SARS-CoV-2 and COVID-19

For a recent comprehensive review of COVID-19, see (Wiersinga, JAMA)

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); serial interval and reproduction number (R0) are not fixed properties of an outbreak but change with the implementation of control measures, particularly case isolation (Ali, Science); Inter-individual contact data can be used to estimate R0 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 12-17% among household contacts, higher in adults/spouses and lower in children (Li, Clin Infect Dis; Jing, Lancet 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 (Dingen, 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); young children (< 5 yrs) may have higher upper respiratory tract viral loads despite mild symptoms (Heald-Sargent, JAMA Pediatr); 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; Levin, NEJM; Felsenstein, Lancet Rheumatol); children with MIS-C vs severe COVID-19 may be distinguished by differences in TNFα and IL-10 levels (Diorio, J Clin Invest); tends to occur in older children compared with classical Kawasaki disease and has a higher rate of cardiac involvement and macrophage-activation syndrome, often treated with IVIG, corticosteroids and sometimes other immunomodulators such as tocilizumab or anakinra (Verdoni, Lancet; Feldstein, N Engl J Med; Riollano-Cruz, J Med Virol; Pain, Lancet Rheumatol); the prognosis for children treated with IVIG with or without steroids appears to be generally favorable (Belhadjer, Circulation), but PICU admission is frequently required (Davies, Lancet Child Adolesc Hlth); GI involvement is common in children with MIS-C of all ages but younger children are more likely to have mucocutaneous involvement while older children are more likely to have cardiac involvement (Dufort, N Engl J Med); children with MIS-C are usually seropositive but sometimes PCR-negative, consistent with an immune-mediated process
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; Hao, Nature); a systematic review estimates that 15% of infections are truly asymptomatic but 40-60% of new infections are transmitted from presymptomatic individuals (Buitrago-Garcia, MedRxiv), whereas another review concluded that as many as 40-45% of SARS-CoV-2 infections may be asymptomatic (Oran, Ann Intern Med); some models suggest that most transmission is mediated by asymptomatic or presymptomatic individuals (Li, Science; Moghadas, PNAS); methods used to measure asymptomatic/presymptomatic transmission (case studies, viral dynamics, serial interval) are subject to different methodological limitations and bias, but in aggregate provide compelling evidence of asymptomatic and presymptomatic transmission (Savvides, MedRxiv); presymptomatic transmission 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); in a study of 11 Maryland LTCFs, universal screening found that 55% of PCR-positive cases were asymptomatic (Bigelow, 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), and most asymptomatic patients identified on the Diamond Princess cruise ship remained asymptomatic (Sakurai, 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); ~10-20% of individuals appear to be responsible for ~80% of secondary transmission (Endo, Wellcome Open Res) and social exposures produce 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); a 44% attack rate was observed among attendees of an overnight camp in which mask use and social distancing were not observed (Szablewski, MMWR); transmission risk in train passengers was found to correlate with co-travel time and seats adjacent to index cases (Hu, Clin Infect Dis); most super-spreading events occur outside of household settings (Xu, Clin Infect Dis) and include crowded workplace settings such as call centers (Park, Emerg Infect Dis); an analysis of 61 COVID-19 case-clusters found that heavy breathing in close proximity to other persons (karaoke parties, cheering at clubs, conversing in bars, exercising in gyms) were high risk activities; the authors recommend avoiding the “three Cs”: closed poorly-ventilated spaces, crowds and close-contact settings; 41% of identified primary cases were asymptomatic/presymptomatic at the time of transmission (Furuse, Emerg Infect Dis); an air conditioning system was believed to potentiate the spread of airborne droplets in a restaurant-associated outbreak (Lu, Emerg Infect Dis)

**Viral Shedding.** High pharyngeal viral shedding on day zero is seen with a subsequent decline, more like influenza than SARS (He, Nat Med; 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); seroprevalence in Puget Sound region 1.1% compared to 6.9% in NYC (Mar 23-Apr 1) (Havers, JAMA Intern Med); 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); numerous outbreaks have occurred in meat and poultry processing facilities, where physical distancing is not possible and workers frequently share workspace, transportation and housing (Waltenburg, MMWR), and 4,913 cases of COVID-19 with 20 deaths have been 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 was 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); 122,300 excess deaths in US as of May 30 exceeds the 95,235 deaths officially attributed to COVID-19 and probably represents a more accurate estimate of the burden of the pandemic (Weinberger, JAMA Intern Med).

Nursing Homes. Skilled nursing facilities are particularly vulnerable to COVID-19, and residents are at risk for severe outcomes (Patel, Clin Infect Dis nursing homes; Fisman, JAMA Netw Open). However, aggressive surveillance and control measures have been effective in this setting (Roxby, MMWR; Roxby, JAMA Intern Med).

