cause of ketosis-prone diabetes, including other coronaviruses that bind to ACE2 receptors.[5] Greater incidences of fasting glycemia and acute-onset diabetes have been reported among patients with SARS coronavirus 1 pneumonia than among those with non-SARS pneumonia.[5]

In the aggregate, these observations provide support for the hypothesis of a potential diabetogenic effect of Covid-19, beyond the well-recognized stress response associated with severe illness. However, whether the alterations of glucose metabolism that occur with a sudden onset in severe Covid-19 persist or remit when the infection resolves is unclear. How frequent is the phenomenon of new-onset diabetes, and is it classic type 1 or type 2 diabetes or a new type of diabetes? Do these patients remain at higher risk for diabetes or diabetic ketoacidosis? In patients with preexisting diabetes, does Covid-19 change the underlying pathophysiology and the natural history of the disease? Answering these questions in order to inform the immediate clinical care, follow-up, and monitoring of affected patients is a priority.

To address these issues, an international group of leading diabetes researchers participating in the CoviDIAB Project have established a global registry of patients with Covid-19–related diabetes (covidiab.e-dendrite.com). The goal of the registry is to establish the extent and phenotype of new-onset diabetes that is defined by hyperglycemia, confirmed Covid-19, a negative history of diabetes, and a history of a normal glycated hemoglobin level. The registry, which will be expanded to include patients with preexisting diabetes who present with severe acute metabolic disturbance, may also be used to investigate the epidemiologic features and pathogenesis of Covid-19–related diabetes and to gain clues regarding appropriate care for patients during and after the course of Covid-19. Given the very short history of human infection with SARS-CoV-2, an understanding of how Covid-19–related diabetes develops, the natural history of this disease, and appropriate management will be helpful. The study of Covid-19–related diabetes may also uncover novel mechanisms of disease.

Francesco Rubino, M.D.
Stephanie Amiel, M.D.
King's College London
London, United Kingdom
francesco.rubino@kcl.ac.uk

Paul Zimmet, M.D.
Monash University
Melbourne, VIC, Australia

and Others

Drs. Rubino, Amiel, and Zimmet contributed equally to this letter.

A complete list of authors is available with the full text of this letter at NEJM.org.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on June 12, 2020, at NEJM.org.

1. Chee YJ, Ng SJH, Yeoh E. Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. Diabetes Res Clin Pract 2020 April 24 (Epub ahead of print).
2. Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. Diabetes Obes Metab 2020 April 20 (Epub ahead of print).
3. Ren H, Yang Y, Wang F, et al. Association of the insulin resistance marker TyG index with the severity and mortality of COVID-19. Cardiovasc Diabetol 2020;19:58.
4. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus: a first step in understanding SARS pathogenesis. J Pathol 2004;203:631-7.
5. Yang J-K, Lin S-S, Ji X-J, Guo L-M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47:193-9.

DOI: 10.1056/NEJMc2018688

Randomized Trial of Lactin-V to Prevent Recurrence of Bacterial Vaginosis

TO THE EDITOR: In their trial of *Lactobacillus crispatus* CTV-05 (Lactin-V), Cohen et al. (May 14 issue) offer hope for the prevention of bacterial vaginosis.[1] The protective effect of the treatment was modest, similar to twice-weekly metronidazole,[2,3] but the *L. crispatus* CTV-05 strain could still be detected in 48% of participants 13 weeks after the last administration. This finding is encouraging, but in order to interpret the effects of Lactin-V properly, we would like to see additional data. First, previous trials of lactobacilli-containing vaginal probiotics have shown large variability in treatment responses among women, as well as fluctuations in response in individual women, over time.[4] Cohen et al. report a cumulative incidence according to treatment group, thereby over-

looking these variabilities. Second, sequencing or other data on the composition of the molecular vaginal microbiome — preferably quantified — are essential for interpretation.[3,4] Unlike microscopy, molecular methods can differentiate between autologous and biotherapeutic lactobacilli, which enables microbiome data obtained at all trial visits, including those that occurred during treatment with Lactin-V, to be used in longitudinal modeling. Molecular methods also enable estimation of the relative abundance of lactobacilli and bacterial vaginosis–associated anaerobes over time. Clinical symptoms are important outcomes in their own right, but microscopy-based Amsel criteria and Nugent scores should be accompanied by molecular data.

