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The Self Learning Committee has created this special issue of the Self Learning Program as an educational resource on COVID-19 pandemic, available at no cost to all CFPC members. We hope it serves to update you on the latest medical research on the current pandemic, while introducing you to all that the Self Learning Program has to offer. Self Learning is an innovative educational program from the College of Family Physicians of Canada (CFPC). It offers subscribers the opportunity to learn any time, anywhere, with a focus on information that is timely and relevant to family medicine. Each issue contains clinical questions based on recent articles from a wide variety of peer-reviewed journals. The questions are developed by more than 50 family physician volunteers. This issue contains questions drawn from recent issues of Self Learning with practice-changing information on COVID-19. We encourage you to apply the same critical appraisal to articles featured in the program as you would when reading articles in any medical journal. The educational points are not consensus statements about how best to conduct your practice; rather, they are items selected by your peers in family practice as being relevant and challenging.

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Instructions

Each question requires a selection of one best answer from either three or four possible choices, or a choice of true or false. For quick reference, the answers alone appear on page 36.

Educational Points and References
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Journals Used in this Issue

American Family Physician
American Journal of Emergency Medicine
Annals of Internal Medicine
BMJ
Canadian Family Physician
Clinical Infectious Diseases
CMAJ
Drug and Alcohol Review
JAMA
J. Pediatrics
Journal of Hospital Medicine
Journal of Palliative Medicine
NEJM
The Medical Letters

Abbreviations Used in this Issue

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<td>FODMAP</td>
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<td>number needed to harm</td>
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<td>SARS-CoV-2</td>
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<td>SNRI</td>
<td>serotonin-norepinephrine reuptake inhibitor</td>
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<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
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<td>UTI</td>
<td>urinary tract infection</td>
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Acknowledgements

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*see page iv for disclosures.
All others have no conflicts of interests to declare
## Conflict of Interest Disclosure

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<thead>
<tr>
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<tbody>
<tr>
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<td>I am the recipient of research grants from the Newfoundland and Labrador Medical Association and the College of Family Physicians of Canada.</td>
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Q1 Dexamethasone and COVID-19 Mortality

Mortality is decreased in hospitalized patients with COVID-19 who do not require respiratory support and are given dexamethasone.

☐ 1. True  ☐ 2. False

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), emerged in China in late 2019 from a zoonotic source. The majority of COVID-19 cases either are asymptomatic or result in only mild disease. However, in a substantial percentage of patients, a respiratory illness requiring hospital care develops, and such infections can progress to critical illness with hypoxemic respiratory failure requiring prolonged ventilatory support. Among patients with COVID-19 who have been admitted to hospitals in the United Kingdom, the case fatality rate has been approximately 26%, a percentage that has increased to more than 37% among patients who were undergoing invasive mechanical ventilation. Although remdesivir has been shown to shorten the time until recovery in hospitalized patients, no therapeutic agents have been shown to reduce mortality.

The pathophysiological features of severe COVID-19 are dominated by an acute pneumonic process with extensive radiologic opacity and, on autopsy, diffuse alveolar damage, inflammatory infiltrates, and microvascular thrombosis. In other severe viral pneumonias, such as highly pathogenic avian influenza, SARS, and pandemic and seasonal influenza, the host immune response is thought to play a key role in the pathophysiological effects of organ failure.

The RECOVERY trial was designed to evaluate the effects of potential treatments in patients hospitalized with COVID-19 at 176 National Health Service organizations in the United Kingdom.

Hospitalized patients were eligible for the trial if they had clinically suspected or laboratory-confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put patients at substantial risk if they were to participate in the trial.

Eligible and consenting patients were assigned in a 2:1 ratio to receive either the usual standard of care alone or the usual standard of care plus oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to ten days (or until hospital discharge if sooner).

Of the 11,303 patients who underwent randomization from March 19 to June 8, 2020, a total of 9355 patients (83%) were eligible to receive dexamethasone. Of these patients, 6425 underwent randomization to receive either dexamethasone (2104 patients) or usual care alone (4321 patients).

The mean (±SD) age of the patients in this comparison was 66.1±15.7 years, and 36% of the patients were female. A history of diabetes was present in 24% of the patients, heart disease in 27%, and chronic lung disease in 21%, with 56% having at least one major coexisting illness recorded. In this analysis, 89% of the patients had laboratory-confirmed SARS-CoV-2 infection, and 0.4% were currently awaiting the result. At randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non-invasive ventilation), and 24% were receiving neither.
Mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group, with deaths reported in 482 of 2104 patients (22.9%) and in 1110 of 4321 patients (25.7%), respectively (rate ratio, 0.83; 95% CI, 0.75 to 0.93; P < 0.001).

In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and in those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; RR, 0.82; 95% CI, 0.72 to 0.94). However, there was no clear effect of dexamethasone among patients who were not receiving any respiratory support at randomization (17.8% vs. 14.0%; RR, 1.19; 95% CI, 0.91 to 1.55).

It is likely that the beneficial effect of glucocorticoids in severe viral respiratory infections is dependent on a selection of the right dose, at the right time, in the right patient. High doses may be more harmful than helpful, as may such treatment given at a time when control of viral replication is paramount and inflammation is minimal. Slower clearance of viral RNA has been observed in patients with SARS, MERS, and influenza who were treated with systemic glucocorticoids, but the clinical significance of these findings is unknown. Unlike with SARS, in which viral replication peaks in the second week of illness, viral shedding in SARS-CoV-2 appears to be higher early in the illness and declines thereafter. The greater mortality benefit of dexamethasone in patients with COVID-19 who are receiving respiratory support and among those recruited after the first week of their illness suggests that at that stage the disease may be dominated by immunopathological elements, with active viral replication playing a secondary role.

Correct answer is 2.


PMID: 32678530


Q2 COVID-19 Symptoms in Nursing Home Residents

Patients dying of COVID-19 in nursing homes have lower symptom prevalence than those dying in hospital.

☐ 1. True
☐ 2. False

Educational Point: The COVID-19 pandemic is creating fear not only among the public but also in health care staff, due to the alarming reports of large groups of dying patients with acute respiratory distress syndrome (ARDS). Symptoms at admission to hospitals are frequently reported, but little is written about symptom relief in the dying patients.

In studies so far, including a recent study on 5700 patients hospitalized in the New York City area, focus has mainly been on describing initial symptoms such as fever and cough, risk factors, including comorbidities, laboratory findings, and prognostic factors. With few exceptions, reports on deaths have been from hospitals and/or ICUs, where multivariable analyses have highlighted independent risk factors such as age, comorbidities, organ failure, elevated markers, for example, d-dimer. These data are important, especially for the development of COVID-19 care. However, from the individual, dying patient's point of view, symptom prevalence and the possibility to relieve distressing symptoms are even more important.
In hospital and ICU studies, the mean age is relatively low. In two Chinese studies, the median age at admission to hospital and ICU were 56 and 47 years, respectively. In the recent New York study, median age at admission was 63 years. However, emerging statistics show that when all deaths in COVID-19 are considered, the mean age is substantially higher. Recent data indicate that about 40–50% of deaths occur among elderly people in nursing homes, but little is known about the way they die.

Increasing numbers of people dying from COVID-19 are reported, but data are lacking on the way they die. In order to study symptoms and symptom relief during the last week of life, comparing nursing homes with hospitals, the Swedish Register of Palliative Care with national coverage was used. Breakthrough symptoms were registered as Yes/No. Symptom relief was recorded on a 3-grade scale as complete—partial—no relief.

All deaths in COVID-19 were contrasted to deaths in a reference population (deaths 2019). Deaths at nursing homes were compared with deaths in hospitals. All deaths in hospitals or nursing homes (n = 490) were analyzed. Deaths in other settings (specialized palliative care wards [n = 11], in palliative home care [n = 2], or in their own homes [n = 8]) were excluded (n = 21). Only patients with expected deaths (n = 390) were entered in the final analysis.

Breathlessness as a breakthrough symptom was more common in COVID-19 patients than in the 2019 reference population (P < 0.001) and relief of breathlessness, as well as anxiety, delirium, and death rattles was less successful in COVID-19 patients (P < 0.05 to P < 0.01 in different comparisons). Patients were older in nursing homes than in hospitals (86.6 years vs. 80.9 years, P < 0.001) and more often female (48% vs. 34%, P < 0.001). Breakthrough of breathlessness was much more frequently reported in hospital settings than in nursing homes, 73% versus 35% (P < 0.0001), and complete relief was more rarely possible in hospitals, 20% versus 42% (P < 0.01). The proportion of partial relief+complete relief was comparable, 92% versus 95% (ns). Also, anxiety and pain were more often completely relieved in nursing homes (P < 0.01 in both comparisons).

The lower symptom prevalence in nursing homes may be explained by elderly frail residents dying already in the first phase of the COVID-19 disease, before acute respiratory distress syndrome develops.

Correct answer is 1.


PMID: 32746685

Q3 Management of Post-acute COVID-19 in Primary Care

Which one of the following statements about post-acute COVID-19 is false?

- 1. Around 10% of patients who have tested positive for SARS-CoV-2 virus remain unwell beyond three weeks.
- 2. There are no evidence based treatments for fatigue after COVID-19.
- 3. Intense cardiovascular exercise must be avoided for three months in all patients after pericarditis.

Educational Point: This article, intended for primary care clinicians, relates to the patient who has a delayed recovery from an episode of COVID-19 that was managed in the community or in a standard hospital ward.

In the absence of agreed definitions, for the purposes of this article the authors define post-acute COVID-19 as extending beyond three weeks from the onset of first symptoms and chronic COVID-19 as extending beyond 12 weeks. Since many people were not tested, and false negative tests are common, the authors suggest that a positive test for COVID-19 is not a prerequisite for diagnosis.

Around 10% of patients who have tested positive for SARS-CoV-2 virus remain unwell beyond three weeks, and a smaller proportion for months. This is based on the UK COVID-19 Symptom Study, in which people enter their ongoing symptoms on a smartphone app. A recent US study found that only 65% of people had returned to their previous level of health 14-21 days after a positive test.

It is not known why some people’s recovery is prolonged. Persistent viraemia due to weak or absent antibody response, relapse or reinfection, inflammatory and other immune reactions, deconditioning, and mental factors such as post-traumatic stress may all contribute. Long term respiratory, musculoskeletal, and neuropsychiatric sequelae have been described for other coronaviruses (SARS and MERS), and these have pathophysiological parallels with post-acute COVID-19.

Post-acute COVID-19 symptoms vary widely. Even so-called mild COVID-19 may be associated with long term symptoms, most commonly cough, low grade fever, and fatigue, all of which may relapse and remit. Other reported symptoms include shortness of breath, chest pain, headaches, neurocognitive difficulties, muscle pains and weakness, gastrointestinal upset, rashes, metabolic disruption (such as poor control of diabetes), thromboembolic conditions, and depression and other mental health conditions. Skin rashes can take many forms including vesicular, maculopapular, urticarial, or chilblain-like lesions on the extremities (so called COVID toe). There seems to be no need to refer or investigate these if the patient is otherwise well.

