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Evidence-based summaries of the latest research in internal medicine [ALERT]

ABSTRACT & COMMENTARY

The COVID-19 Pandemic: What Comes Next? Lessons from Seasonal Coronaviruses

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: In temperate regions other than China, human seasonal coronaviruses circulate most heavily during the winter months, overlapping with influenza and respiratory syncytial virus. This may be the eventual pattern for SARS-CoV-2.

SOURCE: Li Y, Wang X, Nair H. Global seasonality of human seasonal coronaviruses: A clue for post-pandemic circulating season of SARS-CoV-2 virus? *J Infect Dis* 2020; July 21:jiaa436. doi:10.1093/infdis/jiaa436. [Online ahead of print].

Speculation regarding the behavior of COVID-19 after the virus is brought under some semblance of stability continues. This is of great importance for the future of this disease and the response to it. It is unlikely that SARS-CoV-2 will disappear, thus leaving two major possibilities: ongoing, year-round transmission (with occasional regional spikes) or seasonal transmission, as has occurred after the appearance of influenza pandemic strains. One source of information that potentially can inform the debate on this issue is the behavior of the four endemic coronaviruses that primarily cause symptoms of a common cold.

Li et al performed a systematic review to assess the global seasonality of existing seasonal human coronavirus infections (sCoV). They found that in temperate regions other than China, the winter months accounted for high sCoV activity, as measured by the annual average percentage. In China, sCoV activity occurred year-round.

In examining temperate regions (excluding China), researchers found 53.1% of sCoV cases occurred during the influenza season and 49.6% occurred during the respiratory syncytial virus season. Lesser overlap occurred in tropical regions, as well as in temperate China (20% and 29% overlap, respectively). An examination of meteorological factors revealed that higher proportions of sCoV cases were associated with periods of low temperature and higher relative humidity.

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[INSIDE]

Internal Medicine
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■ COMMENTARY

The authors of a previous modeling study concluded that if, as has been demonstrated with sCoV, immunity to SARS-CoV-2 is not long-lasting, it will begin its circulation pattern beginning in 2021 or 2022 and will synchronize with circulation of the four human sCoV.[1] Thus, as also indicated by the empiric evidence discussed above, SARS-CoV-2 will cocirculate not only with sCoV but with influenza and respiratory virus infections.

Since symptoms of infections caused by these viruses overlap, clinical diagnoses cannot be relied on. Accurate, rapid turnaround and (preferably) point-of-care tests will be needed. Get ready for a long, complicated, and never-ending ride. ■

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ABSTRACT & COMMENTARY

Repeat Infections with Endemic Coronaviruses and Possible Implications for COVID-19

By Stan Deresinski, MD, FACP, FIDSA

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Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Repeat infection with endemic seasonal coronavirus occurs commonly and raises concerns about immunity to SARS-CoV-2 as well as about the efficacy of vaccines in the protection against infection because of this virus.

SOURCE: Galanti M, Shaman J. Direct observation of repeated infections with endemic coronaviruses. *J Infect Dis* 2020; July 7. doi:10.1093/infdis/jiaa392. [Online ahead of print].

Galanti et al examined data from the Virome project carried out in Manhattan from October 2016 to April 2018 to determine the frequency of recurrent infection with endemic coronaviruses. In this study, 214 healthy individuals underwent regular sampling for respiratory virus infection, with self-reporting of symptoms and episodes of clinical care. The cohort included children attending two daycare centers, as well as their parents and siblings; students and teachers from a high school; adults working in EDs at a pediatric and an adult hospital; and adults working at a university medical center.

Nasopharyngeal samples were collected weekly. Using a respiratory virus panel, researchers tested these samples for the presence of nucleic acid from 18 respiratory viruses, including the α-coronaviruses 229E and NL63 and the β-coronaviruses HKU1 and OC43. Participants also self-reported symptoms each day.

Of 191 participants who contributed samples at least six times in the same season, 86 exhibited evidence of at least one episode of infection by a coronavirus, with OC43 the most frequently identified. The probability of a test-positive episode of OC43 infection during the 80 weeks of the study was 0.47. Twelve of 86 tested positive for the same virus during at least two episodes, with OC43 accounting for nine of these 12. Of the nine people with repeated OC43 episodes, six people experienced two episodes and three experienced three such episodes. The median interval between episodes was 37 weeks (range, 4 to 48 weeks).

Repeat episodes did not appear to be associated with either worse or milder symptoms, but there was a significant association between symptom severity and inclusion within the same family cluster. In individuals whose initial coronavirus infection was asymptomatic, all subsequent infections with the same virus also were asymptomatic.

