# TreatmentUpdate 236

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# I COVID-19

## A. About coronaviruses and SARS-CoV-2

Coronaviruses get their name because of their appearance under the microscope. There are many coronaviruses and, in general, they tend to cause respiratory infections in people and intestinal infections in animals.

Coronaviruses naturally circulate in animals in the wild, such as bats and mice. Before they develop the ability to infect people, coronaviruses seem to first need what scientists call "an intermediate species" of animal. Different coronaviruses infect different intermediate species, including camels, cows, civets and pigs. Once the coronavirus has infected an intermediate species, it mutates and can develop the ability to infect people. A person who encounters an intermediate species can become infected and pass on the virus to other people. Until about two decades ago, scientists found that most coronaviruses that could infect people would generally cause mild respiratory illness in healthy adults.

### SARS

However, in 2002 an outbreak of a new disease appeared—severe acute respiratory syndrome (SARS). A virus called SARS-coronavirus (SARS-CoV) caused this syndrome. The virus that caused SARS was likely spread from bats to palm civets and then to people. It caused a flu-like illness in people, including fever, cough and shortness of breath. In severely affected people it could cause a

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lethal form of pneumonia. Ultimately, SARS-CoV infected about 8,000 people worldwide, about 10% of whom died. There have been no further cases of SARS identified since that initial outbreak.

## MERS

Middle East respiratory syndrome (MERS) is spread by a coronavirus called MERS-CoV, likely from bats to camels and then to humans. Cases of MERS were first documented in 2012 in the Middle East and still occur there from time to time. Initial symptoms of MERS are similar to SARS and COVID-19. Overall, MERS has caused about 2,500 infections and 774 deaths.

## COVID-19

In late 2019, cases of severe pneumonia first appeared in Wuhan, China, and then quickly spread around the world. A virus called SARS-CoV-2 was isolated from affected people and identified as the cause of associated symptoms—coronavirus disease 2019 (COVID-19).

SARS-CoV-2 tends to cause either no symptoms or mild symptoms in most (80%) infected people. These symptoms are similar to a mild cold or flu. In other people, particularly the elderly and those with underlying conditions (such as heart disease, higher-than-normal blood pressure, chronic respiratory diseases, diabetes, kidney disease, obesity), symptoms of COVID-19 can be more severe. Such people can feel as if they have a severe cold or flu. A minority of people with severe COVID-19 can develop pneumonia and problems breathing and may require hospitalization.

## Inside the lungs

One of the puzzles about infection with SARS-CoV-2 is: Why does infection cause severe disease only in a minority of people? A clue about this has emerged from experiments with lung tissue.

Scientists in Hong Kong have performed experiments with lung tissue and two viruses—SARS-CoV and SARS-CoV-2. They have found the following:

- Both viruses infect several groups of critical cells in the lungs—the cells involved in absorbing oxygen and releasing carbon dioxide; the cells involved in producing mucus to help keep lung cells healthy; and the cells of the immune system that patrol the lungs on the lookout for germs.
- SARS-CoV-2 infection of lung tissue subsequently resulted in the production of three-fold more viruses than SARS-CoV infection.
- SARS-CoV-2 infection did not appear to trigger the production of interferon. Furthermore, this virus caused only low levels of inflammation in lung tissue, at least in the short term. The experiments lasted for 48 hours.

## Bear in mind

The results from the Hong Kong scientists suggest that SARS-CoV-2 may have a way to subvert the immune system's defenses, at least in the lungs in the short term.

Previous research with other coronaviruses suggests that this family of viruses can produce proteins that can suppress the immune system. However, as this issue of *TreatmentUpdate* goes to press, no scientific team has yet found such proteins associated with SARS-CoV-2.

## Research issues

Since SARS-CoV-2 is new to science, there are many issues that are unresolved and will remain unresolved or unclear for months to come. Cases of COVID-19 have overwhelmed health systems in many countries and caused a public health emergency. As a result, the science of many aspects of clinical research on COVID-19 has not been, at least initially, as rigorous as it might have been with other chronic and well-established conditions. Many of the studies on people with COVID-19 are retrospective in nature; that is, data were collected for one purpose and then later analyzed for another purpose. Such methods can cause scientists to inadvertently draw biased conclusions about a set of findings. However, such is the nature of research when a pandemic suddenly occurs. Over time, the state of knowledge and research on COVID-19 will improve and issues will be clarified.

