SARS-CoV-2 and COVID-19

EPIDEMIOLOGY

Transmission Dynamics. Person-to-person transmission documented with mean incubation period 5.2 d, serial interval 7.5 d, reproductive number approximately 2.2 (Li, NEJM); inter-individual contact data can be used to estimate R0 (reproduction number) in health care facilities to inform infection control measures (Temime, MedRxiv)

Families. Family clusters observed (Chan, Lancet); estimated transmission risk ranges from 1-16% among household contacts (Wu CROI presentation, https://special.croi.capitalreach.com/; Li, Clin Infect Dis); family gatherings may facilitate community spread (Ghinai, MMWR)

Children. Infection is common in children but most are asymptomatic or mild, including early neonatal infections (Cai, Clin Infect Dis; Lu, NEJM; Dong, Pediatrics; Qiu, Lancet Infect Dis; Zeng, JAMA Pediatr; Wei, JAMA; Castagnoli, JAMA Pediatr; Parri, NEJM); children may still contribute to transmission and have viral loads comparable to adults (Jones, Charite preprint)

Asymptomatic Transmission. Asymptomatic or pre-symptomatic transmission makes an important contribution to spread (Rothe, NEJM; Yu, J Infect Dis; Bai, JAMA; Tong, Emerg Infect Dis; Li, Science; Xia, MedRxiv; Tao, MedRxiv; Qian, Clin Infect Dis; Wei, MMWR); this is further supported by comparison of the transmission interval and incubation period in China, Japan and Singapore (Nishiura, Int J Infect Dis; Tindale, MedRxiv); over half of PCR-positive residents of Life Care Center of Kirkland were asymptomatic on initial testing, and viral load did not correlate with the presence of symptoms (Kimball, MMWR; Arons, NEJM), which has also been noted in Italy (Cereda, ArXiv); contact tracing and testing revealed 20% of secondary cases to be asymptomatic at the time of first clinical assessment (Bi, Lancet Infect Dis); 43% of SARS-CoV-2-positive persons detected in population-based screening in Iceland denied symptoms (Gudbjartsson, NEJM); containment measures, movement restrictions and increased awareness may shorten the window of transmission (Zhang, Lancet Infect Dis)

Superspreaders. Superspreader events appear to be associated with explosive growth and sustained transmission of COVID-19 (https://wwwnc.cdc.gov/eid/article/26/6/20-0495_article); closed environments may promote superspreading, as transmission is 19-times more likely in a closed environment than in open air (Nishiura, MedRxiv), and possible aerosol transmission has occurred in crowded and poorly ventilated enclosures (Li, MedRxiv); out of 318 outbreaks outside of Hubei province, only 1 occurred outdoors; most occurred in homes or transport, but the largest occurred in a shopping mall (Qian, MedRxiv)

Viral Shedding. High pharyngeal viral shedding on day zero is seen with a subsequent decline, more like influenza than SARS (He, MedRxiv; Zou, NEJM; To, Lancet Infect Dis), but some patients may continue to be PCR-positive (Lan, JAMA); PCR-positivity persists for 7-12 days in
mild-moderate cases but longer in severe cases (Wu CROI presentation
https://special.croi.capitalreach.com/arc/audD3b/o1)

**Washington State.** First US cases in Washington State described (Holshue, NEJM; Arentz, JAMA); COVID-19 detected in all 50 states by early March, and genomic epidemiology suggests the importance of cryptic domestic spread (Fauver, MedRxiv; Bedford, MedRxiv); surveillance by the Seattle Flu Study detected early SARS-CoV-2 circulation (Chu, NEJM); Life Care Center of Kirkland outbreak ended up involving 101 residents, 50 HCWs and 16 visitors (McMichael NEJM); links with other LTCFs involving shared staff or patients were identified

**Community Prevalence.** High prevalence found when screening homeless shelter residents and staff in Boston, Seattle and San Francisco (Baggett, JAMA; Mosites, MWR); a mobile community, crowding, asymptomatic transmission and lack of face coverings are thought to contribute to the high rates of COVID-19 in homeless shelters (Tobolowsky, MMWR); a survey estimated SARS-CoV-2 seroprevalence to be 2.8% in Santa Clara County (Bendavid, MedRxiv), which is unexpectedly high (but concerns have been raised regarding sampling bias, inconsistency with rates of SARS-CoV-2 spread and mortality in other communities, and the likelihood of false-positive results)

**Cruise Ships.** Recent outbreaks on cruise ships resulted in more than 800 infections and 10 deaths (Moriarty, MMWR)

**Seasonal Factors.** Inverse relationship observed between temperature/humidity and transmission (Wang, MedRxiv; Ma, MedRxiv; Oliveira, MedRxiv; Araujo, MedRxiv; Neher, MedRxiv; Sajadi, SSRN; Bukhari, SSRN)

**Environmental Stability.** SARS-CoV-2 may remain detectable in aerosols for at least 3 h and is more stable on plastic/steel than on copper/cardboard; inactivated by 70% ethanol, 0.5% hydrogen peroxide or 0.1% bleach but less reliably by benzalkonium chloride or chlorhexidine (Kampf, J Hosp Infect; van Doremalen, NEJM)