■ COMMENTARY

Seroconversion to one or more of the endemic seasonal coronaviruses first occurs at an early age. Overall, more than nine in 10 people in the general population are seropositive. Although limited evidence indicates pre-existing antibodies may correlate with some degree of protection, the occurrence of repeat infection with the same serotype suggests any protection is limited.

To the extent these data are relevant to COVID-19, they raise concern regarding the long-term protective nature of antibody to SARS-CoV-2, with obvious implications for dealing with this infection and for the efficacy of vaccines. Although almost all patients who recover from COVID-19 develop antibodies to the virus, and these antibodies often are neutralizing, evidence indicates their serum levels rapidly decay, at least in those with mild or asymptomatic infection.

Ibarrondo et al found the serum half-life of IgG antibody in patients with clinically mild COVID-19 was only 36 days. Long et al found 40% of patients with asymptomatic infection and 12% of those whose infection was symptomatic lost detectable serum antibody during the early convalescent period.[1,2] The finding by Galanti et al of clustering within families of symptomatic infection because of seasonal endemic coronaviruses suggests the possibility of human genetic influences on the inflammatory response elicited via the innate immune system. Some evidence suggests genetic factors affecting that system may play a role in COVID-19. Van der Made et al evaluated two sets of brothers in the Netherlands who, despite their youth and good health, required mechanical ventilation for their management.[3] They were found to have putative loss-of-function mutations in the gene encoding TLR7, which was associated with an impaired interferon response to agonists of this toll-like receptor. Just as with endemic coronaviruses, the necessary elements of immune protection against SARS-CoV-2 remain undefined. ■

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3. van der Made CI, Simons A, Schuurs-Hoeijmakers J, et al. Presence of genetic variants among young men with severe COVID-19. *JAMA* 2020; July 24. doi: 10.1001/jama.2020.13719. [Online ahead of print].

ABSTRACT & COMMENTARY

DASH Is Revisited and Updated, Lowering Subclinical Cardiac Injury Markers

By Jeffrey H. Baker, MD, FAAFP, DABIHM, DABMA

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Dr. Baker reports no financial relationships relevant to this field of study.

SYNOPSIS: In individuals without pre-existing cardiovascular disease, the Dietary Approaches to Stop Hypertension diet plan and a diet consisting of fruits and vegetables, given over eight weeks, lowered biomarkers for cardiac strain and injury.

SOURCE: Juraschek SP, Kovell LC, Appel LJ, et al. Associations between dietary patterns and subclinical cardiac injury. *Ann Intern Med* 2020;172:786-794.

Clinicians continue to search for ways to aid patients in long-term disease prevention, whether by primary or secondary actions. A primary focus is continuing to reduce cardiovascular disease (CVD) risk. Although many interventions exist, elevated blood pressure (BP) is a main factor influencing the development of CVD. Therefore, prevention and control are on the list of clinical concerns.[1,2]

Twenty-four years have passed since the Dietary Approaches to Stop Hypertension (DASH) study was published, showing that dietary interventions could lower systolic BP (SBP) and diastolic BP (DBP), as well as low-density lipoprotein (LDL) cholesterol.[3] Using current testing profiles on historic and curated specimens reveals new information regarding the importance of this diet plan. Juraschek et al hypothesized dietary intervention would reduce cardiovascular injury and aid in primary prevention of CVD. They studied stored samples from a subpopulation of the original DASH trial participants to assess the effects of diet on three biomarkers of subclinical cardiac injury. They examined high-sensitivity troponin I (hs-cTnI) as a marker of cardiac myocyte damage, N-terminal pro-B-type natriuretic peptide (NT-proBNP) as a marker of cardiac strain,

and high-sensitivity C-reactive protein (hs-CRP) as a marker for inflammation. These three markers have been shown to predict risk for vascular events in adults without known CVD.[4-6] The authors of the DASH trial, conducted between September 1994 and March 1996, compared the influence of three isocaloric dietary styles (plans) on SBP.[3] The plans used were:

- a control, typical of American consumption at that time;
- a "fruit and vegetable" diet;
- the DASH diet, supported by the American Heart Association for "managing blood pressure and reducing risk of heart attack, stroke, and other blood pressure-related health threats."[7,8]

Four clinical research centers were involved, selecting 459 participants and randomly assigning them to one of three iso-caloric, prepared dietary plans following a three-week run-in period of the control plan. The control dietary plan consisted of a fiber and macronutrient content of average consumption, with potassium, magnesium, and calcium levels close to the 25th percentile of U.S. consumption. The fruit and vegetable diet plan contained higher quantities of fiber, potassium, and magnesium levels, close to the 75th percentile of human consumption.