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; Oliveiraos, MedRxiv; Araujo, MedRxiv; Neher, MedRxiv; Sajadi, JAMA Network Open; Bukhari, SSRN); vitamin D deficiency correlates with severity in men (De Smet, MedRxiv); a large UK database found no correlation between vitamin D levels and COVID-19 (Hastie, Diabet Metab Synd), but others have found low 25(OH)-vitamin D levels to be associated with an increased risk of COVID-19 (Merzon, FEBS J).

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); a clinical
trial may be required to definitively determine whether BCG vaccination confers protection against COVID-19 (Escobar, PNAS)

**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); features of coronaviruses associated with higher pathogenicity are enhanced nuclear localization signals in the nucleocapsid protein and inserts in the spike glycoprotein (Gussow, PNAS); recent phylogenetic data are most consistent with an origin for SARS-CoV-2 in *Rhinolophus* spp. bats, most likely from Yunnan province in China (Latinne, BioRxiv); the sarbecovirus lineage giving rise to SARS-CoV-2 appears to have been circulating unnoticed in bats for decades (Boni, Nat Microbiol)

**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 have been identified (Tang, Nat Sci Rev; Xi, MedRxiv; Su, BioRxiv). and designations of discrete SARS-CoV-2 lineages have been proposed (Rambaut, Nat Microbiol); the D614G spike variant has become the dominant pandemic form of SARS-CoV-2, growing to higher titers in culture, attaining higher viral loads in patients, and perhaps exhibiting enhanced fitness in communities (Korber, Cell); G614 spike variant may correlate with a higher case-fatality rate (Becerra-Flores, IJCP); a review of 80 S protein variants and 26 glycosylation site modifications has confirmed that D614G variants are more infectious, but other variants are also more or less infectious, some are resistant to
neutralizing Ab, and glycosylation variants also affect infectivity (Li, Cell); S protein G614 and ORF1ab L4715 variants correlate with country-wide fatality rates— notably, WA state has a relative low fatality rate and a lower incidence of both alleles (Toyoshima, J Hum Genet); pseudovirus expressing D614G spike protein infects ACE2-expressing cells more efficiently (Zhang, BioRxiv); greater infectivity in vitro may be attributable to more efficient proteolysis of the D614G mutant S protein (Hu, BioRxiv; Daniloski, BioRxiv), although 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), and disease severity results from an aberrant immune response rather than viral burden (Broggi, Science); proinflammatory cytokine production, T cell exhaustion/apoptosis and endothelial activation are associated with a more severe clinical course (De Biasi, Nat Commun; Bouadma, MedRxiv); 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; Weiskopf, Sci Immunol; Braun, Nature); possible immunopathological mechanisms include antibody-dependent enhancement and promotion of Th2 responses (Peeples, PNAS); the immune signature associated with SARS-CoV-2 infection includes both protective and pathological responses (CXCL10/IP10, T cell proliferation, basophil/plasmacytoid DC depletion (Laing, MedRxiv)

**Immune Evasion.** Transcriptomic response suggests a muted antiviral response compared to other respiratory viruses (Blanco-Melo, Cell); relatively weak induction of interferon responses is observed (Chu, Clin Infect Dis; O’Brien, Clin Infect Dis) and SARS-CoV-2 may have unique mechanisms to evade type I interferon responses (Sa Ribero, PLoS Pathog); however, SARS-CoV-2 is sensitive to type I IFN responses in cultured cells, although it does not elicit them (Lokugamage, BioRxiv)-- early interferon responses are associated with coronavirus clearance, while delayed responses are associated with viral persistence and inflammation (Park, Cell Host Microbe); a loss-of-function mutation in TLR7 associated with a loss of type I/II interferon responses is associated with severe COVID-19 (Van Der Made, JAMA); in a mouse model, type III IFNλ produced lung DCs induces barrier damage, suggesting potential risks from the therapeutic use of type III IFN (Broggi, Science); immunophenotyping indicates that severe
cases exhibit a combination of type I IFN responses co-existent with TNF/IL-1beta-driven inflammation (Lee, Sci Immunol); marked T cell activation, senescence, exhaustion and TH17 skewing may be observed (De Biasi, Nat Commun); 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); T cell exhaustion and depletion are seen in other subacute viral infections and are not unique to COVID-19 (Vardhana, J Exp Med); one contributing factor in lymphopenia may be deficient IL-2-JAK1-STAT5 signaling (Shi, Cell Death Dis); single-cell RNA sequencing of PBMCs correlated a heterogenous interferon response, HLA class II down regulation and a developing neutrophil population with respiratory failure (Wilk, Nat Med); 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); immune profiling may identify patients progressing to severe illness-- recovering patients express growth factors, whereas deteriorating patients simultaneously express multiple cytokine/chemokine patterns (Lucas, Nature); 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 IFNα (Dinnon, BioRxiv); replication-deficient adenoviruses encoding human ACE2 allow productive respiratory tract infections in mice which can be mitigated by neutralizing Ab (Hassan, Cell)

