

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 44-year-old man presented with a 4-day history of an itchy rash and a 2-day history of fever and malaise. The rash had first appeared on the scalp and then spread across the body within 24 hours. What is the most likely diagnosis? You are offered: Cutaneous t-cell lymphoma, Dengue fever, Disseminated gonococcal infection, Varicella infection and Smallpox. Can you see any vesicles in this picture? I could not.

Aspirin reduces the incidence of colorectal adenoma and colorectal cancer among high-risk persons. Aspirin irreversibly binds to COX2. COX2 prostanoids are involved in PI3K-pathway activation. Observational studies suggest that aspirin may also improve disease-free survival after diagnosis, particularly among patients with tumors harboring somatic PIK3CA mutations. However, data from randomized trials are lacking. Investigators conducted a double-blind, randomized, placebo-controlled trial involving patients with stage I, II, or III rectal cancer or stage II or III colon cancer with somatic alterations in PI3K pathway genes. The patients were assigned in a 1:1 ratio to receive 160 mg of aspirin or matched placebo once daily for 3 years. Patients with prespecified PIK3CA hotspot mutations in exon 9 or 20 (group A alterations) and those with other moderate- or high-impact somatic variants in PIK3CA, PIK3R1, or PTEN (group B alterations) were eligible for randomization. The primary end point was colorectal cancer recurrence, assessed in a time-to-event analysis, in patients with group A alterations. Secondary end points included colorectal cancer recurrence in patients with group B alterations, disease-free survival, and safety. In patients with genetic variants in PIK3CA and pathway, aspirin slowed the time to cancer recurrence.

Oral GLP-1 agonists are under development. Orforglipron is a small-molecule, nonpeptide glucagon-like peptide-1 (GLP-1) receptor agonist in clinical development for type 2 diabetes and weight management. Additional data on the efficacy and safety of orforglipron are needed. In a phase 3, double-blind, placebo-controlled trial, investigators randomly assigned participants in a 1:1:1:1 ratio to receive orforglipron at one of three doses (3 mg, 12 mg, or 36 mg) or placebo once daily for 40 weeks. Orforglipron reduced HbA1C by at least 1.5%, as well as body weight and BMI. Oral

semaglutide at a dose of 25 mg may provide an alternative treatment option to injectable semaglutide (2.4 mg) and higher-dose oral semaglutide (50 mg) for persons with overweight or obesity. In a 71-week, double-blind, randomized, placebo-controlled trial conducted at 22 sites in four countries, investigators enrolled persons without diabetes who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher or a BMI of 27 or higher with at least one obesity-related complication. Body weight dropped by about 15%. In critically ill patients, acceleration of liberation from mechanical ventilation is important in order to reduce the risk of complications and to improve long-term outcomes. Whether the use of proportional-assist ventilation with load-adjustable gain factors (PAV+) results in a shorter time to successful liberation from mechanical ventilation than pressure-support ventilation (PSV) is unclear. In an international clinical trial, investigators randomly assigned adult patients who had been receiving mechanical ventilation for at least 24 hours and were able to undergo partial ventilatory support with PSV but were not yet ready for liberation from ventilation to undergo PAV+ (which targeted normal work of breathing) or PSV (which targeted a normal respiratory rate and tidal volume). The primary outcome was the time from randomization to successful liberation from mechanical ventilation. PAV could not beat PSV; the outcomes were invariably the same. The N Engl J Med review is on the tumor-lysis syndrome. Beware of potassium, phosphate, uric acid etc. Put prophylactic strategies into operation. The weekly patient is an 11-year-old girl with chest pain, bone pain and a few small liver lesions on imaging. She recently was given a kitten. David Carrion and Alberto Barton elucidated her disease >100 years earlier. In the Lancet, we first confront PCSK9, an adapter protein for the LDL receptor. PCSK9 is responsible for removing the LDL receptor from the cell surface to be degraded via the proteasome. Inhibiting PCSK9 with an antibody (evolocumab) markedly reduces LDL cholesterol. Bypass grafts are commonly harvested from the saphenous vein. They eventually close over time. Would evolocumab reduce saphenous-vein bypass closure? A randomized trial shows that evolocumab reduces LDL cholesterol by >50% but the antibody did not alter saphenous vein bypass closures in the same patients. Parent-focused behavioral interventions in obese children have achieved much attention and generated negative results. A meta-analysis of more than 30 trials involving more than 30,000 obese

subjects again underscore the finding that these interventions were of no value. Lancet next reviews noncommunicable disease (NCD) worldwide. There has been some reduction, particularly amongst the rich countries but otherwise progress on NCDs overall has been limited. The Lancet reviews are about typhoid fever and oncolytic viruses. An oncolytic virus is a virus, naturally occurring or genetically modified, that selectively infects and destroys cancer cells while leaving healthy cells unharmed. In Science Magazine we learn that broad adoption of hydrogen as a versatile energy carrier is primarily hampered by a lack of safe and compact hydrogen storage. Hydrogen is often stored as compressed gas or cryogenic liquid, which requires high pressures or extremely low temperatures. To free hydrogen from solid storage requires very high temperatures. The energy requirements are prohibitive. We learn about a new method, an approach that electrochemically “pumps” hydrogen in the form of hydride ions (H<sup>-</sup>) through a solid electrolyte into-, or out of-, a metal hydride. This method elegantly circumvents the requirement of high temperature to free hydrogen from the metal hydride, offering a pathway to harness high-capacity hydrogen storage under practical release conditions. Friday for futures, please take notice. Are you having trouble falling asleep at night? Washington Post reviews an earlier Nature paper showing that warm feet result in a far shorter time falling asleep at nights. So try a warm bath or socks. Join me on Wednesday, September 24 for the above and more in another stunning, orally presented, clinical journal club, 16:00 in English and 17:00 in German.

Sincerely, Fred Luft

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