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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

# Ethical Issues Affecting COVID-19 Vaccination

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

SYNOPSIS: The world waits eagerly for a COVID-19 vaccine. But the supply of vaccine is unlikely to initially meet the demand. Ethical issues are important as individuals and groups are prioritized for early vaccination.

SOURCE: Persad G, Peek ME, Emanuel EJ. Fairly prioritizing groups for access to COVID-19 vaccines. *JAMA* 2020; Sept. 10. doi: 10.1001/jama.2020.18513. [Online ahead of print].

There is optimism about the coming availability of SARS-CoV-2 vaccines. However, supplies are likely to be limited, at least initially. Thus, various groups have suggested prioritization schemes to allocate limited vaccine supplies.

In a viewpoint article, Persad et al suggest that three main ethical issues relate to vaccine allocation, and they discuss these issues in light of COVID-19. First, they claim that providing benefit while limiting harm is a universal value and that a vaccine could reduce illness and death while also mitigating unemployment, poverty, and educational deprivation. Second, they believe that it is fundamental to prioritize disadvantaged populations, including the medically vulnerable who risk earlier death if infected, as well as those who have been subject to socioeconomic deprivation and oppression. Third, they suggest that differences of race, gender, and religion should not enter into consideration in simplistic ways that could actually harm or de-prioritize disadvantaged population groups — while, of course, not ignoring relevant differences.

The authors point out that the vaccine allocation plan proposed by the U.S. National Academy of

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[INSIDE]

Infectious Disease [ALERT]

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Medicine also valued reciprocity, the recognition of past good behavior to justify earlier vaccination. This principle encourages that previous organ donors be prioritized to receive organs if they subsequently are in need, and the National Academy of Medicine applies this principle to COVID-19 vaccination as well. However, the authors propose that reciprocity be subordinate to the greater values of preventing harm and helping disadvantaged groups. The authors see the assignment of worth to past good behavior as too difficult and controversial to be implemented fairly.

The viewpoint authors believe that their main ethical principles support individual and societal benefit when prioritized immunization is targeted for healthcare workers, people in high transmission settings, and medically vulnerable individuals who have medical conditions that put them at risk of poorer outcomes if they were to be infected with SARS-CoV-2. Focusing on healthcare workers would reduce iatrogenic spread of illness and provide reduced risk for patients with risk factors who frequent healthcare settings and live in medical housing situations. Focusing on people working in high transmission settings would reduce direct harm and minimize spread; this would include school personnel, childcare providers, and food supply workers. It is reported that 200 million people in the United States have high-risk medical conditions, so further prioritization within the high-risk groups also will be necessary.

The authors stress that it is important to be careful not to harm disadvantaged populations by the choice of "high risk" individuals prioritized for early vaccination. For instance, although it is true that the risk of poor COVID outcomes increases after age 65 years, 30% of non-white people who die as a result of COVID are younger than 65 years of age, while only 13% of whites who lose their lives to COVID are younger than 65 years of age. The risk of death in a healthy older person who can shelter in place in a single-family residence is significantly less than that of a similarly aged person with medical comorbidities who lives in crowded housing. Prioritizing all older people also would lead to some younger people being relatively more likely to become ill and succumb, with the resulting loss of many more total years of remaining life.

Others, applying the principle of reciprocity, have suggested that participants in vaccine research studies should be prioritized for vaccination when good vaccines become available. The authors point out that this approach is problematic since vaccine studies have tended to include people who are unlikely to live or work in high transmission settings, and vaccine studies have included relatively few people with either medical conditions or backgrounds in racial and ethnic minority groups.

The authors of this viewpoint article go on to caution against prioritizing vaccine allocation based on racial and ethnic background. They accurately claim that the statistical risk of poor COVID outcomes is less the result of genetics and more because of the consequences of structural racism that have left some racial and ethnic groups more likely to work or live in crowded settings where social distancing is particularly difficult.

Thus, the authors urge that COVID-19 vaccines be allocated to prevent harm, prioritize those who are disadvantaged, and achieve equal treatment. They caution against simplistic schemes that prioritize only the elderly or those of certain racial groups without considering the individual's actual risk factors for becoming infected or suffering extreme illness if infected. They then practically propose that the vaccine be allocated so that half the supply goes to frontline healthcare workers, with one-fourth of the initial vaccine supply going to people living and working in high-risk settings, and the final fourth going to other people. Within those categories, priority would be given to individuals with high-risk medical conditions.

## ■ COMMENTARY

Believing in individualized medicine, we often select diagnostic testing and therapeutic interventions based on what is deemed best for each individual patient. Early in the COVID-19 pandemic, however, it became shockingly clear that resources were not infinite and that even

resource-rich societies needed to think through priorities of allocating limited resources. With at least 25 vaccines currently being evaluated, and even as we anticipate the availability of COVID-19 vaccines, our consideration of vaccine delivery systems must go beyond infection and immunity, beyond safety and efficacy.[1] We will need to consider the ethics of allocation of limited vaccine supplies.