**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); dysmorphic infected pneumocytes form the syncytia, and infected endothelial cells are associated with macro- and micro-thrombi (Bussani, MedRxiv); distinctive patterns of lung pathology have been classified as: (a) epithelial (with diffuse alveolar damage), (b) vascular (microvascular damage and thrombosis) and (c) fibrotic, but multiple patterns may exist concurrently or sequentially, with virus demonstrated
within endothelial cells and pneumocytes (Polak, Mod Pathol; Bösmüller, Virchows Arch); virus in pneumocytes and ciliated airway cells is seen during the acute phase of lung injury but not during the organizing phase of alveolar damage (Schaefer, Mod Pathol); spleens and lymph nodes show lymphocyte depletion and virus-infected macrophages producing IL-6 (Feng, MedRxiv), which are implicated in the pathogenesis of the so-called “cytokine storm” (Merad, Nat Rev Immunol); the striking presence of capillary congestion and microthrombi is 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; Calabrese, Virchows Archiv); some patients show pulmonary sepsal 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); different pathological patterns in different geographic regions is presently unexplained: autopsies of Washington State patients, many of whom were from a long-term care facility, reported diffuse alveolar damage and virus in type I and II pneumocytes but no microthrombi (Bradley, Lancet), and a series from Germany predominantly showed alveolar damage (Schaller, JAMA), whereas another reported evidence of widespread endothelial inflammation, thrombosis with microangiopathy, and intussusceptive angiogenesis (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 also reported 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); symptoms most associated with mild COVID-19 are cough, sore throat, fever, diarrhea, headache, myalgias/arthralgias, fatigue, and disturbance of smell or taste, whereas more severe illness is associated with breathlessness, anorexia, confusion, chest pain and high fever (Struyf, Cochrane Rev); 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); males exhibit higher inflammatory responses (IL-8, IL-18, CCLS, non-classical monocytes) and lower levels of T cell activation (Takahashi, MedRxiv); 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), and extrapulmonary involvement in COVID-19 includes the heart, kidneys, GI tract, liver, CNS and skin (Gupta, Nat Med); 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); a systematic review found that only 12% of patients with COVID-19 have GI symptoms but 41% have viral RNA detected in GI tract (Parasa, JAMA Network Open); 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; Mercante, JAMA Otolaryngol); loss of taste/smell is the fourth most common COVID-19 symptom and has the highest (83%) positive predictive value (Dawson, Clin Infect Dis); most patients with anosmia/dysgeusia recover quickly (Levinson, Medriv), and 89% of patients with altered taste or smell had experienced improvement or resolution by 4 weeks (Boscolo-Rizzo, JAMA Otolaryngol); 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); the pathogenesis of COVID-19-associated chilblains is uncertain but vasculitis is variably present in biopsy material, sometimes with immunohistochemical evidence of SARS-CoV-2 (Colmenero, Br J Dermatol; Herman, JAMA Dermatol); retiform purpura is only seen in critical cases (Freeman, MedRxiv)

**Post-COVID-19 Symptoms.** A majority of patients report persistent symptoms after hospital discharge, particularly fatigue, dyspnea and arthralgia (Carfi, JAMA); a survey found that 35% of symptomatic adults had not yet returned to their usual state of health 2-3 wks after diagnosis, including young adults without comorbidities (Tenforde, MMWR)

**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/Om9VTacb6VM; 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 (Lesure, 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; Java, JCI Insight); 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; increased platelet activation and aggregation has been reported (Manne, Blood; 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; markers of endotheliopathy (e.g., VWF antigen, soluble thrombomodulin) are commonly elevated and correlate with mortality (Goshua, Lancet Haematol); 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); 16% of patients hospitalized with COVID-19 in a large NYC cohort had a thrombotic event, and elevated D-dimer at presentation was predictive (Bilaloglu, JAMA); pulmonary arterial thrombosis may be observed in fatal cases despite prophylactic anticoagulation (Lax, Ann Intern Med); high risk of venous thromboembolism and pulmonary embolism in patients with severe COVID-19, with adverse outcomes (Lodigiani, Thromb Res), even on therapeutic anticoagulation (Llitjos, J Thromb Haemost; Ren, Circulation; Zhang, Circulation); most patients admitted to ICU with COVID-19 may have DVT (Nahum, JAMA Network Open; Voicu, JACC)
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; Yang, MedRxiv fatality risk); 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), but frailty may be a better predictor of mortality than age or comorbidity (Hewitt, Lancet Public Hlth); 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, Nature); large increases in mortality from heart disease, diabetes and other conditions coincide with the COVID-19 pandemic, potentially due to delayed access to health care or extra-respiratory manifestations of COVID-19 (Woolf, JAMA); 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); higher in-hospital mortality in Blacks hospitalized with COVID-19 has been attributed to demographic characteristics and greater severity at presentation (Price-Haywood, NEJM), and the disproportionate impact of COVID-19 on racial and ethnic minorities may be due to long-standing disparities that result in a higher prevalence of chronic medical conditions and lower health care access (Tai, Clin Infect Dis); 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).
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(Argenziano, BMJ); mortality in patients requiring ICU admission may be ~25% or more (Grasselli, JAMA); high SOFA score is predictive of mortality (OR 5.65; Zhou, Lancet); 28-day survival of 61% has been reported in patients requiring ICU admission (Wang, AJRCCM); reported mortality in patients requiring mechanical ventilation has varied widely from 17-88%, but it is unclear whether patient populations are comparable and some estimates may be inflated due to incomplete follow-up (Richardson, JAMA; Auld, MedRxiv; Petrilli, BMJ; Docherty, MedRxiv; Ziehr, NEJM); out of 2,215 patients admitted to ICUs in the US, 40% died, but the risk-adjusted proportion of patients who died varied widely among institutions, from 7-81% (Gupta, JAMA Intern Med); out of 3,988 COVID-19 patients admitted to ICUs in Lombardy, Italy, 87% required invasive mechanical ventilation and 53% died in-hospital (Grasselli, JAMA Intern Med); 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); a nationwide study in Germany, which did not have a shortage of ICU beds, found 53% in-hospital mortality for patients who required invasive mechanical ventilation, which rose to 72% in those 80 years or older (Karagiannidis, Lancet Respir Med); patients requiring mechanical ventilation frequently require vasopressor support (Goyal, NEJM); risk factors for severe illness and mortality are age, obesity, comorbidities, dyspnea/tachypnea, hemoptysis, hypotension, loss of consciousness, O2 sat <88% and elevated D-dimer/IL-6/ferritin/CRP/NLR, azotemia/elevated LFTs/troponin (Petrilli, BMJ; Lighter, Clin Infect Dis; Wang, MedRxiv; Liang, JAMA Intern Med; Mikami, J Gen 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 more likely to have respiratory failure, and type O has a protective effect; (Ellinghaus, NEJM); a 3p21.31 gene cluster was also identified as a possible genetic susceptibility locus

