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CME ELIGIBLE ACTIVITY

Mastering COVID-19 — Harnessing Post-Exposure Prophylaxis for Primary Care Excellence

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Learning Objectives

Gain insight into the current burden of COVID-19 and develop an enhanced understanding of evolving viral variants, changing symptom patterns, and the significance of viral load.

Increase understanding of the clinical significance and implementation of PEP for COVID-19.

Expand knowledge of current, emerging, and investigational COVID-19 treatment options.

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Introduction

Post-exposure prophylaxis (PEP) is a treatment strategy that entails the prompt administration of medication to individuals who have been exposed to an infectious pathogen but have not yet shown symptoms of illness.[1] It aims to prevent systemic infection or reduce disease severity by early intervention when the pathogen load and host inflammatory response are still minimal.[1] PEP often uses the same drugs that are used for active treatment.

In the context of coronavirus-19 (COVID-19), PEP serves as a critical strategy to control the viral transmission and reduce case burden, particularly amid the emergence of the highly contagious variants.[2] It is especially valuable for people who are elderly, immunocompromised, or have comorbidities (e.g., asthma), as these groups have a higher risk of COVID-related morbidity and mortality.[1]

Understanding COVID-19 and Its Current Burden

Overview of COVID-19

Caused by the single-stranded RNA virus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), COVID-19 is a highly contagious respiratory disease. Primarily spread through respiratory droplets via direct, indirect, or close contact with infected individuals (e.g., on inhalation or through other deposition on the nasal, conjunctival, or oral mucosa), the virus then binds to the receptors found primarily on epithelial cells in the respiratory tract, allowing entry and replication.[3] Within approximately 5 days of infection, individuals typically become contagious to others.[3]

Infection can be asymptomatic or cause clinical manifestations that range from mild upper respiratory infection (URI) to severe and life-threatening conditions. Besides its direct effects on health, COVID-19 and long-COVID contribute to significant functional and socioeconomic burden on patients, such as absenteeism from work or school and greater healthcare resource utilization.[4]

Dominant SARS-CoV-2 Strains and Current Burden of COVID-19

COVID-19 vaccines, a form of pre-exposure prophylaxis (PrEP), reduce the likelihood of severe illness from certain SARS-CoV-2 variants and have played a key role in lowering case numbers and death rates, thus supporting the return to daily life like it was pre-pandemic for most people.[4] However, emerging mutant variants, while generally causing milder illness, are often more transmissible and can partially evade immunity from vaccines developed for earlier strains, contributing to periodic surges in infections and hospitalizations.[5]

According to the Centers for Disease Control and Prevention (CDC), the circulating Omicron subvariants in the United States in 2025 included XFG (Strauss), NB.1.8.1 (Nimbus), LP.8.1, XEC, and KP.3.1.1s.[6] Among these, Strauss accounted for approximately 85% of cases, making it the dominant strain, followed by Nimbus at approximately 7%.[7,8]

The estimates from the CDC for October 1, 2024, through September 27, 2025, as listed in Table 1, illustrate the continued burden of COVID-19 in the United States.[9]

Importance of Early Intervention and Preventive Strategies for COVID-19

Primary prevention measures (e.g., wearing a facemask, social distancing, good hand hygiene practices) aim to prevent COVID-19 in healthy individuals.[10] However, the rising household secondary attack rate (~81%) with highly transmissible Omicron variants, coupled with

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Table 1. Estimates of COVID-19 Burden in the United States (adapted from CDC data).[9]

Category	Estimates
COVID-19 Illness	13.8 million – 20.3 million
COVID-19 Outpatient Visits	3.3 million – 4.8 million
COVID-19 Hospitalizations	380,000 – 540,000
COVID-19 Deaths	44,000 – 63,000

declining vaccination rates and waning immunity, has made management and containment of COVID-19 increasingly challenging.[11] In response to the ongoing viral evolution, the United States has adopted an annual COVID-19 booster strategy coordinated each fall with the seasonal influenza vaccination campaign.[12] Despite this recommendation, booster uptake has remained low, with fewer than 25% of Americans receiving the updated dose in the past seasons.[12] Consequently, the burden of COVID-19 remains a significant concern, even if the "global emergency" has passed.

