SARS-CoV-2 and COVID-19

EPIDEMIOLOGY

Transmission Dynamics. Person-to-person transmission documented with mean incubation period 5.2 days, serial interval 7.5 days, 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, Clin Infect Dis)

Families. Family clusters have been 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); cats may be infected and exhibit asymptomatic transmission to other cats, but it is unknown if they can transmit SARS-CoV-2 to humans (Halfmann, NEJM); cats and ferrets are susceptible to SARS-CoV-2 infection but dogs, pigs, chickens and ducks do not support efficient replication (Shi, Science)

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); a serosurvey in Seattle found <1% of children to be seropositive, and most were asymptomatic (Dingens, MedRxiv); most children requiring hospitalization for COVID-19 have comorbidities (Shekerdemian, JAMA Pediatr); obesity is associated with worse clinical outcomes in children as in adults (Zachariah, JAMA Pediatr); children may still contribute to transmission and have viral loads comparable to adults (Jones, Charite); a recent association with Kawasaki Disease-like inflammatory syndrome called “MIS-C” or Multisystem Inflammatory Syndrome in Children has been reported (Jones, Hosp Pediatr; Riphagen, Lancet; Licciardi, Pediatrics), which tends to occur in older children compared with classical Kawasaki disease and has a higher rate of cardiac involvement and macrophage-activation syndrome, which may require steroid therapy (Verdoni, Lancet); the prognosis for children treated with IVIG with or without steroids appears to be generally favorable (Belhadjer, Circulation); some children with MIS-C are PCR-negative-seropositive, consistent with an immune-mediated process (Perez-Toledo, MedRxiv); children of African ancestry may be at increased risk (Toubiana, BMJ); elevated cytokines are observed (IL2R, IL16, IL-18, CXCL9) (Cheung, JAMA); complications include myocardial injury, shock and coronary artery aneurysms (Whittaker, JAMA), but the epidemiology differs from classical Kawasaki’s Disease (McCrindle, JAMA)

Asymptomatic Transmission. Asymptomatic or pre-symptomatic transmission makes an important contribution to SARS-CoV-2 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; Cheng, JAMA Intern Med; Furukawa, Emerg Infect Dis; Huff, Clin Infect Dis); 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 the 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); symptom screening found to be inadequate for case detection in skilled nursing facilities, so early surveillance recommended (Roxby, JAMA Intern Med); SARS-CoV-2 spread prior to symptom onset or by patients with mild atypical symptoms has been documented (Bohmer, Lancet Infect Dis), and possible transmission by hand shaking and face-to-face contact by a presymptomatic individual reported (Hijnen, Emerg Infect Dis); contact tracing and testing revealed 20% of secondary cases to be asymptomatic at the time of first clinical assessment (Bi, Lancet Infect Dis); 23% of a cohort of asymptomatic PCR-positive contacts remained asymptomatic and some were able to transmit SARS-CoV-2 to others despite lack of symptoms and a normal CT scan (Wang, Clin Infect Dis); a prospective study found that patients with asymptomatic infection cleared their infections more rapidly but secondary transmission was still observed (Chau, Clin 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](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); ~10-20% of individuals appear to be responsible for ~80% of secondary transmission (Endo, Wellcome Open Res) and and social exposures produced more secondary cases than family or work exposures (Adam, Research Sq); 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); 87% of attendees at a choir rehearsal in Skagit County were infected by a single asymptomatic index patient, resulting in 2 deaths (Hamner, MMWR), and a high attack rate was also observed in church-related events in Arkansas (James, MMWR).

**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 suggested the importance of cryptic domestic spread (Fauver, MedRxiv; Bedford, MedRxiv); however, contrary to the conclusions of Bedford et al., phylogenetic outbreak simulations suggest that the initial Jan. 2020 SARS-CoV-2 introduction into WA state was not transmitted further, but rather a second introduction of a similar but non-identical virus occurred in Feb. 2020 and led to the regional outbreak (Worobey, 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; mortality in the initial group of hospitalized patients at the UW-affiliated hospitals as been high (33%), possibly because of advanced age (median 69 years) and frequent comorbidities (hypertension, cardiovascular disease, diabetes)

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); meat and poultry facilities appear to be high-risk settings: 4,913 cases of COVID-19 with 20 deaths reported in 115 U.S. facilities (Dyal, MMWR); surveys estimated SARS-CoV-2 seroprevalence to be 2.8% in Santa Clara County (Bendavid, MedRxiv) and 4.65% in LA County (Sood, JAMA), 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, and another Bay Area serosurvey found only 0.26% in patients hospitalized for non-respiratory indications and 0.1% in blood donors (Ng, MedRxiv); may already have been spreading in France in late December (Deslandes, Int J Antimicrob Agents); evidence for multiple introductions of SARS-CoV-2 into NYC from Europe and other parts of the U.S. (Gonzalez-Reiche, Science)

