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Internal Medicine

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ABSTRACT & COMMENTARY

Long COVID and the Clinical Reality of Chronic Infections

By Joseph E. Scherger, MD, MPH

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SYNOPSIS: Long COVID is the latest entry into a long list of potentially chronic, pandemic-associated infections. For many long COVID patients, some symptoms may be the result of a reactivation of an Epstein-Barr infection.

SOURCE: Gold JE, Okyay RA, Licht WE, Hurley DJ. Investigation of long COVID prevalence and its relationship to Epstein-Barr virus (EBV) reactivation. *Pathogens* 2021;10:763.

Persistence of symptoms after the acute phase of COVID-19 infection is common. The CDC is documenting and studying post-COVID conditions, and the list of symptoms and organ systems involved is growing.[1] The Advisory Board estimates nearly 25% of patients who test positive for COVID-19 experience post-COVID symptoms, even if the initial infection was mild or asymptomatic.[2]

Long et al investigated long COVID prevalence among 185 randomly surveyed COVID-19 patients. They found 56 patients (30.3%) exhibited symptoms of long COVID. The unique finding of this study was 66.7% of long COVID patients experienced reactivation of Epstein-Barr virus (EBV), which may explain some of their symptoms.

COMMENTARY

The explosion of HIV in the 1980s made clinicians and the public aware that we may carry serious viral infections long term. Virologists have learned this always has been the case, with more than 90% of individuals worldwide testing positive for EBV.[3] Hepatitis B and C are other examples of long-term viral infections. With better anti-virus medications, some of these long-term infections can be eradicated.

In a recently published book on infectious disease, the authors described how Lyme and many other similar infections become "long-haul" conditions.[4] Both authors nearly died of Lyme disease and have dedicated themselves to informing the public of chronic infections.

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This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

At this point, long COVID is not described as a chronic infection associated with the virus. That likely will change soon as the identification of the active virus in patients becomes more accessible. COVID-19 will become the latest entry into a long list of chronic infections that may sap human health. Vaccines, better medications, and a robust immune system free of common chronic diseases like type 2 diabetes will help us survive and stay healthy. While we may not like to dwell on it, our survival is us vs. the pathogens. ■

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LITERATURE REVIEW

Common Herbal and Dietary Supplements for Patients with Type 2 Diabetes

By Clipper F. Young, PharmD, MPH, CDCES, BC-ADM, BCGP, APh, and Matthew Wai, DO

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Diabetes mellitus (DM), especially type 2 DM, is a major public health concern that affects about 34.1 million people in the United States.[1] This chronic health condition, if not properly managed, can cause long-term complications as well as considerable morbidity and mortality in the affected population.[2] In 2018, an estimated 1.5 million new cases of diabetes were diagnosed in U.S. adults ≥ age 18 years, with more than half of these new cases in adults age 45-64 years.[1]

With cases rising, clinicians also are encountering more patients who are turning to complementary and alternative medicine (CAM) to help control their glucose levels. In a 2015 National Consumer Survey on the Medication Experience and Pharmacist Roles, 35% of 26,157 respondents reported using at least one herbal medicine.[3] In all, 3,050 respondents had diabetes, and 41.2% reported using a dietary supplement.[3] The data revealed respondents with diabetes were associated with higher herbal medicine use vs. respondents without chronic diseases (41% vs. 34%; $P < 0.001$).[3] The results also showed herbal medicine use rose as age increased among the respondents.[3]

Since the FDA regulates CAM products as dietary supplements, the effectiveness and safety of these products are regulated after they are available in the market, which means the quality and safety of these supplements can be highly variable.[4] As more people with diabetes are reporting CAM product use in conjunction with prescription medications, it is important clinicians understand what role these products play in diabetes management with the available evidence. By reviewing the current evidence behind these alternative therapies, medical practitioners will be better equipped to distill information for their patients and address the utility of these proposed diabetes supplements.

The following is a review of the current literature regarding commonly used herbal and dietary supplements among people with diabetes.

