COVID-19 Evidence Digest 01/29/21

Invasive Mold Disease in Fatal COVID-19: A Systematic Review of Autopsies (MedRxiv)

Bottom Line: Though several studies have found an association between invasive mold disease or COVID-19-associated pulmonary aspergillosis and COVID-19 mortality, it's likely uncommon in patients with fatal COVID-19 infection.

Details: This was a systematic review of autopsy studies examining evidence of invasive mold disease (IMD; infection caused by mold which usually affects the upper respiratory system, with the most common cause being *aspergillosis*) among patients with COVID-19. Most cases of IMD among COVID-19 patients that have been reported are COVID-19-associated pulmonary aspergillosis. Authors searched PubMed, Web of Science, OVID (Embase), and MedRxiv for English or French studies published between January 1, 2019 and September 26, 2020. Authors found 51 case series with a total of 702 autopsies. Of these, 430 had individual-level data and were included. The median age of those included was 72 years. Common conditions included diabetes (32%), lung disease (22%), and other immunocompromising conditions (32%). The length of hospital stay was 10 days. 52% of them were on mechanical ventilation for a median of 9 days. Treatments included were immunomodulation (usually steroids or tocilizumab, 14%) and antifungals (10%). Of all autopsies, 2% had confirmed IMD. Among those who were on mechanical ventilation, 3% had IMD. The most common type of IMD among autopsied patients was COVID-19 associated pulmonary aspergillosis (n=6). The study was not able to examine the risk of IMD among those with immunocompromised status and invasive mechanical ventilation due to inconsistent reporting among studies.

Key Takeaways:

- Most cases of IMD among COVID-19 patients had COVID-19-associated pulmonary aspergillosis.
- Rates of IMD, and more specifically, COVID-19-associated pulmonary aspergillosis, may be most common among those with severe COVID-19 infections, particularly among those that were on mechanical ventilation. However, the rates of IMD were found to be quite low and likely uncommon.

Effect of Bamlanivimab as Monotherapy or in Combination with Etesevimab on Viral Load in Patients with Mild to Moderate COVID-19: A Randomized Clinical Trial (JAMA)

Bottom line: This phase 2/3 randomized clinical trial found a statistically significant reduction in SARS-CoV-2 viral load at day 11 in non-hospitalized patients with mild to moderate COVID-19 illness treated with a combination of bamlanivimab and etesevimab, compared with placebo. No reduction was seen for patients treated with bamlanivimab only. Ongoing clinical trials are assessing the clinical benefits.

Details:
This is an original investigation of the BLAZE-1 study, a phase 2/3 randomized clinical trial of 613 non-hospitalized patients who tested positive for SARS-CoV-2 infection and had 1 or more mild to moderate symptoms from 49 US outpatient centers. Patient enrolled and randomized between June 17 and August 21, 2020 received either the bamlanivimab monotherapy (single infusion of 700mg [n=101], 280 mg [n=107], or 7000 mg [n=101]) or placebo. Participants enrolled between August 22- and September 3, 2020 received either a combination of bamlanivimab and etesevimab (2800mg of each [n=112]) or placebo. A total of 156 participants

received placebo. The primary endpoint was a reduction in log SARS-CoV-2 viral load at day 11 (± 4 days). Secondary endpoints included additional measures of viral load and symptoms, and the proportion of patients with a COVID-19-related hospitalization, ED visit, or death by day 29. Of the 577 patients randomized and treated, 92.4% completed the study through day 29. The reduction in log viral load at day 11 compared to baseline was –3.72 for 700 mg, –4.08 for 2800 mg, –3.49 for 7000 mg, –4.37 for combination treatment, and –3.80 for placebo. The difference in the change log viral load compared to placebo was as follows: 0.09 (95% CI, –0.35 to 0.52; P = .69) for 700 mg, –0.27 (95% CI, –0.71 to 0.16; P = .21) for 2800 mg, 0.31 (95% CI, –0.13 to 0.76; P = .16) for 7000 mg, and –0.57 (95% CI, –1.00 to –0.14; P = .01) for combination treatment. The following number (%) of ED or hospitalization events occurred in each group: 1 event (1%) in the 700 mg group, 2 (1.9%) in the 2800 mg group, 2 (2.0%) in the 7000 mg group, 1 (0.9%) in the combination group, and 9 (5.8%) events in the placebo group. No deaths occurred during the study. A total of 9 patients (6 in the mono treatment group and 2 in the combination group) experienced immediate hypersensitivity.

