A 29-year-old woman with a history of systemic lupus erythematosus (SLE) and herpes simplex virus type 2 infection presented to a Boston-area urgent care clinic in the early fall with a 6-day history of diarrhea; the diarrhea had initially been accompanied by nausea and vomiting, which had resolved after 2 days. The woman described the diarrhea as five to eight watery bowel movements, without blood or mucus, per day. On the morning of presentation, she reported chills, diffuse myalgias, malaise, and a fever (temperature of 38.7°C). She had not had any abdominal pain, a change in diet, recent travel, contact with sick persons, or known exposure to animals or insects.

This patient has acute-onset diarrhea, which is defined as three or more unformed stools per day, with a duration of less than 2 weeks. Given that the diarrhea in this case is accompanied by fever and was initially accompanied by nausea and vomiting, infectious gastroenteritis appears to be the most probable diagnosis. A thorough history of stool characteristics (e.g., visible blood), associated symptoms, and possible exposures can be helpful in identifying the cause. Viral gastroenteritis, which is most often due to noroviruses, is very common and typically manifests with watery diarrhea, nausea, vomiting, and fever; her myalgias and malaise are also consistent with this diagnosis. However, the patient's history of SLE suggests that she has had increased exposure to health care facilities and may be receiving or has recently received immunosuppressive medications. Therefore, in addition to the possibility that common viral pathogens could be causing gastroenteritis, a broader differential diagnosis should be considered, including other infectious causes such as those related to exposure to health care facilities, opportunistic pathogens if she is immunosuppressed, complications of her underlying lupus, and, depending on her current medication regimen, a drug-related adverse effect.

The patient had received the diagnosis of SLE 14 years earlier, when she presented with cutaneous lesions, arthralgias, and fever; she was initially treated with hydroxychloroquine, glucocorticoids, and methotrexate. One year before the current presentation, discoid lesions developed on her ears, face, and chest wall, and she was again treated with hydroxychloroquine and methotrexate. Four months before presentation, she received a diagnosis of class IV lupus nephritis in conjunction with proteinuria and was treated with rituximab, high-dose methylprednisolone, and mycophe-
nolate mofetil. Her medications at the time of the current presentation included hydroxychloroquine, mycophenolate mofetil, prednisone (6 mg per day, as part of a regimen that involved tapering of the dose), and prophylactic treatment with trimethoprim–sulfamethoxazole. She had no known drug or environmental allergies. Her family history was notable for gastric cancer in a paternal grandfather. She had no family history of autoimmune disease. She was born in East Asia but had lived in the United States for more than 10 years and, at the time of presentation, was attending school in the Boston area. She did not smoke cigarettes, consume alcohol, or use illicit substances.

The patient's medical history and immunosuppressive medication regimen substantially broaden the differential diagnosis. Her exposure to glucocorticoids, mycophenolate mofetil (which impairs cellular immunity), and rituximab (which impairs humoral immunity) arouses concern for opportunistic pathogens, and her ongoing use of antibiotic agents increases the risk of Clostridium difficile. Lupus enteritis (mesenteric vasculitis) should also be considered, although it is a rare condition and is a less likely diagnosis in this case, given the absence of abdominal pain. Finally, mycophenolate mofetil is often associated with gastrointestinal side effects and may cause colitis, which most commonly manifests with watery diarrhea.

On physical examination, the patient's temperature was 39°C, heart rate 121 beats per minute, blood pressure 109/73 mm Hg, respiratory rate 16 breaths per minute, and oxygen saturation 97% while she was breathing ambient air. She appeared to be fatigued but in no distress and was fully oriented and able to converse. Her mucous membranes appeared dry, but no thrush or oral lesions were present. Her neck was supple, and there was no cervical lymphadenopathy. Both lungs were clear to auscultation. The cardiac examination was notable only for tachycardia. Her abdomen was soft, nontender, and nondistended, with normal bowel sounds and no appreciable organomegaly. The skin was warm and dry. The patient had hyperpigmented patches on her chest that were consistent with previously described discoid lesions from her lupus. There was no edema in the legs or feet. The joints were nontender and without swelling. Motor strength and sensation in the arms and legs were normal.

