Dr. Leo's COVID Corner
August 2022

1. IM Evusheld decreased risk of severe COVID or death from 9% to 4% in unvaccinated individuals
2. Maternal vaccination was associated with a reduced risk of hospitalization including critical illness
3. Paxlovid was associated with a 67% reduction in Covid-19 hospitalizations and an 81% reduction in Covid-19 mortality in patients 65 years and above
4. Liver manifestation in children with Long COVID
5. reported "rebound phenomenon" of COVID after Paxlovid therapy reported to be low in a cohort of 400+ pts described in CID.
6. tixagevimab-cilgavimab, a neutralizing monoclonal Ab combination against COVID, reduced risk of severe COVID and death in outpt COVID pts from 9% to 4% with a relative safe profile
7. 12% of pts with COVID had rheumatic conditions at 12 months follow up
8. Time to blood positivity in S. pyogenes bacteremia as a predictor of mortality - TTP blood culture of 8-10 hours associated with 10% 30-day mortality.
9. vaccine effectiveness of Pfizer in 5-12 year olds against infection and symptomatic infection was approximately 50%
10. Treatment with Remdesivir was associated with lower mortality rates compared to standard of care.
11. Readmission rate of hospitalized COVID pts is 3.6%. Readmitted pts are more likely to have DM, HTN, CVD, and AKI on CKD. Mortality rate on readmission for these pts is 12.3%
12. Post-mortem pathologic description of neurovascular injury after COVID. Antibody-mediated cytotoxicity directed against the endothelial cells is the most likely initiating event that leads to vascular leakage, platelet aggregation, neuroinflammation and neuronal injury.
13. Pre-omicron COVID infection provided little protection against BA4. BA.5 infections (15 - 25% protection effectiveness) - Omicron COVID infection provided 75 - 79% effectiveness in protection
14. Vaccine effectiveness of 4th dose of COVID vaccine against all-cause mortality was 71%
15. In hospitalized pts with COVID during 2/2021 and 9/2021, Tixagevimab-cilgavimab decreased mortality risk from 12% to 9% with similar side effect profile.

Lancet - 6/7/2022 -Efficacy and safety of Evusheld	• Between Jan 28, 2021, and July 22, 2021, 1014 participants were enrolled, of whom 910 were randomly assigned to a treatment group (456 to receive tixagevimab–cilgavimab and 454 to receive placebo). The mean age of participants was 46·1 years (SD 15·2). ○ either a single tixagevimab–cilgavimab 600 mg dose (two consecutive 3 mL intramuscular injections, one each of 300 mg tixagevimab and 300 mg cilgavimab

	• Severe COVID-19 or death occurred in 18 (4%) of 407 participants in the tixagevimab–cilgavimab group versus 37 (9%) of 415 participants in the placebo group (relative risk reduction 50·5% [95% CI 14·6–71·3]; p=0·0096). The absolute risk reduction was 4·5% (95% CI 1·1–8·0; p<0·0001). Adverse events occurred in 132 (29%) of 452 participants in the tixagevimab–cilgavimab group and 163 (36%) of 451 participants in the placebo group, and were mostly of mild or moderate severity. There were three COVID-19-reported deaths in the tixagevimab–cilgavimab group and six in the placebo group • A single intramuscular tixagevimab–cilgavimab dose provided statistically and clinically significant protection against progression to severe COVID-19 or death versus placebo in unvaccinated individuals and safety was favorable • https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00180-1/fulltext
Lancet - 6/3/2022 - efficacy of safety of Favipiravir, Camostat and Ciclesonide combination therapy.	• Of 121 enrolled patients, 56 received monotherapy and 61 received combination therapy. Baseline characteristics were balanced between the groups. The median time of hospitalization was 10 days for the combination and 11 days for the monotherapy group. The median time to discharge was statistically significantly lower in the combination therapy vs monotherapy group (HR, 1·67 (95% CI 1·03–2·7; P = 0·035). The hospital discharge rate was statistically significantly higher in the combination therapy vs monotherapy group in patients with less severe COVID-19 infections and those who were ≤60 years. There were no significant differences in clinical findings between the groups at 4, 8, 11, 15, and 29 days. Adverse events were comparable between the groups. There were two deaths, with one in each group • Combination oral Favipiravir, camostat and, ciclesonide therapy could decrease the length of hospitalization stays without safety concerns in patients with moderate COVID-19 pneumonia. • https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(22)00214-0/fulltext
NEJM - 6/22/2022 - Maternal vaccination and risk of hospitalization for COVID 19	• A total of 537 case infants (181 of whom had been admitted to a hospital during the delta period and 356 during the omicron period; median age, 2 months) and 512 control infants were enrolled and included in the analyses; • 16% of the case infants and 29% of the control infants had been born to mothers who had been fully vaccinated against Covid-19 during pregnancy. ○ Among the case infants, 113 (21%) received intensive care (64 [12%] received mechanical ventilation or vasoactive infusions).