**Possible Effects of BCG.** Attributable mortality is lower in BCG vaccine-using countries (Miller, MedRxiv; Shet, MedRxiv); however, the purported relationship between BCG and COVID-19 susceptibility is being heavily criticized because of testing, time and selection bias (Szigeti, MedRxiv) and failure to control for confounding by population age (Kirov, MedRxiv)

**VIROLOGY**

**SARS-CoV-2 Virus.** Description of SARS-CoV-2 (Zhu, NEJM; Lu, Lancet; Wu, Nature)

**Relation to Other Coronaviruses.** 88-96% similarity to bat coronaviruses (Zhou, Nature); pangolin suggested as reservoir host (Zhang, Curr Biol; Lam, Nature), used for food and
traditional Chinese medicine, but pangolin coronaviruses lack a furin cleavage site found in SARS-CoV-2

**Binding.** Structure of spike protein and binding to ACE2 (Wrapp, Science; Yan, Science; Hoffmann, Cell; Walls, Cell); the distribution of tissue ACE2 expression may explain higher viral loads in the lower respiratory tract; ACE2 expressed in airways, cornea, GI tract, liver, heart, kidney, testis (Sungnak, Nat Med); productive infection of human gut epithelial cells has been demonstrated (Lamers, Science)

**Furin Cleavage.** Furin-like cleavage site in the spike glycoprotein may broaden cell tropism (Coutard, Antiviral Res)

**Subtypes.** Possible subtypes with differences in virulence (Tang, Nat Sci Rev; Xi, MedRxiv; Su, BioRxiv; Korber, BioRxiv)

**Immune Response.** Increased antibody-secreting cells (ASCs), follicular helper T cells (T_{FH} cells), activated CD4+/CD8+ T cells and IgM/IgG SARS-CoV-2-binding antibodies were observed in a patient with non-severe COVID-19 prior to recovery, suggesting that they might provide a correlate of favorable outcomes and protective immunity (Thevarajan, Nat Med); possible immunopathological mechanisms include antibody-dependent enhancement and promotion of Th2 responses (Peeples, PNAS)

**Immune Evasion.** Transcriptomic response suggests a muted antiviral response compared to other respiratory viruses (Blanco-Melo, BioRxiv); weak induction of interferon responses is observed (Chu, Clin Infect Dis; O’Brien, Clin Infect Dis); STAT2 signaling appears to play a role in both antiviral defense and immunopathology in a hamster model, suggesting that immunomodulators may potentially have mixed effects (Boudewijns, BioRxiv); like other subacute viral infections, may cause T-cell exhaustion as well as depletion (Vardhana, J Exp Med)

**Complement Activation.** Viral N protein induces complement activation, which may contribute to acute lung injury (Gao, MedRxiv)

**Interaction with Olfactory Epithelium.** Sustentacular cells in the olfactory neuroepithelium express the ACE2 receptor and TMPRSS2 protease required for viral attachment and entry (Fodoulian, BioRxiv); this may help to explain COVID-19-associated anosmia

**Animal Models.** Syrian hamsters can be used to study transmission, pathogenesis, treatment and immunization (Chan, Clin Infect Dis); SARS-CoV-2 replicates throughout the respiratory tract in a macaque model (Rockx, Science)

**Autopsy Pathology.** Autopsy findings in patients with COVID-19-associated ARDS shows edema, proteinaceous exudate, focal reactive pneumocyte hyperplasia, patchy inflammatory cellular infiltration, and multinucleate giant cells consistent with diffuse alveolar damage similar
to SARS/MERS (Xu, Lancet Respir Med; Liu, J Med Virol); Spleens and lymph nodes show lymphocyte depletion and virally-infected macrophages producing IL-6 (Feng, MedRxiv); a striking finding is thrombotic microangiopathy, generally but not always restricted to the lungs (Fox, MedRxiv; Dolhnikoff, J Thromb Haemost; Carsana, MedRxiv; Marini, JAMA suppl), although autopsies of Washington State patients, many of whom were from a long-term care facility, found diffuse alveolar damage and virus in type I and II pneumocytes but no microthrombi (Bradley, MedRxiv); some patients show pulmonary septal capillary injury with complement/fibrin deposition in the microvasculature rather than classic ARDS (Magro, Transl Res); endothelial infection by SARS-CoV-2 may promote microvascular dysfunction and thrombosis (Varga, Lancet)

**CLINICAL**

**Incubation.** Incubation period usually 4-5 d, most within 14 d (Chan, Lancet; Lauer, Ann Intern Med); incubation period may range up to 24 d in exceptional cases (Nie, J Infect Dis)

**Usual Clinical Presentation.** Male > female, median age 49 y, fever, cough, myalgia, fatigue, dyspnea, lymphopenia, ARDS, cardiac injury; myalgias, confusion, headache, sore throat, coryza, chest pain, secondary infection infrequent (Huang, Lancet; Chen, Lancet; Wang, JAMA; Xu, BMJ; Guan, NEJM); rates of hospitalization and mortality higher in men (Garg, MMWR; Lewnard, MedRxiv)

