

SARS-CoV-2 and COVID-19

Chapter 205 | Part 5: Infectious Diseases

KEY CLINICAL POINTS

- 1 SARS-CoV-2 is a Betacoronavirus (Betacoronavirus pandemicum) that emerged in 2019, causing the COVID-19 respiratory disease.
- 2 Viral entry is mediated by the S protein binding to hACE2, primed by TMPRSS2.
- 3 Key risk factors for severe disease include age (>45 years), high BMI (Overweight ≥ 25 , Obesity ≥ 30 , Severe ≥ 40), and specific comorbidities like lung disease or immunodeficiency.
- 4 Hospitalization criteria: O₂ saturation <94%, respiratory rate >30/min, PaO₂/FiO₂ <300 mmHg, or lung infiltrates >50%.
- 5 Nirmatrelvir-ritonavir is the primary outpatient antiviral, administered within 5 days of symptom onset.
- 6 Long COVID is defined as a condition persisting for at least 3 months with varied symptoms (fatigue, cognitive deficits).
- 7 VTE prophylaxis is recommended for all hospitalized patients.
- 8 ACE inhibitors and ARBs should generally be continued in patients with COVID-19.
- 9 Antibiotics are not generally indicated unless bacterial superinfection is suspected.
- 10 Vaccines have evolved to include bivalent (BA.4/BA.5) and monovalent (XBB, JN.1) formulations.

DEFINITION & CLASSIFICATION

- **Definition (Harrison's 20e):** SARS-CoV-2 is the cause of a respiratory disease called COVID-19.
- **Classification:**
 - Member of the Betacoronavirus genus (includes SARS-CoV-1, MERS-CoV, HCoV-OC43, and HCoV-HKU1).
 - Enveloped, positive-sense RNA viruses.
 - Genome: $\approx$ 30,000 nucleotides.
- **Viral Structure:**
 - Four structural proteins: S (spike), E (envelope), M (membrane), and N (nucleocapsid).
 - Large polyprotein cleaved into 16 nonstructural proteins.
- **Entry Mechanism:**
 - Trimeric S protein primed by TMPRSS2 $\rightarrow$ facilitates entry.
 - S protein mediates attachment via receptor-binding domain (RBD) binding to human angiotensin-converting enzyme 2 (hACE2).

Historical Context

- **WHO Status:**
 - Public Health Emergency of International Concern: January 30, 2020.
 - Pandemic Declaration: March 11, 2020.

- End of Global Emergency: May 5, 2023.
- **Impact (as of Sept 2024):** >700 million cases and >7 million deaths worldwide.

Viral Structure & Replication

- **Mutation:** RNA-dependent RNA polymerases are error-prone → frequent variants.
 - Most mutations have no effect or are deleterious.
 - Specific variations affect transmission, severity, antigenicity, and diagnostic sensitivity.
- **Monitoring:** WHO Technical Advisory Group on SARS-CoV-2 Virus Evolution tracks variant evolution.

EPIDEMIOLGY

- **Origin:** Likely existed in a bat reservoir prior to 2019.
- **Transmission:**
 - First detected in humans: 2019, Wuhan, China.
 - Rapid human-to-human spread.
 - Basic reproduction number (R) ≈ 6 (vs. influenza 1–2).
- **Risk Environments:**
 - High transmission: Prisons, cruise ships, nursing homes, airplanes, large indoor gatherings.
 - Lower transmission: Outdoor settings.
- **High-Risk Groups:** Healthcare workers, dental workers, and "superspreaders."
- **School Setting:** Not a primary driver of population transmission; children have lower rates of severe disease.

Risk Factors for Severe Illness

- **Age:** Primary risk factor.
 - >95% of deaths in patients >45 years.
 - >80% of deaths in patients >65 years.
- **Demographics:**
 - Social/health disparities (disability, minority groups) increase risk.
 - Male sex associated with higher risk (OR ≈ 1.8).
- **BMI:** Risk increases with BMI.
 - Overweight: BMI >25 but <30.
 - Obesity: BMI ≥ 30 but <40.
 - Severe obesity: BMI ≥ 40 .
- **Other Factors:** Substance use (alcohol, opioid, cocaine), smoking, and pregnancy (increased severity).

