Good morning

Today I summarize the OSHA guidance for Covid-19. I next review a randomized controlled open-label trial to assess the effectiveness of a comprehensive preventive intervention for a mass-gathering indoor event (a live concert) based on systematic same-day screening of attendees with Ag-RDTs, use of facial masks, and adequate air ventilation. Next a review on mucor in India during their Covid-19 surge. The next article looks at tofacitinib, another a Janus kinase inhibitor (JAK), in the treatment of severe Covid-19. I end with two articles on treatment of MIS-C.

Have a great day

Ed

Protecting Workers: Guidance on Mitigating and Preventing the Spread of COVID-19 in the Workplace
OSHA June 10, 2021, Highlights

- Unless otherwise required by federal, state, local, tribal, or territorial laws, rules, and regulations, most employers no longer need to take steps to protect their fully vaccinated workers who are not otherwise at risk from COVID-19 exposure. This guidance focuses only on protecting unvaccinated or otherwise at-risk workers in their workplaces.
- Except for workplace settings covered by OSHA's ETS and mask requirements for public transportation, most employers no longer need to take steps to protect their workers from COVID-19 exposure in any workplace, or well-defined portions of a workplace, where all employees are fully vaccinated. Employers should still take steps to protect unvaccinated or otherwise at-risk workers in their workplaces, or well-defined portions of workplaces.
    - Employers should engage with workers and their representatives to determine how to implement multi-layered interventions to protect unvaccinated or otherwise at-risk workers and mitigate the spread of COVID-19, including: (1) Grant paid time off for employees to get vaccinated. (2) Instruct any workers who are infected, unvaccinated workers who have had close contact with someone who tested positive for SARS-CoV-2, and all workers with COVID-19 symptoms to stay home from work. (3) Implement physical distancing for unvaccinated and otherwise at-risk workers in all communal work areas. (4) Provide unvaccinated and otherwise at-risk workers with face coverings or surgical masks unless their work task requires a respirator or other PPE. (5) Educate and train workers on your COVID-19 policies and procedures using accessible formats and in a language they understand. (6) Suggest that unvaccinated customers, visitors, or guests wear face coverings. (7) Maintain Ventilation Systems. (8) Perform routine cleaning and disinfection. (9) Record and report COVID-19 infections and deaths. (10) Implement protections from retaliation and set up an anonymous process for workers to voice concerns about COVID-19-related hazards.

Same-Day SARS-CoV-2 Antigen Test Screening in an Indoor Mass-Gathering Live Music Event: A Randomized Controlled Trial
Lancet Infect Dis published online May 27, 2021
doi.org/10.1016/ S1473-3099(21)00268-1
This is a randomized controlled open-label trial to assess the effectiveness of a comprehensive preventive intervention for a mass-gathering indoor event (a live concert) based on systematic same-day screening of attendees with Ag-RDTs, use of facial masks, and adequate air ventilation. The event took place in the Sala Apolo, Barcelona, Spain. Adults aged 18-59 years with a negative result in an Ag-RDT from a nasopharyngeal swab collected immediately before entering the event were randomized 1:1

(block randomization stratified by age and gender) to either attend the indoor event for 5 hours or go home. Nasopharyngeal specimens used for Ag-RDT screening were analyzed by real-time reverse-transcriptase PCR (RT-PCR) and cell culture (Vero E6 cells). 8 days after the event, a nasopharyngeal swab was collected and analyzed by Ag-RDT, RT-PCR, and a transcription-mediated amplification test (TMA). The primary outcome was the difference in incidence of RT-PCR-confirmed SARS-CoV-2 infection at 8 days between the control and the intervention groups, assessed in all participants who were randomly assigned, attended the event, and had a valid result for the SARS-CoV-2 test done at follow-up.