**Other Signs and Symptoms.** A prospective study of 16,749 people with COVID-19 in the UK found distinct respiratory, systemic and enteric presentations (Docherty, MedRxiv); may present with mild URI symptoms, particularly in young healthy persons (Arashiro, Emerg Infect Dis; Woelfel, Nature); GI symptoms infrequent in some series but may be the primary presenting symptoms in a subset of patients (Pan, Am J Gastroenterol; D’Amico, Clin Gastroenterol Hepatol) and can include abdominal pain in absence of fever (Gahide, Clin Med); GI symptoms may be associated with milder illness (Nobel, Gastroenterology; Han, Am J Gastroenterol; Buscarini, MedRxiv) but have also been reported to be a risk factor for hospitalization (Cholankeril, Am J Gastroenterol); >85% of patients with mild-moderate COVID-19 may report alteration or loss of taste/smell (Iacobucci, BMJ; Lechien, Eur Arch Oto-Rhinol Laryngol; Spinato, JAMA); most patients with anosmia/dysgeusia recover quickly (Levinson, MedRiv); ocular signs may include conjunctival hyperemia, chemosis, epiphora or ocular secretions (Wu, JAMA Ophthalmol); cutaneous findings include acral erythema, vesicular eruptions, urticaria, maculopapular rash and livedo or necrosis (Casas, Br J Dermatol)

**Course of Pre-symptomatic Infections.** Pre-symptomatic cases detected on screening usually result in mild disease (Wang, J Infect Dis)

**Fever.** Although fever is a common feature of COVID-19, only half of Seattle patients requiring ICU admission for severe COVID-19 were febrile on admission (Bhatraju, NEJM); a biphasic illness is seen in severe cases, with fever at the onset of illness and again in the second week of
illness at the time of acute deterioration and ARDS (https://youtu.be/Om9VTacb6VM; Kujawski, Nat Med); in patients with acute deterioration, viral load may indicate whether antiviral or immunomodulatory therapy is more likely to be beneficial (Lescure, Lancet Infect Dis; Joynt, Lancet Infect Dis)

**Laboratory Findings.** Lymphopenia (Tan, MedRxiv), eosinopenia (Li, MedRxiv) and elevated NLR (neutrophil-to-lymphocyte ratio, Qin, Clin Infect Dis; Liu, J Infect) are predictive of more severe illness; elevated LDH, ferritin, LFTs, IL-2R/IL-6/IL-10/TNFα and reduced CD4+/CD8+ T cells common (Chen, J Clin Invest; Pedersen, J Clin Invest; Wang, JCI Insight), procalcitonin may be elevated; Lymphopenia, elevated D-dimer ≥2.0 mcg/ml, CRP, procalcitonin predictive of mortality (Paranjpe, MedRxiv; Zhang, J Thromb Haemost)

**Hypercoagulable State.** Abnormal coagulation parameters are common and associated with increased mortality risk (Tang, J Thromb Haemost; Lillicrap, J Thromb Haemost; Violi, Throm Haemost); coagulopathy, endothelial damage and inflammation can promote thrombosis (Connors, Blood); anti-phospholipid antibodies or lupus anticoagulant may be detected in the setting of coagulopathy and multifocal thrombosis (Zhang, NEJM; Harzallah, J Thromb Haemost); thromboelastography more consistent with an inflammatory hypercoagulable state than with DIC (Panigada, J Thromb Haemost; Spiezia, Thromb Haemost); ~30% incidence of thrombotic complications in ICU patients with COVID-19 (Klok, Thromb Res); high risk of venous thromboembolism and pulmonary embolism in patients with severe COVID-19 (Lodigiani, Thromb Res), even on therapeutic anticoagulation (Llitjos, J Thromb Haemost)

**Radiographic Findings.** Chest CT shows multifocal ground-glass opacities, but findings overlap with other causes of viral pneumonitis (Chung, Radiology; Zhou, AJR; Shi, Lancet Infect Dis; Li, AJR); most discriminating chest CT features of COVID-19 pneumonia are peripheral distribution, ground glass opacities and vascular thickening (Bai, Radiology); may be abnormal in asymptomatic individuals (Hu, Sci China Life Sci); consensus guidelines for the use of chest imaging are available (Rubin, Radiology); electrical impedance tomography suggests distinctive pulmonary physiology in some patients with severe COVID-19 with more ventilated/nonperfused units, consistent with vasculopathy (Mauri, Crit Care Med)

