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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

SARS-CoV-2 Antibodies and Multisystem Inflammatory Syndrome in Children

By Philip R. Fischer, MD, DTM&H

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SYNOPSIS: SARS-CoV-2-related multisystem inflammatory syndrome in children (MIS-C) can be severe and life-threatening. New data suggest that the degree of elevation of spike protein receptor-binding domain antibodies could serve as a diagnostic marker of MIS-C as well as point to potential pathogenic processes.

SOURCE: Rostad CA, Chahroudi A, Mantus G, et al. Quantitative SARS-CoV-2 serology in children with multisystem inflammatory syndrome (MIS-C). *Pediatrics* 2020;146:e2020018242.

SARS-CoV-2 infection often is asymptomatic or mild in children. However, some children go on to develop a Kawasaki disease-like condition with hemodynamic instability, cardiac dysfunction, and respiratory failure. The clinical features of this condition, now commonly termed multisystem inflammatory syndrome in children (MIS-C), have been described, but serologic correlates had not been described.

Thus, Rostad and colleagues measured various SARS-CoV-2-related antibodies in the serum of 10 children hospitalized with MIS-C, 10 children with symptomatic COVID-19 who did not meet Centers for Disease Control and Prevention criteria for having MIS-C, five children with Kawasaki disease (three with complete and two with incomplete Kawasaki disease), and four hospitalized control children in Atlanta from March to May 2020.

The median age of studied children was 8.5 years (interquartile range 6.5-12 years). The children with MIS-C were mostly boys, Black, previously healthy, and of normal body mass index. By contrast, most children with COVID-19 without MIS-C had an underlying medical comorbidity, and three of the 10 were immunocompromised due to chemotherapy for malignant disease.

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Infectious Disease [ALERT]

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Laboratory test features linked to having MIS-C included elevated D-dimer levels, lymphopenia, and thrombocytopenia. Gastrointestinal (GI) symptoms predominated at the time of diagnosis, but some children also had respiratory symptoms. Children with MIS-C were more likely than the others to require intensive care and to require vasodilator therapy for shock. All of the children with MIS-C survived with improvement in health, but two of the children with COVID-19 and cancer died of presumed bacterial sepsis.

All 10 children with MIS-C and nine of the 10 with COVID-19 had detectable immunoglobulin G (IgG) antibodies to SARS-CoV-2 spike protein receptor-binding domain (RBD). Children with Kawasaki disease and the control children did not have marked antibody elevations. RBD IgG levels were significantly higher in children with MIS-C than in the others ($P < 0.001$ for each group). RBD immunoglobulin M (IgM) levels were higher in MIS-C patients than in hospitalized controls but not in comparison to COVID-19 patients.

Neutralization titers to SARS-CoV-2 were found in 100% of MIS-C patients and in 30% of COVID-19 patients. SARS-CoV-2 full length spike and nucleocapsid antibody titers also were higher in children with MIS-C than in children with COVID-19 (and also higher than in Kawasaki and control patients).

RBD IgG antibody titers in children with MIS-C were positively correlated with erythrocyte sedimentation rates (but not peak C-reactive protein levels), total length of hospitalizations, and the duration of intensive care unit stays.

Rightly, the authors concluded that RBD IgG serological testing might helpfully differentiate patients with MIS-C from those with COVID-19 or Kawasaki disease. The degree of elevation of these antibody titers also was linked with an inflammatory marker and the duration of hospitalization and, thus, might be a predictive measure of disease severity and prognosis.

Interestingly, none of the MIS-C patients had a recent history of a respiratory and/or febrile illness (despite having SARS-CoV-2 antibodies), but two had positive polymerase chain reaction (PCR) tests for SARS-CoV-2 when they presented with MIS-C. It seems that MIS-C follows or is concurrent to SARS-CoV-2 infection, whether or not that infection caused symptoms prior to the onset of MIS-C.

■ COMMENTARY

The pathophysiology of COVID-19-related MIS-C is poorly understood, and it often is clinically challenging to differentiate this condition from "simple" COVID-19 and Kawasaki disease. The new data from Rostad and colleagues give clues to a possible pathophysiologic mechanism and provide potential help with diagnostic testing. In addition, these data raise hypothetical concern about the safety of some COVID-19 vaccines in children.

The pathophysiology of MIS-C is not clear, but the condition does seem to represent a hyperinflammatory response to SARS-CoV-2 infection. It could be that the development of higher RBD antibody titers with the initial SARS-CoV-2 infection could put some patients at greater risk of developing MIS-C. If this is the case, one might want to screen convalescent serum, when that is used therapeutically, to give serum with higher neutralizing antibody levels and lower RBD antibody levels.

Clinicians might want to measure RBD antibody titers in patients presenting with severe multisystem problems. This might help clarify whether the patient actually has MIS-C or not, and this might help prognosticate the severity of illness in those who do have MIS-C.

