. Rosenberg** (Pathology): Dr. Barbash, would you tell us what the team was thinking when they first saw this patient?

**Dr. Barbash:** The team’s differential diagnosis was similar to Dr. Rhee’s; for the reasons he discussed, the leading diagnosis on admission was TPP.

### Table 2. Characteristics of Familial Hypokalemic Periodic Paralysis and Thyrotoxic Periodic Paralysis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Familial Hypokalemic Periodic Paralysis</th>
<th>Thyrotoxic Periodic Paralysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Inheritance</td>
<td>Autosomal dominant (reduced penetrance among women)</td>
<td>Sporadic*</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>&lt;20</td>
<td>20–50</td>
</tr>
<tr>
<td>Racial predominance</td>
<td>White</td>
<td>Asian</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Low urinary potassium excretion</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Normal acid–base status</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Provoked by high carbohydrate intake</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Some persons with thyrotoxic periodic paralysis have been shown to have a mutation in Kir2.6, an inwardly rectifying potassium channel.16

## CLINICAL DIAGNOSIS

Thyrotoxic periodic paralysis.

## DR. EUGENE P. RHEE’S DIAGNOSIS

Thyrotoxic periodic paralysis.

## PATHOLOGICAL DISCUSSION

**Dr. Anand S. Dighe:** Blood drawn when the patient was in the emergency room showed a very low thyrotropin level, at 0.01 μU per milliliter (reference range, 0.4 to 5.0). Results of thyroid tests showed an elevated free thyroxine (T₄) level (3.4 ng per deciliter [43.8 pmol per liter]; reference range, 0.9 to 1.8 ng per deciliter [11.6 to 23.2 pmol per liter]) and an elevated total triiodothyronine level (307 ng per deciliter [4.7 nmol per liter]; reference range, 60 to 181 ng per deciliter [0.9 to 2.8 nmol per liter]). These levels were consistent with hyperthyroidism, and the patient was assessed for autoimmune thyroid disease by measurement of autoantibodies directed against the following thyroid antigens: thyroid peroxidase, thyroglobulin, and the thyrotropin receptor.

The level of antithyroid-peroxidase antibodies was greatly elevated (>1000 IU per milliliter; reference interval, <35), and the level of antithyroglobulin antibodies was not elevated (<20 IU per milliliter; reference interval <40). The precise role of antithyroid-peroxidase and antithyroglobulin anti-
bodies in the pathogenesis of autoimmune thyroid disease remains unclear, but these antibodies may represent epiphenomena, being markers of the thyroiditis common to many forms of autoimmune thyroid disease, such as Graves’ disease and Hashimoto’s thyroiditis.

The presence of thyrotropin-receptor antibodies was assessed with the thyroid-stimulating immunoglobulin (TSI) bioassay. With the TSI assay, the patient’s serum can be examined for the presence of antibodies capable of activating the thyrotropin-receptor signaling pathway. Results of sensitive TSI assays show that virtually all patients with active, untreated Graves’ hyperthyroidism have an elevated TSI index (the ratio of the stimulating activity of the patient to that of the control subject).31 This patient’s TSI index was 2.7 (reference value, ≤1.3). The elevated TSI index, the high thyroid hormone level, and the very low thyrotropin level are consistent with a diagnosis of Graves’ disease. However, on rare occasions, patients with Hashimoto’s thyroiditis may present with an initial hyperthyroid phase that has a similar laboratory presentation to that of Graves’ disease, including, in some cases, an elevated TSI index.32 The clinical course, histologic examination, presence of the extrathyroidal features of Graves’ disease (ophthalmopathy and dermopathy), and radioiodine-uptake scans may all provide useful information in distinguishing between these two diagnoses.

Dr. Rosenberg: Dr. Barbash, would you tell us your team’s initial approach?

Dr. Barbash: The patient did not receive any further potassium supplementation. He was started on methimazole and metoprolol on the advice of the inpatient endocrinology team. After the potassium level had remained normal for several days, he was discharged from the hospital. Shortly thereafter, a technetium-99m pertechnetate scan of the thyroid was obtained at an outpatient facility associated with this hospital. Dr. Scott will review the images.

Dr. James A. Scott: The technetium-pertechnetate scan (Fig. 2) showed an enlarged thyroid with diffusely increased uptake of the pertechnetate (twice the upper limit of the normal range), features consistent with Graves’ disease.

Dr. Rosenberg: Dr. Barbash, would you describe the rest of the patient’s course?

Dr. Barbash: Repeat thyroid-function tests performed approximately 3 weeks later revealed a free T4 level of 1.1 ng per deciliter (14.2 pmol per liter), and his endocrinologist decreased his dose of methimazole. Two months later, the free T4 level was low and the thyrotropin level was elevated, so thyroid hormone–replacement therapy was begun. Recently, laboratory studies revealed normal free T4 and thyrotropin levels. The patient was admitted without a primary care doctor, so I, as his admitting intern, became his primary care physician. I have seen him in the clinic several times, and it is rewarding to have found a readily fixable problem and reassuring to know that the patient can proceed to live a normal life. His endocrinologist plans to perform radioactive iodine ablation soon.

A Physician: How do you control the symptoms in the familial cases?

Dr. Rhee: Avoiding triggers, such as prolonged exercise and meals that are high in carbohydrates, can be helpful. Nonselective beta-blockers can prevent catecholamine-induced activation of the Na+/K+–ATPase, and for reasons that are unclear, acetazolamide may also be effective in reducing episodes of paralysis. Unfortunately, familial hypokalemic periodic paralysis, unlike TPP, is associated with a progressive myopathy, despite these preventive measures.

Dr. Lloyd Axelrod (Endocrinology): It is worth noting that the patient’s potassium level and symptoms were corrected with only 120 mmol of...
11. When the potassium level is below 2 mmol per liter in the most common forms of hypokalemia, the total-body deficit is 400 or 500 mmol. Commonly, 40 or 80 mmol of potassium will raise the potassium level transiently, but hours or days later, it will plummet again as that potassium is redistributed into the intracellular pool. The fact that 120 mmol of potassium was sufficient in this patient supports the diagnosis of TPP, indicating that the hypokalemia was due to transcellular potassium shift rather than total-body depletion.

REFERENCES


Presentation of Case

Dr. Carlos Fernandez-Robles: A 39-year-old man with a recent diagnosis of human immunodeficiency virus (HIV) infection was transferred to this hospital from another hospital because of fever, sweats, and psychosis.

The patient had been well until 4 months before admission, when fevers with temperatures up to 40.6°C, night sweats, and chills developed. During the next 3 months, anorexia, nonproductive cough, and unintentional weight loss (7 to 14 kg) occurred, associated with early satiety, epigastric burning that improved with eating, and abdominal pain that was intermittent, mild, and crampy. Two courses of antibiotics were reportedly administered, without improvement.

Six days before admission, the patient was seen in the emergency department at the other hospital. The evaluation was reportedly negative; a skin test for tuberculosis was administered, and he was discharged. The next day, he saw his internist. Computed tomography (CT) of the abdomen, after the administration of contrast material, revealed a thick-walled mass near the duodenum (7 cm by 2.2 cm, with air in its center), scattered lymph nodes near the porta hepatis, a thickened gallbladder wall, and mild splenomegaly (13.5 cm). The patient was admitted to the other hospital.

On examination, the patient was alert, oriented, cooperative, and thin, with shaking chills. The temperature was 38.5°C, the blood pressure 135/76 mm Hg, the pulse 106 beats per minute, the respiratory rate 20 breaths per minute, and the oxygen saturation 93% while he was breathing ambient air. There was mild epigastric and right-upper-quadrant tenderness, with no induration at the site of the skin test for tuberculosis. The hematocrit was reportedly 31.9%, the white-cell count 4600 per cubic millimeter (with 75% neutrophils and 14% lymphocytes), the blood level of alkaline phosphatase 233 U per liter, and the level of aspartate aminotransferase 47 U per liter. Broad-spectrum antibiotics and intravenous pantoprazole were administered.

During the next 2 days, the temperature rose to 39.4°C and the stools became black and tarry; the hematocrit was 28.3%. Magnetic resonance imaging (MRI) of the abdomen, after the administration of contrast material, revealed a thick-walled...
lesion that was contiguous with the posteromedial wall of the duodenum, mild distention of the gallbladder, and a small amount of fluid adjacent to the gallbladder wall. A unit of red cells was transfused. On the fourth day, esophagogastroduodenoscopy revealed a duodenal ulcer and gastritis. Testing for antibody to HIV was positive. During that night, the patient became agitated, reporting a nightmare in which he was dying. On the fifth day, he appeared tense, speaking with his teeth and fists clenched and his eyes staring ahead; religious delusions developed. Psychiatric consultation was obtained, and olanzapine was prescribed. The patient was transferred to this hospital.

The patient had had herpes zoster of the thoracic dermatome 4 years before admission and again 3 months before admission. He had no known allergies. He had immigrated to the United States from a Caribbean country more than a decade earlier. Testing for HIV and syphilis had reportedly been negative 11 years before admission. He had a history of alcohol abuse and did not smoke or use intravenous drugs. He lived with his partner and her children. He had biologic children who lived in his native country. A bird and a turtle were in the home. His parents and siblings were healthy, with no family history of psychiatric illness.

On admission, the patient was awake but initially unresponsive. The temperature was 37.6°C and the blood pressure 148/81 mm Hg; other vital signs and the remainder of the physical examination were normal. He became agitated and continued to have bizarre delusions. Olanzapine and haloperidol were administered. On psychiatric examination later that day, the agitation had resolved. He was not oriented to date and was found not to have the capacity to sign out against medical advice. Twenty-four-hour accompaniment was begun. Blood levels of platelets, bilirubin, amylase, lipase, calcium, phosphorus, magnesium, vitamin B₁₂, folic acid, thyrotropin, and ammonia were normal, as were the results of tests of renal function and urinalysis; tests for toxic drugs and hepatitis B and C viruses were negative. Other test results are shown in Table 1.

On formal psychiatric examination on the second day, the patient had disorganized and guarded behavior, flat affect, thought blocking, and bizarre nihilistic delusions, including statements that he had died and was dead. Although the cognitive examination was limited in scope because of the patient’s lack of cooperation, it revealed deficits in attention (inability to name months of the year backward), anterograde memory (inability to orally recall three objects), and the performance of visuospatial tasks (Fig. 1) in the absence of fluctuations in the level of consciousness.

On the third day, the patient appeared lucid and somber and had appropriate speech content. The maximum temperature was 40.3°C. There were white plaques on the tongue, scars from zoster on the right thorax, and small, rubbery lymphadenopathy in the left axilla. Blood tests for IgG antibodies to toxoplasma and cytomegalovirus (CMV) was positive, and testing for syphilis, CMV antigen, strongyloides antibody, cryptococcal antigen, and urine histoplasma antigen was negative. The aspartate aminotransferase level increased to 155 U per liter. Broad-spectrum antibiotics were stopped, and nystatin was begun orally. Respiratory-isolation measures were instituted. A portable chest radiograph was normal; CT of the abdomen and pelvis obtained after the administration of contrast material showed upper abdominal, retroperitoneal, and pelvic lymphadenopathy; splenomegaly; a duodenal diverticulum; and gallbladder-wall thickening.

During the next 9 days, psychiatric symptoms persisted. Fevers occurred daily, with temperatures up to 40.1°C, and extrapyramidal side effects developed. CT of the brain showed no clinically significant abnormality. CT of the chest without contrast material revealed a few nonspecific nodules and multiple supraclavicular, mediastinal, and upper abdominal lymph nodes, up to 12 mm in diameter. MRI scans of the brain obtained before and after the administration of contrast material showed multiple punctate foci of enhancement, up to 4 mm in diameter, in the right and left cerebral hemispheres, with mild surrounding hyperintensity on fluid-attenuated inversion recovery (FLAIR) images. The distribution of the lesions was predominantly intraaxial and involved white matter and the junction of the gray and white matter, although one lesion appeared extraaxial and another lesion appeared to involve cortical gray matter. The results of portable electroencephalography were normal, with overlying beta activity and no evidence of epileptiform activity. Three induced-sputum specimens showed hyphae on fungal wet preparation and were negative for acid-fast bacilli. Cultures of sputum grew Candida...
Cultures of sputum, urine, and blood for mycobacteria and fungi remained negative. Lumbar puncture was performed, and analysis of the cerebrospinal fluid (CSF) was normal. The HIV RNA level was 3010 copies per milliliter of CSF, with no malignant cells on cytologic examination.

On the ninth day, fine-needle aspiration of the peripancreatic lymph node showed no malignant cells, and flow cytometry revealed T lymphocytes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Adults†</th>
<th>On Admission, This Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>41.0–53.0 (men)</td>
<td>32.2</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.5–17.5 (men)</td>
<td>11.0</td>
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<tr>
<td>White-cell count (per mm³)</td>
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<tr>
<td>Differential count (%)</td>
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<tr>
<td>Neutrophils</td>
<td>40–70</td>
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<tr>
<td>Lymphocytes</td>
<td>22–44</td>
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<tr>
<td>Monocytes</td>
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<tr>
<td>Mean corpuscular volume (μm³)</td>
<td>80–100</td>
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<td>Smear description</td>
<td>1+ Microcytes</td>
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<tr>
<td>Absolute lymphocyte count (per mm³)</td>
<td>950–2967</td>
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<tr>
<td>CD4 T-cell count (per mm³)</td>
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<td>CD8 T-cell count (per mm³)</td>
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<td>Activated partial-thromboplastin time (sec)</td>
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<td>Prothrombin time (sec)</td>
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<td>International normalized ratio</td>
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<td>Sodium (mmol/liter)</td>
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<td>Potassium (mmol/liter)</td>
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<tr>
<td>Protein (g/dl)</td>
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<tr>
<td>Total</td>
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<td>Albumin</td>
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<td>Globulin</td>
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<tr>
<td>Alkaline phosphatase (U/liter)</td>
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<td>Aspartate aminotransferase (U/liter)</td>
<td>10–40</td>
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<tr>
<td>Alanine aminotransferase (U/liter)</td>
<td>10–55</td>
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<tr>
<td>Lactate dehydrogenase (U/liter)</td>
<td>110–210</td>
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<tr>
<td>IgG (mg/dl)</td>
<td>614–1295</td>
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<tr>
<td>HIV antibodies (by enzyme-linked immunosorbent assay)</td>
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<td>Positive, confirmed by Western blot analysis</td>
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<tr>
<td>HIV nucleic acid (copies per ml of plasma, by RT-PCR)</td>
<td></td>
<td>893,000</td>
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</table>

* To convert the values for glucose to millimoles per liter, multiply by 0.05551. HIV denotes human immunodeficiency virus, and RT-PCR reverse-transcriptase polymerase chain reaction.
† 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.
with an inverted ratio of CD4 T cells to CD8 T cells and no monoclonal B cells. Ophthalmologic examination showed retinal lesions, including superficial whitening and fluffy white infiltrate, findings consistent with retinopathy from CMV or HIV. Transthoracic echocardiography was normal.

Haloperidol was stopped, and olanzapine and lorazepam were administered as needed for agitation. Treatment with antiretroviral medications (emtricitabine, tenofovir, atazanavir, and ritonavir) and prophylactic trimethoprim–sulfamethoxazole was begun.

On the 12th day, a diagnostic procedure was performed.

**Differential Diagnosis**

*Dr. Oliver Freudenreich:* I am aware of the diagnosis in this case. May we review the imaging studies?

*Dr. Mykol Larvie:* The abdominal CT scan (Fig. 2A) shows a structure posterior to the second part of the duodenum that is typical in appearance for a duodenal diverticulum, although it initially raised concern for a mass, either inflammatory or malignant. There are enlarged, low-density lymph nodes, including aortocaval and periaortic nodes (Fig. 2B), some of which were originally worrisome for a parapancreatic mass. The gallbladder wall is thickened with a small amount of pericholecystic fluid.

CT of the brain revealed no clinically significant abnormality. A tiny punctate intraaxial calcification was a nonspecific and nonacute finding. MRI of the brain (Fig. 3) revealed multiple predominantly punctate, enhancing, hyperintense foci on T2-weighted images, including one focus in the right medial temporal lobe and another in the inferior left frontal lobe, with no evidence of mass effect. Although the images are degraded by motion artifact, there is no gross evidence of hemorrhage or abscess.

*Dr. Freudenreich:* This patient has new-onset psychosis. He also made repeated statements about having died and being dead that are consistent with nihilistic delusions (termed the Cotard syndrome), which occur when the self becomes unfamiliar, leading to a delusion of being dead.

Psychosis is a symptom, not a diagnosis, and can be organized into primary and secondary (organic) psychoses. Unfortunately, there is no easy way to reliably differentiate primary from secondary psychoses on the basis of the characteristics of the psychosis itself, and assessment of the overall clinical situation is very important in narrowing the differential diagnosis and determining the degree of urgency.

**Delirium**

The first question we must ask is whether this patient’s new-onset psychosis is caused by an underlying, life-threatening medical condition, such as delirium. Psychosis is common in patients with delirium. The clinical diagnosis of delirium hinges on the presence of two cardinal features: disruption of attention and disruption of the sleep–wake cycle, which leads to fluctuation in symptoms over the course of a day. A delirium can be easily missed if ancillary features such as psychosis overshadow the core problem of inattention. An electroencephalogram (EEG) that shows diffuse slowing is suggestive of a delirium, but as in this patient, a normal EEG is not sensitive enough to reliably rule out a delirium.

The sudden onset of psychosis in a patient with fluctuating mental status and fevers is a delirium
until proved otherwise. In this patient, our differential diagnosis and evaluation must focus on his advanced HIV infection. Therefore, a thorough evaluation involving CSF analysis and MRI is warranted for ruling out infection and a malignant condition of the central nervous system.

**HIV-ASSOCIATED DEMENTIA**

Delirium often occurs in patients with cognitive impairment and dementia. Since this patient has advanced HIV infection, he is at risk for HIV-associated dementia, which was a common problem before the introduction of highly active antiretroviral therapy (HAART). The typical presentation is a progressive dementia with subcortical features (apathy, inattention, and loss of retentive memory) and abnormalities of motor function, such as psychomotor slowing. When psychosis occurs in patients with HIV-associated dementia, it is characterized by prominent agitation, irritability, and delusions (all of which were present in this patient) and is often part of a manic syndrome that has been called “AIDS mania.”

HIV-associated dementia is a diagnosis of exclusion, supported by findings on CSF analysis and MRI. This patient almost certainly has some degree of brain involvement by HIV infection, as suggested by the severe immunosuppression and presence of HIV RNA in the CSF. The extent of his cognitive impairment will require reexamination with a full battery of neuropsychological tests after his acute illness has resolved. Most likely, he is in an early stage of HIV-associated dementia, since he did not have focal findings and his history showed no cognitive decline.

**PSYCHOSIS DUE TO GENERAL MEDICAL CONDITIONS**

Psychosis can occur in patients with delirium and in those with dementia. It may also occur as a direct manifestation of an underlying medical condition, such as HIV infection. The common clinical features of HIV-associated psychosis include sudden onset without prodrome, delusions (87% of patients), hallucinations (61%), and mood symptoms (81%). In HIV-associated psychosis, neurologic findings are typically limited and CT findings are nonspecific; however, EEGs are abnormal in 50% of cases. Cognitive impairment has consistently been described as a feature of HIV-associated psychosis, although it cannot be distinguished from a first episode of schizophrenia. Since substance abuse is a common coexisting disorder in HIV-infected patients and can further impair cognition, it is important to rule out the use of alcohol or other drugs as a contributing cause.

I would not diagnose HIV-associated psychosis in a patient with a delirium, which some of the patients cited in the literature might have had.

**PRIMARY PSYCHIATRIC DISORDERS**

A primary psychiatric disorder such as schizophrenia, without HIV as a causative factor, develops in some patients who have established HIV infection. In this patient, a first episode of schizophrenia is unlikely, since the onset of schizophrenia is typically not sudden but instead involves a prodromal period of several years, with gradual loss of function and social competence. This patient was married, had children, and at the age of 39 years would be unusually old to be having a first episode of schizophrenia, since men typically...
become ill in their 20s. However, psychosis is a feature of other psychiatric disorders besides schizophrenia. For example, the very sudden onset of psychosis during the course of a day or so has been called “reactive psychosis,” in response to stressors, and may occur in patients with HIV infection.\(^1^5\) This patient’s delirium is a sufficient explanation for his psychosis, and psychiatric causation does not need to be invoked.

To summarize, the clinical history (sudden onset of psychosis in a patient with constitutional symptoms and fevers) and results of the serial mental status examination (characterized by delusions, attentional problems, and disorientation at times) suggest a delirium in this patient with AIDS and severe immune suppression. The non-specific MRI findings and the lumbar puncture that showed HIV viral replication but no other infection suggest one of the HIV-associated neurocognitive disorders as a vulnerability factor for the delirium. The small lesions seen on MRI are not sufficient to explain this patient’s psychosis, particularly given the clear evidence that he had a delirium, most likely from systemic infection.

**LATE DIAGNOSIS OF HIV INFECTION**

Dr. Nesli Basgoz: I am aware of the diagnosis in this case. In any patient with fever and sudden changes in mental status, infection or a malignant condition of the central nervous system must be considered. In this patient with HIV infection and a low CD4 T-cell count, our differential diagnosis has to include processes that cause central nervous system disease in immunosuppressed hosts. Cerebral toxoplasmosis is possible, since the patient has serologic evidence of past infection. However, no brain abscess was identified on MRI, making this diagnosis unlikely. Cryptococcal meningitis is another possibility. Results of CSF analysis are often bland in cryptococcal meningitis, since the organism may not elicit a robust inflammatory response. The absence of cryptococcal antigen in the CSF of this patient makes this diagnosis unlikely. Infection with *Mycobacterium tuberculosis* may cause chronic central nervous system disease. This patient does not have evidence of tuberculous meningitis or a tuberculoma. Although MRI may reveal gross disease, it is not particularly sensitive for the detection of invasion of the central nervous system; therefore, tuberculosis affecting the central nervous system cannot be ruled out. CMV infection should also be considered, especially given the abnormalities seen on retinal examination. Testing for CMV in the blood and CSF was negative, and this makes CMV encephalitis unlikely although not impossible. This patient is also at risk for progressive multifocal leukoencephalopathy or lymphoma associated with...
Epstein–Barr virus, but there is no imaging evidence to support these diagnoses.

In this profoundly immunosuppressed patient, multiple opportunistic infections may be involved, since the laws of medical parsimony do not apply to patients with low CD4 T-cell counts. The range of possible opportunistic infections is vast, but most disease is caused by a relatively small number of organisms. The two most important predictive factors in this case are the CD4 T-cell count of 30 per cubic millimeter and the fact that the patient comes from an island in the Caribbean where tuberculosis is endemic. His fever, chills, sweats, cough, and lymphadenopathy are all consistent with disseminated tuberculosis. Although he had a negative purified protein derivative skin test for tuberculosis, this test lacks sensitivity in normal hosts and is likely to be uninformative in this patient with a low CD4 T-cell count. We also need to consider fungal infections that behave like tuberculosis, including histoplasmosis.

During the patient’s hospital course, he had a persistently high aspartate aminotransferase level. Since the initial review of the lymph-node aspirate did not show acid-fast bacilli or fungi, the next step was a liver biopsy.

**Dr. Oliver Freudenreich and Dr. Nesli Basgoz’s Diagnoses**

- Acute psychosis with Cotard’s delusion, most likely superimposed on a mild HIV-associated neurocognitive disorder.
- Delirium due to the systemic effects of an opportunistic infection or malignant condition, most likely *M. tuberculosis*.

**Pathological Discussion**

Dr. Joseph Misdraji: Examination of the liver-biopsy specimen revealed several epithelioid granulomas, some of them necrotizing (Fig. 4A and 4B). Histochemical staining for acid-fast organisms revealed numerous acid-fast bacilli (Fig. 4C). The diagnosis was mycobacterial infection of the liver with necrotizing granulomatous inflammation. Shortly after the diagnosis was made, various cultures were reported as positive for *M. tuberculosis* complex, including the liver biopsy, peripancreatic lymph-node aspirate, sputum, blood, and urine. Therefore, the final anatomical diagnosis is disseminated *M. tuberculosis* infection. The large number of bacilli and the somewhat looser arrangement of the histiocytes are features consistent with the immunodeficient status of the patient.

After the diagnosis of *M. tuberculosis* was confirmed, we took another look at the peripancre-
atic lymph-node aspirate to see whether we could find acid-fast bacilli. Review of the aspirate revealed lymphocytes and small amounts of amorphous granular debris in which acid-fast bacilli were identified. This case underscores the fact that the identification of acid-fast bacilli is challenging, and organisms can be overlooked. Therefore, when there is a high clinical suspicion of mycobacterial disease, it is important to notify the pathologist so that extra time can be spent reviewing the slide stained for acid-fast bacilli.

### Discussion of Management

#### Management of HIV-Associated Psychosis

**Dr. Fernandez-Robles:** Reversal of organic psychosis involves treatment of the underlying disorder and symptomatic treatment with antipsychotic agents. This patient had markedly less agitation after 2 days of treatment with olanzapine, an antipsychotic agent. This drug was initially chosen because of its proven efficacy and relatively low risk of causing extrapyramidal symptoms and tardive dyskinesia, which are highly prevalent among patients with HIV.\(^\text{16-19}\) This sensitivity is thought to be related to HIV-associated damage to the dopaminergic basal ganglia system and to increased plasma levels of antipsychotic agents because of interactions with antiretroviral drugs.\(^\text{20,21}\) Dysfunction of the basal ganglia also heightens the risk for neuroleptic malignant syndrome, which has been well documented to occur in patients with HIV.\(^\text{22}\)

On day 5, extrapyramidal symptoms developed, requiring the administration of lorazepam and a reduction in the dose of olanzapine. Because of the development of extrapyramidal symptoms, persistent high fever, and changes in mental status, we became concerned about the possibility of neuroleptic malignant syndrome. We closely followed the creatine kinase levels, which remained normal. On discharge, most of the patient’s psychotic symptoms had resolved, except for a persistently flat affect and mildly monotonous speech.