The patient appears to be dehydrated, as evidenced by dry mucous membranes and tachycardia, although the latter may also be explained by her fever. Given that her nausea has resolved, I would anticipate that she can be given oral hydration, and I would favor this route of fluid repletion over intravenous fluids. Given the unremarkable abdominal examination, a diagnosis of lupus enteritis is very unlikely. No skin or joint manifestations of a flare-up of lupus are present, making this diagnosis less likely, although laboratory evaluation is still warranted.

Laboratory studies revealed a potassium level of 3.0 mmol per liter; the remainder of her basic metabolic panel and liver function tests were unremarkable. The lactate level was within normal limits. The complete blood count was notable only for a hematocrit of 35.7%, which was similar to previous measurements. The double-stranded DNA antibody level was stably elevated at 109 units. The serum complement factor 3 and serum complement factor 4 levels were normal. A urine pregnancy test was negative.

Her initial laboratory test results are reassuring. There are no changes to suggest a flare-up of lupus, such as worsening cytopenias, acute elevation in antibodies to double-stranded DNA, or hypocomplementemia. Despite the relatively reassuring physical examination and laboratory assessment, I would admit her to the hospital for further evaluation, given her level of immunosuppression. In the absence of evidence of a flare-up of lupus, I would favor withholding mycophenolate mofetil, given ongoing concern about an infectious cause for her presentation, as well as the possibility that the drug may be contributing to her diarrhea. I would obtain specimens for blood and stool cultures and test for C. difficile and cytomegalovirus.

The patient was admitted to the hospital for further evaluation. Administration of mycophenolate mofetil was discontinued at the time of admission. The diarrhea abated initially, but the fevers persisted. One day after admission, she reported a diffuse headache. The next day, she became...
lethargic and had a precipitous decline in mental status; she would open her eyes in response to loud voices but could not consistently follow simple commands. Blood, urine, and stool cultures were negative. A polymerase-chain-reaction (PCR) blood test for cytomegalovirus was negative. Examination of a stool specimen did not reveal ova or parasites. Stool testing for C. difficile antigen and toxin was negative.

The decline in the patient's mental status is alarming and, in a patient with a presumed infectious process, arouses concern for nervous system involvement. She should be reexamined with specific attention paid to features suggestive of meningitis or encephalitis.

A neurologic examination showed a decreased level of consciousness, with noxious stimulation required to obtain and maintain arousal. The patient was unable to follow most commands, but the examination was notable for meningismus and the presence of Brudzinski's sign. No abnormalities were observed with respect to her assessable cranial nerves, motor strength, distal sensation to light touch, or deep tendon reflexes. The plantar reflexes were equivocal.

The interval development of meningeal signs and the altered mental status arouse concern for meningoencephalitis. Although the clinical assessment favors a viral meningitis or encephalitis, empirical treatment for bacterial meningitis and for treatable causes of viral meningitis should be initiated, given the degree of immunosuppression and the patient's precipitous clinical decline. Lupus cerebritis, although a much less likely diagnosis, should be considered if an infectious cause is not identified. Lumbar puncture is indicated for further evaluation. The procedure should be avoided in patients who have coagulopathy, possible cardiopulmonary abnormalities, or signs of cerebral herniation from increased intracranial pressure. In patients with focal neurologic signs, computed tomography (CT) should be performed before proceeding with lumbar puncture.

CT of the head without contrast did not reveal any intracranial abnormalities. A lumbar puncture was performed, with an opening pressure of 23 cm of water. The cerebrospinal fluid (CSF) was clear and colorless; xanthochromia was not present. There were 94 nucleated cells per cubic millimeter, with 73% lymphocytes, 19% monocytes, and 8% neutrophils. No red cells were present. The glucose level was 40 mg per deciliter (2.2 mmol per liter; reference range, 40 to 70 mg per deciliter [2.2 to 3.9 mmol per liter]), and the protein level was 100.5 mg per deciliter (reference range, 10 to 44). Empirical treatment with vancomycin, cefepime, ampicillin, and acyclovir was initiated for possible bacterial infection and herpes simplex virus (HSV) encephalitis.