Various COVID-19 vaccines are being deployed around the world, but currently more for adults than for children. It is possible that children would be adequately protected and less at risk of MIS-C if the vaccine(s) used for children do not provoke strong anti-RBD responses. ■

ABSTRACT & COMMENTARY

Early Convalescent Plasma for Treatment of COVID-19 in Elderly Patients with Mild Symptoms

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: Administration of convalescent plasma obtained from survivors of COVID-19 within 72 hours of onset of mild symptoms in elderly patients with COVID-19 was associated with a significant reduction in the risk of development of severe respiratory disease.

SOURCE: Libster R, Pérez Marc G, Wappner D, et al; Fundación INFANT–COVID-19 Group. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med* 2021; Jan 6. doi: 10.1056/NEJMoa2033700. [Online ahead of print].

In this clinical trial performed in Argentina, 160 patients with COVID-19 underwent randomization to receive a single infusion of either convalescent plasma that had been obtained with high titers (> 1:1,000) of immunoglobulin G (IgG) antibody to SARS-CoV-2 spike protein from individuals who had recovered from COVID-19 or a normal saline placebo. Study entry required that patients were symptomatic for ≤ 72 hours and were either 65-74 years of age with one of a series of specified comorbid conditions or were > 75 years of age with or without a comorbid condition. There were several exclusion criteria, including, e.g., severe respiratory disease, primary hypogammaglobulinemia, lymphoproliferative disorders, cancer with treatment in the previous six months, immunosuppressive therapy, solid organ transplant, chronic liver or lung disease, and receipt of anticoagulants.

The primary endpoint of the trial was the development of severe respiratory disease, defined as a respiratory rate ≥ 30 breaths per minute, an oxygen saturation < 93% while breathing ambient air, or both. A power analysis had estimated a requirement to enroll a total of 210 patients to achieve an 80% power to detect a difference between treatment groups at an $\alpha = 0.05$. Enrollment was discontinued after only 76% of the target population was enrolled as the local epidemic waned.

The mean age of the cohort was 77.2 ± 8.6 years (55% were ≥ 75 years of age) and 60% were women; approximately four-fifths of the cohort had comorbidities. In an intent-to-treat analysis, severe respiratory disease occurred in 13 (16%) of 80 patients assigned convalescent plasma and 25 (31%) of 80 patients assigned placebo, resulting in a calculated relative risk of 0.52 (95% confidence interval [CI], 0.29 to 0.94; $P = 0.03$). This represented a 48% risk reduction and a number needed to treat of 7. In modified intent-to-treat analysis that excluded six patients who reached the primary end point prior to receiving their designated infusion, relative risk favoring plasma was 0.40 (95% CI, 0.20 to 0.81). The response was greater in those who received plasma with the highest antibody titers. No adverse reactions were observed.

■ COMMENTARY

This study provides evidence that a highly selected group of patients with COVID-19 benefit from receipt of convalescent plasma. These include patients with mild symptoms of no more than 72 hours duration who were > 75 years of age and/or 65-74 years of age with limited specified comorbidities. It excluded patients with a very large list of other comorbidities, a factor that significantly limits the applicability of the results.

The results also may be considered possibly surprising based on prior published experience. Thus, in a supplementary appendix, the authors listed five previous randomized controlled trials that enrolled between 81 and 333 patients and that failed to demonstrate benefit from administration of convalescent plasma in the treatment of patients with COVID-19. However, Libster and colleagues pointed out that those studies enrolled adults as young as 18 years of age and that the median duration of symptoms prior to enrollment in these studies ranged from eight to 30 days. In addition, the evaluation of convalescent plasma in COVID-19 patients admitted to intensive care as part of the REMAP-CAP adaptive trial was halted recently because of futility.

In contrast to these negative results, the apparent benefit of monoclonal antibodies, bamlanivimab as well as the combination of casirivimab and

imdevimab, is more modest than that seen with convalescent plasma in the study reviewed here. In their trials, however, they were administered to a population that was as young as 18 years of age, and could be affected by a variety of comorbidities. In addition, the participants received their infusions after a median duration of symptoms of 4.0 days and 3.0 days — meaning that more than half of the subjects would not have been eligible for the convalescent plasma study, in which the plasma was administered within 72 hours of symptom onset. Of note is that the emergency use authorizations for these monoclonals allow for infusion to patients with symptom durations as long as 10 days.

Thus, convalescent plasma with high IgG antibody titers should be considered for administration to patients who match the entry/exclusion criteria in the study by Libster and colleagues. Furthermore, their results may provide lessons for the use of monoclonals until there is more direct evidence related to the use of these products. Among these is that there is a greater likelihood of benefit the earlier the infusion is administered. This knowledge would be especially useful in circumstances of shortage, as currently exist. It also is apparent from the study evaluating casirivimab/imdevimab that patients who lack antibody at the time of intervention are most likely to benefit — but this would require the availability of an antibody test with rapid turnaround time.

