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CME Review

Zoonotic coronavirus epidemics
Severe acute respiratory syndrome, Middle East respiratory syndrome, and coronavirus disease 2019

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Key Messages
- Severe acute respiratory syndrome, Middle East respiratory syndrome, and coronavirus disease 2019 (COVID-19) are zoonotic epidemics caused by members of the Coronaviridae family of enveloped, single-stranded, RNA viruses.
- The diagnosis of severe acute respiratory syndrome, Middle East respiratory syndrome, and COVID-19 relies on nucleic acid amplification tests, which are highly specific, but their sensitivity depends on many clinical factors, including the timing from symptom onset and sample type relative to disease.
- COVID-19 has broad clinical manifestations and can affect almost every organ system in the body.
- Although asthma and atopy do not seem to predispose patients to COVID-19 infection, their effects on COVID-19 clinical outcomes remain uncertain. It is recommended that effective therapies, including inhaled corticosteroids and biologic therapy, be continued to maintain disease control.
- There are no reports of COVID-19 among patients with primary innate and T-cell deficiencies. The presentation of COVID-19 among patients with primary antibody deficiencies is variable, with some experiencing mild clinical courses and others experiencing fatal infection despite multimodal therapy.
- The landscape of treatment for COVID-19 is rapidly evolving. The main classes of therapy include antivirals and immunomodulators, and there are drugs from each category demonstrating efficacy in the management of COVID-19.

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ABSTRACT

Objective: To review the virology, immunology, epidemiology, clinical manifestations, and treatment of the following 3 major zoonotic coronavirus epidemics: severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and coronavirus disease 2019 (COVID-19).

Data Sources: Published literature obtained through PubMed database searches and reports from national and international public health agencies.

Study Selections: Studies relevant to the basic science, epidemiology, clinical characteristics, and treatment of SARS, MERS, and COVID-19, with a focus on patients with asthma, allergy, and primary immunodeficiency.

Results: Although SARS and MERS each caused less than a thousand deaths, COVID-19 has caused a worldwide pandemic with nearly 1 million deaths. Diagnosing COVID-19 relies on nucleic acid amplification tests, and infection has broad clinical manifestations that can affect almost every organ system. Asthma and atopy do not seem to predispose patients to COVID-19 infection, but their effects on COVID-19 clinical outcomes remain mixed and inconclusive. It is recommended that effective therapies, including inhaled corticosteroids and biologic therapy, be continued to maintain disease control.

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corticosteroids and biologic therapy, be continued to maintain disease control. There are no reports of COVID-19 among patients with primary innate and T-cell deficiencies. The presentation of COVID-19 among patients with primary antibody deficiencies is variable, with some experiencing mild clinical courses, whereas others experiencing a fatal disease. The landscape of treatment for COVID-19 is rapidly evolving, with both antivirals and immunomodulators demonstrating efficacy.

Conclusion: Further data are needed to better understand the role of asthma, allergy, and primary immunodeficiency on COVID-19 infection and outcomes.

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Introduction

There are 4 common coronaviruses that cause mild upper respiratory illness in humans. Over the past 20 years, there have been 3 major zoonotic coronavirus (CoV) epidemics with 3 other highly pathogenic CoV: (1) severe acute respiratory syndrome (SARS) caused by SARS-CoV, (2) Middle East respiratory syndrome (MERS) caused by MERS-CoV, and now (3) coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2. SARS and MERS each caused fewer than a thousand deaths, but COVID-19 has infected nearly 50 million patients and caused more than a million deaths. Since then, there have only been a few sporadic cases of SARS reported, mostly associated with laboratory breaches. The main mode of transmission for SARS-CoV is by means of respiratory droplets and possibly fomites. Nosocomial transmission was well documented.

Clinical Manifestations

The incubation period for SARS is approximately 5 days (range 2-14 days). The most common presenting symptoms are fever (99%-100%), chills (15%-73%), cough (62%-100%), shortness of breath (40%-42%), headache (20%-56%), and myalgia (31%-61%). Gastrointestinal symptoms (nausea, vomiting, or diarrhea) occur in less than a third of patients. Asymptomatic infection is uncommon.

Diagnosis

SARS-CoV was detected using polymerase chain reaction (PCR) on respiratory, blood, and stool specimens, often using a combination of specimens given the imperfect sensitivity (80% at best) of a single nasopharyngeal sample. Serologic testing was used for epidemiologic surveillance.

Treatment and Vaccines

Supportive care was the mainstay of management for SARS. Multiple drugs were tried for treatment, but few randomized controlled trials (RCTs) were done. Ribavirin did not have clinical efficacy and led to hemolysis in many patients. Retrospective studies revealed possible benefits from lopinavir/ritonavir, IFN, and convalescent plasma. Steroids seemed to be harmful, leading to increased mortality and prolonged viremia. There were early vaccine trials in macaques and mice, but no completed human trials.
Middle East respiratory syndrome (MERS)

Virology and Immune Response

MERS-CoV is another Betacoronavirus in the same genus SARS-CoV that infects humans and camels. Although bats serve as a MERS-CoV reservoir, the immediate host is the dromedary camel that then infects humans. MERS-CoV differs in host binding receptor dipeptidyl peptidase 4 (also known as CD26), which is found on epithelial and endothelial cells of the human lung, kidney, small intestine, liver, and prostate. The host immune response to MERS-CoV is characterized by elevated proinflammatory cytokines (e.g., interleukin [IL]-6 and CXCL-10) followed by TH1 and type 1 cytotoxic T-cell responses during convalescence.

Epidemiology and Transmission

The first MERS case was reported in September 2012 in Saudi Arabia, and there have been more than 2400 cases and 800 deaths reported to the World Health Organization (WHO). Cases have occurred predominantly in persons residing in or traveling from the Arabian Peninsula. The median age was 52 years (interquartile range, 37-65 years), and 79% were men. Transmission primarily occurs by close contact between dromedary camels and humans. Although human-to-human transmission has been confirmed, humans are considered transient or terminal hosts with no sustained human-to-human transmission.