Key Takeaways:

- There was a decrease in SARS-CoV-2 log viral load at day 11 (between-group difference, –0.57 [95% CI, –1.00 to –0.14], P = .01) for participants treated with a combination of bamlanivimab and etesevimab compared to placebo.
- The following number (%) of ED or hospitalization events occurred in each group: 1 event (1%) in the 700 mg, 2 (1.9%) in the 2800 mg, 2 (2.0%) in the 7000 mg, 1 (0.9%) in the combination group, and 9 (5.8%) events in the placebo group.
- Clinical trials are ongoing to further assess the clinical benefits.

Neutralization of SARS-CoV-2 lineage B.1.1.7 pseudovirus by BNT162b2 vaccine-elicited human sera (bioRxiv)

Bottom Line: A preprint article compared the neutralizing titers to SARS-CoV-2-S pseudovirus bearing either the Wuhan reference strain or the newly emerged B.1.1.7 lineage among the immune sera of 16 participants drawn from the previously reported Pfizer-BioNTech COVID-19 vaccine BNT162b2 trial. The study found no biologically significant difference in the neutralizing titers, suggesting that the vaccine efficacy will likely be preserved against the B.1.1.7 lineage.

Details: The newly emerged SARS-CoV-2 lineage B.1.1.7, originally detected in the UK, was reported to be more transmissible than other strains, and has raised concerns over the effectiveness of the Pfizer-BioNTech COVID-19 vaccine BNT162b2 towards this specific strain due to multiple mutations in its spike protein. In this preprint article, the authors generated VSV-SARS-CoV-2-S pseudoviruses bearing either the Wuhan SARS-CoV-2 reference strain or the B.1.1.7 variant spike protein, and compared the neutralization of the two strains using a 50% neutralization assay ($pVNT_{50}$) at 21 days after the booster immunization with 30 µg BNT162b2 among 16 participants (18-55 yrs: n = 8; 56-85 yrs: n = 8) drawn from the previously reported German phase 1/2 trial. No biologically significant difference in neutralization activity against the two pseudoviruses were found (median ratio of $pVNT_{50}$ between SARS-CoV-2 lineage B.11.7 and Wuhan reference strain spike-pseudotyped VSV = 0.79). The authors suggested that, based on this evidence and coupled with the combined immunity involving humoral and cellular effectors induced by the vaccine, it was unlikely the B.1.1.7 lineage will escape the vaccine-mediated protection. However, the use of non-replicating pseudovirus systems may be a limitation of this study. Future studies and continuous monitoring of the impact on the efficacies

of currently authorized vaccines caused by significant mutations of the COVID-19 virus will be needed.

Key Takeaways:

- Efficacy of the Pfizer-BioNTech COVID-19 vaccine BNT162b2 will likely be preserved against the newly emerged B.1.1.7 variant based on a preprint study comparing the neutralizing titers to the Wuhan reference strain and the B.1.1.7 lineage using pseudovirus systems among 16 participants drawn from the BNT162b2 vaccine trial.
- Future studies and continuous monitoring of the new COVID-19 mutation's impact on vaccine efficacy will be needed.

COVID-19 Evidence Digest 01/29/21

Duration of Culturable SARS-CoV-2 in Hospitalized Patients with COVID-19 (NEJM)

Bottom Line: This small study of 21 patients with COVID-19 found that while, on average, SARS-CoV-2 PCR tests remained positive for 34 days, viable virus was not cultured from any patient sample after 12 days post-symptom onset.