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, Cardiov 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); evidence of cardiac injury may be seen in ~22% of critically ill patients with COVID-19 (Clerkin, Circulation); 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 (Cree-Bulos, NEJM); stress cardiomyopathy (also called Takotsubo syndrome) can be a complication of COVID-19 (Jabri, JAMA Network Open); cardiac MRI may detect abnormalities in a large percentage of patients recently recovered from COVID-19, suggesting possible long-term cardiovascular consequences (Puntmann, JAMA Cardiol); 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; Ellul, Lancet Neurol; Paterson, Brain); neuropsychiatric presentations include acute psychosis (Varatharaj, Lancet
Psychiatr); neuropathology of patients who died with COVID-19 found evidence of acute hypoxic injury but no encephalitis or evidence of infection of neurons, glia, endothelium or immune cells (Solomon, NEJM); microvascular and hypoxic injury are the most characteristic neuropathological findings (Jaunmuktane, Acta Neuropathol)

**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; Pearce, Exp Opin Ther Target), although some have questioned characterizing the hyperinflammatory state in COVID-19 as a “cytokine storm” since IL-6 levels are considerably less markedly elevated compared to sepsis/ARDS (Sinha, JAMA Intern Med); 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 (Minotti, J Infect; Tschopp, Am J Transpl), 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; Garassino, 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, Nat Med); 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.** Only very rare evidence of intrauterine or transplacental transmission (Chen, Lancet; Schwartz, Arch Pathol Lab Med; Chen, NEJM), but pregnant women have an increased risk of hospitalization, ICU admission and mechanical ventilation (Ellington, MMWR); transplacental transmission from a viremic mother who was infected in the third trimester and developed placental infection (Vivanti, Nat Commun); in another case of congenital SARS-CoV-2 infection, 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) and pregnancy loss has also been reported (Galang, Obstet Gynecol); 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); breastfeeding by SARS-CoV-2-positive mothers appears to be safe if appropriate precautions are taken (Salvatore, Lancet Child Adolesc Health)

**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, E Clinical Medicine); 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; Caruana, Clin Microbiol Infect); 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 presentation may be predictive of disease severity and prognosis (Liu, Lancet Infect Dis; Pujadas, MedRxiv; Magleby, Clin Infect Dis), but a study at NYU failed to find a relationship between initial viral load and clinical progression or mortality (Argyropoulos, Am J Pathol); 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); panels with multiple RT-PCR targets can mitigate the risk of loss of sensitivity due to genomic variants (Penarrubia, IJID); 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, Clin Infect Dis; Williams, 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-turbinates 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; Wong, Clin Infect Dis; McCulloch, JAMA Netw Open); 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 or viral load in saliva (Becker, MedRxiv) or oropharyngeal swab samples (Hung, Lancet Infect Dis; Patel, Clin Infect Dis); plasma viral load (RNAemia) correlates with disease severity, lymphopenia, organ damage, inflammation/elevated IL-6 and in-hospital mortality (Fajnzylber, MedRxiv; Chen, MedRxiv; Xu, Clin Infect Dis RNAemia)