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; Oliveiros, MedRxiv; Araujo, MedRxiv; Neher, MedRxiv; Sajadi, SSRN; Bukhari, SSRN); vitamin D deficiency correlates with severity in men (De Smet, MedRxiv), but a large UK database found no correlation between vitamin D levels and COVID-19 (Hastie, Diabet Metab Synd)

Environmental Stability. SARS-CoV-2 may remain detectable in aerosols for at least 3 hours 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 has been criticized because of testing, time and selection bias (Szigeti, MedRxiv) and failure to control for confounding by population age (Kirov, MedRxiv); BCG-vaccinated or unvaccinated adults in Israel had similar rates of COVID-19 infection (Hamiel, JAMA)

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); the closest match to SARS-CoV-2 to date is an isolate from a bat collected in Yunnan Province in China, but this isolate has low sequence identity in the receptor-binding domain of the Spike protein (Zhou, Curr Biol); pangolin suggested as reservoir host (Zhang, Curr Biol; Lam, Nature; Xiao, Nature), used for food and traditional Chinese medicine, but pangolin coronaviruses lack a furin cleavage site found in SARS-CoV-2 and pangolin coronaviruses are genetically related but distinct from SARS-CoV-2 (Liu, PLoS Pathog); SARS-CoV-2 receptor binding motif appears to have arisen from recombination with pangolin coronaviruses (Li, Sci Adv)

Binding. Structure of spike protein and binding to ACE2 (Wrapp, Science; Yan, Science; Hoffmann, Cell; Walls, Cell), which is encoded by an interferon-stimulated gene (Ziegler, Cell); the distribution of tissue ACE2 expression may explain a variable distribution of viral load in the respiratory tract—ACE2 is most highly expressed in the nose, ciliated epithelium and type 2 pneumocytes (Hou, Cell); ACE2 is also expressed in cornea, GI tract, liver, heart, kidney, testis (Sungnak, Nat Med); productive infection of human gut epithelial cells has been demonstrated (Lamers, Science); lower nasal ACE2 expression in children might relate to their lower incidence of severe illness (Bunyavanich, JAMA)

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

Sequence Variants. Increasing SARS-CoV-2 diversification observed (Castells, J Med Virol); subtypes with possible differences in transmissibility or virulence proposed (Tang, Nat Sci Rev; Xi, MedRxiv; Su, BioRxiv; Korber, BioRxiv), and a comparison of the case-fatality rate in countries with the G614 spike variant has found a correlation with a higher case-fatality rate (Becerra-Flores, IJCP); however, an analysis of descendants of SARS-CoV-2 sequenced isolates with recurrent mutations did not provide support for higher transmissibility (van Dorp, BioRxiv), and distinct viral lineages identified early in the Wuhan outbreak did not appear to be associated with different degrees of virulence—host factors (age, lymphocyte count, cytokines) appeared to correlate better with clinical outcomes (Zhang, Nature); nevertheless, patients in Chicago were found to have three distinct clades of SARS-CoV-2; clade 1 related to NYC was associated with higher viral loads, clade 3 is related to WA State isolates (Lorenzo-Redondo, MedRxiv)

Immune Response. The distinctive immune responses to SARS-CoV-2 play a major role in disease severity and mortality (Vabret, Immunity); 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 correlate with favorable outcomes and protective immunity (Thevarajan, Nat Med); virus-specific T cells detected in recovered patients, which correlated with neutralizing Ab titers (Ni, Immunity); reappearance of effector and memory T cells correlates with recovery (Odak, MedRxiv); SARS-CoV-2-specific CD4+ and CD8+ T cell responses are detected in convalescing COVID-19 patients, but also to a lesser extent in in unexposed individuals, which
may represent cross-reactivity with seasonal respiratory coronaviruses (Grifoni, Cell; Braun, MedRxiv); 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, Cell); weak induction of interferon responses is observed (Chu, Clin Infect Dis; O’Brien, Clin Infect Dis)-- early interferon responses are associated with coronavirus clearance, while delayed responses are associated with viral persistence and inflammation (Park, Cell Host Microbe); 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, COVID-19 may cause T-cell exhaustion as well as depletion (Vardhana, J Exp Med); one contributing factor in lymphopenia may be deficient IL-2-JAK1-STAT5 signaling (Shi, Cell Death Dis); immune profiling of patients with COVID-19 or influenza found profound immunosuppression in most patients with COVID-19 with a small subset developing a hyper-inflammatory phenotype associated with respiratory failure (Mudd, MedRxiv); production of inflammatory cytokines in COVID-19 inversely correlates with cytotoxic perforin-expressing NK and CD3+ T cells (Bordoni, Clin Infect Dis)

**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 (Bilinska, ACS Chem Neuro; 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 and recapitulates features of moderate human COVID-19 (Rockx, Science; Munster, Nature); causes interstitial pneumonia in transgenic mice expressing human ACE2 (Bao, Nature; Jiang, Cell); a mouse-adapted model in which the spike protein and ACE2 protein have been modified to allow efficient interaction recapitulates SARS-CoV-2 replication in the respiratory tract, more severe illness in aged mice, and protection by IFNλ (Dinnon, BioRxiv)