How much safety and efficacy data will be enough to begin widespread vaccination? Even moving at "warp speed," scientific processes should be respected. Sadly, a review of the initial nine months of COVID-19 research data revealed 33 papers that were deemed "unsuitable for public use" and had to either be retracted, withdrawn, or labeled as concerning.[2] The desire to quickly control the pandemic should not prompt acceptance of rushed or incompletely vetted research findings. And, even after licensing and widespread vaccination are achieved, post-marketing surveillance will be needed; the dangers of an initial rotavirus vaccine and an early dengue fever vaccine were not recognized until large population groups had been vaccinated.

In the medical field, we often espouse a "do no harm" approach. Of course, risks and benefits must be balanced carefully. Almost no medical intervention carries zero risk of harm, and new rapidly produced interventions should be recognized as inherently risky.

How much effectiveness is enough to warrant widespread immunization? Malaria vaccines offering children 30% protection for up to four years have not been seen as effective enough to warrant widespread use. One hopes the COVID-19 vaccines will have better efficacy than the current malaria vaccine candidates.

The authors of the viewpoint article wisely look beyond race in considering the prioritization of vaccination. Clearly, race is related to poor outcomes with COVID-19, and new data confirm this finding.[3] But race is, to at least some degree, a marker for risk factors rather than a fully independent risk factor. Even in the county where I live, recent pre-publication epidemiologic data suggest that COVID-19 is, indeed, more common in minority racial groups, but the geospatial clustering of cases reveals that the risk actually is associated with living in crowded housing (apartment buildings and trailer parks) and with neighborhoods with lower socioeconomic levels.[4] Race is a statistical marker for risk, but considering race alone would lead decision-makers to inappropriately include many low-risk individuals (those of racial minority groups who have high socioeconomic status and live in single-family dwellings) in the "high risk" category.

Well-intentioned, ethics-based research regulations also can hinder research for appropriately studying vulnerable populations. Although incarcerated individuals are at particularly high risk of infection and poor outcomes with SARS-CoV-2, it is not likely that prisoners will be included in COVID-19 vaccine trials.[5]

Children are at risk of becoming ill with COVID-19, and they also are at risk of becoming asymptomatic "super spreaders" as schools open. One could wonder if children should be mandated to receive vaccines, even as other vaccines are mandated through school systems. However, careful review of the situation reveals that more data are needed before deciding if children should be prioritized for early or mandated vaccination.[6]

Another ethical issue has been raised about a few of the candidate COVID-19 vaccines. As with some routine childhood vaccines, some of the adenovirus vector-based COVID-19 vaccines have used decades-old cell lines from aborted fetal tissue during the manufacturing process.[7] "Moral complicity" is the notion that using the products of an unethical act, as some see abortion, makes one complicit to the initial act. Moral complicity was a major concern in past generations when execution rates seemed to increase when "justified" by the use of victims' bodies "for science."[8] Does the use of abortion-derived vaccines make vaccinators and vaccine recipients complicit with and "guilty of" the initial abortion? A similar issue was raised when the popular press realized that researchers were benefitting from studies involving

HeLa cell lines that had been used without the patient's consent. Most of us do not see the moral complicity argument as a limitation to the use of specific vaccines any more than we see a kidney transplant recipient who received an organ from a deceased murder victim as being complicit with or guilty of the murder of the organ donor.

Already, governments of some wealthy countries have purchased huge stocks of not-yet-produced COVID-19 vaccines, with more than 2 billion doses already bought.[9] The World Health Organization recommends that richer nations ensure that resource-limited countries receive early access to vaccines, too.[10] It is hoped that national and international law will serve as a means, rather than as a barrier, to just and equitable distribution of vaccines around the globe.[11] ■


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## ABSTRACT & COMMENTARY

# First There Was MIS-C, Now There Is MIS-A


***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: Multisystem inflammatory syndrome in adults (MIS-A), similar to multisystem inflammatory syndrome in children (MIS-C), is described by the Centers for Disease Control and Prevention.

SOURCE: Morris SB, Schwartz NG, Patel P, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection — United Kingdom and United States, March–August 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1450-1456.


The occurrence of the multisystem inflammatory syndrome in children (MIS-C) has been linked to SARS-CoV-2 infection. The case definition of this illness, which may resemble Kawasaki disease, includes the presence of fever, laboratory evidence of an inflammatory response, and illness severe enough to require hospitalization with involvement of at least two organ systems in an individual younger than 21 years of age — all without a reasonable alternative diagnosis. Also required is a positive current or recent SARS-CoV-2 real time polymerase chain reaction (RT-PCR), antigen, or serology — or exposure within the previous four weeks to an individual with suspected or confirmed COVID-19.

Beginning in June 2020, case reports of a similar illness began to be reported in adults, but with at least one major difference — the lack of severe respiratory illness. This syndrome has been called the multisystem inflammatory syndrome in adults (MIS-A).