The combination DASH diet contained the same higher levels of calcium, potassium, and magnesium, but also included low-fat dairy foods and lower amounts of saturated fat, total fat, and cholesterol compared to the control.

All three plans limited salt to 3 g per day to reduce sodium's potential effects on SBP. The trial duration for participants was eight weeks. The original study revealed the DASH diet could significantly lower SBP, DBP, and LDL cholesterol.[3]

Juraschek et al used blood samples curated by the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) from three of the four original sites submitting samples in the DASH trial, totaling 326 of the 459 trial participants. Of these 326 participants, 108 were assigned to the control plan, 109 to the fruit and vegetable plan, and 109 to the DASH diet plan.

The three markers of cardiac injury were analyzed from the baseline and eight-week samples. As in the original trial, the mean age of participants was 45.2 years. Of the participants, 52% were men, 48% were women, and 49% were Black.

Exclusions for the original DASH trial (and this analysis) included adults with diabetes mellitus, those taking antihypertensive medications, a body mass index greater than 35 kg/m^2, renal insufficiency, or self-reported alcoholic beverage intake of greater than 14 drinks per week. Statistically significant changes in values of hs-cTnI and NT-proBNP from baseline to eight weeks were seen in both the DASH and fruit and vegetable diet, but not in hs-CRP levels.

Compared with the control diet, the DASH plan reduced hs-cTnI levels by 0.5 ng/L (95% confidence interval [CI], -0.9 to 0.1 ng/L) and NT-proBNP levels by 0.3 pg/mL (95% CI, -0.5 to -0.04 pg/mL), while the fruit and vegetable plan lowered hs-cTnI levels by 0.5 ng/L (95% CI, -0.9 to -0.2 ng/L) and NT-proBNP levels by 0.3 pg/mL (95% CI, -0.5 to -0.1 pg/mL). There were no differences noted among the plans regarding hs-CRP.

The authors acknowledged both the DASH and the fruit and vegetable plans lowered markers equally for myocyte damage and strain during the eight-week period. They suggested these plans were higher in fiber, magnesium, and potassium, leading to the effects, but noted further research is needed to confirm these findings. The authors observed patient weight is a principal determinant of elevated hs-CRP levels in obese adults, because this dietary intervention did not result in weight reduction, unlike other studies that showed reduction in hs-CRP with weight loss.

Juraschek et al conceded several limitations to their study analysis. Not all specimens were available from the DASH trial, and the findings were only observational in association with the injury markers, not to effects on clinical outcomes. The study lasted only eight weeks, again, without effect on clinical outcomes. There was concern over the freeze-thaw of samples, causing drift in the test levels, especially hs-CRP.

However, the authors argued their study showed strengths in the original control and administration of diet plans and the use of individuals without CVD. The diets were calorie-controlled, minimizing weight change factors on the markers. Therefore, the recent demonstration of changes in markers of cardiac injury and strain imply that in even the short term of eight weeks, the effect on future CVD events can occur from dietary interventions.

■ COMMENTARY

DASH established the importance of aiding BP reduction by increasing the amount of fresh fruits and vegetables in the diet and reducing saturated fats, thereby increasing magnesium and potassium. The work by Juraschek et al alerted clinicians to techniques to reduce pre-event markers for cardiovascular damage and perhaps the events that change lives. There may be no new tests to order for reassurance or concern, but

there is more meaningful knowledge and conceptual information to pass on to patients to help them be healthy. The concepts, research, plans, and guides for the DASH dietary plan are readily available in books and online as technology apps and classes.

The scientific evidence supports the DASH diet in helping control many aspects of heart disease, and even all-cause mortality.[9] In the recent report of the White House Conference on Food, Nutrition, and Health, listed in the number of priority executive recommendations, was, "Equip health professionals with effective nutrition interventions and better nutrition knowledge."[10] Many medical specialty colleges and academic groups support good nutrition to prevent chronic diseases. Nutrition is one of the six pillars of the American College of Lifestyle Medicine in supporting the prevention and treatment of chronic diseases, including CVD.

Analyzing NHANES data collected between 2007 and 2012 and comparing intake of nine nutrients to target amounts, Kim and Andrade found hypertensive patients scored poorly (2.6 out of a possible 9 score in accordance to DASH targets), and that the reported diet was associated with increased consumption of sodium, saturated fat, total fat, and protein.[11]

Certainly, financial hurdles and regular access to fresh foods in rural or urban areas described as "food deserts" are becoming more apparent. Consuming fresh vegetables and fruit, as well as lean and grass-fed, free-range meats, is an expensive change. But the diet can be adopted in low-income communities at reasonable cost.[12,13]

The DASH plan has not been sold as a "quick fix" for the upcoming wedding or prom, but as a lifelong lifestyle approach to good health. It is not an eating style that is as fast or convenient as the population generally desires. It takes time, commitment, and discipline for individual change to occur.