Transmission primary occurs by means of close contact between dromedary camels and humans. Although human-to-human transmission has been confirmed, humans are considered transient or terminal hosts with no sustained human-to-human transmission. Reported R0 estimates vary significantly (0.45-8.1), with increased spreading described in nosocomial outbreaks. Primary modes of transmission are droplet and contact, with potential for aerosol spread in close unprotected contact.

Clinical Manifestations

The average incubation period for MERS is 5 to 7 days. The most common clinical presentation is severe pneumonia and acute respiratory distress syndrome in an adult. Among 47 patients with MERS-CoV infection in Saudi Arabia, fever (98%) and cough (83%) were present in most; less common symptoms included myalgia, diarrhea, and sore throat. All patients had abnormal chest imaging, but there were no clear characteristic laboratory findings. Approximately 89% of patients required intensive care and 72% required mechanical ventilation, with a case fatality rate of 60%.

Diagnosis

Real-time reverse-transcriptase PCR (RT-PCR) testing is the main diagnostic for MERS-CoV. Given the severity of disease and risk for human-to-human transmission, a combined approach to
testing is favored with PCR testing of the lower respiratory tract, upper respiratory tract, and serum (in order of preference).15,26,35

Treatment and Vaccines

There are no therapeutic agents with proven clinical efficacy for MERS-CoV, and supportive care is the mainstay of therapy. Retrospective studies of antiviral agents (ribavirin or IFN) and steroids among critically ill patients with MERS have exhibited either statistically nonsignificant trends toward benefit or suggested increased mortality.36-38 Although convalescent plasma,39 monoclonal antibodies,40,41 and novel antivirals (fusion inhibitor42; nucleotide analog43) exhibited promise in animal studies, these therapies were not studied in humans.

Coronavirus Disease 2019 (COVID-19)

Virology and Immune Response

SARS-CoV-2 is a novel Betacoronavirus that is related to but distinct from SARS-CoV and MERS-CoV.44 SARS-CoV-2 is closely related to bat and pangolin coronaviruses44,45; it has been theorized that bats are the natural reservoir of the virus and the pangolin, an endangered and frequently trafficked mammal, may have served as an intermediate host.45 Although a market in Wuhan, People’s Republic of China, was initially thought to be the source of the outbreak, this has not been definitely proven.45

The lifecycle of SARS-CoV-2 is believed to be similar to that of SARS-CoV and other coronaviruses (Fig 1). The spike protein on the virion surface binds to the angiotensin-converting enzyme 2 (ACE2) receptor on host cells.46 The virus is then internalized by means of endocytosis, which is mediated by spike protein cleavage by the serine protease transmembrane serine protease 2.47 The viral genome is then translated into a polyprotein that is cleaved by both host and viral proteases; a viral RNA-dependent RNA polymerase then amplifies the genome, and virions are assembled and released.48 It is notable that the ACE2 receptor has broad tissue distribution, including the lungs, upper airway, myocardium, gastrointestinal tract, kidneys, and vascular endothelial cells in most tissues.49,50 This likely, in part, explains the broad clinical manifestations of COVID-19.

SARS-CoV-2 induces a limited type I and type III IFN response but high chemokine and proinflammatory cytokine gene expression. This exuberant inflammatory response is thought to play a role in more severe disease given the association between elevated inflammatory markers and mortality.51

Epidemiology and Transmission

Since the first reports of COVID-19 cases in Wuhan, People’s Republic of China, in late 2019, the SARS-CoV-2 virus has spread worldwide, infecting nearly 30 million patients and causing close to 1 million deaths.1,52 Older patients and those with comorbidities are at increased risk for severe COVID-19 disease.53-55 Data from multiple countries have exhibited incrementally higher rates of hospitalization and mortality with increasing age.56-58 In the People’s Republic of China, patients with COVID-19 who were in the age range of 70 to 79 years and 80 years or older experienced case fatality rates of 8% and 15%, respectively, compared with the overall case fatality rate of 2.3%.59 Other established epidemiologic risk factors for severe COVID-19 include diabetes, hypertension, cardiovascular disease, chronic lung disease, and obesity.56-58,60 In a large prospective cohort from the United Kingdom, significantly increased mortality was seen among COVID-19 patients with cardiovascular disease (hazard ratio [HR], 1.16), liver disease (HR, 1.51), obesity (HR, 1.33), and chronic kidney disease (HR, 1.33).60 Immunosuppressed patients with malignancy and solid organ transplant recipients seem to be at increased risk of severe COVID-19 disease and death, whereas for those with other types of immunocompromise, current evidence is less clear.61 Within the United States, there are significant racial disparities in COVID-19 disease and death likely as a result of social conditions and systemic health inequities among racial groups.62

The current understanding of SARS-CoV-2 transmission is incomplete. Person-to-person transmission by means of close-range respiratory droplets is considered the predominant mode of transmission (Fig 2).63,64 Although SARS-CoV-2 can be transmitted as an airborne aerosol,65-67 this has not been clearly

Figure 3. The clinical course of COVID-19. Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.