Centers for Disease Control and Prevention (CDC) investigators identified cases of MIS-A from voluntary reports and published case reports, with the former yielding nine cases and the latter yielding seven cases. These 16 patients ranged in age from 21 to 50 years; nine were women; nine were African-American, and one was of African origin but was from the United Kingdom. Nine had no reported comorbidity.

Twelve patients had measured or subjective fever on hospital admission. All 16 patients had cardiac abnormalities, including arrhythmias, elevated troponin, and/or echocardiographic evidence of ventricular dysfunction. Gastrointestinal symptoms were present in 13 patients, and five patients had dermatologic manifestations and/or mucositis. Respiratory symptoms were, by definition, at most minimal, but chest imaging identified ground glass opacities in 10 patients, while four patients had pleural effusions. Lymphocytopenia was present in 10 patients. One or more inflammatory markers, including C-reactive protein (CRP) and ferritin, were greatly elevated in all 16 patients, and D-dimer also was elevated.

Treatment, each administered to varying numbers of patients, included corticosteroids, intravenous immunoglobulin, and tocilizumab. Ten patients required intensive care, seven patients received inotropes or vasopressors, three required mechanical ventilation, and one received extracorporeal membrane oxygenation (ECMO). Two of the 16 patients died. An additional 11 patients with illness consistent with MIS-A, but with incomplete information, were identified in three published case series. In one report, all seven patients developed mixed cardiogenic and vasogenic shock. In a second report, both patients had large vessel strokes, and a third report described two patients with endothelitis with associated complement deposition. Overall, eight (30%) of the 27 patients had negative PCR tests but positive antibody tests — a proportion comparable to the 45% reported in MIS-C.

■ COMMENTARY

This CDC study suggests that a syndrome quite similar to MIS-C, which by definition was limited to those younger than 21 years of age, also may occur in adults and which they have called MIS-A. In contrast to the frequent presence of severe respiratory abnormalities in MIS-C, however, adults with such findings were excluded from MIS-A to distinguish this group from those who simply had severe COVID-19 or whose extrapulmonary multi-organ dysfunction was caused by hypoxemia, at least in part.

The fact that the SARS-CoV-2 test is negative in the majority of cases of MIS-A, with the remainder being seropositive, suggests that it may result from immunologic/inflammatory post-infectious mechanisms. Of note is that in patients who reported a prior episode of "typical" COVID-19 symptoms, the interval to the development of MIS-A was two to five weeks. The pathologic mechanisms may result in many tissue injuries, including, e.g., endothelial damage and procoagulant effects.

Morris and colleagues indicated that both virologic and antibody testing should be performed in suspected cases. Fortunately, 24 of 27 of the patients described by this group survived, despite their complex and severe disease. The anti-inflammatory treatment they received seems reasonable, but whether it is effective remains undetermined. ■

ABSTRACT & COMMENTARY

# Corticosteroid Bursts and Subsequent Sepsis

***By Stan Deresinski, MD, FACP, FIDSA***

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

SYNOPSIS: Short-term (< 14 days) administration of oral corticosteroids is associated with an increased risk of adverse events, including an approximately two-fold risk of sepsis.

SOURCE: Yao TC, Huang YW, Chang SM, et al. Association between oral corticosteroid bursts and severe adverse events: A nationwide population-based cohort study. *Ann Intern Med* 2020;173:325-330.

Investigators in Taiwan examined claims from their country's National Health Insurance Research Database to examine the relationship between administration of "bursts" of oral corticosteroid and associated adverse events. A burst was defined as administration for < 14 days. The study covered three years ending Dec. 31, 2015.

During that time, 2,623,327 (16.5%) of 15,859,129 individuals received such bursts and met selection criteria, although overall, 25% had received glucocorticoid bursts. Most bursts were administered to treat dermatologic conditions (24.1% of top 10 diagnoses) or upper respiratory tract infections (33.6%). The incidence rates per 1,000 patient-years

for gastrointestinal (GI) bleeding and heart failure were 27.1 and 1.3, respectively, while for sepsis it was 1.5 (95% confidence interval [CI], 1.4-1.6). The incidence rate ratios were 1.80 for GI bleeding, 2.37 for heart failure, and 1.99 (95% CI, 2.13-2.63) for sepsis during the five- to 30-day period after steroid administration, but subsequently diminished.

## ■ COMMENTARY

Approximately 8% of Taiwanese adults receive a glucocorticoid burst prescription each year. The incidence of short-term (< 30 days) glucocorticoid prescriptions for adults in the United States is approximately 7%, with upper respiratory tract infections the most frequent reason.[1]

Several years ago, a physician spontaneously told me he routinely gave his children corticosteroids when they developed symptoms of upper respiratory infection, and I was astounded. In fact, it appears this may be a common phenomenon and one that apparently has been promoted. In 2017, an expert panel made a weak recommendation for administration of a single dose of glucocorticoid in the management of patients with sore throats, reasoning that it shortens the duration of symptoms by approximately one day and is unlikely to cause harm.[2]

Whether a single dose may cause harm is unknown, but it would appear to be a possibility. The study reviewed here indicates that steroid bursts lasting < 14 days are associated with 1.8- to 2.4-fold increased risk of GI bleeding, heart failure, or sepsis — with, for our specific interests, a two-fold risk of sepsis. Clinicians should carefully consider the potential adverse effects of their prescriptions for short-term use of oral corticosteroids. ■

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ABSTRACT & COMMENTARY

# Chronic Low-Dose Corticosteroids and Infection Risk


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



SYNOPSIS: The prolonged use of low-dose oral corticosteroids (including < 5 mg prednisone equivalent doses) in rheumatoid arthritis patients is associated with an increased risk of infection.