Clinical trials are underway to test potential treatments for COVID-19. As well, many companies have established teams to develop a vaccine against

SARS-CoV-2. However, a safe, highly effective vaccine is unlikely to become available until sometime in 2021.

In this issue of *TreatmentUpdate*, we review key biological and clinical reports on SARS-CoV-2 and COVID-19. This will give readers some idea of what generally happens with this new disease as well as some relevant virus research. Many of the reports we highlight will have come from China and the United States.

A future issue of *TreatmentUpdate* will have information on emerging treatments.

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## B. An overview of illnesses seen in people with COVID-19

The Chinese Center for Disease Control and Prevention (CDC) has published the largest analysis to date of people with COVID-19. Here is a summary of its findings, based on data collected between December 2019 and February 2020.

Information from a total of 72,314 cases was analyzed. The breakdown of the cases as defined by the Chinese CDC is as follows:

- 44,672 people had SARS-CoV-2 confirmed by RNA testing
- 16,186 people were diagnosed with COVID-19 based on symptoms and exposure; they could not be tested for infection with SARS-CoV-2 infection due to a shortage of tests
- 10,567 people were diagnosed with COVID-19 based on symptoms, exposure to people already diagnosed with COVID-19 and CT scans suggestive of coronavirus pneumonia; no RNA testing for SARS-CoV-2 was performed
- 889 people tested positive for SARS-CoV-2 but were free from symptoms associated with the virus

### Age

Most people in the analysis were between the ages of 30 and 79 years. The Chinese CDC provided the following age distribution of the 44,672 confirmed cases:

- 1% of people were younger than 10 years old
- 1% of people were aged 10 to 19 years
- 8% of people were aged 20 to 29 years
- 87% of people were aged 30 to 79 years
- 3% of people were aged 80 and older

The spectrum of disease among 44,415 people was as follows:

- 81% of people had what the Chinese CDC called mild symptoms – no pneumonia or, at worst, mild pneumonia
- 14% of people had more severe issues – shortness of breath, rapid breathing, less-than-normal levels of oxygen in their blood, rapid development of lung injury
- 5% of people were in a critical state – their vital organs were failing and they required invasive ventilation

### Deaths

Among 46,672 confirmed cases of COVID-19, overall, 2.3% of people died. The distribution of deaths by age was as follows:

- 80 years and older – 15%
- 70 to 79 years – 8%

(No further age distribution for adults was provided.)

No deaths occurred in mild or severe cases, only in critical cases. The scientists further stated that no deaths occurred among children aged 9 years and younger.

### Underlying conditions and death

The distribution of deaths in people who had certain underlying conditions prior to the development of COVID-19 was as follows:

- cardiovascular disease – 11%
- diabetes – 7.3%
- chronic respiratory disease – 6.3%
- higher-than-normal blood pressure – 6%
- cancer – 6%

The issue of underlying diseases and its connection to severe COVID-19 has puzzled doctors. Later in this issue of *TreatmentUpdate* we revisit underlying issues and theories about why they make some people more susceptible to severe illness with COVID-19.

REFERENCE:

Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020; 323(13):1239-1242.

## C. Focus on COVID-19 in 1,000 people in China

Doctors in 552 medical centres across China pooled their data about people hospitalized with COVID-19. This allowed them to analyze features held in common by patients and could be used to form a picture of which patients are at heightened risk for further interventions (such as being placed in an intensive care unit), in need of mechanical ventilation or dying.

Of 1,099 people with virologically confirmed COVID-19, their distribution was as follows:

- admitted to the intensive care unit (ICU) – 5%
- underwent mechanical ventilation – 2.3%
- died – 1.4%

These figures are broadly in line with what has been reported in other studies of people with COVID-19.

### Study details and results

Doctors analyzed medical records collected between December 11, 2019 and January 29, 2020.

The age distribution of patients was as follows:

- less than 14 years – 1%
- 15 to 49 years – 55%
- 50 to 64 years – 29%
- 65 years and older – 15%

The gender distribution of patients was 58% men, 42% women.