**Ultrasound.** Lung ultrasound may show pleural thickening, B lines and consolidation (Peng, Intensive Care Med)

**Risk Factors and Outcomes.** Case-Fatality Rate 1.38% with a strong age-gradient (Verity, MedRxiv; Wu, Nature Med); most deaths occur in patients with co-morbidities including cardiovascular/pulmonary disease and diabetes (Wu, JAMA; Zhou, Lancet; Guan, MedRxiv; COVID-19 Response Team, MMWR); higher CFR reported in Italy, attributable to more patients ≥70 years of age (Onder, JAMA); although CFR is highest in older patients, a substantial number of patients aged 20-64 are requiring hospitalization and ICU admission (COVID-19 Response Team, MMWR; Myers, JAMA); dyspnea, ARDS and cardiac injury (elevated troponin T) are associated with fatal outcomes (Chen, BMJ; Guo, JAMA Cardiol; Gupta, JAHA); hyperkalemia, acute kidney injury and hypoxic encephalopathy may also be seen; mortality in patients
requiring ICU admission may be ~25% (Grasselli, JAMA); high SOFA score is predictive of mortality (OR 5.65; Zhou, Lancet); 28d survival 61% in patients requiring ICU admission (Wang, AJRCCM); reported mortality in patients requiring mechanical ventilation has varied widely from 17-88%, but unclear if patient populations are comparable and some estimates inflated due to incomplete follow-up (Richardson, JAMA; Auld, MedRxiv; Petrilli, MedRxiv; Docherty, MedRxiv; Ziehr, NEJM); patients requiring mechanical ventilation nearly always require vasopressor support (Goyal, NEJM); risk factors for severe illness are obesity, O2 sat <88% and elevated D-dimer/ferritin/CRP (Petrilli, MedRxiv; Lighter, Clin Infect Dis); from Feb-Apr 2020, COVID-19 was calculated to have caused 21 times more deaths than seasonal influenza in NYC (Faust, MedRxiv)

Cardiac and Neurologic Complications. Cardiac injury more common in severe illness (Hui, MedRxiv), which can be accompanied by arrhythmias and may be due to the presence of ACE2 on cardiac myocytes (Zheng, Nat Rev Cardiol; Wang, JAMA clinical); cardiac injury is an independent risk factor for in-hospital mortality (Shi, JAMA Cardiology); 58% increase in out-of-hospital cardiac arrest observed during the COVID-19 outbreak in Italy (Baldi, NEJM); neurologic abnormalities are not uncommon but may result from indirect mechanisms (Mao, JAMA Neurol); acute CVA may be a presentation of COVID-19, including patients <50 yrs of age (Oxley, NEJM); Guillain-Barré Syndrome has been reported (Toscano, NEJM)

Cytokine Storm. Cytokine storm and elevated IL-6 levels seen in severe illness (Wang, Clin Infect Dis; Chen, MedRxiv; Wang (2), MedRxiv; Yang, MedRxiv; Moore, Science; Tay, Nat Rev Immunol); IL-6 levels ≥80 pg/ml associated with 22-fold increased risk of respiratory failure (Herold, MedRxiv)

Immunocompromised Hosts. Rates of hospitalization in patients on immunosuppressive therapy in NYC were comparable to the general population (Haberman, NEJM); some immunocompromised populations have been reported to have a generally favorable prognosis (Minotti, J Infect), but a higher case-fatality rate has been observed for patients with cancer in NYC (Mehta, Cancer Discov), and kidney transplant recipients in NYC had a high early mortality (28% at 3 wks) (Akalin, NEJM)

Pregnancy. Clinical course similar in pregnant women without definitive evidence of intrauterine or transplacental transmission (Chen, Lancet; Schwartz, Arch Pathol Lab Med; Chen, NEJM); detection of antibodies including IgM in newborns of SARS-CoV-2-infected mothers suggests possible in utero infection, but virus not detected (Dong, JAMA; Zeng, JAMA; Kimberlin, JAMA); may be an increased risk of preterm delivery (Mullins, Ultrasound Obstet Gynecol; Wang, Clin Infect Dis); 88% of COVID-positive pregnant women admitted for delivery during the NYC epidemic were asymptomatic (Sutton, NEJM)

Impact on Surgical Outcomes. Asymptomatic patients with COVID-19 who undergo elective surgery may have unexpectedly poor outcomes, with 44% requiring ICU care and 21% mortality (Lei, EClinicalMedicine)
LABORATORY DIAGNOSIS

Diagnostic Tests. Diagnostic testing plays an extremely important role in COVID-19 control, but there are still major unmet needs in the diagnostic pipeline (Cheng, Ann Intern Med); Demographic data, labs (CRP, LDH, ferritin, neutrophil/lymphocyte counts) and x-ray/CT can be used for a presumptive diagnosis of COVID-19 with 96% sensitivity and 95% specificity (Kurstjens, MedRxiv)