Figure 4. Computed tomography findings from three patients with COVID-19 (A–C). Bilateral ground-glass opacities can be seen, often with a peripheral distribution.
Table 1
Percentage and Number of Patients With Asthma Among Patients With COVID-19 and Reports of Clinical COVID-19 Outcomes Associated With Asthma

| Author, year | N   | Age, y | Hospitalized | With asthma, % (n) | Study location | Asthma associated with |
|--------------|-----|--------|--------------|--------------------|----------------|----------------------------|
| Adult        |     |        |              |                    |                |                            |
| Zhang et al,223 2020 | 140 | 57 (25-87) median (range) | 140 | 0.0 (0) | Wuhan, People’s Republic of China |                              |
| Zhang et al,224 2020 | 290 | 57 (22-88) median (range) | 290 | 0.3 (1) | Wuhan, People’s Republic of China |                              |
| Li et al,225 2020 | 548 | 60 (48-69) median (IQR) | 548 | 0.9 (5) | Wuhan, People’s Republic of China |                              |
| Song et al,225 2020 | 961 | — | 961 | 2.3 (22) | Wuhan, People’s Republic of China |                              |
| Guan et al,226 2020 | 1590 | 49 | — | 0.0 (0) | People’s Republic of China |                              |
| Lee et al,227 2020 | 303 | 25 (22-36) median (IQR) | 1 | 0.3 (1) | Cheonan, South Korea | Increased risk for intubation, ICU admission, death |
| Yang et al,228 2020 | 7340 | ≥20 | — | 9.9 (725) | South Korea | Lower but not significantly different mortality rate |
| Garcia-Pachon et al,229 2020 | 376 | 54 (42-69) median (IQR) | 158 | 2.7 (10) | Alicante, Spain | No difference in length of admission, oxygen supplementation needs, need for intubation or ICU level of care |
| San-Juan et al,230 2020 | 32 | 32 ± 7 mean ± SD | 29 | 12.5 (4) | Madrid, Spain |                              |
| Beurnier et al,231 2020 | 768 | 54 (42-67) median (IQR) | 768 | 4.8 (37) | Paris, France |                              |
| Grandbastien et al,232 2020 | 106 | 64 (54-72) median (IQR) | 106 | 21.7 (23) | Strasbourg, France |                              |
| Avdeev et al,233 2020 | 1307 | 62 (34-83) median (range) | 1307 | 1.8 (23) | Moscow, Russia |                              |
| Almaziedi et al,234 2020 | 1096 | 41 | median | 1096 | 3.9 (43) | State of Kuwait |                              |
| Ferguson et al,235 2020 | 72 | 60 (43-71) median (IQR) | 72 | 9.7 (7) | California |                              |
| Duanmu et al,236 2020 | 100 | 45 (32-65) median (IQR) | 24 | 10.0 (10) | California |                              |
| Gold et al,237 2020 | 305 | 60 | median | 305 | 10.5 (32) | Georgia |                              |
| Chhiba et al,238 2020 | 1526 | — | — | 853 | 14.4 (220) | Illinois | No difference in risk for hospitalization |
| Mahdavinia et al,239 2020 | 935 | — | — | 25.8 (241) | Illinois | Longer intubation time |
| Corsini Campioli et al,240 2020 | 251 | 53 | median | 62 | 18.3 (46) | Minnesota | No difference in mortality rate |
| Lovinsky-Desir et al,241 2020 | 1298 | ≤65 | — | 1298 | 12.6 (163) | New York | Lower likelihood of achieving cessation of viral RNA shedding 3 weeks after symptom onset |
| Singer et al,242 2020 | 1651 | 50 | median | — | 6.0 (99) | New York | No difference in length of admission, need for intubation, length of intubation, need for tracheostomy, hospital readmission, mortality |
| Richardson et al,243 2020 | 5700 | 63 | median | — | 9.0 (513) | New York | No difference in mortality rate |
| Lieberman-Cribbin et al,244 2020 | 6259 | 57 | median | — | 4.4 (272) | New York | No difference in mortality rate |
| Andrikopoulou et al,245 2020 | 158 | — | — | 87 | 11.4 (18) | New York | No difference in mortality rate |
| Salacup et al,246 2020 | 242 | 66 (58-76) median (IQR) | 242 | 7.4 (18) | Pennsylvania | No difference in mortality rate |
| Bhatraju et al,247 2020 | 24 | 64 (23-97) mean (range) | 24 | 14.0 (3) | Washington | No difference in need for PICU level of care |
| Pediatric |     |        |              |                    |                |                            |
| Du et al,248 2020 | 182 | 6 (0-15) median (range) | 182 | 0.5 (1) | Wuhan, People’s Republic of China |                              |
| Ibrahim et al,249 2020 | 4 | 13 ± 5 mean ± SD | 0 | 25 (1) | Melbourne, Australia |                              |
| Chao et al,250 2020 | 67 | 21 | median (IQR) | 46 | 23.9 (11) | New York | No difference in need for PICU level of care |
| Otto et al,251 2020 | 424 | 10 (1-15) median (IQR) | 77 | 20.5 (87) | Pennsylvania | No difference in need for PICU level of care |
| DeBlassi et al,252 2020 | 177 | 10 (0-34) median (range) | 44 | 19.8 (35) | Washington, District of Columbia | No difference in need for PICU level of care |

Abbreviations: B, benralizumab; COVID-19, coronavirus 2019; D, dupilumab; ICU, intensive care unit; IQR, interquartile range; M, mepolizumab; O, omalizumab; PICU, pediatric ICU; R, reslizumab.

*Studies that reported specifically on pregnant women only.

*This study reported the number of asthma patients only among hospitalized patients with COVID-19.

*Ages were rounded to the nearest whole number in years.
exhibited in the real world, including among health care workers. Although SARS-CoV-2 has been detected in nonrespiratory specimens (stool, blood, semen, ocular fluid), the likelihood of bloodborne or nonmucous membrane transmission seems to be low.

The duration and degree of infectivity of an individual with COVID-19 depend on multiple factors. Asymptomatic or presymptomatic transmission plays a large role, with several studies documenting transmission up to 6 days before symptom onset. A persistent positive PCR for SARS-CoV-2 does not necessarily indicate the presence of a live infective virus, but viral load as assessed by PCR cycle threshold may. Risk of infection is also related to the type and duration of exposure, with prolonged close contact in closed or crowded settings conveying the highest risk.