On admission to hospital, common symptoms were as follows:

- cough – 68%
- fever – 44%
- nausea or vomiting – 5%
- diarrhea – 4%

These symptoms were assessed as severe in 16% of people.

Among the 1,099 people, 24% had an underlying condition—most commonly higher-than-normal blood pressure or diabetes.

People with severe symptoms of COVID-19 were more likely to have an underlying condition (39%) than people who did not have severe symptoms (21%).

### CT scans

On admission to the hospital, 975 people had CT scans of their chest. In 86% of scans, abnormalities

of the lungs were found, suggestive of some degree of pneumonia.

### Lab tests

Analysis of blood samples found many abnormalities, such as the following:

- less-than-normal levels of lymphocytes – 83%
- less-than-normal levels of platelets – 36%

Many patients had elevated levels of proteins suggestive of a high degree of inflammation:

- c-reactive-protein – 61%
- lactate dehydrogenase (LDH) – 41%

About one-fifth of patients had elevated levels of liver enzymes, suggestive of liver injury:

- AST (aspartate aminotransferase) – 22%
- ALT (alanine aminotransferase) – 21%

A large proportion of patients had elevated levels of a protein called d-dimer, suggesting elevated inflammation and also that there was a heightened risk of blood clots forming.

People with severe symptoms of COVID-19 were more likely to have highly abnormal lab test results.

### Clinical outcomes

- admitted to the intensive care unit (ICU) – 5%
- underwent mechanical ventilation – 2.3%
- died – 1.4%

Among the 1,099 people in this study, the risk of having severe outcomes listed above was about 4%. However, among people who had severe symptoms of COVID-19, the risk was 21%.

On average, people were hospitalized for 13 days.

### Treatment

People who are ill with COVID-19, like other people with severe respiratory infections, can also develop bacterial and in some cases fungal infections. Not surprisingly, 58% of the 1,099 people in the study received intravenous antibiotics. A total of 43% received oxygen delivered by nasal tube or mask. Mechanical ventilation was given to 2.3% of people.

Additional interventions included the use of steroids (methylprednisolone) in 19% of people. Nearly 36% received the anti-flu drug oseltamivir, as doctors hoped that it might help them fight the underlying infection (SARS-CoV-2). In the early days of the pandemic, doctors would use a wide range of antiviral drugs in the hope that they might provide benefit and save the lives of people with COVID-19.

### Bear in mind

This report on 1,099 patients is a snapshot of the early part of the COVID-19 pandemic. It focuses on very ill patients. It is likely that people who had no symptoms or very mild symptoms would not have sought care and were not represented in this group of patients.

REFERENCE:

Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *New England Journal of Medicine*. 2020; *in press*.

## D. Underlying conditions in some people in the U.S. with COVID-19

The U.S. Centers for Disease Control and Prevention (CDC) has received information from clinics across that country on 7,162 people diagnosed with COVID-19 who had laboratory confirmed infection with SARS-CoV-2. The CDC scientists focused on underlying conditions and potential risk factors (such as smoking) that increase the chances for respiratory diseases.

The CDC found the following:

- underlying conditions were common – found in 38% of people
- the proportion of people with underlying conditions was greater among those who were admitted to the hospital in general (71%) and to the ICU in particular (78%)

The most commonly reported underlying conditions were as follows:

- type 2 diabetes
- chronic lung disease – this included people with asthma, chronic obstructive lung disease (COPD) and emphysema
- cardiovascular disease

The CDC scientists stated that their findings are "consistent with findings from China and Italy, which suggest that patients with underlying health conditions and risk factors, including but not limited to diabetes, hypertension, COPD, coronary artery disease, cerebrovascular disease, chronic [kidney] disease and smoking might be at higher risk for severe disease or death from COVID-19."

### Controlled conditions

Many people who are diagnosed with underlying conditions, such as higher-than-normal blood pressure, cardiovascular disease, type 2 diabetes and so on, are prescribed medicines that can help bring these conditions under control. Unfortunately, due to the overwhelmed nature of health systems, detailed data capture has not been possible so far. As a result, the CDC scientists stated:

"It is not yet known whether the severity or level of control of underlying health conditions affects the risk for severe disease associated with COVID-19."