Clinical Specimens for Viral Detection. Sequential utility of specimen types: upper respiratory specimens more sensitive early in illness, lower respiratory tract specimens more sensitive later, fecal specimens remain positive the longest (Song, J Med Virol); PCR of Sputum or BALF is more sensitive than upper respiratory specimens (Wang, JAMA: Han, Lancet Infect Dis; Lin, MedRxiv; Loeffelholz, Emerg Microbes Infect; Cheng, Ann Intern Med); PCR sensitivity parallels higher viral load in sputum compared to nasopharyngeal or throat swabs (Zou, NEJM; Yu, Clin Infect Dis); viral load at the time of admission may be predictive of disease severity and prognosis (Liu, Lancet Infect Dis); self-collected tongue, nasal, saliva or mid-turbinate swabs reported to be as or more sensitive than health care worker-collected nasopharyngeal swabs (Tu, MedRxiv; Wehrhahn, MedRxiv; Kojima, MedRxiv; Wyllie, MedRxiv; Williams, J Clin Microbiol); differences observed in the sensitivity of primer-probe sets used to detect SARS-CoV-2, with E gene (Charité), ORF1 (HKU) and N1 (US CDC) more sensitive than RdRp-SARSr (Charité) (Vogels, MedRxiv)

Limitations of PCR. A negative NP/OP swab does not rule-out COVID-19 (Winichakoon, J Clin Microbiol; Long, Eur J Radiol); PCR assays may revert to positive in a minority of patients, clinical significance of this is unknown (Yuan, Clin Infect Dis)

Other Specimens. Virus detected in urine, blood, anal swabs, saliva (To, Clin Infect Dis; Peng, MedRxiv; Tang, J Clin Microbiol)

Viral Shedding. PCR may continue to detect viral RNA for weeks, but cultures of respiratory secretions in patients with mild illness become negative after 8 days (Woelfel, MedRxiv); severely ill patients may continue to exhibit detectable viral RNA in lower respiratory tract specimens for weeks to months (Huang, AJRCCM; Zheng, BMJ; Xiao, Clin Infect Dis); viral RNA can also be found in stool for weeks, but there is currently little evidence of fecal-oral transmission (Pan, Lancet infect Dis; Gu, Gastroenterology; Wu, Lancet Gastroenterol Hepatol; Chan, Ann Intern Med; Cheung, Gastroenterology; Xu, Nat Med)

Co-Infections. Co-infections may be present (Lin, Sci China Life Sci; Kim, JAMA)

Adjunctive Role of CT Scanning. Chest CT may show abnormalities even when PCR is negative (Fang, Radiology; Ai, Radiology); dual-energy CT may detect regions of decreased perfusion surrounded by a halo of higher perfusion indicative of disrupted pulmonary vasoregulation (Lang, Lancet Infect Dis)
Serology. Serologic tests vary in sensitivity and specificity (Okba, MedRxiv; Whitman, MedRxiv); IgG more sensitive than IgM, but IgM and IgG exhibit similar kinetics (Jin, Int J Infect Dis; Xiang, Clin Infect Dis); combination of RT-PCR and serology may enhance case detection (Guo, Clin Infect Dis; Zhao, Clin Infect Dis 2; Zhang, J Infect Dis); many patients seroconvert within 14 d of symptom onset, and most seroconvert by 20d (Long, MedRxiv; To, Lancet Infect Dis; Lou, MedRxiv); Ab titers correlate with disease severity (Zhao, Clin Infect Dis); commercial assays exhibit considerable variation in sensitivity and specificity (Lassauniere, MedRxiv); neutralizing Ab titers in recovered patients are variable and correlate with CRP and lymphopenia (Wu, MedRxiv); False negative serologies may result from waning antibody levels, and sensitivity of serology in subclinical infection is presently unknown, but seroconversion may not occur in some asymptomatic infections (Zhang, Emerg Microbes Infect); antibody titers do not necessarily mean immunity, and protection may be transient (Huang, MedRxiv)

Biosafety. Clinical lab safety recommendations have been published (Iwen, Am J Clin Pathol)

TREATMENT

Investigational Agents. A large number of potential therapeutic agents is under investigation (Sanders, JAMA); the importance of maintaining standards in clinical research despite the urgency of a pandemic has been emphasized (London, Science); timing of antiviral, immunomodulatory and anticoagulant interventions must take into account the sequential progression of illness from viral to pulmonary to inflammatory and hypercoagulable phases of illness (Liu, Circulation; Siddiqi, J Heart Lung Transpl)

Remdesivir. Remdesivir is a potent inhibitor of SARS-CoV-2 RNA-dependent RNA polymerase (Gordon, J Biol Chem) that causes chain termination (Yin, Science) and is active in vitro (Wang, Cell Res); effective when given prophylactically or therapeutically in a macaque model of MERS-CoV (de Wit, PNAS) and when given early in a macaque model of COVID-19 (Willamson, MedRxiv); results of compassionate use of remdesivir reported in 63 patients (Grein, NEJM): clinical improvement observed in 68%, and 57% of intubated patients were able to be extubated, but no control group or viral load measurement, and adverse events seen in 60% (including elevated LFTs); a double-blind placebo-controlled RCT in China found no benefit from remdesivir, although there was a trend toward more rapid clinical improvement in patients with symptoms ≤ 10d (Wang, Lancet)