Janneke H.H.M. van de Wijgert, M.D., Ph.D.
University Medical Center Utrecht
Utrecht, the Netherlands
j.h.h.vandewijgert@umcutrecht.nl

Marijn C. Verwijs, M.D., Ph.D.
Canisius Wilhelmina Hospital
Nijmegen, the Netherlands

No potential conflict of interest relevant to this letter was reported.

1. Cohen CR, Wierzbicki MR, French AL, et al. Randomized trial of Lactin-V to prevent recurrence of bacterial vaginosis. N Engl J Med 2020;382:1906-15.
2. Sobel JD, Ferris D, Schwebke J, et al. Suppressive antibacterial therapy with 0.75% metronidazole vaginal gel to prevent recurrent bacterial vaginosis. Am J Obstet Gynecol 2006;194:1283-9.
3. van de Wijgert JHHM, Verwijs MC, Agaba SK, et al. Intermittent lactobacilli-containing vaginal probiotic or metronidazole use to prevent bacterial vaginosis recurrence: a pilot study incorporating microscopy and sequencing. Sci Rep 2020;10(1):3884.
4. van de Wijgert J, Verwijs MC. Lactobacilli-containing vaginal probiotics to cure or prevent bacterial or fungal vaginal dysbiosis: a systematic review and recommendations for future trial designs. BJOG 2020;127:287-99.

DOI: 10.1056/NEJMc2021832

TO THE EDITOR: Cohen et al. report on a potential treatment for recurrent bacterial vaginosis. Women arrived at the trial screening clinic. (I could not find a description of the way in which they were recruited.) Bacterial vaginosis was diagnosed on the basis of the Amsel criteria and the Gram's staining–based Nugent score; the presence of symptoms was not required for diagnosis. I could not find how many participants had symptoms at entry nor whether treatment affected the symptoms in the participants who had them. Some symptoms of bacterial vaginosis were reported as adverse events in some participants.

The U.S. Preventive Services Task Force recommends against screening for bacterial vaginosis in pregnant women who are not at risk for preterm delivery; for pregnant women who have such a risk, no recommendation is made, because current evidence is insufficient.[1] I could find no recommendation for or against screening in nonpregnant women.

Thomas E. Finucane, M.D.
Massachusetts General Hospital
Boston, MA
tfinucane@mgh.harvard.edu

No potential conflict of interest relevant to this letter was reported.

1. U.S. Preventive Services Task Force. Bacterial vaginosis in pregnant persons to prevent preterm delivery: screening. April 7, 2020 (https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/bacterial-vaginosis-in-pregnancy-to-prevent-preterm-delivery-screening).

DOI: 10.1056/NEJMc2021832

THE AUTHORS REPLY: Van de Wijgert and Verwijs raise questions about individual and temporal variability in responses to Lactin-V treatment, as well as about the use of molecular methods. A preliminary quantitative polymerase-chain-reaction assay distinguished the *L. crispatus* CTV-05 strain we evaluated from endogenous *L. crispatus*. To assess sustained colonization at relevant concentrations and fluctuations over time in relation to the presence of competing lactobacillus strains (such as *L. iners*) and other bacteria, we are currently performing additional analyses on vaginal samples obtained at all trial visits using molecular methods. The aim of DNA and RNA sequencing of the vaginal microbiome is to identify associations of clinical, microbial, host genetic, and ecological factors with loss or retention of *L. crispatus* CTV-05 and with recurrence of bacterial vaginosis. We agree that molecular methods should routinely be included in future clinical trials of treatment and prevention of bacterial vaginosis to allow for interpretation of findings in greater depth and to advance our understanding of the female genital microbiome.

In response to Finucane: Recruitment strategies varied across the trial sites. Many women learned of the trial through social media, Google searches, and flyers in local clinics and in locations frequented by women, and they referred themselves after recognizing bacterial vaginosis as being relevant to their health. Other women were contacted through mass mailings sent to previous patients who had received a diagnosis of bacterial vaginosis or were referred by clini-

cians who had diagnosed cases of bacterial vaginosis.