Blood tests should be ordered selectively and for specific clinical indications after a careful history and examination; the patient may not need any. Anaemia should be excluded in the breathless patient. Lymphopenia is a feature of severe, acute COVID-19. Elevated biomarkers may include C reactive protein (for example, acute infection), white cell count (infection or inflammatory response), natriuretic peptides (for example, heart failure), ferritin (inflammation and continuing prothrombotic state), troponin (acute coronary syndrome or myocarditis) and D-dimer (thromboembolic disease). Troponin and D-dimer tests may be falsely positive, but a negative result can reduce clinical uncertainty.

Further research is likely to refine the indications for, and interpretation of, diagnostic and monitoring tests in follow-up of COVID-19. For patients who were not admitted to intensive care, British Thoracic Society guidance on follow-up of COVID-19 patients who have had a significant respiratory illness proposes community follow-up with a chest x-ray at 12 weeks and referral for new, persistent, or progressive symptoms. For those with evidence of lung damage (such as persistent abnormal chest x ray and oximeter readings), referral to a respiratory service is recommended; subsequent early referral to pulmonary rehabilitation probably aids recovery.
A degree of breathlessness is common after acute COVID-19. Severe breathlessness, which is rare in patients who were not hospitalised, may require urgent referral. Breathlessness tends to improve with breathing exercises. Pulse oximeters may be extremely useful for assessing and monitoring respiratory symptoms after COVID-19, and the authors could find no evidence that their use in the home leads to increased anxiety. Those who have had significant respiratory illness may benefit from pulmonary rehabilitation.

The profound and prolonged nature of fatigue in some post-acute COVID-19 patients shares features with chronic fatigue syndrome described after other serious infections including SARS, MERS, and community acquired pneumonia. The authors found no published research evidence on the efficacy of either pharmacological or nonpharmacological interventions on fatigue after COVID-19.

Perhaps 20% of patients admitted with COVID-19 have clinically significant cardiac involvement; occult involvement may be even commoner. Cardiopulmonary complications include myocarditis, pericarditis, myocardial infarction, dysrhythmias, and pulmonary embolus; they may present several weeks after acute COVID-19. They are commoner in patients with pre-existing cardiovascular disease, but they have also been described in young, previously active patients. Various pathophysiological mechanisms have been proposed, including viral infiltration, inflammation and microthrombi, and down-regulation of ACE-2 receptors.

Chest pain is common in post-acute COVID-19. The clinical priority is to separate musculoskeletal and other nonspecific chest pain (for example, the symptom described by a large patient-led survey as “lung burn”) from serious cardiovascular conditions. Clinical assessment of the post-acute COVID-19 patient with chest pain should follow similar principles to that for any chest pain: a careful history, taking account of past medical history and risk factors, a physical examination, backed up as indicated by investigations.

COVID-19 is an inflammatory and hypercoagulable state, with an increased risk of thromboembolic events. Many hospitalised patients receive prophylactic anticoagulation. Recommendations for anticoagulation after discharge vary, but higher risk patients are typically discharged from hospital with ten days of extended thromboprophylaxis. If the patient has been diagnosed with a thrombotic episode, anticoagulation and further investigation and monitoring should follow standard guidelines. It is not known how long patients remain hypercoagulable following acute COVID-19.

Left ventricular systolic dysfunction and heart failure after COVID-19 can be managed according to standard guidelines. Intense cardiovascular exercise must be avoided for three months in all patients after myocarditis or pericarditis; athletes are advised to take three to six months of complete rest from cardiovascular training followed by specialist follow-up, with return to sport guided by functional status, biomarkers, absence of dysrhythmias, and evidence of normal left ventricular systolic function.

Ischaemic stroke, seizures, encephalitis, and cranial neuropathies have been described after COVID-19, but these all seem to be rare. A patient suspected of these serious complications should be referred to a neurologist. Common non-specific neurological symptoms, which seem to co-occur with fatigue and breathlessness, include headaches, dizziness, and cognitive blunting (“brain fog”). Until evidence based guidance appears on how to manage or when to refer such symptoms, the authors recommend supportive management and symptom monitoring in primary care.

Correct answer is 4.


PMID: 32784198 Link: https://www.bmj.com/content/370/bmj.m3026.long
Q4 COVID-19 and Multisystem Inflammatory Syndrome in Children

Which one of the following statements about children with COVID-19 and multisystem inflammatory syndrome (MIS-C) is false?

- ☐ 1. Most children with SARS-CoV-2 infection have mild COVID-19 that does not lead to medical intervention.
- ☐ 2. The majority of patients admitted with MIS-C test positive for SARS-CoV-2.
- ☐ 3. The gastrointestinal system is the organ system most commonly involved.
- ☒ 4. Among patients with MIS-C and recorded COVID-19 symptoms, MIS-C symptom onset usually occurs within three days of COVID-19 symptom onset.

Educational Point: Severe lung involvement with acute respiratory failure is the most common complication of COVID-19 in adults, but many have complications in multiple organs, including the heart. Adults with severe COVID-19 typically present during the second week of illness, a time coinciding with declining viral loads and increasing markers of inflammation. In contrast, most children and adolescents with SARS-CoV-2 infection have mild COVID-19 that does not lead to medical intervention. In late April 2020, clinicians in the United Kingdom reported a cluster of eight previously healthy children presenting with cardiogenic shock, fever and hyperinflammation. The case definition of multisystem inflammatory syndrome in children (MIS-C) includes six criteria: serious illness leading to hospitalization, age less than 21 years, fever > 38.0°C or report of fever lasting at least 24 hours, laboratory evidence of inflammation, multisystem organ involvement, and laboratory-confirmed SARS-CoV-2 infection or an epidemiologic link to a person with COVID-19.

The authors conducted prospective and retrospective surveillance of 234 patients with MIS-C admitted to 53 centers from March 15, 2020 to May 20, 2020. Most patients with MIS-C have involvement of at least four organ systems. The most commonly involved organ systems were the gastrointestinal (92%), cardiovascular (80%), hematologic (76%), mucocutaneous (74%) and respiratory (70%) systems. Most patients were cared for in an intensive care unit, and 20% received invasive mechanical ventilation. As of May 20, 2020 70% had been discharged alive, 28% were still hospitalized, and four (2%) had died.

The majority of patients (70%) tested positive for SARS-CoV-2 infection, and 30% had an epidemiologic link to a person with COVID-19. Among the 14 patients with recorded COVID-19 symptoms before the onset of MIS-C, the median interval from COVID-19 symptom onset to MIS-C symptom onset was 25 days (range, 6 to 51).

In this case series, a majority of patients were treated with immunomodulatory drugs, most commonly intravenous immune globulin (77%) and systemic glucocorticoids (49%).

Correct answer is 4.


PMID: 32598831

COVID-19 infection can be ruled out with an appropriately timed and negative polymerase chain reaction test, even if clinical suspicion is high.

☐ 1. True
☐ 2. False

**Educational Point:** Tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) based on reverse transcriptase polymerase chain reaction (RT-PCR) are often used to rule out infection among high-risk persons, such as exposed inpatients and health care workers. Hence, it is critical to understand how the predictive value changes in relation to time since exposure or symptoms, especially when using the results of these tests to make decisions about whether to stop using personal protective equipment or allow exposed health care workers to return to work. The sensitivity and specificity of PCR-based tests for SARS-CoV-2 are poorly characterized, and the “window period” after acquisition in which testing is most likely to produce false-negative results is not well known.

As part of a broader effort to provide critical evaluation of emerging evidence, the Novel Coronavirus Research Compendium at the Johns Hopkins School of Public Health did a literature review to identify preprint and peer-reviewed articles on SARS-CoV-2 diagnostics.

From the broader search, the authors identified articles that provided data on RT-PCR performance by time since symptom onset or exposure using samples derived from nasal or throat swabs among patients tested for SARS-CoV-2. Inclusion criteria were use of an RT-PCR–based test, sample collection from the upper respiratory tract, and reporting of time since symptom onset or exposure. The authors identified seven studies (two preprints and five peer-reviewed articles) with a total of 1330 respiratory samples analyzed by RT-PCR.

Over the four days of infection before the typical time of symptom onset (day 5), the probability of a false-negative result in an infected person decreases from 100% (95% CI, 100% to 100%) on day 1 to 67% (CI, 27% to 94%) on day 4, although there is considerable uncertainty in these numbers. On the day of symptom onset, the median false-negative rate was 38% (CI, 18% to 65%). This decreased to 20% (CI, 12% to 30%) on day 8 (3 days after symptom onset) then began to increase again, from 21% (CI, 13% to 31%) on day 9 to 66% (CI, 54% to 77%) on day 21.

Translating these results into a post-test probability of infection, a negative result on day 3 would reduce our estimate of the relative probability that a case patient was infected by only 3% (CI, 0% to 47%) (for example, from 11.2%, the rate seen in a large study of household contacts, to 10.9%). Tests done on the first day of symptom onset are more informative, reducing the inferred probability that a case patient was infected by 60% (CI, 33% to 80%).

When the authors assumed a high pretest probability of infection (4 times the attack rate observed in a large cohort study), the post-test probability of infection was at minimum 14% (CI, 9% to 20%) eight days after exposure. When the authors assumed a lower pretest probability of 5.5% (half the observed attack rate), the negative post-test probability of infection was still minimal eight days after exposure (1.2% [CI, 0.7% to 2.0%]).

Tests for SARS-CoV-2 based on RT-PCR added little diagnostic value in the days immediately after exposure. This is consistent with a window period between acquisition of infection and detectability by RT-PCR seen in other viral infections, such as HIV and hepatitis C. This study suggests a window period of three to five days, and the authors would not recommend making decisions regarding removing contact precautions or ending quarantine on the basis of results obtained in this period in the absence of symptoms. Although the false-negative rate is minimized one week after exposure, it remains high at 21%.
If clinical suspicion is high, infection should not be ruled out on the basis of RT-PCR alone, and the clinical and epidemiologic situation should be carefully considered. In many cases, time of exposure is unknown and testing is done on the basis of time of symptom onset. The false-negative rate is lowest three days after onset of symptoms, or approximately eight days after exposure. Clinicians should consider waiting one to three days after symptom onset to minimize the probability of a false-negative result.

Correct answer is 2.


PMID: 32422057 Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7240870/

Q6 Alcohol Policies During the COVID-19 Pandemic

During the COVID-19 pandemic, many national governments have, explicitly or implicitly, deemed the supply of alcohol to be essential and some have even argued that doing so prevents cases of alcohol withdrawal swamping hospitals. Which one of the following statements about the impact of alcohol on health systems or patients is false?

- 1. Alcohol withdrawal admissions pre-pandemic likely accounted for about 5% of alcohol attributable hospitalizations in Canada.
- 2. Estimates of alcohol-attributable emergency room visits in Canada exceeds by a factor of about seven all the known cases of COVID-19 in the first wave of the pandemic in Canada.
- 3. Heavy drinking increases risk for severe lung infections (including both viral and bacterial pneumonia).
- 4. In South Africa during the COVID-19 pandemic, public policies that resulted in reduced alcohol availability resulted in increased acute-care utilization.