**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 virus-infected macrophages producing IL-6 (Feng, MedRxiv), which are implicated in the pathogenesis of a “cytokine storm” (Merad, Nat Rev Immunol); a striking finding is capillary congestion and microthrombi, generally but not always restricted to the lungs (Fox, Lancet Respir Med; Dolhnikoff, J Thromb Haemost; Carsana, Lancet Infect Dis;
Marini, JAMA suppl; Menter, Histopathology), 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) and play a central role in severe vascular complications (Teuwen, Nat Rev Immunol), although the “viral-like particles” described in EM by Varga et al. may actually be rough endoplasmic reticulum (Goldsmith, Lancet; Varga, Lancet reply); a recent autopsy series from Germany predominantly showed alveolar damage (Schaller, JAMA), while another reported evidence of widespread endothelial inflammation, thrombosis with microangiopathy, and intussceptive angiogenesis in contrast to the pathology of H1N1 influenza (Ackermann, NEJM); a NYC autopsy series also showed microthrombi and large pulmonary emboli, hemophagocytosis, and the presence of viral particles (Bryce, MedRxiv); clinically unsuspected deep venous thrombosis and pulmonary embolism have also been noted (Wichmann, Ann Intern Med); SARS-CoV-2 found in kidneys, liver, heart and brain (Puelles, NEJM)

CLINICAL

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

Usual Clinical Presentation. As many as 40-45% of SARS-CoV-2 infections may be asymptomatic (Oran, Ann Intern Med); male > female, median age 49 years, 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, BMJ; Prieto-Alhambra, MedRxiv); females may be more susceptible to infection but less likely to develop severe disease or death (Qian, Clin Infect Dis gender); SARS-CoV-2-positive patients in the ED are more likely to report fever, fatigue or myalgias, and to have lymphopenia/CXR infiltrates (Shah, MedRxiv); another series found predictors of COVID-19 to include exposure history, fatigue, leukopenia or lymphopenia and ground glass opacities on imaging (Mao, Lancet Digital Health); “silent” hypoxia with minimal symptoms may be a sign of impending deterioration (Wilkerson, Am J Emerg Med)

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 and complications (Cholankeril, Gastroenterology; Mao, Lancet Gastroenterol Hepatol); >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; Luers, Clin Infect Dis); most patients with anosmia/dysgeusia recover quickly (Levinson, MedRiv); recommendations for assessment and treatment of persistent olfactory dysfunction have been made (Whitcroft, JAMA); ocular signs may include conjunctival hyperemia, chemosis, epiphora or ocular secretions (Wu, JAMA Ophthalmol); cutaneous findings include acral erythema/pernio/chilblains, vesicular eruptions, urticaria, morbilliform/maculopapular rash, papulosquamous lesions and livedo or necrosis (Casas, Br J Dermatol; de Masson, JAAD); retiform purpura is only seen in critical cases (Freeman, MedRxiv)

**Course of Asymptomatic or Pre-symptomatic Infections.** Pre-symptomatic cases detected on screening usually result in mild disease (Wang, J Infect Dis); the estimated proportion of asymptomatic infections varies from 11-45% (Beale, MedRxiv; Oran, Ann Intern Med); patients with asymptomatic SARS-CoV-2 infections have less depression of CD4+ T cell counts and shorter duration of viral shedding (Yang, JAMA Network Open)

**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/Om9VTac6VM; Kujawski, Nat Med), and a biphasic need for intubation (on day 3-4 and again on around day 9 after symptom onset) (Argenziano, BMJ); 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.** A variety of hematologic, biochemical, inflammatory and coagulation biomarkers have been identified (Henry, Clin Chem Lab Med; Ponti, Crit Rev Clin Lab Sci); 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); soluble urokinase plasminogen activator (suPAR) has been suggested as an early predictor of respiratory failure (Rovina, Crit Care)

**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); inflammatory thrombotic process primarily in the lungs is common to SARS and COVID-19 (McGonagle, Lancet Rheumatol); anti-phospholipid antibodies or lupus anticoagulant may be detected in the setting of coagulopathy and multifocal thrombosis (Zhang, NEJM; Harzallah, J Thromb Haemost; Bowles, NEJM); thromboelastography more
consistent with an inflammatory hypercoagulable state than with DIC (Panigada, J Thromb Haemost; Spiezia, Thromb Haemost; Lawicki, MedRxiv) and correlates with thrombotic events; hypercoagulability may result from increased angiotensin II expression, resulting in increased expression of plasminogen activator inhibitor C-1, as well as from COVID-19-related inflammation (Mortus, JAMA Network Open); ~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); most patients admitted to ICU with COVID-19 may have DVT (Nahum, JAMA Network Open)