SOURCE: George MD, Baker JF, Winthrop K, et al. Risk for serious infection with low-dose glucocorticoids in patients with rheumatoid arthritis: A cohort study. *Ann Intern Med* 2020; Sept. 22. doi: 10.7326/M20-1594. [Online ahead of print].


George and colleagues set out to quantify the risk for hospitalized infection associated with the use of low-dose glucocorticoid therapy in adults with rheumatoid arthritis who were also receiving a disease-modifying antirheumatic drug (DMARD) for more than six months. A hospitalized infection was considered to have occurred if there was an ICD-9 diagnostic code indicating infection among all the discharge diagnoses from an acute care hospital. The primary outcome was the time to first such infection. They used the Medicare national claims data from 2006 to 2015 and the Optum Clinformatics Data Mart from 2001 to 2015 covering individuals with commercial health insurance. The investigators identified 247,297 and 44,118 qualifying medication courses in the Medicare Optum databases, respectively. At six months of stable DMARD use, 47.1% and 39.5%, respectively, were receiving glucocorticoids, most at doses of < 5 mg per day.

The one-year cumulative incidences of hospitalized infection in Medicare patients receiving glucocorticoids in daily doses (as prednisone equivalents) of < 5 mg, 5 mg to 10 mg, and > 10 mg were 11.0%, 14.4%, and 17.7%, respectively, while it was only 8.6% in those not receiving glucocorticoids. The incidences were lower in the Optum database cases involving a younger population: 5.2%, 8.1%, and 10.6% at the three doses, respectively, while it was 4.0% in those not receiving glucocorticoids. Each of

the differences achieved statistical significance. The most frequent infections involved the urinary tract, as well as pneumonia, bacteremia or septicemia, and skin or soft tissue infections.

■ COMMENTARY

Glucocorticoid administration is an important element of the treatment for many patients with rheumatoid arthritis and is believed to be effective for durations of as much as six months. The risk-benefit ratio of longer durations is uncertain, at least in part because of the risk of drug-associated adverse effects, such as osteoporosis and infection. The study reviewed here demonstrates an increased risk of dose-dependent infection.

The massive number of observations in this analysis lend strength to the result, but the nature of the study leaves open the possibility of several confounders. For instance, the diagnosis of hospitalized infection relied on discharge ICD-9 codes, raising issues of accuracy. Thus, it is certain that many coded as a urinary tract infection were, in fact, instances of asymptomatic bacteriuria. Nonetheless, the authors pointed out that the overall results were concordant with similar studies. They also noted that the risk associated with a daily dose of < 5 mg is similar to that reported with biologic therapies in previous studies.

Thus, there is an infection risk associated with prolonged use of even very low doses of glucocorticoids. These results provide support to recommendations that their long-term use be minimized, to the extent possible. They also inform decisions regarding choices between chronic prednisone administration and the use of biologics. ■

ABSTRACT & COMMENTARY

# Hospitalized COVID-19 Patients: SARS-CoV-2 RNA in Plasma Associated with ICU Admission and Mortality

***By Richard R. Watkins, MD, MS, FACP, FIDSA, FISAC***

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

SYNOPSIS: A prospective cohort study found that SARS-CoV-2 plasma RNA was detected more often, and the levels were higher, in patients who were admitted to the intensive care unit and/or who died.

SOURCE: Prebensen C, My Hre PL, Jonassen C, et al. SARS-CoV-2 RNA in plasma is associated with ICU admission and mortality in patients hospitalized with COVID-19. *Clin Infect Dis* 2020; Sept. 5. doi:10.1093/cid/ciaa1338. [Online ahead of print].

SARS-CoV-2 can disseminate to multiple organs besides the lungs, including the heart, brain, kidneys, and gastrointestinal tract. However, the clinical significance of detecting viral ribonucleic acid (RNA) in the bloodstream is unknown. Prebensen and colleagues sought to quantify SARS-CoV-2 RNA in the plasma and upper respiratory tract of patients hospitalized with COVID-19 and to determine the association between viral RNA loads and disease severity.

The study was a prospective cohort that included adult patients admitted to a single center in Norway with COVID-19 confirmed by real time polymerase chain reaction (RT-PCR). The study's primary endpoint was a composite of intensive care unit (ICU) admission for more than 24 hours and in-hospital mortality. RT-PCR detected SARS-CoV-2 RNA in plasma samples and upper respiratory tract swabs. Researchers estimated plasma RNA levels using the cycle threshold (Ct) value. The RNA was quantified and expressed as log10 copies/mL in plasma samples that were positive on PCR.

