SARS-CoV-2 and COVID-19

EPIDEMIOLOGY

Person-to-person transmission documented with mean incubation period 5.2 d, serial interval 7.5 d, reproductive number approximately 2.2 (Li, NEJM)

Family clusters have been observed (Chan, Lancet), but transmission risk is only 1-5% among close contacts (Wu CROI presentation, https://special.croi.capitalreach.com/); family gatherings may facilitate community spread (Ghinai, MMWR)

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); children may still contribute to transmission

Asymptomatic or pre-symptomatic transmission makes an important contribution to spread (Rothe, NEJM; Yu, J Infect Dis; Bai, JAMA; Tong, Emerg Infect Dis; Li, Science; Xia, MedRxiv; Tao, MedRxiv; Qian, Clin Infect Dis; Wei, MMWR); this is further supported by comparison of the transmission interval and incubation period in China, Japan and Singapore (Nishiura, Int J Infect Dis; Tindale, MedRxiv); Over half of PCR-positive residents of Life Care Center of Kirkland were asymptomatic on initial testing, and viral load did not correlate with the presence of symptoms (Kimball, MMWR), which has also been noted in Italy (Cereda, ArXiv); containment measures, movement restrictions and increased awareness may shorten the window of transmission (Zhang, Lancet Infect Dis)

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

First US cases in Washington State described (Holshue, NEJM; Arentz, JAMA); COVID-19 detected in all 50 states by early March, and genomic epidemiology suggests the importance of cryptic domestic spread (Fauver, MedRxiv; Bedford, MedRxiv); 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

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

Inverse relationship observed between temperature/humidity and transmission (Wang, MedRxiv; Ma, MedRxiv; Oliveira, MedRxiv; Araujo, MedRxiv; Neher, MedRxiv; Sajadi, SSRN; Bukhari, SSRN)
SARS-CoV-2 may remain detectable in aerosols for at least 3 h and is more stable on plastic/steel than on copper/cardboard; inactivated by 70% ethanol, 0.5% hydrogen peroxide or 0.1% bleach but less reliably by benzalkonium chloride or chlorhexidine (Kampf, J Hosp Infect; van Doremalen, NEJM).

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

**Virology**

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

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

Structure of spike protein and binding to ACE2 (Wrapp, Science; Yan, Science; Hoffmann, Cell; Walls, Cell); the distribution of tissue ACE2 expression may explain higher viral loads in the lower respiratory tract.

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


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

Transcriptomic response suggests a muted antiviral response compared to other respiratory viruses (Blanco-Melo, BioRxiv).

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

Sustentacular cells in the olfactory neuroepithelium express the ACE2 receptor and TMPRSS2 protease required for viral attachment and entry (Fodoulian, BioRxiv); this may help to explain COVID-19-associated anosmia.
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); a striking finding is thrombotic microangiopathy restricted to the lungs (Fox, MedRxiv)

**CLINICAL**

Incubation period usually 4-5 d, most within 14 d (Chan, Lancet; Lauer, Ann Intern Med)

Male > female, median age 49 y, fever, cough, myalgia, fatigue, dyspnea, lymphopenia, ARDS, cardiac injury; myalgias, confusion, headache, sore throat, coryza, chest pain, secondary infection infrequent (Huang, Lancet; Chen, Lancet; Wang, JAMA; Xu, BMJ; Guan, NEJM)

However, 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); >85% of patients with mild-moderate COVID-19 may report alteration or loss of taste/smell (Iacobucci, BMJ; Lechien, Eur Arch Oto-Rhinol Laryngol); ocular signs may include conjunctival hyperemia, chemosis, epiphora or ocular secretions (Wu, JAMA Ophthalmol)

Pre-symptomatic cases usually result in mild disease (Wang, J Infect Dis)

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); Shanghai intensivists describe a biphasic illness in severe cases, with fever at the onset of illness and again at the time of acute deterioration and ARDS (https://youtu.be/Om9VTacb6VM); in patients with acute deterioration it may be important to distinguish those with declining or increasing viral loads to determine appropriate management (Lescure, Lancet Infect Dis; Joynt, Lancet Infect Dis)

Lymphopenia (Tan, MedRxiv), eosinopenia (Li, MedRxiv) and elevated NLR (neutrophil-to-lymphocyte ratio, Qin, Clin Infect Dis) 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), procalcitonin may be elevated

Abnormal coagulation parameters are common and associated with increased mortality risk (Tang, J Thromb Haemost; Lillicrap, J Thromb Haemost); anti-phospholipid antibodies may be detected in the setting of coagulopathy and multifocal thrombosis (Zhang, NEJM)

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); may be abnormal in asymptomatic individuals (Hu, Sci China Life Sci); consensus guidelines for the use of chest imaging are available (Rubin, Radiology)
Lung ultrasound may show pleural thickening, B lines and consolidation (Peng, Intensive Care Med)

Case-Fatality Rate 1.38% with a strong age-gradient (Verity, MedRxiv; Wu, Nature Med); most deaths occur in patients with co-morbidities including cardiovascular/pulmonary disease and diabetes (Wu, JAMA; Zhou, Lancet; Guan, MedRxiv; COVID-19 Response Team, MMWR); higher CFR reported in Italy, attributable to more patients ≥70 years of age (Onder, JAMA); although CFR is highest in older patients, a substantial number of patients aged 20-64 are requiring hospitalization and ICU admission (COVID-19 Response Team, MMWR); dyspnea, ARDS and cardiac injury are associated with fatal outcomes (Chen, BMJ); hyperkalemia, acute kidney injury and hypoxic encephalopathy may also be seen; mortality in patients requiring ICU admission may be ~25% (Grasselli, JAMA); high SOFA score is predictive of mortality (OR 5.65; Zhou, Lancet); 28d survival 61% in patients requiring ICU admission (Wang, AJRCCM); a cross-sectional analysis of 1,999 hospitalized COVID-19 patients in NYC found that 15% died or were discharged to hospice; 36% of those requiring mechanical ventilation died; risk factors for severe illness were O2 sat <88% and elevated D-dimer/ferritin/CRP (Petrilli, MedRxiv)