Participant enrollment took place during the morning of the day of the concert, Dec 12, 2020. Of the 1140 people who responded to the call and were deemed eligible, 1047 were randomly assigned to either enter the music event (experimental group) or continue with normal life (control group). Of the 523 randomly assigned to the experimental group, 465 were included in the analysis of the primary outcome (51 did not enter the event and eight did not take part in the follow-up assessment), and of the 524 randomly assigned to the control group, 495 were included in the final analysis (29 did not take part in the follow-up). At baseline, 15 (3%) of 495 individuals in the control group and 13 (3%) of 465 in the experimental group tested positive on TMA despite a negative Ag-RDT result. The RT-PCR test was positive in one case in each group and cell viral culture was negative in all cases. 8 days after the event, two (<1%) individuals in the control arm had a positive Ag-RDT and PCR result, whereas no Ag-RDT nor RT-PCR positive results were found in the intervention arm. The Bayesian estimate for the incidence between the experimental and control groups was -0·15% (95% CI -0·72 to 0·44).

Comment: This study provides preliminary evidence on the safety of indoor mass-gathering events during a COVID-19 outbreak under a comprehensive preventive intervention. This study provides preliminary evidence on the effectiveness of same-day point-of-care screening with Ag-RDT, combined with face mask-wearing and active air ventilation, to create safe indoor environments with no need for physical distancing measures. Future studies with a larger capacity of attendees and assistants and done during periods of increased transmission of COVID-19 are needed. Participants could have modified their behavior during the event due to their awareness of being observed, having signed an informed consent, and participating in a clinical trial [Hawthorne effect]. In addition, the planned number of participants (1000 per study arm) had to be halved due to restrictions issued by local healthcare authorities.

Multicenter Epidemiologic Study of Coronavirus Disease-Associated Mucormycosis, India
Emerg Infect Dis, early release September 2021
doi.org/10.3201/eid2709.210934
In this study, the prevalence of CAM (Covid-19 associated mucormycosis) was 0.27% in patients managed in hospital wards and 1.6% in patients managed in ICUs. We found a 2.1-fold increase in mucormycosis cases during September-December 2020 than the same months of 2019; they attribute the increase to COVID-19. Most CAM cases were diagnosed ≥8 days after COVID-19 diagnoses. Hypoxemia due to COVID-19 and inappropriate use of glucocorticoid drugs were independently associated with development of late CAM. The mortality rate for CAM patients was high (44%) but was comparable to rates for non-CAM (49%) patients. Older age (>54 years), admission to an ICU, and pulmonary or brain involvement by Mucorales were independently associated with a higher risk for death. The sequential use of antifungal drugs at any site was associated with improved survival at 6 and 12 weeks, irrespective of anatomical site of mucormycosis. They found diabetes mellitus was the most common underlying disease for both CAM and non-CAM patients.

They found inappropriate glucocorticoid use was independently associated with late CAM. Among 187 CAM cases, 61 (32.6%) had COVID-19 as the only underlying disease; 13 of those cases were not treated with glucocorticoid or other immunomodulatory therapies. Whether COVID-19 itself causes immune dysregulation and predisposes patients to invasive mucormycosis remains an unproven possibility. They did not find that COVID-19 was an independent predictor of late CAM, possibly because of the lower numbers of patients in our cohort with COVID-19 as the only underlying disease without any other risk factor. The persisting immune dysregulation during the recovery phase of COVID-19 infection also confers additional risk. Tocilizumab use in COVID-19 has been reported as a risk factor for invasive candidiasis. However, only 2.7% of the CAM patients in this study received tocilizumab.