#### Management of Tuberculosis and HIV Infection

**Dr. Basgoz:** This patient has at least two life-threatening infections, HIV and tuberculosis, both of which require complex treatment regimens. His subsequent clinical course highlights an unresolved clinical question regarding the timing of the initiation of antiretroviral therapy in patients with a low CD4 T-cell count and concurrent opportunistic infection.\(^\text{23-29}\)

This patient was initially started on a standard four-drug antiretroviral regimen, and approximately 1 week later, therapy directed against tuberculosis was initiated. Within 6 days after the initiation of antituberculous therapy, high temperature, cough, and tachypnea developed, with worsening malaise. Severe scrotal pain also developed, with swelling, tenderness, and induration. Ultrasound examination of the scrotum showed a complex testicular mass with epididymal enlargement that was thought to be consistent with involvement by disseminated tuberculosis. During this time, there was also an increase in the alkaline phosphatase level, from 185 U per liter to 722 U per liter, suggesting worsening of the patient’s liver disease. This constellation of findings is consistent with the immune reconstitution inflammatory syndrome (IRIS), a paradoxical worsening of inflammation caused by the reconstitution of immune function while on antiretroviral therapy. As his immune function started to recover, the patient mounted an exuberant inflammatory response, probably directed against antigens liberated from dead or dying mycobacteria.

For treatment of IRIS, we added prednisone to the patient’s regimen. He had a rapid clinical response, with a decrease in alkaline phosphatase levels and an improvement in fever. However, he had reactivation of a latent CMV infection and required treatment with ganciclovir. As we tapered the dose of prednisone, fever recurred, but the pattern of fever was relatively constant, lacking the normal diurnal variation that is typical of infection. The patient looked and felt well, which suggested that the fever might be medication-related. We discontinued rifabutin, which was part of his antimycobacterial regimen, and the fever resolved.

After discontinuation of prednisone, asymptomatic hypercalcemia developed, with calcium levels measured as high as 13.5 mg per deciliter (3.4 mmol per liter). We assumed that this was caused by a parathyroid-hormone–independent mechanism related to the production of 1,25-dihydroxyvitamin D by the macrophages in reaction to the tuberculosis infection. Hypercalcemia is much more commonly seen in other granulomatous diseases, such as sarcoidosis, than in tuberculosis. We restarted low-dose prednisone,
and the hypercalcemia rapidly resolved with ketoconazole, which inhibits a step in the production of 1,25-dihydroxyvitamin D. The patient was discharged after 4 weeks in the hospital, at which time he was medically stable and had a markedly improved mental status. He continued therapy for tuberculosis and HIV.

On examination by the retina service, the patient was noted to have bilateral retinopathy, which was considered to be due to CMV or HIV. However, there was a focal area of chorioretinitis in the left eye that was not considered typical of CMV retinitis and was thought to possibly be a granulomatous lesion from tuberculosis. Approximately 14 months after discharge, at the time of his last eye examination, the eye lesions were quiescent and there was no evidence of active retinitis.

Thirty months after discharge, the patient is doing exceptionally well medically, feels strong, and exercises frequently. His last CD4 T-cell count was 231 per cubic millimeter, and plasma HIV RNA was not detected.

Dr. Freudenreich: I saw the patient in outpatient psychiatry for follow-up 6 months after his acute illnesses had resolved. He had made a remarkable recovery but had residual cognitive problems, particularly in processing speed, recall memory, and frontal-lobe functions, all of which might have functional ramifications. His clock drawing was intact. Of note, he scored 7 out of 16 on the HIV Dementia Scale (with scores of 10 or less indicating HIV-associated dementia).

This case exemplifies the effect that HIV infection may have on the brain, particularly late in the course of infection. Early diagnosis and treatment of HIV infection may help to limit brain disease. Therefore, I consider HIV testing in any patient presenting with psychosis or with cognitive problems.

Dr. Theodore A. Stern (Psychiatry): In light of the patient’s episodic belief that he was dead, should we consider the possibility that this thought or feeling was derived from a complex partial seizure in the temporal lobe? The theme of death in complex partial seizures has been described in the literature.

Dr. Freudenreich: An EEG was obtained to rule out seizures and was normal in this patient. I do not think it is possible to establish causality between this patient’s lesion in the temporal lobe and his psychosis.

***

**Final Diagnoses**

Disseminated infection with *Mycobacterium tuberculosis*, including the liver, peripancreatic lymph node, sputum, blood, and urine, with delirium and acute psychosis with Cotard’s delusion.

Mild HIV-associated neurocognitive disorder.

Presented at the Psychiatry Grand Rounds.

Dr. Freudenreich reports receiving consulting fees from Beacon Health Strategies and Transept Pharmaceuticals, grant money from Pfizer, and honoraria from Reed Medical Education. Dr. Basgoz reports receiving stock options and income for board membership from Forest Laboratories. 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.

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**References**


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Secondary Prevention after Ischemic Stroke or Transient Ischemic Attack

Stephen M. Davis, M.D., and Geoffrey A. Donnan, M.D.

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

A 62-year-old woman is seen 1 week after an ischemic stroke. She had presented to another hospital with dysphasia and right-sided weakness; magnetic resonance imaging (MRI) showed a recent infarction in the left parietal cortex, and computed tomographic angiography (CTA) showed a high-grade stenosis in the left proximal internal carotid artery with normal intracranial vessels (Fig. 1). She was treated with intravenous recombinant tissue plasminogen activator and discharged home, taking aspirin and a statin. She stopped smoking 12 years ago. On examination, the blood pressure is 145/90 mm Hg. She reports some mild residual clumsiness of her right hand. What would you advise to reduce the risk of stroke recurrence?

The Clinical Problem

Worldwide, stroke is the second most common cause of death after myocardial infarction and is a leading cause of acquired disability. In some regions, the combined incidence of stroke and transient ischemic attacks (TIAs) exceeds the incidence of coronary vascular events. More than 85% of fatal strokes occur in low- and middle-income countries.

Patients with stroke are at high risk for subsequent vascular events, including recurrent stroke (highest risk), myocardial infarction, and death from vascular causes. Because the risk of stroke is highest in the early period after the acute event, prompt initiation of tailored prevention strategies is essential. A meta-analysis showed that the risk of stroke was as high as 12.8% during the first week after a TIA, but the risk was lowest when emergency treatment had been given by specialized stroke services. It is estimated that at least 80% of recurrent events might be prevented with the use of a comprehensive approach that includes dietary modification, exercise, blood-pressure lowering, antiplatelet therapy, and statin therapy.

Strategies and Evidence

Evaluation

Stroke is categorized as ischemic stroke (80% of cases), intracerebral hemorrhage (15%), or subarachnoid hemorrhage (5%). TIAs were traditionally defined as brief neurologic episodes of vascular origin lasting less than 24 hours. More recently, TIAs have been classified as transient neurologic events without signs of acute infarction on imaging. This updated definition is based on the evidence that many strokes detected on imaging, particularly MRI, last less than 24 hours or are clinically silent. This review focuses on secondary prevention after a TIA or ischemic stroke.
In planning secondary prevention, it is important to attempt to identify the pathogenesis of the TIA or ischemic stroke, particularly to detect clinically significant cardiac or large-artery causes that warrant the use of strategies tailored to the individual patient. In clinical practice, the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification for ischemic stroke is useful in delineating major pathogeneses on the basis of clinical findings and investigations. These include cardioembolism (most commonly from atrial fibrillation), large-artery disease, small-vessel occlusion (lacunar stroke), stroke of other determined cause (e.g., arterial dissection, drug-related stroke, or a hypercoagulable disorder), and stroke of undetermined cause (two or more identified causes or negative or incomplete evaluation). Even when fully investigated, up to 30% of cases of cerebral ischemia remain unexplained (“cryptogenic stroke”).

Urgent evaluation is warranted after a stroke or TIA, because many recurrent events occur early. Brain imaging is mandatory for diagnosis, classification, and management. MRI is much more sensitive than computed tomography (CT) in the diagnosis of acute ischemia, although CT is more widely available. Arterial imaging with the use of carotid Doppler ultrasonography, CTA, or magnetic resonance angiography (MRA) is usually necessary. In many centers, CT is now combined with CTA. Electrocardiography is routinely performed. To detect paroxysmal atrial fibrillation, ambulatory monitoring is useful. Transthoracic or transesophageal echocardiography is often used to detect cardiac sources of embolism other than atrial fibrillation. Routine blood tests may reveal predisposing causes, such as polycythemia, renal impairment, electrolyte disturbances, and hyperglycemia.

**MANAGEMENT**

Aggressive risk-factor management and lifestyle advice are essential for all patients. Observational studies of patients with a history of stroke indicate that healthy lifestyle behaviors, including regular exercise and abstinence from smoking, are associated with reduced mortality. In the INTERSTROKE case–control study involving first acute strokes, 10 risk factors accounted for 90% of stroke risk: hypertension, current smoking, a high waist-to-hip ratio, a high dietary risk score, lack of regular physical activity, diabetes mellitus, excess alcohol consumption, psychosocial stress or depression, cardiac causes (e.g., previous myocardial infarction or atrial fibrillation), and a high ratio of apolipoprotein B to apolipoprotein A1. Diabetes and the metabolic syndrome are common in patients with stroke or TIA and may not have been previously recognized.

In secondary prevention, three principal strategies are appropriate for nearly all patients: blood-pressure lowering, cholesterol lowering with statins, and antiplatelet therapy (except in patients in whom anticoagulant therapy is indicated). Other strategies are specific to the cause of stroke (Table 1).

**BLOOD-PRESSURE LOWERING**

Blood pressure is the most important modifiable risk factor in both primary and secondary preven-
tion of stroke. Observational studies and clinical trials support blood-pressure reduction for secondary prevention in most patients, regardless of the initial blood-pressure level. Data are lacking to determine the most effective blood-pressure target and extent of lowering, and guidelines recommend that treatment be individualized, but benefits have been linked to absolute blood-pressure reductions of approximately 10/5 mm Hg.8 Given data suggesting the risks of immediate blood-pressure lowering after stroke, caution is warranted in the acute care setting.8,22

A systematic review of trials of secondary prevention after stroke with the use of agents in various classes of antihypertensive drugs showed reductions in all strokes, nonfatal strokes, myocardial infarction, and all vascular events; the magnitude of the reduction in stroke risk was directly related to the degree of systolic-blood-pressure lowering.23 In the Perindopril Protection against Recurrent Stroke Study (PROGRESS),11 patients with a prior stroke or TIA were randomly assigned to treatment with an angiotensin-converting–enzyme (ACE) inhibitor (plus the diuretic indapamide, at the discretion of the physician) or placebo. There was a 28% lower risk of stroke over a period of 4 years in the ACE-inhibitor group, with an average blood-pressure reduction of 9/4 mm Hg. Data from another large trial involving high-risk patients, including those with a prior stroke, also support blood-pressure lowering with an ACE inhibitor.24

Whether the benefits of blood-pressure lowering depend on the particular class of antihypertensive drugs or simply on the antihypertensive effect of all such drugs remains controversial, although most of the evidence appears to support the latter.25 The PROGRESS trial showed a greater reduction in the risk of stroke and other vascular outcomes among patients treated with a combination of an ACE inhibitor and a diuretic than among those treated with an ACE inhibitor alone, but blood-pressure reduction was greater with combination therapy.11 One secondary-prevention trial showed a reduction in the combined incidence of stroke and TIA with an angiotensin-receptor blocker (ARB) as compared with a calcium antagonist, despite similar effects on blood pressure.26 Yet a much larger trial, the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study, failed to show a significant benefit of an ARB over placebo in reducing the risk of recurrent stroke27; however, the negative results may

Figure 1. Imaging Studies in a Woman with an Ischemic Stroke.
In Panel A, a diffusion-weighted MRI scan shows an acute infarction in the territory of the left middle cerebral artery. In Panel B, CTA shows severe stenosis of the left internal carotid artery (arrow).
**Table 1. Strategies of Proven Benefit for Secondary Prevention of Stroke.**

<table>
<thead>
<tr>
<th>Indication and Strategy</th>
<th>Study</th>
<th>Key Trial or Meta-Analysis</th>
<th>Results†</th>
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<tr>
<td>Blood-pressure lowering</td>
<td>PROGRESS: ACE inhibitor plus diuretic vs. placebo; primary end point: total strokes</td>
<td>RRR, 28.0%; ARR, 4.00 percentage points; NNT, 97</td>
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<td>Cholesterol lowering (statin)</td>
<td>SPARCL: statin vs. placebo; primary end point: first stroke</td>
<td>RRR, 16.0%; ARR, 2.20 percentage points; NNT, 220</td>
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<tr>
<td>Antiplatelet therapy (unless anticoagulation indicated)</td>
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<tr>
<td>Aspirin (first-line therapy)</td>
<td>ATTC: aspirin vs. placebo; primary end points: nonfatal stroke, nonfatal MI, and death from vascular causes</td>
<td>RRR, 13.0%; ARR, 1.00 percentage points; NNT, 100§</td>
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<td>Clopidogrel</td>
<td>CAPRIE: clopidogrel vs. aspirin; primary end points: ischemic stroke, MI, and death from vascular causes</td>
<td>RRR, 8.7%; ARR, 0.51 percentage points; NNT, 196</td>
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<tr>
<td>Aspirin plus dipyridamole</td>
<td>ESPS2: aspirin plus dipyridamole vs. aspirin; primary end point: stroke</td>
<td>RRR, 23.8%; ARR, 2.97 percentage points; NNT, 74</td>
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<td>Symptomatic high-grade stenosis: carotid endarterectomy</td>
<td>NASCET: carotid endarterectomy plus medical treatment vs. medical treatment alone; primary end point: any ipsilateral ischemic stroke</td>
<td>RRR, 65.0%; ARR, 17 percentage points; NNT, 9</td>
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<td>Atrial fibrillation</td>
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<td>Warfarin</td>
<td>EAFT: warfarin vs. placebo; primary end point: all strokes</td>
<td>RRR, 66.0%; ARR, 8.0 percentage points; NNT, 12</td>
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<tr>
<td>Dabigatran</td>
<td>RE-LY: dabigatran vs. warfarin; primary end points: stroke and systemic embolism</td>
<td>RRR, 34.0%; ARR, 0.58 percentage points; NNT, 172¶</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>ROCKET AF: rivaroxaban vs. warfarin; primary end points: stroke and systemic embolism</td>
<td>RRR, 13.0%; ARR, 0.30 percentage points; NNT, 333</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>ARISTOTLE: apixaban vs. warfarin; primary end points: stroke and systemic embolism</td>
<td>RRR, 21.0%; ARR, 0.33 percentage points; NNT, 303</td>
<td></td>
</tr>
</tbody>
</table>

*All trials are based on level 1 evidence. The list of trials is not comprehensive; instead, a definitive trial or meta-analysis is cited for each intervention. The number needed to treat (NNT) to prevent one primary-outcome event (secondary prevention) per year was calculated with the use of data on absolute risk reduction (ARR) during the mean or median trial follow-up period. All values are approximate and derived from previous analyses, Cochrane database reviews, or individual trials if these are the only data available. ACE denotes angiotensin-converting enzyme, ARISTOTLE Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation, ATTC Antithrombotic Trialists’ Collaboration, CAPRIE Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events, EAFT European Atrial Fibrillation Trial, ESPS2 European Stroke Prevention Study 2, MI myocardial infarction, NASCET North American Symptomatic Carotid Endarterectomy Trial, PROGRESS Perindopril Protection against Recurrent Stroke Study, RE-LY Randomized Evaluation of Long-Term Anticoagulation Therapy, ROCKET AF Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation, RRR relative risk reduction, and SPARCL Stroke Prevention by Aggressive Reduction in Cholesterol Levels.

† The RRR and ARR are annualized for all the studies except PROGRESS, SPARCL, ESPS2, and NASCET, for which the RRR and ARR are for the duration of the trial.

‡ The indication is routine in the absence of clinical contraindications.

§ The results are based on a meta-analysis of trials comparing aspirin with placebo in patients with a previous stroke or transient ischemic attack (TIA).

¶ The results are for dabigatran at a dose of 150 mg twice per day.
have been explained by the small reduction in blood pressure with active treatment.27

**CHOLESTEROL LOWERING WITH STATINS**
Cholesterol lowering with statin drugs, which is effective in primary stroke prevention, has also proved effective in secondary prevention after stroke or TIA. A subgroup analysis involving patients with a history of cerebrovascular disease in the Heart Protection Study with an initial total cholesterol level of at least 135 mg per deciliter (3.5 mmol per liter) showed that simvastatin (at a dose of 40 mg per day), as compared with placebo, resulted in a 20% reduction in the risk of all vascular end points and a 25% reduction in the risk of stroke.28 In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study,12 a placebo-controlled trial involving patients with a recent TIA or stroke and baseline low-density lipoprotein (LDL) cholesterol levels of 100 to 190 mg per deciliter (2.6 to 4.9 mmol per liter), those randomly assigned to atorvastatin (at a dose of 80 mg per day) had significant reductions in the risks of stroke and all cardiovascular events (absolute risk reductions, 2.2 percentage points and 3.5 percentage points, respectively, over a period of 5 years). The benefits appear to be greatest in patients with the greatest reductions in LDL levels (50% or more).29 Secondary-prevention guidelines recommend treatment for patients with an LDL cholesterol level of 100 mg per deciliter (2.6 mmol per liter) or higher, with the aim of reducing the level by at least 50% or achieving a target level of less than 70 mg per deciliter (1.8 mmol per liter).4 Despite the overall benefit, statins have been associated with a slightly increased risk of intracerebral hemorrhage, and their use may be contraindicated in patients with the disorder.12,30

**ANTIPLATELET THERAPY**
Unless anticoagulation is indicated, patients should receive antplatelet therapy for secondary stroke prevention. In trials involving high-risk patients, including those with a history of stroke, aspirin reduced the risk of subsequent vascular events overall by about a quarter.13 However, a meta-analysis of trials specifically of aspirin (vs. placebo), limited to patients with a prior stroke or TIA, suggested that aspirin reduced the risk of subsequent vascular events by only 13%.14 Low doses of aspirin (ranging from 75 to 325 mg per day) appear to be as effective as higher doses in reducing the risk of stroke, with a lower risk of gastrointestinal toxic effects.

Secondary-prevention trials have also shown benefits of other antiplatelet strategies. Both clopidogrel (an adenosine diphosphate–receptor inhibitor)35 and the combination of aspirin plus dipyridamole (a phosphodiesterase inhibitor)16,31 were shown in randomized trials to be superior to aspirin, but the absolute benefits were very small. In a trial comparing the combination of aspirin plus dipyridamole with clopidogrel for the prevention of recurrent stroke, outcomes were similar in the two treatment groups.32 Current guidelines indicate that aspirin alone, clopidogrel, and aspirin plus dipyridamole are all acceptable first-line options in secondary stroke prevention.8 Randomized trials have shown no benefit, and increased hemorrhagic risks, with the combined use of clopidogrel and aspirin as compared with clopidogrel alone33 or aspirin alone34 for long-term secondary prevention after stroke. In the Secondary Prevention of Small Subcortical Strokes (SPS3; ClinicalTrials.gov number, NCT00059306) trial, which is evaluating antiplatelet therapy with aspirin plus clopidogrel versus aspirin alone, as well as two approaches to blood-pressure lowering, the combination antiplatelet therapy was recently terminated prematurely owing to excess hemorrhages and deaths.

Short-term use of the combination of aspirin and clopidogrel has been proposed early after stroke or TIA, when the risk of recurrent stroke is highest (Table 2). A brief duration of exposure would be expected to reduce the risks associated with combination therapy. In a randomized, controlled pilot trial, the rate of stroke recurrence at 90 days was 10.8% among patients randomly assigned to aspirin within 24 hours versus 7.1% among those randomly assigned to combined aspirin and clopidogrel; this difference was not significant, but the trial was underpowered.35 A larger trial comparing these regimens is under way (NCT00991029).

**CAROTID ENDARTERECTOMY AND CAROTID-ARTERY STENTING**
Carotid endarterectomy is indicated for the treatment of patients with a history of TIA or nondisabling ischemic stroke who have high-grade (70 to 99%) carotid stenosis or, in selected cases, moderate (50 to 69%) stenosis.17,44-46 In the North
American Symptomatic Carotid Endarterectomy Trial (NASCET), participants with high-grade carotid stenosis who were randomly assigned to endarterectomy had an absolute reduction of 17 percentage points in the risk of stroke over a period of 18 months. Surgery resulted in a more modest benefit (absolute risk reduction of 6.5 percentage points over a period of 5 years) in patients with moderate stenosis and no benefit in those with mild (<50%) stenosis. Careful attention to the results of carotid endarterectomy in any given center is essential to ensure that the surgical risks do not exceed those in the clinical trials.

The timing of carotid endarterectomy after a TIA or ischemic stroke involves balancing the risk of early recurrent events with the risk of reperfusion injury and hemorrhagic transformation. Early intervention, within 2 weeks after the onset of symptoms, is now recommended, given evidence that the benefits of surgery rapidly diminish with increasing time since the ischemic event.

The use of carotid-artery stenting as an alternative to carotid endarterectomy is more controversial. Carotid-artery stenting is less invasive than endarterectomy and is associated with a more rapid recovery and a much lower risk of cranial-nerve palsies. However, studies have shown that the periprocedural risks (chiefly death and recurrent stroke within 30 days) are significantly higher with carotid-artery stenting than with carotid endarterectomy. In the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), these risks were offset by a reduced rate of myocardial infarction in the stenting group, such that overall outcomes (stroke, myocardial infarction, and death) were similar with the two procedures at 30 days and at 4 years. However, the purported equivalence of these procedures has been questioned, given that the longer-term health effects of stroke outweigh those of myocardial infarction. Data from CREST and European stenting trials indicate that the relative benefits and risks of the procedures vary according to age. In patients older than 70 years of age, carotid endarterectomy appears to be superior to carotid-artery stenting, whereas in patients 70 years of age or younger, the periprocedural risks of stroke and death are similar with the two procedures, and carotid-artery stenting (performed by interventionists with acceptable complication rates) is a reasonable alternative to ca-

| Table 2. Controversial or Investigational Secondary-Prevention Strategies.a |
|-----------------------------|-----------------------------|-----------------------------|
| Target                     | Possible Strategy           | Comments                     |
| Early recurrent stroke     | Combined aspirin and clopidogrel for 90 days from stroke onset | Increased risk with combination therapy vs. aspirin or clopidogrel alone, but meta-analysis suggests possible benefit of combination therapy after a TIA or minor stroke; POINT (NCT00991029): combination therapy vs. aspirin, ongoing |
| Carotid stenosis           | Carotid-artery stenting     | Higher risks of periprocedural stroke and death with stenting than with endarterectomy, although risks similar with the two treatments among patients 70 years of age or younger |
| Aortic-arch atheroma       | Antiplatelet therapy vs. anticoagulation | Common cause of stroke; most effective treatment unknown; ARCH (NCT00235248): aspirin plus clopidogrel vs. warfarin, ongoing |
| Intracranial arterial stenosis | Intracranial stenting       | Higher rates of stroke and death with intracranial stenting than with aggressive medical therapy in one trial (SAMMPRIS), but other trials ongoing |
| Carotid dissection         | Antiplatelet therapy vs. anticoagulation | Optimal treatment unclear; CADISS (NCT00238667): aspirin vs. warfarin, ongoing |
| Patent foramen ovale       | Percutaneous closure device vs. medical therapy | No benefit observed with percutaneous closure in CLOSURE I; other trials ongoing |

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a ARCH denotes Aortic Arch Related Cerebral Hazard, CADISS Cervical Artery Dissection in Stroke Study, CLOSURE I Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale, POINT Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke, and SAMMPRIS Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis.
Atrial fibrillation causes at least 15% of cases of ischemic stroke. Dose-adjusted warfarin has been the mainstay of therapy. A meta-analysis of trials comparing warfarin with placebo or aspirin showed reductions in the risk of stroke of 60% and 40%, respectively, although these were chiefly primary-prevention trials. Warfarin has also been shown to be more effective than aspirin or the combination of aspirin plus clopidogrel for secondary prevention of stroke in patients with atrial fibrillation.

Newer oral anticoagulant strategies, which do not require monitoring, are now available and are likely to replace warfarin in many cases, although they are more costly. In a randomized trial of patients with atrial fibrillation (20% of whom had a prior stroke or TIA), dabigatran (a direct thrombin inhibitor), at a dose of 150 mg twice per day, was superior to warfarin in the prevention of stroke or systemic embolism, with a similar risk of overall major bleeding but a significantly lower risk of intracranial hemorrhage. At a lower dose (110 mg twice per day), dabigatran was noninferior to warfarin, with a lower risk of overall major bleeding. Randomized trials have also shown the efficacy of factor Xa inhibitors in reducing stroke risk among patients with atrial fibrillation. Like dabigatran, rivaroxaban was noninferior to warfarin, with a lower risk of bleeding. Apixaban has been shown to be superior to warfarin, with reductions in the risk of bleeding and mortality, and for persons in whom warfarin has unacceptable adverse effects, apixaban has been shown to be superior to aspirin.

Areas of Uncertainty

Patent foramen ovale is more common in patients with cryptogenic stroke than in the general population, and patients with both patent foramen ovale and atrial septal aneurysm appear to be at increased risk for stroke. Antiplatelet therapy is generally recommended for patients with patent foramen ovale after a stroke or TIA. The efficacy and safety of endovascular closure for the prevention of recurrent stroke in such patients remains questionable; one recent trial showed no benefit of endovascular closure.

Studies of secondary-prevention strategies for other conditions associated with an increased risk of stroke, including aortic-arch atheroma and intracranial atherosclerosis, are needed; intracranial atherosclerosis accounts for up to 50% of ischemic strokes in Asian populations. Antiplatelet therapy and intensive risk-factor management are recommended for such patients. A randomized trial comparing warfarin with aspirin in patients with stroke or TIA caused by intracranial stenosis was terminated early owing to higher risks of adverse outcomes with warfarin, and a trial comparing angioplasty and stenting with aggressive medical management in such patients was halted because of increased hazards with stenting.