Chloroquine/Hydroxychloroquine/Azithromycin. Hydroxychloroquine inhibits SARS-CoV-2 replication in vitro (Yao, Clin Infect Dis; Liu Cell Discovery); anecdotal reports of clinical benefit of chloroquine/hydroxychloroquine (Gao, Biosci Trends); a non-randomized French open-label trial reported evidence of an anti-viral effect in vivo, particularly in combination with azithromycin (Gautret, MedRxiv/Int J Antimicrob Agents); however, a small RCT of hydroxychloroquine failed to show a beneficial effect on viral clearance or clinical resolution (Chen, J Zhejiang Univ), while another RCT involving 62 patients observed more rapid clinical
resolution and fewer patients progressing to severe illness in hydroxychloroquine recipients (Chen, MedRxiv HCQ); a subsequent larger study by the French authors has reported a good virologic and clinical outcome in 72 of 74 additional recipients of combination therapy, but without a control group (Gautret, unpublished); concerns have been raised regarding the paper by Gautret, et al. and the use of hydroxychloroquine to treat COVID-19 outside research protocols (Kim, Ann Intern Med; Hulme, MedRxiv; Yazdany, Ann Intern Med); a different French group was unable to demonstrate rapid viral clearance in 11 patients receiving the same regimen of hydroxychloroquine and azithromycin, and one patient had treatment discontinued due to QT prolongation (Molina, Med Mal Infect); acute renal failure is a risk factor for QTc prolongation on hydroxychloroquine/azithromycin, but baseline QTc is not (Chorin, Nat Med); based on PK studies of hydroxychloroquine in patients with COVID-19, a loading dose of 800 mg followed by 200mg BID for 7 days has been suggested (Perinel, Clin Infect Dis)

Additional Studies of Hydroxychloroquine. An RCT of hydroxychloroquine in China (n=75 per group) failed to detect an effect on viral clearance but found more rapid symptomatic improvement and resolution of inflammatory parameters, suggesting a possible immunomodulatory effect (Tang, MedRxiv); a retrospective French study (n=181) of patients with COVID-19 and hypoxemia found no significant reduction in ICU transfers, ARDS or mortality (Mahevas, MedRxiv)—8 patients had to discontinue hydroxychloroquine due to QTc prolongation or AV block; a retrospective of 368 VA patients found higher mortality in recipients of hydrochloroquine (27.8%) or hydrochloroquine plus azithromycin (22.1%) compared to no hydrochloroquine (11.4%), but selection bias and residual confounding cannot be excluded (Magagnoli, MedRxiv); chronic HCQ did not prevent COVID-19 in 14 patients with SLE, 7 of whom required ICU admission with 2 deaths (Mathian, Ann Rheum Dis)

Tocilizumab. Possible benefits of tocilizumab (IL-6RA) or other immunomodulators in patients with severe illness or cytokine storm (Liu, MedRxiv; Xu, PNAS; Mehta, Lancet), although another uncontrolled trial of tocilizumab in 15 patients (8 of whom also received steroids) reported highly variable clinical responses with worsening in 2 and death in 3 (Luo, J Med Virol); a retrospective cohort study (n=59) found lower mortality in tocilizumab recipients (Roumier, MedRxiv); 2 patients treated with tociluzumab still progressed to macrophage activation syndrome, and one developed viral myocarditis (which may have resulted from immunosuppression) (Radbel, Chest); IL-6-driven immune dysregulation with macrophage activation syndrome and impaired antigen presentation is partially rescued by tocilizumab, with an increase in lymphocyte count and HLA-DR expression (Giamarellos-Bourbolis, Cell Host Microbe); a different IL-6 antagonist siltuximab was associated with a decline in CRP but variable clinical responses (Gritti, MedRxiv)

Lopinavir-Ritonavir. No benefit from lopinavir-ritonavir seen in severe COVID-19 (Cao, NEJM)

Treatment of Coagulopathy. ISTH and other societies have endorsed interim guidance on recognition and management of COVID-19-related coagulopathy (Thachil, J Thromb Haemost; Bikdeli, JACC); anticoagulation may be beneficial in patients with coagulopathy and marked D-dimer elevation (Tang 2, J Thromb Haemost); improved oxygenation in response to therapeutic
heparin (Negri, MedRxiv) or tissue plasminogen activator (tPA) (Wang, J Thromb Haemost; Poor, MedRxiv); coagulation studies may support the need for intensive anticoagulation (Panigada, J Thromb Haemost; Ranucci, J Throm Haemost; Connors, J Throm Haemost; Connors, Blood)

**Complement Inhibition.** Complement activation may contribute to thrombotic microangiopathy (Campbell, Circulation; Ciceri, Crit Care Resusc; Magro, Transl Res; Risitano, Nat Rev Immunol); anecdotal evidence that complement inhibition can improve oxygenation and reduce inflammation (Gao, MedRxiv)

**Corticosteroids.** Possible benefits of low-dose corticosteroids (Wu, JAMA Intern Med; Wang, MedRxiv), but this is controversial (Russell, Lancet; Shang, Lancet)