The scientists stated that underlying health conditions are "common" in the U.S. population. For instance, surveys over the past several years found that self-disclosed rates of such conditions were as follows:

- all types of heart disease (except hypertension) – 11%
- diabetes – 10%
- asthma – 8%
- COPD – 6%

The CDC's findings of the high prevalence of these conditions underscores the importance for people with these conditions to take steps to reduce the risk of SARS-CoV-2 infection.

### Bear in mind

The current analysis is preliminary. Health systems are overwhelmed by COVID-19 and unable to collect all the background information on underlying conditions when patients are admitted to the hospital.

If testing for infection with SARS-CoV-2 becomes more widespread, perhaps more people with less severe infection will be documented.

The scientists note that for some underlying health conditions and risk factors "few severe outcomes were reported; therefore, conclusions cannot be drawn about the risk for severe COVID-19 among persons [with the following]":

- neurological disorders
- chronic liver disease
- being a smoker
- pregnancy

REFERENCE:

CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States, February 12–March 16, 2020. *Morbidity and Mortality Weekly Report*. 2020;69:343-346.

## E. HIV and COVID-19

COVID-19 has the remarkable ability to cause serious disease in some people with underlying conditions. HIV infection weakens the immune system and causes chronic inflammation and immune activation. Even with HIV treatment and subsequent virological suppression, the level of immune activation and inflammation does not return to the levels seen in healthy, HIV-negative people. Furthermore, many HIV-positive people have high rates of co-morbidities—particularly issues such as higher-than-normal blood pressure, cardiovascular disease, type 2 diabetes, kidney injury and so on. In theory, all of these issues might make HIV-positive people more susceptible to SARS-CoV-2 infection and severe COVID-19. Yet to date there have not been reports of large numbers of HIV-positive people developing severe symptoms of COVID-19 in Canada, the U.S., East Asia or European Union.

Doctors at Tongji Hospital in Wuhan, China, reported case details of a man who was diagnosed with both SARS-CoV-2 and HIV infection. He has recovered from COVID-19.

### Case details

In late January 2020, a 61-year-old man went to a fever clinic. Such clinics had been established in Wuhan to screen people for SARS-CoV-2 infection. At the clinic the man reported that he had experienced dry cough and fever for the past two days. The man disclosed that he smoked between

20 and 30 cigarettes daily and that he had type 2 diabetes. This latter condition was being managed with the drugs metformin and alogliptin.

At the clinic, doctors performed assessments and found the following:

- a mild fever
- CT scans of his lungs suggested pneumonia
- blood tests revealed modestly decreased levels of lymphocytes

Doctors sent him home with instructions to isolate himself from other family members.

Due to a shortage of tests at the time, it was two weeks before nasal swabs taken at his clinic visit could be tested and revealed that he was infected with SARS-CoV-2.

During this interval, the man developed shortness of breath. Subsequently, another CT scan suggested worsening pneumonia. He was then referred to Tongji Hospital, an institution that treated people with COVID-19.

On admission to the hospital, the man's body temperature had risen to 39°C and the amount of oxygen in his blood was less than normal. Doctors provided him with supplementary oxygen via a mask. While this intervention raised the amount of oxygen in his blood, it still remained below normal.

The total number of lymphocytes in the man's blood continued to decrease and the proportion of lymphocytes that were CD4+ cells was extremely low (4.75%). The doctors did not publish CD4+ or CD8+ cell counts.

For reasons that are not clear, the doctors tested the man for HIV infection and the tests confirmed chronic HIV infection.

Since SARS-CoV-2 infection was life threatening, doctors focused on treating that virus. They prescribed Kaletra (lopinavir-ritonavir) for 12 consecutive days in the hope that it would work against the coronavirus. Kaletra is approved in many countries as a treatment for HIV. At the time, Chinese guidelines suggested that doctors could use Kaletra as a potential treatment for coronavirus infection and Kaletra was widely used in China during the initial stages of the COVID-19 pandemic.

No additional anti-HIV drugs were prescribed. In addition, the man was given the following:

- the antibiotic moxifloxacin, 400 mg once daily
- an intravenous infusion of broad-spectrum antibodies (gamma globulin)
- an intravenous infusion of the steroid methylprednisolone, 0.8 mg/kg of body weight once daily for three consecutive days

On the 5th day of hospitalization, doctors reported that the man showed "a remarkable clinical improvement." Another CT scan of his chest showed a decrease in lung inflammation and pneumonia. The level of oxygen in his blood approached normal.