Educational Point: During the COVID-19 pandemic global, national and local infections and deaths have been tracked daily and communicated to us in real time via multimedia. Citizens of most countries have endured extraordinary restrictions to try and contain viral spread, reduce deaths and relieve the strain on frontline health-care workers. During this time, most governments have also taken steps to ensure continued and convenient access to alcohol, despite its demonstrated impacts on these same health-care services and it causing some three million deaths each year.

Alcohol use poses special problems in relation to the COVID-19 pandemic which have implications for public health and health care. Firstly, heavy drinking increases risk for severe lung infections (including both viral and bacterial pneumonia) and ensuing respiratory problems. Secondly, there are many reports of domestic violence spiking around the world as people are required to spend long hours together in their homes. Alcohol use increases the risk that interpersonal conflicts will result in violent behaviour. Alcohol use in the home may also compromise children’s welfare. Alcohol is a significant risk factor for depression and suicide, which may be more prevalent during this time of enforced social isolation. Finally, it is implausible that being impaired with alcohol will do anything other than make it harder for people to attend to basic precautions for avoiding infection, such as physical distancing, hand washing and not touching one’s face.

Many national governments have, explicitly or implicitly, deemed the supply of alcohol to be ‘essential’ and some have even argued that doing so prevents cases of alcohol withdrawal swamping hospitals. In fact, presentations to hospitals for alcohol withdrawal are only a small proportion of all those attributable to alcohol—and they would most likely be reduced if alcohol restrictions were introduced. In 2017, the Canadian Institute for Health Information identified 77,000 hospital admissions wholly caused by alcohol (which they noted as a higher number than for those due to heart attacks). Of these 100% alcohol-attributable admissions, 23% were attributed to alcohol withdrawal, but this estimate excludes
the many more cases partly caused by alcohol, for example from cancer, road traffic accidents, violence and liver disease. In 2017, 100% alcohol-attributable hospitalisations accounted for 22% of all alcohol hospitalisations; thus cases involving alcohol withdrawal will involve only about 5% of the total.

Alcohol’s impact on the delivery of health services is substantial. In most countries, alcohol’s contribution is in the region of 20% of all presenting injuries, while alcohol’s contribution to non-injury emergency department presentations averages 11.5%. It was estimated that in 2014 there were 4,976,136 alcohol-related emergency room presentations in the USA (a rate over time not dissimilar to those of confirmed COVID-19 cases of any severity detected in the USA). The Canadian Substance Use Costs and Harms study estimates of alcohol-attributable emergency room visits in Canada for 2017 (700,140) exceeds by a factor of about seven all the known cases of COVID-19 as of 8 July 2020 (100,818).

The 20th century provides many examples where restricted alcohol supply led to substantial reductions in alcohol-related health problems and hence demand on health-care services. For example, alcohol monopoly strikes in Canada and the Nordic countries were associated with significant reductions in public intoxication, crime and demand for withdrawal treatment. Wine rationing during World War II, Gorbachev era restrictions and even US Prohibition all led to improved health outcomes. It seems likely, therefore, that reducing not maintaining alcohol’s availability is the best way to limit the burden on health-care services at this and any other time. Recent experience from South Africa bears this point out, where it was estimated that trauma units received 5000 fewer visits every week as a result of the country’s COVID-19 alcohol ban, with more lives saved from alcohol-related causes than lives lost to COVID-19.

Alcohol’s impact on global health is substantial and of a similar order of magnitude to that from COVID-19. Despite the current importance of protecting health-care services, most governments have deemed alcohol sales to be as essential as food, fuel and pharmaceuticals. In many countries, alcohol is now more readily available and affordable than ever before, a situation global alcohol producers benefit from and have helped engineer. The authors argue that to protect frontline health-care services and public health more generally, it is essential that modest, evidence-based restrictions on alcohol prices, availability and marketing are introduced. In particular, the authors recommend increases in excise taxation coupled with minimum unit pricing to both reduce impacts on health-care services and provide much-needed revenues for governments at this critical time.

Correct answer is 4.


Q7 Elevated D-Dimer in COVID-19

Increased D-dimer levels measured on hospital admission are significantly correlated with the severity of COVID-19 pneumonia.

◉ 1. True
◉ 2. False

Educational Point: COVID-19 has infected millions of people worldwide, but definite prognostic factors and treatment regimens have not been adequately defined. COVID-19 manifests with enteric, hepatic, nephrotic, neurological and cardiac symptoms, causing multiple organ failure and a high risk of death. Arterial and venous thrombotic complications and coagulopathies including disseminated intravascular coagulopathy (DIC) have become a major cause of morbidity and mortality particularly in patients with comorbid conditions, prolonged hospitalization, intensive care unit (ICU) admission, and mechanical ventilation (MV). Excessive inflammation, platelet activation, endothelial
dysfunction, and stasis play a significant role in the development of thrombotic complications. D-dimer is the degradation product of fibrin and reflects the activation of both thrombotic and fibrinolytic pathways. Many descriptive studies have reported elevated D-dimer levels in COVID-19 patients although the prognostic value of D-dimer levels, particularly those measured on admission and the threshold levels for treatment modifications, have not been well described.

In this systematic review and meta-analysis, the authors aimed to investigate the prognostic value of D-dimer levels measured on admission in COVID-19 patients. The authors performed a comprehensive literature search from several databases. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in abstracting data and assessing validity. Quality assessment was performed using the Newcastle-Ottawa quality assessment scale (NOS). D-dimer levels were pooled and compared between severe/non-severe and surviving/non-surviving patient groups. Weighted mean difference (WMD), risk ratios (RRs) and 95% confidence intervals (CIs) were analyzed.

Thirty-nine studies reported on D-dimer levels in 5750 non-severe and 2063 severe patients and 16 studies reported on D-dimer levels in 2783 surviving and 697 non-surviving cases. D-dimer levels were significantly higher in patients with severe clinical status (WMD: 0.45 mg/L, 95% CI: 0.34–0.56; \( P < 0.0001 \)). Non-surviving patients had significantly higher D-dimer levels compared to surviving patients (WMD: 5.32 mg/L, 95% CI: 3.90–6.73; \( P < 0.0001 \)). D-dimer levels above the upper limit of normal (ULN) was associated with higher risk of severity (RR: 1.58, 95% CI: 1.25–2.00; \( P < 0.0001 \)) and mortality (RR: 1.82, 95% CI: 1.40–2.37; \( P < 0.0001 \)).

This meta-analysis evaluated the clinical data of 11,054 COVID-19 patients and indicated that patients with more severe presenting symptoms and patients with a higher risk of mortality have higher levels of D-dimer levels on admission. The clinical progress of COVID-19 may vary from asymptomatic disease to rapid progression to death due to acute respiratory distress syndrome (ARDS) and thromboembolic and hemorrhagic complications. The findings of this meta-analysis provide robust evidence that D-dimer levels may be used for risk stratification of patients with COVID-19. In emergency settings, risk stratification is as important as diagnosis especially if testing all patients with suspected COVID-19 is not possible. Reverse transcription polymerase chain reaction assays usually yield results within 24 hours which is relatively long for triage of suspected COVID-19 patients. However, D-dimer testing is widely available and results can be obtained within one hour. D-dimer testing may be reserved for all patients with suspected COVID-19 in emergency departments. **Increased levels of D-dimer levels measured on admission are significantly correlated with the severity of COVID-19 pneumonia** and may predict mortality in hospitalized patients.

Correct answer is 1.


PMID:

Q8 SARS-CoV-2 Among Children

Which one of the following statements about SARS-CoV-2 among children is false?

- ☐ 1. Children can carry very high viral loads even before symptoms develop.
- ☐ 2. Children with multisystem inflammatory syndrome (MIS-C) exhibit high levels of viral load on nasopharyngeal or oropharyngeal viral testing.
- ☐ 3. Symptoms are nonspecific and overlap considerably with non-COVID-19-related illnesses.
- ☐ 4. Only one half of children with acute SARS-CoV-2 infection present with fever.

**Educational Point:** The manner in which children contribute to the spread of SARS-CoV-2 is unclear. Children are less likely to become seriously ill from SARS-CoV-2; however, asymptomatic carriers, including children, can spread infection and carry virus into their household. Understanding infectious burden and the potential for transmissibility within the pediatric population is critical for developing both short- and long-term responses, including public health policies, to the current pandemic.

The authors sought to describe the pediatric impact of COVID-19, specifically focusing on viral burden, susceptibility to disease, and immune responses.

Children ages 0–22 years with suspected severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) infection presenting to urgent care clinics or being hospitalized for confirmed/suspected SARS-CoV-2 infection or multisystem inflammatory syndrome in children (MIS-C) at Massachusetts General Hospital were offered enrollment in the Massachusetts General Hospital Pediatric COVID-19 Biorepository. Enrolled children provided nasopharyngeal, oropharyngeal, and/or blood specimens. SARS-CoV-2 viral load, ACE2 RNA levels, and serology for SARS-CoV-2 were quantified.

A total of 192 children (mean age, 10.2 ±7.0 years) were enrolled. Forty-nine children (26%) were diagnosed with acute SARS-CoV-2 infection; an additional 18 children (9%) met the criteria for MIS-C. Only 25 children (51%) with acute SARS-CoV-2 infection presented with fever; symptoms of SARS-CoV-2 infection, if present, were nonspecific. Nasopharyngeal viral load was highest in children in the first two days of symptoms, significantly higher than hospitalized adults with severe disease ($P = .002$).

The authors concluded that children can carry high levels of virus in their upper airways, particularly early in an acute SARS-CoV-2 infection, yet they display relatively mild or no symptoms. Moreover, when present, the symptoms of SARS-CoV-2 are nonspecific and overlap considerably with non- COVID-related illnesses. Identifying SARS-CoV-2 infection in children will become even more challenging during pollen allergy season and influenza season this fall.

Further, some children carry very high viral loads even before symptoms develop. In contrast, children with severe symptoms, such as MIS-C, do not have high levels of viral load on nasopharyngeal or oropharyngeal viral testing, nor do they have detectable viremia. Overall, the lack of correlations between viral load and symptoms will complicate infection control strategies for children.

These findings suggest that it would be ineffective to rely on symptoms or temperature monitoring to identify SARS-CoV-2 infection. Instead, infection control measures should minimize the possibility of viral spread, with focus on strategies including social distancing precautions, mask use, and/or remote learning.

**Correct answer is 2.**

*PMID:* 32827525  
*Link:* [https://www.jpeds.com/article/S0022-3476(20)31023-4/fulltext](https://www.jpeds.com/article/S0022-3476(20)31023-4/fulltext)
Discontinuing angiotensin-converting enzyme inhibitors for 30-days improves mortality in patients admitted to hospital with mild to moderate COVID-19.