The CSF profile indicates an inflammatory condition. The findings of fewer than 100 white cells per cubic millimeter with a predominance of lymphocytes, the elevated protein level, and the low-normal glucose level are most consistent with viral meningoencephalitis. Although bacterial meningitis would be expected to be associated with a much higher white-cell count with neutrophil predominance, empirical treatment with antibiotics is appropriate, especially in light of the patient's degree of immunosuppression, until final results of the CSF culture are available. In patients with HSV encephalitis, red cells are typically present in the CSF, but I would continue to treat this patient with empirical acyclovir for now. In rare cases, SLE is associated with an aseptic meningitis, which is most commonly attributed to medications used for the treatment of lupus (such as nonsteroidal anti-inflammatory drugs). Central nervous system vasculitis in a person with lupus can also lead to abnormal CSF results (including lymphocytic pleocytosis and elevated protein level) and is typically associated with focal abnormalities on magnetic resonance imaging (MRI) of the head. MRI of the head may, therefore, be informative, because it can show features associated with vasculitis (such as ischemic regions) or because it can reveal abnormalities associated with specific viruses (such as temporal lobe abnormalities in patients with HSV encephalitis or thalamic abnormalities in patients with respiratory viral or arboviral infections).

MRI of the head showed hyperintense signals on T2-weighted fluid-attenuated inversion recovery (FLAIR) images in both thalami (Fig. 1) and cere-
bral peduncles, without contrast enhancement or diffusion restriction. Intracranial magnetic resonance angiography did not show any abnormalities of the intracranial vessels.

Abnormal signal intensity on T₂-weighted images in both thalami, without contrast enhancement or restricted diffusion, is suggestive of a viral encephalitis, particularly respiratory viral infection or arboviral infection. West Nile virus is the most common arboviral cause of viral encephalitis in New England (and across the United States). St. Louis encephalitis virus can manifest with similar clinical and radiographic findings, although it is less likely in this case because its incidence has decreased dramatically in the past decade, with no recent reported cases in New England. The usual test for West Nile virus involves analysis of CSF for the presence of IgM antibodies against the virus, which usually appear within days after the onset of symptoms. In this case, however, the recent administration of rituximab may impair antibody production. PCR testing for West Nile virus RNA should be performed in this patient, even though such testing is generally considered to be less sensitive than CSF analysis.

Because of the patient’s rapidly declining mental status, she was transferred to the neurocritical care unit for close monitoring. A serum test for Lyme disease was negative. Gram’s staining of spinal fluid, bacterial culture, fungal culture, and a Venereal Disease Research Laboratory test were all negative. A multiplex PCR assay of the CSF was negative for Escherichia coli K1, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, S. pneumoniae, cytomegalovirus, enterovirus, Herpes simplex virus types 1 and 2, human parechovirus, varicella zoster virus, and Cryptococcus neoformans. CSF testing for IgM and IgG antibodies to La Crosse virus, eastern equine encephalitis, St. Louis encephalitis, and western equine encephalitis was also negative. PCR testing of the CSF for West Nile virus was positive; antibody testing of the CSF for West Nile virus was not performed.

Administration of empirical antibacterial and antiviral agents can be discontinued because they have no role in the treatment of West Nile virus. There is no approved therapy for neuroinvasive West Nile virus, and current treatment typically involves supportive care alone. Although intravenous administration of immune globulin has been proposed as a possible treatment on the basis of the prevalence of West Nile virus neutralizing antibodies in plasma, it is not routinely recommended for the treatment of neuroinvasive West Nile virus. This patient, however, is critically ill and has probable impairment of her humoral immunity as a result of her recent receipt of rituximab; thus, intravenous administration of immune globulin in this case would be reasonable.