Clinical Manifestations

Approximately 40% to 45% of SARS-CoV-2 infections are asymptomatic. For the remaining patients with symptomatic infection, approximately 80% are mild (not requiring hospitalization), 15% are moderate to severe (requiring hospitalization), and 5% are critical (requiring intensive care unit [ICU] care). COVID-19 can involve almost every system in the body. The median incubation period between infection and symptom onset is 5 days. Patients often do not manifest signs and symptoms of a severe disease until the second week of illness. Of note, 2 recent reports describe that a significant proportion of patients have persistent symptoms weeks to months after recovery from acute infection, even in young patients with no comorbidities.

Systemic and Respiratory Manifestations

The main systemic manifestations of COVID-19 are fever (>75%), myalgias (10%-50%), and fatigue (20%-40%). Cough is seen in 45% to 80% of patients (usually dry) and dyspnea in 20% to 55%. Headache and symptoms of upper respiratory tract infection (sore throat and rhinorrhea) are seen in less than 20% of patients. Gastrointestinal Manifestations

Diarrhea or nausea/vomiting is seen in only 5% to 9% of patients. More importantly, gastrointestinal symptoms can rarely be the only presenting symptoms (ie, without respiratory complaints) of COVID-19.

Cardiac Manifestations

Arrhythmias have been described in 7% to 17% of hospitalized patients and cardiac injury (defined by elevation in troponin level) in 7% to 28%. Multiple studies have found that there is no association between the use of ACE inhibitors and angiotensin receptor blockers and the risk of SARS-CoV-2 acquisition or the risk for more severe disease.

Head and Neck Manifestations

Disorders of taste (dysgeusia, ageusia) and smell (hyposmia, anosmia) are quite common in COVID-19, ranging anywhere from 34% to 89% of patients. These symptoms can manifest before other respiratory symptoms and can be present without nasal congestion, raising the possibility that disorders of taste and smell may at least be in part a direct effect of the virus rather than solely because of nasal inflammation and obstruction. Ocular symptoms have been described in 1% to 32% of patients, with conjunctivitis being most common.

Neurologic Manifestations

Neurologic findings have been described in 36% to 57% of hospitalized patients. The most common symptoms were dizziness, headache, and impaired consciousness; stroke was seen in
| Author, year | Patient diagnoses (N) | Geographic location | Study design | Number with COVID-19 | Symptoms | Clinical severity (%) | COVID-19 treatment (%) | Outcomes (%) |
|-------------|----------------------|---------------------|--------------|---------------------|----------|-----------------------|------------------------|--------------|
| Meyts et al, 2020 | PID/IEI 53 | International Argentina, Chile, Brazil, France, Italy, Mexico, Spain, The Netherlands, United Kingdom, United States | Retrospective study | Total 94 | Asymptomatic, fever, dyspnea, cough, upper respiratory symptoms, GI symptoms, myalgias | Home (36), Asymptomatic (11), Hospitalized (63), ICU (19) | Antibiotics (51), IVIG (11), hydroxychloroquine/chloroquine (33), corticosteroids (21), mAbs (tocilizumab, anakinra) (9), antivirals (lopinavir and ritonavir) (13), remdesivir (10), favipiravir (1), anticoagulants (13), convalescent plasma (5) | Recovered (90), Died (10) |
| Quinti et al, 2020 | XLA (1), ARA (1), CVID (5) | Italy | Case series | 7 | Asymptomatic, fever, dyspnea, cough | Home (14), Hospitalized (86), ICU (43) | Antibiotics (71), Antivirals (100), hydroxychloroquine (100), IVIG (100), tocilizumab (43) | Recovered (100), Recovered (86), died (14—1 CVID patient) |
| Soresina et al, 2020 | XLA (2) | Italy | Case series | 2 | Fever, dyspnea, cough | Hospitalized (100) | Antibiotics (100), hydroxychloroquine (100), IVIG (100), lopinavir/ritonavir (50) | Recovered (100) |
| Jin et al, 2020 | XLA (3) | United States (NY) | Case series | 3 | Fever, dyspnea, cough | Hospitalized (100) | Antibiotics (100), anticoagulants (57), convalescent plasma (100), IVIG (100), remdesivir (33) | Recovered (100) |
| Fil et al, 2020 and Aljaberi et al, 2020 | CVID (1) | United States (OH) | Case report | 1 | Fever, dyspnea, cough, nausea/vomiting, diarrhea | ICU | Antibiotics, home hydroxychloroquine increased from 200 mg twice daily to thrice daily, IVIG | Recovered (100) |
| Mullur et al, 2020 | CVID (1) | United States (MA) | Case report | 1 | Fever, dyspnea, cough | ICU | Antibiotics, Convalescent plasma, IVIG, remdesivir | Died (75) |
| Ho et al, 2020 | CVID (9), hypogammaglobulinemia (1), IgA-IgG2 deficiency (1), XLA (3), XHGM (1), interferon gamma receptor 2 deficiency 16 | United States (NY) | Case series | 16 | Fever, cough, dyspnea, diarrhea, emesis, stomatitis | Home (25), Hospitalized (75), ICU (31) | Antibiotics, hydroxychloroquine, corticosteroids, investigational agent, convalescent plasma | Recovered (75), Died (25) |
| Abraham et al, 2020 | NFKB2 loss of function (1) | United States (OH) | Case report | 1 | Fever, cough, dyspnea, UR symptoms, anemia | ICU | Remdesivir, tocilizumab, IVIG, convalescent plasma | Recovered (100) |
| Dinkelbach et al, 2020 | FNI1P1 deficiency (1) | Germany | Case report | 1 | Fever, dyspnea, cough | ICU | Antibiotics, prednisolone, remdesivir | Recovered (100) |
| van der Made et al, 2020 | TLR7 deficiency (4) | Netherlands | Case series | 4 | Fever, dyspnea, cough, vomiting | ICU (100) | Antibiotics (100), chloroquine (50), corticosteroids (25), anticoagulation (25) | Recovered (75), Died (25) |

Abbreviations: ARA, autosomal recessive agammaglobulinemia; CID, combined immunodeficiency; CVID, common variable immune deficiency; FNI1P1, folliculin interacting protein 1; GI, gastrointestinal; ICU, intensive care unit; IEI, idiopathic environmental intolerance; IVIG, intravenous immunoglobulin; mAbs, monoclonal antibodies; NFKB2, nuclear factor kappa B subunit 2; PID, primary immunodeficiencies; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; XLA, X-linked agammaglobulinemia.