- 1. True
- 2. False

Educational Point: Membrane-bound angiotensin-converting enzyme 2 (ACE2), an enzyme that physiologically counters renin-angiotensin-aldosterone system (RAAS) activation, is the functional receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the coronavirus disease 2019 (COVID-19) pandemic. Select preclinical investigations have shown upregulation of ACE2 expression by RAAS inhibitors, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), raising concerns about their safety in patients with COVID-19.

Conversely, observational data have demonstrated an association between use of ACEIs or ARBs and better outcomes in patients with COVID-19, leading to speculation that ACEIs or ARBs decrease acute lung damage and prevent angiotensin II–mediated pulmonary permeability, inflammation, and fibrosis.

This was a multicenter, registry-based, open-label randomized clinical trial with blinded end-point assessment that included patients hospitalized with COVID-19 who were taking ACEIs or ARBs prior to hospital admission to determine whether discontinuation of these drugs compared with continuation of these drugs affects the number of days alive and out of the hospital. Patients aged 18 years or older with a confirmed diagnosis of COVID-19 who were taking ACEIs or ARBs prior to hospital admission were eligible for the trial. Eligible patients were randomized using a 1:1 allocation ratio to either discontinue or continue ACEI or ARB therapy for 30 days.

The primary outcome was the number of days alive and out of the hospital from randomization through 30 days. The secondary outcomes included: length of hospital stay (days), death (during the 30-day follow-up period), in-hospital death, cardiovascular death, COVID-19 progression (worsening of clinical severity during hospitalization in relation to baseline severity), and others.

A total of 659 randomized patients from 29 hospitals (28% being academic hospitals) in Brazil were included in the primary analysis, with 334 patients assigned to discontinue use of ACEIs or ARBs and 325 patients assigned to continue use of ACEIs or ARBs. The 30-day follow-up was completed for 100% of patients and no data were missing for the primary outcome.

The mean number of days alive and out of the hospital for patients randomized to discontinue use of ACEIs or ARBs was 21.9 days (SD, 8.0 days) vs. 22.9 days (SD, 7.1 days) for those randomized to continue use of ACEIs or ARBs. For days alive and out of the hospital, the between-group mean ratio was 0.95 (95% CI, 0.90 to 1.01; \( P = .09 \)) and the between-group mean difference was −1.10 days (95% CI, −2.30 to 0.13 days). The median number of days alive and out of the hospital at 30 days was 25 days for both groups and the between-group median difference was 0 days (95% CI, −1 to 1 days). The proportion of patients alive and out of the hospital at 30 days was 91.9% in the discontinuation group and 94.8% in the continuation group. In the on-treatment analysis, 9.7% of patients in the discontinuation group had 0 days alive and out of the hospital compared with 3.0% in the continuation group; the between-group mean ratio was 0.91 (95% CI, 0.84 to 0.96).

In this pragmatic, registry-based randomized clinical trial, discontinuing ACEI or ARB therapy for 30 days did not affect the number of days alive and out of the hospital in patients hospitalized with mild to moderate COVID-19. These results were generally consistent across major subgroups. There were no significant between-group differences in death, cardiovascular outcomes, or COVID-19 progression.

Correct answer is 2.
Q10 Monoclonal Antibodies for COVID-19

Bamlanivimab, a monoclonal antibody, is authorized for use in patients who require oxygen therapy because of COVID-19.

☐ 1. True
☐ 2. False

Educational Point: The investigational neutralizing IgG1 monoclonal antibody bamlanivimab (LY-CoV555) has been granted an Emergency Use Authorization (EUA) by the FDA and Health Canada for treatment of recently diagnosed mild to moderate COVID-19 in patients who are ≥12 years old, weigh at least 40 kg, and are at high risk for progressing to severe disease and/or hospitalization. Bamlanivimab is not authorized for use in patients who are hospitalized or require oxygen therapy because of COVID-19.

Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Bamlanivimab binds to the receptor binding domain of the spike protein of SARS-CoV-2, blocking the spike protein's attachment to the human ACE2 receptor.

In an interim analysis of an ongoing phase two trial (BLAZE-1), 452 outpatients with recently diagnosed mild or moderate COVID-19 (within three days of first positive test) were randomized to receive a single IV infusion of one of three doses of LY-CoV555 or placebo. The primary endpoint was the decrease from baseline in SARS-CoV-2 viral load on day 11. The decrease was significantly greater with a 2800-mg dose of the antibody than with placebo, but not with 700- and 7000-mg doses, possibly because most patients, including those treated with placebo, had effectively cleared the virus by day 11.

The predefined secondary endpoint of hospitalization or emergency department visit for COVID-19 by day 29 occurred in 1.6% of antibody recipients and 6.3% of placebo recipients. In a post-hoc analysis of patients at high risk (BMI ≥35 or ≥65 years old) for disease progression, 4 of 95 patients (4%) who were treated with LY-CoV555 were hospitalized or visited the emergency department, compared to 7 of 48 (15%) of those treated with placebo.

In the BLAZE-1 trial, nausea occurred in 3.9%, dizziness in 3.2%, and mild infusion reactions in 2.3% of antibody recipients, compared to 3.5%, 2.1%, and 1.4%, respectively, of placebo recipients. According to the FDA’s fact sheet for the EUA, one anaphylactic reaction and one serious infusion-related reaction were reported with infusion of bamlanivimab in ongoing, blinded trials.

Bamlanivimab is authorized for administration as a single 700-mg IV infusion over at least 60 minutes. The drug should be given as soon as possible after a SARS-CoV-2 positive test result and within ten days of COVID-19 symptom onset. Patients should be treated in a facility staffed and equipped to manage anaphylaxis and they should be monitored for hypersensitivity reactions during administration of the drug and for at least one hour after completion of the infusion.
The diluted solution for infusion should be used immediately after it is prepared. If immediate use is not possible, it can be stored in the refrigerator for up to 24 hours or at room temperature for up to seven hours, including infusion time.

The investigational IV monoclonal antibody bamlanivimab (LY-CoV555) has been granted an Emergency Use Authorization (EUA) from the Health Canada based on its association with a reduction in emergency department visits and hospitalizations in recently diagnosed patients with mild or moderate COVID-19 considered to be at high risk of progressing to severe disease and/or hospitalization. The drug needs to be infused over one hour in a facility equipped to manage anaphylaxis. Bamlanivimab has not been beneficial in hospitalized patients.

Correct answer is 2.

PMID: 33443490 Link: https://secure.medicalletter.org/w1612a

Q11 Pediatric Inflammatory Multisystem Syndrome and COVID-19

Which one of the following statements about Pediatric Inflammatory Multisystem Syndrome temporally associated with COVID-19 is false?

❍ 1. Features include prolonged fever, multiorgan dysfunction and laboratory evidence of hyperinflammation.
❍ 2. The history of an illness compatible with acute SARS-CoV-2 infection one week prior.
❍ 3. Blood vessels are thought to be the primary target of endothelial inflammation triggered by SARS-CoV-2.
❍ 4. The immunobiology mirrors that seen in Kawasaki disease.

Educational Point: On April 25, 2020, the United Kingdom National Health Service sent a public health alert to doctors advising of the emergence of an unusual disorder of multisystem inflammation in children with varying cardiac and gastrointestinal involvement, with features of Kawasaki disease and toxic shock syndrome. Since then, there has been an alarming increase in the number of cases along with several case definition and names proposed, including pediatric inflammatory multisystem syndrome temporally associated with COVID-19 and multisystem inflammatory syndrome in children. Common elements to these definitions are the presence of prolonged fever, multiorgan dysfunction, laboratory evidence of hyperinflammation, with or without SARS-CoV-2 infection or exposure, and no alternative cause to explain the clinical presentation.

Although pediatric inflammatory multisystem syndrome is epidemiologically related to COVID-19, interestingly not all case definitions require evidence of SARS-CoV-2 infection or exposure. Most reported cases in other countries have identified positive serologic evidence of SARS-CoV-2 infection, with a small percentage of children having a positive result for the virus on nasopharyngeal swab PCR testing. Other exposure criteria include a preceding illness compatible with acute SARS-CoV-2 infection 4–6 weeks before, suspected or confirmed exposure or contact, and residing in areas with high COVID-19 caseloads.

Blood vessels are thought to be the primary target of endothelial inflammation and injury triggered by SARS-CoV-2, mirroring the immunobiology identified in Kawasaki disease. Although the exact pathophysiology of pediatric inflammation multisystem syndrome has yet to be determined, the presence of SARS-CoV-2 antibodies, specific T-cell response and delayed presentation after the peak of acute infection points to a potential role for acquired immunity such as enhancement of viral entry or a pro-inflammatory response mediated by antibodies or immune complexes. This possibility has important implications for vaccine development and is an area of active study.
In severe cases, a dysregulated immune response can result in overactive monocyte-derived macrophages with an increased production of cytokine and chemokines similar to that seen in macrophage activation syndrome. Macrophage activation syndrome is a cytokine storm syndrome secondary to uncontrolled activation and proliferation of T cells and macrophages that is characterized by non-remitting fever, cytopenia, hyperferritinemia, liver dysfunction and coagulopathy. Patients are unwell with hemodynamic instability and multiorgan involvement, and their condition can deteriorate rapidly—a clinical scenario seen in children with pediatric inflammatory multisystem syndrome.

Correct answer is 2.


PMID: 32907819 Link: https://www.cmaj.ca/content/192/38/E1093.long

Q12 COVID-19 and C-Reactive Protein

In hospitalized patients with COVID-19 who received corticosteroid treatment, C-Reactive protein (CRP) responders (≥50% CRP level reduction) had reduced risk of death compared with risk among CRP non-responders.

☐ 1. True
☐ 2. False

Educational point: The clinical presentation of COVID-19 varies widely, with the most severe presentation characterized by acute respiratory distress syndrome and a marked systemic inflammatory response. Corticosteroids have emerged as a potential therapeutic option in a subset of patients. Results from the recently published RECOVERY trial suggest a substantial mortality benefit of dexamethasone in patients who require mechanical ventilation, with a risk reduction of approximately 33%.

Levels of C-Reactive protein (CRP) have been shown to correlate with outcomes in COVID-19 and bacterial pneumonias. Reduction in CRP levels following the institution of therapy, known as CRP response, has been shown to predict outcomes in other inflammatory conditions, such as osteomyelitis, hidradenitis suppurativa, and some cases of bacterial pneumonia. Whether the CRP response as a response to therapeutics in COVID-19 is associated with improved outcomes remains unknown.

In this retrospective cohort study, the charts of patients who were admitted to Montefiore Medical Center between March 10, 2020, and May 2, 2020 for the management of COVID-19 were examined. Of all patients who met inclusion criteria, patients who received corticosteroid treatment were categorized as CRP responders (≥50% CRP level reduction) and CRP nonresponders (<50% CRP level reduction) based on change in CRP within 72 hours of corticosteroid treatment initiation. The outcomes of interest were two-fold: (1) CRP response after treatment with corticosteroid, and (2) differences in mortality among patients with CRP response compared those without.