Pediatric Considerations

- **MIS-C / PMIS:** Multisystem inflammatory syndrome in children.
 - Symptoms: Persistent fever, multi-organ involvement (GI, dermatologic, cardiac, renal, hematologic, neurologic), elevated inflammatory markers.
 - High-risk group (US): Black and Latino children age 3–12 years.
- **MIS-A:** Similar syndrome in adults (rare).

ETIOLOGY & PATHOPHYSIOLOGY

- **Mechanism:** Driven by direct viral pathogenesis and associated immune response.
- **Immune Response:** Excessive proinflammatory host response contributes to pulmonary pathology and severity.
- **Autoimmunity:** Manifestations mediated by autoantibodies reported.
- **Secondary Infections:** Bacterial or fungal infections occur (bacteremia, respiratory infections).
- **Primary Driver:** Tissue inflammation and systemic inflammatory responses > direct viral cytopathic effect.

Immune Response & Cytokine Storm

- **Systemic Findings:** Lymphopenia, thrombocytopenia.
 - Inflammatory markers: IL-6, TNF- α , ferritin, CRP.
 - Organ damage markers: Elevated liver enzymes, LDH, D-dimer, prothrombin time, troponin, creatine phosphokinase.

CLINICAL FEATURES

- **Timeline:** Symptoms typically 4–5 days post-exposure; almost always within 14 days.
- **Symptoms:** Cough, fever, myalgia, headache, dyspnea, sore throat, GI symptoms (nausea, vomiting, diarrhea).
- **Sensory Loss:** Sudden onset of dysgeusia and anosmia (often resolves in weeks/months).
- **Dermatologic:** Diverse findings reported.
- **Geriatric:** Decline of health status or worsening of dementia in older individuals.
- **Mental Health:** Fatigue, depression, anxiety, sleep disturbances, cognitive deficits, PTSD, substance abuse.

Disease Severity Spectrum

- **Asymptomatic:** $\approx 1/3$ of cases; can still transmit.
- **Mild:** Most symptomatic infections (no pneumonia).
- **Severe:** Requires hospitalization, involves pneumonia, radiographic involvement of >50% lung, or hypoxia (O_2 saturation $\leq 94\%$).
- **Critical:** Respiratory failure requiring mechanical ventilation, multiorgan failure, or shock.

Long COVID

- **Definition:** Chronic condition after SARS-CoV-2 infection present for ≥ 3 months.
 - Symptoms: Fatigue, cognitive deficits, cough, dyspnea, chest pain.
 - Physical: Persistent respiratory or cardiac impairment in those with acute injury.
 - Mental Health: Altered mental health, decreased brain function, increased suicidal ideation.

DIFFERENTIAL DIAGNOSIS

- **Common Respiratory Viruses:** Influenza, RSV (most common).
 - Others: hMPV, PIV3, rhinoviruses.

- **Immunity:** Healthy adults usually develop partial immunity to these pathogens.
- **High-Risk Groups for Severe Disease:** Immunocompromised patients, institutionalized frail elderly, patients with COPD.

Bacterial Superinfection

- **Assessment:** Evaluate for bacterial complications of respiratory tract viral illness.
 - Frequency: Bacterial complications are unusual.
 - Antibiotics: Not generally indicated.
 - Exception: If diagnosis is uncertain, consider empiric regimens for CAP or HAP.

DIAGNOSTIC APPROACH

1. **Initial Screening:** Perform during respiratory symptoms or ≥ 5 days post-exposure without symptoms.
2. **Sample Collection:** Nasopharyngeal swab (most common) or saliva sample.
3. **Test Selection:**
 - **Antigen Tests:** Detect proteins; used for screening/at-home; less accurate than molecular tests in asymptomatic exposed persons.
 - **Molecular Tests (NAAT/RT-PCR):** Detect genetic material; higher sensitivity; performed in professional settings.
4. **Imaging:**
 - **Chest Radiograph:** May show bilateral consolidation or ground-glass opacities (GGO). Often normal despite respiratory compromise.
 - **Chest CT:** Shows GGO, pleural thickening, interlobular septal thickening, air bronchograms. Used for management of respiratory disease, not primary diagnosis.
 - **Lung Ultrasound:** Detects B-lines and pleural effusion.