**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); other chest CT findings include air-bronchograms, crazy paving pattern, consolidation, patchy infiltrates, spider-web sign, or cord-like and nodular lesions; pleural thickening sometimes seen but lymphadenopathy and pleural effusions are rare (Zhu, J Med Virol); 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); crude CFR in US and Canada was 5.4% and 4.9%, respectively, and estimated to be 1.6% and 1.78% after adjustment for survival and reporting bias (Abdollahi, CMAJ); 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); a large UK study analyzing health records of >17 million adults found a strong correlation between mortality and age, sex, obesity, diabetes, recent diagnosis of malignancy and organ transplant (Williamson, MedRxiv); better glucose control was associated with more favorable clinical outcomes in diabetics with COVID-19 (Zhu, Cell Metab); illness may be more severe in Blacks (Gold, MMWR); increased in-hospital mortality in Blacks hospitalized with COVID-19 might be attributable to demographic characteristics and greater severity at presentation (Price-Haywood, NEJM); 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); hypoxemia is independently associated with mortality (Xie, Mayo Clin Proc) and monitoring of oxygen saturation (SpO2/FiO2) has been recommended (Von Vopelius-Feldt, MedRxiv); 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; a New York study of 5,449
patients admitted to a New York hospital system with COVID-19 found acute kidney injury in 37%, temporally associated with respiratory failure, which carried a poor prognosis (35% died, 39% still hospitalized) (Hirsch, Kidney Int; another NYC study found that most COVID-19 patients in the ICU developed acute kidney injury, and 35% required dialysis (Argenziano, BMJ); mortality in patients requiring ICU admission may be ~25% (Grasselli, JAMA); high SOFA score is predictive of mortality (OR 5.65; Zhou, Lancet); 28-day survival 61% in patients requiring ICU admission (Wang, AJRCCM); 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, BMJ; Docherty, MedRxiv; Ziehr, NEJM); 22% of COVID-19 patients at two NYC hospitals were critically ill; at follow-up, 79% required mechanical ventilation, 39% had died and 37% remained hospitalized (Cummings, Lancet); patients requiring mechanical ventilation frequently require vasopressor support (Goyal, NEJM); risk factors for severe illness are age, obesity, comorbidities, dyspnea, hemoptysis, loss of consciousness, O2 sat <88% and elevated D-dimer/ferritin/CRP/NLR, azotemia/elevated LFTs (Petrilli, BMJ; Lighter, Clin Infect Dis; Wang, MedRxiv; Liang, JAMA Intern Med); from Feb-Apr 2020, COVID-19 was calculated to have caused 21 times more deaths than seasonal influenza in NYC (Faust, MedRxiv); individuals with the type A-positive blood group are 45% more likely to have respiratory failure, and type O has a protective effect (Ellinghaus, MedRxiv)

**Cardiac and Neurologic Complications.** Pre-existing cardiovascular disease is a risk factor for more severe disease, and COVID-19 can have a variety of cardiovascular complications (Driggin, JACC; Guzik, Cardiovasc Res); 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); cor pulmonale may occur, most likely due to thromboembolic disease (Creel-Bulos, 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); ischemic stroke is an unusual complication of COVID-19 and most cases are cryptogenic (Yaghi, Stroke); Guillain-Barré Syndrome has been reported (Toscano, NEJM); other neurologic presentations include headache, impaired consciousness, seizures and encephalopathy (Zubair, JAMA Neurol)

**Cytokine Storm.** Cytokine storm and elevated IL-6 levels produced by macrophages seen in severe illness (Wang, Clin Infect Dis; Chen, MedRxiv; Wang (2), MedRxiv; Yang, MedRxiv; Moore, Science; Tay, Nat Rev Immunol; Merad, Nat Rev Immunol); IL-6 levels ≥80 pg/ml associated with 22-fold increased risk of respiratory failure (Herold, J Allerg Clin Immunol); elevated IL-6 and TNFα are predictive of severe disease and death and can inform the use of immunomodulatory agents (Del Valle, 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
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); patients with cancer are more likely to develop severe illness, particularly if they have recently received chemotherapy (Kuderer, Lancet; Tian, Lancet Oncol; Yang, Lancet Oncol); among cancer patients with COVID-19, age ≥65 and treatment with immune checkpoint inhibitors are risk factors for hospitalization and severe outcomes (Robilotti, MedRxiv); clinical presentation in patients with HIV is variable and largely dependent on other comorbidities (Blanco, Lancet HIV; Gervasoni, Clin Infect Dis; Vizcarra, Lancet HIV) and HIV-infected patients of Black ethnicity may be at higher risk for severe outcomes (Childs, Clin Infect Dis); others have reported that immunocompromised patients (autoimmune disease, cancer, organ transplant) are less likely to develop moderate-severe ARDS (Monreal, Res Sq preprint).