This data underscores the importance of secondary prevention strategies (SPSs) that aim to reduce disease severity through early detection and intervention (Figure 1) in asymptomatic or pre-symptomatic individuals exposed to confirmed cases. PEP, a key SPS, can help ease the overall disease burden by providing an additional layer of protection against COVID-19.

Clinical Features

Symptoms Currently Observed with COVID-19

Symptom patterns are evolving with successive mutations in SARS-CoV-2. Current viral variants cause milder respiratory symptoms, with patients experiencing a mild cough, shortness of breath, throat irritation, nasal congestion, and occasional mild wheezing.[13] At the same time, neurological and cognitive symptoms, such as brain fog, anosmia, and ageusia, are increasingly prominent.[13] Gastrointestinal manifestations, including nausea, diarrhea, and abdominal discomfort, are also more frequent and may precede respiratory signs. Subtle cardiovascular and systemic effects, such as palpitations, persistent fatigue, and muscle aches, are also being reported.[13]

Long COVID and Exacerbation of Existing Conditions

According to the CDC, long COVID encompasses a wide range of new, returning, or ongoing health problems that people experience for at least 3 months after SARS-CoV-2 infection.[14] Patients with pre-existing chronic conditions, such as cardiovascular disease, diabetes, and renal disease, are more susceptible to long COVID and a poor prognosis.[14,15] PEP is a potentially effective approach to reduce the risk of these complications after exposure.

Diagnostic Challenges

Despite widespread public awareness campaigns, the timely and accurate diagnosis of COVID-19 remains difficult. Some infections may not be detected or reported because individuals may remain asymptomatic.[16] Conversely, other cases may feature abnormalities on chest imaging inconsistent with COVID-19 before symptom onset or confirmation by testing, further complicating diagnosis. Additionally, COVID-19 symptoms frequently overlap with those of other viral respiratory illnesses such as influenza and respiratory syncytial virus (RSV), further expanding the differential diagnosis.[16] The wide spectrum of symptoms and severity, which often shifts during the course of illness, adds another layer of complexity and contributes to underreporting.

Diagnostic Tools

Measuring the quantity of virus present in a specific volume of bodily fluid – that is, viral load monitoring – is vital for assessing the severity of infection, guiding treatment decisions, and predicting the effectiveness of therapy.[17] A decline in viral load during antiviral treatment indicates effective viral suppression, while an undetectable viral load is associated with improved clinical outcomes.[17]

Treatment Timing

PEP should be considered as a SPS to reduce the risk of hospitalization and death for patients with mild to moderate COVID-19 and who have at least one risk factor for severe disease. Treatment should be initiated ideally within 5-7 days of symptom onset.[18]

Role of PEP in COVID-19 Management

COVID-19 management is challenging due to a wide spectrum of symptoms, severity, high transmissibility, morbidity, and mortality.[19] Declining vaccination rates and waning immunity further compound the challenge. By attenuating severe infection and associated complications, PEP can be a crucial strategy for treating individuals at higher risk, limiting secondary transmission, and reducing the overall burden of COVID-19.

COVID-19 Treatment Landscape

Approved COVID-19 Treatments

Remdesivir is the first US Food and Drug Administration (FDA)-approved antiviral for treating COVID-19 in adults and children. In the ACTT-1 study, a randomized, double-blind, placebo-controlled, phase 3 clinical trial hospitalized patients with confirmed SARS-CoV-2 infection and COVID-19 disease. The patients received 100 mg of remdesivir for 10 days.[20] Treatment with remdesivir was associated with a shorter time to recovery (9–11 days), improved recovery rate (recovery rate ratio 1.20–1.37), reduced progression to severe disease,

Figure 1. Levels of prevention of a health problem

Primordial	Primary	Secondary	Tertiary
Reduces risk factors in an entire population	Avoids the onset of a disease in healthy individuals	Prevents progression by early detection and treatment of disease in people at risk of a health problem	Prevents or reduces complications in individuals with an existing health problem
Healthy Population	Healthy Individuals	At-risk Individuals	Established Disease

and decreased time on supplemental oxygen.[20] While remdesivir acts primarily as a treatment, it can indirectly prevent disease progression, representing a form of clinical prevention. However, since remdesivir is administered intravenously to hospitalized patients, its use is primarily limited to individuals with active, moderate-to-severe COVID-19[20] and is not suitable for PEP or in outpatient settings.