We performed an electronic literature search on the American Diabetes Association website based on the recommendation from the American Association of Diabetes Educators (now named Association of Diabetes Care and Education Specialists) to discover what had been written about herbal products relating to diabetes management.[5] We cross-referenced these findings with the Natural Medicines Database and Complementary & Alternative Medicine Supplement Use in People with Diabetes: A Clinician's Guide regarding the identified products' safety and effectiveness.[6]

Keywords included dietary supplements, herbal supplements, type 2 diabetes mellitus, *Aloe vera*, alpha-lipoic acid, chromium, cinnamon, fenugreek, ginseng, ginger, gymnema, magnesium, nopal, and psyllium. The search was limited to studies published in English and from date of inception until 2019. We included systematic reviews; meta-analyses; and randomized, controlled trials. We excluded abstract-only articles, conference presentations, editorials, and studies with fewer than five participants. Articles were screened independently by the authors and included based on relevancy.

The most popular supplements taken by patients are herbal ones derived from natural sources, as opposed to other forms, such as vitamin or mineral mixtures.[7] The authors have identified 11 herbal and dietary supplements — *Aloe vera*, alpha-lipoic acid, chromium, cinnamon, fenugreek, garlic, ginseng, magnesium, psyllium, gymnema, and nopal — that are used commonly among patients with diabetes.

However, because of limited quality control in dietary supplements, it is difficult to make firm recommendations without reviewing the current evidence on efficacy and proposed mechanisms by which these products work in patients with diabetes. In this review, we focus on *Aloe vera* and alpha-lipoic acid.

ALOE VERA

There are more than 300 species in the Aloe genus, and one is extremely well-known worldwide. *Aloe barbadensis*, otherwise known as *Aloe vera*, is a renowned plant of the Liliaceae family, known for its many medicinal properties.[8] The spiky succulent plant contains gel and juice, which has become a commercial supplement and cosmetic. It is believed *Aloe vera* possesses antioxidant, anticancer, anti-inflammatory, laxative, and anti-atherosclerotic properties.[9]

There are multiple existing hypotheses on why *Aloe vera* can be a useful diabetes management tool. One hypothesis indicates *Aloe vera* lowers blood glucose levels through its anti-inflammatory effects. Type 2 DM is an inflammatory disease associated with oxidative stress of the pancreas, which leads to beta-cell dysfunction and insulin resistance.[10] Clinical research shows *Aloe vera* can reduce fasting blood glucose levels by 30 mg/dL to 46.6 mg/dL and hemoglobin A1c (HbA1c) by 0.41% to 1.05% in adults with prediabetes and diabetes.[11-13]

Another hypothesis suggests a constituent of the *Aloe vera* plant, glucomannan, is the agent that possesses the hypoglycemic effects.[14] Glucomannan is a hydrosoluble agent believed to promote satiety and delaying intestinal absorption because of its increased viscosity.[15] There has been a variety of doses and dosage forms, ranging from 100 mg to 1,000 mg of its powder to 15 mL to 150 mL of its juice formulation, suggested to be efficacious in lowering blood glucose.[11-13] However, because of the heterogeneity of the available studies, the mixed evidence on *Aloe vera*'s effectiveness hinders the validity of the reported findings.

ALPHA-LIPOIC ACID

Alpha-lipoic acid (ALA) is an antioxidant that could improve carbohydrate disturbances.[15,16] ALA is a naturally occurring antioxidant that promotes the transport of glucose into cells of muscles.[16] Additionally, it might alleviate peripheral neuropathy in patients with type 2 diabetes.[17] The suggested effective dose to improve insulin sensitivity and fasting blood glucose is 600 mg to 1,800 mg/day orally for four to eight weeks.[16] However, conflicting evidence exists, which suggests no effect on insulin sensitivity.[12] Dosages of 600 mg to 1,800 mg daily have shown benefits for patients experiencing pain, numbness, and prickling of extremities associated with neuropathy.[18]

■ DISCUSSION

Compared to patients without diabetes, patients with diabetes are 1.6 times more likely to include CAM as a component of their diabetes management plans; thus, they are more prone to negative consequences (e.g., side effects and drug interactions) resulting from herbal and dietary supplement usage.[19] These products often are purchased over the counter or through the mail. Consumers with DM might be confused about the product contents and labels, adding to the list of safety concerns. For that reason, patients might be at risk of purchasing products that do not match their stated claims if the products have not gone through a third-party verification process.