Another factor that has not been evaluated in this context relates to the usual disappearance of viable (replication competent) SARS-CoV-2 after approximately eight days, at least in patients without severe immunocompromise. Presumably, antibody administration would have little or no benefit if the virus is no longer replicating, something that can be determined using a polymerase chain reaction (PCR) test specific for negative-strand ribonucleic acid (RNA). ■

ABSTRACT & COMMENTARY

Healthcare Workers with Antibody to SARS-CoV-2 Have Strong Protection Against Reinfection

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: A study of healthcare workers demonstrated that the presence of antibody to SARS-CoV-2 spike protein or to nucleocapsid provides strong protection against infection with this virus for up to six months.

SOURCE: Lumley SF, O'Donnell D, Stoesser NE, et al; Oxford University Hospitals Staff Testing Group. Antibody status and incidence of SARS-CoV-2 infection in health care workers. *N Engl J Med* 2020; Dec 23:NEJMoa2034545. doi: 10.1056/NEJMoa2034545. [Online ahead of print].

Lumley and colleagues at the Oxford University Hospitals prospectively evaluated the incidence of the occurrence of SARS-CoV-2 positive polymerase chain reaction (PCR) tests in healthcare workers (HCWs) who, at baseline, either had or lacked antibody to the virus to assess the protection provided by the presence of antibody.

At baseline, 11,364 (90.6%) of 12,541 HCWs had negative tests for the presence of immunoglobulin G (IgG) anti-spike antibody, while 1,177 (9.4%) were seropositive and another 88 seroconverted during the 31 weeks of the study. HCWs were followed for a median of 200 days after a negative test and 139 days after a positive test. Follow-up testing of the 11,364 HCWs who were seronegative for antibody to spike protein at baseline detected 223 who subsequently had a positive PCR, for an incidence of 1.09 per 10,000 days at risk. The positive PCR occurred in the presence and absence of symptoms in 123 (55.2%) and 100 (44.8%) subjects, respectively.

Among the 1,265 who were seropositive (including the 88 who first became seropositive after the baseline assessment), only two subsequently had a positive PCR test, each at a time when they were asymptomatic, for an incidence of 0.13 per 10,000 days at risk. Comparing those who were seropositive to those who were seronegative, the risk ratio for a subsequent positive PCR test was 0.12 (95% confidence interval [CI], 0.03 to 0.47; $P = 0.002$). There were no symptomatic PCR-confirmed infections in the

seropositive cohort, while, among the seronegatives, the incidence was 0.60 per 10,000 days at risk.

Similar risk ratio results were seen with analyses of anti-nucleocapsid IgG antibody. Confirming the protective role of antibodies, the incidence of occurrence of positive PCR tests was inversely correlated with the titers of antibody to the spike protein ($P < 0.001$). In fact, this protection extended to individuals who had detectable antibody but at levels too low to meet the threshold used to declare a test as positive.

■ COMMENTARY

This study confirms that the presence of antibody to SARS-CoV-2 as the result of natural infection is protective against subsequent infection, especially against symptomatic infections. This protective effect lasts at least six months, a finding consistent with recent evidence of the persistence of immunological memory for at least eight months.

These findings have important implications for understanding protection associated with COVID-19 vaccines. It also provides information that is valuable to the safety of HCWs with naturally acquired immunity as well as to their patients. The rare occurrence of a positive PCR test, however, indicates that protection is not complete (something already known from the very rare occurrence of reinfection in individuals who have recovered from COVID-19), and there is a potential danger that they may transmit infection even when they are asymptomatic. ■

ABSTRACT & COMMENTARY

Candidemia in the United States

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: Candidemia, a common bloodstream infection in the United States, is associated with high mortality. There is concern about increasing resistance to antifungals.

SOURCE: Tsay SV, Mu Y, Williams S, et al. Burden of candidemia in the United States, 2017. *Clin Infect Dis* 2020;71:e449-e453.

The Centers for Disease Control and Prevention (CDC) examined cases of *Candida* bloodstream infections using surveillance data for the year 2017 from the Emerging Infections Program (EIP) conducted in 45 counties with a total population of 17 million in nine states. The states represented were California, Colorado, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee. This program identified 1,226 cases of candidemia in 1,140 patients (taking into account recurrent episodes). Individuals > 65 years of age accounted for 41.5% of cases and had, by far, the highest incidence rate (20.1 per 100,000 persons). Blacks also were overrepresented, accounting of 31.6% of cases, with a rate of 12.3 per 100,000. All-cause in-hospital mortality was 25% (31% in those ≥ 65 years of age) and was 15% within seven days of the onset of candidemia.