**Pregnancy.** Clinical course similar in pregnant women with only very rare evidence of intrauterine or transplacental transmission (Chen, Lancet; Schwartz, Arch Pathol Lab Med; Chen, NEJM); a single case of congenital SARS-CoV-2 infection has been reported, and the newborn did well (Kirtsman, CMAJ); detection of antibodies including IgM in newborns of SARS-CoV-2-infected mothers has also suggested possible in utero infection, but virus was not detected (Dong, JAMA; Zeng, JAMA; Kimberlin, JAMA); may be an increased risk of preterm delivery (Mullins, Ultrasound Obstet Gynecol; Wang, Clin Infect Dis); a case of preeclampsia in the 2nd trimester associated with placental infection reported (Hosier, MedRxiv); 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); a higher incidence of post-operative pulmonary complications is seen in patients with perioperative COVID-19 (COVIDSurg Collaborative, Lancet); this warrants routine pre-operative screening.

**LABORATORY DIAGNOSIS**

**Diagnostic Tests.** Diagnostic testing plays an extremely important role in COVID-19 control, but there are still major unmet needs in the domestic diagnostic pipeline (Cheng, Ann Intern Med); testing availability in the U.S. has been uneven and inadequate (Schneider, NEJM); 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); RT-PCR is the standard method for SARS-CoV-2 detection, and sensitive commercial assays are available (Zhen, J Clin Microbiol); IDSA diagnostic guidelines have been published (Hanson, IDSA guidelines); point-of-care (POC) tests are under development or being assessed (Loeffelholz, Emerg Microbes Infect; Joung, MedRxiv); answers to FAQs may be found in (Fang, Clin Infect Dis).
Clinical Specimens for Viral Detection by Nucleic Acid Amplification Tests (NAAT). 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); some false negatives are probably due to improper sampling technique (Piras, Otolaryngol Head Neck Surg); 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; Wu, Travel Med Infect Dis) and 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); 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); most commercial assays are comparably sensitive and specific (Lieberman, J Clin Microbiol), but the Abbott ID NOW rapid NAAT assay is reported to have lower specificity than conventional PCR assays (Basu, J Clin Microbiol)

Limitations of PCR. Sensitivity of RT-PCR is highest during first few days of symptoms (Kucirka, Ann Intern Med); a negative NP/OP swab does not rule-out COVID-19 (Winichakoon, J Clin Microbiol; Long, Eur J Radiol; Woloshin, NEJM); yield of re-testing depends on local prevalence (Green, MedRxiv; Long, MedRxiv); PCR assays may revert to positive in a minority of patients, clinical significance of this is unknown (Yuan, Clin Infect Dis) but patients who re-test positive have no obvious signs of disease recurrence, progression or transmission (An, MedRxiv)

Other Specimens. Virus detected in urine, blood, anal swabs, saliva (To, Clin Infect Dis; Peng, MedRxiv; Tang, J Clin Microbiol); has been detected in breast milk, but the clinical significance is uncertain (Tam, Clin Infect Dis); self-collected tongue, nasal, saliva or mid-turbinate swabs appear comparable to health care worker-collected nasopharyngeal swabs and can reduce PPE use and patient discomfort (Tu, NEJM; Wehrhahn, MedRxiv; Kojima, MedRxiv; Wyllie, MedRxiv; Williams, J Clin Microbiol; Jamal, MedRxiv; Berenger, MedRxiv); viral loads in saliva reportedly comparable to those in nasopharyngeal swabs and may be detected up to 20 days post-symptom onset, correlating with illness severity (Khurshid, MedRxiv; McCormick-Baw, J Clin Microbiol), but others have found lower sensitivity of saliva (Becker, MedRxiv)

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); respiratory samples from COVID-19 patients with ≥8 days of symptoms are culture-negative, suggesting a lack of infectivity despite PCR-positivity (Bullard, Clin Infect Dis), and correlate with lower quantitative PCR values (E gene Ct ≥24); more 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; Wajnberg, MedRxiv; Xiao, J Clin Virol), but persistent viral PCR positivity is not associated with recurrent symptoms or transmission (Wu, JAMA Network Open); viral RNA can also be found in stool for weeks; although 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),
Culturable SARS-CoV-2 has been recovered from fecal samples (Wang, JAMA; Xiao, Emerg Infect Dis)

Co-Infections. Co-infections may be present (Lin, Sci China Life Sci; Kim, JAMA); see also Co-Infections section under TREATMENT below