Arterial dissection is one of the most common causes of stroke in young adults; the most effective therapy after a dissection remains unclear. A large trial comparing aspirin and warfarin in such patients is under way (NCT00238667).
REFERENCES


44. European Carotid Surgery Trialists’ Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 1991;337:1235-43.


Lichen Planus

Laurence Le Cleach, M.D., and Olivier Chosidow, M.D., Ph.D.

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

A 53-year-old woman presents with intensely itchy skin lesions and burning in her mouth, which makes eating difficult. These signs and symptoms have become progressively evident during the past several weeks. Examination of her skin and oral cavity reveals violaceous, polygonal papules, mainly on the flexural aspect of the wrists and ankles and in the lumbar region, as well as erosions associated with a lace-like, white-line network apparent in the posterior buccal mucosa. How should this case be managed?

THE CLINICAL PROBLEM

Lichen planus is a mucocutaneous inflammatory disease of unknown origin. The skin and oral mucosa are the most frequently involved areas. Other mucous membranes (including the genitalia, esophagus, and conjunctiva) and skin appendages (e.g., scalp hair and nails) can also be affected. One or several areas can be involved, either concomitantly or sequentially.

The clinical presentation of lichen planus varies depending on the area involved (Fig. 1A through 1F and Table 1). Cutaneous lichen planus is characterized by flat-topped, violaceous papules (Fig. 1A and 1B), the appearance of which may cause embarrassment and which in some cases can be intensely itchy. The lesions may result in long-standing residual hyperpigmentation, especially in dark-skinned patients. (Less common variants of cutaneous disease are shown in the figure in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Oral lichen planus is characterized by symmetric reticular lesions that resemble a white, lanacike network, as well as by papules, plaques, erythematous lesions, and erosions (Fig. 1C); it is a chronic disease, and its erosive form is painful. The clinical characteristics of anogenital lichen planus (Fig. 1D and 1E) are typically similar to those of both the cutaneous and the oral forms. The erosive form of mucosal lichen planus may result in fibrosis, with vulvar scarring, vaginal stenosis, phimosis, esophageal stricture, blindness, or obstruction of the lachrymal canal. Progressive scarring can also affect the nails and scalp.

According to population-based data from Sweden, the prevalence of cutaneous lichen planus among men is 0.3% and the prevalence of oral lichen planus is 1.5%; the respective prevalences among women are 0.1% and 2.3%. A large study of patients who presented with oral lesions revealed prior or current cutaneous lesions in 16% and genital disease in 19%, with rare cases of esophageal, nail, or conjunctival disease, whereas substantially higher rates of concomitant genital or esophageal disease have been noted on systematic histologic examination in patients with oral or cutaneous disease.
Women account for 60 to 75% of patients with oral lichen planus and 50% of those with cutaneous lichen planus. The mean age at diagnosis is between 50 and 60 years for oral disease and between 40 and 45 years for the cutaneous form. Lichen planus is uncommon in children (accounting for less than 5% of cases).

Oral lichen planus is generally considered a potentially premalignant condition; a 1% incidence of squamous-cell carcinoma has been reported among patients with this condition in both retrospective and prospective cohort studies. However, the true risk remains controversial, given the heterogeneous diagnostic criteria for lichen planus across studies (and the difficulty in discriminating it from other premalignant conditions), the variation in the duration of follow-up, and the potential confounding by associated risk factors (e.g., alcohol consumption and smoking). Case reports have also described squamous-cell carcinomas arising from chronic anogenital, esophageal, or hypertrophic cutaneous lichen planus lesions.

Although the pathogenesis of lichen planus remains unclear, it appears to be an autoimmune disease. The basal keratinocyte degeneration observed in lichen planus is attributed to cytotoxic CD8+ T lymphocytes, which are the major component of the infiltrates located within the epithelium and adjacent to damaged keratinocytes. The triggering antigen is not known. The existence of rare cases of familial lichen planus and the overrepresentation of certain HLA haplotypes (e.g., HLA-DR1 in cutaneous lichen planus) suggest that genetic factors have a role in susceptibility to this disease. Several autoimmune disorders, particularly alopecia areata and ulcerative colitis, have been reported to occur more frequently in patients with lichen planus than in control populations.

There is a significant association between lichen planus and infection with hepatitis C virus (HCV). In two meta-analyses, patients with lichen planus were reported to be approximately 5 times as likely as controls to be HCV-seropositive; moreover, lichen planus was 2.5 to 4.5 times as likely to develop in the HCV-seropositive patients.

Lichen planus has adverse effects on both quality of life and psychological status. Factors that contribute to these detrimental effects include pain and difficulties with eating and with sexual function in association with mucosal disease.

**KEY CLINICAL POINTS**

**LICHEN PLANUS**

- Lichen planus is a mucocutaneous inflammatory disease of unknown origin that involves mainly the skin and oral mucosa.
- The major burdens of lichen planus are itching and residual hyperpigmentation in the cutaneous form and pain and difficulties with eating in the oral erosive form.
- With the exception of the cutaneous form, which generally heals within 1 year, lichen planus is a chronic condition.
- Given reports of a significant association between lichen planus and infection with the hepatitis C virus (HCV), HCV serologic testing should be considered in all affected patients.
- In the case of lesions that persist despite treatment, biopsy specimens should be assessed for early dysplasia or squamous-cell carcinoma, since these conditions have been reported in association with lichen planus.
- Data from randomized, controlled trials are limited, and management choices are based mainly on clinical experience.
- Superpotent topical glucocorticoids are the usual first-line treatment for lichen planus.
Figure 1. Clinical Presentations of Lichen Planus.
Panel A shows widespread eruption of violaceous, shiny, isolated, flat-topped papules and plaques, which are most profuse on the ankles and in the lumbar region; the legs and neck are also frequently involved. As shown in Panel B, polygonal, violaceous papules, with a lacelike, white-line network (arrow), are most frequently seen on the inner aspect of the wrist. Panel C shows the oral lesions of lichen planus, which are bilateral and symmetric and are associated with a network of white-lined plaques (left arrowhead) and erosive lesions (arrow) in the posterior buccal mucosa and with a white-line network (right arrowhead) on the top of the tongue. Areas of the oral mucosa mainly affect the posterior lining of the cheek (in 73% and 91% of cases), the gingiva (33% and 57%), and the tongue (44% and 54%).\textsuperscript{3,4} Panel D shows a white-line network within an erosive plaque on the glans penis. Panel E shows a white-line network on the internal aspects of the labia minora and majora, which are the sites that are usually affected in anogenital lichen planus; the vagina is involved in about 50% of cases\textsuperscript{5} and the perianal area in about 20% of cases.\textsuperscript{5} Panel F shows nail thinning, with longitudinal ridging and distal splitting linked to matrix involvement in these two fingernails; fingernails are involved more frequently than toenails. Panel G shows follicular, violaceous erythema and acuminated keratotic plugs surrounding the zone of alopecia. The plaques are multifocal and occur most frequently on the vertex; other hairy areas can also be involved. The skin specimen in Panel H shows the characteristic histologic features of lichen planus: thickening of the stratum corneum, with orthokeratosis (thick arrow), accentuation of the granular-cell layer (thin arrow), liquefactive degeneration of the basal-cell layer (arrowhead), and bandlike inflammatory-cell infiltrate (asterisk) (hematoxylin and eosin).
diagnoses, which vary depending on the clinical presentation, are reviewed in Table 1 in the Supplementary Appendix.

Drug-induced lichen planus, also known as lichenoid drug eruption, is uncommon and may be indistinguishable from typical idiopathic lichen planus\(^ {25-29}\) (Table 1 in the Supplementary Appendix). A careful drug history is routinely warranted; in rare cases, drugs that have been taken for as long as 2 years before cutaneous lesions develop have been considered to be the likely cause of the lesions.

Histologic examination of skin or mucosal biopsy specimens is useful to confirm the diagnosis in atypical cases, as well as to avoid inappropriate treatment in cases of severe disease. Histologic findings are the same, regardless of the area involved (Fig. 1H). For persistent lesions that do not disappear with treatment, biopsy should be performed to rule out early dysplasia or squamous-cell carcinoma.\(^ {18}\)

Given the recognized associations between lichen planus and HCV infection, screening for anti-HCV antibodies with the use of an enzyme-linked immunosorbent assay (ELISA) is recommended. Some experts believe that for purposes of cost-effectiveness, such screening should be reserved for patients known to be at risk for acquiring HCV (e.g., intravenous drug abusers),\(^ {30}\) whereas other experts recommend screening all patients with

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**Table 1. Typical Symptoms and Particular Patterns of Lichen Planus, with Possible Outcomes and Complications.**

<table>
<thead>
<tr>
<th>Location</th>
<th>Symptoms</th>
<th>Particular Patterns</th>
<th>Outcomes and Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body</td>
<td>Itching</td>
<td>Koebner’s phenomenon: lesion at site of traumatic injury (e.g., from scratching); soles affected more frequently than palms, with bilateral involvement; seen as erythematous scaly plaques, hyperkeratosis</td>
<td>Spontaneous healing, usually within 1 yr; long-lasting residual pigmentation</td>
</tr>
<tr>
<td>Mouth</td>
<td>Soreness, pain, burning, swelling, irritation, bleeding; isolated reticular form usually asymptomatic</td>
<td>White forms (reticular, papular, plaquelike); white, lacy like net-work, papules, plaques; seen in 35%(^ 3) and 59%(^ 4) of cases; red forms (eroseive, atrophic, bullous); erythematous lesions with or without erosive lesions associated with reticular lesions; seen in 41%(^ 3) and 64%(^ 4) of cases</td>
<td>Poor tendency to heal spontaneously in about 2.5%(^ 6); periods of exacerbation</td>
</tr>
<tr>
<td>Genital area</td>
<td>Burning, itching, pain, dyspareunia, impaired sexual function</td>
<td>Vulvovaginogingival or penogingival syndrome: association between erosive genital lichen planus and gingivitis</td>
<td>Vulvar scarring in erosive forms (95% frequency)(^ 3); synchiase with vaginal stenosis and labia minora aggluti-nation in females, phimosis in males</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Odynophagia, dysphagia</td>
<td>Endoscopic findings: stricture mainly located in whitish papules, erythema, mucosal sloughing</td>
<td>Chronic stricture</td>
</tr>
<tr>
<td>Scalp</td>
<td>Itching, pain and burning during inflammatory phase</td>
<td>Frontal fibroging alopecia: progressive frontal–temporal hairline recession in postmenopausal women; Lassueur–Graham-Little–Piccardi syndrome: patchy, scarring alopecia associated with follicular lichenoid eruption and loss of axillary and pubic hair</td>
<td>Chronic and progressive; atrophic, scarring alopecia with absence of follicular units</td>
</tr>
<tr>
<td>Nails</td>
<td>Pain, burning</td>
<td>Lichen planus of the nail bed leading to onycholysis and subungual hyperkerato-sis</td>
<td>Recovery with treatment, but with frequent relapses; in rare cases, nail loss or pterygium unguis (permanent advancement of medial skin over the nail plate, bisecting the nail)</td>
</tr>
</tbody>
</table>
lichen planus; the choice of screening approach should be based on the local seroprevalence of HCV. Routine screening for other immune-mediated conditions is not thought to be warranted, although these disorders should be considered in patients with suggestive symptoms or signs.

**MANAGEMENT**

Therapeutic objectives depend on the location and severity of the lesions. Since data from randomized, controlled trials are limited, treatment choices are guided largely by clinical experience. Table 2 summarizes commonly used therapies and their indications. (See Table 2 in the Supplementary Appendix for an expanded list, including therapies used for nail and scalp lichen planus, as well as systemic immunosuppressive therapies.)

**Cutaneous Lichen Planus**

Because the cutaneous form of lichen planus may resolve spontaneously, the goals of therapy are to shorten the time between onset and resolution of the lesions and to reduce itching. In one study, clearing of lesions occurred within 1 year in two thirds of patients with cutaneous disease who were treated with various regimens. Topical glucocorticoids are used as the first-line treatment, although their efficacy has not been demonstrated in well-designed, randomized, controlled trials. Data from studies in which various topical glucocorticoids are compared are lacking. Topical retinoids are not prescribed for this condition because of the risk of irritation.

When topical glucocorticoids are ineffective, oral glucocorticoid therapy is sometimes used. In a small, randomized, controlled trial in which hydrocortisone 17-butyrate cream alone was compared with oral prednisolone (30 mg per day for 10 days) in combination with twice-daily administration of hydrocortisone 17-butyrate cream, similar numbers of patients in the two treatment groups were reported to have clearing of lesions at 18 weeks, but the time to clearing was significantly shorter in the group given prednisolone (18 weeks, vs. 29 weeks in the group given the topical cream alone); the limitations of this study preclude reliable conclusions.

Oral retinoids are also used. If these agents are prescribed to women of childbearing age, adequate contraception is mandatory (Table 2). In a randomized, controlled trial, the rates of lesion regression or remission at 8 weeks were significantly higher with acitretin (30 mg per day for 8 weeks) than with placebo.

Another option is phototherapy, although this treatment should be used cautiously in dark-skinned patients, who have an increased risk of residual hyperpigmentation. In a small trial involving 10 patients, psoralen and ultraviolet A (PUVA) therapy three times weekly on one side of the body was compared with no treatment on the other side of the body. After a mean period of 6 weeks, complete clearance (nonpalpable lesions) was noted in half the patients on the treated side only; 2 patients with no response had flares while taking the therapy. Data from randomized trials of narrow-band ultraviolet B therapy are lacking. In a retrospective, observational study, 70% of patients who were treated with narrow-band ultraviolet B therapy had a complete response within a mean of 11 weeks.

**Oral Lichen Planus**

Reticular oral lichen planus is usually asymptomatic and does not require treatment. For erosive oral lichen planus, the goals of treatment are to heal erosive lesions and to lessen pain and the associated difficulty in eating and drinking. Topical glucocorticoids are the first-line therapy. In two small, randomized, placebo-controlled trials — one of fluocinonide and the other of betamethasone valerate — the rates of cure or attenuation were significantly higher in the active-treatment group than in the placebo group (80% with fluocinonide vs. 30% with placebo, and 66% with betamethasone vs. 18% with placebo).

Oral glucocorticoids (e.g., prednisone, at a dose of 0.5 to 1.0 mg per kilogram of body weight per day, typically given for 4 to 6 weeks) are generally used for erosive lesions that do not respond sufficiently to topical glucocorticoids and as first-line therapy for severe erosive oral lichen planus associated with eating difficulties. However, data showing the efficacy of this approach are lacking, and side effects are common. In one randomized trial, in which topical triamcinolone was compared with low-dose oral betamethasone (5 mg per day for 3 months, followed by a slow taper during the ensuing 3 months), the only significant between-group difference was a shorter time to healing in the group of patients treated with systemic glucocorticoids (15.5 weeks, vs. 19.0 weeks with triam-
Table 2. Therapies Commonly Used for Lichen Planus.*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Uses and Recommendations</th>
<th>Potential Harmful Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical glucocorticoids†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superpotent topical glucocorticoids</td>
<td>For symptomatic oral lichen planus: first-line treatment applied with gloved finger 3 times daily; patient should avoid eating and drinking for 1 hr after application; for anogenital lichen planus: first-line treatment applied once daily; for thickened lesions of cutaneous lichen planus: first-line treatment applied once daily (under an occlusive bandage for hypertrophic lichen planus)</td>
<td>Oral or genital candidiasis; long-term use can lead to epidermal atrophy and systemic effects (e.g., suppression of the hypothalamic–pituitary–adrenal axis, cushingoid features, diabetes mellitus, bone loss, avascular necrosis)</td>
<td>Glucocorticoids are not formulated for oral or vaginal mucosa, and no randomized, controlled trials have compared the different formulations available; if no improvement after 6 wk, change therapeutic strategy; tailor maintenance therapy to patient’s clinical course: reduce frequency of application, use a less potent glucocorticoid, or both</td>
</tr>
<tr>
<td>Potent topical glucocorticoids</td>
<td>For less severe forms of lichen planus or for maintenance therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone tablet soluble in water</td>
<td>For widespread oral lichen planus: used as mouthwash, 5 mg in 15 ml water, 3 times daily</td>
<td></td>
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</tr>
<tr>
<td>Hydrocortisone suppositories, foam, or</td>
<td>For vaginal lichen planus: applied every other day</td>
<td></td>
<td></td>
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<tr>
<td>cream</td>
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<td></td>
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<tr>
<td><strong>Systemic glucocorticoids</strong></td>
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<tr>
<td>Oral prednisone, 0.5 to 1.0 mg/kg of body weight/day, for 4 to 6 wk; or intramuscular triamcinolone acetonide</td>
<td>For severe mucosal erosive lichen planus or for nail lichen planus that involves more than three nails: first-line treatment; for severe lichen planus that is resistant to topical glucocorticoids: second-line treatment</td>
<td>Characteristic side effects of systemic glucocorticoids</td>
<td>After remission, taper slowly</td>
</tr>
<tr>
<td><strong>Topical retinoids</strong></td>
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<tr>
<td>Retinoic acid or isotretinoin lotion or gel (0.1%)</td>
<td>For oral lichen planus with papular and plaquelike form (without erosive lesions): first-line treatment, either alone or with topical glucocorticoids, 2 times daily</td>
<td>Burning sensation after application; prohibited during pregnancy and breastfeeding; requires adequate birth control</td>
<td>Not indicated for lichen planus at other sites</td>
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cinolone), and half the patients had side effects (twice the rate in the topical-therapy group).

Topical calcineurin inhibitors (cyclosporine, pimecrolimus, and tacrolimus), although proposed as possible therapy for this disorder, are not recommended. They are not approved by the Food and Drug Administration (FDA) for this indication, and current FDA labeling states that these drugs should not be given to treat premalignant conditions. A recent Cochrane review concluded that evidence to support the contention that topical cyclosporine reduces pain and clinical signs of oral lichen planus is weak and unreliable and that there is no evidence to support the notion that pimecrolimus reduces pain, as compared with topical glucocorticoids or placebo.

For papular and plaquelike lichen planus without erosive lesions, either topical glucocorticoids or topical retinoids are used as first-line treatment. In two small, randomized, placebo-controlled trials in which 0.1% tretinoin lotion was applied for 4 months, twice daily, and 0.1% isotretinoin gel was applied for 8 weeks, twice daily, both the active treatments were superior to placebo. Attenuation was observed in 97% of the lotion-treated patients versus 21% of those given placebo and in 90% of the gel-treated patients versus 10% of those given placebo. A randomized trial comparing a topical glucocorticoid (0.1% fluocinolone acetonide) with topical 0.05% retinoic acid for patients with atrophic and erosive oral lichen planus showed the former treatment to be significantly more effective, with complete resolution in 90% of the glucocorticoid group versus 40% of the retinoid group.

Anogenital Lichen Planus

For erosive genital lesions, the major therapeutic aims are to prevent or limit scarring. In a prospective cohort study of women with erosive vulvar lichen planus, symptoms were attenuated in 71% of the women who applied 0.05% clobetasol propionate ointment (a superpotent topical glucocorticoid) twice daily, but complete resolution (except for scarring) was uncommon. Synechiae formation may be prevented with the use of vaginal dilators, and, for uncircumcised men, foreskin retraction. When adhesions form, surgery may be required, but it should be delayed in order to avoid complications with healing. Since lichen planus has been reported to occur less frequently in circumcised men than in uncircumcised men, circumcision may be indicated in patients with refractory vulvar or penile lesions.

Systemic Retinoids

Acitretin, 30 mg/day, for 8 wk

Teratogenicity, elevation of liver enzymes, hyperlipidemia

For women of childbearing age, two effective forms of contraception are mandatory during treatment and for 3 yr afterward.

Phototherapy

PUVA or narrow-band ultraviolet B therapy: 2 or 3 times a week, for a total of 12 sessions (i.e., 1 cycle)

Increased risk of skin cancer (but does not appear to be significant if therapy is limited to 1 or 2 cycles of 12 sessions each); increased risk of residual pigmentation

* Levels of evidence for specific choices of treatment are described in the text. (An expanded version of this table is available in the Supplementary Appendix.) PUVA denotes psoralen and ultraviolet A.

† Gloves should be worn when one is applying topical glucocorticoids in order to prevent side effects of the medication.

‡ Superpotent glucocorticoids in Orabase (Colgate), as a commercial formulation or one prepared by a pharmacist, can also be used.

§ For cutaneous lichen planus, the choice among second-line therapies should be based on the presence or absence of concomitant erosive mucosal lichen planus, the severity of the lesions, childbearing potential, and the availability of phototherapy.

For cutaneous lichen planus, the choice among second-line therapies should be based on the presence or absence of concomitant erosive mucosal lichen planus, the severity of the lesions, childbearing potential, and the availability of phototherapy.
uncircumcised men,\textsuperscript{43} removal of the foreskin is usually recommended.

**Nail Lichen Planus**
The objectives of treatment in lichen planus of the nails are to lessen pain and to prevent or limit scarring. In two retrospective case series, a total of 142 patients were treated with systemic glucocorticoids (intramuscular injection or oral administration), local glucocorticoids (intraleisional injection or topical application), or both.\textsuperscript{10,11} Cure or major improvement was reported in two thirds of the patients after an average treatment period of 6 months; however, relapses were common.

**Scalp Lichen Planus**
Topical glucocorticoids, either alone or combined with an intraleisional glucocorticoid injection, are the first-line treatment for lichen planopilaris.\textsuperscript{12,44} In a retrospective chart review, 20 of 30 patients who were treated with topical glucocorticoids (potency level not specified) were found to have complete clearing of lesions after 12 weeks.\textsuperscript{45} Lichen planopilaris that is severe or is resistant to local glucocorticoid therapy is commonly treated with systemic glucocorticoids, although data on the efficacy of this approach are lacking.

### AREAS OF UNCERTAINTY

It remains uncertain whether, and if so to what extent, lichen planus is an independent risk factor for the development of squamous-cell carcinoma, as well as whether, and if so how, patients with lichen planus should be monitored for this neoplasm.\textsuperscript{7,17} Randomized trials are needed to provide better guidance in the choice of the various therapies available for the different types of lichen planus\textsuperscript{31,39} and to assess the benefits and risks of several medications that have been described to be effective in case reports or small case series. Examples of such medications include topical rapamycin (now known as sirolimus)\textsuperscript{46} and extracorporeal photochemotherapy\textsuperscript{47} for erosive oral lichen planus; methotrexate for cutaneous lichen planus\textsuperscript{48}; a peroxisome proliferator–activated receptor agonist for lichen planopilaris\textsuperscript{49}; and anti-CD20 monoclonal antibody for oral, genital, and esophageal lichen planus.\textsuperscript{50} Two randomized, controlled trials comparing aloe vera with placebo for the treatment of oral lichen planus yielded inconsistent results,\textsuperscript{51,52} so further study is warranted. It remains unclear how long maintenance treatment should be continued for mucosal, scalp, nail, and esophageal disease, for which there are currently no curative therapies.

### GUIDELINES

Guidelines for managing oral lichen planus have been published by the British Society for Oral Medicine,\textsuperscript{53} and guidelines for managing vulvar lichen planus have been published by the British Association for Sexual Health and HIV.\textsuperscript{54} The recommendations provided below are generally consistent with these guidelines.

### CONCLUSIONS AND RECOMMENDATIONS

The woman described in the vignette has oral and cutaneous lesions that appear to be consistent with a diagnosis of lichen planus. In such patients, complete examination of the skin, including the scalp and nails, and of oral, genital, anal, and ocular areas, as well as a thorough gynecologic examination, should be performed to detect any evidence of lichen planus elsewhere. Serologic testing for HCV should be considered. Good oral hygiene should be recommended, and the patient should be told to avoid cigarette smoking, alcohol consumption, and the ingestion of spicy or acidic foods or beverages that can be painful in the presence of oral lesions.

We would initiate treatment with topical 0.05% clobetasol propionate ointment applied three times daily on erosive areas of the oral mucosa (an approach supported by data from randomized trials) and once daily, at night, on involved skin (an approach based largely on clinical experience), with a reevaluation after 6 weeks. If there is no response to treatment or if the response is insufficient and difficulties with eating persist, we would recommend oral glucocorticoids (e.g., prednisone at a dose of 0.5 to 1.0 mg per kilogram per day for 4 to 6 weeks, followed by a slow taper, to minimize the risk of relapse), although data from randomized trials assessing the efficacy of this therapy or comparing it with alternative approaches are lacking. If the patient has intense pain or loses weight, systemic rather than topical glucocorticoids can be considered as first-line treatment. Biopsy is war-
ranted if healing does not occur with treatment. Patients should be educated regarding the potential side effects of glucocorticoids and should be monitored to detect any such effects. Moreover, patients should understand the potentially chronic and relapsing course of oral lichen planus, as well as the need for long-term clinical surveillance.

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Whistling in the Dark

Daniel A. Solomon, M.D., Christopher H. Fanta, 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.

A 38-year-old woman living in Florida presented to her primary care physician with shortness of breath, fever, and cough productive of yellow sputum soon after the birth of her third child. She received a course of antibiotics for a presumed respiratory tract infection, and her symptoms resolved. Soon thereafter, however, she returned to her physician with an intermittent, nonproductive cough, wheezing, and shortness of breath. She was unable to identify any specific exposures that might have provoked these symptoms, although she noted that her symptoms tended to worsen at night. She reported no fever, orthopnea, leg swelling, or aspiration with swallowing, but she had a history of episodic retrosternal burning that was consistent with gastroesophageal reflux.

Recurrent episodes of shortness of breath, cough, and wheezing suggest a diagnosis of asthma. Nocturnal worsening of symptoms is consistent with this diagnosis. Atypical features, opening the possibility of alternative diagnoses, are the relatively late age at onset and the absence of identifiable triggers for the symptoms. Other potential causes of her symptoms include recurrent respiratory tract infections (due to being the mother of young children), gastroesophageal reflux with microaspiration of gastric contents, and congestive heart failure, including that resulting from valvular heart disease or diastolic dysfunction, which may cause “cardiac asthma.”