**Viral Shedding.** Nasopharyngeal viral load declines over time regardless of clinical severity (Huang, Clin Infect Dis); PCR may continue to detect viral RNA for weeks (Ridgway, ICHE), but cultures of respiratory secretions in patients with mild illness become negative after 8 days (Woelfel, Nature); respiratory samples from COVID-19 patients with ≥8 days of symptoms are often 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); one study has found viral shedding to last for 0-20 days post-symptom onset, with viral loads >7 log_{10} RNA copies/mL associated with detection of infectious virus, and a neutralizing Ab titer ≥1:20 associated with the absence of infectious SARS-CoV-2 (Van Kampen, MedRxiv); others have reported that the ability to recover virus in culture correlates with viral loads of 5.4-6.0 log_{10} genome copies/mL (Huang, J Clin Microbiol), and lower loads may not represent the presence of intact genomes; one study has defined a relationship between Ct value and likelihood of culture-positivity, ranging from 0% (Ct 34) to 50% (Ct 29) to 100% (Ct 18) (La Scola, Eur J Clin Micro Infect Dis); duration of viral shedding correlates with illness severity, even though neutralizing Ab may be detected after 10d post-symptom onset and tend to be higher in severe cases (Wang, J Clin Invest); 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), and more prolonged shedding of cultivable virus has been reported in patients with more severe illness (Folgueira, MedRxiv), 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
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Dis), and virions have been observed by electron microscopy in intestinal tissue (Qian, Clin Infect Dis intestine)

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); unequivocal evidence of SARS-CoV-2 reinfection is presently lacking, but some possible reinfections have been observed (Duggan, Am J Emerg Med); Ab begins to be detected as viral load declines (Sethuraman, JAMA), so a combination of RT-PCR and serology may enhance case detection (Guo, Clin Infect Dis; Zhao, Clin Infect Dis 2; Zhang, J Infect Dis; Miller, MedRxiv); 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); nearly 50% of symptomatic patients in NYC were IgG-positive (Reifer, MedRxiv); sensitivity of serology is only 30% after 1 week but rises to over 90% in week 3 (Deeks, Cochrane; 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, Lancet); commercial assays exhibit considerable variation in sensitivity and specificity (Lassaunier, MedRxiv), but SARS-CoV-2 serological tests in general do not appear to cross-react with seasonal coronaviruses (Amanat, Nat Med); antibodies directed to the receptor-binding domain (RBD) of the spike protein correlate with neutralizing antibodies (Premkumar, Sci Immunol); Ab directed against multiple sites on the S-protein, not only the receptor-binding domain, appear to be able to neutralize SARS-CoV-2 (Brouwer, Science); neutralizing antibodies prevent viral engagement with the ACE2 receptor by steric hindrance (Ju, Nature) and protect hamsters from SARS-CoV-2 challenge (Rogers, Science); antibodies capable of cross-neutralization of SARS-CoV and SARS-CoV-2 have been identified from B cells obtained from an individual with prior SARS (Wec, Science); 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); although most patients develop neutralizing Ab, higher titers correlate with more severe clinical illness (Wang, Clin Infect Dis neutralizing Ab; Wang, BioRxiv); most convalescent sera do not contain high titers of neutralizing antibodies, although some RBD-specific antibodies have potent antiviral activity (Robbiani, Nature); assays for Ab to nucleocapsid protein may be more sensitive than assays of Ab to spike protein (Burbelo, J Infect Dis); however, anti-spike Ab may correlate with recovery, whereas anti-nucleocapsid Ab may correlate with progression (Atyeo, Immunity); 28% of blood donors in Lombardy had evidence of COVID-19 infection, but few had high titers of neutralizing antibodies (Percivalle, Euro Surveill); mild COVID-19 is associated with a more delayed Ab response with lower titers of neutralizing Ab (Rijkers, 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 or may be less durable (Zhang, Emerg Microbes Infect; Long, Nat Med asymptomatic); 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); 2-9% of individuals in one study failed to seroconvert; non-seroconverters tend to be young with fewer comorbidities (Staines, MedRxiv); 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; the durability of antibody responses is uncertain--although seroconversion is observed in most symptomatic individuals, Ab responses may wane by 3 mos post-infection (Seow, MedRxiv); IgG targeting RBD correlates with neutralizing Ab and can still be detected 75d post-symptom onset (Iyer, MedRxiv), but SARS-CoV-2 antibodies decline rapidly in persons with mild COVID-19 (half-life 36d, Ibarrondo, NEJM); predominantly Th1 T cell responses appear early in patients with severe COVID-19 and increase over time (Weiskopf, Sci Immunol); some patients with mild COVID-19 develop T cell responses without seroconversion (Gallais, MedRxiv); although antibody responses may be relatively short-lived, T cell responses appear to be more lasting (Altmann, Sci Immunol); long lasting memory T cell responses are detected in patients following SARS or COVID-19 (Le Bert, Nature)

**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); although many therapeutic trials for COVID-19 have been initiated, many are overlapping and potentially underpowered (Kouzy, JAMA Netw Open); 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; Matheson, Science; Schiffer, OFID); whether investigational or approved,
treatment decisions must carefully consider the individual physiology of the patient and the timing of the intervention, with guidance from biomarkers and immunophenotype (Fang, Clin Infect Dis evidence; Garcia-Vidal, Clin Infect Dis; Hall, Clin Infect Dis; Mathew, Science); 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)