Of 2,707 patients admitted during the study period, 324 received corticosteroid treatment. Of patients who received corticosteroid treatment, CRP responders had reduced risk of death compared with risk among CRP nonresponders (25.2% vs 47.8%; unadjusted odds ratio [OR], 0.37; 95% CI, 0.21-0.65; P < .001). This effect remained strong and significant after adjustment for potential confounders (adjusted OR, 0.27; 95% CI, 0.14-0.54; P < .001).
The authors found that therapy with corticosteroids in patients with COVID-19 is associated with a substantial reduction in CRP levels within 72 hours of therapy, and for those patients in whom CRP levels decrease by 50% or more, there is a significantly lower risk of inpatient mortality. Future studies are needed to validate these findings in other cohorts and to determine whether markers other than CRP levels may be predictors of a therapeutic response or whether CRP non responders would benefit from other targeted therapies.


PMID: 33617431


Q13 mRNA Vaccine Allergy

Which one of the following statements about allergic reaction to mRNA vaccine is false?

- 1. Most anaphylactic reactions occur in persons with a previous history of anaphylaxis.
- 2. Acute allergic reactions occur in about 2% of recipients.
- 3. Acute anaphylactic reactions occur in about 2 in 10,000 recipients.
- 4. The mean time to anaphylaxis onset is at 17 minutes.

Educational Point: Anaphylaxis to the mRNA COVID-19 vaccines is currently estimated to occur in 2.5 to 11.1 cases per 1 million doses, largely in individuals with a history of allergy. Allergic concerns contribute to vaccine hesitancy; the authors investigated acute allergic reaction incidence after more than 60 000 mRNA COVID-19 vaccine administrations.

The authors prospectively studied Mass General Brigham (MGB) employees who received their first dose of an mRNA COVID-19 vaccine. For 3 days after vaccination, employees completed symptom surveys through a multipronged approach including email, text message, phone, and smartphone application links. Acute allergic reaction symptoms solicited included itching, rash, hives, swelling, and/or respiratory symptoms.

Of 64 900 employees who received their first dose of a COVID-19 vaccine, 25 929 (40%) received the Pfizer-BioNTech vaccine and 38 971 (60%) received the Moderna vaccine. At least 1 symptom survey was completed by 52 805 (81%).

Acute allergic reactions were reported by 1365 employees overall (2.10% [95% CI, 1.99%-2.22%]), more frequently with the Moderna vaccine compared with Pfizer-BioNTech (2.20% [95% CI, 2.06%-2.35%] vs 1.95% [95% CI, 1.79%-2.13%]; P = .03). Anaphylaxis was confirmed in 16 employees (0.025% [95% CI, 0.014%-0.040%]): 7 cases from the Pfizer-BioNTech vaccine (0.027% [95% CI, 0.011%-0.056%]) and 9 cases from the Moderna vaccine (0.023% [95% CI, 0.011%-0.044%]) (P = .76).
Individuals with anaphylaxis were a mean age of 41 (SD, 13) years, and 15 (94%) were female; 10 (63%) had an allergy history and 5 (31%) had an anaphylaxis history. Mean time to anaphylaxis onset was 17 (SD, 28; range, 1-120) minutes. One patient was admitted to intensive care, 9 (56%) received intramuscular epinephrine, and all recovered. Three employees, with prior anaphylaxis history, did not seek care.

In this prospective cohort of health care employees, 98% did not have any symptoms of an allergic reaction after receiving an mRNA COVID-19 vaccine. The remaining 2% reported some allergic symptoms; however, severe reactions consistent with anaphylaxis occurred at a rate of 2.47 per 10,000 vaccinations. All individuals with anaphylaxis recovered without shock or endotracheal intubation.

Most of the vaccine recipients with anaphylaxis had allergy histories, with 31% having prior anaphylaxis. However, given that approximately 5% of adults have severe food allergy histories and 1% of adults have severe drug allergy histories, this MGB employee cohort likely included almost 4000 individuals with severe food or medication allergy histories who were safely vaccinated.

Correct answer is 1.


PMID: 33683290 Link: https://jamanetwork.com/journals/jama/fullarticle/2777417

Q14 Transfusion of COVID-19 Convalescent Plasma

Early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduces the progression of COVID-19.

☐ 1. True
☐ 2. False

Educational Point: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic agent of COVID-19, causes a particularly severe illness in older adults. The percentage of these patients who are hospitalized is high, and most deaths from COVID-19 worldwide occur in this age group. Various coexisting conditions adversely affect the prognosis in patients with COVID-19, regardless of age. These conditions include hypertension, diabetes, cardiovascular disease, obesity, chronic renal failure, and COPD.

Treatments for COVID-19 in the early stages of the disease remain elusive. Few strategies provide benefit, several have failed, and others are being evaluated. Among the strategies under investigation is the infusion of specific antibodies that are present in the plasma of convalescent patients. Plasma infusions have not been commonly associated with adverse events and have been associated with improved outcomes in patients who have had other diseases. However, antibodies in plasma must be administered soon after infection in order to be effective. In hospitalized patients with COVID-19, the infusion of convalescent plasma against SARS-CoV-2 late in the course of illness has not shown clear benefits and, consequently, the most appropriate antibody concentrations for effective treatment are unclear. The authors evaluated whether convalescent plasma with high IgG titers against SARS-CoV-2, administered within 72 hours after the onset of mild symptoms, would be efficacious in preventing progression to severe disease in older adult patients with COVID-19.
A total of 160 patients 75 years of age or older, or between 65 and 74 years of age with at least one of the coexisting conditions noted above, were randomized in this double-blind, placebo-controlled trial. The primary end point was severe respiratory disease, defined as a respiratory rate of 30 breaths per minute or more, an O₂ saturation of less than 93% while the patient was breathing ambient air, or both. In the intention-to-treat population, severe respiratory disease developed in 13 of 80 patients (16%) who received convalescent plasma and 25 of 80 patients (31%) who received placebo (RR, 0.52; 95% CI, 0.29 to 0.94; P=0.03), with a relative risk reduction of 48%. No adverse effects were observed. The authors conclude that early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduces the progression of COVID-19.

Correct answer is 1.


PMID: 33406353


Q15 Post-COVID Syndrome

Which one of the following statements about outcomes among those discharged following an admission to hospital with COVID-19 is false?

- 1. There is an increased risk of readmission compared with individuals with similar personal and clinical characteristics.
- 2. Rates of major adverse cardiovascular events are increased compared to a matched control group.
- 3. Patients older than age 70 have a greater relative risk of death compared to those under 70 years.
- 4. Rates of new diagnosis of diabetes are increased compared to a matched control group.

Educational Point: Since SARS-CoV-2 infection was recognised in late 2019, the academic and clinical emphasis has been on respiratory manifestations. Increasing evidence exists for direct multiorgan effects, however, and indirect effects on other organ systems and disease processes, such as cardiovascular diseases and cancers, through changes in healthcare delivery and patient behaviours. Although the long-term effects of COVID-19 on individuals and health systems are becoming clear, investigation across organ systems is urgently needed. Long COVID or post-COVID syndrome, is not one condition, and is defined by the National Institute for Health and Care Excellence (NICE) as “signs and symptoms that develop during or after an infection consistent with COVID-19 which continue for more than 12 weeks and are not explained by an alternative diagnosis.”

The authors conducted an observational, retrospective, matched cohort study of individuals admitted to hospital with COVID-19. Individuals were followed up from the index date to 30 September 2020 or the date of death (whichever was earlier) for all cause mortality, all cause hospital readmission (admission after discharge for patients and admission after the index date for controls), respiratory disease, major adverse cardiovascular event (a composite of heart failure, myocardial infarction, stroke, and arrhythmia), diabetes (type 1 or 2), chronic kidney disease stages 3-5 (including dialysis and kidney transplant), and chronic liver disease.

The authors matched patients to controls on potential confounders of the relation between hospital admission for COVID-19 and outcomes, established from electronic health records over a 10 year look back period (1 January 2010 to 31 December 2019). Of 86955 individuals in hospital with COVID-19 during the study period, 53795 (61.9%) had been discharged alive by the end of the study. After excluding individuals whose age or sex was not known and those
who could not be matched to a control, 47780 patients with COVID-19 (4745 admitted to the intensive care unit and 43035 not requiring admission to the intensive care unit) were included in the analysis, representing 90.8% of those discharged alive with known age and sex. Mean follow-up was 140 days (standard deviation 50 days, maximum 253 days) for patients with COVID-19 and 153 days (33 days, 253 days) for controls.

Of 47 780 individuals in hospital with COVID-19 over the study period, 29.4% were readmitted and 12.3% died after discharge. These events occurred at rates of 766 (95% confidence interval 753 to 779) readmissions and 320 (312 to 328) deaths per 1000 person years, which were 3.5 (3.4 to 3.6) and 7.7 (7.2 to 8.3) times greater, respectively, than those in matched controls. Diabetes, major adverse cardiovascular event, chronic kidney disease, and chronic liver disease were diagnosed after discharge in 4.9%, 4.8%, 1.5%, and 0.3% of individuals with COVID-19, respectively, occurring at rates of 127 (122 to 132) for diabetes, 126 (121 to 131) for major adverse cardiovascular event, 15 (13 to 17) for chronic kidney disease, and 7 (6 to 9) for chronic liver disease diagnoses per 1000 person years. The authors saw a similar pattern when only new onset diagnoses were considered, but at lower rates of 29 (26 to 32) for diabetes, 66 (62 to 70) for major adverse cardiovascular event, 15 (13 to 17) for chronic kidney disease and 4 (3 to 5) for chronic liver disease diagnoses per 1000 person years. Those with COVID-19 were diagnosed with major adverse cardiovascular event, chronic liver disease, chronic kidney disease, and diabetes after discharge from hospital 3.0 (2.7 to 3.2), 2.8 (2.0 to 4.0), 1.9 (1.7 to 2.1), and 1.5 (1.4 to 1.6) times more frequently, respectively, than in the matched control group.

Rates of all outcomes after discharge were greater in individuals with COVID-19 aged 70 or more than in those aged less than 70, whereas rates of all outcomes other than diabetes were greater in the white ethnic group than in the non-white group. Rate ratios comparing patients with COVID-19 and matched controls were greater in individuals aged less than 70 than those aged 70 or more for all outcomes, however. The largest differences in rate ratios were for death (14.1 (95% confidence interval 11.0 to 18.3) for age <70 years vs 7.7 (7.1 to 8.3) for ≥70) and respiratory disease (10.5 (9.7 to 11.4) for age <70 vs 4.6 (4.3 to 4.8) for ≥70). Differences in rate ratios between men and women were generally small.