The patient’s other active medical problems included depression and seasonal allergic rhinitis. She had smoked cigarettes for approximately 10 years and quit 10 years before presentation. She was not employed and lived at home with three children and two golden retrievers. She had no history of aspirin intolerance or recurrent sinusitis. Her examination was notable for her body-mass index (BMI, the weight in kilograms divided by the square of the height in meters), which was 45.4, and loud, diffuse expiratory wheezing in both lungs.

The wheezing supports a possible diagnosis of asthma. Risk factors for adult-onset asthma include a history of cigarette smoking, atopy (suggested by her seasonal allergic rhinitis), and obesity. Aspirin-exacerbated respiratory disease is also a possibility because it often presents in adulthood with a characteristic sequence of recurrent sinusitis, followed by the development of asthma and then the recognition of exacerbations of asthma precipitated by ingestion of aspirin or any other cyclooxygenase-1 inhibitor. Her young age and limited smoking history (less than 20 pack-years) diminish the likelihood of a diagnosis of chronic obstructive pulmonary disease (COPD) in the absence of alpha1-antitrypsin deficiency.
Given her history and the findings on physical examination, the patient received an empirical diagnosis of asthma and was started on controller therapy with an inhaled glucocorticoid and a long-acting beta-agonist bronchodilator, together with a short-acting beta-agonist bronchodilator for the relief of acute symptoms. On skin tests for allergies, she reacted only to antigens from the house-dust mite.

A presumptive diagnosis of asthma was made on the basis of the patient’s symptoms, the findings on physical examination, and the initial improvement in her condition with antiasthma therapy. However, confirmatory evidence was lacking; specifically, the presence of airflow obstruction on pulmonary-function testing that abates over time or in response to the use of a quick-acting bronchodilator.

During the ensuing 5 years, the patient remained active but required hospitalization as often as once yearly for episodes of severe shortness of breath and wheezing, typically provoked by respiratory tract infections. The leukotriene-receptor antagonist montelukast was added to her treatment regimen but had little effect on her symptoms.

After a move from Florida to New Hampshire, her symptoms worsened. During the next 3 years, she required hospitalization every 3 to 4 months for respiratory distress, and on one occasion she required a brief period of mechanical ventilation for respiratory failure.

The patient now has severe disease that is refractory to seemingly appropriate treatment. At this point, the treating physician must make a systematic assessment of the possible reasons for the failure of treatment that is highly effective in most patients with asthma. Are there inciting factors, such as allergens or cigarette smoke, in the patient’s home (or work or school) environment that are intensifying the underlying inflammation in the airways? Could the lack of responsiveness to treatment be due to aggravating coexisting conditions (gastroesophageal reflux, uncontrolled rhinosinusitis, allergic bronchopulmonary aspergillosis, or Churg–Strauss syndrome) or aggravating agents (beta-blocker medications or illicit inhaled drugs)? Is the patient adhering to the treatment regimen, or is a lack of comprehension of the regimen, a lack of access to medications, fear of medication side effects, or an unconventional view of health care contributing to nonadherence? Is the diagnosis of asthma correct, or is an alternative disease mimicking asthma?

In an effort to reduce the frequency of disease flares, anti-IgE monoclonal antibody therapy was initiated and evoked a modest response. In addition, the patient was treated with multiple courses of oral glucocorticoids and ultimately with 15 mg of prednisone daily. Intermittent attempts to reduce the dose of prednisone resulted in symptomatic worsening. Despite treatment with daily systemic glucocorticoids, she received little relief, reporting a persistent barklike cough, wheezing on an almost daily basis, and severe exertional dyspnea. She was admitted to our hospital for further evaluation.

Despite maximal therapy, the patient’s symptoms have progressively worsened to the point that she takes oral glucocorticoids daily for symptom control. However, the worsening of symptoms when steroid doses are tapered does not necessarily indicate increased airway inflammation and obstruction. A range of symptoms can be associated with a dose reduction in patients who have undergone long-term treatment with systemic glucocorticoids, including weakness, lethargy, depression, decreased appetite, myalgias, and arthralgias, and such symptoms might have contributed to the difficulty in changing her treatment regimen. Objective measurement of lung function can help to distinguish the increased airflow obstruction characteristic of worsened asthma from the side effects of the withdrawal of glucocorticoids. Spirometry is preferable to peak-flow measurement in this circumstance because the patient’s effort is more readily assessed in the graphic display of the test results and because it is possible to distinguish a low peak flow that is caused by restriction (i.e., something other than asthma) from a low peak flow that is caused by obstruction. An objective assessment of airflow is warranted before the initiation of additional therapy, with its attendant costs and possible harms.

On admission to the hospital, the patient’s weight was approximately 128 kg (282 lb) and her height approximately 168 cm (66 in.); her blood pressure was 148/89 mm Hg, and her pulse 103 beats per minute and regular. She was afebrile. Her oxygen saturation was 96% at rest while breathing ambient air. Her breathing appeared uncomfortable,
but she was in no acute respiratory distress. Notable physical findings were a prolonged expiratory phase during respiration and diffuse expiratory wheezes that were audible with and without a stethoscope, with the loudest wheezing heard over the trachea and upper chest. The remainder of her examination was normal; she had no nasal polyps, jugular venous distention, heart murmurs, or peripheral edema.

The cause of the patient’s loud expiratory wheezing, which can be heard easily without a stethoscope, may be diffuse intrathoracic airway obstruction, such as occurs during a severe asthma attack, or obstruction of the upper or central airways, from which the sounds are transmitted throughout all lung fields. The source of the obstruction can be determined with the use of pulmonary-function testing, in which the characteristic patterns produced in flow-volume curves serve to distinguish upper-airway obstruction from diffuse intrathoracic airway obstruction.

The intermittent nature of her symptoms also raises the possibility of vocal-cord dysfunction (i.e., the occurrence of a functional abnormality in a structurally normal larynx). Wheezing results when air flows through the narrow residual glottic opening made when the vocal cords inappropriately adduct during breathing. This condition may occur as an abnormal response to stress or be a manifestation of various psychiatric disorders. Symptoms may also be triggered by laryngeal irritants, such as laryngopharyngeal reflux and postnasal drip. When it is inspiratory, the wheezing of vocal-cord dysfunction mimics stridor; when expiratory, it is often mistaken for asthma. Direct inspection of the vocal cords at a time when the patient is actively wheezing can establish or rule out the diagnosis.

The patient had a normal complete blood count and normal findings on chest radiography. Pulmonary-function testing showed a forced vital capacity (FVC) of 3.62 liters (91% of the predicted value) and a forced expiratory volume in 1 second (FEV₁) of 2.67 liters (83% of the predicted value), with a normal FEV₁:FVC ratio of 0.73. Total lung capacity was measured at 6.03 liters (102% of the predicted value), with a residual volume of 2.41 liters (122% of the predicted value). The flow-volume loop was normal (Fig. 1). Computed tomography (CT) of the chest showed clear lungs without evidence of airway or parenchymal abnormalities. Direct fiberoptic laryngoscopy revealed normal vocal-cord movement and no structural abnormalities in the upper airway.

It is surprising to observe unobstructed airflow on spirometry and normal vocal-cord movement in a patient with loud, nonfocal expiratory wheezing. These findings suggest that the source of wheezing may be the intrathoracic trachea. Further investigation should include CT with dynamic imaging of the trachea or fiberoptic bronchoscopy with direct tracheal inspection. Potential causes of airflow obstruction in the central airways, particularly in the trachea, include endobronchial tumors, aspirated foreign bodies, extrinsic compression, strictures, and malacia.

The findings on subsequent fiberoptic bronchoscopy were abnormal. The trachea narrowed dramatically during exhalation, particularly when the patient coughed, leaving only a thin crescentic lumen for airflow. Anterior bulging of the posterior membranous sheath extended throughout the length of the trachea, and there was expiratory narrowing of both main-stem bronchi (Fig. 2).
Normally, the posterior membranous sheath (pars membranacea) of the intrathoracic trachea bows slightly inward on exhalation and to a greater degree with cough, the result of positive pleural (and mediastinal) pressure that is greater than intratracheal pressure. Healthy persons may have a wheezy cough or may wheeze on forced exhalation as the anterior bulging of the posterior membranous sheath narrows the tracheal lumen to a thin crescent. In tracheomalacia and other conditions in which there is excessive airway collapse on exhalation, the exaggerated dynamic movement of the posterior membrane can compromise the airway lumen on exhalation, even during tidal breathing.

A diagnosis of excessive dynamic airway collapse, presumably resulting from tracheomalacia, ties together many aspects of the patient’s presentation: dyspnea and a barklike cough that is unresponsive to conventional asthma therapy, diffuse expiratory wheezes heard most easily over the neck and upper chest, and normal results on chest imaging and pulmonary-function tests. Unlike our patient, many patients with tracheomalacia have airflow obstruction that can be detected on spirometry; typically, there is reduced peak expiratory flow and notching or repeated oscillations along the expiratory limb of the flow-volume curve.

A Y-shaped silicone stent was placed in the trachea and main bronchi by means of rigid bronchoscopy. However, the patient had difficulty clearing secretions through the stented segment of the airway (as documented on bronchoscopy) and asked for the stent to be removed. At a subsequent visit, a metal tracheobronchial stent was placed. She noted initial improvement in her breathing, but 3 weeks later, when respiratory difficulty developed during a respiratory tract infection, the stent was removed. Thereafter, she elected to proceed with surgical tracheoplasty. At a follow-up visit 6 months after surgery, the patient’s condition was much improved. She noted minimal wheezing, had begun to taper the dose of systemic glucocorticoids, and was starting to pursue an active lifestyle.

**COMMENTARY**

In this 38-year-old woman who presented with recurrent wheezing, coughing, and shortness of breath, a diagnosis of asthma initially seemed reasonable. The early abatement of symptoms and the improvement in physical findings with the use of bronchodilators and inhaled and oral glucocorticoids were consistent with this presumptive diagnosis. However, there was no confirmatory evidence on pulmonary-function testing that airflow obstruction had abated over time or in response to the use of bronchodilators. This case illustrates how the absence of appropriate diagnostic testing can lead to a long delay in reaching the correct diagnosis, and in this instance, to an extended course of costly and potentially harmful treatment. The management of severe, refractory asthma calls for a systematic approach that includes assessment of the accuracy of the diagnosis, with consideration of other conditions that can mimic asthma, including tracheomalacia.

Although in our patient the diagnosis of tracheomalacia was made with the use of fiberoptic bronchoscopy, the speed of image collection on modern multidetector CT equipment makes chest CT a useful alternative means of diagnosis. Images should be obtained during inspiration and expiration and then compared (Fig. 3). For images collected during expiration, the goal is to maximize the abnormal movement of the posterior tracheal wall (or any other malacic portion of the wall). The best time to obtain the image is...
near but not at the end of exhalation (i.e., there should still be expiratory airflow), when the pleural pressure is still positive, rather than during the period when exhalation is complete and inhalation has yet to begin. At this point in respiration pleural pressure returns to a level just below the atmospheric pressure. Precise criteria for radiographic diagnosis of tracheomalacia have not yet been defined, but many radiologists use a luminal narrowing of 50% on exhalation as a benchmark.

In adults, the most common cause of tracheomalacia is prolonged mechanical ventilation; high pressures in the endotracheal tube cuff may cause localized ischemic injury to the tracheal wall (the cartilage and the membranous sheath). Other causes of segmental tracheomalacia include prolonged external pressure on the tracheal wall, such as may be caused by a large substernal goiter or a congenital vascular sling (e.g., a right-sided aortic arch with an aberrant subclavian artery). More diffuse tracheomalacia is encountered in patients with the rare conditions of tracheobronchomegaly (Mounier–Kuhn syndrome) and relapsing polychondritis. In patients with advanced COPD, there may be development of a distinctive form of tracheomalacia in which distortion of the cartilaginous rings leads to a lateral narrowing of the trachea, known as saber-sheath trachea, which becomes exaggerated on exhalation. In other patients, similar to ours, diffuse anterior bulging of the posterior tracheal wall develops, leading to a crescent shape on cross-sectional imaging or direct endobronchial inspection. The pathogenesis is uncertain, although limited autopsy data suggest that the atrophy of longitudinal elastic fibers is a contributing factor. Reported risk factors include cigarette smoking and long-term use of glucocorticoids. In some patients with less severe disease, symptoms related to tracheomalacia appear only

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**Figure 3. Radiographic Imaging of Tracheomalacia.**
CT images captured at 5-mm intervals above, at, and below the main carina on inspiration (left panels) and exhalation (right panels) reveal dramatic expiratory airway narrowing (arrows). (These images are not from the case patient.)
in the context of an acute infection of the lower respiratory tract. During a bout of tracheobronchitis, intraluminal secretions cannot be effectively cleared past the involved segment and cause critical obstruction at this site. Supportive care during acute respiratory infections is often sufficient, but continuous positive airway pressure, administered through a nasal or full-face mask, may be used to provide a pneumatic stent for the central airways during exhalation.9

For more severe tracheomalacia, treatment options supported by evidence from case series include the surgical repair of areas of localized disease (tracheal resection and reconstruction), the placement of tracheal stents, and surgical tracheoplasty. The use of a tracheal stent for extensive tracheomalacia is for the most part a short-term solution.10,11 Complications include stent migration, the development of granulation tissue in response to the rubbing of the tips of the stent against the mucosa during respiration, and the accumulation of airway secretions inside the stent (which lacks normal mucociliary clearance mechanisms). Tracheoplasty is currently performed through a right thoracotomy. Polyethylene mesh is sewn to the outside of the posterior membrane, reducing its mobility while at the same time reducing the compliance of the trachea by shortening the distance between the tips of the cartilaginous rings.12 This surgical procedure does not provide access to the subglottic trachea (which requires a separate cervical approach) or address malacia in the distal bronchi.

The present case underscores the need to consider a broad differential diagnosis for wheezing, especially when findings are atypical for asthma or when symptoms fail to subside as expected in response to conventional therapy. This case also highlights the importance of measuring lung function both when attempting to confirm (or rule out) a diagnosis of asthma if it is suspected and when adjusting medications in patients with established asthma. In our patient, pulmonary-function testing (performed after a prolonged course of illness attributed to “refractory asthma”) failed to confirm the diagnosis. Further testing led to the identification of tracheomalacia as the cause of symptoms and, with appropriate therapy, to clinical improvement.

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.

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Uncomplicated Urinary Tract Infection

Thomas M. Hooton, M.D.

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

A 30-year-old woman calls you to report a 2-day history of worsening dysuria and urinary urgency and frequency. She reports having no fever, chills, back pain, or vaginal irritation or discharge. One month ago, you treated her with a 3-day course of trimethoprim–sulfamethoxazole for presumptive cystitis, and her symptoms resolved. She is otherwise healthy, but this is her third episode in the past year. How should her case be managed?

THE CLINICAL PROBLEM

INCIDENCE

Urinary tract infection is the most common bacterial infection encountered in the ambulatory care setting in the United States, accounting for 8.6 million visits (84% by women) in 2007.1 The self-reported annual incidence of urinary tract infection in women is 12%, and by the age of 32 years, half of all women report having had at least 1 urinary tract infection.2 The incidence of cystitis (bladder infection) was 0.70 episodes per person-year in a study of college women starting a new contraceptive method3 and 0.07 episodes per person-year in a population-based study of postmenopausal women.4 Among young, healthy women with cystitis, the infection recurs in 25% of women within 6 months after the first urinary tract infection,5 and the recurrence rate increases with more than 1 prior urinary tract infection.6,7 Acute uncomplicated pyelonephritis is much less common than cystitis (estimated ratio, 1 case of pyelonephritis to 28 cases of cystitis),7 with a peak annual incidence of 25 cases per 10,000 women 15 to 34 years of age.8

CLASSIFICATION

Episodes of acute cystitis and pyelonephritis occurring in healthy premenopausal, nonpregnant women with no history suggestive of an abnormal urinary tract are generally classified as uncomplicated, whereas all others are classified as complicated. This distinction has been used to guide the choice and duration of antimicrobial treatment, with broader-spectrum agents and longer courses of treatment often recommended for persons with complicated urinary tract infections. However, this classification scheme does not account for the diversity of complicated urinary tract infection syndromes and misclassifies as complicated many urinary tract infections that can be managed with short-course treatment regimens (Table 1). A classification scheme that stratifies patients with urinary tract infection into multiple, homogeneous categories has been proposed by European experts, but it is not routinely used in practice.9

PATHOGENESIS

Symptomatic urinary tract infection in a healthy woman is a complex event. It is initiated when potential urinary pathogens from the bowel, or in some cases from the va-
gina (as a result of direct inoculation during sexual activity), colonize the periurethral mucosa and ascend through the urethra to the bladder and in some cases through the ureter to the kidney. (The circumstances under which this occurs remain unclear; pyelonephritis is rare in women with untreated cystitis and in men and women with untreated asymptomatic bacteriuria.) Uropathogenic *Escherichia coli*, the predominant pathogens in uncomplicated urinary tract infection, are a specific subset of extraintestinal pathogenic *E. coli* that have the potential for enhanced virulence. Virulence and fitness factors include fimbriae, flagella, diverse adhesins, siderophores, toxins, polysaccharide coatings, and other properties that assist the bacteria in avoiding or subverting host defenses, injuring or invading host cells and tissues, and stimulating a noxious inflammatory response.10,11 However, the triggers for development of urinary symptoms are not entirely clear.

The vast majority of episodes of recurrent cystitis in healthy women, up to two thirds of which are recurrences involving the same strain of bacteria that caused the initial infection, are thought to be reinfections.12 Uropathogenic strains can persist in the fecal flora for years after elimination from the urinary tract and can cause recurrent urinary tract infections. Laboratory studies in a mouse model show that inoculated *E. coli* invade the epithelium, resist clearance with antimicrobial agents, and develop quiescent epithelial reservoirs that can result in recurrent bacteriuria.13 Evidence that this phenomenon occurs in humans is sparse, but intracellular biofilm-like collections of bacteria, similar to those seen in the mouse model, have been identified in exfoliated cells in the urine of women with cystitis.14

**RISK FACTORS**

Risk factors for uncomplicated sporadic and recurrent cases of cystitis and pyelonephritis include sexual intercourse, use of spermicides, previous urinary tract infection, a new sex partner (within the past year), and a history of urinary tract infection in a first-degree female relative.3,15-17 Case-control studies have shown no significant associations between recurrent urinary tract infection and precoital or postcoital voiding patterns, daily beverage consumption, frequency of urination, delayed voiding habits, wiping patterns, tampon use, douching, use of hot tubs, type of underwear, or body-mass index,16 but at least some of these null findings might reflect a misclassification of behaviors (particularly if behavioral changes were made after the diagnosis of recurrent urinary tract infection). A genetic predisposition to recurrent urinary tract infection is suggested by the strong association between a history of urinary tract infection in one or more first-degree female relatives and an increased risk of recurrent cystitis and pyelonephritis;7 marked familial clustering of cases of acute pyelonephritis among the relatives of pyelonephri-
Complicated urinary tract infections (UTIs) are heterogeneous in that the risks of infection and of treatment failure vary. Current classification schemes are overly simplistic, especially for patients with complicated infections, but the value of more complex classification schemes has not yet been shown. MRSA denotes methicillin-resistant Staphylococcus aureus.

Response to treatment
Predictable with appropriate agent for recommended treatment duration; persistent symptoms or early recurrence suggests presence of a complicating factor

Less predictable regardless of antimicrobial susceptibility; may require instrumentation for cure

*Complicated urinary tract infections (UTIs) are heterogeneous in that the risks of infection and of treatment failure vary. Current classification schemes are overly simplistic, especially for patients with complicated infections, but the value of more complex classification schemes has not yet been shown. MRSA denotes methicillin-resistant Staphylococcus aureus.

† Short-course regimens are likely to be effective for mild-to-moderate cystitis in healthy, ambulatory, compliant women who are elderly, have catheter-associated UTIs, are pregnant, or have mild diabetes.

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**Microbiology**

In women, *E. coli* causes 75 to 95% of episodes of uncomplicated cystitis and pyelonephritis; the remaining cases are caused by other Enterobacteriaceae, such as *Klebsiella pneumoniae*, and gram-positive bacteria such as *Staphylococcus saprophyticus*, *Enterococcus faecalis*, and *Streptococcus agalactiae* (group B streptococcus). However, the latter two organisms, when isolated from voided urine from women with symptoms of uncomplicated cystitis, often represent contamination of the voided specimen.

**Diagnosis**

Cystitis is usually manifested as dysuria with or without frequency, urgency, suprapubic pain, or hematuria. Clinical manifestations suggestive of pyelonephritis include fever (temperature >38°C), chills, flank pain, costovertebral-angle tenderness, and nausea or vomiting, with or without symptoms of cystitis. Dysuria is also common with urethritis or vaginitis, but cystitis is more likely when symptoms include frequency, urgency, or hematuria; when the onset of symptoms is sudden or severe; and when vaginal irritation and discharge are not present. The probability of cystitis is greater than 50% in women with any symptoms of urinary tract infection and greater than 90% in women who have dysuria and frequency without vaginal discharge or irritation. The only finding on physical examination that increases the probability of urinary tract infection is costovertebral-angle tenderness (indicating pyelonephritis).

Assessment for pyuria and bacteriuria is often performed with the use of commercially available dipsticks that test for leukocyte esterase, an enzyme released by leukocytes, and for nitrites, since some bacteria reduce urinary nitrates to nitrites. The dipstick test is most accurate for predicting UTI when the presence of either leukocyte esterase or nitrite is positive.

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Uncomplicated</th>
<th>Complicated*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical patient</td>
<td>Otherwise healthy, ambulatory women with no history suggestive of anatomical or functional abnormality of the urinary tract</td>
<td>Men, women, or children with functional, metabolic, or anatomical conditions that may increase the risk of treatment failure or serious outcomes (e.g., obstruction, stone, pregnancy, male sex, diabetes, neurogenic bladder, renal insufficiency, immunosuppression)</td>
</tr>
<tr>
<td>Clinical spectrum</td>
<td>Mild cystitis to severe pyelonephritis</td>
<td>Mild cystitis to life-threatening urosepsis</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Infection suspected on the basis of typical symptoms; urinalysis and urine culture not routinely needed for suspected cystitis but recommended for pyelonephritis</td>
<td>Typical symptoms or symptoms that are atypical and subtle (e.g., owing to catheterization, impaired sensation, or altered mental status); urinalysis and urine culture indicated</td>
</tr>
<tr>
<td>Antimicrobial resistance</td>
<td>Common but generally predictable (antimicrobial resistance alone does not warrant the designation complicated UTI)</td>
<td>Multidrug resistance common and less predictable; fluoroquinolone resistance not uncommon</td>
</tr>
<tr>
<td>Empirical antimicrobial treatment</td>
<td>For cystitis: first-line short-course antimicrobial regimen; for pyelonephritis: first-line oral or intravenous antimicrobial regimen for 5 to 14 days, depending on severity and need for hospitalization</td>
<td>For cystitis: 7-day or longer course of fluoroquinolone preferred†; for pyelonephritis: broad-spectrum antimicrobial agent (e.g., piperacillin–tazobactam or carbapenem, plus vancomycin with either of these agents if MRSA suspected); limited data on duration, but 14-to-21-day duration recommended in general</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>Predictable with appropriate agent for recommended treatment duration; persistent symptoms or early recurrence suggests presence of a complicating factor</td>
<td>Less predictable regardless of antimicrobial susceptibility; may require instrumentation for cure</td>
</tr>
</tbody>
</table>

---

* Complicated urinary tract infections (UTIs) are heterogeneous in that the risks of infection and of treatment failure vary. Current classification schemes are overly simplistic, especially for patients with complicated infections, but the value of more complex classification schemes has not yet been shown. MRSA denotes methicillin-resistant *Staphylococcus aureus*.† Short-course regimens are likely to be effective for mild-to-moderate cystitis in healthy, ambulatory, compliant women who are elderly, have catheter-associated UTIs, are pregnant, or have mild diabetes.
ase or nitrite is considered a positive result, with a sensitivity of 75% and a specificity of 82%. However, results of the dipstick test provide little useful information when the history is strongly suggestive of urinary tract infection, since even negative results for both tests do not reliably rule out the infection in such cases.

A urine culture is performed to confirm the presence of bacteriuria and the antimicrobial susceptibility of the infecting uropathogen. This test is indicated in all women with suspected pyelonephritis but is not necessary for the diagnosis of cystitis, given the reliability of the patient’s history in establishing the diagnosis and the delayed availability of culture results. Moreover, studies comparing voided urine specimens and bladder-aspirate specimens in women with cystitis have shown that the traditional criterion for a positive culture of voided urine (10^5 colony-forming units per milliliter) is insensitive for bladder infection, and 30 to 50% of women with cystitis have colony counts of 10^2 to 10^4 colony-forming units per milliliter in voided urine. Since most clinical laboratories do not quantify bacteria below a threshold of 10^3 colony-forming units per milliliter in voided urine specimens, a culture report of “no growth” in a woman with urinary symptoms should be interpreted with caution.

Given the accuracy of a diagnosis that is based on the patient’s symptoms, in selected women with symptoms of cystitis, the infection can be successfully managed without in-person assessment. However, in women who have symptoms of cystitis along with vaginal discharge or irritation, it is reasonable to delay antimicrobial treatment until vaginal examination has been performed and the results of a urine culture are available.