Steinberg et al, in a viewpoint statement, addressed the economic hurdles and those of the clinician in providing counseling support for their hypertensive patients. They noted clinicians often are too busy to tackle the details of lifestyle nutrition in a short office visit, advocating for sodium reduction at a minimum and referring patients to registered dieticians who are suited for dietary counseling. Although the emergence of self-management health tools for cellphones are a unique opportunity to help educate, the authors argued a limited number of tools truly are evidence-based.[14]

Twenty-four years after the original study, the DASH diet plan continues to resonate as a clinician's tool in facilitating CVD risk reduction. Considering the evidence accumulated, it is an easy recommendation to make to all patients at risk for hypertension as well as those already working to reduce their hypertensive burden. Juraschek et al provided further data to support that dietary lifestyle adherence potentially reduces preclinical damage and CVD risk. Using this information to support patients' individual efforts to improve or maintain their health status will be well worth the time and effort in doing so. ■

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BRIEF REPORT

'Hygiene Theater'

By Carol A. Kemper, MD, FACP

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Dr. Kemper reports no financial relationships relevant to this field of study.

SOURCES: Thompson D. Hygiene theater is a huge waste of time. *The Atlantic,* July 27, 2020.
Goldman E. Exaggerated risk of transmission of COVID-19 by fomites. *Lancet Infect Dis* 2020;20:892-893.

I received an email from clinic administrators in which they asked whether disinfection of the chairs in the waiting room every 30 minutes during the COVID-19 pandemic was sufficient. Two fabric paintings, gifted by a patient, were removed from the walls, and the magazines in the waiting room were confiscated, lest the SARS-CoV-2 virus jump off and infect visitors. The New York subway system is spraying seats, walls, and poles with disinfectant. Yet, people are still riding the subway and standing next to each other.

In an immediate notice on May 22, the CDC sought to assuage people's fears by attempting to clarify that although surface contamination resulting in COVID-19 may be possible, most people acquire infection through person-to-person spread.[1] Sadly, this statement did not go far enough, and my friend is still washing her store-bought fruits and vegetables with soap and water. My sister lets her groceries sit in the garage for two days before unpacking them. My neighbor is wearing gloves to get the mail. It reminds me of those televised scenes of the Chinese government spraying disinfectant throughout the city streets during H1N1 crisis in 2009.

This "hygiene theater" is completely misguided, mistakenly making some people feel safer while obscuring the real risk for infection: contact with other people. Such activities also waste time, energy, and valuable resources. The real risk is friends, family, and co-workers, not the mail.

The press has made much about the risk of COVID-19 viral particles surviving for days on surfaces and objects. However, none of the relevant studies are based in realistic scenarios of viral surface contamination or on the common understanding of respiratory infections. The longest survival of SARS-CoV-2 on surfaces required a large laboratory inoculation of 10^7 viral particles, and viable virus was found out to six days. Another study applied 10^6 viral particles to surfaces, and retrieved viable virus four days later. Aerosols spiked with a large inoculum of 10^5 to 10^7 of SARS-CoV-2 particles found viable virus on surfaces two days later. This would be like 100 people sneezing on that surface, immediately followed by one licking the surface.

In a study of surfaces contaminated by an actual patient, no viable virus could be found. Similar studies of common community coronavirus found the virus survived less than one to three hours after drying on various surfaces, including surgical gloves and aluminum. People's fears have been exaggerated by bad science and worse public policy.

Theoretically, high-touch surfaces may pose a risk. Realistically, fomites carrying small amounts of virus that have not been in contact with their owner for more than one or two hours do not. Ask how many cases of COVID-19 have been traced to fomites as the cause for infection. As the columnist states, "the extreme infrequency of evidence may indeed be evidence of extreme infrequency." ■

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PHARMACOLOGY UPDATE

Teprotumumab-trbw Injection (Tepezza)

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

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Drs. Elliott and Chan report no financial relationships relevant to this field of study.

Earlier this year, the FDA approved the first drug for the treatment of thyroid eye disease (Graves' orbitopathy or thyroid-associated ophthalmopathy). Teprotumumab is a fully human IgG1 that is an inhibitor of insulin-like growth factor-1 receptor (IGF-1R).[1] It received priority review and fast track, breakthrough, and orphan designations. Teprotumumab is distributed as Tepezza.