Antimicrobial therapy was discontinued, and the patient received two doses of intravenous immune globulin. Her mental status improved rapidly, and she was transferred out of the neurocritical care unit. She continued to have marked nonfocal weakness, which was attributed in part to deconditioning during her hospitalization. She was discharged to an acute rehabilitation facility, where her condition continued to improve. At a follow-up visit at her primary care practice 1 month after discharge, she reported complete recovery in her cognition and marked improvement in her strength.
Although this patient’s initial presentation was consistent with a benign viral gastroenteritis, her underlying lupus and substantial immunosuppressive therapy necessitated a very broad initial differential diagnosis that nonetheless did not specifically include the ultimate diagnosis. Her subsequent hospital course was clinically consistent with a viral meningoencephalitis. A multiplex PCR assay for common bacterial, viral, and fungal pathogenic causes of meningoencephalitis allows for rapid diagnosis of some pathogens both in immunocompetent and in immunocompromised patients but does not specifically test for arboviral infection, which should be considered in any patient with viral encephalitis, particularly during seasons of peak incidence. PCR–based testing for West Nile virus infection has low sensitivity (approximately 57%) but may be particularly useful in patients with impaired humoral immunity, which may lead to false negative serologic testing. In this case, serologic testing was not performed, but PCR testing led to the diagnosis of West Nile virus.

West Nile virus has been observed throughout the continental United States and is by far the most common domestic cause of arboviral infection. After amplification in birds, West Nile virus is transmitted to humans by mosquitoes, with incidence peaking during the warmer months of the summer and early fall. Climate change is projected to result in increases in the geographic and temporal range of West Nile virus infections. Rare cases of transmission through blood transfusion or solid-organ transplantation have been reported.

After inoculation, the incubation period varies from 3 days to 3 weeks; only approximately 25% of patients report symptoms. When symptoms are present, they tend to be nonspecific and can include acute onset of fever, chills, malaise, headache, vomiting, diarrhea, and myalgias. In some cases, a maculopapular rash develops on the trunk; this finding is more common among children than among adults. In the absence of neuroinvasive disease, West Nile virus infection generally has a benign course. Neuroinvasive disease occurs in approximately 1 in 150 cases of West Nile virus infection and appears to be more common among older adults (with the highest incidence among persons 70 years of age or older) and among immunocompromised persons. Neuroinvasive West Nile virus infection can manifest as meningitis (with fever, headache, nuchal rigidity, and photophobia), encephalitis (with impaired mental status), or meningoencephalitis. In addition, some patients with neuroinvasive disease have presented with acute flaccid paralysis caused by a poliomyelitis-like syndrome, with inflammation of the anterior horn of the spinal cord and focal loss of anterior-horn neurons. Prospective cohort studies have shown that neurologic symptoms, including fatigue, muscle weakness, memory issues, and loss of concentration, may last for months to years. The mortality rate among patients with neuroinvasive disease is reported to be 2 to 20%, with advanced age and coexisting medical conditions leading to poorer outcomes.

No specific antiviral treatments for West Nile virus infection are currently available. A retrospective analysis showed a higher mortality rate among patients who received ribavirin as antiretroviral therapy than among those who did not. In preclinical models, intravenous immune globulin (either from populations with antibodies against West Nile virus or specifically high-titer West Nile virus immune globulin) showed a protective effect, but in a small, randomized, placebo-controlled trial, it did not show clinical efficacy. Therefore, intravenous immune globulin is not routinely administered but may be considered in specific circumstances, such as West Nile virus neuroinvasive disease in a critically ill patient with suspected humoral immunodeficiency, as was the case with the current patient.

In this case, it was not until the initially nonspecific viral presentation evolved to a clinical picture that suggested meningoencephalitis that arbovirus infection was considered. PCR–based testing of the CSF led to specific identification of West Nile virus as the causative pathogen and allowed for the subsequent discontinuation of empirical antimicrobial therapy.

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