The combination of nirmatrelvir (an active 3C-like protease inhibitor) and ritonavir (a CYP3A inhibitor) is given orally to treat COVID-19 in adults and children older than 12 years of age (>88 lbs) within 5 days of the onset of symptoms.[21] However, it failed to significantly improve symptoms in patients experiencing moderate to severe long COVID in the STOP-PASC study.[22] In addition, there have been instances of rebound, characterized by a recurrence of COVID-19 symptoms or a positive viral test after a person has begun to recover and initially tested negative.[23] This reappearance of symptoms typically occurs within 2–8 days after completing the standard 5-day course of the medication.[23] To avoid drug-drug interactions, it should not be taken with a number of other medications (e.g., statins).[21] Some of the interaction checkers for COVID-19 drug-drug interactions are listed in Table 2.

Molnupiravir, a nucleoside analogue, is used orally to treat COVID-19 in adults within 5 days of the onset of symptoms.[27] In late 2021, it received Emergency Use Authorization (EUA) by the FDA for treatment of adults with mild-to-moderate COVID-19 who are at risk for progression to severe illness when alternative FDA-approved or -authorized COVID-19 treatments are not accessible.[27]

Pipeline COVID-19/PEP Treatments

In early 2024, the FDA issued an EUA for a preventive monoclonal antibody, pemivibart, for people who are age 12 years and older (>88 pounds) and moderately or severely immunocompromised.[28] In addition to vaccination, it may provide another layer of protection against COVID-19, as it can be given as early as 2 weeks after receiving a COVID-19 vaccine.[28] However, pemivibart is given as a single intravenous infusion over 60 minutes in an outpatient clinic or healthcare facility, limiting its utilization in most communities.[28] Additionally, if continued protection is needed, additional doses should be administered every 3 months.[28]

In the SCORPIO-PEP phase 3 placebo-controlled trial, ensitrelvir, an investigational oral 3CL protease inhibitor, demonstrated a 67% reduction in the risk of developing COVID-19 in uninfected individuals treated after exposure, compared to a placebo at day 10.[29] It also has been observed that early treatment with ensitrelvir (<72 hours after symptom onset) shortens the time to resolve typical COVID-19 symptoms by approximately a day.[30]

Table 2. Interaction checkers for COVID-19 drug-drug interactions

Interaction Checker Tool	Link to the Tool
COVID-19 drug-drug interactions	https://www.covid19ddi.com[24]
Liverpool COVID-19 interactions	https://www.covid19-druginteractions.org/checker[25]
Drug interaction checker	https://www.pfizermedical.com/drug-interaction-checker[26]

Clinical Implications for Family Medicine

Despite declining rates of severe illness, COVID-19 continues to present family medicine (FM) specialists with challenges because of highly transmissible mutants, variable symptoms, and waning vaccine-acquired immunity. Clinicians must stay up to date on the current burden of COVID-19 and evolving symptoms to evaluate the risk of severe illness in high-risk patients. Long COVID complications underscore the need for early intervention to prevent acute infection. PEP with antivirals is emerging as an important option to protect high-risk patients and may become a crucial strategy for primary care practitioners to effectively manage COVID-19. A deeper understanding of viral load can also guide decisions on infectiousness, disease severity, and infection control. As therapies and preventive strategies evolve, their implementation in clinical practice is crucial for improved COVID-19 management.

Future Outlook

Despite considerable advancement in the prevention and treatment strategies for COVID-19, clinical challenges remain in identifying patients who may benefit from emerging interventions, selecting therapy, and optimizing the timing of treatment. The effectiveness of the COVID-19 therapies depends on various factors such as comorbidities, vaccination status, and circulating variants. This highlights the need for evidence appraisal and personalized patient treatment for efficient COVID-19 management.

Conclusion

Even after years of mainstream attention, social debate, and scientific research, COVID-19 remains a persistent challenge in FM and other specialties, with evolving highly transmissible variants and a growing burden of long-term complications. While vaccination continues to be an important tool to prevent severe complications, waning immunity and vaccine hesitancy leave many patients vulnerable. Oral antivirals and emerging PEP strategies offer powerful tools to reduce infection risk, hospitalization, and long-term complications, but they remain underutilized in clinical practice. For FM clinicians, the priority is to identify at-risk patients promptly, offer intervention early, and explore the promise of available or emerging treatments to reduce the disease burden.

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