**Immunostimulators.** Interferon/ribavirin/lopinavir-ritonavir was superior to lopinavir-ritonavir alone (Hung, Lancet); early reports of inhaled interferon-beta are reportedly promising (https://clinicaltrials.gov/ct2/show/NCT04385095); IL-7 has been reported to restore lymphocyte count and function in patients with COVID-19 (Laterre, JAMA Netw Open)

**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); a review of the RCT data has concluded that low certainty evidence suggests that remdesivir may reduce time to improvement and decrease mortality but probably has no important impact on the need for invasive ventilation and may have little effect on hospital LOS (Rochwerg, BMJ); 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
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); some supporting data reported from a multicenter retrospective observational study in Michigan (n=2,541), in which hydroxychloroquine use was associated with reduced mortality (13.5% vs 26.4%), but treatment was non-randomized (Arshad, IJID); 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; an RCT of 504 patients with confirmed mild-moderate COVID-19 failed to detect a benefit of hydroxychloroquine with or without azithromycin (Calvacanti, NEJM); the RECOVERY trial involving 4,716 patients hospitalized with COVID-19 found that hydroxychloroquine was associated with a reduced likelihood of being discharged from the hospital alive at 28d (60.3% vs 62.8%) (Horby, MedRxiv); a double-blind placebo-controlled RCT found that prophylactic hydroxychloroquine fails to prevent symptomatic infection after SARS-CoV-2 exposure (Boulaye, NEJM); an RCT of hydroxychloroquine in China (n=75 per group) failed to detect an effect on viral clearance (Tang, BMJ); an open-label multicenter RCT in Spain found that early hydroxychloroquine treatment failed to reduce nasopharyngeal viral load or shorten the time to symptom resolution (Mitja, Clin Infect Dis); 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%), although 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); HCQ was ineffective in hamster and macaque models of SARS-CoV-2 infection (Rosenke, BioRxiv; Kaptein, BioRxiv).

**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, improving oxygenation and reducing the need for mechanical ventilation (Liu, MedRxiv; Xu, PNAS; Mehta,
Lancet; Price, Chest; McCarthy, Respirology), although clinical responses may be variable (Luo, J Med Virol); preliminary results or Roche phase III COVACTA trial of tocilizumab failed to meet its primary endpoint, although a positive trend in time to discharge was observed (Roche, Covacta press release); retrospective studies have found lower mortality in tocilizumab recipients (Roumier, MedRxiv; Klopfenstein, Med Mal Infect; Somers, MedRxiv) and a reduced risk of invasive ventilation or death and shorter duration of vasopressor support (Guaraldi, Lancet Rheumatol; Kewan eClinicalMedicine); 2 patients treated with tociluzumab still progressed to macrophage activation syndrome, and one developed viral myocarditis (which may have resulted from immunosuppression) (Radbel, Chest); elevations in D-dimer following tocilizumab have also been reported (Price, 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 sarulimab 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); IL-1 is upstream of IL-6 production, and early IL-1 receptor blockade with anakinra can also reduce CRP, oxygen requirements and days of ventilatory support (Cauchois, PNAS); anakinra was 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 recipients of baricitinib (JAK kinase inhibitor with both immunomodulatory and antiviral actions) (Cantini, J Infect); baricitiniib was associated with recovery in 11 of 15 patients with moderate-severe COVID-19, but superinfections and thrombotic events were also reported (Titanji, Clin Infect Dis); a reduction in IL-1/IL-6/TNFα with more rapid development of specific Ab has also been observed following baricitinib treatment (Bronte, MedRxiv); combined JAK1/2 (ruxolitinib) and complement (eculizumab) inhibition has been reported to result in clinical improvement and reduced evidence of coagulopathy (Giudice, Front Pharmacol); acalabrutinib, a Bruton’s tyrosine kinase inhibitor, appeared to reduce inflammation and improve oxygenation in patients with severe COVID-19 (Roschewski, Sci Immunol); a small RCT of colchicine reported reduced progression in hospitalized patients (Deftereos, JAMA Network Open); a retrospective study found lower mortality in patients receiving statins after propensity score matching (Zhang, Cell Metab)

**Lopinavir-Ritonavir.** No benefit from lopinavir-ritonavir seen in severe COVID-19 (Cao, NEJM); interferon/ribavirin/lopinavir-ritonavir was 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, Clin Transl Med); 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); circulating endothelial cells, a sign of endothelial damage, are detected in patients with COVID-19 but appear to be reduced in patients receiving therapeutic anticoagulation (Khider, J Thromb Haemost)