To ensure safety from the standpoint of clinicians, it is crucial to ask patients at every visit whether any herbal or dietary supplements were added since the last medical appointment to identify potential drug-supplement interactions, side effects, or additive effects when used with antidiabetic medications. Although *Aloe vera* has been used for skin treatment and incorporated into

drugs as laxatives, there is no long-term evidence yet to suggest its effectiveness in diabetes management. ALA — functioning similarly to B-complex vitamin — has been used in peripheral neuropathy treatment, even that secondary to diabetes.[20] ■

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ABSTRACT & COMMENTARY

Another Way Antibiotic Therapy Can Kill You

By Michael H. Crawford, MD

Professor of Medicine, Lucy Stern Chair in Cardiology, University of California, San Francisco

SYNOPSIS: An analysis revealed fluoroquinolone antibiotic use was associated with later aortic diseases and mortality in patients without known aortic disease.

SOURCE: Chen SW, Chan YH, Chien-Chia Wu V, et al. Effects of fluoroquinolones on outcomes of patients with aortic dissection or aneurysm. *J Am Coll Cardiol* 2021;77:1875-1887.

Fluoroquinolone antibiotics (FA) have been associated with diseases of the aorta in some general population studies, but little data exist on their effect on patients with known aortic disease or a genetic predisposition to aortic disease (e.g., Marfan syndrome).

Investigators interrogated the Taiwan National Health Insurance Research Database to identify patients admitted to hospitals for aortic diseases from 2001 through 2013 using ICD-9 codes. Chen et al excluded patients younger than age 20 years, those with previously diagnosed aortic disease, and those who died during index admission. Among these patients on at least three days of FA or amoxicillin (AM) as a control, use was assessed every two months. Three study designs were used: self-control, comparing outcomes on FA vs.

not on FA; active control, comparing outcomes on FA vs. those on AM; and confounding by indication, where only periods where an infection was diagnosed are used to compare outcomes on FA and AM. The primary outcomes were all-cause mortality, aortic disease mortality, aortic surgery, or aortic stent placement.

The study population consisted of 31,570 patients (mean age, 70 years; 73% men) with 697,171 episodes of aorta disease: aortic dissection (AD) in 43% and aortic aneurysm (AA) in 57%. During the study period, the incidence of AD and AA increased from 4.4% and 6.5%, respectively, to 6.9% and 9.9% ($P < 0.001$). Also, the use of FA and AM in the two months before index hospital admission increased from 3.6% and 7.1% to 11.5% and 8.8%, respectively ($P < 0.001$).

Over the entire study period, FA and AM were prescribed to 24% and 36%, respectively of the study population. On FA, after a mean follow-up of 3.5 years, the adjusted hazard ratio of all-cause mortality on FA was 1.61 (95% CI, 1.50-1.73), 1.80 for aortic death (95% CI, 1.50-2.15), 1.49 for aortic surgery (95% CI, 1.24-1.79), and 1.64 for aortic stenting (95% CI, 1.30-2.06). AM use was not associated with any of these outcomes. When only active infection periods were considered, the results were similar. Sensitivity analyses did not show FA associations with traumatic fractures or strokes. Also, these results were not different for patients with AD or AA. The authors concluded the use of FA, but not AM, increased the risk of all-cause mortality and adverse aortic outcomes. Further, they suggested FA should not be used in patients with known AD unless there are no other suitable treatment options available.

■ COMMENTARY

FAs, such as levofloxacin and ciprofloxacin, are some of the most frequently prescribed antibiotics in the world. They are used for a long list of infectious diseases, from anthrax to urinary tract infections. It is estimated FAs represent about 25% of all antibiotics prescribed, and that 10% of adults will receive one in their lifetime. Considering this ubiquity, rare complications are more likely to be seen. Thus, it is important physicians know their potential serious adverse effects, such as torsade de pointes, hepatic toxicity, and connective tissue disorders. The latter include atraumatic Achilles tendon rupture, retinal detachment, and aortic and mitral valve regurgitation. Experience with general population surveys have suggested an increase in aortic diseases, but some are concerned that the increase in imaging performed when an infection is suspected may have produced confounding by indication. Also, such studies lack a control group. The study by Chen et al addresses these concerns and others. Among the three analyses of the data was the active comparator design, in which AM was used as a control group and no association with aortic disease was found. Also, the authors reduced confounding by indication by only including periods when an infection was present when comparing FA to AM. Therefore, for a retrospective, observational study, it was robust.

However, there were limitations beyond study design. The authors used ICD-9 codes to establish diagnoses, which are subject to human error. There were no data on adherence to therapy. This was an East Asian study population; the results here may not be applicable to other populations. Finally, Chen et al did not provide any data on patients with known connective tissue disorders, such as Marfan syndrome.