Three major findings were found in this large study examining post-COVID syndrome in 47 780 patients admitted to hospital with COVID-19 in England, matched to controls. Firstly, admission to hospital for COVID-19 was associated with an increased risk of readmission and death after discharge compared with individuals with similar personal and clinical characteristics in the general population over the same period. Secondly, rates of multiorgan dysfunction after discharge were raised in individuals with COVID-19 compared with those in the matched control group, suggesting extrapulmonary pathophysiology. Diabetes and major adverse cardiovascular events were particularly common, whether incident or prevalent disease. Thirdly, the absolute risk of death, readmission, and multiorgan dysfunction after discharge was greater for individuals aged 70 or more than for those aged less than 70, and for individuals of white ethnic background than non-white individuals. Compared with outcome rates that might be expected to occur in these groups in the general population, however, younger patients and ethnic minority individuals had greater relative risks than those aged 70 or more and those in the white ethnic group, respectively.

Post-COVID syndrome adds to current healthcare challenges, particularly sustainable high quality care for long term conditions: inequalities in health, access, and provision; incomplete pathways across community and hospital care; and the need to translate research into clinical practice with sufficient resources.

Correct answer is 3.


PMID: 33789877 Link: https://www.bmj.com/content/372/bmj.n693.long
Q16 Long-term Sequelae of COVID-19

Which one of the following statements about long-term sequelae of COVID-19 four months after hospital discharge is false?

❖ 1. Half of patients report at least one symptom that did not exist before COVID-19.
❖ 2. Cognitive symptoms are reported in about 20% of patients.
❖ 3. Computed tomographic lung-scan abnormalities are common.
❖ 4. New-onset dyspnea is reported in more than half of patients.

Educational Point: The possible long-term sequelae of COVID-19 have become an increasing concern. The inflammatory storm that characterizes severe forms of the disease suggests that serious tissue sequelae may affect various organ systems. Other coronaviruses have been shown to induce long-term effects, especially in the lungs. Although the long-term sequelae of individual organ damage have been reported, there have been few comprehensive evaluations of long-term consequences of COVID-19. In addition, most of the studies have included patients who actively decided to participate in follow-up.

The authors systematically assessed, 4 months after discharge, the clinical status of survivors of COVID-19 disease requiring hospitalization. In a prospective uncontrolled cohort study, survivors of COVID-19 who had been hospitalized in a university hospital, underwent a telephone assessment 4 months after discharge. Patients with relevant symptoms and all patients hospitalized in an intensive care unit (ICU) were invited for further assessment at an ambulatory care visit.

Respiratory, cognitive, and functional symptoms were assessed by telephone with the Q3PC cognitive screening questionnaire and a checklist of symptoms. At the ambulatory care visit, patients underwent pulmonary function tests, lung computed tomographic scan, psychometric and cognitive tests (including the 36-Item Short-Form Health Survey and 20-item Multidimensional Fatigue Inventory), and, for patients who had been hospitalized in the ICU or reported ongoing symptoms, echocardiography.

Among 834 eligible patients, 478 were evaluated by telephone (mean age, 61 years [SD, 16 years]; 201 men, 277 women). During the telephone interview, 244 patients (51%) declared at least 1 symptom that did not exist before COVID-19: fatigue in 31%, cognitive symptoms in 21%, and new-onset dyspnea in 16%. There was further evaluation in 177 patients (37%), including 97 of 142 former ICU patients. The median 20-item Multidimensional Fatigue Inventory score (n = 130) was 4.5 (interquartile range, 3.0-5.0) for reduced motivation and 3.7 (interquartile range, 3.0-4.5) for mental fatigue (possible range, 1 [best] to 5 [worst]). The median 36-Item Short-Form Health Survey score (n = 145) was 25 (interquartile range, 25.0-75.0) for the subscale “role limited owing to physical problems” (possible range, 0 [best] to 100 [worst]). Computed tomographic lung-scan abnormalities were found in 108 of 171 patients (63%), mainly subtle ground-glass opacities. Fibrotic lesions were observed in 33 of 171 patients (19%), involving less than 25% of parenchyma in all but 1 patient. Fibrotic lesions were observed in 19 of 49 survivors (39%) with acute respiratory distress syndrome. Among 94 former ICU patients, anxiety, depression, and posttraumatic symptoms were observed in 23%, 18%, and 7%, respectively. The left ventricular ejection fraction was less than 50% in 8 of 83 ICU patients (10%). New-onset chronic kidney disease was observed in 2 ICU patients. Serology was positive in 172 of 177 outpatients (97%).

Four months after hospitalization for COVID-19, a cohort of patients frequently reported symptoms not previously present, and lung-scan abnormalities were common among those who were tested. These findings are limited by the absence of a control group and of pre-COVID assessments in this cohort. Further research is needed to understand longer-term outcomes and whether these findings reflect associations with the disease.

Correct answer is 4.
Comparing with the standard of care or placebo, ivermectin reduces mortality in COVID patients.

- 1. True
- 2. False

**Educational Point:** The coronavirus disease 2019 (COVID-19) pandemic represents a global sanitary, social, and economic challenge. However, scientific advances have also amplified deficiencies and misinformation. Biological plausibility, pathophysiological considerations, in vitro research, observational studies, and/or clinical trials with heterogeneous quality were used to evaluate several repurposed drugs repurposed for indications different from the approved ones. Some policy makers and regulatory institutions authorized emergency use of unproven COVID-19 treatments; the use of some of these treatments has been heavily politized in some regions.

Ivermectin (IVM) is a semisynthetic, anthelminthic agent for oral administration, and derived from the avermectins of *Streptomyces avermitilis*. IVM and its analogues selectively open inhibitory glutamate-gated chloride ion channels in the cell membranes of nematodes. In addition, IVM prevents the filarial ability to release inhibitors of the host immune response. In tissue cultures, at concentrations higher than anthelmintic concentrations, IVM showed antiviral (eg, in dengue), antiparasitic (eg, in malaria), and anticancer (eg, in epithelial ovarian cancer) effects. However, these in vitro results have not been clinically demonstrated.

In March 2020, researchers from Australia showed IVM to be active against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cell cultures by drastically reducing viral RNA at 48 hours. Concentrations were equivalent to >50-fold the normal maximum concentration achieved with a standard single dose of IVM 200 μg/kg, raising concerns about the efficacious dose of IVM for treating or preventing SARS-CoV-2 infection in humans and its tolerability. However, theoretical considerations, experimental and observational evidence, misinformation, self-medication, and the wide availability of IVM led to its use as treatment of COVID-19 in low- and middle-income countries, assuming a priori efficacy and safety.

Three systematic reviews on the effect of IVM on clinical outcomes have been published. Padhy et al included only 3 small observational studies. Siemieniuk et al conducted a living systematic review of all treatments for COVID-19, but details were scarce, and the quality of evidence (QoE) was very low. Finally, Kow et al evaluated 6 RCTs, 5 from Asia and one from Latin America. Other systematic reviews or narrative reviews of IVM effects have been disseminated only as preprints or on Web sites.

IVM is currently approved by the Food and Drug Administration (FDA) to treat people with intestinal strongyloidiasis and onchocerciasis. The European Medicines Agency and the FDA have not approved IVM for the treatment of COVID-19. World Health Organization (WHO) and Infectious Diseases Society of America guidelines do not recommend IVM for treatment of COVID-19 outside randomized controlled trials (RCTs).

In this study the authors systematically assessed benefits and harms of the use of ivermectin (IVM) in patients with coronavirus disease 2019.
Published and preprint randomized controlled trials (RCTs) assessing the effects of IVM on adult patients with COVID-19 were searched until 22 March 2021. Primary outcomes were all-cause mortality rate, length of hospital stay (LOS), and adverse events (AEs). Secondary outcomes included viral clearance and severe AEs (SAEs). Ten RCTs (n = 1173) were included. The controls were the standard of care in 5 RCTs and placebo in 5. COVID-19 disease severity was mild in 8 RCTs, moderate in 1, and mild and moderate in 1. IVM did not reduce all-cause mortality rates compared with controls (relative risk [RR], 0.37 [95% confidence interval, .12–1.13]; very low QoE) or LOS compared with controls (mean difference, 0.72 days [95% confidence interval, −.86 to 2.29 days]; very low QoE). AEs, SAEs, and viral clearance were similar between IVM and control groups (low QoE for all outcomes). Compared with the standard of care or placebo, IVM did not reduce all-cause mortality, LOS, or viral clearance in RCTs in patients with mostly mild COVID-19. IVM did not have an effect on AEs or SAEs and is not a viable option to treat patients with COVID-19.

IVM is generally safe at conventional doses for approved indications. However, its safety became a concern owing to longer use and/or higher doses in patients with COVID-19. IVM was found to be similar to placebo in safety and tolerability, even at 10 times the highest FDA-approved dose of 200 μg/kg in healthy volunteers, but not in patients with COVID-19. In addition, the use of IVM needs further analysis when IVM is combined with other agents for COVID-19. In several settings, it was wrongly assumed that the potential benefits of using repurposed drugs outweigh their potential harms. Well-designed RCTs with longer treatment and higher doses are necessary to further evaluate the safety of IVM in patients with COVID-19.

Correct answer is 2.


PMID: 34181716 Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8394824/

Q18 Myocarditis with the mRNA COVID-19 Vaccines

The risk of myocarditis and pericarditis following administration of mRNA-based COVID-19 vaccines is higher in males.

☐ 1. True
☐ 2. False

Educational Point: On June 25, 2021, the FDA added a warning to the Fact Sheets for the mRNA-based COVID-19 vaccines manufactured by Pfizer/BioNTech (Comirnaty) and Moderna (Spikevax) about an increased risk of myocarditis and pericarditis following administration of the vaccines.

The warning was issued after a review of reports to the Vaccine Adverse Events Reporting System submitted between December 29, 2020 and June 11, 2021 identified 1226 cases of myocarditis following administration of an mRNA vaccine. Cases occurred most commonly in males (76%), in persons <30 years old (58%), and after administration of the second vaccine dose (76%). Symptoms usually developed within a few days after vaccination. At the time of the review, about 296 million doses of mRNA-based COVID-19 vaccines had been administered in the US, including 52 million doses in persons <30 years old.

A CDC analysis of 323 cases of myocarditis following mRNA vaccination in persons 16-29 years old found that 90% of cases were in males and 96% required hospitalization. The median time to symptom onset after vaccination was 2 days. Most cases were mild in severity, and none of the 304 patients with known clinical outcomes died. The CDC estimates that, for every 1 million males 12-29 years old who receive a 2-dose mRNA-based COVID-19 vaccination series, 560 hospitalizations due to COVID-19 would be prevented and 39-47 cases of myocarditis would occur.
The Advisory Committee on Immunization Practices concluded in a June 23, 2021 meeting that the benefits of mRNA-based COVID-19 vaccination still clearly outweigh the risks for all persons ≥12 years old. Adolescents and young adults who experience acute chest pain, shortness of breath, or palpitations after vaccination should be assessed with an ECG, a troponin level, and inflammatory marker testing (e.g., C-reactive protein level, erythrocyte sedimentation rate).

Correct answer is 1.


PMID: 34544112 Link: https://secure.medicalletter.org/scripts/articlefind.cgi?issue=1629&page=e9

Q19 COVID-19 Brain Impacts

Mild cases of COVID-19 may be associated with cognitive deficits months after recovery.