6.1 Diagnostic Criteria & Indications

1. Hospitalization Decision (NIH Guidelines):

ullet Oxygen Saturation $< 94\%$ on room air $\rightarrow$ Hospitalize

ullet Respiratory Rate > 30 breaths/min $\rightarrow$ Hospitalize

ullet $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg $\rightarrow$ Hospitalize

ullet Lung Infiltrates $> 50\%$ of lung fields $\rightarrow$ Hospitalize

MANAGEMENT & TREATMENT

1. General Principles:

ullet Focus on severe respiratory illness and systemic disease.

ullet Antibiotics: Not generally indicated unless bacterial infection is suspected.

ullet Anticoagulation: Recommended for all hospitalized patients due to VTE risk.

ullet Antipyretics: Preferred agent is acetaminophen; avoid NSAIDs if possible (due to potential, though unconfirmed, association with worse outcomes).

ullet Chronic Meds: Continue aspirin, statins, ACE inhibitors, or ARBs.

2. Outpatient Management:

ullet Support care for mild disease.

ullet Antiviral Selection: Based on risk factors (age ≥ 65 , immunocompromised, multiple comorbidities, or age > 50 and unvaccinated).

ullet **Antiviral Therapy (Nirmatrelvir-ritonavir):**

- Administer as soon as possible.
- Timing: Within 5 days of symptom onset.
- Dose: 300 mg + 100 mg orally twice daily for 5 days.
- Adjustment: Adjust for renal function; avoid in severe renal dysfunction.

3. Inpatient Management:

ullet Initial assessment: Identify comorbidities, immunocompromise, and organ dysfunction.

ullet Fever control: Preferred with acetaminophen.

ullet Anticoagulation: Therapeutic dose for all hospitalized patients.

ullet **Antiviral (Remdesivir):** For patients with severe disease and low-flow O₂.

- Dose: 3 IV doses over 3 days.

ullet **Corticosteroids:** Dexamethasone or Prednisone for anti-inflammatory treatment.

- Monitor for hyperglycemia.

ullet **Immunomodulators (for escalation):**

- Criteria: If oxygen requirement escalates in first 4 days + severe disease + high inflammatory markers.
- Options: Baricitinib (JAK inhibitor) or Tocilizumab (IL-6 blocker).
- Tocilizumab: Humanized mAb against IL-6 receptor; used for patients requiring high-flow O₂, NIV, mechanical ventilation, or ECMO.
- Alternatives: Abatacept or Infliximab if first-line not available.

7.3 Antibody-Based Therapies

- **Convalescent Plasma:** Low effectiveness/reproducibility due to low antibody titers.
- **Human Monoclonal Antibodies (mAbs):**

- Used for outpatients with mild-to-moderate infection.
- Preliminary data: Vaccinated patients less likely to have Long COVID.

- **Long-Acting Antibody (LAAB) Combinations:**

- Tixagevimab + Cilgavimab: FDA expired EUA in 2023 due to escape variants.
- Pemivibart: Current EUA for immunocompromised patients unlikely to mount response to vaccine.
- Requirement: Only if variant frequency with reduced susceptibility $\leq 90\%$.
- Dose: 4.5 g IV (for adults/adolescents ≥ 12 years, weight ≥ 40 kg).

7.4 Treatment of Complications

- **Systemic Effects:** Hyperinflammatory and hypercoagulable states lead to ARDS, viral sepsis, cardiac injury, arrhythmias, AKI, and shock.
 - **Antibiotics:** No evidence for routine empiric broad-spectrum therapy; deescalate if no bacterial infection evidence.
 - **Specialized Care:** Replacement solutions for CRRT, sedation drugs in ICU, and expert consultation for complex anticoagulation.
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PROGNOSIS & COMPLICATIONS

- **Recovery Time:** Influenced by severity, comorbidities, and age.

ullet Symptomatic infection: Resolves in $\approx$ 2 weeks in 80% of patients (mild/moderate).

ullet Severe disease: Requires several months for recovery.