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COVID–19
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Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin, a phase 2 randomized trial[1]

An open-label, randomized, phase 2 trial examined the effect of a triple combination regimen of interferon beta-1b, lopinavir plus ritonavir, and ribavirin, compared with lopinavir plus ritonavir alone. The investigators enrolled 127 patients with COVID-19 admitted to six hospitals in Hong Kong. On average, treatment was started on day five of symptoms, which is earlier than most previous trials. Overall symptom level was mild to moderate with only five patients requiring the ICU and only one intubated, and no mortality observed in the trial. The primary endpoint was time to negative nasopharyngeal swab for SARS-CoV-2 PCR and secondary endpoints were time to symptom resolution and hospital length of stay. Triple therapy was associated with a significant reduction in the duration of viral shedding (time to negative nasopharyngeal swab seven days in the combination group vs. 12 days in the control group). Symptom alleviation was also shorter with triple therapy (4 days vs. 8 days), and duration of hospital stay (9–0 days vs. 14–5 days). This significant difference was sustained in a subgroup analysis of patients who were enrolled within less than seven days of symptom onset but not in the subgroup of patients enrolled later than seven days from symptom onset. This along with the early time of enrollment may be important points. Multiple trials of various agents which failed to show benefit enrolled patients later in their disease course, at a time when much of the viral load may have cleared and the ongoing symptoms were possibly related to cytokine storm and not ongoing viral replication. Although only a small phase 2 trial, these encouraging early results suggest the need for a larger phase 3 trial as well as trials with other antiviral therapies beginning earlier in the disease course.

Skin manifestations vary with COVID-19 infections

Since the onset of the COVID-19 pandemic, clinical manifestations of the disease have been reported as single cases and larger case series. The dermatologic features of COVID-19 were recently characterized from a cohort of 375 patients from Spain with suspected or confirmed SARS-CoV-2 and skin findings.[2] The authors created five categories of skin lesions:

- Acral areas of erythema with vesicles or pustules (pseudo-chilblain) affected 19% of patients. Lesions could be itchy or painful and tended to be asymmetrical.
- Vesicular eruptions affected 9%. Vesicles could appear on trunk and/or limbs, may have hemorrhagic content, and could become large or diffuse.
- Urticarial lesions affected 19%. Mostly lesions distributed on trunk, but could be dispersed or only on the palms.
- Maculopapular eruptions affected 47%. Some were described as similar to pityriasis rosea in appearance. Purpura could also be present.
- Livedo reticularis (a mottled discoloration of the skin in a reticular pattern), or necrosis affected 6%. These patients had different degrees of vascular disease causing areas of truncal or acral ischemia.

The vesicular eruptions tended to present early in the course of the disease; the pseudo-chilblain appeared late in the disease in this series. Other publications have found a chilblains-like rash as the initial feature of SARS-CoV-2 infection.[3] The remaining skin manifestations appear as the other symptoms of COVID-19 evolve.

Skin findings are characterized by other published reports as well. After excluding patients who had recently started a new medication, 18 (20.4%) of 88 hospitalized patients had cutaneous manifestations. Skin findings developed with the onset of typical COVID-19 symptoms (8 patients) or after hospitalization (10 patients) and appeared similar to skin findings with other common viral infections, including erythematous rash (14 patients), urticaria (3 patients), and chickenpox-like vesicles (1 patient).[4]

Lastly, two patients with COVID-19 presented with transient livedo reticularis[5] and a third was initially misdiagnosed as dengue fever[6] after presenting with a rash and petechiae typical of dengue. Laboratory testing was not published, but a transient microthrombotic disorder was hypothesized as the cause of livedo reticularis. Disseminated intravascular coagulation (DIC) was demonstrated in four of seven critically ill patients with COVID-19 and signs of acro-ischemia, including finger and toe cyanosis, skin bulla, and dry gangrene.[7]

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EDUCATIONAL FORUM

Gastrointestinal symptoms in COVID-19 infection[8]