On the 9th day of hospitalization, swabs from the man's nose and throat tested negative for COVID-19.

On the 11th day of hospitalization, the man was sent home with instructions to stay home for two consecutive weeks as a precaution against infecting others with SARS-CoV-2. He was also referred to a clinic for HIV treatment.

This is only one case, so no firm conclusions can be drawn about co-infection with HIV and SARS-CoV-2 or its treatment.

### Resources

Further reports about COVID-19 and HIV appear on our website here.

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Zhu F, Cao Y, Xu S, Zhou M. Co-infection of SARS-CoV-2 and HIV in a patient in Wuhan city, China. *Journal of Medical Virology*. 2020; *in press*.

## F. ACE2 and the health of major organs

The cause of COVID-19 is a virus called SARS-CoV-2. This virus uses a receptor on the surface of cells in order to gain entry to and infect cells. The receptor is called ACE2. Once inside a target cell, SARS-CoV-2 engages with enzymes in the cell to cause infection.

## Distribution of ACE2

In 2003-04, scientists were trying to understand how a related virus, SARS-CoV (the cause of severe acute respiratory syndrome), was able to enter cells. They found that SARS-CoV also used ACE2.

ACE2 is found on many different types of cells in different parts of the body, including the following, which we have grouped together as they have a related function:

- mouth, nose, throat and lungs
- stomach and intestinal tissues, including the colon
- bone marrow, lymph nodes, spleen and thymus gland
- liver
- brain
- cells lining the arteries, the heart
- testicles

Although ACE2 is found on the surface of many cells in the body, research has found especially high levels of ACE2 on tissues from the cardiovascular system, intestines and kidneys. These high levels of ACE2 may, in theory, make these tissues more susceptible to infection and injury from SARS-CoV-2.

## In sickness and in health

The normal role of ACE2 is to help break down a hormone called angiotensin II to angiotensin. This conversion of angiotensin II helps to reduce tightening of blood vessels and signals the kidneys to remove sodium from the blood, helping to reduce blood pressure. Thus, ACE2 has a protective effect on the cardiovascular system and kidneys. ACE2 also has other protective roles, such as anti-inflammatory effects and likely reducing the risk of excessive formation of blood clots.

## Back to the virus

Once SARS-CoV-2 infects a cell, it is somehow able to get the cell to reduce expression of ACE2 on its surface. If many cells in an organ-system are infected and reduce their expression of ACE2 on their surface, the result is that there are insufficient levels of ACE2 to protect cells from inflammation-related injury.

In the case of SARS-CoV-2-infected lung tissue, scientists think that the subsequent loss of ACE2 expression could increase the risk of lung injury arising from infection by this virus and/or bacteria.

## The heart and blood vessels

SARS-CoV-2 can infect the heart and cells lining blood vessels. People with severe symptoms of COVID-19 have elevated levels of proteins in the blood, suggestive of heart injury (we will have more details about these proteins in another article in this issue of *TreatmentUpdate*). It is at least plausible that the loss of ACE2 arising from SARS-CoV-2 infection of the heart and blood vessels could contribute to cardiac injury—abnormal heart rhythms, heart failure and other issues—that has been reported in some people with severe symptoms of COVID-19. Doctors have found that people with underlying cardiovascular injury seem to be at elevated risk for severe COVID-19 associated problems.

## Theories about ACE2

There are several theories about ACE2 and its role in COVID-19. These theories are largely based on data collected from past experiments with cells and with animals and have not been done in the context of the current pandemic.

### Genes

Not everyone has the same level of ACE2 expression in their body. Scientists have found that there are differences in populations concerning ACE2 expression and the risk for cardiovascular disease. This risk may be related to differences in genetic makeup between groups of people. This difference in expression of ACE2, related to genes, may be one reason why some people are more susceptible to COVID-related injury of organs.

### Gender

Women have two X chromosomes (written as XX) and men have one X and one Y chromosome (written as XY). The ACE2 gene is associated with the X chromosome. Since the cells of women have two copies of this chromosome, they may have higher levels of ACE2 than men. This difference may, in part, explain some reports that men seem to be significantly more affected by severe COVID-19 than women. However, this idea needs further exploration in well-designed analyses.