The determination of whether a woman has asymptomatic or symptomatic bacterial vaginosis drives decisions in clinical practice; often, only women who report symptoms will receive treatment. Although only half of women with bacterial vaginosis have symptoms,[1] whether a woman has symptoms does not seem to affect the association of bacterial vaginosis with sexually transmitted infections, including human immunodeficiency virus infection.[2] As has been the case in other recent clinical trials,[3-5] we enrolled women with or without patient-reported symptoms of bacterial vaginosis at screening as long as bacterial vaginosis was subsequently diagnosed on the basis of the Amsel criteria and the Nugent score.

Although women were not specifically queried about symptoms of bacterial vaginosis at screening, one can assume that most of the women scheduled a screening visit because of current or recent symptoms of bacterial vaginosis such as abnormal vaginal discharge and odor. At screening, 165 of the 228 participants (72.4%) had abnormal vaginal discharge, as recorded by the trial investigators.

Craig R. Cohen, M.D., M.P.H.
University of California, San Francisco
San Francisco, CA
craig.cohen@ucsf.edu

Thomas Parks, Ph.D.
Osel
Mountain View, CA

Anke Hemmerling, M.D., M.P.H.
University of California, San Francisco
San Francisco, CA

Since publication of their article, the authors report no further potential conflict of interest.

1. Koumans EH, Sternberg M, Bruce C, et al. The prevalence of bacterial vaginosis in the United States, 2001-2004; associations with symptoms, sexual behaviors, and reproductive health. Sex Transm Dis 2007;34:864-9.
2. Gosmann C, Anahtar MN, Handley SA, et al. Lactobacillus-deficient cervicovaginal bacterial communities are associated with increased HIV acquisition in young South African women. Immunity 2017;46:29-37.
3. Hillier SL, Nyirjesy P, Waldbaum AS, et al. Secnidazole treatment of bacterial vaginosis: a randomized controlled trial. Obstet Gynecol 2017;130:379-86.
4. Schwebke JR, Morgan FG Jr, Koltun W, Nyirjesy P. A phase-3, double-blind, placebo-controlled study of the effectiveness and safety of single oral doses of secnidazole 2 g for the treatment of women with bacterial vaginosis. Am J Obstet Gynecol 2017;217(6):678.e1-678.e9.
5. Balkus JE, Srinivasan S, Anzala O, et al. Impact of periodic presumptive treatment for bacterial vaginosis on the vaginal microbiome among women participating in the Preventing Vaginal Infections Trial. J Infect Dis 2017;215:723-31.

DOI: 10.1056/NEJMc2021832

Pulmonary Disease Related to E-Cigarette Use

TO THE EDITOR: Layden et al. (March 5 issue)[1] reported the results of a public health investigation of e-cigarette, or vaping, product use–associated lung injury (EVALI). Surveillance for cannabis use with precise analytical data is paramount in the evolving EVALI epidemic. More than 60% of cannabis users report vaping,[2] and 89% of patients with EVALI in the study by Layden et al. reported having used tetrahydrocannabinol (THC) vaping products. It is unclear whether any clinical laboratory or drug testing corroborating this information was ever obtained for this study. Our inpatient toxicology service has found that all six patients whose conditions have met the Centers for Disease Control and Prevention (CDC) definition of EVALI have presented with urinary 11-nor-9-carboxy-Δ^9-THC (THC-COOH) levels higher than 200 ng per milliliter; in the majority of patients, the levels were higher than the available laboratory assay limit (500 ng per milliliter). Two thirds of the patients had evidence of hyperemesis cannabinoid syndrome, and one had signs of cannabis withdrawal during his hospital stay. Existing studies[3] of urinary concentrations of THC-COOH after cannabis vaping have shown a mean maximum concentration of approximately 40 ng per milliliter — well below the levels we observed. Given this finding and the fact that cannabis levels may indicate vitamin E acetate exposure,[4,5] we suggest that further surveillance and clinical evaluation protocols target precise measurements of cannabis and metabolite levels.

Joseph Kennedy, M.D.
Jerrold Leikin, M.D.

Toxikon Consortium
Chicago, IL
jmw227@gmail.com

No potential conflict of interest relevant to this letter was reported.