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# Forum for Evidence-Based Medicine

***Special COVID Edition 12***
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**COVID–19**
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## Multisystem inflammatory (Kawasaki-like) syndrome in children appears to be related to SARS-CoV-2 infection

Investigators in France recently published a study that characterized clinical findings of the multisystem inflammatory (Kawasaki-like) syndrome and explored the temporal relationship with SARS-CoV-2.[1] Twenty-one children and adolescents (median age 7.9 years) with multisystem inflammatory syndrome were admitted over a two-week period. Ninety percent had IgG antibodies to SARS-CoV-2, suggesting that the initial infection occurred at least 2–3 weeks earlier. A Kawasaki-like shock syndrome was present in 57%, 76% had myocarditis and 81% required intensive care support. Echocardiography detected that coronary artery abnormalities were present in over a third of patients, including some with increased coronary artery visibility and coronary artery dilatations. All patients had gastrointestinal symptoms and high levels of inflammatory markers including leukocytosis with a neutrophil predominance and elevations of C-reactive protein, procalcitonin and serum interleukin 6. Lymphopenia was present in 81%, and anemia, hyponatremia and hypoalbuminemia were commonly observed. D-dimer was increased in most patients. Over half had transient kidney failure. All patients received low-dose aspirin. Fourteen patients needed inotropic medicines for cardiac dysfunction for a median duration of 3 days. The median hospital stay was 8 days. None of the patients died. All were discharged home.

In England, 58 hospitalized children (median age 9 years) met UK, CDC or WHO criteria for multisystem inflammatory syndrome.[2] Seventy-eight percent of patients had evidence of current or prior SARS-CoV-2 infection: PCR was positive in 26% and IgG testing was positive in 87%. All children had fever. Rash was present in 52%, and conjunctival injection in 45%. Multiple laboratory markers for inflammation were elevated across patients. Half of the patients developed shock and required inotropic support and fluid resuscitation. Echocardiography demonstrated coronary artery dilatation or aneurysm in 14%. Overall, 22% met criteria for the American Heart Association definition of Kawasaki disease, and 40% had fever and signs of inflammation without features of shock or Kawasaki criteria.

The CDC[3] and WHO[4] have developed criteria for multisystem inflammatory syndrome in children (MIS-C).

| CDC case definition for MIS-C |
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| • An individual aged <21 years presenting with fever ≥38°C for ≥24 hours, laboratory evidence of inflammation (e.g., elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6 (IL-6), also elevated neutrophils, reduced lymphocytes and low albumin), and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND<br>• No alternative plausible diagnoses; AND<br>• Current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms. |
| **WHO preliminary case definition for MIS-C** |
| Children and adolescents 0–19 years of age with fever >3 days; AND<br>• Two of the following: rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet); hypotension or shock; features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP); evidence of coagulopathy (by PT, PTT, elevated D-dimers); acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain); AND<br>• Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin; AND<br>• No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes; AND<br>• Evidence of COVID-19 (RT-PCR, antigen test or serology positive) or likely contact with patients with COVID-19. |

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EDUCATIONAL FORUM

## Hydroxychloroquine update

Seemingly, not a week goes by without some swirl around the use of hydroxychloroquine (HCQ). Although this week is no different, the literature remains clear without any new data showing a benefit to treatment. There were three notable developments this week.

Most important was the analysis of the RECOVERY Trial.[5] This trial enrolled patients hospitalized with COVID-19 infection in the UK. The study randomized 3,200 usual care patients and 1,500 HCQ patients. Because of controversy surrounding The Lancet retraction noted below, the RECOVERY investigators performed an interim analysis and published the results in The British Medical Journal this week. The mortality in the HCQ cohort was 26% compared to 23% in the usual care cohort. This was the largest well conducted randomized trial to date. It supports the data of the other four trials that have evaluated the use of HCQ and showed either no benefit or an increased mortality. Based on this interim analysis, the HCQ arm of the RECOVERY trial was discontinued. The lead author stated, "There are hundreds of thousands, potentially millions, of patients around the world being treated with hydroxychloroquine. This treatment does not reduce the risk of dying from COVID-19 among hospital patients — that clearly has a significant importance for the way that patients are treated not only in the UK but around the world."