among infants.	Two case infants died from Covid-19; neither infant's mother had been vaccinated during pregnancy. • The effectiveness of maternal vaccination against hospitalization for Covid-19 among infants was 52% (95% confidence interval [CI], 33 to 65) overall, 80% (95% CI, 60 to 90) during the delta period, and 38% (95% CI, 8 to 58) during the omicron period. Effectiveness was 69% (95% CI, 50 to 80) when maternal vaccination occurred after 20 weeks of pregnancy and 38% (95% CI, 3 to 60) during the first 20 weeks of pregnancy • Maternal vaccination with two doses of mRNA vaccine was associated with a reduced risk of hospitalization for Covid-19, including for critical illness, among infants younger than 6 months of age • https://www.nejm.org/doi/full/10.1056/NEJMoa2204399?query=featured_coronavirus
JPGN - 6/10/2022 - Long-COVID Liver manifestation in children	• We report five pediatric patients who recovered from COVID-19 and later presented with liver injury. • Two types of clinical presentation were distinguishable. Two infants aged 3 and 5 months, previously healthy, presented with o acute liver failure that rapidly progressed to liver transplantation. Their liver explant showed massive necrosis with cholangiolar proliferation and lymphocytic infiltrate. o Three children, two aged 8 years and one aged 13 years, presented with hepatitis with cholestasis. Two children had a liver biopsy significant for lymphocytic portal and parenchyma inflammation, along with bile duct proliferations. All three were started on steroid treatment; liver enzymes improved, and they were weaned successfully from treatment. For all five patients, extensive etiology workup for infectious and metabolic etiologies were negative • We report two distinct patterns of potentially long COVID-19 liver manifestations in children with common clinical, radiological, and histopathological characteristics after a thorough workup excluded other known etiologies • https://journals.lww.com/jpgn/Abstract/9900/Long_COVID_19_Liver_Manifestation_in_Children.84.aspx
6/14/2022 - rebound phenomenon after Paxlovid therapy for COVID	• In a cohort of 483 high-risk patients treated with nirmatrelvir/ritonavir for coronavirus disease-2019, o two patients (0.4%) required hospitalization by day 30. o Four patients (0.8%) experienced rebound of symptoms, which were generally mild, at median of 9 days after treatment, and all resolved without additional COVID-19-directed therapy

	○ https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciac481/6607746?redirectedFrom=fulltext
Lancet - 6/7/2022 - Safety and efficacy of tixagevimab-cilgavimab for outpatient COVID Tx.	• Between Jan 28, 2021, and July 22, 2021, 1014 participants were enrolled, of whom 910 were randomly assigned to a treatment group (456 to receive tixagevimab–cilgavimab and 454 to receive placebo). The mean age of participants was 46·1 years (SD 15·2). • Severe COVID-19 or death occurred in 18 (4%) of 407 participants in the tixagevimab–cilgavimab group versus 37 (9%) of 415 participants in the placebo group (relative risk reduction 50·5% [95% CI 14·6–71·3]; p=0·0096). The absolute risk reduction was 4·5% (95% CI 1·1–8·0; p<0·0001). • Adverse events occurred in 132 (29%) of 452 participants in the tixagevimab–cilgavimab group and 163 (36%) of 451 participants in the placebo group, and were mostly of mild or moderate severity. There were three COVID-19-reported deaths in the tixagevimab–cilgavimab group and six in the placebo group • https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00180-1/fulltext
OFID - 6/2022 - Rheumatic conditions following COVID	• In total, 1296 of 2469 discharged patients with COVID-19 were enrolled in this study. • Among them, 160 (12.3% [95% confidence interval {CI}, 10.6%–14.3%]) suffered from rheumatic symptoms following COVID-19 at 12-month follow-up. • The most frequently involved joints were the knee joints (38%), followed by hand (25%) and shoulder (19%). Rheumatic symptoms were independent of the severity of illness and corticosteroid treatment during the acute phase, while elderly age (odds ratio [OR], 1.22 [95% CI, 1.06–1.40]) and female sex (OR, 1.58 [95% CI, 1.12–2.23]) were identified as the risk factors for this condition • considerable proportion of rheumatic symptoms following COVID-19 in discharged patients • https://doi.org/10.1093/ofid/ofac170
OFID - 6/2022 - Time to blood culture positivity - predictor of	• A total of 347 episodes of *S pyogenes* bacteremia were identified, of which 61 were excluded, resulting in 286 included episodes. • Median TTP was 10.4 (interquartile range, 8.4–11.4) hours. ○ Thirty-day mortality was 10%. • Median TTP was shorter in patients who died within 30 days compared to survivors (8.6 vs 10.4 hours; *P* < .001). • In a multivariable logistic regression, shorter TTP was associated with 30-day mortality when adjusting for age, Charlson Comorbidity Index, and