Of the 123 COVID-19 patients who had blood samples available, 35 (28%) reached the primary end point. Thirty-one patients were admitted to the ICU, 29 patients received mechanical ventilation, and four died. An additional four patients who had do-not-intubate orders died on regular hospital floors. All patient admissions to the ICU and deaths were attributable to COVID-19 infection.

SARS-CoV-2 RNAemia was detected in at least one sample in 58/123 (47%) patients. It also was detected in a significantly higher proportion of the patients who were admitted to the ICU or who died (80% vs. 34%, $P < 0.001$). Forty-eight out of 123 (39%) of patients had RNAemia detected at baseline, a median 0 [-1, 3] days before admission to the ICU. Twenty-four patients (41%) with detectable RNAemia had Ct values > 38, below the quantitation limit of 2.70 log10 copies/mL. After nine patients with baseline samples taken after ICU admission were excluded, baseline RNAemia and RNA load both were associated significantly with ICU admission and/or death. The association persisted after adjusting for age, sex, race, body mass index (BMI), diabetes mellitus, and symptom duration. No correlation was identified between days from symptom onset and RNAemia frequency or RNA load at baseline. Moreover, no correlations were found between upper respiratory Ct values and RNAemia frequency or plasma RNA loads, nor between the number of days from symptom onset to ICU admission. Finally, there was no difference in the titers of anti-SARS-CoV-2 total Ig or IgG at any time point between patients who reached the primary endpoint and those who did not.

## ■ COMMENTARY

The investigators found a high proportion of SARS-CoV-2 RNA in the blood of patients who were hospitalized with COVID-19, and they found a significantly higher frequency and level of RNAemia in the patients admitted to the ICU and in those who died. The key takeaway is the possible utility of SARS-CoV-2 RNAemia as a prognostic marker. Indeed, with the current availability of remdesivir and potentially other antiviral agents in the near future, identifying patients with early markers of severe disease is important for deciding when to initiate treatment. This is because early initiation is a crucial factor in antiviral drug efficacy.

There has not been a consistent association found between SARS-CoV-2 RNA in the nasopharynx and asymptomatic vs. symptomatic disease, or with symptomatic disease severity. Moreover, viral RNA at a local site of initial infection does not give an accurate measure of viral replication in the lower respiratory tract or dissemination of the virus via the bloodstream to other organs. Longitudinal samples from patients with a range of illness severity would provide additional insights into the utility of SARS-CoV-2 RNAemia as a prognostic marker. However, this raises the question of whether viral nucleic acid indicates the presence of viral particles and/or infected cells. Also, does detection of viral RNA in the blood indicate uncontrolled infection and a risk for complications, thus necessitating earlier intervention, i.e., antiviral therapy? These and other questions about the pathogenesis of extra-pulmonary SARS-CoV-2 will need to be elucidated to improve the precision of antiviral and anti-inflammatory therapies.

There are some limitations to the study worth mentioning. First, not every patient diagnosed with COVID-19 during the study period was included, making selection bias a concern. Second, as mentioned earlier, the presence of viral RNA does not necessarily indicate there is replication-competent virus. Third, the time between baseline testing and ICU admission was short, which limits the prognostic time window for SARS-CoV-2 RNAemia. Finally, the findings cannot determine whether RNAemia represents direct viral involvement causing extra-pulmonary pathology or whether it is just spillover from an intense pulmonary infection.

In summary, SARS-CoV-2 RNAemia may prove to be a useful clinical marker in patients with COVID-19. But further studies on the pathophysiological significance of circulating viral RNA are needed to inform prognosis and optimize therapeutic decisions. ■

ABSTRACT & COMMENTARY

# Gut Microbiome in Patients at Risk for Parkinson's Disease

*By Harini Sarva, MD*

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**Dr. Sarva reports that she is a consultant for Accorda Therapeutics, Amneal Pharmaceuticals, and Merz Pharma.**

SYNOPSIS: Certain risk factors and prodromal markers of Parkinson's disease (PD), such as constipation and rapid eye movement sleep behavior disorder, are associated with specific bacterial compositions of the gut. However, the value of gut microbiome data to predict the risk of PD development needs further investigation.

SOURCE: Heinzel S, Aho VT, Suenkel U, et al. Gut microbiome signatures of risk and prodromal markers of Parkinson's disease. *Ann Neurol* 2020;88:320-331.

Stool samples were obtained from 745 participants of the Tubingen Evaluation of Risk Factors for Early Detection of Neurodegeneration (TREND) study. Participants of this study were chosen based on the presence of olfactory loss, depression, and/or possible rapid eye movement (REM) sleep behavior disorder (RBD), all of which increase the risk of Parkinson's disease (PD) development based on criteria established by the International Parkinson's Disease and Movement Disorders Society. Nine risk factors (male gender, diabetes, and smoking, among others) and nine prodromal factors (constipation, depression, RBD, and olfactory loss) based on the new criteria were chosen for evaluation of possible association with gut microbiota.