☐ 1. True
☐ 2. False

Educational Point: Research presented at the Alzheimer’s Association International Conference suggests even mild cases of COVID-19 may be associated with cognitive deficits months after recovery.

One Argentinian study of 234 seniors who previously had COVID-19 found that more than half showed some degree of cognitive impairment months later. One in three had severe “dementia-like” impairments in memory, attention and executive function - a much higher proportion than the 5%–8% of seniors in the general population who have dementia at a given time.

The study didn’t look at participants’ cognitive performance prior to infection. However, those who lost their sense of smell while sick with COVID-19 tended to have more severe cognitive impairments months later, even if their other symptoms had been mild.

One British study of 81,337 people in EClinicalMedicine found that those who previously had COVID-19 tended to score lower on measures of intelligence, reasoning, problem-solving and planning than people who were never infected.

In another study of 57 Americans receiving inpatient rehabilitation after hospitalization for COVID-19, four in five had mild to severe cognitive impairments. More than half had deficits in working memory, while two in five had impaired processing speed, divided attention, and trouble switching between mental tasks.

Similar deficits have also been noted in patients after recovery from other coronaviruses. A 2020 systematic review and meta-analysis found that delirium was common in the acute stage of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19. Following up with patients six weeks to 39 months later, more than 15% reported sleep disorders, mood swings, trouble concentrating, impaired memory and other mental challenges.

Correct answer is 1.


PMID: 34462298 Link: https://www.cmaj.ca/content/193/34/E1360.long
Q20 Saliva Based COVID Testing

Which one of the following statements about saliva PT-PCR test for SARS-CoV-2 infection is false?

- 1) Saliva sensitivity is highest in samples collected during the first week of infection.
- 2) The sensitivity is much higher in symptomatic patients.
- 3) Higher viral load is associated with higher odds of a positive test.
- 4) After 10 days of infection a positive RT-PCR result confirms remaining infectivity.

Educational Point: While real-time reverse transcriptase–polymerase chain reaction (RT-PCR) on nasopharyngeal swabs is the current standard for SARS-CoV-2 detection, saliva is an attractive alternative for diagnosis and screening due to ease of collection and minimal supply requirements. Studies on the sensitivity of saliva-based SARS-CoV-2 molecular testing have shown considerable variability. The authors conducted a prospective, longitudinal study to investigate the testing time frame that optimizes saliva sensitivity for SARS-CoV-2 detection.

A convenience sample of 889 paired nasopharyngeal swab-saliva samples from 404 participants exposed to a household member with RT-PCR–confirmed SARS-CoV-2 within 2 weeks were recruited from Children’s Hospital Los Angeles and nearby community testing sites. Paired nasopharyngeal and saliva samples were collected every 3 to 7 days for up to 4 weeks or until 2 negative nasopharyngeal test results.

Ninety-three participants (36.3%) were asymptomatic throughout their infection; 126 (77.3%) of 163 symptomatic individuals reported mild severity.

Saliva sensitivity was highest in samples collected during the first week of infection at 71.2% (95% CI, 62.6%-78.8%) but decreased each subsequent week. Participants who presented with COVID-19–associated symptoms on the specimen collection day during week 1 of infection had significantly higher saliva sensitivity compared with asymptomatic participants (88.2% [95% CI, 77.6%-95.1%] vs 58.2% [95% CI, 46.3%-69.5%]; P < .001).

Saliva sensitivity remained significantly higher in symptomatic participants in week 2 (83.0% [95% CI, 70.6%-91.8%] vs 52.6% [95% CI, 42.6%-62.5%]; P < .001). No difference was observed more than 2 weeks after COVID-19 onset. Sensitivities did not significantly differ for never-symptomatic (34.7% [95% CI, 27.3%-42.7%]), presymptomatic (57.1% [95% CI, 31.7%-80.2%]), and post symptomatic (42.9% [95% CI, 36.8%-49.1%]) time points (P = .26).

For each day after COVID-19 onset, the odds ratio for saliva detection was 0.94 (95% CI, 0.91-0.96) compared with the previous day (P < .001). Participants presenting with COVID-19–associated symptoms at the time of specimen collection or with high nasopharyngeal viral loads had 2.8 (95% CI, 1.6-5.1; P < .001) and 5.2 (95% CI, 2.9-9.3; P < .001) higher odds of having a saliva-positive RT-PCR result compared with those with asymptomatic presentation or low nasopharyngeal viral loads, respectively.

Saliva was sensitive for detecting SARS-CoV-2 in symptomatic individuals during initial weeks of infection, but sensitivity in asymptomatic SARS-CoV-2 carriers was less than 60% at all time points. As COVID-19 testing strategies in workplaces, schools, and other shared spaces are optimized, low saliva sensitivity in asymptomatic infections must be considered. This study suggests saliva-based RT-PCR should not be used for asymptomatic COVID-19 screening. A positive RT-PCR result from any sample past 10 days of infection may not be predictive of viral replication or infectivity.

Correct answer is 4.


PMID: 34387653 Link: https://jamanetwork.com/journals/jama/fullarticle/2783249
Q21 Tofacitinib in COVID-19 Pneumonia

Treatment with tofacitinib reduces the combined outcome of death or respiratory failure in patients hospitalized with COVID-19 pneumonia who are not receiving non-invasive or invasive ventilation.

❍ 1. True
❍ 2. False

Educational Point: Severe manifestations of Sars-CoV-2 infection are associated with an exaggerated immune response driven by interleukin-2 and other cytokines in a pattern called a cytokine storm. Tofacitinib is an orally administered selective inhibitor of Janus kinase (JAK), that blocks intracellular transduction pathways after a cytokine is bound to its receptor. The authors conducted a multicenter, randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of tofacitinib in hospitalized patients with COVID-19 pneumonia who were not receiving non-invasive or invasive ventilation. They randomly assigned, in a 1:1 ratio, hospitalized adult patients with COVID-19 pneumonia to receive either tofacitinib at a dose of 10 mg or placebo twice daily for up to 14 days or until hospital discharge. The primary outcome was the occurrence of death or respiratory failure through day 28. All-cause mortality and safety were also assessed.

A total of 289 patients underwent randomization at 15 sites in Brazil. Overall, 89.3% of the patients received glucocorticoids during hospitalization. The cumulative incidence of death or respiratory failure through day 28 was 18.1% in the tofacitinib group and 29.0% in the placebo group (RR, 0.63; 95% CI, 0.41 to 0.97; P=0.04). Death from any cause through day 28 occurred in 2.8% of patients in the tofacitinib group and in 5.5% of those in the placebo group (HR, 0.49; 95% CI, 0.15 to 1.63). Serious adverse events occurred in 20 patients in the tofacitinib group and in 17 in the placebo group.

The authors conclude that among patients hospitalized with COVID-19 pneumonia, tofacitinib leads to a lower risk of death or respiratory failure through day 28 than placebo.

Correct answer is 1.


COVID-19 mRNA vaccines are associated with significant reductions in sperm count in healthy males.

☐ 1. True
☐ 2. False

Answer: False

Educational Point: Two mRNA vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), received Emergency Use Authorization from the US Food and Drug Administration. Despite high efficacy and few adverse events found in clinical trials, only 56% of individuals in the US reported wanting to receive the vaccine. One of the reasons for vaccine hesitancy is the potential negative effect on fertility. Because reproductive toxicity was not evaluated in the clinical trials and SARS-CoV-2 has been associated with decreases in sperm parameters, the authors assessed sperm parameters before and after mRNA vaccine administration. This single-center prospective study at the University of Miami recruited healthy volunteers aged 18 to 50 years scheduled for mRNA COVID-19 vaccination through flyers posted throughout the university hospital and internal list serve emails.

Between December 17, 2020, and January 12, 2021, 45 men volunteered (median age, 28 years [IQR, 25-31]); follow-up samples were obtained at a median of 75 days (IQR, 70-86) after the second dose. The study ended on April 24, 2021. Baseline samples were obtained after a median abstinence period of 2.8 days (IQR, 2-3) and follow-up samples after a median of 3 days (IQR, 3-4). Of the 45 men, 21 (46.7%) received BNT162b2 and 24 (53.3%) received mRNA-1273. Baseline median sperm concentration and total motile sperm count (TMSC) were 26 million/mL (IQR, 19.5-34) and 36 million (IQR, 18-51), respectively. After the second vaccine dose, the median sperm concentration significantly increased to 30 million/mL (IQR, 21.5-40.5; P = .02) and the median TMSC to 44 million (IQR, 27.5-98; P = .001). Semen volume and sperm motility also significantly increased. Eight of the 45 men were oligospermic before the vaccine (median concentration, 8.5 million/mL [IQR, 5.1-12]). Of these 8, 7 men had increased sperm concentration to normozoospermic range at follow-up (median concentration, 22 million/mL [IQR, 17-25.5]), and 1 man remained oligospermic.

No man became azoospermic after the vaccine.

In this study of sperm parameters before and after 2 doses of a COVID-19 mRNA vaccine, there were no significant decreases in any sperm parameter among this small cohort of healthy men.

Correct answer is 2.


PMID: 34137808 Link: https://jamanetwork.com/journals/jama/fullarticle/2781360
Q23 SAMP Type 2 Diabetes During COVID-19

Three months ago, you saw a 69-year-old male with diabetes for his routine follow-up. At that time, his A1C was 7.5% and his blood pressure was normal. You notice that your secretary has left a message near your door: your patient has cancelled his visit today because he is afraid of exposing himself to COVID-19. You decide to call him during your planned visit.

1. What can be assessed virtually for this patient? List three.

2. What can the patient self-monitor? List three.

Your patient is relieved that you called him and answers all your questions. You agree to another virtual visit in three months. However, one week before your next visit, the patient leaves a message that his blood pressure has been significantly higher with his home machine.

3. Which one of the following statements concerning blood pressure targets is true?
   a. An office target of < 130/80 mmHg means a home target of < 135/85
   b. An office target of < 130/80 mmHg means a home target of < 130/80
   c. An office target of < 130/80 mmHg means a home target of < 125/75
   d. An office target of < 130/80 mmHg means a home target of < 120/70
After assessing his blood pressure, you decide to initiate an ACEI and follow-up in person.

4. How many in-person visits should occur annually for this patient?

5. What should the physician focus on during this in-person visit in order to minimize time in the clinic? List three.

Educational Point: Type 2 diabetes is one of the most common chronic conditions managed in primary care. But how primary care teams provide care and support to people with diabetes needs to change because of new risks posed by the coronavirus disease 2019 (COVID-19) pandemic.

Before the COVID-19 pandemic, usual practice was to see patients with diabetes in the office every three to six months to review bloodwork results, conduct a focused physical examination, and provide treatment and self-management advice. Primary care clinicians supported patients to reduce their risk of diabetes-related complications through glycemic and blood pressure control, lipid management, smoking cessation, diet, exercise, and timely screening for renal, foot, and retinopathy complications—evidence-based interventions recommended by the Diabetes Canada clinical practice guidelines.