### Blood pressure treatment

Many medicines for treating higher-than-normal blood pressure and cardiovascular disease raise levels of ACE2 on the surface of cells. In theory, this could provide more opportunities for SARS-CoV-2 to infect such cells. However, the consensus among leading cardiovascular and kidney specialists and their professional societies is that the benefit of these drugs on a person's overall health outweighs any theoretical concerns about enhancement of SARS-CoV-2 infection.

Well-designed clinical trials will be needed to explore the issue of blood pressure medicines and COVID-19. Examples of such trials that are planned or underway include the following:

- a medicine called losartan that has been used to treat hypertension
- intravenous infusions of ACE2

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## G. The heart and COVID-19

Reports from China, Italy and the U.S. suggest that some people with underlying cardiovascular disease are at heightened risk for severe illness associated with COVID-19. There are also reports of increased risk for cardiovascular complications in some people with COVID-19.

Cardiologists at Zonghan Hospital in Wuhan, China, have been studying cardiovascular complications in people with COVID-19. Their study focused on proteins in the blood associated with heart injury. In some severe cases of COVID-19 with cardiovascular complications, levels of these proteins in the blood were elevated.

### Study details

The cardiologists reviewed data collected from 187 people who were hospitalized and diagnosed with COVID-19 in January and February 2020. A total of 144 people survived and were able to leave the hospital, while 43 people died. The doctors collected information about signs, symptoms, lab tests and other assessments.

Two lab tests were a particular focus of their research:

- TnT (cardiac-specific troponin) – this protein is released from dying or dead heart cells
- NT-proBNP (N-terminal pro B-type natriuretic peptide) – this is a small molecule produced by the heart that is released into circulation when heart failure occurs

When participants were first admitted to the hospital and evaluated, the doctors stated that there was no evidence of the following:

- heart attack
- chronic liver disease
- problems with excessive clotting of blood
- rheumatism

## Results

The cardiologists found that more deaths occurred in people with elevated levels of TnT (60%) than in people with normal TnT levels (9%).

Furthermore, the doctors found that people with elevated TnT levels were more likely to have underlying health issues, such as the following:

Higher-than-normal blood pressure
- with elevated TnT – 64%
- with normal TnT – 21%

Coronary heart disease
- with elevated TnT – 32%
- with normal TnT – 3%

Enlarged heart
- with elevated TnT – 15%
- with normal TnT – 0%

Diabetes
- with elevated TnT – 31%
- with normal TnT – 9%

Chronic Obstructive Pulmonary Disease (COPD)
- with elevated TnT – 8%
- with normal TnT – 0%

Rates of smoking and cancer were not different between people with elevated TnT and those with normal TnT.

As reported in other studies of COVID-19, lab tests revealed elevated levels of proteins associated with inflammation, such as high-sensitivity C-reactive protein (hsCRP). Such markers were higher in people who had elevated levels of TnT.

People with elevated levels of TnT in the present study tended to have less-than-normal levels of oxygen in their blood. During the course of hospitalization, doctors found that people with elevated TnT levels developed "more frequent complications," including the following:

- severe lung injury
- abnormal heart rhythms that became life threatening
- excessive formation of blood clots
- acute kidney injury

Although liver injury occurred in some of the people in the cardiology study (this was found by detection of elevated liver enzymes in blood samples), there was no connection to TnT levels.

## Interventions

As data were captured during an evolving approach to the management of COVID-19, patients received a wide variety of treatments, including the following:

- antiviral drugs such as oseltamivir and ribavirin
- antibiotics such as moxifloxacin for respiratory infections
- steroids such as methylprednisolone

Also, some patients required invasive mechanical ventilation because of severe lung injury. More people with elevated TnT required this intervention.

## Risk of dying

The doctors found that the risk of death was distributed as follows:

- normal TnT and no underlying cardiovascular disease – 8%
- normal TnT and underlying cardiovascular disease – 13%
- elevated TnT and no underlying cardiovascular disease – 38%
- elevated TnT and underlying cardiovascular disease – 69%

## Changes

Over the course of hospitalization, levels of TnT and NT-proBNP successively rose in people who subsequently died. However, among people who survived, there was no increase in levels of these markers.