Of 1,122 isolates analyzed at CDC, *Candida albicans* accounted for 38% and *Candida glabrata* for 30%, followed by *Candida parapsilosis* (14%) and *Candida tropicalis* (7%). Overall, 6% of *Candida* isolates were resistant to fluconazole, with variability by species: 0.5% in *C. albicans*, 7% in *C. glabrata*, and 9% in *C. parapsilosis*. Only 2% (mostly *C. glabrata*) were resistant to an echinocandin.

Based on these data, the authors estimated that 22,600 cases of candidemia occurred in the United States in 2017, with an incidence of 7.0 per 100,000 persons, with almost one-half of the cases occurring in individuals > 65 years of age and almost one-fourth occurring in Blacks. The geographic rates of candidemia ranged from a low of 5.9 cases per 100,000 in Pacific states to 7.7 and 7.9 per 100,000 in the South Atlantic and East South Central states, respectively.

■ COMMENTARY

These data point out the large burden of candidemia in the United States. It should be recognized that blood cultures are estimated to be positive in only approximately one-half of patients with invasive candidiasis.

The reason for the higher rates of candidema in South Atlantic and East South Central states may be related to the injection drug use epidemic as well as the excessive use of antibacterials in those states. The overall rates of resistance to fluconazole

and to echinocandins were relatively low, but, as pointed out by the authors, varied greatly among institutions. At Stanford in 2017, fluconazole resistance was identified in 3% of *C. albicans*, 14% of *C. glabrata*, 15% of *C. tropicalis*, and 0% of *C. parapsilosis*. The last is quite different from the 9% recorded in the CDC study. The only resistance to an echinocandin (caspofungin) noted among these four species at Stanford was a 7% incidence of resistance of *C. glabrata* to caspofungin. Given the changing demographics of the country, the incidence of candidemia (and other forms of invasive candidiasis) is likely to increase, as is the incidence of antifungal resistance, including to echinocandins.

Among *Candida* resistant to antifungals there is, of course, great concern regarding multidrug-resistant *Candida auris*. This organism first appeared in the United States in the middle of 2015 and, by early 2019, had been identified as the cause of > 300 bloodstream infections. It can be anticipated that this number is increasing. ■

ABSTRACT & COMMENTARY

Malaria and Anemia — Chemoprophylaxis Helps

By Philip R. Fischer, MD, DTM&H

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SYNOPSIS: For young children in Africa who return home after hospitalization for severe anemia, monthly long-acting malaria prophylaxis can reduce the rates of readmission and death during the three months following hospitalization.

SOURCE: Kwambai TK, Dhabangi A, Idro R, et al. Malaria chemoprevention in the postdischarge management of severe anemia. *N Engl J Med* 2020;383:2242-2254.

Realizing that part of the morbidity and mortality associated with severe anemia occurs during the months following initial inpatient care, Kwambai and colleagues in Kenya and Uganda studied the effect of post-discharge monthly courses of dihydroartemisinin–piperaquine on hospital readmission rates and death rates during the six months after the initial admission.

Preschool-age children hospitalized for severe anemia (hemoglobin less than 5 gm/dL) without concurrent sickle cell disease or cancer were randomized to receive either placebo or dihydroartemisinin-piperaquine as a three-day treatment course two, six, and 10 weeks after the initial admission. (Each course of this treatment is known to provide four weeks of malaria prevention.) This was a double-blind, placebo-controlled trial. Iron supplements (2 mg/kg/day) also were given for the first four weeks. Bed net use was advised. Outcomes were followed for six months.

From May 2016 through May 2018, 1,049 children were included in the study. The anemia was thought to be caused by malaria in more than three-fourths of the study participants. Overall, 97% were compliant with the study treatment, and 7% of participants were lost to follow-up. There were no serious adverse events attributed to the intervention, but asymptomatic prolongation of the QT interval was noted in the medication-treated children.

Thirty percent of children were readmitted and/or died during the six months of follow-up: 26% of the chemoprophylaxis group and 34% of the placebo group. There were 31 deaths in the placebo group and 12 in the treatment group. The rate of readmission or death was 35% lower in the chemoprophylaxis group ($P < 0.001$) than in the placebo group. The difference in both readmissions and deaths was significant during the first three months but not during the second half of the six-month follow-up period.

The authors stated that it is not known if ongoing treatment beyond 10 weeks would have extended the benefit. Similarly, they do not know if further iron supplementation or more aggressive mosquito avoidance measures might have further reduced the risks of subsequent readmission and death.

■ COMMENTARY

Malaria still is a major killer, with more than 400,000 deaths globally per year.[1] Children in sub-Saharan Africa are disproportionately affected.[1] During the years I worked in a rural medical center in incompletely resourced central Africa, we frequently saw preschool-age children with severe anemia. Most

days, at least one child would present with high fever, fatigue, tachycardia, tachypnea, and pallor. Hemoglobin levels were in the range of 3 gm/dL to 5 gm/dL. Malaria smears were strongly positive. We would treat the malaria and provide careful blood transfusions. For the short-term, the children did well. Unfortunately, though, some of these children returned with subsequent similar bouts of malaria with severe anemia.

