

Dear friends of clinical journal club - load the file down at <https://www.mdc-berlin.de/cjc>. This website also gives you access to my seminar on Wednesdays 16:00 English and 17:00 German. You need to click on *Besprechung beizutreten*. If it fails to work immediately, keep on clicking.

A 96-year-old woman presented to the emergency department with a 1-day history of pleuritic chest pain 4 days after a single-chamber transvenous pacemaker had been implanted. A chest radiograph and computed tomographic scan of the chest showed the tip of the right ventricular lead in the left pleural space. What rhythm does the electrocardiogram show? You are offered: Atrial fibrillation, Complete heart block, Second-degree heart block, Ventricular-paced rhythm, and Wandering atrial pacemaker. Hint: inspect the rhythm strip. Determine the ventricular rate and the atrial rate. Is there any relationship between the two? We have discussed Crispr/Cas-9 gene editing many times. Exagamglogene autotemcel (exa-cel) is a nonviral Crispr cell therapy designed to reactivate fetal hemoglobin synthesis by means of gene editing of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) at the erythroid-specific enhancer region of BCL11A. Fetal hemoglobin has two alpha chains and two gamma chains. BCL11A suppresses gamma chain synthesis at birth so that beta chains are made. With Crispr, BCL11A can be shut off, restoring fetal hemoglobin. Investigators conducted a phase 3, single-group, open-label study of exa-cel in patients 12 to 35 years of age with sickle cell disease who had had at least two severe vaso-occlusive crises in each of the 2 years before screening. These sickle-cell patients then make hemoglobin F, which does not sickle. Vaso-occlusive crises were essentially eliminated in the patients. Beta thalassemia is another beta-chain disease, in which faulty beta chains result in a microcytic hemolytic anemia. The patients with severe disease can only survive with continuous blood transfusions. Investigators conducted an open-label, single-group, phase 3 study of exa-cel in patients 12 to 35 years of age with transfusion-dependent β -thalassemia and a β^0/β^0 , β^0/β^0 -like, or non- β^0/β^0 -like genotype. CD34+ HSPCs were edited by means of CRISPR-Cas9 with a guide mRNA. Before the exa-cel infusion, patients underwent myeloablative conditioning with pharmacokinetically dose-adjusted busulfan. The primary end point was transfusion independence, defined as a weighted average hemoglobin level of 9 g per deciliter or higher without red-cell transfusion for at least 12 consecutive months.

Total and fetal hemoglobin concentrations and safety were also assessed. The exa-cel therapy dropped the transfusion requirements dramatically in these patients. The use of thrombectomy in patients with acute stroke and a large infarct of unrestricted size has not been well studied. Investigators assigned, in a 1:1 ratio, patients with proximal cerebral vessel occlusion in the anterior circulation and a large infarct (as defined by an Alberta Stroke Program Early Computed Tomographic Score of ≤ 5 ; values range from 0 to 10) detected on magnetic resonance imaging or computed tomography within 6.5 hours after symptom onset to undergo endovascular thrombectomy and receive medical care (thrombectomy group) or to receive medical care alone (control group). The primary outcome was the score on the modified Rankin scale at 90 days (scores range from 0 to 6, with higher scores indicating greater disability). The primary safety outcome was death from any cause at 90 days, and an ancillary safety outcome was symptomatic intracerebral hemorrhage. The Rankin scale was improved significantly; however, at the cost of more hemorrhages. In patients with immune thrombotic thrombocytopenic purpura (iTTP), autoantibodies against the metalloprotease ADAMTS13 lead to catastrophic microvascular thrombosis. However, the potential benefits of recombinant human ADAMTS13 (rADAMTS13) in patients with iTTP remain unknown. Investigators now report the clinical use of rADAMTS13, which resulted in the rapid suppression of disease activity and complete recovery in a critically ill patient whose condition had proved to be refractory to all available treatments. The rADAMTS13 therapy was a success and greatly improved the iTTP in this patient. The N Engl J Med next reviews the physiology of taste and its relationship to metabolism. The N Engl J Med patient is a 30-year-old woman, who develops glutamic acid-decarboxylase 65 autoantibody-associated “stiff-person” syndrome. In the Lancet, we review the IVUS-ACS trial, in which patients with acute coronary syndromes were randomized to standard coronary catheterization or to that plus intravascular ultrasound (IVUS) in assessing their coronary lesions. IVUS led to better outcomes and subsequent major adverse cardiovascular events (MACE) were reduced. Anti P2Y12 platelet inhibition is routine after stenting. Ticagrelor is commonly given, but whether-or-not concomitant aspirin is necessary or just leads to more bleeding is unknown. In the ULTIMATE-DAPT trial, after stenting patients with randomized to dual antiplatelet treatment or ticagrelor alone. MACE events were the

same, but bleeding was more common in the group that also received aspirin. We next inspect a measles and rubella vaccine study relying on a microneedle patch delivery strategy. It was successful. Craniometaphyseal dysplasia is a Mendelian disease involving a mutation in the *ANKH* gene. The Lancet case describes a young girl with an *ANKH* mutation, who is successfully treated with an allogeneic bone marrow transplant from her father. Next, a Lancet Commission reports on breast cancer worldwide. The commission reviews health-care inequities in the management of these patients. In Science Magazine, we observe that magnetic resonance imaging was described 50 years ago. The routine MRI involves a scanner with 1.8 Tesla strength and 7 Tesla MRI is in service. The devices require a separate building. But imagine a 0.05 Tesla MRI that scans within 8 minutes with a permanent magnet so that the device is about the size of a kitchen table and can be plugged into any outlet? Chinese investigators have now designed such a scanner that can be used anywhere with acceptable imaging results. In the Washington Post, we learn that Highway 1 in California is falling into the sea. Goodbye to the great Big-Sur bike rides. Read the file and join me on May 15 for the next oral presentation.

Best regards, Fred Luft, at <https://www.mdc-berlin.de/cjc>