M A N A G E M E N T

Acute uncomplicated cystitis is a benign condition, with early resolution of symptoms observed in 25 to 42% of women — and only rare cases of progression to pyelonephritis — in the placebo groups in randomized, controlled trials. However, cystitis is associated with considerable morbidity, and antimicrobial drugs are routinely prescribed, the primary goal being the rapid resolution of symptoms. The choice of regimen has become more complicated as antimicrobial resistance among the uropathogenic strains of E. coli has increased worldwide. Recent large, international studies of the in vitro susceptibility of E. coli strains that cause uncomplicated urinary tract infection have revealed rates of resistance to amoxicillin of 20% or higher in all regions and similar rates of resistance to trimethoprim–sulfamethoxazole in many regions. Rates of resistance to fluoroquinolones, oral cephalosporins, and amoxicillin–clavulanate are generally lower than 10%, but resistance to the fluoroquinolones is increasing; the lowest rates of resistance are to nitrofurantoin, fosfomycin, and mecillinam (for which pivmecillinam is the prodrug). (Mecillinam and pivmecillinam are not available in the United States.) Uncomplicated urinary tract infections caused by extended-spectrum beta-lactamase–producing (beta-lactam–resistant) strains of E. coli are increasingly being reported worldwide. Most of these strains are also resistant to the fluoroquinolones and trimethoprim–sulfamethoxazole, but limited data show that fosfomycin, nitrofurantoin, and to a lesser extent, amoxicillin–clavulanate have in vitro and clinical activity.

The recently updated guidelines of the Infectious Diseases Society of America (IDSA) emphasize the importance of considering ecologic adverse effects of antimicrobial agents (i.e., selection for colonization or infection with multidrug-resistant organisms — so-called “collateral damage”) when one is selecting a treatment regimen. Thresholds are suggested for the prevalence of resistance in a community above which a drug is not recommended (20% for trimethoprim–sulfamethoxazole and 10% for fluoroquinolones); however, clinicians rarely have access to such information. Local resistance rates reported in hospital antibiograms often reflect cultures obtained from inpatients or those with complicated or recurrent infections and probably overestimate the rates of resistance among patients with uncomplicated urinary tract infections.

Cystitis

Recommended empirical treatment regimens for acute uncomplicated cystitis are shown in Table 2. Short-course regimens (ranging from a single dose to a 5-day regimen, depending on the antimicrobial agent) are recommended as first-line treatment, since they are as effective as longer regimens in achieving symptomatic cure and have fewer adverse effects. Given the benign nature of uncomplicated cystitis along with its high frequency, the guidelines give equal weight to the risk of ecologic adverse effects and drug effectiveness in the recommendations. Nitrofurantoin is well tolerated and has good efficacy when the mono-
Table 2. Empirical Treatment of Acute Uncomplicated Cystitis.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Antimicrobial Regimen</th>
<th>Efficacy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin monohydrate macrocrystals, 100 mg twice daily for 5 days (with meals)\textsuperscript{†}</td>
<td>Clinical efficacy of 5-to-7-day regimen: 93% (84 to 95%); a 3-day regimen appears to be less effective than longer regimens; minimal in vitro resistance to \textit{E. coli}</td>
<td>Minimal ecologic adverse effects; avoid if pyelonephritis is suspected; common side effects include nausea, headache, and flatulence</td>
</tr>
<tr>
<td>TMP-SMX, 160 mg and 800 mg twice daily for 3 days\textsuperscript{‡}</td>
<td>Clinical efficacy of 3-day TMP-SMX regimen: 93% (90 to 100%); similar efficacy with trimethoprim alone, 100 mg twice daily for 3 days; avoid if resistance rate is greater than 20% or if exposure occurred within prior 3 to 6 mo</td>
<td>Probably fewer ecologic adverse effects than seen with fluoroquinolones; common side effects include nausea, vomiting, anorexia, rash, urticaria, hematologic complications, and photosensitivity</td>
</tr>
<tr>
<td>Fosfomycin trometamol (Monurol), 3-g sachet in a single dose\textsuperscript{†}</td>
<td>Clinical efficacy: 91% based on a single, randomized trial\textsuperscript{,28} but fosfomycin appears to be less effective than TMP-SMX or fluoroquinolones\textsuperscript{28,32}; minimal in vitro resistance, but most laboratories do not test for resistance</td>
<td>Minimal ecologic adverse effects; avoid if pyelonephritis is suspected; common side effects include diarrhea, nausea, headache, and vaginitis</td>
</tr>
<tr>
<td>Pivmecillinam, 400 mg twice daily for 3 to 7 days</td>
<td>Clinical efficacy of 3-to-7-day regimens: 73% (55 to 82%); minimal in vitro resistance</td>
<td>Minimal ecologic adverse effects; avoid if pyelonephritis is suspected; common side effects include nausea, vomiting, and diarrhea; not available in United States</td>
</tr>
<tr>
<td><strong>Second-line therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones: ciprofloxacin, 250 mg twice daily for 3 days; levofloxacin, 250 mg or 500 mg once daily for 3 days\textsuperscript{‡}</td>
<td>Clinical efficacy: 90% (85 to 98%); minimal in vitro resistance, but prevalence in United States is rising; high prevalence of in vitro resistance in some regions of the world</td>
<td>Propensity for ecologic adverse effects; when possible, reserve for uses other than cystitis; common side effects include nausea, vomiting, diarrhea, headache, drowsiness, and insomnia</td>
</tr>
<tr>
<td>Beta-lactams (e.g., amoxicillin–clavulanate, cefdinir, cefaclor, and cefpodoxime–proxetil) for 3 to 7 days\textsuperscript{†}</td>
<td>Clinical efficacy of 3-to-5-day regimens: 89% (79 to 98%); less effective than TMP-SMX or fluoroquinolones\textsuperscript{28,32}; few efficacy data on narrow-spectrum cephalosporins (e.g., cephalaxin); avoid empirical amoxicillin or ampicillin</td>
<td>Probably fewer ecologic adverse effects than seen with parenteral broad-spectrum cephalosporins; common side effects include diarrhea, nausea, vomiting, rash, and urticaria</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Efficacy rates and ranges and antimicrobial recommendations are based on the Infectious Diseases Society of America guidelines.\textsuperscript{28,32} Cure rates should not necessarily be compared across agents, owing to differences among trials and varying local patterns of antimicrobial resistance. TMP-SMX denotes trimethoprim–sulfamethoxazole. The costs of these antimicrobial agents vary considerably; in general, TMP-SMX and ciprofloxacin are the least expensive, with nitrofurantoin and levofloxacin being relatively higher in cost and fosfomycin (nongeneric) and the beta-lactam regimens shown here being the most expensive.

\textsuperscript{†} This regimen presents no clear risk to the fetus, on the basis of studies in animals, humans, or both (pregnancy category B).

\textsuperscript{‡} Studies in animals have shown an adverse effect of this regimen on the fetus (pregnancy category C); use only if the potential benefit justifies the potential risk to the fetus.

The choice of an antimicrobial agent should be individualized on the basis of the patient’s allergy and compliance history, local practice patterns, the prevalence of resistance in the local community (if known), availability, cost, and patient and provider threshold for failure.\textsuperscript{28} If a first-line antimicrobial agent is not a good choice on the basis of one or more of these factors, fluoroquinolones or beta-lactams are reasonable alternatives, although it is preferable to minimize their use because of concerns about ecologic adverse effects and, with respect to beta-lactams, efficacy.\textsuperscript{28} Unfortunately, U.S. surveys show that fluoroquinolones are the...
most commonly used antimicrobials for urinary tract infection in the ambulatory setting.\textsuperscript{35} Given increasing antimicrobial resistance and the benign nature of cystitis, antimicrobial-sparing management strategies are of increasing interest (e.g., antiinflammatory drugs or delayed treatment, \textit{etc.}) and antimicrobial-sparing management strategies are of increasing interest (e.g., antiinflammatory drugs or delayed treatment, \textit{etc.})

<table>
<thead>
<tr>
<th>Table 3. Outpatient Empirical Treatment of Acute Uncomplicated Pyelonephritis.\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimicrobial Regimen</strong></td>
</tr>
<tr>
<td>Fluoroquinolones: ciprofloxacin, 500 mg given orally twice daily; or 1 g (extended-release) given orally once daily, for 7 days; levofloxacin, 750 mg given orally once daily for 5 days.</td>
</tr>
<tr>
<td>TMP-SMX, 160 mg and 800 mg orally twice daily for 14 days.</td>
</tr>
<tr>
<td>Oral beta-lactams (specific agents not listed in IDSA guidelines)\textsuperscript{28,32} for 10 to 14 days</td>
</tr>
</tbody>
</table>

\textit{a} Efficacy rates and antimicrobial recommendations are based on the Infectious Diseases Society of America (IDSA) guidelines.\textsuperscript{30,32} FDA denotes Food and Drug Administration.

\textit{b} If tolerance or resistance to the oral medication is a concern because the prevalence of resistance in the community exceeds 10% (fluoroquinolone) or is unknown (trimethoprim–sulfamethoxazole [TMP-SMX]), because exposure has occurred in the past 3 to 6 months, or be-cause an oral beta-lactam is used, an initial intravenous dose of ceftriaxone, 1 g, or gentamicin, 5 to 7 mg per kilogram of body weight, should be given. (If tolerance to oral fluoroquinolone is a concern, intravenous ciprofloxacin, 400 mg, can also be given.)

\textit{c} Studies in animals have shown an adverse effect of this regimen on the fetus (pregnancy category C); use only if the potential benefit justifies the potential risk to the fetus.

**Pyelonephritis**

Most episodes of acute uncomplicated pyelonephritis are now treated in the outpatient setting.\textsuperscript{8,24} Table 3 lists recommended outpatient empirical treatment regimens.\textsuperscript{8,36,39} (For information about inpatient treatment regimens, see Expanded Table 3 in the Supplementary Appendix, available with the full text of this article at NEJM.org.) A urine culture and susceptibility test should be performed to guide treatment. Women should be admitted if pyelonephritis is severe, if there is hemodynamic instability or any complicating factor (e.g., diabetes, renal stone, or pregnancy), if oral medications are not tolerated, or if there is concern regarding potential nonadherence to treatment.\textsuperscript{22} Empirical treatment should have broad-spectrum in vitro activity against likely uropathogens and be started quickly to minimize progression. Fluoroquinolones are the only oral antimicrobials recommended for the outpatient empirical treatment of acute uncomplicated pyelonephritis.\textsuperscript{28} When there is concern about antimicrobial resistance or tolerance of oral medications, one or more doses of a broad-spectrum parenteral antimicrobial are recommended until in vitro activity can be assured.

**Recurrent Cystitis**

Urinary symptoms that persist or recur within a week or two of treatment for uncomplicated cystitis suggest infection with an antimicrobial-resistant strain or, rarely, relapse. In such women, a urine culture should be performed and treatment should be initiated with a broader-spectrum antimicrobial agent, such as a fluoroquinolone. Episodes of...
cystitis that occur at least 1 month after successful treatment of a urinary tract infection should be treated with a first-line short-course regimen (Table 2). If the recurrence is within 6 months, one should consider a first-line drug other than the one that was used originally, especially if trimethoprim–sulfamethoxazole was used, because of the increased likelihood of resistance. 22

The goal of long-term management of recurrent cystitis should be to improve the quality of life while minimizing antimicrobial exposure. Table 4 lists nonantimicrobial preventive strategies for women who have recurrent cystitis. 40-42 Although data supporting the effectiveness of these strategies are sparse or nonexistent, they carry a low risk of adverse effects and may be helpful. Antimicrobial prophylaxis (Table 5), 43-45 on the other hand, has been shown to reduce the risk of recurrence by approximately 95%. 12,24; however, such treatment should be limited to women who have had three or more urinary tract infections in the past 12 months or two or more urinary tract infections in the past 6 months (at least one of which was confirmed by a positive culture) in whom nonantimicrobial strategies have not been effective and who prefer prophylactic antimicrobial therapy. The strategy of self-diagnosis and self-treatment is a useful non-preventive antimicrobial strategy for many women with recurrent cystitis (Table 5). Antimicrobial management strategies should be assessed periodically to determine whether they continue to be appropriate.

Follow-up after Uncomplicated Cystitis or Pyelonephritis

After treatment for uncomplicated cystitis or pyelonephritis, a urine culture is unnecessary if symptoms have resolved, except in pregnant women (for whom treatment of persistent asymptomatic bacteriuria is recommended). 46 In women with recurrent uncomplicated cystitis or pyelonephritis, routine urologic evaluation (with the use of ultrasonography or computed tomography) has a low diagnostic yield and is not recommended. 12 However, it should be considered in women who have persistent hematuria or multiple early recurrences.

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Table 4. Strategies for Nonantimicrobial Prevention of Recurrent Acute Uncomplicated Cystitis. 22

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioral counseling</strong></td>
<td></td>
</tr>
<tr>
<td>Recommend abstinence or reduction in frequency of intercourse</td>
<td>Sexual intercourse is the strongest risk factor for uncomplicated UTIs; often this behavioral strategy is not feasible</td>
</tr>
<tr>
<td>If spermicides are used, recommend changing to another method for contraception or prevention of infection</td>
<td>Spermicide use, including use of spermicide-coated condoms, is a strong risk factor, especially if used with a diaphragm; spermicides alter the vaginal flora and favor the colonization of uropathogens</td>
</tr>
<tr>
<td>Recommend that patient urinate soon after intercourse, drink fluids liberally, not routinely delay urination, wipe front to back after defecation, avoid tight-fitting underwear, avoid douching</td>
<td>In case–control studies, none of these strategies have been shown to be associated with a reduced risk of recurrent UTIs, and none have been studied prospectively; however, it is reasonable to suggest them to the patient, since they pose a low risk and might be effective</td>
</tr>
<tr>
<td><strong>Biologic mediators</strong></td>
<td></td>
</tr>
<tr>
<td>Cranberry juice, capsules or tablets</td>
<td>Biologic plausibility is based on the inhibition of uropathogen adherence to uroepithelial cells; clinical data supporting a protective effect have been limited by design flaws; a recent randomized, placebo-controlled trial showed no benefit from cranberry juice 41</td>
</tr>
<tr>
<td>Topical estrogen</td>
<td>In some postmenopausal women, topical estrogen normalizes the vaginal flora and reduces the risk of recurrent UTIs; oral estrogens are not effective</td>
</tr>
<tr>
<td>Adhesion blockers (D-mannose, available in health-food stores and online, is occasionally used as preventive therapy)</td>
<td>UTIs caused by E. coli are initiated by adhesion of the bacteria to mannosylated receptors in the uroepithelium by means of FimH adhesin located on type 1 pili; theoretically, mannosides could block adhesion; however, D-mannose has not been evaluated in clinical trials</td>
</tr>
</tbody>
</table>

* Counseling about the pros and cons of these strategies is appropriate for women who have one or more recurrent UTIs or who have questions about any of the strategies.
of cystitis involving the same strain of bacteria. In women with pyelonephritis who have severe or worsening illness, persistent fever 48 to 72 hours after the initiation of appropriate antimicrobial treatment, or symptoms suggestive of a stone, abscess, or obstruction, urologic evaluation should be performed to rule out these latter abnormalities. It is also reasonable to perform imaging studies in women who have two or more recurrences of pyelonephritis.

### Areas of Uncertainty

Several areas of uncertainty warrant further investigation, including the ecologic adverse effects of cystitis involving the same strain of bacteria. In women with pyelonephritis who have severe or worsening illness, persistent fever 48 to 72 hours after the initiation of appropriate antimicrobial treatment, or symptoms suggestive of a stone, abscess, or obstruction, urologic evaluation should be performed to rule out these latter abnormalities. It is also reasonable to perform imaging studies in women who have two or more recurrences of pyelonephritis.

### Guidelines

Recently, the IDSA updated its guidelines for the use of antimicrobial treatment in acute uncomplicated cystitis and pyelonephritis in women. The recommendations in this article are largely consistent with these guidelines. International consensus guidelines for the management of uncomplicated urinary tract infection, which are similar to the IDSA guidelines, have also been published recently.
CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette appears to have recurrent cystitis on the basis of her symptoms and history. A 3-day course of trimethoprim–sulfamethoxazole is generally my choice of a first-line empirical regimen for cystitis in women who are not allergic to the medication, given that it is inexpensive and effective and that there are no reliable data in my community to suggest a high prevalence of resistance. In this case, however, I would prescribe a different first-line antimicrobial agent, nitrofurantoin (5-day course), since the patient’s recent exposure to trimethoprim–sulfamethoxazole increases the likelihood that the current infecting strain will be resistant to this agent.

I would also offer her a urinary analgesic (e.g., phenazopyridine [over-the-counter], three times daily as needed) until her dysuria diminishes, which often occurs within a few hours after the start of antimicrobial therapy.53 An office visit is not required for management, and there is no need for a follow-up urine culture if her symptoms resolve.

The patient should be counseled concerning nonantimicrobial preventive approaches that may reduce the risk of recurrence (e.g., avoidance of spermicides [as appropriate], urination soon after intercourse, and liberal fluid intake) (Table 4); although data on the efficacy of these measures are mostly lacking, they pose little risk. If the patient continues to have recurrences, self-diagnosis and self-treatment with antimicrobial agents could be considered, since this approach has been shown to be an effective management strategy; other options include postcoital antimicrobial prophylaxis and, as a last resort, continuous antimicrobial prophylaxis.

Dr. Hooton reports receiving consulting fees from Pinnacle Pharmaceuticals, Pfizer, and Alita Pharmaceuticals. 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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Presentation of Case

Dr. Clayton Knox (Medicine): A 45-year-old man with a history of alcoholism was admitted to this hospital because of rapid cognitive decline and worsening jaundice. During the previous 3 months, increasing fatigue and cough productive of yellow sputum and flecks of blood had developed, with post-tussive vomiting. Eleven days earlier, the patient had traveled to Europe for a week for a family event, during which he had consumed 10 to 20 alcoholic beverages per day. He had stopped drinking alcohol on his return, 3 days before admission, when nausea and vomiting developed. The next day, he called his physician's office. He reported no recent alcohol use and no fever, headache, diarrhea, or abdominal pain. Azithromycin was prescribed, and fluids and follow-up were advised. During the 36 hours before admission, jaundice developed, his urine darkened, and somnolence, slow and slurred speech, difficulty putting words together, and repetitions of questions and phrases developed. His girth gradually increased and his appetite decreased, without weight loss, tremulousness, or seizure activity. He was taken to the emergency department at a local affiliated hospital.

On examination, the patient was lethargic but oriented to person, place, and time and able to follow simple commands. The vital signs and oxygen saturation while he was breathing ambient air were normal. Scleral icterus, bilateral facial telangiectasias, and crackles in the right lower lung were evident, as was abdominal distention, with the edge of the liver palpable and slight tenderness in the right upper quadrant. The remainder of the physical and neurologic examination was normal. The blood levels of glucose, alanine aminotransferase, lipase, amylase, troponin I, and ammonia were normal, as were the results of renal-function tests; testing for hepatitis B and C viruses, alcohol, and salicylates was negative. Other results are shown in Table 1. An electrocardiogram was normal. A chest radiograph showed findings consistent with atelectasis in the base of the right lung, unchanged from 5 years earlier, and was otherwise normal. Computed tomography (CT) of the head obtained without the administration of contrast material revealed hypodensity and mass effect in the right temporal lobe and insula, with preservation of the adjacent cortex and without
intracranial herniation or hydrocephalus. Magnetic resonance imaging (MRI) after the administration of contrast material revealed a solitary lesion (2.6 cm in diameter) in the right insula, with thin, smooth, peripheral enhancement and extensive surrounding edema and mild mass effect. The patient was transferred to this hospital.

The patient reported no fever, chills, diarrhea, abdominal pain, chest pain, dyspnea, weakness, numbness, tingling, paresthesias, or altered sensation, taste, or smell. He had a history of elevated results of liver-function tests, anxiety, depression, gout, erectile dysfunction, and bursitis of the right shoulder; he had undergone a hemorrhoidectomy 7 years earlier after an episode of rectal bleeding and iron-deficiency anemia requiring hospitalization. He had a long history of alcohol abuse (up to 1 liter of vodka per day). He had declined detoxification treatment, disulfiram therapy, and referral to support groups for alcoholism. He did not smoke or use illicit drugs. Medications included allopurinol, citalopram, sildenafil, and vitamins; he had taken celecoxib for bursitis for 3 months, stopping 3 months earlier. He had no known allergies. He grew up on a farm in Europe, immigrated to the United States two decades ago, returned to Europe often for family events, lived with his wife and children, and had worked in the food-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Adults†</th>
<th>On Presentation, Other Hospital</th>
<th>On Admission, This Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>41.0–53.0 (men)</td>
<td>32.2</td>
<td>32.2</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.5–17.5 (men)</td>
<td>11.1</td>
<td>10.7</td>
</tr>
<tr>
<td>White-cell count (per mm$^3$)</td>
<td>4500–11,000</td>
<td>3800</td>
<td>3500</td>
</tr>
<tr>
<td>Differential count (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>40–70</td>
<td>66</td>
<td>68</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>22–44</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>Monocytes</td>
<td>4–11</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0–8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count (per mm$^3$)</td>
<td>150,000–400,000</td>
<td>104,000</td>
<td>111,000</td>
</tr>
<tr>
<td>Mean corpuscular volume (μm$^3$)</td>
<td>80–100</td>
<td>100.0</td>
<td>103</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin (pg/red cell)</td>
<td>26.0–34.0</td>
<td>34.5 (ref 27–34)</td>
<td>34.4</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration (g/dl)</td>
<td>31.0–37.0</td>
<td>34.5</td>
<td>33.3</td>
</tr>
<tr>
<td>Red-cell distribution width (%)</td>
<td>11.5–14.5</td>
<td>14.6</td>
<td>13.7</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>0.5–2.5</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Activated partial-thromboplastin time (sec)</td>
<td>22.1–34.0</td>
<td>36.0</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>10.8–13.4</td>
<td>17.1</td>
<td>16.6</td>
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<tr>
<td>International normalized ratio</td>
<td></td>
<td>1.4</td>
<td>1.5</td>
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<tr>
<td>Sodium (mmol/liter)</td>
<td>135–145</td>
<td>129</td>
<td>126</td>
</tr>
<tr>
<td>Potassium (mmol/liter)</td>
<td>3.4–4.8</td>
<td>4.2</td>
<td>3.4</td>
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<tr>
<td>Chloride (mmol/liter)</td>
<td>100–108</td>
<td>96</td>
<td>97</td>
</tr>
<tr>
<td>Carbon dioxide (mmol/liter)</td>
<td>23.0–31.9</td>
<td>26</td>
<td>23.4</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.0–1.0</td>
<td>12.6</td>
<td>13.4</td>
</tr>
<tr>
<td>Direct</td>
<td>0.0–0.4</td>
<td>9.6</td>
<td>9.6</td>
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<tr>
<td>Protein (g/dl)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6.0–8.3</td>
<td>8.5</td>
<td>7.7</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.3–5.0</td>
<td>2.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Globulin</td>
<td>2.6–4.1</td>
<td>5.3</td>
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service industry and with heavy machinery. His mother, 89 years of age, had cancer, and his father died at 84 years of age with bone cancer; a cousin had tuberculosis.

On examination, the blood pressure was 142/89 mm Hg; other vital signs were normal. The conjunctivae were icteric, the tongue was smooth and dry, and there was dried blood in the mouth. A systolic murmur, grade 2/6, was heard at the apex, radiating toward the axilla. The abdomen was distended, with periumbilical striae, bulging flanks, and a prominent venous pattern over the upper abdomen, without tenderness, rebound, or guarding. The edge of the liver was four fingerbreadths below the right costal margin in the midclavicular line. The skin was jaundiced, and there were petechiae on the legs. The patient followed commands and spoke fluently and spontaneously, without aphasia or dysarthria. The pupils constricted briskly (the right pupil from 5 mm to 4 mm, and the left pupil from 4 mm to 3 mm), and the remainder of the examination was normal.

Blood levels of phosphorus, magnesium, alanine aminotransferase, lactate dehydrogenase, iron, vitamin B₁₂, and folate were normal. Serum protein electrophoresis and immunofixation showed five small bands (two IgG kappa, one IgG lambda, and two IgM kappa, all <0.25 g per deciliter), features consistent with an oligoclonal immune response. Other test results are shown in Table 1. The urine contained 3+ bilirubin and trace urobilinogen, glucose, and ketones; screening for toxins in the urine revealed lorazepam. Thiamine, folic acid, allopurinol, citalopram, levetiracetam, and multivitamins were administered.

During the next 3 days, the patient was intermittently lethargic, with slurred speech. Testing for IgG antibodies to Epstein–Barr virus (EBV) capsid antigen and nuclear antigen was positive; the level of EBV DNA was 1000 copies per milliliter by polymerase chain reaction. Testing for IgM antibodies to EBV; antibodies to cytomegalovirus and smooth muscle; and hepatitis A, B and C viruses was negative, as was a skin test for tuberculosis. Ultrasonography of the abdomen showed hepatic and splenic enlargement and a thickened gallbladder wall. CT of the chest revealed scattered nodules, 2 to 5 mm in diameter, in the middle lobe and a minor fissure of the right lung, bilateral hilar lymphadenopathy, and trace pleural effusions.

Table 1. (Continued.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Adults†</th>
<th>On Presentation, Other Hospital</th>
<th>On Admission, This Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.5–10.5</td>
<td>8.6</td>
<td>8.0</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/liter)</td>
<td>45–115</td>
<td>155</td>
<td>129</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/liter)</td>
<td>10–40</td>
<td>181</td>
<td>156</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>140–200</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Total iron-binding capacity (μg/dl)</td>
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<td></td>
<td>150</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>30–300</td>
<td></td>
<td>574</td>
</tr>
<tr>
<td>Immunoglobulins (mg/dl)</td>
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<td></td>
<td></td>
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<tr>
<td>IgA</td>
<td>69–309</td>
<td></td>
<td>478</td>
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<tr>
<td>IgG</td>
<td>614–1295</td>
<td></td>
<td>3248</td>
</tr>
<tr>
<td>IgM</td>
<td>53–334</td>
<td></td>
<td>449</td>
</tr>
<tr>
<td>Free kappa light chain (mg/liter)</td>
<td>3.3–19.4</td>
<td></td>
<td>129.0</td>
</tr>
<tr>
<td>Free lambda light chain (mg/liter)</td>
<td>5.7–26.3</td>
<td></td>
<td>97.8</td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td></td>
<td>Positive at 1:320 dilution, speckled pattern</td>
<td></td>
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</tbody>
</table>

* To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for 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 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.
bilaterally. CT of the abdomen showed hepatosplenomegaly, mild lymphadenopathy, and a small amount of ascites. On the third day, repeat MRI of the brain obtained after the administration of contrast material showed a $T_2$-weighted hyperintense lesion (3.4 cm in diameter) with thin, smooth peripheral enhancement and heterogeneous foci of restricted diffusion centrally. Lactulose was administered.