Interestingly, these children were rarely jaundiced. Although the malaria-induced hemolysis was enough to tip the children into enough anemia to cause mild heart failure, there was not enough hemolysis to cause jaundice. We surveyed healthy children in the community and found that the mean hemoglobin level was about 8 gm/dL and that iron deficiency was common. It seemed that many seemingly asymptomatic children had chronic iron deficiency anemia and then got malaria with high fever and enough hemolysis to push them into cardiovascular decompensation. To prevent future episodes of severe decompensation and to treat the underlying nutritional deficiency, we gave iron supplements. Again, this seemed to work well — until malaria recurred.

Of course, there is an interaction between *Plasmodium* parasites and iron in children. Iron supplements seem to help foster parasite multiplication before they restore iron sufficiency.[2] Thus, it is important to make sure that children in malaria-endemic areas who receive iron also are using bed nets and trying to avoid mosquito bites. And, as with severe acute malnutrition, new iron supplementation can be delayed until infections are managed and initial nutritional rehabilitation is established.[3]

Now, though, Kwambai and colleagues extend our two-pronged battle against both malaria and anemia a step further. They clearly showed that adding antimalarial chemoprophylaxis to the post-transfusion regimen in children with severe malarial anemia is effective in reducing hospitalizations and death during the subsequent three months.

For those working in or advising about the care of children in sub-Saharan Africa, attention must be given to managing both malaria and anemia. Children hospitalized with severe anemia should receive the benefit not only of iron supplementation but also of prophylactic malaria medication. Malaria chemoprophylaxis after acute malaria treatment and blood transfusion reduces the risks of death and readmission. ■

REFERENCES

1. World Health Organization. Malaria. https://www.who.int/news-room/fact-sheets/detail/malaria
2. Moya-Alvarez V, Bodeau-Livinec F, Cot M. Iron and malaria: A dangerous liaison? *Nutr Rev* 2016;74:612-623.
3. Ashworth A, Khanum S, Jackson A, Schofield C. Guidelines for the inpatient treatment of severely malnourished children. World Health Organization 2013: 16. https://www.who.int/nutrition/publications/guide_inpatient_text.pdf

ABSTRACT & COMMENTARY

Does the Addition of IV Metronidazole Improve Outcomes of Severe *Clostridioides difficile* Infection?

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

SYNOPSIS: These studies indicate that the addition of intravenously administered metronidazole in the treatment of severe *Clostridioides difficile* infection is unwarranted.

SOURCES: Wang Y, Schluger A, Li J, et al. Does addition of intravenous metronidazole to oral vancomycin improve outcomes in *Clostridioides difficile* infection? *Clin Infect Dis* 2020;71:2414-2420.

Vega AD, Heil EL, Blackman AL, et al. Evaluation of addition of intravenous metronidazole to oral vancomycin therapy in critically ill patients with non-fulminant severe *Clostridioides difficile* infection. *Pharmacotherapy* 2020;40:398-407.

Wang and colleagues performed a retrospective study at two centers designed to examine the relative benefit of the addition of intravenously administered metronidazole to orally administered vancomycin in adult inpatients with *Clostridioides difficile* infection (CDI). Treatment must have been

initiated within a four-day window (two days before or after) of a positive test for *C. difficile*. The primary outcome was a composite of the occurrence of death or colectomy within the 90 days after the positive test.

The total cohort consisted of 2,114 patients: 1,121 who received vancomycin monotherapy and 993 who received combination therapy. Using the Infectious Diseases Society of America (IDSA) criteria, CDI was classified as non-severe in 34%, severe in 41%, and fulminant in 25% (hypotension accounted for this designation in most cases). As expected, those who received combination treatment had a greater severity of illness.

The primary outcome occurred in 23% of the entire cohort, with death in 1% and colectomy in 22%. In addition, recurrence subsequently occurred in 11% of survivors. In a crude analysis, death occurred significantly more frequently in those who received vancomycin alone. However, with adjustment for disease severity, there was no association between combination therapy and 90-day death or colectomy (adjusted odds ratio, 1.07; 95% confidence interval [CI], 0.79 to 1.45). Neither stratifying by severity (fulminant vs. non-fulminant) nor restricting the analysis to intensive care unit (ICU) patients changed the finding of a lack of significant relative benefit from combination therapy.

In a smaller study, Vega and colleagues examined the cases of 138 ICU patients with severe but non-fulminant CDI, 60 (43.5%) of whom received combination therapy. Although overall mortality proved to be higher in those receiving both drugs, the 30-day mortality rate in the monotherapy arm (12.8%) did not significantly differ from that in the group that received combination therapy (18.3%; $P = 0.371$). A subset analysis with matching by APACHE-II score also found no significant difference.