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); an independent risk factor for in-hospital morality (Shi, JAMA Cardiology)

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

Clinical course similar in pregnant women without definitive evidence of intrauterine or transplacental transmission (Chen, Lancet; Schwartz, Arch Pathol Lab Med); detection of antibodies including IgM in newborns of SARS-CoV-2-infected mothers suggests possible in utero infection, but virus not detected (Dong, JAMA; Zeng, JAMA; Kimberlin, JAMA); may be an increased risk of preterm delivery (Mullins, Ultrasound Obstet Gynecol; Wang, Clin Infect Dis)

Asymptomatic patients with COVID-19 who undergo elective surgery may have unexpectedly poor outcomes, with 44% requiring ICU care and 21% mortality (Lei, EclinicalMedicine)

**DIAGNOSIS**

PCR of Sputum or BALF is more sensitive than upper respiratory specimens (Wang, JAMA: Han, Lancet Infect Dis; Lin, MedRxiv; Loeffelholz, Emerg Microbes Infect); parallels higher viral load in sputum compared to nasopharyngeal or throat swabs (Zou, NEJM; Yu, Clin Infect Dis); viral load at the time of admission may be predictive of disease severity and prognosis (Liu, Lancet Infect Dis); self-collected tongue, nasal or mid-turbinate swabs reported to be as sensitive as health care worker-collected nasopharyngeal swabs (Tu, MedRxiv; Wehrhahn, MedRxiv); 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)

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

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

Can be found in stool but little evidence of fecal-oral transmission (Pan, Lancet Infect Dis; Gu, Gastroenterology); viral RNA may be detected in stool for weeks (Wu, Lancet Gastroenterol Hepatol)

Viral co-infections may be present (Lin, Sci China Life Sci)

Chest CT may show abnormalities even when PCR is negative (Fang, Radiology; Ai, Radiology)

Serologic tests are investigational and vary in sensitivity and specificity (Okba, MedRxiv); many patients seroconvert within 14 d of symptom onset, and most seroconvert by 20d (Long, MedRxiv; To, Lancet Infect Dis); Ab titers correlate with disease severity (Zhao, Clin Infect Dis); Neutralizing Ab titers in recovered patients are variable and correlate with CRP and lymphopenia (Wu, MedRxiv)

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

PCR may continue to detect viral RNA for weeks, but cultures of respiratory secretions in patients with mild illness become negative after 8 days (Woelfel, MedRxiv)

**TREATMENT**

No benefit from lopinavir-ritonavir (Cao, NEJM)

Remdesivir active in vitro (Wang, Cell Res) but uncertain efficacy of remdesivir in early U.S. cases and some possible hepatotoxicity (Kujawski, MedRxiv); effective when given prophylactically or therapeutically in a macaque model of MERS-CoV (de Wit, PNAS); 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)

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

ISTH has published interim guidance on recognition and management of COVID-19-related coagulopathy (Thachil, J Thromb Haemost); anticoagulation may be beneficial in patients with coagulopathy and marked D-dimer elevation (Tang 2, J Thromb Haemost); anecdotal of improved oxygenation in response to tissue plasminogen activator (tPA) (Wang, J Thromb Haemost)

Complement activation may contribute to thrombotic microangiopathy (Campbell, Circulation); anecdotal evidence that complement inhibition can improve oxygenation and reduce inflammation (Gao, MedRxiv)

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

Possible benefits of tocilizumab (IL-6RA) or other immunomodulators in patients with severe illness or cytokine storm (Liu, MedRxiv; Xu, ChinaXiv; Mehta, Lancet), although another IL-6 antagonist siltuximab was associated with a decline in CRP but variable clinical responses (Gritti, MedRxiv)

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); a clinical trial of convalescent serum will be initiated (Casadevall and Pirofski, J Clin Invest; Bloch J Clin Invest)

COVID-19, patients taking ACE inhibitors or angiotensin receptor blockers are less likely to develop severe pneumonia (Feng, MedRxiv)

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

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)

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)

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

PREVENTION

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 can be effective (Anderson, Lancet; Cowling, MedRxiv) and is more effective in reducing demand for ICU beds if instituted early (Li, MedRxiv); modeling of King County indicates that strong intervention can stop the exponential rise in infections (Klein, working paper); drastic social distancing interventions in Wuhan drove the effective reproductive number from 3.86 to 0.32 (Wang, MedRxiv); 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)

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)

Potential vaccine platforms include RNA, DNA, recombinant proteins, viral vector-based vaccines, live attenuated virus and inactivated virus (Amanat, Immunity); challenges include elicitation of durable immunity and potential immune enhancement (Peeples, PNAS)
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.

The need for airborne vs droplet precautions is controversial and may be based on outdated biophysical concepts of respiratory emissions (Bourouiba, JAMA); the University of Nebraska found viral contamination of commonly used items, toilets and air samples, suggesting that airborne precautions are appropriate (Santarpia, MedRxiv).

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); surgical masks worn by individuals with infections can also reduce the risk of transmission (Leung, Nat Med); universal cloth face masks have been advocated for infection prevention in the community (Abeluck, SSRN).

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

**EMERGENCY MANAGEMENT**

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

This summary was compiled by Ferric C. Fang, M.D. and does not necessarily represent the views of the University of Washington or its affiliated institutions.
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Last updated 12 April 2020


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Last updated 12 April 2020


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