On the fifth hospital day, the level of total bilirubin was 18.6 mg per deciliter (318 μmol per liter), and the direct bilirubin 11.8 mg per deciliter (202 μmol per liter).

A test result was received, and a diagnostic procedure was performed.

**Differential Diagnosis**

Dr. Tracey A. Cho: This 45-year-old man with chronic alcoholic liver disease presented with subacute fatigue, cough, and hemoptysis; acute liver decompensation; and fluctuating mental status. He had variable somnolence, slow and slurred speech, difficulty putting words together, and frequent repetition during conversational speech. Results of his mental-status examination and his level of arousal fluctuated, without clear focal deficits, but note was made of anisocoria, with the right pupil larger than the left pupil, and worsening somnolence.

**Syndromic Diagnosis**

Neuroanatomical localization is fairly broad at this point. Somnolence may result from abnormalities in the bilateral cortices, reticular activating system (rostral brain stem), or bilateral medial thalami. Slow speech and difficulty putting words together may be indicative of aphasia due to dominant frontal-lobe or temporal-lobe dysfunction or could represent bradyphrenia, which may be caused by global, diffuse subcortical, extrapyramidal, or psychiatric dysfunction. Alternatively, difficulty putting words together could represent impaired attention resulting from global dysfunction, lesions in the prefrontal cortex, parietal lesions, or a psychiatric cause. Conversational repetition could be explained by impaired attention or by short-term memory impairment, attributable to the medial temporal lobe and limbic circuits (thalami, mammillary bodies, and their connections). Slurred speech or dysarthria may be due to lesions in the corticobulbar tract, brain-stem motor nuclei, cranial nerves, cerebellum, extrapyramidal system, or vocal cords. The findings of somnolence (in the absence of signs of aphasia or amnesia), slow speech, difficulty putting words together, conversational repetition, and slurred speech suggest global hemispheric dysfunction. However, anisocoria with the right pupil larger than the left pupil suggests dysfunction of the right pupillary constrictor muscles, the parasympathetic component of the right oculomotor nerve, or the left sympathetic pathway.

Many features of the patient’s history and laboratory data could be accounted for by liver disease and a subacute confusional state. The differential diagnosis includes five major syndromes: hepatic encephalopathy, Wernicke’s encephalopathy, alcohol withdrawal, occult seizures, and infection. However, the anisocoria seen on examination raises the possibility of mass effect on the right midbrain, which would compromise parasympathetic input to the pupil through the oculomotor nerve. In patients who are immunocompromised to any degree, such as this patient with liver disease, alterations in mental status should prompt CT of the head without the administration of contrast material, since multiple processes (e.g., both diffuse and focal mass lesions) may occur simultaneously.

May we review the imaging studies?

Dr. Mykol Larvie: The CT scan of the head without the administration of contrast material (Fig. 1A) shows hypodensity involving the right insula and temporal lobe and extending superiorly into the corona radiata. There is mild mass effect, with slight effacement of the right lateral ventricle. $T_2$-weighted images from MRI of the head (Fig. 1D) show a region of relatively mild hyperintensity centered in the right insula, as well as confluent hyperintensity in the adjacent parenchyma that is consistent with edema. The pattern suggests a central lesion with perilesional edema. There is no evidence of hemorrhage, and mild, heterogeneous restricted diffusion corresponds to the mildly hyperintense region seen on $T_2$-weighted imaging. Images obtained after the administration of contrast material (Fig. 1C) show a lesion that is delineated by thin, smooth peripheral enhancement and that is centered in the right insula. The lesion extends to involve the insular cortex and, together with the associated edema, causes mild mass effect on adjacent structures. In broad terms, the lesion has features of an
infectious abscess, although a tumor could have this appearance; an inflammatory or demyelinat-
ing process is much less likely.

The imaging studies confirm Dr. Cho’s obser-
vations. The mass effect from the lesion in the insula slightly effaces the perimesencephalic cis-
terns and impinges on the brain stem, which could account for impairment of the oculomotor-nerve nuclei in the brain stem and the resulting aniso-
coria. Regions of the ventral attention network — the right temporoparietal region and the right ventral frontal lobe — are markedly perturbed by the lesion and the surrounding edema, possibly contributing to the fluctuating mental sta-
tus and attention difficulties. Involvement of the right temporal lobe, which may be the language-
dominant region in a minority of people, could account for both language impairment and defi-
cits in spatial orientation and memory. Although none of these correlations is sensitive or specific,
Dr. Cho has presented some excellent insights into what can be discerned from the relatively nonfocal findings on the neurologic examination.

CT of the abdomen (Fig. 2) shows marked hepatomegaly and mild splenomegaly. There is also mild portacaval, paraaortic, iliac, and mesenteric lymphadenopathy. A small amount of ascites surrounds the liver and extends into the pelvis. A CT scan of the chest showed subcentimeter pulmonary nodules in the right middle lobe, a very nonspecific finding.

**Dr. Cho:** Four major categories of disease could lead to the brain lesion identified on MRI. These are neoplastic, infectious, inflammatory, and vascular processes. The clinical presentation and additional radiographic sequences rule out inflammatory processes (e.g., tumefactive multiple sclerosis, acute disseminated encephalomyelitis, and sarcoidosis) and vascular processes (e.g., subacute ischemic stroke, hemorrhage, and thrombosed arteriovenous malformation).

### Neoplastic Processes

The differential diagnosis of a peripherally enhancing brain lesion should always include the following neoplastic processes: metastatic tumors, primary glial tumors, and primary lymphoma of the central nervous system. Although tumor metastases may cause a solitary peripherally enhancing lesion, such lesions are more commonly multifocal, and this patient had no evidence of a systemic malignant condition. High-grade glioma may cause a solitary, rim-enhancing lesion as the relatively rapid tumor growth outstrips the blood supply, leading to central necrosis. However, both anaplastic astrocytoma and glioblastoma are more typically heterogeneously enhancing and often cross the midline. Primary lymphoma of the central nervous system, usually diffuse large B-cell lymphoma, may occur in otherwise healthy persons. Alternatively, it may occur as part of advanced infection with the human immunodeficiency virus (HIV), in which case it is characteristically associated with detectable EBV DNA in the cerebrospinal fluid. It is usually homogeneously enhancing, although cases involving patients who are HIV-positive may be heterogeneous or peripherally enhancing. The presence of peripheral low-level EBV viremia in this patient is nonspecific; this viremia may occur in systemic inflammatory states due to lysis of chronically infected B cells, and it is known to occur in immunosuppressed patients, without being predictive of lymphoma. Assessing this patient’s cerebrospinal fluid for the presence of EBV would be more specific but is precluded by the risk of uncal herniation. The most important argument against a malignant condition is the rapid enlargement of the mass lesion, over a period of hours to days, which would be unusual for any of these neoplastic processes.

### Infectious Causes

The radiographic appearance is classic for an abscess, but imaging studies cannot distinguish among pyogenic bacteria, fungi, mycobacteria, or parasites as the cause.

**Pyogenic Bacterial Abscess**

Solitary brain abscesses may occur in patients with otitis, sinusitis, or dental infection, typically by local extension of the infection to the temporal, frontal, or frontal and temporal regions, respectively. Abscesses due to hematogenous dissemin-
nation are most often multiple and distributed in the region of the middle cerebral artery at the junction of the gray matter and white matter. There are no findings on the patient's history, physical examination, or imaging studies to suggest risk factors for pyogenic abscess. However, the occurrence of cryptogenic pyogenic abscess may be independent of liver disease or advanced HIV infection; therefore, this diagnosis remains a possibility.4

Fungal Abscess
Aspergillosis may cause pulmonary infection in alcoholic persons in particular, leading to hemoptysis and nonspecific pulmonary infiltrates. The manifestations of aspergillosis vary with the status of the immune system.5 In patients who are moderately immunocompromised, invasive aspergillosis may cause a solitary rim-enhancing brain lesion (aspergilloma).6 Serum tests for galactomannan (specific for aspergillosis) and 1,3-β-d-glucan (a nonspecific fungal marker) might be useful to assess this possibility. The most common fungal pathogen in the central nervous system in immunocompromised patients is cryptococcus, which typically causes meningitis. However, cryptococcomas may occur in the Virchow–Robins perivascular subarachnoid spaces at the base of the brain as a result of direct extension from the meningitis.7 Serum cryptococcal antigen would be a sensitive test for active cryptococcal infection but would be nonspecific for the brain lesion.

Mycobacterium tuberculosis
Focal brain lesions due to Mycobacterium tuberculosis are uncommon in developed countries but may occur as part of a primary infection or reactivation. This patient's European origin (tuberculosis is endemic in Eastern Europe); his syndrome of subacute fatigue, cough, and hemoptysis; and the bilateral hilar lymphadenopathy with pulmonary nodules and effusions raise this possibility. Although this patient had a negative tuberculin skin test, the sensitivity of skin testing in a patient with central nervous system tuberculosis is low, ranging from 10 to 65%. Furthermore, sensitivity is reduced in an immunocompromised patient who has poor nutritional status.

Parasitic Infection
Brain abscess may be due to parasitic infection. Neurocysticercosis is endemic in parts of Eastern Europe and may cause a solitary peripherally enhancing brain lesion in the context of early cystic degeneration (colloidal stage). However, these lesions are usually smaller than the lesion in this patient, have only moderate surrounding edema, and are often accompanied by other foci of calcification. A serum assay for cysticercosis antibody is insensitive in a patient with a solitary lesion and would not be likely to add diagnostic value.8

Toxoplasma is a protozoon that rarely causes serious illness in normal hosts. In patients with advanced HIV infection, however, it is the most common cause of focal brain mass lesions.9 Patients with toxoplasma encephalitis typically present subacutely with headache, fever, changes in mental status, and focal neurologic deficits. Imaging studies of the brain reveal characteristic rim-enhancing lesions that are usually multifocal but may be solitary in up to 30% of cases. Lesions are typically less than 4 cm in diameter. Serologic testing for toxoplasma IgG would be helpful, since this test has high sensitivity for toxoplasma exposure. However, antibodies may be lost in patients with profound immunosuppression, and seroprevalence is higher in Europe than in the United States.10 These lesions characteristically improve rapidly with appropriate treatment.11 Therefore, if the clinical scenario allows observation, a trial of specific antimicrobial agents may be both therapeutic and diagnostic.

Diagnostic Considerations
Because of the focal brain lesion that is visible on the MRI scans, the presence of HIV infection would drastically change the differential diagnosis and should be tested for immediately. Already, the circumstantial evidence for advanced HIV infection includes macrocytic anemia without vitamin B12 or folate deficiency, thrombocytopenia with splenomegaly, lymphopenia, and elevated globulin levels. On the basis of this patient's presumed immunocompromised state, the rapid progression of symptoms, and the MRI findings, the brain lesion is most likely an abscess.

In patients with advanced HIV infection, the most common causes of focal brain lesions with mass effect are toxoplasmosis and lymphoma. Tuberculosis and neurocysticercosis should also be considered in patients who are from regions where these diseases are endemic. In this patient, the most likely causes of the brain lesion are toxoplasmosis or tuberculosis; lymphoma is less likely.
Serum testing for toxoplasma and tuberculosis is not reliable in patients with advanced HIV infection. In this patient, lumbar puncture is precluded, given the anisocoria and the mass effect on the right midbrain. Glucocorticoids may temper the edema but might compromise the diagnostic potential of a brain biopsy, especially in the case of lymphoma. Most patients who receive empirical treatment for toxoplasma improve within 2 weeks and therefore can avoid undergoing a biopsy. However, if a patient is rapidly worsening or does not have a response to empirical treatment for toxoplasma, a brain biopsy is essential for accurate diagnosis, specimens for microbial culture and sensitivity, and therapeutic drainage.

Dr. Nancy Lee Harris (Pathology): Dr. Knox, would you tell us what the clinical thinking was at the time?

Dr. Knox: The team, which was led by Dr. Dan Hunt, arrived at a clinical diagnosis of acute liver failure due to alcoholic hepatitis and a brain abscess due to bacterial infection or toxoplasmosis, possibly associated with HIV infection.

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**CLINICAL DIAGNOSES**

Acute liver failure due to chronic alcoholic liver disease.

Brain abscess due to either pyogenic bacteria or toxoplasma.

Possible HIV infection.

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**DR. TRACY A. CHO’S DIAGNOSIS**

Acute liver failure superimposed on chronic alcoholic liver disease.

Brain abscess due to toxoplasma.

Advanced HIV infection.

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**PATHOLOGICAL DISCUSSION**

Dr. Di Tian: The diagnostic procedure was a brain biopsy, which revealed a necrotizing inflammatory process with several large areas of necrosis. The areas of the biopsy specimen consisting of viable brain tissue (Fig. 3A) showed scattered lymphocytes, some polymorphonuclear leukocytes, activated elongated microglia, and reactive astrocytes. In addition, there were many isolated or clustered round-to-oval organisms throughout the brain parenchyma (Fig. 3A, arrow); these organisms were strongly immunoreactive for a polyclonal antibody against toxoplasma (Fig. 3B). Special stains and immunohistochemical stains for other infectious organisms, such as bacteria, fungi, herpes simplex virus type 1 and type 2, and cytomegalovirus, were all negative. Cultures were also negative.

Dr. Mari Mino-Kenudson: A liver biopsy was also performed (Fig. 3C through 3F). Examination of the specimen showed mild (<5%) steatosis; widespread hepatocyte ballooning, with prominent Mallory’s hyaline and focal neutrophilic satellitosis; prominent lobular inflammation with lymphocytes and neutrophils; mild portal inflammation and ductular duplication; and stage 5 fibrosis (on a scale of 0 to 6, with 0 indicating normal and 6 cirrhosis) on trichrome stain. The overall features are consistent with a diagnosis of chronic toxic hepatitis, which in this patient is consistent with alcoholic hepatitis, with evolving cirrhosis. Changes indicative of acute hepatitis were not seen in the sampled tissue.

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**MANAGEMENT AND FOLLOW-UP**

Dr. Emily P. Hyle (Infectious Disease): The medicine team performed testing for HIV on hospital day 1. Standard HIV testing involves two steps. The initial test is enzyme-linked immunosorbent assay (ELISA), which is an extremely sensitive test for the antibody. If the test is positive, it is repeated. If the second test is also positive for the presence of antibody, then the more specific Western blot analysis is performed to confirm the diagnosis. It is important to perform both types of tests, because the ELISA has a high false positive rate. In this case, the ELISA for HIV antibody was positive, and the Western blotting confirmed the diagnosis. Analysis of the T-cell subsets showed that the absolute CD4 T-cell count was 78 per cubic millimeter (16.2%), which meets the definition of acquired immunodeficiency syndrome (AIDS) (i.e., a CD4 T-cell count of <200 per cubic millimeter). The HIV RNA level, also known as the viral load, was greater than 100,000 copies per milliliter. Together, these results were consistent with long-standing HIV infection. As a result, the patient was at extreme risk for not just one but several opportunistic infections.

The patient’s mental status declined in tandem with worsening liver and renal failure. Although he was counseled extensively by the general medicine team regarding his HIV status, it was only after several days of discussion that he permitted disclosure to his wife.
As part of the initial workup for newly diagnosed HIV infection, the medicine team ordered serologic tests for hepatitis B and hepatitis C, a rapid plasma reagin test for syphilis, and a test for cryptococcal antigen, all of which were negative. An ophthalmologic examination was normal.
In anticipation of antiretroviral therapy, HIV genotyping was performed to evaluate for drug resistance, and tissue typing for HLA B5701 was performed to determine whether the patient was at risk for hypersensitivity to abacavir.

Serologic tests for toxoplasmosis were negative for IgM and positive for IgG, findings consistent with previous infection. Thus, the clinical presentation and findings in this case were consistent with a reactivation of toxoplasmosis in a patient with AIDS.

First-line treatment for cerebral toxoplasmosis includes pyrimethamine and sulfadiazine, with folinic acid (leucovorin) to reduce the hematologic adverse effects from the antimicrobial agents. Sulfadiazine is often contraindicated in cases of renal failure, and this patient had an elevated creatinine level, at 2 mg per deciliter (177 μmol per liter). Nevertheless, the concern about the severity of his presentation prompted treatment with pyrimethamine, sulfadiazine, and folinic acid and close monitoring of his renal function. The administration of glucocorticoids was discontinued.

Unfortunately, the patient’s renal function continued to worsen; therefore, sulfadiazine was discontinued on postoperative day 3. Second-line therapy was initiated, which involved the administration of clindamycin, pyrimethamine, and folinic acid. In the absence of sulfadiazine therapy, atovaquone was added for prophylaxis against *Pneumocystis jiroveci* pneumonia, since the patient’s CD4 T-cell count was below 200 per cubic millimeter.

The patient was discharged home on postoperative day 9 to complete a 6-week course of clindamycin, pyrimethamine, and folinic acid for cerebral toxoplasmosis. Atovaquone was continued for prophylaxis against *P. jiroveci* pneumonia.

Early initiation of antiretroviral therapy in patients with some opportunistic infections has been shown to improve outcomes; therefore, this patient was to begin antiretroviral therapy on an outpatient basis when the results of the HIV genotyping and HLA-B5701 tissue typing were available and his renal function and liver function had stabilized.

After discharge, the patient spent 4 days at home, cared for by his wife. She grew concerned that he was becoming increasingly jaundiced and took him to his primary care physician. Laboratory investigations revealed advancing liver and renal failure, which prompted readmission to the first hospital.

Dr. Koushik Das (Medicine): On readmission, progressive liver, renal, and central nervous system failure developed. The total bilirubin level was 35.0 mg per deciliter (371 μmol per liter), the creatinine level 4.7 mg per deciliter (415 μmol per liter), and the prothrombin time 15.9 seconds; encephalopathy persisted despite treatment with lactulose. The patient’s Model for End-Stage Liver Disease score (which ranges from 6 to 40, with higher scores indicating more severe disease), adjusted for alcoholic hepatitis, was 37, corresponding to a 90-day mortality rate of 83%. The next day, renal function worsened, with the serum creatinine level increasing to 8.5 mg per deciliter (751 μmol per liter), an increase thought to be due to the hepatorenal syndrome. Through discussions with the patient’s wife and family and in view of the patient’s poor clinical prognosis and ineligibility for liver transplantation, it was decided that the goals of his care should be driven primarily by comfort. The patient died on hospital day 3, before he could be transferred to inpatient hospice.

Dr. Hasan Bazari (Medicine): What is the reservoir from which reactivation of toxoplasmosis occurs?

Dr. Eric S. Rosenberg (Pathology): There are two known reservoirs: the myocardium, which is why reactivation of toxoplasmosis is a problem in recipients of cardiac transplants, and the brain.

Dr. Cho: When the patient is relatively stable and not at immediate risk for permanent neurologic compromise, a trial of antitoxoplasmosis therapy can be useful, particularly when tests for toxoplasma IgG are positive, the lesion is in an inaccessible location, and there is no suggestion of other processes. There is a published algorithm for the diagnosis of focal mass lesions in patients with advanced HIV infection that incorporates factors such as whether the patient is already taking trimethoprim–sulfamethoxazole (reducing the likelihood of toxoplasmosis) or whether EBV is detected in the cerebrospinal fluid (raising the risk of lymphoma).

Dr. Rajesh T. Gandhi (Infectious Disease): This case is a good reminder that of the 1.1 million...
U.S. residents who have HIV infection, 21% do not know they have it. Do we know whether this patient was ever tested for HIV before?

Dr. Hyle: He had not been tested previously for HIV and repeated that he did not know of any previous exposures to HIV.

A Physician: Was an explanation ever found for his respiratory symptoms, hemoptysis, and the findings on lung imaging?

Dr. Hyle: Unfortunately, he died so soon after the diagnosis was established that further investigation for other opportunistic infections or malignant conditions was not possible. An autopsy was not performed.

ANATOMICAL DIAGNOSES
Alcoholic liver disease with fibrosis.
Brain abscess due to toxoplasma.
Advanced HIV infection.

REFERENCES
Aspirin for Preventing the Recurrence of Venous Thromboembolism

Cecilia Becattini, M.D., Ph.D., Giancarlo Agnelli, M.D., Alessandro Schenone, M.D., Sabine Eichinger, M.D., Eugenio Bucherini, M.D., Mauro Silingardi, M.D., Marina Bianchi, M.D., Marco Moia, M.D., Walter Ageno, M.D., Maria Rita Vandelli, M.D., Elvira Grandone, M.D., and Paolo Prandoni, M.D., Ph.D., for the WARFASA Investigators*

**ABSTRACT**

**BACKGROUND**
About 20% of patients with unprovoked venous thromboembolism have a recurrence within 2 years after the withdrawal of oral anticoagulant therapy. Extending anticoagulation prevents recurrences but is associated with increased bleeding. The benefit of aspirin for the prevention of recurrent venous thromboembolism is unknown.

**METHODS**
In this multicenter, investigator-initiated, double-blind study, patients with first-ever unprovoked venous thromboembolism who had completed 6 to 18 months of oral anticoagulant treatment were randomly assigned to aspirin, 100 mg daily, or placebo for 2 years, with the option of extending the study treatment. The primary efficacy outcome was recurrence of venous thromboembolism, and major bleeding was the primary safety outcome.

**RESULTS**
Venous thromboembolism recurred in 28 of the 205 patients who received aspirin and in 43 of the 197 patients who received placebo (6.6% vs. 11.2% per year; hazard ratio, 0.58; 95% confidence interval [CI], 0.36 to 0.93) (median study period, 24.6 months). During a median treatment period of 23.9 months, 23 patients taking aspirin and 39 taking placebo had a recurrence (5.9% vs. 11.0% per year; hazard ratio, 0.55; 95% CI, 0.33 to 0.92). One patient in each treatment group had a major bleeding episode. Adverse events were similar in the two groups.

**CONCLUSIONS**
Aspirin reduced the risk of recurrence when given to patients with unprovoked venous thromboembolism who had discontinued anticoagulant treatment, with no apparent increase in the risk of major bleeding. (Funded by the University of Perugia and others; WARFASA ClinicalTrials.gov number, NCT00222677.)
The risk of recurrence of venous thromboembolism persists for many years after anticoagulant treatment is withdrawn.\textsuperscript{1,2} This risk is particularly high among patients with unprovoked venous thromboembolism,\textsuperscript{2} about 20\% of whom have a recurrence within 2 years after treatment with vitamin K antagonists has been discontinued.\textsuperscript{3-6} Extending treatment with these agents reduces the risk of recurrence but is associated with an increased risk of bleeding, as well as the inconvenience and expense of laboratory monitoring and dose adjustments.\textsuperscript{7}

The role of aspirin in the primary prevention of venous thromboembolism has been evaluated in various clinical settings.\textsuperscript{8-11} In these studies, aspirin was associated with a risk reduction ranging from 20 to 50\%. A potential benefit from antiplatelet therapy in the secondary prevention of venous thromboembolism first became evident with the results of a randomized study involving only 39 patients.\textsuperscript{12}

The aim of the Aspirin for the Prevention of Recurrent Venous Thromboembolism (the Warfarin and Aspirin [WARFASA]) study was to assess the clinical benefit of aspirin for the prevention of recurrence after a course of treatment with vitamin K antagonists in patients with unprovoked venous thromboembolism.

**METHODS**

**PATIENTS**

Patients older than 18 years of age were eligible for the study if they had been treated for 6 to 18 months with vitamin K antagonists (with a target international normalized ratio [INR] of 2.0 to 3.0) for first-ever, objectively confirmed, symptomatic, unprovoked proximal deep-vein thrombosis, pulmonary embolism, or both. Venous thromboembolism was considered to be unprovoked when it occurred in the absence of any known risk factor for this event. The main exclusion criteria can be found in the Supplementary Appendix, available with the full text of this article at NEJM.org.

**STUDY DESIGN AND INTERVENTION**

WARFASA was a multicenter, investigator-initiated, randomized, double-blind clinical trial. Eligible patients were randomly assigned to aspirin, 100 mg once daily, or placebo for 2 years, with the option of extending the study treatment. Randomization occurred within 2 weeks after vitamin K antagonists had been withdrawn.

**OUTCOME MEASURES**

All suspected study outcome events were assessed by a central, independent adjudication committee whose members were unaware of the group assignments and who reviewed the imaging results. The primary efficacy outcome was symptomatic, objectively confirmed recurrence of venous thromboembolism, defined as the composite of deep-vein thrombosis or nonfatal or fatal pulmonary embolism.\textsuperscript{13,14} (Criteria for the diagnosis of recurrence are provided in the Supplementary Appendix.) Pulmonary embolism was considered to be the cause of death if it was confirmed on autopsy or if death was preceded by a diagnosis of either pulmonary embolism (objectively confirmed on computed tomography or lung scanning) or deep-vein thrombosis (objectively confirmed on compression ultrasonography) and whenever the cause could not be attributed to an alternative diagnosis.\textsuperscript{15} Deaths were classified as being due to pulmonary embolism, bleeding, or other causes. Secondary efficacy outcomes included nonfatal myocardial infarction, unstable angina, stroke, transient ischemic attack, acute ischemia of the lower limbs, and death from any cause.

The principal safety outcome was major bleeding. An overt bleeding event was defined as major if it was fatal, occurred in a critical location (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular [leading to a compartment syndrome]), or was associated with a decrease in the hemoglobin level of at least 2.0 g per deciliter or required a transfusion of 2 or more units of whole blood or red cells. Clinically relevant, nonmajor bleeding, defined as any overt bleeding that required a medical intervention and did not meet any of the criteria for major bleeding, was a secondary safety outcome.

**SURVEILLANCE AND FOLLOW-UP**

Patients were reexamined every 3 months during the first year after randomization and every 6 months thereafter. Patients were instructed to report to the study center immediately if they had symptoms suggestive of recurrent venous thromboembolism.
boembolism or bleeding complications. In cases of suspected recurrence, objective testing was required.