mortality in S. pyogenes bacteremia.	focus of infection (odds ratio, 3.7 [95% confidence interval, 1.2–11.3]; *P* = .02). There was no statistically significant difference in TTP between patients with sepsis within 48 hours and those who did not have sepsis. Additionally, there was no statistically significant difference in TTP between patients with disease deterioration compared to those who did not deteriorate • Knowledge on TTP might be a tool to determine the prognosis of a given patient with *S pyogenes* bacteremia. • https://doi.org/10.1093/ofid/ofac163
NEJM - 6/29/22 - Pfizer vaccine effectiveness for 5-12 year olds.	• Among 136,127 eligible children who had been vaccinated during the study period, 94,728 were matched with unvaccinated controls. • The estimated vaccine effectiveness against documented infection was 17% (95% confidence interval [CI], 7 to 25) at 14 to 27 days after the first dose and 51% (95% CI, 39 to 61) at 7 to 21 days after the second dose. The absolute risk difference between the study groups at days 7 to 21 after the second dose was 1905 events per 100,000 persons (95% CI, 1294 to 2440) for documented infection and 599 events per 100,000 persons (95% CI, 296 to 897) for symptomatic Covid-19. • The estimated vaccine effectiveness against symptomatic Covid-19 was 18% (95% CI, −2 to 34) at 14 to 27 days after the first dose and 48% (95% CI, 29 to 63) at 7 to 21 days after the second dose. We observed a trend toward higher vaccine effectiveness in the youngest age group (5 or 6 years of age) than in the oldest age group (10 or 11 years of age). • https://www.nejm.org/doi/full/10.1056/NEJMoa2205011?query=featured_coronavirus
CID - 6/2022 - Remdesivir and mortality in patients with Coronavirus	• A total of 1138 patients were enrolled, including 286 who received RDV and 852 treated with BSC, 400 of whom received Hydroxychloroquine. Corticosteroids were used in 20.4% of the cohort (12.6% in RDV and 23% in BSC). • Comparing persons receiving RDV with those receiving BSC, the hazard ratio (95% confidence interval) for death was 0.46 (.31–.69) in the univariate model (*P* < .001) and 0.60 (.40–.90) in the risk-adjusted model (*P* = .01). In the subgroup of persons with baseline use of low-flow oxygen, the hazard ratio (95% confidence interval) for death in RDV compared with BSC was 0.63 (.39–1.00; *P* = .049) • Treatment with RDV was associated with lower mortality rates than BSC • https://doi.org/10.1093/cid/ciab698
CID - 6/2022 - Factors associate	• Among 29 659 patients, 1070 (3.6%) were readmitted. • Readmitted patients were more likely to have ○ diabetes, hypertension, cardiovascular disease (CVD), or chronic kidney disease (CKD) vs those not readmitted (*P* < .0001) and to

d with readmission in the US following hospitalization with COVID	present on first admission with acute kidney injury (15.6% vs 9.2%), congestive heart failure (6.4% vs 2.4%), or cardiomyopathy (2.1% vs 0.8%) (*P* < .0001). • Higher odds of readmission were observed in patients aged >60 vs 18–40 years (odds ratio [OR], 1.92; 95% confidence interval [CI], 1.48–2.50) and those admitted in the Northeast vs West (OR, 1.43; 95% CI, 1.14–1.79) or South (OR, 1.28; 95% CI, 1.11–1.49). • Comorbidities including diabetes (OR, 1.34; 95% CI, 1.12–1.60), CVD (OR, 1.46; 95% CI, 1.23–1.72), CKD stage 1–5 (OR, 1.51; 95% CI, 1.25–1.81), and CKD stage 5 (OR, 2.27; 95% CI, 1.81–2.86) were associated with higher odds of readmission; 12.3% of readmitted patients died during second hospitalization • https://doi.org/10.1093/cid/ciab464
Brain - 6/5/2022 - neurovascular injury and complement activation in COVID	• The underlying mechanisms by which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leads to acute and long-term neurological manifestations remains obscure. We aimed to characterize the neuropathological changes in patients with coronavirus disease 2019 and determine the underlying pathophysiological mechanisms. • In this autopsy study of the brain, we characterized the vascular pathology, the neuroinflammatory changes and cellular and humoral immune responses by immunohistochemistry. • All patients died during the first wave of the pandemic from March to July 2020. All patients were adults who died after a short duration of the infection, some had died suddenly with minimal respiratory involvement. Infection with SARS-CoV-2 was confirmed on ante-mortem or post-mortem testing. Descriptive analysis of the pathological changes and quantitative analyses of the infiltrates and vascular changes were performed. • All patients had multifocal vascular damage as determined by leakage of serum proteins into the brain parenchyma. This was accompanied by widespread endothelial cell activation. • Platelet aggregates and microthrombi were found adherent to the endothelial cells along vascular lumina. Immune complexes with activation of the classical complement pathway were found on the endothelial cells and platelets. • Perivascular infiltrates consisted of predominantly macrophages and some $CD8^+$ T cells. Only rare $CD4^+$ T cells and $CD20^+$ B cells were present. Astrogliosis was also prominent in the perivascular regions. Microglial nodules were predominant in the hindbrain, which were associated with focal neuronal loss and neuronophagia. • Antibody-mediated cytotoxicity directed against the endothelial cells is the most likely initiating event that leads to vascular leakage, platelet