**Complement Inhibition.** Complement activation is a common feature of severe COVID-19 and may contribute to inflammation, thrombotic microangiopathy and tissue injury (Campbell, Circulation; Ciceri, Crit Care Resusc; Magro, Transl Res; Risitano, Nat Rev Immunol; Lo, J Immunol); a longitudinal immunophenotyping study correlated C5a/C5aR1 levels with disease severity, implicating complement cascade activation in severe COVID-19 (Carvelli, Nature); anecdotal evidence that complement inhibition can improve oxygenation and reduce inflammation (Gao, MedRxiv)

**Corticosteroids.** Possible benefits of low-dose corticosteroids have been suggested (Wu, JAMA Intern Med; Wang, MedRxiv), but caveats have also been raised (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); the open-label RECOVERY trial involving 6,425 patients hospitalized with COVID-19 found that dexamethasone was associated with lower 28d mortality (23% vs 26%), particularly in those requiring mechanical ventilation (29% vs 41%) (Horby, NEJM), so corticosteroids are now the standard of care for hospitalized patients with severe COVID-19; a systematic review of RCT data to date concludes that corticosteroids probably reduce mortality and mechanical ventilation but effectiveness of other interventions is uncertain (Siemieniuk, BMJ)

**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 in convalescent plasma recipients, including circulatory overload, lung injury, allergic reactions (Joyner, Mayo Clin Proc)

**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; Fosbøl, JAMA); 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); continuation of ACE inhibitors or angiotensin receptor blockers is associated with reduced ICU admissions and mortality compared to discontinuation (Lam, J Infect Dis); 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); favipiravir has weak antiviral activity in a hamster model (Kaptein, BioRxiv)

**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 relatively 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 (Sepulveda, MedRxiv); invasive pulmonary aspergillosis may occur as a late and often lethal complication, particularly in Europe (Van Arkel, AJRCCM; Bartoletti, 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; Ceruti, MedRxiv; Price, Eur Heart J); a high incidence of barotrauma in mechanically ventilated COVID-19 patients is seen compared to conventional ARDS, associated with increased mortality (McGuinness, Radiology); hospitalized patients with COVID-19 exhibit anomalous reductions in the volume of small pulmonary blood vessels consistent with vasoconstriction or microvascular thrombosis (Lins, MedRxiv), which correlates with hypoxemia (De Backer, MedRxiv); severe hypoxemia with preserved lung compliance and elevated deadspace is suggested to represent a distinctive subtype of ARDS with prominent hypercoagulability, thrombosis, and vascular pathology/perfusion abnormalities warranting specific interventions (Rello, Eur Respir J; Mangalmurti, AJRCCM; Patel, AJRCCM); others favor standard ARDS protocols (Ziehr, AJRCCM; Berlin, NEJM; Barbeta, Annals ATS); prone positioning improves oxygenation 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); an analysis of 149 countries or regions found that physical distancing is associated with a 13% reduction in COVID-19 incidence (Islam, BMJ); another study of 211 U.S. counties found social distancing to be the most important determinant of reproduction number, with a 70% reduction in visits to nonessential businesses associated with a fall in R0 < 1 in nearly all cases (Rubin, JAMA Netw Open); 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); a combination of distancing, self-isolation and contact tracing is more likely to result in R0<1 than any measure alone (Kucharski, Lancet Infect Dis); analysis of contact survey data in China indicates that social distancing alone may be sufficient to control COVID-19; school closures may delay and reduce peak incidence (Zhang, Science), although modeling suggests a limited impact of interventions targeting children on transmission (Davies, Nat Med); statewide school closures have been associated with reductions in COVID-19 incidence and mortality, although confounding by other interventions cannot be excluded (Auger, JAMA); 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, seroprevalence was only 5% in Spain, one of the European countries most affected by the pandemic, and at least one-third of infections were asymptomatic (Pollan, Lancet); 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); in one model, rapid testing every 2 days and strict behavioral interventions were required to keep R0<2.5 in a college campus setting (Paltiel, JAMA Netw Open); 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); near real-time genome sequencing may enhance recognition of transmission links (Rockett, Nat Med; Oude Munnink, Nat Med); 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); current leading vaccine candidates are being developed by Moderna, BioNTech/Fosun/Pfizer, Merck/IAVI, J&J/Janssen and AstraZeneca/Oxford University (O’Callaghan, JAMA); challenges include elicitation of durable immunity and potential immune enhancement (Peeples, PNAS); antibody-dependent enhancement has been shown experimentally for spike protein Ab in SARS and MERS but has not been shown or excluded for SARS-CoV-2 (Ulrich, Cytometry); 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); a recombinant vaccine based on
the receptor binding domain of the S protein is immunogenic and elicits protective responses in non-human primates correlated with neutralizing Ab and CD4 T cell responses (Yang, Nature); 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; a phase 1 study of an mRNA vaccine found it to be safe and immunogenic, with neutralizing Ab detected in all participants (Jackson, NEJM); the mRNA-1273 vaccine elicits robust neutralizing Ab responses, protection from respiratory tract challenge and no lung pathology in non-human primates (Corbett, NEJM); although a Department of Defense study suggested that influenza vaccination might increase the risk of other respiratory viruses due to viral interference (Wolff, Vaccine. 2020 Jan 10;38(2):350-354), a comprehensive analysis of influenza vaccine coverage in the U.S. has actually found a protective effect in the elderly population against COVID-19 mortality (Zanettini, MedRxiv)