To date, the only review of GI symptoms in COVID-19 infection was a population of patients in China. That study showed that nausea and vomiting were seen in <1% of patients, with diarrhea occurring more frequently. As we gain experience in managing patients in the United States, anorexia and nausea have emerged as frequent symptoms. Last week, a study was pre-published in gastroenterology. It looked at a U.S. cohort of 318 patients with confirmed infection, hospitalized at one of nine Massachusetts hospitals. At presentation 61% of patients had at least one GI symptom. Anorexia and diarrhea were each seen in about a third of patients, and nausea was seen in about a quarter, with vomiting seen in 15%. GI symptoms were the predominant presenting complaint in 20% of patients and the initial presenting complaint in 14%. Other than the above GI symptoms, the cohort resembled those patients without GI symptoms in terms of severity of illness, laboratory studies and clinical course. Overall, these symptoms resembled those reported in the series from China with the exception that vomiting was present in 15% of patients in the U.S. series.

Are children less likely to transmit COVID-19?

In a recent publication, investigators performed a series of mathematical models to investigate the potential differences in transmission of COVID-19 by age and the effects of school contacts on the epidemic spread of the infection.[9] The study used contact data collected from Wuhan and Shanghai before and during the outbreak in China. The number of person-to-person contacts was significantly reduced during the outbreak period, from an average of 14.6 to 2 contacts per day in Wuhan and 18.8 to 2.3 per day in Shanghai. The reduction in contacts was present in all age groups. Most contacts during the outbreak consisted of other household members.

Next, COVID-19 contact tracing information was used to analyze potential differences in infection susceptibility by age. The investigators found that SARS-CoV-2 infections appeared to increase with age. Younger individuals (0–14 years) had a significantly lower infection risk than older individuals (15–64 years) with an odds ratio of 0.34, and the oldest age group (65 years and older) had the highest infection risk.

Lastly, the modeling was applied to the effects of school closure during the pandemic. The basic reproduction number (R_0) represents the average number of infections caused by an index case in a fully susceptible population. R_0 values for COVID-19 have been estimated at 2 to 3.5, meaning that with an R_0 of 2, one person with the infection would go on to infect an average of 2 other people. Modeling indicated that limiting contact patterns to school-aged children during school vacations would interrupt overall transmission and reduce the R_0 down to 1.5, and removing all school contacts would further interrupt transmission and reduce the R_0 down to 1.2. The investigators concluded that although school closures cannot halt transmission of COVID-19 on their own, they can reduce peak incidence by 40–60% and delay progression of the epidemic.

Importantly, their modeling used the lower infection risk in children (odds ratio 3.4). But others have found no differences in infections with SARS-CoV-2 based on age.[10,11] Using a screening population, Jones and colleagues showed that infected children probably have similar viral loads as infected adults, based on RT-PCR.[11] Since virus concentration in the respiratory tract correlates with infectivity, transmission of the virus would be similar in children and adults. If true, school-aged contacts would have a similar effect as adult contacts on viral transmission, and school closures could have a larger effect on delaying the epidemic.

Given the current considerations for reopening schools in many districts across the United States, close monitoring (and more research) is recommended to prevent a large surge of new COVID-19 cases.

Hyperinflammatory shock in children and a possible association with COVID-19

A national alert was sounded when a cluster of eight pediatric patients presented to intensive care in London, UK with signs and symptoms of atypical Kawasaki disease, Kawasaki disease shock syndrome, or toxic shock syndrome over a 10-day period.[12] The typical number had been one to two cases per week. Four of the children had known family exposure to COVID-19. Initial testing for SARS-CoV-2 from broncho-alveolar lavage or nasopharyngeal aspirate was negative in all patients. Following PICU discharge, two patients subsequently tested positive (one of whom had died). One child was positive for adenovirus and human endogenous retrovirus.