■ COMMENTARY

Current IDSA/Society for Healthcare Epidemiology of American (SHEA) guidelines (which are under revision) call for the addition of intravenous (IV) metronidazole to oral vancomycin in the treatment of patients with fulminant CDI as defined by the presence of hypotension, ileus, or megacolon. In contrast to earlier studies on which this recommendation rested, the results of more recent studies have been inconclusive or negative with regard to the benefit of such combination therapy.

Wang et al pointed out that vancomycin, to which *C. difficile* is very rarely resistant, achieves enormous concentration in the fecal stream, even in the presence of ileus. In contrast, the metronidazole concentration achieved after IV administration is quite modest. Furthermore, the efficacy of metronidazole given alone is minimal, and its presence likely adds little or nothing to vancomycin.

The authors concluded that the use of combination therapy "merits reconsideration." I think they are being overly polite. Let's wait and see what IDSA/SHEA say. ■

ABSTRACT & COMMENTARY

Neurotropism of COVID-19: What Is New?

By Alexander E. Merkler, MD

Assistant Professor of Neurology and Neuroscience, Weill Cornell Medical College, and Assistant Attending Neurologist, New York-Presbyterian Hospital

SYNOPSIS: SARS-CoV-2 may gain access to the brain via the olfactory epithelium. The olfactory epithelium and bulbs may serve as an entry point for SARS-CoV-2 infection into the central nervous system.

SOURCES: Matschke J, Lutgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: A post-mortem case series. *Lancet Neurol* 2020;19:919-929.

Chiesa-Estomba CM, Lechien JR, Radulesco T, et al. Patterns of smell recovery in 751 patients affected by the COVID-19 outbreak. *Eur J Neurol* 2020;27:2318-2321.

The COVID-19 worldwide pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Neurological involvement in COVID-19 is common, occurring in approximately one-third of patients hospitalized with COVID-19.[1] Both the central and peripheral nervous system can

be affected. One major area of uncertainty is the route that SARS-CoV-2 uses to gain access to the central nervous system (CNS).

In the current study, Matschke et al evaluated the neuropathological features in the brains of patients with COVID-19 who died in Hamburg, Germany.[2] Forty-three patients were included in the analysis. The median age was 76 years and 37% were women; the cause of death was attributed to respiratory illness in the majority of individuals. SARS-CoV-2 was detected via polymerase chain reaction (PCR) in 21 (53%) of the 40 patients with adequate samples.

In addition, there was evidence for an inflammatory response in all examined brains, with prominent involvement of the brainstem. Interestingly, the neuropathological evidence of SARS-CoV-2 was not associated with the severity of the neuroinflammatory response. Finally, evidence of acute cerebral infarction was found in 14% of the patients, consistent with prior reports suggesting that COVID-19 is associated with a heightened risk of stroke.[3] Whether SARS-CoV-2 causes direct neurological injury, or whether SARS-CoV-2 leads to a neuroinflammatory response remains to be determined and requires further study.

How does SARS-CoV-2 gain access to the CNS? Whether SARS-CoV-2 gains entry via neurotropism and direct invasion or, rather, indirectly through systemic SARS-CoV-2 infection remains uncertain. In data from Wuhan, China, olfactory and gustatory dysfunction was reported in 5% of hospitalized patients with COVID-19.[1] Since then, other reports have found that olfactory and gustatory dysfunction is common in non-severe cases of patients infected with SARS-CoV-2 and can be the initial or only symptom of COVID-19 disease.[4] The current study by Chiesa-Estomba et al enrolled ambulatory and hospitalized patients with confirmed SARS-CoV-2 via nasal PCR or serum immunoglobulin G/immunoglobulin M.[5] Data regarding olfactory dysfunction was acquired via completion of survey responses. Overall, among the 751 participants with COVID-19 who completed the study, olfactory dysfunction was reported in 83%. After a mean follow up of 48 ± 7 days, 37% reported persistent subjective loss of smell, 14% reported partial recovery, and 49% reported complete recovery. The mean duration of olfactory dysfunction was 10 ± 6 days among the participants with complete olfactory recovery.

■ COMMENTARY

Given the frequency of olfactory dysfunction in COVID-19, the olfactory epithelium has been suggested to represent a gateway to the CNS for SARS-CoV-2. Cells of the olfactory epithelium express angiotensin converting enzyme 2 (ACE2) receptor, which may allow for access of SARS-CoV-2 into the olfactory bulbs and, subsequently, the CNS.[6] Given the density of SARS-CoV-2 in the nares (via inhalation of the virus), this may explain why olfactory dysfunction is so prevalent in patients with COVID-19. ■

REFERENCES

1. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;77:683-690.
2. Matschke J, Lutgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: A post-mortem case series. *Lancet Neurol* 2020;19:919-929.
3. Merkler AE, Parikh NS, Mir S, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. *JAMA Neurol* 2020;77:1-7.
4. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): A multicenter European study. *Eur Arch Otorhinolaryngol* 2020;277:2251-2261.
5. Chiesa-Estomba CM, Lechien JR, Radulesco T, et al. Patterns of smell recovery in 751 patients affected by the COVID-19 outbreak. *Eur J Neurol* 2020;11:2318-2321.
6. Bilinska K, Jakubowska P, Von Bartheld CS, Butowt R. Expression of the SARS-CoV-2 entry proteins, ACE2 and TMPRSS2, in cells of the olfactory epithelium: Identification of cell types and trends with age. *ACS Chem Neurosci* 2020;11:1555-1562.