Details: This study serially tested 21 patients hospitalized with COVID-19 for SARS-CoV-2 using PCR and viral culture in order to assess the length of time patients shed viable virus; cycle threshold results from PCR and results from viral culture, drawn simultaneously, were reported. 165 samples were tested using real-time RT-PCR; 89/165 were cultured for SARS-CoV-2. The median time from symptom onset to negative viral culture was 7 days, while the median time from symptom onset to negative real-time RT-PCR was 34 days. No patient sample tested positive for viral culture after 12 days post-symptom onset. Viable virus was only found in samples with a cycle threshold of <28.4. All patients with cycle threshold values below 20 had positive viral cultures at the same time; conversely, no patients with cycle threshold values above 30 had positive viral cultures at the same time. This study also found that some patients had positive, followed by negative, and then (again) positive viral culture. Another reported fever later on in course of illness, suggesting that using time since symptom resolution to determine when isolation should end may be misleading.

Key Takeaways:

- In this study, all patients with cycle threshold values below 20 always had positive viral cultures at the same time; conversely, no patients with cycle threshold values above 30 had positive viral cultures at the same time.
- Symptoms such as fever were often reported later on in course of illness among patients in this study, suggesting that using time since symptom resolution to determine when isolation should end may be misleading.

COVID-19 Cases and Transmission in 17 K–12 Schools — Wood County, Wisconsin, August 31–November 29, 2020 (MMWR)

Bottom Line: In this study of within-school transmission risk in K-12 settings in a Wisconsin county, new COVID-19 cases among students and staff were 37% lower than in the county overall, and of 191 identified cases, only 7 were linked to in-school transmission.

Details: This report sought to characterize in-school SARS-CoV-2 transmission risk in a setting of widespread community transmission, when preventive measures are put in place. 17 K-12 schools in a rural Wisconsin county reopened, with guidance to wear masks, keep students in small cohorts (maximum of 20 students), maintain 6 feet of distance from staff, and quarantine post-exposure. The study period was 8/31-11/29/20, during which COVID-19 cases, transmission, and mask compliance were investigated among 4,876 students and 654 staff participating in in-person learning. Student mask-wearing reported by teachers was high (>92%). New COVID-19 cases among students and staff were 37% lower than in the county overall (3,453 vs 5,466 per 100,000). Of 191 cases identified in students, teachers, and staff, 7 (3.7%, 5 elementary school and 2

secondary school students) were linked to in-school transmission. No transmission between separate classroom cohorts was reported. Importantly, no transmission was known to have occurred to or from staff in school.

Key Takeaways:

- Findings suggest that schools may be able to safely reopen with minimal risk of in-school SARS-CoV-2 transmission if effective layered mitigation strategies, including student cohorting and requirements to wear masks, are in place.

Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge (JAMA Network Open)

Bottom Line: In this study of over 200 patients hospitalized with COVID-19, over half experienced a significant reduction in the lungs' ability to transfer gas from inspired air to the blood stream or functional impairment, and 20% had symptoms of post-traumatic stress.

Details: This cohort study sought to characterize the post-discharge prevalence of issues with lung function, functional impairment, and mental health sequalae among patients hospitalized with severe COVID-19. 238 patients were enrolled in the study (median age = 61, 60% men, median comorbidities = 2). 219/238 completed both lung function tests and a measure of diffusing lung capacity for carbon monoxide (the lung's ability to transfer gas from inspired air to the blood stream) 4 months post-discharge. In 51.6% of patients (n=113), diffusing lung capacity for carbon monoxide was less than 80% of the estimated value; it was less than 60% in 15.5% of patients (n=34). In a functional impairment test (SPPB score), 22% of patients (n=53) had scores suggesting limited mobility; an additional 75 patients did not perform according to expectations for age and sex in a 2-minute walk test, for a total of 128 patients with functional impairment. Lastly, 17% (n=41) of patients reported symptoms of post-traumatic stress.

Key Takeaways:

- In this study, a significant proportion of patients experienced pulmonary, functional, and psychological issues 4 months post-discharge from the hospital for severe COVID-19.