	aggregation, neuroinflammation and neuronal injury. Therapeutic modalities directed against immune complexes should be considered • https://academic.oup.com/brain/advance-article/doi/10.1093/brain/awac151/6621999?searchresult=1&login=false
MedRxIv - protection of COVID natural infection against reinfection with BA.4 and BA.5	• Effectiveness of a previous pre-Omicron infection against symptomatic BA.4/BA.5 reinfection was 1**5.1%** (95% CI: -47.1 to 50.9%), and against any BA.4/BA.5 reinfection irrespective of symptoms was **28.3%** (95% CI: 11.4 to 41.9%). • Effectiveness of a previous Omicron infection against symptomatic BA.4/BA.5 reinfection was **76.1% (**95% CI: 54.9 to 87.3%), and against any BA.4/BA.5 reinfection was **79.7% (**95% CI: 74.3 to 83.9%). Results using all diagnosed infections when BA.4/BA.5 dominated incidence confirmed the same findings. Sensitivity analyses adjusting for vaccination status confirmed study results. Protection of a previous infection against BA.4/BA.5 reinfection was modest when the previous infection involved a pre Omicron variant, but strong when the previous infection involved the Omicron BA.1 or BA.2 subvariants. Protection of a previous infection against BA.4/BA.5 was lower than that against BA.1/BA.2, consistent with BA.4/BA.5 greater capacity for immune system evasion than that of BA.1/BA.2 • https://www.medrxiv.org/content/10.1101/2022.07.11.22277448v1
Lancet - 7/13/2022 - effectiveness of 4th dose of COVID vaccine against all-cause mortality	• From 7 days after baseline and onwards, there were 1119 deaths in the LTCF cohort during a median follow-up of 77 days and a maximum follow-up of 126 days. • During days 7 to 60, the VE of the fourth dose was 39% (95% CI, 29-48), which declined to 27% (95% CI, -2-48) during days 61 to 126. • In the cohort of all individuals **aged ≥80 years**, there were 5753 deaths during a median follow-up of 73 days and a maximum follow-up of 143 days. During days 7 to 60, the VE of the fourth dose was 71% (95% CI, 69-72), which declined to 54% (95% CI, 48-60) during days 61 to 143. The VE of the fourth dose seemed stronger when it was compared to third-dose recipients where at least four months had passed since vaccination ($P < 0{\cdot}001$ for interaction). • https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(22)00162-4/fulltext
Lancet - 7/8/2022 - Tixagevimab-	• From Feb 10 to Sept 30, 2021, 1455 patients were randomly assigned and 1417 in the primary modified intention-to-treat population were infused with tixagevimab–cilgavimab (n=710) or placebo (n=707). The estimated cumulative incidence of sustained recovery was 89% for tixagevimab–cilgavimab and 86% for placebo group participants at day

cilgavimab for treatment of COVID in hospitalized pts.	90 in the full cohort (recovery rate ratio [RRR] 1·08 [95% CI 0·97–1·20]; p=0·21). Results were similar in the seronegative subgroup (RRR 1·14 [0·97–1·34]; p=0·13). • Mortality was lower in the tixagevimab–cilgavimab group (61 [9%]) versus placebo group (86 [12%]; hazard ratio [HR] 0·70 [95% CI 0·50–0·97]; p=0·032). The composite safety outcome occurred in 178 (25%) tixagevimab–cilgavimab and 212 (30%) placebo group participants (HR 0·83 [0·68–1·01]; p=0·059). Serious adverse events occurred in 34 (5%) participants in the tixagevimab–cilgavimab group and 38 (5%) in the placebo group • Among patients hospitalized with COVID-19 receiving Remdesivir and other standard care, tixagevimab–cilgavimab did not improve the primary outcome of time to sustained recovery but was safe and mortality was lower • https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00215-6/fulltext