But the benefits of an in-person visit now need to be balanced with the risk of patients acquiring severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when traveling to and attending a clinic visit. This risk is particularly relevant given that some studies suggest people with diabetes have a higher risk of COVID-19–related complications and death.

Primary care clinicians need a new approach to delivering diabetes care—one that continues to support evidence-based interventions but does so in a way that balances the risks and benefits of in-person and virtual visits. To address this need, we have developed virtual-first recommendations to support family physicians and other primary care professionals in managing their patients with type 2 diabetes during COVID-19.

This guidance was developed by a group of practising family physicians and endocrinologists in collaboration with the Centre for Effective Practice, using the 2018 clinical practice guidelines from Diabetes Canada as a foundation.

In a virtual-first approach to diabetes care during COVID-19, virtual assessments (by telephone or video) should be done every three to six months and can address most aspects of care. More frequent virtual touchpoints might be needed for complex issues or if guiding the patient through change. **In-person visits should still occur at least annually.** In-person assessments should be more frequent if a patient’s risk factor control is suboptimal or his or her capacity to engage in virtual care is limited.
Where feasible, patients should be encouraged to assess their blood pressure, weight, and feet at home. Supporting patient self-assessment makes virtual visits more effective and in-person visits more efficient and thereby safer. **Blood pressure targets need to be adjusted for home monitoring (e.g., an office target of <130/80 mm Hg means a home target of <125/75 mm Hg).**

Some investigations can be deferred during the COVID-19 pandemic based on individual patient characteristics and risk. **In-person care should focus on blood pressure measurement (and home machine calibration), foot assessment, immunizations, and review of a blood glucose log if relevant.** Even with in-person visits, relevant information can be collected virtually before the appointment to minimize the time in clinic.

### Managing type 2 diabetes during COVID-19: a guide for primary care providers

During the COVID-19 pandemic, we should be taking a virtual-first approach to diabetes care. The relative benefits and risks of an in-person versus virtual diabetes visit will depend on several factors, including an individual’s capacity for using technology, the extent of their disease and local COVID-19 prevalence. Regardless, most diabetes care and support can be delivered through virtual visits, phone, video or secure messaging. This resource is meant to supplement the Diabetes Canada guidelines by indicating ways to adapt care for type 2 diabetes during COVID-19. It may also be useful for people with pre-diabetes. See guidelines.diabetes.ca for full guidelines and decision support tools for diabetes management.

**Self-management is a core element of effective diabetes care and** is essential during COVID-19. Two virtual resources to support self-management in people with diabetes and pre-diabetes include:

- **1-800-BANTING (226-8464):** People living with diabetes can call to speak with live diabetes educators
- **Canadian Diabetes Prevention Program:** People living with pre-diabetes can self-enroll in this free, online, 1-year healthy behavior coaching program

### Schedule

<table>
<thead>
<tr>
<th>Virtual visit (every 3-6M)</th>
<th>In-person visit (at least annually**)</th>
<th>Lab testing and referrals</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Assess glycemic control using A1C and/or smart glucose self-monitoring, and assess for hypoglycemia.</td>
<td>- Review glucose meter and log results</td>
<td>- A1C: Every 6-9M if &lt;8%; every 3M if ≥8%</td>
</tr>
<tr>
<td>- BP measured at home*</td>
<td>- Foot examination (if concerns present on self-screening or unable to self-screen)</td>
<td>- Cholesterol: Annually if above target; every 3Y if on target, and med adherence is good</td>
</tr>
<tr>
<td>- Assess cholesterol medication adherence and the need for lipid testing</td>
<td>- BP machine calibration (if concerns with home BP)</td>
<td>- eGFR, urine ACR: Annual</td>
</tr>
<tr>
<td>- Assess appropriateness of drugs for CVD risk reduction</td>
<td>- Self-screening for feet using Ipswich Touch Test</td>
<td>- ECG: Defer if no symptoms</td>
</tr>
<tr>
<td>- Exercise, healthy eating, and weight check</td>
<td>- Smoking cessation</td>
<td>- Retinopathy screening: Defer to a 3-year interval for those with no previous eye disease and A1C &lt;8%</td>
</tr>
<tr>
<td>- Self-screening for symptoms on home machine (SMBG) as a proxy.</td>
<td>- Self-management support (provide apps, connect to resources, support medication adherence, extend prescription refills until next scheduled visit)</td>
<td>- Defer screening ECGs (for those with no symptoms)</td>
</tr>
<tr>
<td>- Foot examination and assessment (if concerns present)</td>
<td></td>
<td>- Defer retinopathy screening to a 3-year interval (for those with no previous eye disease and A1C &lt;8%)</td>
</tr>
</tbody>
</table>

* If a patient is unable to measure BP at home, then measure BP in-person in the clinic, Q6-9 mo if BP is near target and stable

**Patients may require more frequent in-person visits depending on risk factor control and their capacity to engage in virtual care.

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Acceptable Answers:

1. Glucose self-monitoring
   - Hypoglycemia
   - Blood pressure at home
   - Medication adherence
   - Appropriateness of drugs for cardiovascular disease risk reduction
   - Exercise
   - Healthy eating habits
   - Weight
   - Self-screening for feet
   - Smoking cessation
   - Self-management support

2. Blood pressure
   - Weight
   - Feet assessment

3. C.

4. At least once a year

5. Review glucose meter and log results
   - Foot examination
   - Blood pressure machine calibration
   - Shots (immunization)


PMID: 33077454  Link: [https://www.cfp.ca/content/66/10/745.long](https://www.cfp.ca/content/66/10/745.long)
Q24 SAMP Virtual Care for COVID-19

A 67-year-old female has a virtual care visit today because she is worried that she may have been recently infected by COVID-19.

1. How long is the incubation period?

2. When do symptoms generally appear after exposure?

During your virtual care visit with this patient, you discover that she has several symptoms of COVID-19 infection. She has fever, dry cough, shortness of breath, and fatigue. She also mentions that she has an altered sense of smell and taste.

3. What test should be done to confirm an acute infection?

4. There are evidence-based treatments for COVID-19 that are appropriate in the outpatient setting.
   - True
   - False

5. Dexamethasone can significantly reduce mortality in hospitalized patients who require supplemental oxygen.
   - True
   - False

6. What percentage of patients have mild illness?
**Educational Point:** The coronavirus disease 2019 (COVID-19) pandemic is caused by an enveloped single-stranded RNA novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first cases were reported in Wuhan City, China, in December 2019; the United States confirmed its first cases one month later. Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome, also caused by coronaviruses, have caused significantly lower global mortality.

The basic reproductive number (infections per index case) of COVID-19 is unknown. One systematic review estimated a range of 1.9 to 6.5. Pathogenic factors contributing to the virulence of SARS CoV-2 include transmissibility via respiratory droplets and asymptomatic spread via healthy-appearing individuals.

Physical distancing of at least 6 ft (1.8 m) slows the spread of infection by decreasing the mean number of people infected per case, particularly when combined with other measures such as mask wearing in public, school closures, and travel restrictions. The Centers for Disease Control and Prevention (CDC) recommends that close contacts of a person with COVID-19 quarantine for 14 days after the last exposure and monitor for fever and other symptoms daily. People suspected of having COVID-19 should isolate within their home to prevent infection spread, stay in a specific “sick room” if they live with others, and use a separate bathroom, if possible.

The CDC recommends wearing face masks when in a public space where appropriate physical distancing may be difficult. This practice may reduce viral transmission (Howard J, et al., and Kai D, et al., unpublished data, 2020), particularly from asymptomatic or presymptomatic individuals. Patients with respiratory symptoms should wear a surgical mask in health care settings. Those without respiratory symptoms should wear a cloth face mask per CDC recommendations.

The incubation period of SARS-CoV-2 is two to 14 days, although symptoms generally appear within five days of exposure. Common presenting symptoms include fever, dry cough, shortness of breath, and fatigue; however, patients may have a wide range of symptoms representing a spectrum of mild to severe illness. Moderate to severe anosmia and altered taste are commonly reported. Symptoms in children tend to be milder than in adults and may include fever, cough, and feeding difficulty (Arnaout R, et al., unpublished data, 2020). Pregnant and recently pregnant women are less likely to present with fever and myalgias compared with nonpregnant patients of reproductive age. A high proportion of patients with SARS-CoV-2 infection (about 40%) are asymptomatic, particularly younger patients.

There are multiple testing modalities for COVID-19. **Acute infection should be confirmed with polymerase chain reaction testing using a nasopharyngeal swab.** Antibody testing is most useful for epidemiologic purposes. Point-of-care testing provides rapid results, but the reliability of these tests is not clear. Testing asymptomatic people after an exposure is recommended five to seven days after the exposure based on the median viral incubation period. Testing should not
occur for at least 48 hours after exposure. Asymptomatic contacts with negative test results still must quarantine for 14 days. Retesting can be considered to confirm disease resolution in immunocompromised patients if enough testing capacity exists.

There are no evidence-based treatments for COVID-19 that are appropriate for use in the outpatient setting; management is supportive. In addition to supportive care, there are several investigational drugs being explored for the treatment of COVID-19 in hospitalized patients. Dexamethasone, 6 mg per day for 10 days, significantly reduced mortality in hospitalized patients with COVID-19 who required supplemental oxygen (number needed to treat [NNT] = 29) or mechanical ventilation (NNT = 9), but not in hospitalized patients who did not require supplemental oxygen. Systemic corticosteroids are not recommended for outpatients or for hospitalized patients who do not require supplemental oxygen. Remdesivir was shown in a U.S. randomized trial to significantly reduce time to recovery (11 vs. 15 days) and nonsignificantly reduce mortality (7.1% vs. 11.9%; P = .059) in hospitalized patients with COVID-19. A Chinese study found no significant benefit, but the study was underpowered. Remdesivir has not been studied in outpatients with nonsevere illness and is not recommended for this population. Hydroxychloroquine has not been shown to have clear benefit in patients with mild to severe COVID-19 symptoms, or for postexposure prophylaxis (Horby P, et al., unpublished data, 2020).

International data suggest that 85% of people with COVID-19 have only mild illness, whereas 14% have severe disease requiring hospitalization, including 5% of adults and 2% of children who require admission to an intensive care unit. Children tend to have a better prognosis than adults (Arnout R, et al., unpublished data, 2020). The overall mortality rate from COVID-19 has been estimated to be 0.66% to 0.9%, although estimates are difficult because of the number of undiagnosed cases. Observed rates vary considerably (2.3% to 7.2%) depending on location and test availability. As of July 21, 2020, the Johns Hopkins Center for Health Security reported a U.S. case fatality rate of 3.7%. Case fatality rates increase with age.

Acceptable Answers:

1. Two to fourteen days
2. Within five days of exposure
3. Acute infection should be confirmed with polymerase chain reaction testing using a nasopharyngeal swab.
4. False
5. True
6. 85%


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