STUDY OVERSIGHT
The study was designed by the members of the steering committee. Data were collected, maintained, and analyzed by the Clinical Research Unit of the University of Perugia, Italy. The protocol and amendments were approved by the institutional review board or ethics committee at each study center. During the course of the study, two substantial protocol amendments were made and submitted to the ethics committees in May 2009 and December 2009. The first of these amendments reflected the change to an event-driven design, and the second reflected the change of the primary study end point to venous thromboembolism only. These changes were made so that the study design would be consistent with that of contemporary trials of extended treatment for venous thromboembolism (i.e., the EINSTEIN-Extension study [ClinicalTrials.gov number, NCT00439725] and the RE-SONATE study [NCT00558259]). The study was performed in accordance with the protocol and with the provisions of the Declaration of Helsinki and local regulations. (The protocol and statistical analysis plan are available at NEJM.org.) Written informed consent was obtained from all patients before randomization.

The steering committee had final responsibility for verification and analyses of the data. The writing committee wrote the manuscript and vouches for the accuracy and completeness of the reported data. All authors contributed to the interpretation of the results, approved the final version of the manuscript, and made the decision to submit the manuscript for publication. The study was supported by a grant-in-aid from Bayer HealthCare. Aspirin and placebo tablets were supplied by Bayer HealthCare. Bayer played no role in the design of the study, in data collection or analysis, or in manuscript preparation.

STATISTICAL ANALYSIS
Assuming a 40% relative risk reduction with aspirin,8-11 a total of 70 events would provide a power of 80% to show the superiority of aspirin over placebo at a two-sided alpha level of 0.05. With an expected event rate of 8.0% per year in the placebo group, we calculated that we would need to enroll 400 patients (200 in each study group) to observe the expected number of events.

The primary efficacy analysis, which considered all outcome events occurring from randomization to the end of the study, was performed according to a modified intention-to-treat principle, with all patients who received at least one dose of the assigned study drug after randomization included in the analysis. An “on-treatment” efficacy analysis was also performed, in which recurrences were included if they took place during the treatment period or within 2 days after its withdrawal. Event rates are reported as proportions of patients per year. Hazard ratios, confidence intervals, and P values were calculated with the use of Cox proportional-hazards models and SPSS statistical software, version 11.0, with treatment as the only covariate.

A Cox proportional-hazards model analysis was also performed with adjustment for age, sex, type of index event (pulmonary embolism or deep-vein thrombosis), and duration of anticoagulant treatment before randomization (6 months or >6 months).

The safety analysis included all patients who received at least one dose of the study drug. Bleeding events were included in the analyses if they occurred during the period of administration of the study drug or within 2 days after its discontinuation.

RESULTS

PATIENTS AND STUDY TREATMENT
From May 2004 through August 2010, a total of 403 patients were randomly assigned to a study group; 205 patients received aspirin, 197 received placebo, and 1 patient, who was assigned to the placebo group, did not receive the study drug (Fig. 1). The median period during which the patients participated in the study was 24.8 months in the aspirin group and 24.2 months in the placebo group. The study drug was discontinued prematurely in 16 patients given aspirin and in 15 patients given placebo (Fig. 1). Since the end of the study was event-driven, the duration of treatment was shorter than the intended 2 years for 10 patients in the aspirin group (4.9%) and for 11 patients in the placebo group (5.6%); the treatment period was extended beyond 2 years in 58
patients and 55 patients in the two groups, respectively. The median duration of the study treatment was 24.0 months for the aspirin group and 23.5 months for the placebo group. Three patients in the aspirin group (1.4%) and 4 patients in the placebo group (2.0%) were lost to follow-up. There were no significant between-group differences in baseline characteristics of the patients (Table 1).

**Recurrent Venous Thromboembolism**

A recurrence of venous thromboembolism occurred in 71 patients (8.6% patients per year). Recurrent venous thromboembolism was due to deep-vein thrombosis in 44 patients (ipsilateral in 51% of cases) and to pulmonary embolism in 27 patients (fatal in 2 patients). In 77% of cases, recurrence took place in the absence of any known risk factor for venous thromboembolism. A recurrence in the form of pulmonary embolism was more common among the patients who entered the study because of prior pulmonary embolism than among those who entered because of deep-vein thrombosis (12.7% vs. 3.2%; hazard ratio, 5.52; 95% confidence interval [CI], 2.29 to 13.30; P<0.001).

The primary prespecified outcome, recurrence of venous thromboembolism, occurred in 28 of the 205 patients who received aspirin, as compared with 43 of the 197 patients who received placebo (6.6% vs. 11.2% per year; hazard ratio, 0.58; 95% CI, 0.36 to 0.93; P = 0.02) (Fig. 2A). While taking the study drug, 23 patients in the aspirin group had a recurrence, as compared with 39 patients in the placebo group (5.9% vs. 11.0% per year; hazard ratio, 0.55; 95% CI, 0.33 to 0.92; P = 0.02) (Fig. 2B). Exploratory, post hoc subgroup analyses revealed that 11 of 83 patients in the aspirin group who entered the study had a recurrent event, as compared with 16 of 67 patients in the placebo group (6.7% vs. 13.5% per year; hazard ratio, 0.38; 95% CI, 0.17 to 0.88; P = 0.02). Among the patients who entered the study because of deep-vein thrombosis, 17 of 122 in the aspirin group and 27 of 130 in the placebo group had a recurrent event (6.5% and 10.2% per year, respectively; hazard ratio, 0.65; 95% CI, 0.65 to 1.20; P = 0.17).

An analysis adjusted for age, sex, index event (pulmonary embolism or deep-vein thrombosis), and duration of initial anticoagulant treatment...
confirmed that aspirin treatment reduced the risk of recurrence (adjusted hazard ratio, 0.53; 95% CI, 0.32 to 0.85; P=0.009) (Fig. 2C). Independent risk factors for recurrent venous thromboembolism included an age of more than 65 years (hazard ratio, 2.26; 95% CI, 1.16 to 4.41; P=0.02) and male sex (hazard ratio, 2.02; 95% CI, 1.16 to 3.49; P=0.01). No association was found between recurrent venous thromboembolism and prior anti-coagulant therapy lasting for 6 months, as compared with a more extended duration (hazard ratio, 1.21; 95% CI, 0.73 to 1.99; P=0.46), or between recurrence and pulmonary embolism as the index event (hazard ratio, 1.31; 95% CI, 0.79 to 2.15; P=0.29).

HEMORRHAGIC COMPLICATIONS

There were two episodes of nonfatal major bleeding: one due to gastric ulcer in a patient in the placebo group and one due to bowel angiodysplasia in a patient in the aspirin group. Clinically relevant, nonmajor bleeding occurred in three patients who were randomly assigned to aspirin (gingival bleeding in one patient and cutaneous hematomas in two patients) and in three patients who were randomly assigned to placebo (musculoskeletal bleeding after trauma in two and hemorrhagic gastritis in one).

SECONDARY OUTCOME EVENTS

Death occurred in six patients in the aspirin group (1.4% per year) and in five patients in the placebo group (1.3% per year) (Table 2). Sudden death occurred in two patients (one in each group), and both deaths were adjudicated as being the result of pulmonary embolism. In addition, four patients died from cancer and five from other causes. Arterial events occurred in eight patients in the aspirin group and in five patients in the placebo group (1.9% and 1.3% per year, respectively) (Table 2).

ADDITIONAL OBSERVATIONS

Five patients had an adverse event that was considered to be due to the study treatment and led to discontinuation of the drug. These events were gastric pain in three patients (one in the aspirin group and two in the placebo group), a cutaneous reaction in one aspirin-treated patient, and renal failure in another aspirin-treated patient.

An indication for antiplatelet therapy other than an acute arterial event occurred in five patients in the aspirin group and in three patients in the placebo group, and an indication for anti-coagulant therapy other than recurrent venous thromboembolism occurred in three patients and in two patients in the two groups, respectively.

<table>
<thead>
<tr>
<th>Table 1. Demographic and Clinical Characteristics of the Patients, According to Study Group.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Aspirin (N = 205)</td>
</tr>
<tr>
<td>Age — yr</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
</tr>
<tr>
<td>Body-mass index†</td>
</tr>
<tr>
<td>White race — no. (%)‡</td>
</tr>
<tr>
<td>Index event — no. (%)‡</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Duration of VKA treatment before randomization — no. (%)</td>
</tr>
<tr>
<td>6 mo</td>
</tr>
<tr>
<td>12 mo</td>
</tr>
<tr>
<td>18 mo</td>
</tr>
</tbody>
</table>

6 Plus–minus values are means ±SD. VKA denotes vitamin K antagonist.† The body-mass index is the weight in kilograms divided by the square of the height in meters.‡ Race was self-reported.

DISCUSSION

The WARFASA study shows that in patients with unprovoked venous thromboembolism, aspirin therapy, begun after 6 to 18 months of oral anti-coagulant treatment, reduces the rate of recurrence by about 40%, as compared with placebo. This benefit is achieved with no apparent increase in the risk of major bleeding.

Patients with unprovoked venous thromboembolism are at high risk for recurrence after oral anticoagulant treatment is withdrawn.3,6 Extending anticoagulant therapy reduces the risk of recurrence but only as long as the treatment is continued.3,5,16 In clinical practice, anti-coagulant therapy is generally discontinued when the perceived risk of bleeding or the inconvenience of continuing anticoagulant treatment outweighs the risk of recurrence. Our study shows that aspirin therapy is a potential alternative to extended oral anticoagulant treatment for the long-term secondary prevention of venous thromboembolism.
The reduction in the risk of recurrence of venous thromboembolism that was observed with aspirin treatment in our study is consistent with the reduction shown in previous studies evaluating aspirin for the primary prevention of venous thromboembolism.8-11 In the meta-analysis performed by the Antiplatelet Trialists’ Collaboration, aspirin reduced the incidence of deep-vein thrombosis by 20% and that of pulmonary embolism by 69% in patients at high risk for thromboembolic events.8 However, more recent data showed no effect of aspirin in the prevention of venous thromboembolism among healthy women.17 The efficacy of antiplatelet therapy in the secondary prevention of venous thromboembolism was suggested in a small study that compared aspirin plus dipyridamole with placebo.12

The efficacy of aspirin for primary or secondary prevention of venous thromboembolism is biologically plausible because of the involvement of platelets in the formation of venous thrombi18-20 and the increased levels of markers of platelet21,22 and endothelial23 activation in patients with venous thromboembolism.

As compared with placebo, aspirin was not associated with an increase in the rate of major bleeding, which was about 0.3% per patient-year in both study groups. We used the dose of aspirin recommended for the secondary prevention of cardiovascular or cerebrovascular events. In randomized trials of low-dose aspirin in various clinical settings, the incidence of major intracranial or extracranial bleeding was lower than 1% per year.24 The rate of major bleeding with warfarin for the long-term treatment of venous thromboembolism is estimated to be about 2%.25 With the conventional regimen (INR, 2.0 to 3.0), in two studies of a low-intensity warfarin regi-
men for extended treatment of venous thromboembolism, the rates of major bleeding were 0.9% per patient-year and 1.1% per patient-year. It should be noted that the risk of major bleeding with aspirin therapy may be greater in real-world populations.

Since patients were excluded from our study if they had cancer, clinically significant thrombophilia, or a bleeding event during the period of anticoagulant treatment, the results are not applicable to these groups. However, we estimate that a substantial proportion (probably the majority) of patients with an initial episode of venous thromboembolism would be eligible for aspirin therapy as secondary prevention.

The oral thrombin inhibitor dabigatran and the oral factor Xa inhibitor rivaroxaban were recently evaluated for the extended treatment of venous thromboembolism. As compared with placebo, these agents reduced the risk of recurrent venous thromboembolism by more than 80%. An advantage of these agents over vitamin K antagonists is that they do not require laboratory monitoring and dose adjustments. As expected, the reduction in the risk of recurrence is lower with aspirin than with these new oral agents. All the available antithrombotic strategies for extended treatment of venous thromboembolism have been compared with placebo. The place of aspirin among these strategies remains to be defined in future studies. However, aspirin is low in cost and its side effects are well known, since its safety has been assessed over the years in millions of patients.

Low-intensity warfarin was evaluated for the extended treatment of venous thromboembolism and was found to be associated with a 64% reduction in risk, as compared with placebo. However, this warfarin regimen still requires laboratory monitoring and dose adjustments.

Our study has several limitations. As in the majority of investigator-initiated studies, the recruitment of patients was slower than planned. Indeed, this study took about 6 years to be completed.

### Table 2. Outcome Events According to Study Group.

<table>
<thead>
<tr>
<th>Event</th>
<th>Aspirin (N = 205)</th>
<th>Placebo (N = 197)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total episodes</td>
<td>28</td>
<td>43</td>
<td>0.58 (0.36–0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>11</td>
<td>14</td>
<td>0.70 (0.32–1.54)</td>
<td>0.37</td>
</tr>
<tr>
<td>Fatal pulmonary embolism</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>16</td>
<td>28</td>
<td>0.51 (0.27–0.94)</td>
<td>0.03</td>
</tr>
<tr>
<td>Episodes during treatment</td>
<td>23</td>
<td>39</td>
<td>0.55 (0.33–0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding or clinically relevant nonmajor bleeding</td>
<td>4</td>
<td>4</td>
<td>0.98 (0.24–3.96)</td>
<td>0.97</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>6</td>
<td>5</td>
<td>1.04 (0.32–3.42)</td>
<td>0.95</td>
</tr>
<tr>
<td>Recurrent VTE or death</td>
<td>33</td>
<td>47</td>
<td>0.62 (0.40–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Arterial event</td>
<td>8†</td>
<td>5‡</td>
<td>1.43 (0.47–4.37)</td>
<td>0.53</td>
</tr>
<tr>
<td>Recurrent VTE or arterial event</td>
<td>36</td>
<td>48</td>
<td>0.67 (0.43–1.03)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval, and VTE venous thromboembolism.
† These events included two acute myocardial infarctions (after discontinuation of the study drug), two episodes of unstable angina, two ischemic strokes, one transient ischemic attack, and one episode of acute lower-limb ischemia.
‡ These events included two acute myocardial infarctions (after discontinuation of the study drug), one ischemic stroke, and two episodes of acute lower-limb ischemia.
pleted. Furthermore, it was underpowered for showing an effect of aspirin on the incidence of ischemic heart disease or cerebrovascular disease, both of which are reported to be common among patients with unprovoked venous thromboembolism. In addition, patients with symptomatic atherosclerosis were not included in our study. Thus, our results may not apply to patients who require aspirin for the prevention of arterial events.

Our study also has several strengths. It was a randomized, placebo-controlled, double-blind study, with independent adjudication of outcomes. The study treatment lasted for about 2 years — significantly longer than that in recent studies of extended treatment for venous thromboembolism. All patients who received at least one dose of the study drug after randomization were included in the primary efficacy analysis. The results of the on-treatment analysis were consistent with those of the primary study analysis.

We conclude that aspirin, when given after anticoagulant treatment in patients with unprovoked venous thromboembolism, is effective in preventing recurrence, with no apparent increase in the risk of major bleeding.

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Dr. Agnelli reports receiving consulting fees from Bayer HealthCare, Boehringer Ingelheim, and Daiichi Sankyo and lecture fees from Bayer HealthCare, Bristol-Myers Squibb, and Sanofi-Aventis; Dr. Eichinger, board memberships from Bayer and Boehringer Ingelheim and lecture fees from Bayer, Boehringer Ingelheim, Pfizer, and Sanofi-Aventis; and Dr. Ageno, board memberships from Bristol-Myers Squibb, Pfizer, and Bayer Schering Pharma and lecture fees from GlaxoSmithKline, Sanofi-Aventis, Bayer Schering Pharma, Bristol-Myers Squibb, Pfizer, and Boehringer Ingelheim. No other relevant 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.

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Association of Coffee Drinking with Total and Cause-Specific Mortality

Neal D. Freedman, Ph.D., Yikyung Park, Sc.D., Christian C. Abnet, Ph.D., Albert R. Hollenbeck, Ph.D., and Rashmi Sinha, Ph.D.

ABSTRACT

BACKGROUND
Coffee is one of the most widely consumed beverages, but the association between coffee consumption and the risk of death remains unclear.

METHODS
We examined the association of coffee drinking with subsequent total and cause-specific mortality among 229,119 men and 173,141 women in the National Institutes of Health–AARP Diet and Health Study who were 50 to 71 years of age at baseline. Participants with cancer, heart disease, and stroke were excluded. Coffee consumption was assessed once at baseline.

RESULTS
During 5,148,760 person-years of follow-up between 1995 and 2008, a total of 33,731 men and 18,784 women died. In age-adjusted models, the risk of death was increased among coffee drinkers. However, coffee drinkers were also more likely to smoke, and, after adjustment for tobacco-smoking status and other potential confounders, there was a significant inverse association between coffee consumption and mortality. Adjusted hazard ratios for death among men who drank coffee as compared with those who did not were as follows: 0.99 (95% confidence interval [CI], 0.95 to 1.04) for drinking less than 1 cup per day, 0.94 (95% CI, 0.90 to 0.99) for 1 cup, 0.90 (95% CI, 0.86 to 0.93) for 2 or 3 cups, 0.88 (95% CI, 0.84 to 0.93) for 4 or 5 cups, and 0.90 (95% CI, 0.85 to 0.96) for 6 or more cups of coffee per day (P<0.001 for trend); the respective hazard ratios among women were 1.01 (95% CI, 0.96 to 1.07), 0.95 (95% CI, 0.90 to 1.01), 0.87 (95% CI, 0.83 to 0.92), 0.84 (95% CI, 0.79 to 0.90), and 0.85 (95% CI, 0.78 to 0.93) (P<0.001 for trend). Inverse associations were observed for deaths due to heart disease, respiratory disease, stroke, injuries and accidents, diabetes, and infections, but not for deaths due to cancer. Results were similar in subgroups, including persons who had never smoked and persons who reported very good to excellent health at baseline.

CONCLUSIONS
In this large prospective study, coffee consumption was inversely associated with total and cause-specific mortality. Whether this was a causal or associational finding cannot be determined from our data. (Funded by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics.)
Coffee is one of the most widely consumed beverages, both in the United States and worldwide. Since coffee contains caffeine, a stimulant, coffee drinking is not generally considered to be part of a healthy lifestyle. However, coffee is a rich source of antioxidants and other bioactive compounds, and studies have shown inverse associations between coffee consumption and serum biomarkers of inflammation and insulin resistance.

Considerable attention has been focused on the possibility that coffee may increase the risk of heart disease, particularly since drinking coffee has been associated with increased low-density lipoprotein cholesterol levels and short-term increases in blood pressure. Results from a number of studies have been inconsistent. The heterogeneous findings may be due to differences between case-control and prospective study designs and possibly also to inconsistent control for important confounders such as tobacco smoking. In addition, the numbers of deaths have been small in most studies. Cohort studies do not support a positive association between coffee drinking and mortality, however, and some even suggest a modest inverse association.

Previous studies have also investigated the association between coffee consumption and other major causes of death, and they have shown inverse associations with diabetes, inflammatory diseases, stroke, and injuries and accidents, although associations with cancer have generally been null. The results of studies of coffee consumption and total mortality have been mixed, with associations that have been consistent with either the null hypothesis or a modest inverse effect. Data are lacking to clarify the association between coffee drinking and mortality, to determine whether there is a dose-response relationship, and to assess whether associations are consistent across various subgroups.

We used data from a very large study, the National Institutes of Health (NIH)–AARP Diet and Health Study (ClinicalTrials.gov number, NCT00340015), to determine whether coffee consumption is associated with total or cause-specific mortality. The current analysis, involving more than 400,000 participants and 52,000 deaths, had ample power to detect even modest associations and allowed for subgroup analyses according to important baseline factors, including the presence or absence of adiposity and diabetes, as well as cigarette-smoking status.

**Methods**

**Study Population**

The NIH–AARP Diet and Health Study has been described previously. Between 1995 and 1996, a total of 617,119 AARP members, 50 to 71 years of age, returned a comprehensive questionnaire assessing diet and lifestyle. Participants resided in six states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta and Detroit). Of the respondents, 566,401 completed the questionnaire satisfactorily. Completion of the self-administered questionnaire was considered to imply informed consent to participate in the study.

We excluded from these analyses 15,760 persons whose questionnaires were completed by a spouse or other surrogate correspondent, as well as 51,234 persons with cancer, 65,044 with heart disease, 10,459 who had had a previous stroke, 2082 who did not provide information on coffee use, 15,820 who did not provide information on cigarette smoking, 3731 with an extremely low or high caloric consumption (two times as high as the 75th percentile of caloric intake or two times as low as the 25th percentile of caloric intake), and 11 who died before their completed questionnaire was received. The resulting analytic cohort included 229,119 men and 173,141 women. The NIH–AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the National Cancer Institute.

**Assessment of Exposure**

Participants completed a baseline questionnaire that assessed demographic and lifestyle characteristics and 124 dietary items, as previously described. Consumption of fruits, vegetables, red meat, white meat, and saturated fat were adjusted for total energy intake with the use of the nutrient-density approach (i.e., measured per 1000 kcal per day for food groups and as a percentage of total energy for saturated fat).

Coffee consumption was assessed according to...
Coffee and Mortality

In 10 frequency categories, ranging from 0 to 6 or more cups per day. In addition, 96.5% of coffee drinkers provided information on whether they drank caffeinated or decaffeinated coffee more than half the time, and we used this information to categorize coffee drinkers.

In a subgroup of 1953 study participants who also completed a 24-hour dietary-recall questionnaire on 2 nonconsecutive days, the Spearman coefficient for the correlation between coffee consumption as assessed with this questionnaire and coffee consumption as assessed with the baseline food-frequency questionnaire was 0.80. The respective Spearman correlation coefficients for caffeinated and decaffeinated coffee were 0.64 and 0.48, respectively. Among participants who completed the 24-hour dietary-recall questionnaire, 79% drank ground coffee, 19% drank instant coffee, 1% drank espresso coffee, and 1% did not specify the type of coffee they consumed.

Cohort Follow-up

Participants were followed from baseline (1995–1996) until the date of death or December 31, 2008, whichever came first, by means of linkage to the National Change of Address database maintained by the U.S. Postal Service, specific change-of-address requests from participants, and updated addresses returned during other mailings. Vital status was assessed by periodic linkage of the cohort to the Social Security Administration Death Master File, linkage with cancer registries, questionnaire responses, and responses to other mailings.

Causes of Death

Specific causes of death were obtained through follow-up linkage to the National Death Index Plus, maintained by the National Center for Health Statistics. We used the International Classification of Diseases, Ninth Revision (ICD-9), and International Classification of Diseases, Tenth Revision (ICD-10) codes to classify the underlying cause of death (obtained from death certificates) as follows: cancer (ICD-9, 140–239; ICD-10, C00–C97 and D00–D48), heart disease (ICD-9, 390–398, 401–404, 410–429, and 440–448; ICD-10, 100–113, 120–151, and 170–178), respiratory disease (e.g., pneumonia, influenza, chronic obstructive pulmonary disease, and associated conditions) (ICD-9, 480–487 and 490–496; ICD-10, J10–J18 and J40–J47), stroke (ICD-9, 430–438; ICD-10, I60–I69), injuries and accidents (e.g., accident, suicide, and homicide) (ICD-9, 800–978; ICD-10, V01–X59, Y85–Y86, U03, X60–X84, Y870, U01–U02, X85–Y09, Y35, Y87.1, and Y89.0), diabetes (ICD-9, 250; ICD-10, E10–E14), infections (e.g., tuberculosis, septicemia, and other infectious and parasitic diseases) (ICD-9, 001–139; ICD-10, A00–B99), and all other causes.

State data on the incidence of cancer were obtained from the Arizona Cancer Registry, the Georgia Center for Cancer Statistics, the California Cancer Registry, the Michigan Cancer Surveillance Program, the Florida Cancer Data System, the Louisiana Tumor Registry, the New Jersey State Cancer Registry, the North Carolina Central Cancer Registry, the Pennsylvania Cancer Registry, and the Texas Cancer Registry.

Statistical Analysis

Coffee consumption was tabulated according to a number of dietary and lifestyle factors. Hazard ratios and 95% confidence intervals for mortality associated with coffee consumption were estimated with the use of Cox proportional-hazards regression models, with person-years as the underlying time metric; results calculated with age as the underlying time metric were similar. We tested the proportional-hazards assumption by modeling the interaction of follow-up time with coffee consumption and observed no significant deviations. Analyses were conducted with the use of SAS software, version 9.1. Statistical tests were two-sided, and P values of less than 0.05 were considered to indicate statistical significance.

We present risk estimates separately for men and women. Multivariate models were adjusted for the following baseline factors: age; body-mass index (BMI); race or ethnic group; level of education; alcohol consumption; the number of cigarettes smoked per day, use or nonuse of pipes or cigars, and time of smoking cessation (<1 year, 1 to <5 years, 5 to <10 years, or ≥10 years before baseline); health status; presence or absence of diabetes; marital status; level of physical activity; total energy intake; consumption of fruits, vegetables, red meat, white meat, and saturated fat; and use of any vitamin supplement (yes vs. no). In addition, risk estimates for death from cancer were
adjusted for history of cancer (other than non-
melanoma skin cancer) in a first-degree relative
(yes vs. no). For women, status with respect to
postmenopausal hormone therapy was also in-
cluded in multivariate models. Less than 5% of
the cohort lacked any single covariate; for each
covariate, we included an indicator for missing
data in the regression models, if necessary. In
a sensitivity analysis, we adjusted for propen-
sity scores that reflected associations of cof-
fee consumption with the other variables in the
multivariate-adjusted models. Results obtained
with the use of propensity-score adjustment were
very similar to those from multivariate-adjusted
models (Table 1 in the Supplementary Appen-
dix, available with the full text of this article at
NEJM.org).