Of the 745 samples, 666 were included for analysis. DNA analysis and microbial measures of diversity were performed. The mean age of the sample population was approximately 68 years, the majority were men, one-quarter performed no physical activity, and approximately 13% had RBD. The most common bacteria found in the stool samples included *Bacteroides*, followed by *Faecalibacerium*, *Gemmiger*, *Roseburia*, *Prevotella*, and *Ruminococcus*. Constipation severity and age were positively associated with the alpha-diversity or abundance of a genus in the gut. For the intersample differences in microbial composition, as demonstrated by beta-diversity, age, physical activity, body mass index, and constipation had the greatest effect on variance.

Certain risk factors were associated with bacterial enterotypes. For example, the lowest physical activity and severe constipation were associated with *Firmicutes* enterotype, but high physical activity was associated with *Bacteroides*. Certain factors were associated with lower abundance of bacterial species; for example, severe constipation was associated with a decreased abundance of *Faecalibacterium*.

■ COMMENTARY

Alpha-synuclein pathology is present in the gut in patients with PD, and alterations in the gut microbiome leading to increased inflammation have been well described. This study demonstrated that certain risk factors and prodromal markers of PD were associated with different compositions of gut bacterial species.

Although constipation, RBD, smoking, and subthreshold parkinsonism were more commonly associated with microbial changes, other factors, such as substantia nigra hypoechogenicity, orthostatic hypotension, family history of PD, and olfactory loss, did not demonstrate any associations.

However, it is not clear what effect these microbial associations have on prodromal PD. Medications, lifestyle choices such as diet and exercise, and the presence of other chronic conditions can complicate bowel function and microbial composition and the diversity of the microbiome. Further confirmation of these findings may allow us to distinguish between those with and without PD and potentially help us predict risk when combining stool samples with already established prodromal markers.

In the future, with more data about the gut microbiome, this advancing field of research may help us to predict disease severity of PD patients and help us to customize drug therapies. ■

Infectious Disease [ALERT]

# Updates

By Carol A. Kemper, MD, FACP

## Sex in the Time of COVID-19

SOURCE: De Miguel Buckley R, Trigo E, de la Calle-Prieto F, et al. Social distancing to combat COVID-19 led to a marked decrease in food-borne infections and sexually transmitted disease in Spain. *J Travel Med* 2020; Aug, 25. doi: 10.1093/jtm/taaa134. [Online ahead of print].

Since the first case of COVID-19 in Madrid, Spain, occurred Feb. 25, 2020, the Spanish government has enacted a series of restrictive measures on communal gatherings and travel. Beginning March 15, the citizens of Madrid effectively went into lockdown; public gatherings of more than six people are not allowed, and entry and exit from cities with higher burdens of COVID still is permitted only for work, education, or medical purposes. United States citizens are still barred from travel to Spain. These measures have resulted in a significant drop in local and national travel and activity.

Comparing the first six months of 2020 to the previous semester in 2019, epidemiologic surveillance

data for Madrid demonstrate a dramatic reduction in foodborne infections and sexually transmitted diseases (STDs). Cases of *Campylobacter* and *Salmonella* have dropped 74% to 76.4% from pre-COVID levels. Cases of gonorrhea, chlamydia, and syphilis have dropped 81%, 76%, and 73%, respectively, since 2019.

If this drop in STDs is any reflection of the reduction in circulating SARS-CoV-2 virus in the community, then shelter-in-place and travel restrictions really work. While concern has been raised that this drop in STD cases is the result of under-diagnosis during COVID, when public health personnel and dollars have been diverted to COVID, and outpatient STD services have been reduced, I imagine these data are real. The simple fear of acquiring COVID, along with restrictions in gatherings, nightclubs, and parties, have limited both desire and opportunity. I've heard from several patients that popular gay bars and bathhouses in our area have literally gone out of business during the extended months of closure, unable to pay their bills.

The reduction in foodborne illness during COVID is an interesting "side effect" of COVID — and may be the result of the reliance on more home-cooked meals, limited access to prepared deli foods, and closure of restaurants and bars. Smaller and fewer group gatherings also may have reduced transmission of foodborne illness.

One hates to think it took an epidemic to put a dent in people's sexual activity, or at least their number of partners. Prior to COVID in 2019, STD rates in the United States were at a record high, with up to 115,000 cases of syphilis, 580,000 cases of gonorrhea, and 1.7 million cases of chlamydia. Among newborns, syphilis cases increased 40%. One can hope that the lessons learned from COVID might rub off on other aspects of life, with attention to hand washing and a better understanding of disease transmission and risk. ■

## Serum SARS-CoV-2 and Disease Severity

SOURCE: Hagman K, Hedenstierna M, Gille-Johnson P, et al. SARS-CoV-2 RNA in serum as predictor of severe outcome in COVID-19: A retrospective cohort study. *Clin Infect Dis* 2020; Aug. 28:ciaa1285.