INDICATIONS

Teprotumumab should be prescribed to treat thyroid eye disease.[1]

DOSAGE

The recommended initial dose is 10 mg/kg by IV infusion, followed by 20 mg/kg every three weeks for seven additional infusions.[1] Infusion should occur over a 60- to 90-minute period (90 minutes for the first two infusions). Teprotumumab is available as 500 mg lyophilized powder in a single-dose vial.

POTENTIAL ADVANTAGES

Teprotumumab is the first FDA-approved treatment for thyroid eye disease.

POTENTIAL DISADVANTAGES

Teprotumumab can harm the fetus, cause infusion reactions, and exacerbate inflammatory bowel disease and hyperglycemia.[1] Patients with diabetes should be under appropriate control before initiating treatment with teprotumumab. The most frequent adverse reactions (vs. placebo) include muscle spasm (25% vs. 6%), nausea (17% vs. 9%), alopecia (13% vs. 8%), diarrhea (12% vs. 8%), and fatigue (12% vs. 7%).[1]

COMMENTS

Thyroid-associated ophthalmopathy (TAO) is a rare autoimmune disease of the thyroid gland.[2] It is a disfiguring and potentially sight-threatening condition as the soft tissue around the eyes become inflamed and undergoes remodeling. This results in disfigurement and disability from proptosis and diplopia. IGF-1R is overexpressed in several cell types in TAO and may be involved in the disease process.[2]

Teprotumumab's efficacy and safety were evaluated in two randomized, double-masked, placebo-controlled studies.[1,3,4] Subjects (86% white, 73% female) with thyroid eye disease and who were euthyroid or had thyroxine and free triiodothyronine levels less than 50% above or below normal limits were randomized to teprotumumab (n = 42 in study 1; n = 41 in study 2) or placebo (n = 45 in study 1; n = 42 in study 2). Proptosis ranged from 16 mm to 33 mm, and 73% had diplopia at baseline.

The primary outcome was a proptosis response, defined as a reduction of ≥ 2 mm from baseline in the study eye without a corresponding increase of ≥ 2 mm at week 24 in the nonstudy eye.

Diplopia was evaluated in a subgroup of subjects with diplopia at baseline. Proptosis responses were 71% in study 1 and 83% in study 2 compared to 20% and 10%, respectively, for placebo. The mean changes from baseline were -2.5 mm (vs. 0.2 mm for placebo) in study 1 and -2.8 mm (vs. -0.5 mm) in study 2. Improvement in proptosis was observed in week 6 and continued to improve through week 24. Diplopia improved in 53% of subjects compared to 25% for placebo. In study 1, 53% of responders maintained their proptosis response 51 weeks after the last dose, and 67% of diplopia responders maintained their response.[1]

CLINICAL IMPLICATIONS

TAO is a rare condition affecting more women than men. Before approval of teprotumumab, there were no FDA-approved medical therapies for TAO. Mild disease is characterized by dry eyes, lid retraction, and modest ocular prominence.[5] Generally, this is managed with local supportive measures, such as topical ocular solutions and short-course oral steroids with or without nonsteroidal anti-inflammatory agents.[5]

With moderate to severe disease, periorbital tissue remodeling occurs; corticosteroids usually are administered alone or with orbital radiotherapy, but with limited success. The active disease course is usually one to three years, followed by stable disease.[5] These patients often undergo multiple surgical and cosmetic procedures.[5]

Teprotumumab is the first treatment for TAO that ameliorates several manifestations of TAO, including those that were previously amenable only to surgical rehabilitation.[2] The cost is $14,900 per vial. A treatment course (six months) is estimated to be $343,000.[6] ■

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CME QUESTIONS

1. In temperate regions other than China, human seasonal coronaviruses circulate most heavily during the winter months, overlapping with:
a. pneumonia and strep throat.
b. bronchitis and the common cold.
c. influenza and respiratory syncytial virus.
d. croup and norovirus.

2. Which is correct regarding infections with the four endemic coronaviruses?
a. Infection with one type provides subsequent lifelong protection against all four viruses.
b. Infection with one type provides lifelong protection, but only to that type.
c. Infection fails to provide lifelong protection.
d. Repeat infection is associated with increased severity.

3. In individuals without pre-existing cardiovascular disease, the Dietary Approaches to Stop Hypertension diet plan and a diet consisting of fruits and vegetables, given over eight weeks:
a. lowered biomarkers for cardiac strain and injury.
b. helped some participants lower their blood pressure medication dosage.
c. resulted in weight loss for all participants.
d. alleviated feelings of depression among some participants.

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.