

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 68-year-old man with cirrhosis presented to the emergency department with a 2-day history of severe abdominal pain. On physical examination, hypoactive bowel sounds, pain with palpation, and rebound tenderness throughout the abdomen were noted. Computed tomography of the abdomen with administration of contrast material showed thrombosis of the superior mesenteric vein (left, arrows). What complication of superior mesenteric vein thrombosis was also seen on imaging? You are offered: Ascites, Ischemic Colitis, Portal hypertension, Small-Bowel Perforation, and Small-Bowel Infarction. The CT appearance and the operating-room image are revealing.

Multiple sclerosis is a devastating demyelinating disease. Hematopoietic stem-cell-derived glia are held responsible. These cells feature the Bruton tyrosine kinase (BTK). The BTK is responsible for cell maturation. Ibrutinib is an oral, brain-penetrant Bruton's tyrosine kinase inhibitor that targets myeloid cells (including microglia) and B cells, in both the periphery and central nervous system. There are no approved treatments for nonrelapsing secondary progressive multiple sclerosis. In a phase 3, double-blind, placebo-controlled, event-driven trial, investigators randomly assigned participants with nonrelapsing secondary progressive multiple sclerosis, in a 2:1 ratio, to receive ibrutinib (60 mg once daily) or matching placebo. The primary end point was confirmed disability progression that was sustained for at least 6 months, assessed in a time-to-event analysis. Ibrutinib reduced progression from 33% to 22%. Whether or not ibrutinib might also help the relapsing form of multiple sclerosis are unknown. But for the relapsing form, there is an FDA-approved drug, the immune modulator fingolimod. More data are needed on its efficacy and safety in treating relapsing multiple sclerosis. In two phase 3, double-blind, double-dummy, event-driven trials (GEMINI 1 and GEMINI 2), participants with relapsing multiple sclerosis were randomly assigned in a 1:1 ratio to receive ibrutinib (60 mg once daily) or fingolimod (14 mg once daily), each with matching placebo. The primary end point was the annualized relapse rate. The key secondary end point was confirmed worsening of disability, which was assessed in a time-to-event analysis that

was pooled across trials. BTK inhibition was not shown to be better than teriflunomide. Narcolepsy is a (fortunately) rare genetic disease featuring attacks of sleepiness, falling spells, and hallucinations. The condition also occurs in Doberman Pinchers and so, the orexin peptides (also called hypocretins) were discovered in these dogs. The canine research revealed an entire pathway of central-nervous-system signaling. Oveporexton is an oral, orexin receptor 2-selective agonist and could help persons with type 1 narcolepsy (often with cataplexy and hypnagogic hallucinations). In a phase 2 randomized trial, oveporexton improved wakefulness patterns in persons with narcolepsy type 1. Children living with human immunodeficiency virus (HIV) have limited options for second-line antiretroviral therapy (ART). In an open-label trial with a 2-by-4 factorial design, investigators randomly assigned children with HIV who had first-line treatment failure to receive second-line therapy with tenofovir alafenamide fumarate (TAF)–emtricitabine or standard care (abacavir or zidovudine, plus lamivudine) as the backbone and dolutegravir or ritonavir-boosted darunavir, atazanavir, or lopinavir as the anchor drug. The primary outcome was a viral load of less than 400 copies per milliliter at 96 weeks. The study points to regimens that are acceptable for these children. Remember the dialysis patient in N Engl J Med that received a kidney transplant from a pig? The 62-year-old hemodialysis-dependent man with long-standing diabetes, advanced vasculopathy, and marked dialysis-access challenges, received a gene-edited porcine kidney with 69 genomic edits, including deletion of three glycan antigens, inactivation of porcine endogenous retroviruses, and insertion of seven human transgenes. The xenograft functioned immediately. Unfortunately, the patient has died of heart disease, but the graft showed no signs of rejection at the time of death. The Philadelphia chromosome is a balanced (22-and-9) translocation, in which the Abelson tyrosine kinase is placed adjacent to the break-point-cluster region. The translocation was first described in chronic myelogenous leukemia. The N Engl J Med review is on the importance of the Philadelphia chromosome in acute lymphoblastic leukemia. In this leukemia, the Philadelphia chromosome also commonly occurs and has become a major therapeutic target. The N Engl J Med case is a 29-year-old woman with a sore throat and a peritonsillar mass that proves to be a rare sarcoma. Shoulder dystocia occurs commonly in large for gestational age newborns. Induced early labor and delivery at 38 weeks could

ameliorate the problem. A large, randomized trial of this idea was conducted in UK. Two-thirds of the expectant mothers had BMI >27 but diabetic women were excluded from the study. Alas, the physicians managing the control group “caught on” and conducted early deliveries and so, the trial was terminated because of futility. Adverse events were the same in both groups. The cholesterol-ester transfer protein (CETP) moves lipids from HDL to other lipoprotein particles. Genetic alterations have implicated CETP in atherosclerosis. Obicetrapib inhibits CETP. The Lancet reports that in patients with maximal therapy but still LDL >70 mg/dL, obicetrapib in fixed combination with ezetimibe brings these patients around to ideal values. Hepatitis C remains a worldwide problem, and no vaccine is in sight. However, by treating infected persons, the disease and its spread could be controlled. In an open, non-inferiority trial, effective first-line treatments were identified. The Lancet review is on chronic pain self-management, psychological principles, and neurobiological underpinnings. In Science Magazine, we learn more about astroglia. These star-shaped cells were believed to provide structural roles in the central nervous system. In three Science papers, we learn that astrocytes have G protein-coupled receptors and engage in neuronal signaling to modulate transmission in neurons via ATP-receptors. In the Washington Post, we learn about the extreme women divers from Korea that dive to gather abalone at a depth of 20 m without any external support (like SCUBA). At that level, the external pressure is >2300 mm Hg. How do they do it? They have a superior diving reflex that is genetically determined. Join me on Wednesday, May 21 for another stunning, orally presented, clinical journal club, 16:00 in English and 17:00 in German. Sincerely, Fred Luft

[Friedrich.luft@charite.de](mailto:Friedrich.luft@charite.de)

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