Detection of SARS-CoV-2 ribonucleic acid (RNA) in serum has been postulated as an early marker of COVID-19 disease severity. Higher viral loads may suggest an inability to control viral replication with dissemination to other organs and higher organ burden, possibly leading to greater levels of inflammation and disease severity.

These authors at the Danderyd Hospital in Stockholm, Sweden, examined the relationship between SARS-CoV-2 RNA in serum on presentation to hospital and clinical outcome, as defined by disease progression to critical care and mortality. From April 10 to June 30, 2020, serum samples were collected within three days of hospitalization on 167 patients, and patients were followed for 28 days. The median date of sampling was one day after hospitalization, which corresponded to a median of 10 days after the onset of symptoms. No antivirals or chloroquine derivatives were used in these patients, although some of the patients were enrolled in a clinical trial of convalescent plasma. Disease progression was a composite of intensive care unit (ICU) care and mortality.

Using standard reverse-transcriptase polymerase chain reaction (PCR), SARS-CoV-2 RNA was detected in 61 patients (36.5%) at entry to the study. The median age of those with RNA-positive serum was significantly higher than for those with RNA-negative serum specimens (63 years vs. 53 years, respectively), and the proportion of those with positive RNA PCR in serum increased with age. Three patients with RNA-negative serum (2.8%) and 15 of those with RNA-positive serum (24.6%) died. Disease progression occurred in seven patients with RNA-negative serum (7%) compared with 34 of those with detectable SARS-CoV-2 RNA (44%). Multivariate analysis factoring in age, heart disease, hypertension, C-reactive protein level, and RNA positivity showed that only age and PCR positivity significantly correlated with disease severity and death. The hazard ratios for progression to critical care and all-cause mortality at day 28 were 7.2 (95% confidence interval [CI], 3.0-17) and 8.6 (95% CI, 2.4-30), respectively, for patients with positive serum PCR results compared with those with negative serum PCR.

The use of convalescent plasma did not appear to affect 28-day outcomes. Twenty-eight of 61 PCR-positive patients received convalescent plasma. The proportion of these who died among PCR-positive patients receiving convalescent plasma or not was 21.4 % vs. 27% ($P$ = NS). ■

## Natural History of Untreated Tuberculosis

SOURCE: Ragonnet R, Flegg JA, Brilleman SL, et al. Revising the natural history of pulmonary tuberculosis: A Bayesian estimation of natural recovery and mortality rates. *Clin Infect Dis* 2020; Aug. 7:ciaa602. [Online ahead of print].

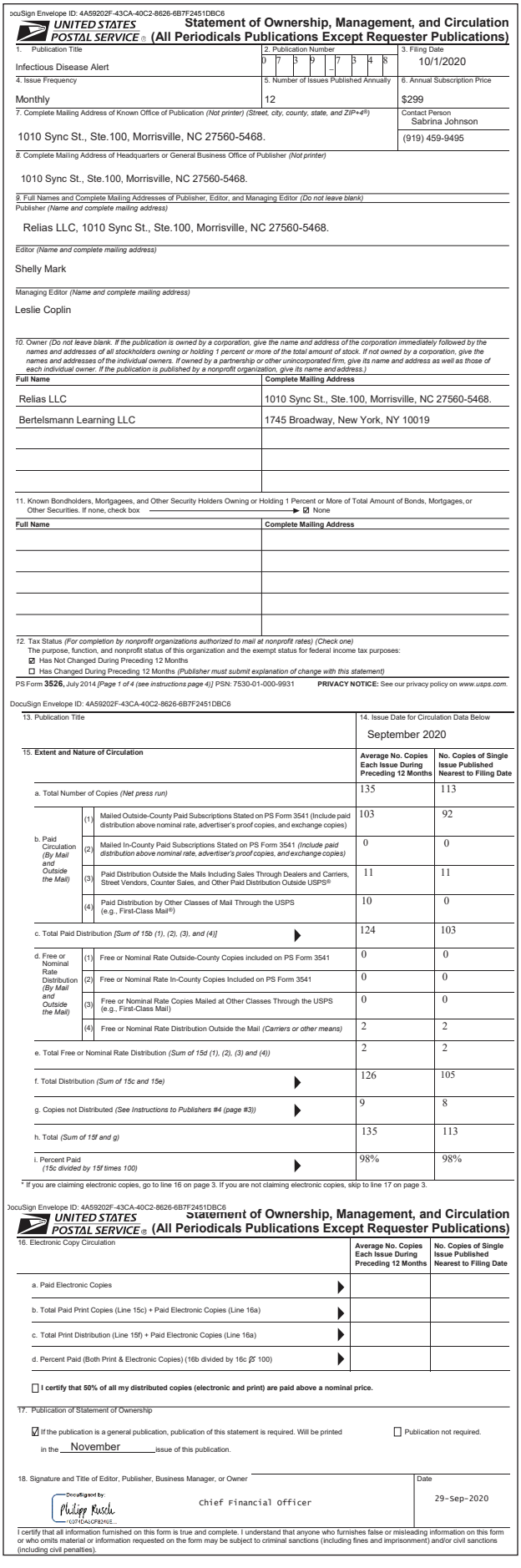
Characterizing the natural history of tuberculosis (TB), including the possibility of spontaneous recovery, disease chronicity and mortality, is important to the determination of worldwide TB