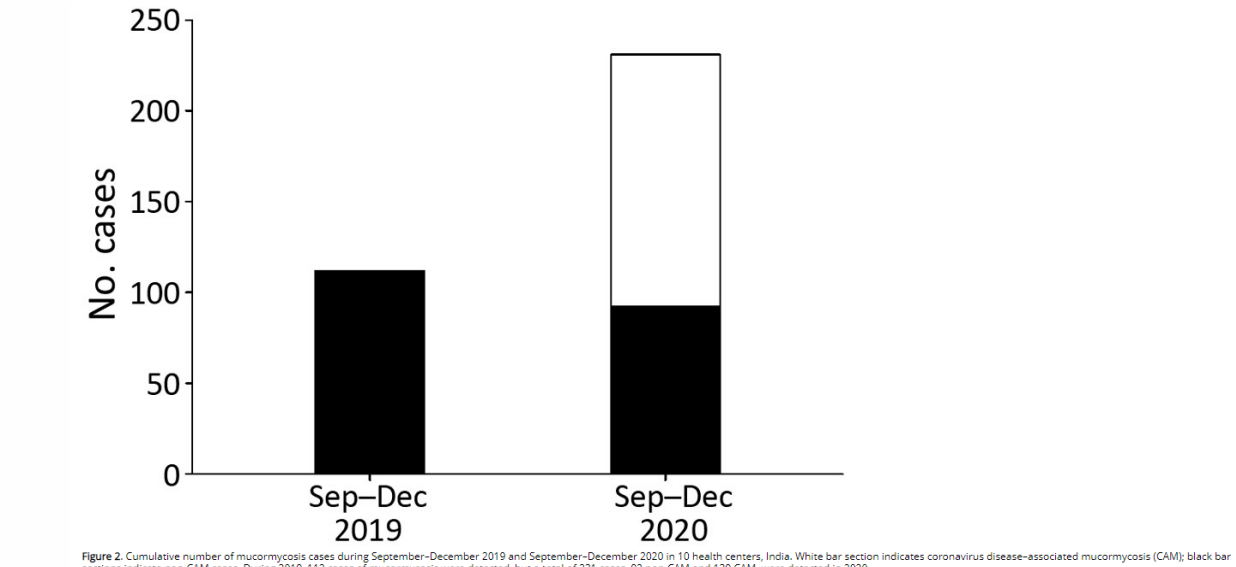


Figure 2. Cumulative number of mucormycosis cases during September–December 2019 and September–December 2020 in 10 health centers, India. White bar section indicates coronavirus disease–associated mucormycosis (CAM); black bar sections indicate non-CAM cases. During 2019, 112 cases of mucormycosis were detected, but a total of 231 cases, 92 non-CAM and 139 CAM, were detected in 2020.

Comment: In the current outbreak, many patients had no history of diabetes. The common denominator seems to be Covid-19 infection and steroids. Many doctors in India prescribed steroids in quantities and for durations that far exceed WHO recommendations. Steroids may have compromised patient immune systems and made Covid-19 patients more susceptible to fungal spores. The steroids may have also increased blood sugar levels, leaving people with diabetes even more vulnerable to mucormycosis.

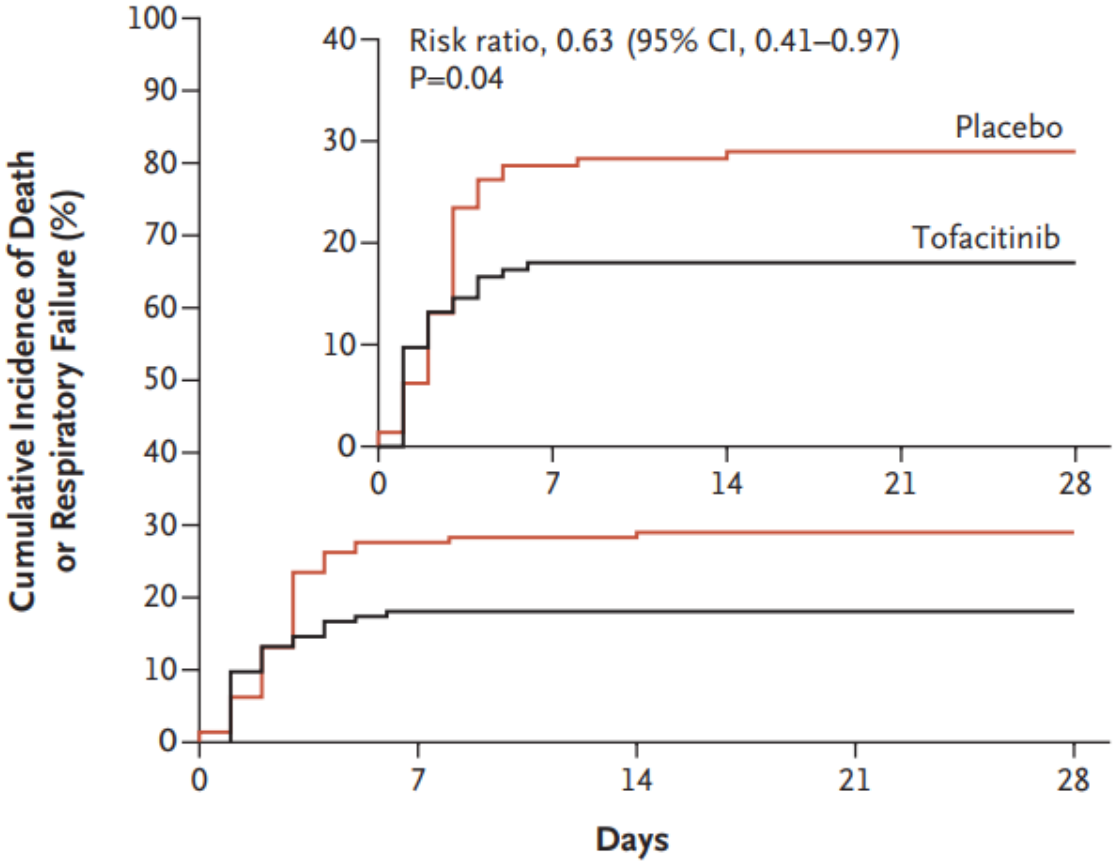
Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia

STOP-COVID N Engl J Med published online June 16, 2021

DOI: 10.1056/NEJMoa2101643

Tofacitinib, is another a Janus kinase inhibitor (JAK). The investigators randomly assigned, in a 1:1 ratio, hospitalized adults with Covid-19 pneumonia to receive either tofacitinib at a dose of 10 mg or placebo twice daily for up to 14 days or until hospital discharge. The primary outcome was the occurrence of death or respiratory failure through day 28 as assessed with the use of an eight-level ordinal scale (with scores ranging from 1 to 8 and higher scores indicating a worse condition). All-cause mortality and safety were also assessed. The trial included patients 18 years of age or older who had laboratory-confirmed SARS-CoV-2 infection as determined by PCR before randomization, who had evidence of Covid-19 pneumonia on radiographic imaging (CT or CXR), and who had been hospitalized for less than 72 hours.

A total of 289 patients underwent randomization at 15 sites. Overall, 89.3% of the patients received glucocorticoids during hospitalization. The cumulative incidence of death or respiratory failure through day 28 was 18.1% in the tofacitinib group and 29.0% in the placebo group (risk ratio, 0.63; 95% confidence interval [CI], 0.41 to 0.97; P=0.04). Death from any cause through day 28 occurred in 2.8% of the patients in the tofacitinib group and in 5.5% of those in the placebo group (hazard ratio, 0.49; 95% CI, 0.15 to 1.63). The proportional odds of having a worse score on the eight-level ordinal scale with tofacitinib, as compared with placebo, was 0.60 (95% CI, 0.36 to 1.00) at day 14 and 0.54 (95% CI, 0.27 to 1.06) at day 28. Serious adverse events occurred in 20 patients (14.1%) in the tofacitinib group and in 17 (12.0%) in the placebo group. Tofacitinib was not associated with a higher risk of secondary infection or thromboembolic events.



Comment: Among patients hospitalized with Covid-19 pneumonia, tofacitinib led to a lower risk of death or respiratory failure through day 28 than placebo. The effects of JAK inhibition in patients with Covid-19 have been assessed previously. In the ACTT-2 Trial, combination treatment with baricitinib and remdesivir was superior to remdesivir treatment alone in shortening the time to recovery, particularly among patients receiving high-flow oxygen or noninvasive mechanical ventilation. [N Engl J Med 2021; 384:795-807] In ACTT-2, only 12% of the participants received glucocorticoid therapy during the trial. In

this trial, the majority (89.3%) of patients were treated with glucocorticoids during hospitalization. The results of ACTT-2 and STOP-COVID provide evidence that JAK inhibition represents an additional therapeutic option for treating Covid-19 pneumonia in patients who are not yet receiving invasive mechanical ventilation. The NIH updated guidance on May 27, 2021. The Panel reviewed the preliminary results (not yet peer-reviewed) from COV-BARRIER, a trial of baricitinib in hospitalized adults. Based on this review, the Panel has updated its recommendations on the use of baricitinib for the treatment of adults with COVID-19:

- The Panel recommends using either baricitinib (BIIa) or tocilizumab (BIIa) (listed alphabetically) in combination with dexamethasone alone or dexamethasone plus remdesivir for the treatment of COVID-19 in hospitalized patients on high-flow oxygen or noninvasive ventilation who have evidence of clinical progression or increased markers of inflammation.
- In the rare circumstance when corticosteroids cannot be used, the Panel recommends using baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized, nonintubated patients who require oxygen supplementation (BIIa).

Based on STOP-COVID results perhaps tofacitinib can be added as another option.

Treatment of Multisystem Inflammatory Syndrome in Children
N Engl J Med published online June 16, 2021
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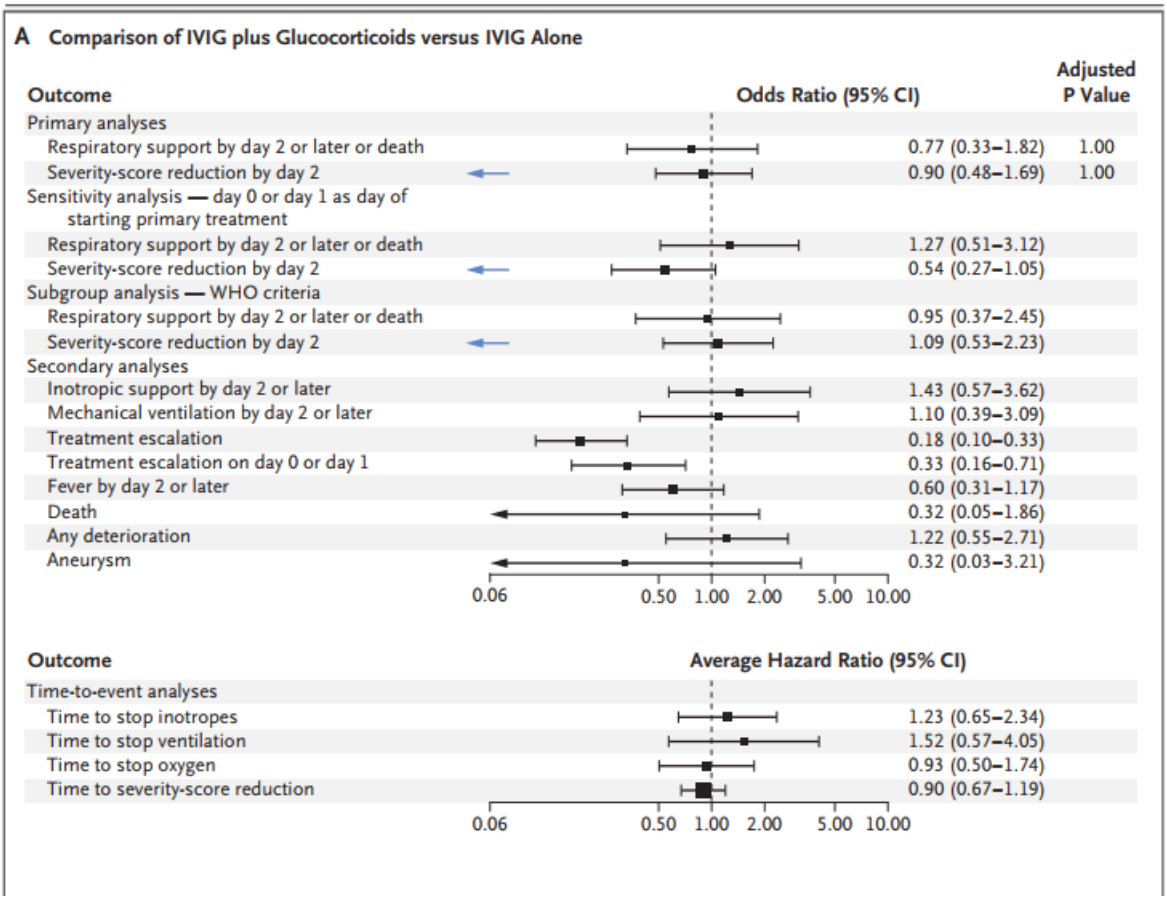
Multisystem Inflammatory Syndrome in Children — Initial Therapy and Outcomes
N Engl J Med published online June 16, 2021
DOI: 10.1056/NEJMoa2102605
The first article is an international observational cohort study of clinical and outcome data regarding suspected MIS-C. The evaluation took place from June 2020 through February 2021. They used inverse-probability weighting and generalized linear models to evaluate intravenous immune globulin (IVIG) as a reference, as compared with IVIG plus glucocorticoids and glucocorticoids alone. There were two primary outcomes: the first was a composite of inotropic support or mechanical ventilation by day 2 or later or death; the second was a reduction in disease severity on an ordinal scale by day 2. Secondary outcomes included treatment escalation and the time until a reduction in organ failure and inflammation. Among children and adolescents with MIS-C, initial treatment with IVIG plus glucocorticoids was associated with a lower risk of new or persistent cardiovascular dysfunction than IVIG alone.