Clinical presentations were similar with fever, rash, conjunctivitis, peripheral edema, extremity pain and gastrointestinal symptoms. All patients received intravenous immunoglobulin; six received aspirin. Although most did not develop respiratory involvement, mechanical ventilation was needed for cardiovascular stabilization in seven patients.

Since submission of the brief report, 12 more pediatric patients presented with similar findings, the first 10 (including the original eight from this report) were found to have SARS-CoV-2 antibodies. The authors suggest an association between SARS-CoV-2 and Kawasaki disease shock syndrome. Details about the SARS-CoV-2 antibody were not provided, including when the antibody was detected during the course of illness or recovery, before or after intravenous immunoglobulin. Additionally, across the United States, there have been 85 similar cases reported. Details of these cases have not yet been systematically described, therefore it is not yet known if these cases would meet the above clinical description. However, many of these children have tested positive for COVID-19.[13]

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More infectious strain of the novel coronavirus dominant in most US locales[14,15]

The novel coronavirus spike protein mediates human infection and is prone to mutation — so far 13 discrete mutations have been identified and tracked over time. Early in the epidemic, a mutation called D614 was predominant in China, Europe and the United States. The presence of a new strain labeled G614 was first reported in Europe and North America in early March, and by the end of March is now the dominant form of infection across both continents.

Clinically, the G614 strain is more transmissible and may lead to higher viral loads but so far does not appear to impact hospitalization or mortality rates. This temporal change in viral transmissibility is independent of the impacts of social policies and human movement and may be impacting models that are now projecting more infections and deaths than they were a month ago.

The incredibly rapid speed with which this new mutation has overtaken the less fit strains across several continents is notable and may hold worrisome implications for vaccine development. Significant and rapid mutation of other viruses (notably influenza) can render vaccines less effective over time.

Development of a monoclonal antibody to spike protein of potential therapeutic use[16]

Ending on a more positive note, a virology group in the Netherlands published a study in Nature Communications looking at an engineered human monoclonal antibody which neutralized the SARS-CoV-2 virus. The antibody binds to a conserved epitope (i.e., one that doesn't frequently mutate and in fact is also present in SARS-CoV-1). This is the first report of a human monoclonal antibody that neutralizes SARS-CoV-2. Neutralizing antibodies can alter the course of infection in the infected host supporting virus clearance or protect an uninfected host that is exposed to the virus. Over the past two decades, we have developed the technology to rapidly develop and scale human monoclonal antibodies for use in a variety of autoimmune diseases. These molecules have proven both safe and effective for a wide range of diseases. It is possible that this approach could be used as a treatment or prophylactic therapy for COVID-19 infection. A similar approach had been in development for both SARS and MERS, but these were never fully developed as these epidemics spontaneously subsided. Several pharma companies are actively working on this approach which could offer the potential to prevent and/or treat COVID-19, and possibly also other future emerging diseases in humans caused by similar viruses. It is anticipated that clinical trials could begin in the next several months.

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Kenneth Roy Cohen, MD, FACP | *Chief Medical Officer*

Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. He has successfully developed and reported numerous clinical quality studies in primary care, including tobacco cessation, osteoporosis, asthma, diabetes, hypertension, and ischemic vascular disease. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of OptumCare. He has served as Chief Medical Officer since 1995. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA | *Senior Medical Director*

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical a medical device startup company and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt is a graduate of the University of Virginia where he played Division 1 soccer. He received his Medical Doctorate from the Medical College of Georgia in 1984 (AOA honors) and completed his Internal Medicine and Infectious Disease Fellowship training at the University of Minnesota Hospital and Clinics. Dr. Hitt completed his MBA at the Carlson School of Management at the University of Minnesota in 2003. He is the proud father of seven children.

Geoffrey Heyer, MD | *Senior Clinical Practice Performance Consultant*

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine. Prior to joining our team, Dr. Heyer was an associate professor of neurology and pediatrics at The Ohio State University and Columbia University Medical Center, specializing in autonomic disorders, headache, and pain management. He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders.

Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.

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