The FDA and the European Medicine Agency have suggested avoiding FAs for patients with genetic diseases that affect the aorta and known aortic disease, but these warnings are based on the general population experience rather than data from high-risk groups.[1] The Chen et al study addressed this deficiency in the data and provided strong support for this warning. ■

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PHARMACOLOGY UPDATE

Ibrexafungerp Tablets (Brexafemme)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

The FDA has approved the first-in-class triterpenoid, or "fungerp," a glucan synthase inhibitor, non-azole, antifungal agent to treat vulvovaginal candidiasis. The FDA classified the solution as a qualified infectious disease product and granted a fast track designation. This oral, one-day treatment course is distributed as Brexafemme.

INDICATIONS

Ibrexafungerp can be prescribed to treat adults and post-menarchal pediatric females with vulvovaginal candidiasis (VVC).[1]

DOSAGE

The recommended dose is 300 mg taken as two 150-mg tablets twice a day for one day.[1] It may be taken without regard to meals. Because ibrexafungerp is metabolized by CYP3A, the dose should be reduced to one 150-mg tablet twice-daily with concomitant use of a strong CYP3A inhibitor (e.g., clarithromycin). Co-administration with CYP3A inducers is not recommended. Ibrexafungerp is available as a blister pack with four 150-mg tablets.

POTENTIAL ADVANTAGES

Ibrexafungerp, which interrupts fungal cell wall formation, demonstrated potent *in vitro* activity against *Candida* species, including certain echinocandin- and azole-resistant isolates.[1,2] In contrast to azoles (e.g., fluconazole), which are fungistatic, ibrexafungerp is fungicidal at normal vaginal pH.[1]

POTENTIAL DISADVANTAGES

Based on animal studies, ibrexafungerp is contraindicated in pregnancy over risk of fetal harm.[1] Pregnancy status should be verified in women of reproductive potential before initiation of treatment. An effective contraception should be used for four days after the last dose. The most frequently reported adverse reactions (> 10% vs. placebo) are diarrhea (16.7% vs. 3.3%), nausea (11.9% vs. 4.0%), and abdominal pain (11.4% vs. 5.1%).[1]

COMMENTS

The safety and efficacy of ibrexafungerp were evaluated in two randomized, placebo-controlled trials that included subjects with a VVC diagnosis.[1] VVC was defined as a minimum composite vulvovaginal signs and symptoms (VSS) score of ≥ 4, positive microscopic evidence of yeast in a vaginal sample, and normal vaginal pH (≤ 4). The composite VSS score was based on vulvovaginal signs (erythema, edema, excoriation) and symptoms (itching, burning, or irritation). These are scored from 0 to 3 (absent, mild, moderate, or severe, respectively). The efficacy endpoint was complete clinical response (i.e., complete resolution of signs and symptoms [VSS score = 0]) at the test of cure (TOC) visit, day 8 to 14 after administration. Additional endpoints were negative *Candida albicans* culture at TOC and complete clinical response at follow-up (day 21 to day 29).

Subjects were randomized 2:1 to ibrexafungerp or placebo (n = 190 and n = 100 in trial 1 and n = 189 and n = 89 in trial 2). Complete clinical responses at TOC were 50.0% vs. 28.0% in trial 1 and 63.5% vs. 44.9% in trial 2. Negative culture rates were 49.5% vs. 19.0% and 58.7% vs. 29.2%, respectively. Complete clinical response rates at follow-up were 59.5% vs. 44.0% and 72.5% vs. 49.4%, respectively.

CLINICAL IMPLICATIONS

VVC or vaginal yeast infection is the second most common type of vaginal infection (after bacterial vaginal infections), affecting generally healthy women of childbearing age.[3,4] Typically, it is caused by an opportunistic fungus, *Candida albicans*. The Infectious Diseases Society of America recommends topical (intravaginal) or oral fluconazole treatment.[5] Effectiveness is similar between vaginal products nightly for seven days and fluconazole as a single oral dose, and similar to those reported for ibrexafungerp.[1,6] Ibrexafungerp may offer clinical advantage in non-albicans species (e.g., *C. glabrata*, *C. auris*) or refractory (azole-resistant) *Candida albicans* in VVC, but that remains to be established. Because of its good oral bioavailability (i.e., suitable for parenteral and oral administration) and in vitro activity, ibrexafungerp might play a role in the treatment of invasive candidiasis infections. The cost for ibrexafungerp is $475 for a treatment course vs. a course of generic fluconazole, which is less than $3. ■