Another important study appeared in the NEJM. This was a randomized trial looking at whether HCQ initiated within four days of moderate to high household or occupational exposure to SARS-CoV-2 would reduce the incidence of subsequent infection.[6] Over 800 subjects were randomized across the United States and Canada with half taking a five-day course of HCQ. Eighty-eight percent reported a high-risk exposure with no PPE and 66% were health care workers. Results showed that new cases of either PCR-confirmed or symptomatically compatible COVID-19 developed in 13.0% of participants during the 14 days of follow-up. The incidence of new illness compatible with COVID-19 did not differ significantly between those receiving hydroxychloroquine at 11.8% compared to those receiving placebo at 14.3% (P=0.35). Two hospitalizations were reported, one in each group. No arrhythmias or deaths occurred. Based upon these results, HCQ does not appear to have any significant benefit post exposure. Studies of pre-exposure prophylaxis in high risk health care workers are ongoing.

The third development was the retraction of two studies which appeared in The Lancet and the NEJM.[7] The Lancet paper was a multinational registry study of over 15,000 patients looking at HCQ therapy alone, or co-administered with azithromycin.[8] The Lancet issued a statement on June 4 saying a study that had suggested hydroxychloroquine was associated with higher rates of ventricular arrhythmia and death in COVID-19 patients — eventually leading to several global hydroxychloroquine trials being halted as a result — has been retracted as three of the authors "can no longer vouch for the veracity of the primary data sources." The studies had relied on data and analyses by a third party, Surgisphere Corporation. When the authors of the original study requested the full data set for independent verification, the request was denied for "contractual reasons" and the authors therefore requested the paper be retracted. Despite this retraction, in addition to the above two new HCQ trials, four other trials have been reported, two observational and two randomized. All four trials have been summarized in prior editions of this Forum and showed either no benefit or an increased mortality with the use of HCQ. Although several of the halted HCQ trials have been resumed, the recommendation continues that HCQ therapy should not be used outside of a randomized controlled trial. The retracted NEJM paper also used the same Surgisphere data base and was retracted for the same reason. It focused on whether ACE/ARB therapy had an impact on COVID-19 infection outcomes. That study showed some benefit to ACE/ARB therapy and there are several other studies supporting this finding such that the retraction of this paper does not fundamentally change the evidence base on this topic.

## Randomized trial of convalescent plasma for severe COVID-19 infection

Whether or not there is a clinical benefit of convalescent plasma for COVID-19 infection remains a critical unanswered question. The largest trial to date was published in JAMA last week.[9] Conducted in Wuhan, China, 103 patients with severe (hypoxic pneumonia) or life-threatening disease (mechanical ventilation or shock) were randomized to placebo vs. convalescent plasma therapy. The trial was scheduled to enroll 200 patients, but it was terminated early due to the rapid decline in new cases in Wuhan by the start of April. The primary endpoint was survival to discharge or a 33% reduction in disease severity at 28 days post therapy. Overall mortality and rate of PCR conversion to negative were secondary outcomes. Patients were enrolled on average 30 days post symptom onset. In the overall group, the primary endpoint was not met. This was due to a lack of benefit in the subgroup with life-threatening disease. In the subset with very severe disease, the primary outcome benefit occurred in 91.3% of those receiving convalescent plasma compared to 68.2% who did not (P = .03). Although there was a trend, there was no significant difference in the secondary outcome of 28-day mortality (15.7% in the convalescent plasma group vs. 24.0% in the control group). The rates of conversion to negative of the SARS-CoV-2 viral PCR in the convalescent plasma group were significantly higher than that of the control group (87.2% vs. 37.5% at 72 hours, P < .001). Thus, looking at this trial in its totality, we still don't have a definitive answer to this important question. There is a signal of benefit which could be clinically meaningful, but will require additional trials for verification.

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## Illness hidden and deferred by COVID-19[10,11,12]

Widespread reductions in non-COVID-19 disease presentation and treatment have been recorded over the last few months. A recent analysis of ICU admissions at the New York City Health and Hospital Corporation, which runs many of New York's public hospitals, adds detail to these observations. COVID-19 positive/suspected ICU census increased from 21 patients on February 15 to 700 by April 15, precipitating a concomitant drop in non-COVID-19 census from 420 to 75 over that same period. There are two explanations for what happened to these missing non-COVID-19 patients — that their concomitant non-COVID-19 illnesses were *hidden* by the COVID-19 diagnosis, or that they avoided medical care entirely for fear of infection *(deferred)*.

The evidence for hidden care is exemplified by ICU census counts for myocardial infarction (MI) only, which dropped from 13 individuals to just two over this time period and was partly counterbalanced by an increase of COVID-19 patients with MI from two to eight. Patients who would have suffered an MI anyway may be contracting COVID-19 and then experiencing the MI as a complication. The evidence for deferred care is exemplified by ICU census counts for heart failure and stroke, which held steady at ~45 and ~35 respectively until March 15, when census dropped quickly to less than half that volume by April 15. It is important to note that schools and businesses in New York were closed on March 15 and 16, along with several high-profile emergency declarations to shelter at home. This conclusion is further supported by ED visit volume data reported by the CDC's National Syndromic Surveillance Program, which showed a roughly 48% decrease in ED visits in the New York and New Jersey region over this time period. In the very different geography of Jackson, Mississippi, over roughly this time period researchers also noted a 50% decline in heart failure admissions, with a sudden drop also corresponding to "state of emergency" announcements.