*Includes some previously reported cases.
*Includes pediatric cases.
*One patient in this report by Soresina et al. was also included in the case series by Quinti et al.
*Includes the same XLA cases as in Jin et al.
only 2% to 3% of patients. It is unclear whether neurologic effects are related to a direct effect of the virus, hypercoagulability or inflammation caused by the virus, or are simply the result of severe medical illness in patients with preexisting vascular risk factors.\textsuperscript{106,109} Several reports have also described Guillain-Barré syndrome in patients with COVID-19.\textsuperscript{110-112}

### Hematologic Manifestations

The incidence of venous thromboembolism (deep vein thrombosis and/or pulmonary embolism) in patients hospitalized with COVID-19 ranges from approximately 15% to 50%, and the risk seems to be higher in patients with elevated D-dimer levels.\textsuperscript{113-119} The role of therapeutic anticoagulation in severe COVID-19 is controversial\textsuperscript{120} the risks and benefits remain unclear and prospective trials are needed.

### Renal Manifestations

Acute kidney injury is seen in 3% to 11% of hospitalized patients, requiring renal replacement therapy in 2% to 7%.\textsuperscript{121,122} It is not clear whether kidney injury is because of direct viral effects (there are high levels of ACE2 expression in the kidney) or whether this is a byproduct of inflammation or hemodynamic shifts.\textsuperscript{121,122}

### Dermatologic Manifestations

Rash has been reported from less than 1% to 20% of patients, depending on the study.\textsuperscript{124-125} The most common morphologies reported are erythematous, urticarial, and vesicular rashes. Chilblain-like lesions (known colloquially as “COVID toes”) have been described typically in patients during the COVID-19 pandemic.\textsuperscript{126,127} However, more recent data argue against a causal link; rather, these lesions may be owing to lifestyle changes (eg, spending more time barefoot) during shelter in place.\textsuperscript{128,129}

### Inflammatory Syndromes

The increased levels of inflammatory markers in patients with severe COVID-19 (discussed in the subsequent sections) have raised the possibility that some manifestations of critical illness in COVID-19 may be caused by a cytokine storm. However, recent data suggest that the levels of inflammatory cytokines are similar in critically ill patients with and without COVID-19.\textsuperscript{130,131} Nevertheless, the inflammatory response in COVID-19 underlies the rationale for trying to treat COVID-19 with anti-inflammatory medications (eg, immunosuppressives and steroids). Another multisystem inflammatory syndrome has recently been described in children, which has similarities to Kawasaki disease but is thought to be a distinct entity.\textsuperscript{132,133}

### Laboratory Findings

Multiple studies have tried to identify factors that could predict disease severity, disease progression, and/or death. Factors that have been identified to date include older age, presence of comorbidities, low oxygen saturation, levels of inflammatory markers (eg, lactate dehydrogenase), and chest computed tomography (CT) severity.\textsuperscript{134-137} However, when and how to use these data from a clinical or triage standpoint is not yet clear.

### Imaging

Chest radiographic findings are abnormal in 60% and chest CT scans in 86% of patients hospitalized with COVID-19.\textsuperscript{13} The most common chest CT findings are ground-glass opacities (83%-87%) that are usually bilateral (78%-80%) and in a peripheral distribution (75%-77%).\textsuperscript{138,139} Consolidations, septal thickening, and crazy paving are also common. Typical CT findings are illustrated in Figure 4.
Clinical Manifestations Among Patients with Allergy and Atopy

Although data are limited, initial studies suggest that asthma and allergies do not particularly predispose patients to coronavirus infections. Asthma exacerbations did not seem to increase during the previous SARS-CoV and MERS-CoV outbreaks. During the current SARS-CoV-2 pandemic, asthma has been reported in 0% to 23.5% of patients with COVID-19 (Table 1). Studies have found asthma prevalence in patients with COVID-19 to be lower than the asthma prevalence reported in respective regions. Similarly, rates of asthma, allergic rhinitis, and atopic dermatitis were all lower in patients with COVID-19 (9.5%, 57.4%, and 1.8%, respectively) compared with the total tested population (14.9%, 63.1%, 3.9%, respectively) in a nationwide Korean cohort study. When 37 major pediatric asthma and allergy centers estimated to treat 1000 patients with asthma in Europe and Turkey were surveyed between September 2019 and July 2020, none reported any symptomatic COVID-19 cases or positive SARS-CoV-2 tests among their patients.

Of note, 3 studies suggest that perhaps asthma rates may be concentrated in pediatric patients with COVID-19. However, data are limited, studies were done in different countries, and definitive conclusions cannot be reached. A higher asthma prevalence was observed among pediatric patients aged 21 years and below (32.6%, 13/55) than in the whole cohort of patients with COVID-19 aged 65 years and below in New York (12.6%, 163/1298). In pediatric patients from Australia, asthma prevalence was higher among patients with COVID-19 (25% [1/4]) than in the whole cohort (10.9%, 47/433), whereas, in adult patients from South Korea, asthma prevalence was lower among patients with COVID-19 (9.9%, 725/7340) than in the whole cohort (14.9%, 32.845/219,959). Data regarding the effect of asthma on COVID-19 outcomes illustrated in Table 1 are mixed and conflicting. Severe asthma was associated with increased risk of COVID-19–related death in 1 study reviewing a health analytics platform with records of 40% of patients from the United Kingdom, but asthma was not necessarily associated with increased mortality in other studies. Interestingly, in at least 2 studies in which asthma was associated with worse clinical outcomes, nonallergic asthma accounted for the increased risk for worse outcomes (severe COVID-19, ICU admission, intubation, and death). The effect of asthma on COVID-19 outcomes may differ on the basis of other patient characteristics, although, again, data are limited. One study found male sex, Asian race, and comorbid chronic obstructive pulmonary disease (COPD) to be risk factors for hospitalization among patients with asthma. Another study from UK Biobank found that asthma was a risk factor for COVID-19 hospitalization among women but not men. Among pregnant women, those with moderate to severe COVID-19 were more likely to have asthma than those with mild COVID-19.