In the second article the investigators analyzed surveillance data on inpatients younger than 21 years of age who had MIS-C and were admitted to U.S. hospitals between March 15 and October 31, 2020. The effectiveness of initial immunomodulatory therapy (day 0, indicating the first day any such therapy for MIS-C was given) with intravenous immune globulin (IVIG) plus glucocorticoids, as compared with IVIG alone, was evaluated with propensity-score matching and inverse probability weighting, with adjustment for baseline MIS-C severity and demographic characteristics. The primary outcome was cardiovascular dysfunction (a composite of left ventricular dysfunction or shock resulting in the use of vasopressors) on or after day 2. Secondary outcomes included the components of the primary outcome, the receipt of adjunctive treatment (glucocorticoids in patients not already receiving glucocorticoids on day 0, a biologic, or a second dose of IVIG) on or after day 1, and persistent or recurrent fever on or after day 2. Unlike the paper above, the investigators found no evidence that recovery from MIS-C differed after primary treatment with IVIG alone, IVIG plus glucocorticoids, or glucocorticoids alone.

Comment: These two publications in the NEJM last week seem to have conflicting findings regarding the efficacy of immunomodulation with IVIG, glucocorticoids, or both. The first article determined that initial MIS-C treatment with IVIG plus glucocorticoids was associated with a lower risk of cardiovascular dysfunction and the initiation of vasopressors and adjunctive therapy than treatment with IVIG alone. In contrast the second article found no statistically significant differences in odds ratios for end points of ventilation, inotropic support, or death or for improvement on an ordinal clinical severity scale for any of three treatments: IVIG alone, a combination of IVIG and glucocorticoids, or glucocorticoids alone. The risk of escalation of immunomodulatory treatment in patients who received IVIG plus glucocorticoids

was significantly lower than the risk in patients who received IVIG alone, a finding that was in line with the other study.

One study included only U.S. patients, whereas the other study encompassed international hospitals, and at least one large U.S. center. Could there be a difference in genetic background, which could be associated with a dysregulated immune response in patients with MIS-C, leading to different responses? The time periods for which the investigators were evaluating surveillance data in these studies differed in two important ways. The U.S. study included only patients who had been hospitalized during the earlier and smaller waves of the Covid-19 pandemic, before any substantial circulation of variants. The international study took place both before and after the emergence of Covid-19 variants in many countries. While investigators in the two trials used statistical methods such as propensity score adjustment to control for confounding factors that might have influenced treatment and for variations in care at multiple centers, these modelings may not be able to fully adjust for such variations. Neither study was powered to include an evaluation of approaches that steer away from broad immunosuppression with glucocorticoids and that focus on more targeted and titratable treatments with biologic agents, such as anakinra and infliximab.