It remains extremely important that we remind our patients they can present for virtual care or triage, especially as higher-risk elderly populations remain afraid to leave their homes as regional movement restrictions are lifted.

## Asymptomatic cases seem to predominate in multiple cohorts

We previously reported in the Forum on the variable, often high, prevalence of COVID-19 in multiple environments characterized by close resident interactions including nursing homes and homeless shelters. Investigators recently reported details surrounding an investigation of one homeless shelter in Boston.[13] All 408 residents were tested for viral RNA using PCR. Thirty-six percent were positive for viral RNA. Importantly, 88% of those who were positive were without symptoms. Investigators from the CDC have shown that prevalence varies in homeless centers across the country.[14] Prevalence ranged from 4% in Atlanta to 66% in San Francisco. Prevalence rates were independent of community prevalence and suggests that the infection began with a point source, followed by progressive person to person spread within the facility. Outbreaks of COVID-19 commonly occur in congregate living arrangements. CDC has recommended baseline testing for all residents and staff in nursing homes and long-term care facilities with continued weekly testing when community presence is more than minimal and/or if there has been a recent case at the facility.[15] A similar approach may be warranted for homeless shelters.

In a related review of PCR testing for SARS-CoV-2 RNA in 16 cohorts (including the homeless shelter above) authors also noted asymptomatic rates ranging from 6 to 96%.[16] In seven of the cohorts the baseline prevalence was low and therefore many of the positive tests may have been false positives, resulting in the asymptomatic percentages to be an overestimate. Notably all of those studies were general population studies. The remaining nine cohorts were from closed populations, characterized by close proximity living or residence. In those nine cohorts prevalence rates varied from 15.4 to 69.8%. Asymptomatic rates, importantly defined as no symptoms at the time of testing ranged from 6.3% to 96%. The highest rate was in inmates and the lowest rate in nursing home residents. The nursing home residents were followed longitudinally. In the nursing home population, 89% of those initially asymptomatic developed symptoms within 96 hours, suggesting that many, if not most individuals who are reported as asymptomatic, are likely pre-symptomatic.

Asymptomatic infection occurs with COVID-19 and across multiple studies and cohorts, seems to occur on average about 40–45% of the time. This seems to be particularly prevalent in situations where closed populations are infected over time. Future studies need to carefully follow patients to distinguish pre-symptomatic and minimally symptomatic patients from those truly asymptomatic.

# Anti-cancer therapy, including chemotherapy, may not increase risk of mortality from COVID-19

Since March, there have been significant reductions in patients pursuing chemotherapy. The CDC currently classifies those actively undergoing cancer therapy as a high-risk COVID-19 cohort. Because limited data is available about the impact of COVID-19 cancer patients, UK researchers created the UK Coronavirus Cancer Monitoring Project (UKCCMP). In five weeks, (March 18 to April 26) researchers accumulated prospective cohort data on over 800 patients with active cancer who contracted Sars-CoV-2 confirmed by RT-PCR.[17]

This is, to date, the largest reported experience of COVID-19 infection outcomes in patients with cancer. "Active cancer" was defined as all patients with:

- Metastatic cancer
- Patients receiving anticancer treatment (curative, radical, adjuvant, or neoadjuvant)
- Patients treated in the last 12 months with surgery, cytotoxic chemotherapy, or radiotherapy

This study has limitations; 22% of patients had their cancer treatment regimens interrupted due to the pandemic and those currently receiving chemotherapy were significantly younger (64 vs. 71 years) than their comparison group, prompting the need for statistical adjustments for age, gender and other comorbidities. After these adjustments, patients with COVID-19 infection who received chemotherapy had a similar mortality rate to those with COVID-19 who completed a course of chemotherapy at least four weeks, and up to a year, prior to infection. Anti-cancer therapies in general did not appear to increase the mortality from COVID-19 infection compared to cancer patients not in active treatment. The quality of evidence for the relative safety of anticancer therapy described here is much higher than the early case series out of China suggesting increased mortality from treatment. Careful consideration should be given before delaying therapy in patients who need it. Although, as noted, the study attempted to control for age and comorbidities, it is nonetheless possible that those at highest risk of a poor outcome from COVID-19 infection are represented in the group of 22% of the patients who had their therapy interrupted due to the pandemic.


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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.

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## 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.

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## 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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