## Bear in mind

Some studies in the pre-COVID-19 era suggest that viral respiratory infections are associated with an increased risk for cardiovascular events—heart attack, stroke and so on.

In 2002-03 when SARS occurred, doctors were able to conduct autopsies of some of the deceased from this complication. They found that 35% of tissue samples taken from hearts of people who died had the virus (SARS-CoV) that caused SARS. Laboratory-based studies done in the past three months suggest that SARS-CoV-2, the cause of COVID-19, can infect heart cells. Therefore, it is at least plausible that some of the cardiovascular problems found in the present study were caused in some way by SARS-CoV-2.

It is also plausible that multiple mechanisms triggered by SARS-CoV-2 infection contributed to the increased risk for cardiovascular problems that have been reported in some people with COVID-19. These other mechanisms could include the following:

- intense levels of inflammation
- changes to expression of a protein called ACE2 found on the surface of some cells (further information about ACE2 is found earlier in this issue of *TreatmentUpdate*)
- less-than-normal levels of oxygen in the blood – this can occur in severe respiratory infections when the lungs become injured
- injury to the lining of blood vessels – this could decrease the flow of blood to organs and also contribute to an increased risk for blood clots

The cardiologists suggested that doctors presently caring for people hospitalized with COVID-19 could screen them for underlying cardiovascular injury with blood tests of key markers (TnT, NT-proBNP) and cardiograms.

The present study was retrospective in design and cannot provide definitive conclusions. However, it provides a foundation for more intensive investigation into the risk for severe cardiovascular events in people with COVID-19. Such investigation can lead to the development of interventions to help people who are ill with COVID-19.

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## H. The brain and nerves in COVID-19

Historically, scientists have thought that coronaviruses generally caused infection of the respiratory tract in people (the wet tissues of the nose, mouth, throat, airways and lungs) and the intestinal tract in animals.

In the outbreak of coronavirus disease that occurred in 2002-03 with severe acute respiratory syndrome (SARS), scientists conducted autopsies of some people who had SARS. They found that the virus that caused SARS, SARS-CoV, was present in many tissues, including brain cells. As this virus is closely related to the virus (SARS-CoV-2) that causes COVID-19, it is possible that SARS-CoV-2 can infect a wide range of tissues, including cells in the brain.

It is not clear how SARS-CoV-2 gains entry to the brain. It is possible that the virus could be transported there via cells of the immune system, as these cells are distributed throughout the body. Cells of the immune system could become infected with SARS-CoV-2 in one location, such as the respiratory tract, and then bring the virus to the brain.

Another possibility is that the virus could get into the brain by infecting nerves that connect different parts of the body to the brain.

Whatever route is used by the virus, it is plausible that in a subset of people, infection with SARS-CoV-2 can affect the functioning of parts of the brain.

### Brain inflammation

Viruses that can infect the brain can cause inflammation of this organ. Doctors at a hospital in Qingdao, China, have documented a case of brain inflammation in a 56-year-old man with SARS-CoV-2. The doctors did not provide clinical details but did note that his spinal fluid contained SARS-CoV-2.

In experiments with mice and another coronavirus (called HCoV-OC43) that can infect people, scientists found that mice that survived the infection had traces of the virus in their brains for several months.

Other scientists have noted that infection with SARS-CoV-2 is associated with headache, nausea and vomiting. In some cases, these symptoms may be due to infection of the brain or the nerves that are in the intestine.

The virus that causes SARS can infect the brain stem. This is a part of the brain that is involved in regulating automatic functions such as breathing, heart rate and alertness/consciousness. As breathing difficulties can be a feature of severe COVID-19, some scientists have speculated that SARS-CoV-2 may have the ability to injure nerves in the lungs or brain stem that affect the health of the lungs.

### Loss of consciousness

The main function of the lungs is to absorb oxygen from the air and release the waste product carbon dioxide. Since COVID-19 is associated with breathing difficulties in severe cases, it is possible that in some of these cases not enough oxygen can enter the tissues of the lungs and, subsequently, blood vessels that connect the lungs to the rest of the circulatory system. As a result, it is possible that vital organs, such as the brain, do not receive enough oxygen, which causes the brain to malfunction. This lack of sufficient oxygen may be one possible explanation for cases in which people with severe COVID-19 have become unconscious.