**Convalescent Plasma.** Possible benefit reported in an uncontrolled trial of convalescent plasma with viral neutralizing activity (Shen, JAMA); in another study, convalescent plasma with neutralizing Ab titers >1:640 was administered to 10 patients with severe COVID-19; clinical improvement was observed with falling viral load, rising lymphocyte counts, improved O2 saturation, and decreased CRP (Duan, PNAS); however, 6 patients with severe COVID-19 received convalescent plasma and cleared their virus, but 5 of them died nevertheless (Zeng, J Infect Dis); a clinical trial of convalescent serum will be initiated (Casadevall and Pirofski, J Clin Invest; Bloch J Clin Invest)

**Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers.** Continuation of ACE inhibitors/ARBs recommended (Patel, JAMA; Vaduganathan, NEJM), and ACEi/ARB are not a risk factor for COVID-19 (Mancia, NEJM; Mehra, NEJM; Reynolds, NEJM); although hypertension is a risk factor for severe COVID-19, patients taking ACE inhibitors or angiotensin receptor blockers may be less likely to develop severe pneumonia (Feng, MedRxiv)

**Ibuprofen.** Avoidance of ibuprofen recommended but with little basis in evidence (Day, BMJ)

**Favipiravir.** Treatment with favipiravir, an RNA polymerase inhibitor, was superior to lopinavir-ritonavir in promoting viral clearance and radiographic improvement in an open-label non-randomized study (Cai, Engineering); patients in both arms also received inhaled IFN-α; nebulized IFN-α2b has been used in China and reported to reduce viral shedding in the respiratory tract in parallel with reduced inflammatory markers (Zhou, medRxiv)

**Arbidol.** Arbidol is a broad spectrum antiviral that blocks cell entry of enveloped viruses; a small trial found more rapid resolution of viral load and laboratory abnormalities in recipients of arbidol compared to recipients of lopinavir/ritonavir (Zhu, J Infect)

**Co-infections.** Although ventilator-associated pneumonia and other nosocomial infections may occur with prolonged hospitalization, bacterial co-infection appears to be relative infrequent; nevertheless, broad-spectrum antibiotics are frequently administered (Rawson, Clin Infect Dis)
Management of ARDS. General guidance for the treatment of severe COVID-19-associated ARDS has been published (Matthay, Lancet Respir Med; Phua, Lancet Respir Med); European intensivists have stressed differences between ARDS and COVID-19, recommending the use of the lowest possible PEEP to avoid worsening lung injury (Gattinoni, AJRCCM; Gattinoni, Crit Care; Marini JAMA); severe hypoxemia with preserved lung compliance is suggested to represent a distinctive phenotype of COVID-19 resulting from pulmonary vascular pathology, possibly warranting different treatment measures (Rello, Eur Respir J); others have favored standard ARDS protocols (Ziehr, AJRCCM)

IDSA Guidelines. IDSA has published treatment guidelines regarding hydroxychloroquine/azithromycin, lopinavir/ritonavir, corticosteroids, tocilizumab and convalescent plasma (Bhimraj, IDSA)

PREVENTION

Travel Restrictions. Travel restrictions gain time but only effective if combined with measures to reduce community transmission (Chinazzi, Science; Wells, PNAS; Kucharski, Lancet Infect Dis)

Social Distancing. Social distancing can be effective (Anderson, Lancet; Cowling, MedRxiv) and is more effective in reducing demand for ICU beds if instituted early (Li, MedRxiv); modeling of King County indicates that strong intervention can stop the exponential rise in infections (Klein, working paper); drastic social distancing interventions in Wuhan drove the effective reproductive number from 3.86 to 0.32 (Wang, MedRxiv) and less dramatically in WA/CA (Lewnard, MedRxiv); social distancing combined with visitor restriction and hand hygiene has been effective in limiting COVID-19 spread in a senior indepencent and assisted living setting (Roxby, MMWR)

Beyond Social Distancing. Sustained suppression is likely to be more effective than mitigation (Ferguson, Imperial College report); temporary non-pharmaceutical interventions may ultimately be ineffective unless accompanied by reinforcement of critical care capacity to ensure adequate care for the most severely ill patients until more definitive strategies (vaccines, new therapeutics, aggressive contact tracing and quarantine) can be implemented (Kissler, DASH); one proposal for eventual restoration of social interaction suggests sequential phases in which widespread surveillance, testing and containment capabilities are established, followed by the application of effective vaccines or therapeutics and the bolstering of public health infrastructure (Gottlieb, AEI); modeling predicts that recurrent wintertime SARS-CoV-2 outbreaks may occur, requiring repeated episodes of social distancing through 2022 (Kissler, Science); intensive control strategies require extensive diagnostic capability; current gaps in diagnostic testing include widespread surveillance, screening of asymptomatic persons and monitoring shedding in convalescence (Cheng, Ann Intern Med); ~60% of the population may need to be immune for adequate herd immunity (Altmann, Lancet); a CIDRAP report describes three potential pandemic scenarios (peaks & valleys/fall peak/slow burn) (Moore, CIDRAP)
**Vaccines.** Potential vaccine platforms include RNA, DNA, recombinant proteins, viral vector-based vaccines, live attenuated virus and inactivated virus (Amanat, Immunity; Lurie, NEJM); challenges include elicitation of durable immunity and potential immune enhancement (Peeples, PNAS); an inactivated vaccine candidate has been shown to induce neutralizing Ab in mice, rats and non-human primates, neutralizes different strains, and protects macaques from challenge without evidence of antibody-dependent enhancement (Gao, BioRxiv)