**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, and a national database analysis has confirmed the increased risk to HCWs (Mutambudzi, MedRxiv); in a study of 99,795 HCWs and 2,035,395 community individuals, front-line HCWs had increased risk of SARS-CoV-2 acquisition compared with the general community (aHR 3.40 after adjustment for testing rates) (Nguyen, Lancet Public Hlth); 36% of HCWs at a NYC hospital were seropositive, most of whom had minimal symptoms (Mansour, MedRxiv); even serologic testing may underestimate mild COVID-19 cases in HCWs due to low Ab titers (Eyre, MedRxiv antibodies); in another NYC study, 33% of symptomatic HCWs and 8% of asymptomatic HCWs in NYC were PCR-positive, with declining rates over time possibly reflecting efficacy of PPE (Nagler, Clin Infect Dis); an analysis of 9,684 HCWs in China also documented COVID-19 acquisition in 1%, with the highest risk during the initial days of the outbreak in hospital areas thought to be low-risk (Lai, JAMA Netw Open); infection rates among HCWs have correlated inversely with levels of PPE (Eyre, MedRxiv); HCWs can be a source of transmission to patients: an outbreak of 66 hospital-acquired COVID-19 cases representing 15% of COVID-positive admissions was associated with a 36% case fatality rate, and HCWs were consider to be a likely source of some of the infections (Rickman, Clin Infect Dis); 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, Lancet Public Hlth); 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), and 239 clinicians, epidemiologists, engineers and aerosol scientists have published a commentary calling for greater attention to the role of airborne SARS-CoV-2 transmission (Morawska, Clin Infect Dis); aerosol transmission is most likely to occur in poorly ventilated spaces and/or at close range (Somsen, Lancet Respir Med); modeling suggests that droplet and airborne routes of infection are more important than contact for transmission to HCWs, and airborne transmission primarily occurs when HCWs are near patients and rates of emission are high (Jones, J Occup Environ Hyg); the University of Nebraska found viral contamination of commonly used items, toilets and air samples, suggesting that airborne precautions are appropriate (Santarpia, Sci Rep); culturable virus and intact virions seen by EM could be detected in <4 µm aerosol samples in rooms housing COVID-19 patients (Santarpia, MedRxiv aerosol); 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); SARS-CoV-2 RNA detected in 25% of samples from hospital heating, ventilation and HVAC systems, concerning for potential airborne spread (Horve, MedRxiv); 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); use of PPE with medical masks for patient care and N95 respirators for aerosol-generating procedures reduced but did not eliminate COVID-19 acquisition by HCWs in a French
study (Contejean, Clin Infect Dis); a meta-analysis supports physical distancing, face masks (N95 > surgical masks) and eye protection to prevent SARS-CoV-2 transmission (Chu, Lancet); some advocate the use of N95 respirators for all COVID-19 inpatient care on the basis of existing evidence (Dau, Ann Intern Med), and note that none of 420 health care providers deployed to Wuhan who were given PPE including N95 respirators developed COVID-19 (Liu, BMJ); a synthesis of available information concludes that viruses may be carried by small aerosolized particles as well as by larger droplets, and HCWs should be protected from potentially infectious aerosols when working in close proximity to patients, i.e. N95 respirators with face shields or goggles, or PAPRs (Fennelly, Lancet Respir Med)

**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); institution of universal masking at MGH was associated with a lower rate of SARS-CoV-2 positivity in HCWs (Wang, JAMA; Brooks, JAMA); 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); inoculum size may be an important but neglected determinant of infection severity (Guallar, IJID), and individuals wearing face masks, including HCWs, may be more likely to have mild or asymptomatic infection if they become infected, due to a reduced viral inoculum (Gandhi, J Gen Intern Med); 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); facemasks reduce SARS-CoV-2 transmission in a hamster model and are more effective when the index case rather than the naïve recipient is masked (Chan, Clin Infect Dis masks); universal cloth face masks have been advocated for infection prevention in the community (Abeluck, SSRN; https://rs-delve.github.io/addenda/2020/07/07/masks-update.html), 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); no transmission to 139 clients was reported from two symptomatic hair stylists working in salons in which both stylists and clients wore face coverings (Hendrix, MMWR); asymptomatic transmission means that symptom-based case detection is insensitive and supports universal face mask usage (Gandhi, NEJM); a narrative review of the benefits of public face mask-wearing may be found in (Howard, Preprints)

**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.
CITED REFERENCES


Becker D, et al. Saliva is less sensitive than nasopharyngeal swabs for COVID-19 detection in the community setting. medRxiv. https://doi.org/10.1101/2020.05.11.20092338.


Last updated 2 August 2020


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.


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.


Last updated 2 August 2020


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.


Xia W, et al. Transmission of coronavirus 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.


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