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CME QUESTIONS

1. In the Gold et al study, how prevalent were long COVID symptoms in patients who tested positive for COVID-19?
a. 10%
b. 30%
c. 60%
d. 75%

2. Using alpha-lipoic acid helps manage which diabetes-related complication?
a. Diabetic retinopathy
b. Diabetic peripheral neuropathy
c. Diabetic nephropathy
d. Diabetic autonomic neuropathy

3. A population-based study of patients with diseases of the aorta showed fluoroquinolone antibiotics use compared to ampicillin use resulted in:
a. increased all-cause mortality rate.
b. fewer aortic surgery cases.
c. fewer infection relapses.
d. lower aortic disease mortality rate.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

Internal Medicine [ALERT]

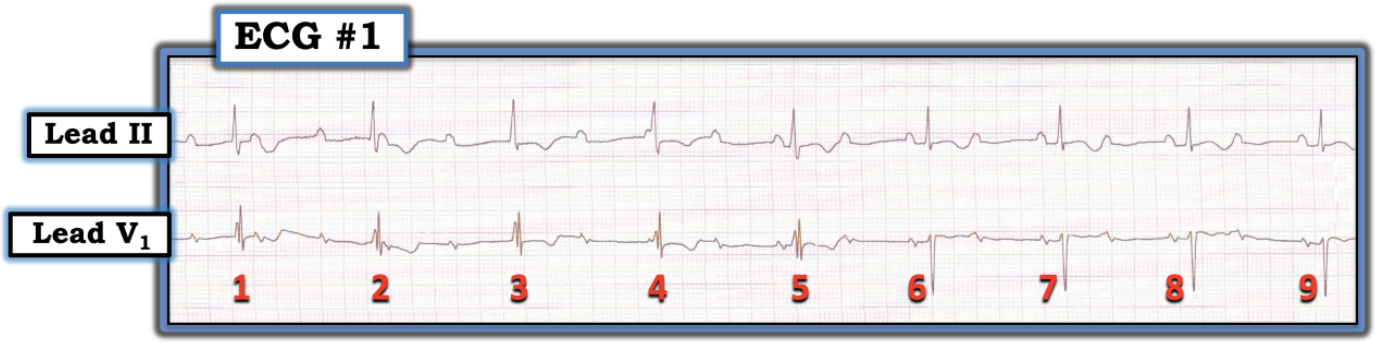
ECG Review

By Ken Grauer, MD

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

Is AV Block Complete?

The dual lead rhythm strip in the figure below was obtained from an elderly patient with syncope. Is there AV dissociation? Is there complete AV block? This is a challenging tracing because a different diagnosis is suggested by the first five beats in the rhythm strip, compared to the last four beats.



Looking first at the initial five beats in the tracing, the QRS complex in lead V1 is notched and appears to be slightly widened. Although some P waves are partially (or totally) hidden by the QRS complex, the underlying atrial rhythm appears to be regular at ~100-110 beats/minute. However, the PR interval preceding each of the first five beats is changing constantly. This tells us there is AV dissociation because none of the P waves for this first portion of the tracing are related to neighboring QRS complexes.

Things change for the last four beats in the tracing. The underlying regular atrial rhythm continues and is easier to appreciate because P waves do not fall so close to neighboring QRS complexes. The QRS itself has narrowed, and QRS morphology has changed. The most important difference is the PR interval preceding each of the last four beats now is constant, which tells us beats 6, 7, 8, and 9 are sinus-conducted. The P wave that falls near the middle of the R-R interval of beats 6-7, 7-8, and 8-9 is not conducted, which defines the conduction defect for these last four beats as second-degree AV block with 2:1 AV conduction.

Importantly, AV dissociation is not the same as complete AV block. Although there is complete AV dissociation for the first five beats on this tracing, this does not represent complete AV block. Proof that this is not complete AV block is forthcoming by clear evidence of conduction for the last four beats. In addition to complete AV dissociation, the diagnosis of complete AV block requires P waves to receive adequate opportunities to conduct, yet still fail to do so. The first five beats on this tracing represent less than six seconds of ECG monitoring, which simply was not a long enough period to allow P waves to appear in all parts of the cardiac cycle. With a few more seconds of monitoring, that "magic point" in the cardiac cycle where conduction is possible was found.

For more information about and further discussion on this case, please visit: https://bit.ly/3dXRKwt.