Adjunctive Role of CT Scanning. Chest CT may show abnormalities even when PCR is negative (Fang, Radiology; Ai, Radiology); however, in low prevalence regions, positive predictive value of RT-PCR is far greater than that of chest CT (Kim, Radiology); chest findings consistent with COVID-19 may be detected as an incidental finding when patients with atypical presentations undergo spine/neck or abdomen/pelvis CT scanning (Hossain, 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. Many issues relating to serologic testing remain to be defined (Theel, J Clin Microbiol; Cheng, Ann Intern Med serology), and serological tests will have important applications at both individual and population levels (Bryant, Sci Immunol); limited clinical and experimental data suggest that recovery from COVID-19 may confer immunity to reinfection (Kircaldy, JAMA); Ab begins to be detected as viral load declines (Sethuraman, JAMA); serologic tests vary in sensitivity and specificity, ranging from 68-93% sensitivity for IgM and 65-100% for IgG, with high specificity for most assays (98%) (Okba, MedRxiv; Whitman, MedRxiv; Caini, MedRxiv); validated serologic assays appear to have high sensitivity and specificity (Paiva, BioRxiv); IgG more sensitive than IgM (Dittadi, MedRxiv), but IgM and IgG exhibit similar initial kinetics (Jin, Int J Infect Dis; Xiang, Clin Infect Dis); IgA has lower specificity (Traugott, J 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); nearly 50% of symptomatic patients in NYC were IgG-positive (Reifer, MedRxiv); many patients seroconvert within 14 days of symptom onset, and most seroconvert by 20 days (Long, Nat Med; To, Lancet Infect Dis; Lou, MedRxiv; Traugott, J Infect Dis); based on aggregate data, IgG from 25d-60d post-symptom onset would be an optimal window in which to test for prior exposure (Benny, MedRxiv); some have found that Ab titers correlate with disease severity (Zhao, Clin Infect Dis; Ou, MedRxiv); community seroprevalence comparable in children/middle-aged adults and lower in older adults (Stringhini, MedRxiv); commercial assays exhibit considerable variation in sensitivity and specificity (Lassauniere, MedRxiv); neutralizing Ab may be detected within 6 days of diagnosis (Suthar, MedRxiv), but titers are variable in recovered patients 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); 20% of PCR-positive cases in a children’s and women’s hospital failed to seroconvert by 3 weeks (Brandstetter, Ped Allerg Immunol), but subclinical seroconversion was observed among HCWs and patients in a pediatric dialysis unit (Hains, JAMA); antibody titers do not necessarily mean immunity, and protection may be transient (Huang, MedRxiv), but SARS-CoV-2 infection protects macaques from rechallenge (Chandrashekar, Science), suggesting that natural infection elicits protective immunity
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); modeling based on viral dynamics indicates that antiviral therapy is likely to be helpful only if administered very early but is unlikely to have a major effect in severe patients (Gonçalves, MedRxiv); immunostimulation may be beneficial early, while immunosuppression is required later (Jamilloux, Autoimmun Rev)

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 (Williamson, BioRxiv); 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 ≤ 10 days (Wang, Lancet); however, a randomized trial in 1,059 patients with COVID-19 and evidence of pulmonary involvement found that remdesivir shortened the median time to recovery from 15 to 11 days, with a trend toward reduced mortality that did not achieve significance (HR 0.70, 95% CI 0.47-1.04) (Beigel, NEJM); 5 day course of remdesivir appears to be as effective as 10 days (Goldman, NEJM)

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); a follow-up report from the same group reported only 4% poor outcomes with <1% deaths in 1,061 patients treated early with HCQ/AZ, and no adverse cardiac outcomes, but again there was no control group (Million, Travel Med Infect Dis); in contrast, 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.** A growing body of evidence is failing to support a clinical benefit of hydroxychloroquine or chloroquine in COVID-19, with or without azithromycin; a double-blind placebo-controlled RCT found that prophylactic hydroxychloroquine fails to prevent symptomatic infection after SARS-CoV-2 exposure (Boulware, NEJM); an RCT of hydroxychloroquine in China (n=75 per group) failed to detect an effect on viral clearance (Tang, BMJ); 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); receipt of hydroxychloroquine and/or azithromycin was not associated with lower mortality in 1438 patients hospitalized with COVID-19 in New York State, but patients were not randomized (Rosenberg, JAMA); an observational study of 1,446 consecutive patients in a NYC medical center failed to detect a benefit of hydroxychloroquine on prevention of intubation or death (Geleris, NEJM); chronic HCQ does not prevent COVID-19 or severe/fatal outcomes in patients treated for rheumatologic diseases (Mathian, Ann Rheum Dis; Gendelman, Autoimmun Rev; Konig, Ann Rheum Dis)

