

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 (mostly) 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 7-year-old girl was referred to the emergency department for evaluation of abnormal blood work. Her family had recently made an immigration journey to the United States. Physical examination was notable for dental caries, mild conjunctival pallor, and no signs of neurodevelopmental delay. Laboratory studies showed a hemoglobin level of 10.5 g per deciliter (reference range, 11.3 to 14.6), a mean corpuscular volume of 64.4 fl (reference range, 77.8 to 86.5), and a ferritin level of 8 ng per milliliter (reference range, 10 to 320). An abdominal radiograph showed intraluminal radiodensities throughout the colon. Which of the following diagnoses best explains the patient's laboratory and radiographic abnormalities? What we see is flakes of somewhat radio-dense material throughout the gastrointestinal tract. You are offered Bismuth poisoning, Copper deficiency, Lead poisoning, Inflammatory bowel disease, and Thalassemia. The question is directed at paint pica, a condition once common in the US. Pulmonary arterial hypertension (PAH) is a rare but devastating lethal condition. We have learned much from genetics. The primary gene associated with heritable PAH is bone-morphogenic protein-2 (BMP2). Mutations in this gene, which codes for a receptor in the TGF-beta superfamily, are responsible for a significant portion of familial PAH cases. While BMP2 mutations are the most common genetic cause, other genes like ACVRL1, CAV1, KCNK3, and SMAD9 have also been implicated in PAH. Avidin is a TGF-beta-family protein implicated in PAH. Sotatercept (a fusion protein that catches avidin) improves exercise capacity and delays the time to clinical worsening in patients with World Health Organization (WHO) functional class II or III PAH. The effects of add-on sotatercept in patients with advanced PAH and a high risk of death are unclear. In a phase 3 trial, investigators randomly assigned patients with PAH (WHO functional class III or IV) and a high 1-year risk of death, who were receiving the maximum tolerated dose of background therapy to receive add-on sotatercept (starting dose, 0.3 mg per kilogram of body weight; escalated to target dose, 0.7 mg per kilogram) or placebo every 3 weeks. The primary end point was a composite of death from any cause, lung transplantation, or hospitalization ( $\geq 24$  hours)

for worsening PAH. The trial was stopped early because sotatercept was so effective. Semaglutide is administered by weekly subcutaneous injections; the drug is enormously effective. The cardiovascular safety of oral semaglutide, a glucagon-like peptide 1 receptor agonist, has been established in persons with type 2 diabetes and high cardiovascular risk. An assessment of the cardiovascular efficacy of oral semaglutide in persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both is needed. In a double-blind, placebo-controlled, event-driven, superiority trial, investigators randomly assigned participants who were 50 years of age or older, had type 2 diabetes with a glycated hemoglobin level of 6.5 to 10.0%, and had known atherosclerotic cardiovascular disease, chronic kidney disease, or both to receive either once-daily oral semaglutide (maximal dose, 14 mg) or placebo, in addition to standard care. The primary outcome was major adverse cardiovascular events. Oral semaglutide lowered cardiovascular events.

Giant-cell arteritis is a systemic vasculitis with limited treatment options. The efficacy and safety of upadacitinib — a selective Janus kinase (JAK) inhibitor that blocks the signaling of several cytokines, including interleukin-6 and interferon- $\gamma$  — are unknown in patients with giant-cell arteritis. Investigators randomly assigned patients with new-onset or relapsing giant-cell arteritis, in a 2:1:1 ratio, to receive upadacitinib at a dose of 15 mg or 7.5 mg orally once daily plus a 26-week glucocorticoid taper or placebo plus a 52-week glucocorticoid taper. The primary end point was sustained remission at week 52, defined by the absence of signs or symptoms of giant-cell arteritis from week 12 through week 52 and adherence to the protocol-specified glucocorticoid taper. Upadacitinib was effective and steroid use was decreased.

Medicare is a US healthcare insurance plan for elderly and certain disease-states (dialysis for instance), which was introduced by Lyndon Johnson in 1965. The plan provides care for millions of Americans, who otherwise would not be able to pay. Oddly, the Republican Party in the US has been trying to torpedo Medicare ever since 1965. A total of 14 million Medicare beneficiaries are eligible for the Low-Income Subsidy (LIS), which reduces cost sharing in Medicare Part D. Losing the LIS may impede medication access and affect mortality. N Engl J Med publishes a “medicine-and-society” paper on what loss of this coverages means in terms of extra deaths. The weekly review is on cancers of unknown primary. The weekly case is a severe pneumonia patient from Argentina. He

develops ARDS and we learn that he was on a camping trip on month earlier. In the Lancet, we learn that stroke patients receiving thrombolysis therapy are monitored closely thereafter with checks of vital signs, neurological status, and blood pressure for the first 24 hours. Specifically, vital signs and neurological assessments are typically monitored every 15 minutes for the first two hours, then every 30 minutes for the next 6 hours, and every hour thereafter. A simpler, less cumbersome protocol could not be proved to be non-inferior. However, clinically speaking, it was. Angiopoietin-like 4 (Angptl4) is a secreted protein modulating triacylglycerol homeostasis. The protein inhibits the enzyme lipoprotein lipase. In a phase 1 trial, the Lancet presents an antibody against Angptl4 that reduces triglycerides in half and is well tolerated. Supplemental breast cancer screening involves using additional imaging tests, such as tomosynthesis, whole-breast ultrasound, molecular breast imaging, or MRI, in addition to a standard mammogram, to improve breast cancer detection, particularly in women with dense breast tissue. The BRAID study investigates the utility of supplemental imaging in women with dense breasts and presents encouraging preliminary data. Next, a Lancet Commission reports on adolescent health and wellbeing. We learn that in “multi-burden” countries, the goals will likely not be met. In Science Magazine, we review the current status of xenotransplantation. In the Washington Post, we are informed that women are more resilient than men in almost all physical endeavors. I have teaching obligations in June that causes me to move the oral presentations to Tuesday, rather than Wednesday. Join me on Tuesday, June 3 for another stunning, orally presented, clinical journal club, 16:00 in English and 17:00 in German.

Sincerely, Fred Luft

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