Hazard ratios for death associated with cate-
gories of coffee consumption (<1, 1, 2 or 3, 4 or
5, and ≥6 cups per day), as compared with no cof-
fee consumption, were estimated from a single
model. Tests of linear trend across categories of
coffee consumption were performed by assigning
participants the midpoint of their coffee-consump-
tion category and entering this new variable into
a separate Cox proportional-hazards regression
model.

In secondary analyses, we determined risk es-
timates for categories of consumption of caffee-
inated and decaffeinated coffee and examined asso-
ciations among prespecified baseline subgroups
based on the following: follow-up time; age;
cigarette-smoking status; presence or absence of
diabetes; BMI; alcohol consumption; self-reported
health; high or low consumption of red meat,
white meat, fruits, and vegetables; use or nonuse
of any vitamin supplement; and, in women, use or
nonuse of postmenopausal hormone therapy. For
these analyses, we combined the categories of
4 or 5 cups of coffee per day and 6 or more cups
per day to preserve numbers in the top category
of consumption. P values for interactions were
computed by means of likelihood-ratio tests com-
paring Cox proportional-hazards models with and
those without cross-product terms for each level
of the baseline stratifying variable, with coffee
consumption as an ordinal variable. For total
mortality, we performed 12 interaction tests for
men and 13 interaction tests for women. We also
performed interaction tests for smoking status
with eight different outcomes for both men and
women. Several differences (P<0.05) would be
expected by chance alone.

## RESULTS

### ASSOCIATION OF COFFEE CONSUMPTION
WITH DIETARY AND LIFESTYLE FACTORS

Coffee consumption at baseline was associated
with several other dietary and lifestyle factors
(Table 1). As compared with persons who did not
drink coffee, coffee drinkers were more likely to
smoke cigarettes and consume more than three
alcoholic drinks per day, and they consumed more
red meat. Coffee drinkers also tended to have a
lower level of education; were less likely to engage
in vigorous physical activity; and reported lower
levels of consumption of fruits, vegetables, and
white meat. However, coffee drinkers, especially
women who drank coffee, were less likely to re-
port having diabetes. About two thirds of coffee
drinkers reported drinking predominantly caff-
feinated coffee.

### COFFEE CONSUMPTION AND TOTAL MORTALITY

During 14 years of follow-up (median, 13.6 years;
total person-years, 5,148,760), 33,731 men and
18,784 women died. In age-adjusted analyses, cof-
fee consumption was associated with increased
mortality among both men (Table 2) and women
(Table 3). However, after multivariate adjustment
for potential confounders, particularly smoking
(Table 1 in the Supplementary Appendix), a modest
inverse association between coffee drinking and
total mortality was observed for both sexes.

Hazard ratios for death among men who drank
coffee, as compared with men who did not drink
coffee, were as follows: 0.99 (95% confidence inter-
val [CI], 0.95 to 1.04) for less than 1 cup of coffee
per day, 0.94 (95% CI, 0.90 to 0.99) for 1 cup, 0.90
(95% CI, 0.86 to 0.93) for 2 or 3 cups, 0.88 (95% CI,
0.84 to 0.93) for 4 or 5 cups, and 0.90 (95% CI,
0.85 to 0.96) for 6 or more cups (P<0.001 for trend
across categories) (Table 2). Hazard ratios among
women who drank coffee, as compared with those
who did not, were as follows: 1.01 (95% CI, 0.96
to 1.07) for less than 1 cup of coffee per day, 0.95
(95% CI, 0.90 to 1.01) for 1 cup, 0.87 (95% CI,
0.83 to 0.92) for 2 or 3 cups, 0.84 (95% CI, 0.79
to 0.90) for 4 or 5 cups, and 0.85 (95% CI, 0.78 to
0.93) for 6 or more cups (P<0.001 for trend across
categories) (Table 3).
Table 1. Baseline Characteristics of the Study Participants, According to Daily Coffee Consumption.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (N = 229,119)</th>
<th>Women (N = 173,141)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Coffee (N = 21,080)</td>
<td>1 Cup (N = 33,961)</td>
</tr>
<tr>
<td>Age (yr) Median</td>
<td>61.1</td>
<td>63.5</td>
</tr>
<tr>
<td>Age (yr) Interquartile range</td>
<td>56.4–65.7</td>
<td>58.6–67.2</td>
</tr>
<tr>
<td>Non-Hispanic white (%)†</td>
<td>91.1</td>
<td>91.1</td>
</tr>
<tr>
<td>Family history of cancer (%)‡</td>
<td>46.3</td>
<td>46.3</td>
</tr>
<tr>
<td>Currently married (%)</td>
<td>83.0</td>
<td>85.5</td>
</tr>
<tr>
<td>College graduate (%)</td>
<td>53.0</td>
<td>46.7</td>
</tr>
<tr>
<td>Median body-mass index§</td>
<td>26.4</td>
<td>26.5</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>8.4</td>
<td>8.6</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>4.8</td>
<td>6.5</td>
</tr>
<tr>
<td>&gt;3 Alcoholic drinks/day (%)</td>
<td>6.3</td>
<td>10.4</td>
</tr>
<tr>
<td>Vigorous physical activity ≥5 times/wk (%)</td>
<td>24.8</td>
<td>21.3</td>
</tr>
<tr>
<td>Poor or fair self-reported health (%)</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Median total energy intake (kcal/day)</td>
<td>1869</td>
<td>1830</td>
</tr>
<tr>
<td>Median servings of food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits (servings/day)</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Vegetables (servings/day)</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Red meat (g/day)</td>
<td>33.1</td>
<td>34.6</td>
</tr>
<tr>
<td>White meat (g/day)</td>
<td>25.8</td>
<td>26.1</td>
</tr>
<tr>
<td>Use of any vitamin supplement (%)</td>
<td>59.6</td>
<td>58.2</td>
</tr>
<tr>
<td>Previous or current use of postmenopausal hormone therapy (%)</td>
<td>52.4</td>
<td>54.8</td>
</tr>
</tbody>
</table>

* All exposures were associated with coffee drinking, with P=0.001 for trends across categories, except for diabetes in men (P=0.002) and self-reported health status in men (P=0.33).
† Race or ethnic group was self-reported.
‡ Nonmelanoma skin cancer in a first-degree relative was excluded from this category.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
Table 2. Association of Daily Coffee Consumption with Total and Cause-Specific Mortality among 229,119 Men.†

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>All Participants (N = 21,080)</th>
<th>No Coffee (N = 34,710)</th>
<th>&lt;1 Cup (N = 33,961)</th>
<th>1 Cup (N = 97,144)</th>
<th>2 or 3 Cups (N = 32,084)</th>
<th>4 or 5 Cups (N = 10,139)</th>
<th>≥6 Cups (N = 10,139)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No. of deaths (%)</td>
<td>33,731</td>
<td>2766 (13.1)</td>
<td>4931 (14.2)</td>
<td>5049 (14.9)</td>
<td>14,115 (14.5)</td>
<td>4966 (15.5)</td>
<td>1904 (18.8)</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.02 (0.98–1.07)</td>
<td>0.99 (0.94–1.03)</td>
<td>1.03 (0.99–1.07)</td>
<td>1.21 (1.15–1.27)</td>
<td>1.60 (1.51–1.69)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>0.99 (0.95–1.04)</td>
<td>0.94 (0.90–0.99)</td>
<td>0.90 (0.86–0.93)</td>
<td>0.88 (0.84–0.93)</td>
<td>0.90 (0.85–0.96)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No. of deaths (%)</td>
<td>13,402</td>
<td>946 (4.5)</td>
<td>1729 (5.0)</td>
<td>1824 (5.4)</td>
<td>5804 (6.0)</td>
<td>2219 (6.9)</td>
<td>880 (8.7)</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.06 (0.98–1.14)</td>
<td>1.06 (0.98–1.15)</td>
<td>1.25 (1.17–1.34)</td>
<td>1.57 (1.46–1.70)</td>
<td>2.13 (1.95–2.34)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.01 (0.93–1.09)</td>
<td>0.96 (0.89–1.04)</td>
<td>1.00 (0.93–1.07)</td>
<td>1.04 (0.96–1.12)</td>
<td>1.08 (0.98–1.19)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No. of deaths (%)</td>
<td>8,127</td>
<td>712 (3.4)</td>
<td>1193 (3.4)</td>
<td>1243 (3.7)</td>
<td>3353 (3.5)</td>
<td>1184 (3.7)</td>
<td>442 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>0.96 (0.87–1.05)</td>
<td>0.94 (0.86–1.03)</td>
<td>0.95 (0.87–1.03)</td>
<td>1.12 (1.02–1.23)</td>
<td>1.44 (1.28–1.62)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>0.93 (0.85–1.02)</td>
<td>0.92 (0.84–1.01)</td>
<td>0.86 (0.79–0.94)</td>
<td>0.87 (0.79–0.96)</td>
<td>0.88 (0.78–1.00)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Respiratory disease</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No. of deaths (%)</td>
<td>2,512</td>
<td>169 (0.8)</td>
<td>351 (1.0)</td>
<td>352 (1.0)</td>
<td>1046 (1.1)</td>
<td>409 (1.3)</td>
<td>185 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.17 (0.97–1.40)</td>
<td>1.07 (0.89–1.28)</td>
<td>1.21 (1.03–1.43)</td>
<td>1.64 (1.37–1.96)</td>
<td>2.63 (2.13–2.34)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.05 (0.87–1.27)</td>
<td>0.93 (0.77–1.11)</td>
<td>0.83 (0.70–0.98)</td>
<td>0.83 (0.69–1.00)</td>
<td>0.81 (0.65–1.00)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths (%)</td>
<td>1,327</td>
<td>125 (0.6)</td>
<td>221 (0.6)</td>
<td>222 (0.7)</td>
<td>555 (0.6)</td>
<td>141 (0.4)</td>
<td>63 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>0.99 (0.80–1.24)</td>
<td>0.91 (0.73–1.14)</td>
<td>0.87 (0.72–1.06)</td>
<td>0.76 (0.60–0.97)</td>
<td>1.21 (0.89–1.64)</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>0.99 (0.79–1.24)</td>
<td>0.92 (0.73–1.15)</td>
<td>0.84 (0.68–1.02)</td>
<td>0.65 (0.51–1.04)</td>
<td>0.83 (0.61–1.14)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Injuries and accidents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths (%)</td>
<td>1,211</td>
<td>113 (0.5)</td>
<td>186 (0.5)</td>
<td>202 (0.6)</td>
<td>492 (0.5)</td>
<td>168 (0.5)</td>
<td>50 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>0.96 (0.76–1.21)</td>
<td>1.01 (0.80–1.27)</td>
<td>0.90 (0.73–1.10)</td>
<td>1.00 (0.78–1.26)</td>
<td>1.00 (0.72–1.40)</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>0.98 (0.77–1.24)</td>
<td>1.02 (0.80–1.29)</td>
<td>0.88 (0.71–1.09)</td>
<td>0.87 (0.68–1.20)</td>
<td>0.72 (0.51–1.02)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths (%)</td>
<td>850</td>
<td>87 (0.4)</td>
<td>165 (0.5)</td>
<td>154 (0.5)</td>
<td>310 (0.3)</td>
<td>107 (0.3)</td>
<td>27 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.10 (0.85–1.42)</td>
<td>0.98 (0.75–1.27)</td>
<td>0.73 (0.57–0.92)</td>
<td>0.83 (0.62–1.10)</td>
<td>0.71 (0.46–1.10)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.07 (0.82–1.39)</td>
<td>1.00 (0.76–1.31)</td>
<td>0.75 (0.59–0.96)</td>
<td>0.80 (0.60–1.08)</td>
<td>0.60 (0.39–0.94)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
Coffee and Mortality

Coffee Consumption and Cause-Specific Mortality

Specific causes of death were also examined. After multivariate adjustment, coffee appeared to be inversely associated with most major causes of death in both men and women, including heart disease, respiratory disease, stroke, injuries and accidents, diabetes, and infections. In contrast, there was no significant association between coffee consumption and deaths from cancer in women. There was a borderline positive association in men: among 13,402 deaths from cancer, 880 deaths were reported among men who drank 6 or more cups of coffee per day (hazard ratio for the comparison with men who did not drink coffee, 1.08; 95% CI, 0.98 to 1.19; P = 0.02 for trend).

Subgroup Analyses

In analyses stratified according to the predominant type of coffee consumed (caffeinated or decaffeinated), the association of coffee drinking with total mortality and individual causes of death appeared to be similar for the two types of coffee (Fig. 1, and Tables 2 and 3 in the Supplementary Appendix).

Coffee consumption was associated with a number of risk factors for death. Results of subgroup analyses are shown in Figure 2, with more detailed results shown in Tables 4 and 5 in the Supplementary Appendix. Associations between coffee consumption and mortality were generally similar across subgroups stratified according to duration of follow-up and the following baseline factors: age; diabetes (yes vs. no); BMI; alcohol consumption; the number of cigarettes smoked per day, use or nonuse of pipes or cigars, and time of smoking cessation; total energy intake; and use or nonuse of vitamin supplements. In addition, risk estimates for death from cancer were adjusted for history of cancer in first-degree relatives.

We further examined associations between coffee consumption and deaths from cancer and...
Table 3. Association of Daily Coffee Consumption with Total and Cause-Specific Mortality among 173,141 Women.*

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>All Participants (N = 208,865)</th>
<th>No Coffee (N = 30,085)</th>
<th>&lt;1 Cup (N = 31,355)</th>
<th>2 or 3 Cups (N = 68,250)</th>
<th>4 or 5 Cups (N = 17,434)</th>
<th>≥6 Cups (N = 5152)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>18,784</td>
<td>2161 (10.4)</td>
<td>3221 (10.7)</td>
<td>3388 (10.8)</td>
<td>7140 (10.5)</td>
<td>2099 (12.0)</td>
<td>775 (15.0)</td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>0.99 (0.94–1.05)</td>
<td>0.93 (0.88–0.98)</td>
<td>0.93 (0.89–0.98)</td>
<td>1.13 (1.07–1.20)</td>
<td>1.51 (1.39–1.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.01 (0.96–1.07)</td>
<td>0.95 (0.90–1.01)</td>
<td>0.87 (0.83–0.92)</td>
<td>0.84 (0.79–0.90)</td>
<td>0.85 (0.78–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths (%)</td>
<td>7,750</td>
<td>783 (3.8)</td>
<td>1153 (3.8)</td>
<td>1313 (4.2)</td>
<td>3110 (4.6)</td>
<td>1016 (5.8)</td>
<td>375 (7.3)</td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>0.96 (0.86–1.08)</td>
<td>1.02 (0.93–1.11)</td>
<td>1.14 (1.05–1.23)</td>
<td>1.52 (1.38–1.67)</td>
<td>2.00 (1.77–2.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.00 (0.89–1.13)</td>
<td>0.91 (0.81–1.03)</td>
<td>0.85 (0.76–0.95)</td>
<td>0.78 (0.68–0.90)</td>
<td>0.72 (0.59–0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths (%)</td>
<td>3,701</td>
<td>461 (2.2)</td>
<td>673 (2.2)</td>
<td>683 (2.2)</td>
<td>1379 (2.0)</td>
<td>378 (2.2)</td>
<td>127 (2.5)</td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>0.96 (0.86–1.08)</td>
<td>1.02 (0.93–1.11)</td>
<td>1.14 (1.05–1.23)</td>
<td>1.52 (1.38–1.67)</td>
<td>2.00 (1.77–2.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.00 (0.89–1.13)</td>
<td>0.91 (0.81–1.03)</td>
<td>0.85 (0.76–0.95)</td>
<td>0.78 (0.68–0.90)</td>
<td>0.72 (0.59–0.88)</td>
<td>&lt;0.001</td>
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<tr>
<td>No. of deaths (%)</td>
<td>1,791</td>
<td>187 (0.9)</td>
<td>315 (1.0)</td>
<td>279 (0.9)</td>
<td>698 (1.0)</td>
<td>208 (1.2)</td>
<td>104 (2.0)</td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.11 (0.92–1.33)</td>
<td>0.85 (0.71–1.03)</td>
<td>1.03 (0.88–1.22)</td>
<td>1.29 (1.06–1.57)</td>
<td>2.35 (1.85–2.99)</td>
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</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.09 (0.91–1.31)</td>
<td>0.84 (0.69–1.01)</td>
<td>0.79 (0.67–0.93)</td>
<td>0.65 (0.53–0.79)</td>
<td>0.77 (0.61–0.99)</td>
<td>&lt;0.001</td>
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<tr>
<td>Stroke</td>
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<td></td>
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<tr>
<td>No. of deaths (%)</td>
<td>966</td>
<td>115 (0.6)</td>
<td>191 (0.6)</td>
<td>168 (0.5)</td>
<td>369 (0.5)</td>
<td>91 (0.5)</td>
<td>32 (0.6)</td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.09 (0.87–1.38)</td>
<td>0.84 (0.66–1.06)</td>
<td>0.89 (0.72–1.10)</td>
<td>0.92 (0.70–1.21)</td>
<td>1.18 (0.79–1.74)</td>
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<tr>
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<td>1.15 (0.91–1.45)</td>
<td>0.89 (0.70–1.13)</td>
<td>0.93 (0.75–1.15)</td>
<td>0.82 (0.62–1.09)</td>
<td>0.84 (0.56–1.25)</td>
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<td>Injuries and accidents</td>
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<td>No. of deaths (%)</td>
<td>462</td>
<td>57 (0.3)</td>
<td>91 (0.3)</td>
<td>114 (0.4)</td>
<td>153 (0.2)</td>
<td>36 (0.2)</td>
<td>11 (0.2)</td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.07 (0.77–1.49)</td>
<td>1.22 (0.88–1.67)</td>
<td>0.77 (0.57–1.05)</td>
<td>0.74 (0.49–1.12)</td>
<td>0.81 (0.42–1.54)</td>
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<td>1.11 (0.80–1.55)</td>
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<td>0.77 (0.56–1.06)</td>
<td>0.64 (0.42–0.98)</td>
<td>0.57 (0.29–1.10)</td>
<td>&lt;0.001</td>
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<tr>
<td>Diabetes</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>No. of deaths (%)</td>
<td>446</td>
<td>71 (0.3)</td>
<td>95 (0.3)</td>
<td>93 (0.3)</td>
<td>140 (0.2)</td>
<td>38 (0.2)</td>
<td>9 (0.2)</td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>0.90 (0.66–1.22)</td>
<td>0.79 (0.58–1.08)</td>
<td>0.56 (0.42–0.75)</td>
<td>0.63 (0.42–0.93)</td>
<td>0.53 (0.27–1.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.00 (0.73–1.36)</td>
<td>0.91 (0.67–1.25)</td>
<td>0.77 (0.57–1.03)</td>
<td>0.82 (0.54–1.23)</td>
<td>0.57 (0.28–1.16)</td>
<td>0.03</td>
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other causes according to smoking status (Tables 6 and 7 in the Supplementary Appendix). The results were similar for most outcomes across categories of smoking status, with the exception of death from heart disease, with associations that appeared to be null in current smokers (P=0.002 for interaction in men and P=0.05 for interaction in women). We also noted significant interactions between smoking and coffee consumption with respect to the overall risk of death from cancer; associations appeared to be modestly inverse for men and women who had never smoked, but not for those who were former or current smokers. However, associations between coffee consumption and death from cancer were not significant for any single category of coffee consumption.

**Discussion**

In this large, prospective U.S. cohort study, we observed a dose-dependent inverse association between coffee drinking and total mortality, after adjusting for potential confounders (smoking status in particular). As compared with men who did not drink coffee, men who drank 6 or more cups of coffee per day had a 10% lower risk of death, whereas women in this category of consumption had a 15% lower risk. Similar associations were observed whether participants drank predominantly caffeinated or decaffeinated coffee. Inverse associations persisted among many subgroups, including participants who had never smoked and those with a normal BMI and those with a high BMI. Asso-

CI denotes confidence interval. The numbers of deaths are for participants who died during follow-up. Multivariate analyses were adjusted for the following factors at baseline: age; body-mass index; race or ethnic group; level of education; alcohol consumption; the number of cigarettes smoked per day, use or nonuse of pipes or cigars, and time of smoking cessation; marital status; physical activity; total energy intake; consumption of fruits, vegetables, red meat, white meat, and saturated fat; use or nonuse of vitamin supplements; and use or nonuse of postmenopausal hormone therapy. In addition, risk estimates for death from cancer were adjusted for history of cancer (other than nonmelanoma skin cancer) in a first-degree relative (yes vs. no).
Figure 1. Subgroup Analysis of Associations between the Consumption of 4 or More Cups of Coffee per Day and Total and Cause-Specific Mortality.

Hazard ratios for death from all causes and from specific causes are for the comparison of men and women who drank 4 or more cups of coffee per day with those who did not drink coffee. Participants were classified as drinking caffeinated or decaffeinated coffee according to whether they reported drinking caffeinated or decaffeinated coffee more than half the time. Risk estimates for other categories of coffee consumption are shown in Tables 2 and 3 in the Supplementary Appendix. Risk estimates were adjusted for the following factors at baseline: age; body-mass index; race or ethnic group; level of education; alcohol consumption; the number of cigarettes smoked per day, use or non-use of pipes or cigars, and time of smoking cessation (<1 year, 1 to <3 years, 5 to <10 years, or ≥10 years before baseline); health status; diabetes (yes vs. no); marital status; physical activity; total energy intake; consumption of fruits, vegetables, red meat, white meat, and saturated fat; and use or non-use of vitamin supplements. In addition, risk estimates for death from cancer were adjusted for history of cancer (other than nonmelanoma skin cancer) in a first-degree relative (yes vs. no). In women, risk estimates were also adjusted for use or nonuse of postmenopausal hormone therapy. Horizontal lines represent 95% confidence intervals.
Study for Evaluation of Cancer Risk, the hazard ratio for death among men who drank 4 or more cups of coffee per day, as compared with men who drank less than 1 cup per day, was 0.80 (95% CI, 0.68 to 0.95); the corresponding hazard ratio for women was 0.89 (95% CI, 0.66 to 1.20). In the Miyagi Cohort Study, the hazard ratio for death among men who drank 3 or more cups of coffee per day, as compared with men who never drank coffee, was 0.89 (95% CI, 0.74 to 1.08); the corresponding hazard ratio for women was 0.75 (95% CI, 0.53 to 1.05).

We noted inverse associations between coffee drinking and most major causes of death, with the exception of cancer. Associations between coffee drinking and the risk of death from heart disease have been particularly controversial, and several studies have suggested an increased risk among coffee drinkers. Nevertheless, the inverse associations observed in our study are consistent with those in a recent meta-analysis of this association. In that analysis, the relative risk of death among men in the highest category of coffee consumption, as compared with men in the lowest category of coffee consumption, was 0.89 (95% CI, 0.78 to 1.03). Although some previous studies showed differences in risk according to the interval between baseline and the date of death, we observed similar associations for deaths occurring early or late in follow-up.

Our results are concordant with previous studies showing inverse associations between coffee consumption and diabetes, stroke, and death due to inflammatory diseases. In addition, we observed an inverse association of coffee consumption with deaths from injuries and accidents. The mechanism of this association is unclear and could reflect chance or residual confounding, although similar results were reported in the Nurses’ Health Study and the Kaiser Permanente Multiphasic Health Checkup cohorts. In contrast to other outcomes, a modest borderline positive association was observed in men for coffee consumption and mortality from cancer, with a null association observed in women. Findings from previous studies were typically null.

Several explanations for our findings are possible. As in all observational studies, associations could reflect confounding by unmeasured or poorly measured confounders. Although coffee consumption was inversely associated with diabetes, it was also positively associated with a number of behaviors that are considered unhealthy and are associated with an increased risk of death, such as tobacco smoking, consumption of red meat, and heavy alcohol use. Tobacco smoking was the strongest confounder in the multivariate analysis, and the inverse association between coffee consumption and mortality tended to be stronger among persons who had never smoked or were former smokers than among those who were current smokers, suggesting that residual confounding by smoking status, if present, attenuated the inverse associations between coffee drinking and mortality in our study.

Reverse causality is another possible explanation, since persons with chronic disease and poor health might abstain from coffee drinking. However, we excluded persons who had cancer or cardiovascular disease at baseline. Moreover, the results were similar when data from the first 4 or 9 years of follow-up were excluded, and associations were stronger among persons reporting good or very good to excellent health at baseline than among those reporting poor to fair health, arguing against this possibility.

Several limitations of our study should be noted. Coffee consumption was assessed by self-report at a single time point and may not reflect long-term patterns of consumption. The distinction between persons who drank caffeinated coffee and those who drank decaffeinated coffee was subject to misclassification, since these categories were defined on the basis of consumption of either beverage more than half the time. We lacked data on how coffee was prepared (espresso, boiled, or filtered), and the constituents of coffee may differ according to the method of preparation.

Given the observational nature of our study, it is not possible to conclude that the inverse relationship between coffee consumption and mortality reflects cause and effect. However, we can speculate about plausible mechanisms by which coffee consumption might have health benefits. Coffee contains more than 1000 compounds that might affect the risk of death. The most well-studied compound is caffeine, although similar
<table>
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<tr>
<th>Subgroup</th>
<th>Men Hazard Ratio</th>
<th>Women Hazard Ratio</th>
<th>P Value for Interaction</th>
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<td>All</td>
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<td>Years of follow-up</td>
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<td>9 to 14</td>
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<td>≥35</td>
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associations for caffeinated and decaffeinated coffee in the current study and a previous study\(^1\) suggest that, if the relationship between coffee consumption and mortality were causal, other compounds in coffee (e.g., antioxidants, including polyphenols) might be important.\(^1,38\)

In summary, this large prospective cohort study showed significant inverse associations of coffee consumption with deaths from all causes and specifically with deaths due to heart disease, respiratory disease, stroke, injuries and accidents, diabetes, and infections. Our results provide reassurance with respect to the concern that coffee drinking might adversely affect health.

The views expressed in this article are those of the authors and do not necessarily reflect those of the cancer registries. 

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We thank the participants in this study for their outstanding cooperation.

This article is dedicated to the memory of Arthur Schatzkin, the visionary investigator who founded the NIH–AARP Diet and Health Study.

### References


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