It has been hypothesized that reduced ACE2 expression could be protective against COVID-19 infection, although data remain limited and conflicting. Asthma, allergic rhinitis, and increasing severity of allergic sensitization have been associated with reductions in ACE2 expression in airway epithelial cells. Asthma has been associated with lower ACE2 expression and a lower risk of developing severe COVID-19 compared with COPD. IL-13, a cytokine implicated in the pathogenesis of multiple atopic conditions, including asthma, were found to reduce ACE2 and increase transmembrane serine protease 2 expression in airway epithelial cells. Conversely, asthma has also been associated with increased ACE2 expression in bronchial biopsy, bronchoalveolar lavage, and blood. In addition, a study comparing 330 patients with asthma and 79 healthy control patients and a study comparing 77 patients with asthma and 17 healthy control patients found that ACE2 expression was similar between patients with asthma and nonpatients with asthma. Notably, there was higher ACE2 expression among patients with asthma who were men, African American, or had diabetes mellitus, and the authors have suggested that a higher level of monitoring may be needed for these patients. Indeed, African American race and diabetes mellitus were implicated as risk factors for hospitalization in patients with asthma with COVID-19 and non–insulin-dependent diabetes mellitus was observed with a significantly higher prevalence in patients with asthma with COVID-19.

There has also been speculation as to whether inhaled corticosteroids (ICS) could be protective against or provide treatment benefit for COVID-19 infection. Currently, there is no literature clearly indicating whether ICS use is beneficial or detrimental to COVID-19 outcomes. In one study of 1562 patients, ICS use did not seem to affect the risk for hospitalization among patients with asthma in Chicago. There has been a case series of inhaled ciclesonide initiation temporally correlating to improvement in 3 hospitalized patients with COVID-19. In vitro, a combination of glycopyrronium, formoterol, and budesonide seemed to inhibit viral replication in infected nasal and tracheal epithelial cells and ACE2 expression was found to be decreased in sputum cells of patients with asthma and COPD on ICS.

Questions have also been raised regarding the effect of type 2 biologic therapy on COVID-19 infectivity and outcomes. Observational experiences reported to date do not provide evidence that type 2 biologics are associated with increased risk for COVID-19 infection or higher COVID-19 disease severity. To date, reports specifically investigating COVID-19 infectivity and outcomes in patients on type 2 biologic therapy found that among 1938 patients on anti–immunoglobulin E (IgE) (n = 610), anti–IL-5 or anti–IL5R (n = 844), or anti–IL-14/IL-13 (n = 483), COVID-19 infection was observed in 55 (2.8%), with 6 severe cases and 1 mortality. In addition, a recent case report specifically described milder than expected COVID-19 severity in a patient on dupilumab.

In a study specifically investigating risk factors for hospitalization, ICU stay, and mortality among patients with asthma and COVID-19, both ICS and biologic use did not differ between patients with COVID-19 having asthma who needed general vs ICU level of care. Short-acting β agonist—only use was associated with a lower risk for hospitalization.

Multiple position statements (Global Initiative for Asthma, American Academy of Allergy, Asthma, and Immunology, American College of Allergy, Asthma and Immunology, British Thoracic Society, and European Academy of Allergy and Clinical Immunology) have been released recommending continued treatments that are effective for patients with atopy, including type 2 biologics, given the current lack of evidence that type 2 biologics increase infectivity or mortality and the risk of losing disease control if type 2 biologics were to be stopped.

Clinical Manifestations Among Patients with Primary Immunodeficieny

Not all primary immunodeficiencies (PID) are thought to be equally susceptible to SARS-CoV-2 infections and its complications, but this is largely based on knowledge of the immune system function in pathogen response given the limited published reports. COVID-19 data from the People’s Republic of China describe very few patients with immunodeficiencies. Of note, 2 studies of more than a thousand patients with COVID-19 each reported that 0.19% of their study population had an immunodeficiency and milder disease courses, but the specifics of their diagnoses were not elaborated on. Given the lack of robust information regarding COVID-19 in patients with PID, likely owing to the small numbers of such patients, reports from databases and
group studies will particularly helpful to further understanding. The largest report of patients with PID infected with SARS-CoV-2 comes from an international effort among immunologists who described 94 patients with a wide range of PID diagnoses. A total of 59 patients (63%) required hospitalization, and 16% of all patients required intensive care. All adult patients who died from SARS-CoV-2 had preexisting comorbidities.174

The innate immune system is the first line of defense against pathogens, CoV is recognized by pattern recognition receptors—such as toll-like receptors (TLRs), particularly TLR3, TLR4, and TLR7, and retinoic acid–inducible gene 1 (RIG-1)–like receptors—that induce proinflammatory cytokines that help propagate antiviral responses.172 There have been few specific reports of COVID­19 in patients with known innate system immune deficiencies. From the larger international study, innate system immune deficiencies were described in 3 young children younger than 2 years of age that ranged from an asymptomatic child with STAT1 gain-of-function to a one-year-old man with interferon gamma receptor 2 deficiency who required ICU admission.174,176 In New York, the one-year-old boy with interferon gamma receptor 2 deficiency with COVID­19 and a miliary Mycobacterium avium coinfection was treated with steroids in the ICU but recovered.174,176 There was also a report of a young child in Italy who became infected with SARS-CoV-2 and developed mild myocarditis and recovered.174 A case series of 2 pairs of brothers in the Netherlands highlights a potential clinical presentation.177 All 4 patients were healthy and young, with a mean age of 26 years, who developed severe COVID-19 leading to mechanical ventilation.177 One patient died. Whole-exome sequencing performed found X-chromosomal loss-of-function mutations in TLR7, and on stimulation with a TLR7 agonist, type I IFN signaling was transcriptionally down-regulated, as was the production of IFN-α.174