Updates

By Carol A. Kemper, MD, FACP

Excess Deaths During COVID-19

SOURCE: Rossen LM, Branum AM, Ahmad FB, et al. Excess deaths associated with COVID-19, by age and race and ethnicity — United States, January 26-October 3, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69: 1522-1527.

Skeptics have expressed concern that mortality from COVID-19 infection is being overestimated or worse, manipulated. Compared with previous years, it is clear from national data that more people in the United States have died this year than anticipated — and not just older patients, but younger age groups have been disproportionately affected.

The measurement of excess deaths, as defined by the number of persons dying from all causes in excess of that anticipated for a given place and time, is useful when questions have been raised about the attribution of death to a given cause — or, in this case, the overall impact of COVID-19 on death rates in the United States. Some of this could be due to unrecognized COVID-19 infection or an indirect effect of the pandemic on the healthcare system and the ability to receive care for other reasons.

[Excess deaths reached their highest points during the weeks ending April 11 and Aug. 8, 2020.]

Mortality data from the Centers for Disease Control and Prevention's National Viral Statistics System was used to examine differences in the number of deaths as defined by age and ethnicity, compared with the same weeks from 2015-2019. The percentage of excess deaths from all causes, as well as that from all deaths excluding that attributed to COVID-19, were estimated. (Expected numbers of deaths were estimated using over-dispersed Poisson regression models, accounting for seasonal trends, and also weighted for possible incomplete reporting in more recent weeks).

Compared with death data for the same weeks from prior years, nearly 300,000 excess deaths have occurred in the United States between the weeks ending Jan. 26 through Oct. 3, 2020. Two-thirds were attributed to COVID-19 (n = 198,081); the remaining deaths were largely attributed to vascular events, respiratory disease, and dementia/Alzheimer's.

Excess deaths reached their highest points during the weeks ending April 11 and Aug. 8, 2020. As imagined, the lowest number of excess deaths occurred in the youngest age group (< 25 years), and the highest number of excess deaths occurred in the oldest age group (75-84 years). However, the greatest percentage change in unanticipated deaths was experienced in those 25-44 years of age (26.5%). The percentage of excess deaths in 2020 compared with averages for the previous five years for other age groups was: 14.4% for ages 45-64 years, 24.1% for ages 65-74 years, 21.5% for ages 75-84 years, and 14.7% for ages > 85 years. The greatest percentage difference in excess deaths occurred in Latinos (53.6%), followed by Asians (36.6%), Blacks (34.6%), and American Indian/Native Americans (28.9%). In contrast, the percentage of excess deaths in whites was 11.9%. This finding is consistent with reported disparities in COVID-19 deaths in Latinos and other minorities.

Subclinical Influenza Infection in Healthcare Workers

SOURCE: Benet T, Amour S, Valette M, et al. Incidence of asymptomatic and symptomatic influenza among healthcare workers: A multicenter prospective cohort study. *Clin Infect Dis* 2020; Aug 4. doi:10.1093/cid/ciaa1109

It happens every year: Patients in the hospital for other reasons suddenly develop a fever and test positive for influenza (or respiratory syncytial virus or other viral illness). Despite all precautions, influenza vaccination, handwashing campaigns, and messaging to staff not to come to work with respiratory symptoms, healthcare workers (HCWs) are an important source of nosocomial influenza and respiratory infection. And now it is happening with COVID-19 — employees with sniffles come to work, thinking they "only have a cold," only to test positive for SARS-CoV-2.

These authors demonstrated just how common subclinical influenza really is in HCWs. A total of 278 HCWs providing active care at five French hospitals were enrolled during the 2016-2017 winter

season. Participants maintained a daily diary of symptoms and were seen for physical examination the first time in October through December before the beginning of the flu season, again in January during peak flu season, and then approximately three weeks following their second visit. Nasopharyngeal swabs for influenza PCR (Virocult) and serologies by hemagglutination inhibition (IHA) for influenza A H3N2- and B Victoria lineage B/Brisbane/60/2008-specific antibodies were obtained. In the event of symptoms, an additional visit with these tests was performed. The median age of participants was 36 years and 84% were female. Vaccine coverage was 42% for 2015-2016 and 49.6% for 2016-2017. Pauci-symptomatic infection was defined as the presence of one or more signs or symptoms for more than one day, with no fever (< 37.8˚F), or the absence of cough and sore throat, whereas symptomatic influenza was defined as fever ≥ 37.8˚F with either cough or sore throat.