**Models.** Even with social distancing, modeling studies predict excess U.S. demand at the pandemic peak in the second week of April to be 64,175 hospital beds, 17,309 ICU beds and 19,481 ventilators, with 81,114 deaths occurring over the next 4 months; IHME model (Murray, MedRxiv https://covid19.healthdata.org/united-states-of-america) has been widely used but also criticized (Jewell, Ann Intern Med)

**Health Care Workers.** Health care workers are at increased risk of infection (Pan, JAMA)—as of April 9, 2020, the CDC reported 9,282 HCWs infected in the U.S. with 723 hospitalizations, 184 ICU admissions and 27 deaths (CDC MMWR HCWs); Screening of health care workers in NYC found 5% positive for SARS-CoV-2; two-thirds were asymptomatic, and prevalence was 7% higher than in non-HCW controls (Barrett, MedRxiv); ED, Anesthesiology and Ophthalmology residents are the specialties at highest risk for COVID-19 acquisition, followed by Surgery, Psychiatry, Medicine and Pediatrics (Breazzano, MedRxiv); the need for airborne vs droplet precautions is controversial and may be based on outdated biophysical concepts of respiratory emissions (Bourouiba, JAMA); the University of Nebraska found viral contamination of commonly used items, toilets and air samples, suggesting that airborne precautions are appropriate (Santarpia, MedRxiv); airborne SARS-CoV-2 RNA could be detected nearby patients' toilets and in areas of crowding (Liu, Nature); IDSA guidelines to protect HCWs recommend N95 or surgical masks in non aerosol-generating settings and N95 or PAPR for aerosol-generating procedures, with alternative methods in crisis settings (Lynch, IDSA Guideline)

**Face Masks.** The use of face masks lowers risk to health care workers— one study found no infections in HCWs using N95 masks to care for high-risk patients, whereas 10/215 HCWs not using masks while caring for patients considered low-risk were infected (Wang, J Hosp Infect); 20% of infected health care providers lack fever, cough or dyspnea as an initial symptom, suggesting that symptomatic screening may be less effective than universal masking of all health care providers (Chow JAMA); in view of PPE shortages, N95 respirators may be decontaminated up to 3 times with UV/H2O2 vapor or up to 2 times with dry heat and re-used (Fischer MedRxiv); surgical masks worn by individuals with infections can also reduce the risk of transmission (Leung, Nat Med); universal cloth face masks have been advocated for infection prevention in the community (Abeluck, SSRN)

**Fomites.** Fomites may contribute to transmission in the hospital environment; SARS-CoV-2 RNA has been detected on printers, keyboards, doorknobs, telephones, medical equipment, gloves and hand sanitizer dispensers (Ye, MedRxiv)

**EMERGENCY MANAGEMENT**
Emergency Response. An overview of the principles of emergency management in the State of Washington and connections to the national emergency response infrastructure has been published (Morris, Prehosp Disast Med)

This summary was compiled by Ferric C. Fang, M.D. and does not necessarily represent the views of the University of Washington or its affiliated institutions.
LITERATURE CITED


Day M. COVID-19: Ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ. 2020 Mar 17;368:m1086. doi: 10.1136/bmj.m1086.


Fodoulian L, et al. SARS-CoV-2 receptor and entry genes are expressed by sustentacular cells in the human olfactory neuroepithelium. bioRxiv. doi: https://doi.org/10.1101/2020.03.31.013268.


Last updated 3 May 2020


Iacobucci G. Sixty seconds on. . . anosmia. BMJ. 24 Mar 2020; 368. doi: https://doi.org/10.1136/bmj.m1202.


Kirov S. Association between BCG policy is significantly confounded by age and is unlikely to alter infection or mortality rates. medRxiv. https://doi.org/10.1101/2020.04.06.20055616.


Oliveiros B, et al. Role of temperature and humidity in the modulation of the doubling time of COVID-19 cases. medRxiv 2020.03.05.20031872.


Poor HD, et al. COVID-19 critical illness pathophysiology driven by diffuse pulmonary thrombi and pulmonary endothelial dysfunction responsive to thrombolysis


Santarpia JL, et al. Transmission potential of SARS-CoV-2 in viral shedding observed at the University of Nebraska Medical Center. MedRxiv. doi: https://doi.org/10.1101/2020.03.23.20039446.


Last updated 3 May 2020


Xia W, et al. Transmission of corona virus disease 2019 during the incubation period may lead to a quarantine loophole. medRxiv 2020.03.06.20031955; doi: https://doi.org/10.1101.2020.03.06.20031955.


Yang Y, et al. Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome. medRxiv 2020.03.02.20029975.