The largest report of patients with PID infected with SARS-CoV-2had preexisting comorbidities.174 There was also a report of a CoV-2 had preexisting comorbidities.174

of 59 patients (63%) required hospitalization, and 16% of all patients was transcriptionally down-regulated, as was the production of TLR7, and on stimulation with a TLR7 agonist, type I IFN signaling performed found X-chromosomal loss-of-function mutations in

hypoimmunoglobulinemia, autoinflammatory syndromes (eg, Mediterranean fever), and immune dysregulation.174 One case report describes a moderately severe case of COVID-19 in a 7-year-old child with a rare foliculin interacting protein 1 deficiency that leads to cardiomyopathy, chronic lung disease, and a B-cell deficiency with hypogammaglobulinemia necessitating immunoglobulin replacement.184 This patient required a high-flow nasal cannula and developed cardiac dysfunction and renal failure but ultimately clinically improved.184 In a study of the Mexican open registry of patients with COVID-19, immunodeficiencies (3.8%) and asthma (3.8%) were the most frequently found preexisting conditions in the 21,161 patients younger than 18 years of age.185 The patients labeled with an immunodeficiency included “transient hypogammaglobulinemia, IgG subclass deficiency, impaired polysaccharide responsiveness, and IgA deficiency.”185 This study concluded that children with immunodeficiencies were associated with mild and moderate forms of COVID-19 disease.185 These findings may be influenced by biased reporting, given that patients with PID and asthma may have better access to medical care than others.

In the few reports describing COVID-19 in adult patients with CVID, X-linked agammaglobulinemia (XLA), and autosomal-recessive agammaglobulinemia, patients with more severe B cell defects seemed to experience a milder clinical course.174,176,181-186 Out of the patients described in these reports, there were 10 patients who were asymptomatic (1 with autosomal-recessive agammaglobulinemia, 1 with XLA, and 1 with hypogammaglobulinemia).174,176,181-185,186-188 In the international study with 94 patients with PID, 26% had mild disease and were treated outpatient, and the most frequently reported PID in that group was predominantly antibody deficiency with 14 patients.174 There are also reports of patients with XLA who had COVID-19-related pneumonia but not needing mechanical ventilation.174,176,186 These cases suggest that B cells are important but not strictly required to overcome infection.

In the literature, there have been approximately a dozen reported fatalities after a SARS–CoV-2 infection described in patients with inborn errors of immunity, predominantly in those with antibody deficiencies.174,176,182 In the international collaboration study, 9 patients in that cohort (7 adults and 2 children) died. All adult patients with PID who died because of SARS-CoV-2 infection had preexisting comorbidities, which included cardiomyopathy, chronic kidney disease, malignancies, chronic lung disease.174 Their PID diagnoses were mostly antibody deficiencies—6 patients with CVID (4), IgG deficiency (1), IgA and IgG2 deficiency (1)—and 1 patient with a syndromic disease.174 The 2 children with X-CGD also had concomitant Burkholderia cepacia and hemophagocytic lymphohistiocytosis, and another child had XIAP deficiency who had severe gut graft vs host disease after hematopoietic stem-cell transplantation, septic shock, and hemophagocytic lymphohistiocytosis. There have also been 2 case reports of death in other patients with CVID, including 1 patient who was a 59-year-old woman with chronic bronchitis and CVID on immunoglobulin replacement and the other a 42-year-old man with asthma, morbid obesity, and CVID who was off of intravenous immunoglobulin (IVIG) for at least 6 months.182,183 The male patient developed COVID-19 pneumonia and acute respiratory distress syndrome. He was treated with convalescent plasma, remdesivir, and antibodies for multiple bacterial infections.183 He was found to be severely hypogammaglobulinemic—IgG 117 mg/dL, IgA 10 mg/dL, and IgM undetectable—and received multiple doses of IVIG, but his SARS-CoV-2 nasopharyngeal PCR swabs remained positive throughout his month-long hospitalization before he died.183 Given this patient’s poor clinical course and that most other patients with CVID and COVID-19 have received IVIG (83%, 5 out of the 6 patients with CVID in the other case series) recovered, maintaining patients on immunoglobulin replacement could be important during these infections potentially to prevent bacterial
suprainfections.\textsuperscript{181-183,187,188} Immunoglobulin replacement has been speculated to potentially be beneficial given its immunomodulatory effects and also potential to provide antibodies that may be cross-reactive with COVID-19, but there are limited data.\textsuperscript{189} There are many other factors present as well that may increase mortality, including age and comorbidities.

These reports are small and additional studies, and RCTs are needed to evaluate the susceptibility to, clinical course, and optimal treatment of SARS-CoV-2 infections in patients with PID. There are current efforts between allergists and immunologists internationally to gather further data through surveys and databases, and there have been joint society statements, which state that there is no current data pointing to whether there is generally an increased risk of severe COVID-19 in PID.\textsuperscript{194,190,191} There may be certain types of PID that are at higher risk of contracting an infection and developing a more severe course, though, and clinician contribution to these studies and the publication of data will be helpful in informing clinical care for patients with PID having COVID-19 because, at this time, there are no formal recommendations for specific therapies in this population.

