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The *N Engl J Med* image of the week concerns a 24-year-old woman with a history of HIV, currently on antiretroviral therapy, who presented with 2 days of severe, burning leg pain. She had a migraine headache 4 days before presentation for which she was taking ergotamine twice daily. Leg pain extended from toes to midthigh. On physical examination, both legs were cold with absent popliteal and dorsalis pedis pulses. What is the diagnosis? You are offered atherosclerosis, ergotism, herniated disc, progressive lumbosacral polyradiculopathy, and thromboangitis obliterans. Hint, the condition is also known as St. Anthony's fire. Trials have evaluated the use of clopidogrel and aspirin to prevent stroke after an ischemic stroke or transient ischemic attack (TIA). In a previous trial, ticagrelor was not better than aspirin in preventing vascular events or death after stroke or TIA. The effect of the combination of ticagrelor and aspirin on prevention of stroke has not been well studied. Investigators conducted a randomized, placebo-controlled, double-blind trial involving patients who had had a mild-to-moderate acute noncardioembolic ischemic stroke, with a National Institutes of Health Stroke Scale (NIHSS) score of 5 or less (range, 0 to 42, with higher scores indicating more severe stroke), or TIA and who were not undergoing thrombolysis or thrombectomy. The patients were assigned within 24 hours after symptom onset, in a 1:1 ratio, to receive a 30-day regimen of either ticagrelor (180-mg loading dose followed by 90 mg twice daily) plus aspirin (300 to 325 mg on the first day followed by 75 to 100 mg daily) or matching placebo plus aspirin. The primary outcome was a composite of stroke or death within 30 days. The combination reduced the primary outcome but increased bleeding. Rheumatoid arthritis, like many inflammatory diseases, is characterized by episodes of quiescence and exacerbation (flares). The molecular events leading to flares are unknown. Investigators established a clinical and technical protocol for repeated home collection of blood in patients with rheumatoid arthritis to allow for longitudinal RNA sequencing (RNA-seq). Specimens were obtained from 364 time points during eight flares over a period of 4 years in an index patient, as well as from 235 time points during flares in three additional patients. The investigators identified transcripts that were differentially expressed before flares and compared these with data from synovial single-cell RNA-seq. Flow cytometry and

sorted-blood-cell RNA-seq in additional patients were used to validate the findings. Anchoring the analysis on disease flares enabled the authors to identify molecular markers that were predictive of imminent flares and to identify transcriptional modules representing activation of naive B cells, which increased in blood approximately 2 weeks before a flare. It further allowed for the identification of a new cell type — termed preinflammatory mesenchymal, or PRIME, cells — that appeared in blood just before disease flares. In contrast to CD45-positive “fibrocytes,” these fibroblast-like PRIME cells are CD45 negative. Systemic oral phosphodiesterase type 4 (PDE-4) inhibitors have been effective in the treatment of inflammatory conditions including psoriasis. Roflumilast cream contains a PDE-4 inhibitor that is being investigated for the topical treatment of psoriasis. In a phase 2b, double-blind trial, investigators randomly assigned adults with plaque psoriasis in a 1:1:1 ratio to use roflumilast 0.3% cream, roflumilast 0.15% cream, or vehicle (placebo) cream once daily for 12 weeks. The primary efficacy outcome was the investigator’s global assessment (IGA) of a status of clear or almost clear at week 6 (assessed on a 5-point scale of plaque thickening, scaling, and erythema; a score of 0 indicates clear, 1 almost clear, and 4 severe). Roflumilast seems to work dose-dependently fairly well. Acute kidney injury (AKI) is common in critically ill patients, many of whom receive renal-replacement therapy. However, the most effective timing for the initiation of such therapy remains uncertain. A large consortium conducted a multinational, randomized, controlled trial involving critically ill patients with severe acute kidney injury. Patients were randomly assigned (about 1500 patients in each group) to receive an accelerated strategy of renal-replacement therapy (in which therapy was initiated within 12 hours after the patient had met eligibility criteria) or a standard strategy (in which renal-replacement therapy was discouraged unless conventional indications developed or acute kidney injury persisted for >72 hours). The primary outcome was death from any cause at 90 days. The determination of kidney injury was defined by a doubling of the serum creatinine level from baseline, a serum creatinine level of 4 mg per deciliter (354 μmol per liter) or more with an increase of 0.3 mg per deciliter (27 μmol per liter) from baseline, or a urine output of less than 6 ml per kilogram of body weight during the preceding 12 hours (about RIF of RIFLE or AKIN Stage 3). In the accelerated-strategy group, clinicians were to start renal-replacement therapy within 12 hours after patients had

met full eligibility criteria. Standard care was based on the usual acidosis, electrolyte disturbance, volume overload, or uremia symptoms criteria. Outcomes of these strategies were not different. However, a greater percentage of survivors who received the accelerated strategy were dependent on renal-replacement therapy at 90 days and they had more adverse events. The N Engl J Med review is on stroke management and fits well with the Lancet review on stroke last week. The weekly case is a woman with newly diagnosed breast cancer who cannot be operated upon promptly because of the Covid-19 pandemic. In the Lancet, urgent (immediate) endoscopic retrograde cholangiopancreatography with sphincterotomy was compared to more conservative management with subsequent elective decisions. Haste made waste; immediate ERCP was not necessary. Dexmedetomidine, a clonidine-like drug, was tested to see whether or not atrial fibrillation and delirium would be reduced after cardiac surgery. Neither were reduced. Next, we learn that carfilzomib (proteasome inhibitor) and daratumumab (CD38 antibody), combined with dexamethasone is a reasonable approach to manage refractory multiple myeloma. The Lancet review is about circulatory support for cardiogenic shock; four techniques are contrasted and compared. Then, on-line in N Engl J Med appears the Oxford Clinical Trials report on dexamethasone in treating hospitalized Covid-19 patients. Those patients with pulmonary problems benefitted most. We close with a 17 year-old transgender man who develops hepatocellular carcinoma, likely aggravated by androgen administration. The oral presentations will be in Wednesday at 16.00 English and 17.00 German.

Yours,

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