disease burden. Several modeling studies have been published, estimating the rates of these outcomes, largely based on historical pre-treatment data. True natural history studies are impossible to perform now, when all patients should receive treatment. One of the best studies of the natural history of untreated TB comes from a 2011 publication, which included 10-year case fatality rates for smear-positive (SP) and smear-negative (SN) pulmonary TB patients (70% and 20% mortality, respectively). However, the interpretation of these data, and their use in mathematical models, has been complicated by the inability to distinguish TB mortality from other causes of death.

These authors examined published literature for the natural history of TB before the advent of anti-tuberculous chemotherapy, identifying 64 cohorts of patients with pulmonary TB, many containing data on mortality. The size of the cohorts varied from as few as eight patients to 2,382 patients, with a median of 379 patients. All of the studies were from Western Europe, patients were followed for up to 31 years, and included six surveys of patients from sanitoriums, six officially notified patient cohorts, and three groups of hospitalized patients. There were 41 cohorts with SP patients and 23 cohorts with SN patients, although four of these latter cohorts reported incomplete data. Forty-seven of 64 cohorts (73%) included patients from sanitoriums and hospitals, with complete follow-up data for almost all of the patients. TB-driven mortality was separated out when possible from non-TB mortality.

The median estimates of TB-specific mortality rates for SP-pulmonary TB and SN-pulmonary TB patients were 0.389 $year^{-1}$ and 0.025 $year^{-1}$. The estimates for self-recovery were 0.231 $year^{-1}$ and 0.130 $year^{-1}$, respectively. With an estimated non-TB mortality rate of 0.014 $year^{-1}$, these rates correspond to an average duration of survival for untreated SP-TB of 1.57 years and for SN-TB of 5.35 years. There was considerable variation in the estimates of TB mortality among the cohorts, and hospitalized patients had the lowest rates of mortality.

An important finding from this newer analysis was the difference in outcomes between SP-TB patients and SN-TB patients, demonstrating the more acute and aggressive nature of SP pulmonary disease in the years before treatment. In contrast, patients with SN pulmonary disease lived four times longer, with a more indolent course. Earlier models underestimated the difference between these two groups. This also means that SN patients probably contributed as much to transmission risk as those with SP disease, since they lived longer with their infection.



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Of course, earlier TB data were based on the detection of acid-fast organisms on smear, since cultures were not invented until the 1930s. Both groups of SP and SN participants may have included patients with other diseases. As I recall from my earlier nontuberculous mycobacteria (NTM) reading, some of the SP patients may have had *M. avium* or *M. kansasii*, which would have been recognized only with appropriate in vitro animal studies demonstrating nonvirulence, which were seldom performed.

SN patients would have been detected clinically or radiographically, and may have had lung problems other than TB. A potential drawback from these earlier studies is the lack of data on sputum smear conversion, since patients may shift back and forth between being SP and SN. An important consideration when modeling disease burden is that the duration of survival in these studies was assessed from the time of diagnosis and not from the onset of symptoms. ■

## CME QUESTIONS

1. **Based on sound ethical principles, initial COVID-19 vaccines should be made most available to which of the following groups?**

   a. All people 65 years of age and older and individuals with complex medical conditions

   b. School children

   c. People in resource-limited countries

   d. Frontline healthcare workers, people living or working in high transmission settings, and medically vulnerable people

2. **By definition, which of the following is absent in patients with multisystem inflammatory syndrome in adults (MIS-A)?**

   a. Cardiac abnormalities

   b. Gastrointestinal symptoms

   c. Dermatologic manifestations

   d. Severe respiratory illness

3. **Which of the following is correct regarding corticosteroid use and risk of infection?**

   a. Short "bursts" of corticosteroid therapy (< 14 days) are associated with a significantly increased risk of sepsis.

   b. Chronic daily administration of < 5 mg prednisone equivalent to patients with rheumatoid arthritis receiving stable disease-modifying antirheumatic therapy (e.g., methotrexate) is not associated with an increased risk of infection.

   c. Chronic daily administration of 5 mg to 10 mg prednisone equivalent to patients with rheumatoid arthritis receiving stable disease-modifying antirheumatic therapy (e.g., methotrexate) is not associated with an increased risk of infection.

   d. Chronic daily administration of > 10 mg prednisone equivalent to patients with rheumatoid arthritis receiving stable disease-modifying antirheumatic therapy (e.g., methotrexate) is not associated with an increased risk of infection.

## CME OBJECTIVES

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

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.