**Diagnosis**

The 2 major categories of SARS-CoV-2 diagnostics are assays detecting viral nucleic acid and serologic response. Interpretation of results depends on the time test is performed.\textsuperscript{192}

**SARS-CoV-2 Nucleic Acid Testing**

Viral nucleic acid detection is the mainstay of testing for active infection. There are multiple assays using RT-PCR technology that amplify and detect regions of the SARS-CoV-2 genome. Although high in specificity and analytical sensitivity SARS-CoV-2, real-life performance depends on the clinical scenario. False-negative results may arise owing to improper sampling or sampling site. For example, a patient with COVID-19 lower respiratory tract infection may be negative by PCR testing of the upper respiratory tract.\textsuperscript{193,194} For this reason, among symptomatic patients who are either hospitalized or in high-risk settings such as congregate living, 1 or more negative nucleic acid amplification testing (NAATs) may not be able to rule out COVID-19.

**SARS-CoV-2 Serology Testing**

Serologic tests detect antibodies to SARS-CoV-2 in the blood, with multiple assays developed against different viral epitopes with varying degrees of diagnostic performance. Both IgG and IgM rise approximately 10 to 14 days into the illness.\textsuperscript{195} Current US Centers for Disease Control and Prevention and WHO guidelines recommend against using antibody tests to diagnose individuals with active SARS-CoV-2 infection.\textsuperscript{196} There are also limited data on whether certain antibodies confer immunity and on the duration of protection of neutralizing antibodies. At this time, serologic testing serves as a public health surveillance tool or as an adjunct to PCR testing for diagnosing active infection.

**SARS-CoV-2 Antigen Testing**

Tests that identify SARS-CoV-2 antigen can be performed rapidly and serve as a rapid point-of-care assay. However, these assays are typically less sensitive than NAATs, with sensitivity ranging from 0% to 94% with an average of 56%.\textsuperscript{197} Antigen tests perform best early in the course of infection when viral load is highest and is currently recommended by the WHO when NAAT is unavailable and within the first 5 to 7 days of infection.

**SARS-CoV-2 Culture**

SARS-CoV-2 viral culture is currently only performed for research purposes.

**Treatment and Vaccines**

The landscape for therapeutics against COVID-19 has changed dramatically since the beginning of the pandemic. Although supportive care remains a cornerstone of therapy, there are now also targeted therapies with data from RCTs to support their use. Here we summarize treatment options for COVID-19.

**Antivirals**

Remdesivir is a nucleoside analog that inhibits the viral RNA-dependent RNA polymerase. Of note, 2 RCTs revealed a clinical benefit in improving recovery in hospitalized patients with COVID-19.\textsuperscript{198,199} The US Food and Drug Administration (FDA) had granted remdesivir emergency use authorization (EUA), and it has become standard of care in the United States for the treatment of COVID-19 in hospitalized patients.\textsuperscript{200} Currently, remdesivir should only be used in hospitalized patients. Although the exact oxygen saturation cutoff for remdesivir use is controversial, it has only been studied in patients with evidence of lower tract respiratory disease from COVID-19.

Although initial uncontrolled trials found a possible benefit for hydroxychloroquine\textsuperscript{201} multiple RCTs now report no clinical benefit for the treatment of or prophylaxis against SARS-CoV-2 infection, and most also exhibit an increased risk of adverse effects.\textsuperscript{202-205} The FDA has revoked its EUA for hydroxychloroquine\textsuperscript{206} and the Infectious Diseases Society of America (IDSA) COVID-19 Guidelines recommend against using hydroxychloroquine.\textsuperscript{207}

Protease inhibitors used for human immunodeficiency viruses, in particular lopinavir/ritonavir, were postulated to act against the proteases of SARS-CoV-2 and were used previously to treat SARS and MERS.\textsuperscript{13} However, randomized control trials have found no benefit of either lopinavir/ritonavir\textsuperscript{208} or darunavir/cohobicstat\textsuperscript{209} Corticosteroids should not be used in patients who do not require oxygen.

**Immunomodulators**

The Randomized Evaluation of COVID-19 Therapy trial, an RCT of more than 6000 hospitalized patients in the United Kingdom, reported a significant mortality benefit for the use of dexamethasone vs placebo, in particular, those who were mechanically ventilated or on supplemental oxygen; there was no mortality benefit (and a trend toward harm) among patients who did not require oxygen.\textsuperscript{210} Although there are some caveats to the study, the IDSA guidelines now recommend dexamethasone for hospitalized patients requiring oxygen.\textsuperscript{207}

Convalescent plasma is believed to have both antiviral (by means of neutralizing antibodies) and immunomodulatory effects (by means of neutralization of cytokines/complement and other effects).\textsuperscript{211} Observational data suggest a possible benefit of convalescent plasma\textsuperscript{212,213} and minimal risk of harm;\textsuperscript{214} although RCT data are limited.\textsuperscript{215} More trials are underway, and the IDSA guidelines currently recommend using convalescent plasma only in the context of a clinical trial.\textsuperscript{216} However, the FDA has issued EUA for convalescent plasma despite the current lack of robust RCT data.\textsuperscript{216}

Tocilizumab is an antibody against the IL-6 receptor that has been used in hopes of dampening the inflammatory response in severe cases of COVID-19. However, a meta-analysis of 7 retrospective studies\textsuperscript{217} and preliminary data from an RCT\textsuperscript{218} both reported no clinical benefit. IDSA guidelines recommend using tocilizumab only in the context of a clinical trial.\textsuperscript{207}

Other immunomodulators are currently under investigation, including other cytokine and Janus kinase inhibitors. IFN beta is also being studied and has exhibited some promise as part of combination therapy in small RCTs.\textsuperscript{219,220}

There are multiple vaccines in development currently using various platforms, including some which use novel messenger RNA (mRNA) technology.\textsuperscript{221,222} The mRNA vaccines rely on the premise...
that the mRNA that codes for a viral antigen can be delivered into human cells, which then leads to the production of antigen within the cell and a robust immunogenic response against it.221

Conclusion
A review of the virology, clinical manifestations, and treatment of SARS, MERS, and COVID-19 has elucidated the similarities and differences among these infections. Additional data are needed to better understand the impact of COVID-19 on patients with asthma, allergy, and PID.

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