**Tocilizumab and Other Immunomodulators.** Multiple targets for immunomodulatory therapeutic intervention (Alijotas-Reig, Autoimmune Rev); 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); retrospective studies have found lower mortality in tocilizumab recipients (Roumier, MedRxiv; Klopfenstein, Med Mal Infect; Somers, 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); however, IL-6 inhibition is associated with an increased risk of secondary infections (Kimmig, MedRxiv; Somers, MedRxiv); other IL-6 antagonists like sarilimab have also been associated with clinical improvement and reduced O2 requirement (De Lusignan, Lancet Infect
Dis), and siltuximab was associated with a decline in CRP but variable clinical responses (Gritti, MedRxiv); Leronlimab (CC5-blocking Ab) given to patients with critical COVID-19 and elevation of IL-6/CCR5 was followed by a rapid decline in inflammatory biomarkers and reduced viral load (Patterson, MedRxiv); anakinra (IL-1 antagonist) associated with clinical improvement in 72% of patients with hyper-inflammation in the setting of COVID-19 (Cavalli, Lancet Rheumatol), as well as reduced need for ventilation and lower mortality (Huet, Lancet Rheumatol); a pilot study suggested an improvement in inflammatory parameters and clinical outcomes in baricitinib (JAK kinase inhibitor) recipients (Cantini, J Infect); acalabrutinib, a Bruton’s tyrosine kinase inhibitor, appeared to reduce inflammation and improve oxygenation in patients with severe COVID-19 (Roschewski, Sci Immunol)

**Lopinavir-Ritonavir.** No benefit from lopinavir-ritonavir seen in severe COVID-19 (Cao, NEJM); interferon/ribavirin/lopinavir-ritonavir superior to lopinavir-ritonavir (Hung, Lancet)

**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); an observational study found that systemic anticoagulation correlated with improved survival in patients requiring mechanical ventilation (Paranjpe, JACC); therapeutic anticoagulation was associated with a lower mortality compared to prophylactic anticoagulation in ventilated ICU patients (Trinh, MedRxiv); improved oxygenation in response to therapeutic heparin (Negri, MedRxiv) or tissue plasminogen activator (tPA) (Wang, J Thromb Haemost; Poor, MedRxiv); coagulation studies may guide the need for intensive anticoagulation (Panigada, J Thromb Haemost; Ranucci, J Throm Haemost; Connors, J Thromb Haemost; Connors, Blood), but serious thrombotic events may still occur despite anticoagulation (Helms, Intensive Care Med)

**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); an early short-course of 0.5-1.0 mg/kg/d methylprednisolone x 3d was associated with clinical improvement and a shorter LOS (Fadel, Clin Infect Dis), and a retrospective analysis with propensity score-matched cohorts suggested reduced in-hospital mortality in patients receiving corticosteroids (Cruz, MedRxiv)

**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; convalescent plasma was associated with improved oxygen requirements and survival (for non-intubated patients) compared to historical matched controls (Liu, MedRxiv); an RCT showed a trend toward more rapid clinical improvement that failed to reach significance, possibly because of early termination (Li, JAMA); convalescent plasma may be more beneficial if administered prior to the need for endotracheal intubation (Liu, MedRxiv); an uncontrolled trial of convalescent plasma found that it is safe in severe COVID-19, and 76% of recipients exhibited improvement by 14 days (Salazar, Am J Pathol); a clinical trial of convalescent serum will be initiated (Casadevall and Pirofski, J Clin Invest; Bloch J Clin Invest); although convalescent plasma is thought to work by neutralizing virus, it may also ameliorate inflammation and the hypercoagulable state of COVID-19 (Rojas, Autoimmun Rev); potential benefits of convalescent plasma include replenishing coagulation proteins and restoring ADAMTS-13 activity (Kesici, PNAS); serious adverse events are infrequent (<1%) in convalescent plasma recipients, including circulatory overload, lung injury, allergic reactions (Joyner, MedRxiv).

**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 or COVID-19-related admission, ICU admission or death (Mancia, NEJM; Reynolds, NEJM; de Abajo, Lancet; Mackey, Ann Intern Med); 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); one study found that ACE inhibitors reduced the risk of hospitalization in Medicare patients, which warrants further study (Khera, MedRxiv).

**Miscellaneous.** Avoidance of ibuprofen recommended but with little basis in evidence (Day, BMJ); receipt of hypnotics has been associated with favorable outcomes (Hu, Clin Infect Dis); a retrospective study suggests that the putative immune response modifier thymosin-α1 may reverse lymphopenia and T cell exhaustion in association with a reduction in mortality in severe COVID-19 (Liu, Clin Infect Dis).

**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).

**Treatment of 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; Lansbury, J Infect; Adler, Lancet); patients may appear septic but have only a 1.6% bacteremia rate, and overutilization of blood cultures can exceed lab capacity.
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; Ceruti, MedRxiv; Price, Eur Heart J); 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; Berlin, NEJM); prone positioning improves oxygenation only in a subset of hypoxemic COVID-19 patients (Elharrar, JAMA).