Sixty-two participants developed influenza infection during the five-month study, with a cumulative incidence of 22.3%. Impressively, 46.8% and 41.9% of these were asymptomatic and pauci-symptomatic, respectively, while only 11.3% developed more classic symptoms. Fever occurred in less than 10% of cases. At the second evaluation in January, people with confirmed influenza reported runny nose (68%), cough (64%), and headache (56%). At the third evaluation, those with confirmed influenza reported runny nose (55%), cough (45%), and headache (36%).

The cumulative incidence of influenza infection did not appear to differ between those who received the 2016-2017 influenza vaccination and those who did not (20.3% vs. 24.3%, $P = 0.38$), although receipt of the 2015-2016 influenza vaccination was protective (16% vs. 27%). Working in a nursing capacity increased the risk of pauci-symptomatic or symptomatic influenza. However, work in the intensive care unit (ICU) setting or the presence of three or more adults in the home was associated with an increased risk of asymptomatic infection.

Nearly nine of 10 hospital staff with confirmed influenza had subclinical infection — and half of these were entirely asymptomatic. Symptoms in 42% were atypical, with at most minor sniffles, headache, or sore throat. Attempts to keep such minimally symptomatic HCWs out of the hospital has been challenging. As our emergency room medical director said the other day, physicians will still come to work with a runny nose — they are just too important and we do not have sufficient staff to keep everyone home with a cold. Although little can be done about asymptomatic infection, we must have some way to rapidly screen minimally symptomatic employees for subclinical serious infections, such as the flu or COVID-19.

Compression Garments Effective in Reducing Cellulitis

SOURCE: Webb E, Neeman T, Bowden FJ, et al. Compression therapy to prevent recurrent cellulitis of the leg. *N Engl J Med* 2020;363:630-639.

This single-site, nonblinded, randomized study examined the benefit of compression garments in patients with lower extremity edema at risk for cellulitis. Eligible patients had significant edema for more than three months in one or both legs, and a history of two or more episodes of cellulitis in the same leg within the previous two years. They could not be using compression garments already for more than four days per week. Patients who were end-of-life or immunosuppressed were excluded.

Participants were assigned to wear compression garments throughout the day, every day. The garments generally consisted of knee-high stockings including the foot (with or without the toes) or leg and foot wraps. Participants were followed every six months for up to three years. Control patients who developed cellulitis were crossed over to the compression therapy group. Clinical characteristics were similar between the two groups at entry to the study. A total of 84 participants were enrolled in study, including 41 in the compression group. During the study, 78% of participants in the compression group reported wearing their compression stockings or wraps five or more days per week, and 88% reported using them at least four days per week.

The trial was stopped prematurely when a large difference in outcomes between the two groups was recognized. At the time the study was stopped, 23 episodes of cellulitis had occurred, including six (15%) in the compression therapy group and 17 (40%) in the control group ($P = 0.002$). Three patients in the compression group (7%) and six patients in the control group (14%) required hospitalization. Three patients died (one in the compression group and two in the control group), and one in each group developed wound infection. Two patients in each group were receiving prophylactic antibacterials at the time of study entry, which were continued. The median duration of follow-up was 209 days in the compression group and 77 days in the control group — simply because patients were removed from the control group when they developed cellulitis. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following is correct regarding the trial of convalescent plasma treatment of patients with COVID-19 by Libster and colleagues?

a. It was most effective in patients receiving mechanical ventilation.

b. It was most effective in patients with symptoms for more than five days.

c. Plasma with high antibody titer to SARS-CoV-2 spike protein were more effective than those with low titer.

d. It was most effective in patients 35-65 years of age.

2. In the study of candidemia in the United States in 2017, which species had the highest frequency of resistance to fluconazole nationally?

a. *Candida tropicalis*

b. *Candida parapsilosis*

c. *Candida glabrata*

d. *Candida albicans*

3. Which of the following is true regarding the treatment of severe *Clostridioides difficile* infection based the results of the study by Wang and colleagues?

a. The addition of intravenous metronidazole to oral vancomycin improved outcomes.

b. Metronidazole given intravenously was as effective as orally administered vancomycin.

c. The addition of intravenous metronidazole to oral vancomycin did not significantly improve outcomes when compared to oral vancomycin alone.

d. The combination of metronidazole with vancomycin results in a strong drug-drug pharmacokinetic interaction that precludes the use of the two together.

4. A 42-year-old woman develops the inability to smell. She is afebrile and without other symptoms. She is evaluated by an otorhinolaryngologist and found to be positive for SARS-CoV-2. What is her prognosis?

a. Her sense of smell should improve or resolve in the ensuing months.

b. Her sense of smell is unlikely to improve or resolve in the ensuing months.

c. She likely will develop a stroke in the ensuing months.

d. She likely will develop other cranial neuropathies in the ensuing months.

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.