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

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); experience in King County indicates that strong intervention can stop the exponential rise in infections (Klein, working paper; Randhawa, JAMA); 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, BMJ); analysis of contact survey data in China indicates that social distancing alone may be sufficient to control COVID-19, but school closures can delay and reduce peak incidence (Zhang, Science); lockdown in France reduced R0 from 2.90 to 0.67 but is predicted to only result in infection of 4.4% of the population, far short of the requirement for herd immunity (Salje, Science); similarly, surveys indicate only 3.2-3.8% seropositivity in Wuhan (Xu, Nat Med serology) and 2.7% in Hong Kong (To, Lancet Microbe); social distancing combined with visitor restriction and hand hygiene has been effective in limiting COVID-19 spread in a senior independent and assisted living setting (Roxby, MMWR); the impact of social interventions on case numbers has a delay of about two weeks (Dehning, Science); non-pharmaceutical interventions are estimated to have prevented 62 million COVID-19 infections in China, South Korea, Italy, Iran, France and the US alone (Hsiang, Nature); a parallel study estimated that 3.1 million deaths were averted by interventions in Europe (Flaxman, Nature).

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; delays in testing or tracing are likely to substantially reduce the effectiveness of contact tracing (Kretzschmar, MedRxiv); current gaps in diagnostic testing include widespread surveillance, screening of asymptomatic persons and monitoring shedding in convalescence (Cheng, Ann Intern Med), although it has been argued that even inaccurate tests may be useful in the surveillance setting (Ramdas, Nat 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, Science); the Oxford ChAdOx1 adenovirus-based vaccine is protective in a macaque model (van Doremalen, BioRxiv); a DNA vaccine expressing S protein protected macaques from SARS-CoV-2 (Yu, Science); a recombinant adenovirus-vectored COVID-19 vaccine was reported to be immunogenic in human subjects (Zhu, Lancet), but pre-existing immunity to the Ad5 factor was associated with diminished antibody and T cell responses

**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), which has risen to more than 63,000 health care providers infected with 299 deaths as of 28 May 2020 (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html); compared to the general community, frontline HCWs are at increased risk of symptomatic COVID-19 acquisition (aHR 11.6), and a national database analysis has confirmed the increased risk to HCWs (Mutambudzi, MedRxiv); 36% of HCWs at a NYC hospital were seropositive, most of whom had minimal symptoms (Mansour, MedRxiv); most positives found in contact tracing of
HCWs with COVID-19 have been asymptomatic (Mandic-Rajcevic, MedRxiv) or had atypical symptoms; one study of HCWs observed both symptomatic and asymptomatic seroconversion, but antibody levels were higher in symptomatic individuals (Shields, MedRxiv); time required for 95% of HCWs to be cleared was 30 days; a large outbreak in a pediatric dialysis unit resulted from an index case HCW with a high viral load (Schwierzeck, Clin Infect Dis); many asymptotically infected HCWs may reflect community rather than hospital transmission (Treibel, Lancet); evidence suggests that PPE (masks, gloves, gowns, eye protection) and hand washing decrease HCW infection risk (Chou, Ann Intern Med); inadequate PPE increased risk, but HCWs with adequate PPE may still have increased risk (Nguyen, MedRxiv); 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); random sampling of 1,032 HCWs by nasal/throat swab found 3% positive in a UK study, of whom more than half were truly asymptomatic/pauci-symptomatic, demonstrating the limitations of symptom-based preventative measures (Rivett, eLife); modeling indicates that universal PPE is more effective than testing and isolation to prevent nosocomial spread (Miller, 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); increasing evidence is pointing to airborne transmission of SARS-CoV-2 (Prather, Science); aerosol transmission is most likely to occur in poorly ventilated spaces and/or at close range (Somsen, Lancet Respir Med); the University of Nebraska found viral contamination of commonly used items, toilets and air samples, suggesting that airborne precautions are appropriate (Santarpia, MedRxiv); SARS-CoV-2 RNA can be detected in exhaled breath condensate from patients with COVID-19 (Ma, MedRxiv); airborne SARS-CoV-2 RNA could be detected nearby patients' toilets and in areas of crowding (Liu, Nature); in another study SARS-CoV-2 RNA was detected on high touch surfaces and air samples in airborne isolation rooms despite 12 air changes per hour (Chia, Nat Commun); ~4 micron droplets generated by speaking could be detected in a closed stagnant air environment for 8-14 minutes, suggesting that SARS-CoV-2 might be transmitted by an airborne route in confined settings (Stadnytskyi, PNAS); upper-room germicidal ultraviolet fixtures might mitigate airborne transmission (Nardell, JAMA); available evidence suggests that airborne precautions will provide optimal protection for HCWs caring for patients with COVID-19 (Bahl, J Infect Dis); 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); a meta-analysis supports physical distancing, face masks (N95 > surgical masks) and eye protection to prevent SARS-CoV-2 transmission (Chu, Lancet)

**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; Klompas, NEJM); 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), as evidence indicates that masks can prevent the spread of respiratory viruses in non-HCWs as well as in HCWs (Liang, Travel Med Infect Dis)

**Fomites.** Fomites may contribute to transmission in the hospital environment; SARS-CoV-2 RNA has been detected in air samples near patients and on floors, printers, keyboards, computer mice, doorknobs, telephones, trash cans, sickbed handrails, medical equipment, gloves and hand sanitizer dispensers (Ye, J Infect; Guo, Emerg Infect Dis)

**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.


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