### Neurological symptoms

Neurologists from three hospitals in China recently reviewed data from 214 people with laboratory confirmed COVID-19. These patients were investigated for possible neurological issues. The doctors found that 36% of these people had symptoms that included at least one of the following:

- dizziness
- headache
- reduced sense of taste
- reduced sense of smell
- nerve pain
- muscle weakness (explained below)

Such symptoms were more likely in people with severe COVID-19.

The doctors stated: "Most neurological manifestations occurred early in the course of illness."

Some of these patients sought medical attention because of stroke or seizure; initially they did not have what the doctors described as typical COVID-19 symptoms (fever, cough, loss of appetite, diarrhea).

Analyses of blood samples from these patients revealed that many with severe COVID-19 had elevated levels of proteins associated with inflammation, including C-reactive protein, D-dimer, elevated levels of liver enzymes and so on.

To help control muscles, many nerves connect muscles to the brain. People with muscle injury associated with COVID-19 had elevated levels of the enzyme creatine kinase in their blood. It is not clear if the virus directly infects muscle cells or how it might otherwise injure them.

### Smell and taste disorders

Doctors in Milan, Italy, interviewed 59 people with COVID-19 about their symptoms. They found that 34% reported "at least one" disorder of taste or smell. In 19% of people, both disorders were reported. Disorders of taste were more common prior to hospitalization. After hospitalization, both disorders could appear with equal frequency.

Note that disorders of a sense of smell can have other causes, such as sinus infections, and by themselves, do not prove that a person has COVID-19.

Due to being overwhelmed by cases of COVID-19, the Italian doctors were unable to conduct further assessments of smell and taste disorders. However, their findings highlight an intriguing consequence of COVID-19, at least in some affected people.

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## I. The gut, liver and COVID-19

Coronaviruses such as SARS-CoV-2, the cause of COVID-19, can cause serious disease in some people, usually affecting the lungs. However, other coronaviruses that also cause serious disease, SARS-CoV and MERS-CoV, can cause intestinal and liver injury. Therefore, it is possible that SARS-CoV-2 can cause similar problems.

In general, studies done in people with SARS in 2002-03 found that elevated levels of liver enzymes (AST and ALT) could occur in the early stages of this disease. In more severe cases of SARS, a greater degree of liver injury was found. In some cases, people with SARS-associated liver injury

also had increased concentrations of the waste product bilirubin and the protein albumin in their blood. Biopsies of liver tissue from people who had SARS suggested that liver injury, caused by SARS-CoV, occurred.

## COVID-19

A review of studies with people who have been diagnosed with COVID-19 has found that between 15% and 53% of such people can have some degree of liver injury. This injury is revealed by the presence of elevated levels of liver enzymes and sometimes bilirubin in their blood samples.

Cells of the liver and bile duct have the protein ACE2 on their surface. This protein serves as a receptor for SARS-CoV-2, allowing the virus entry into cells. Whether this virus directly or indirectly infects the liver remains unclear.

So far, there are no published reports in peer-reviewed journals of large numbers of people with chronic viral hepatitis caused by hepatitis B virus or hepatitis C virus who have also developed COVID-19. However, some doctors are concerned that people with chronic viral hepatitis may experience additional liver injury if they develop serious symptoms of COVID-19.

The role that medicines commonly used in managing complications of COVID-19 have on the liver needs to be investigated. Such medicines include antibiotics and steroids such as prednisolone.

A team of doctors at the Shanghai Public Health Clinical Center reviewed medical records of 148 people (75 men, 73 women) who sought help because of COVID-19. All patients were positive for SARS-CoV-2 RNA. The doctors found that about 37% of patients had elevated levels of liver enzymes in their blood. People with elevated levels of liver enzymes also had proteins in their blood suggestive of generalized inflammation, such as C-reactive protein. However, what is noteworthy is that the doctors found an association between the use of Kaletra (lopinavir-ritonavir) and an increased level of liver enzymes.

Kaletra was approved almost 20 years ago as part of combination therapy for HIV. Due to the crisis nature of the COIVID-19 pandemic, doctors in many countries have used drugs that are approved for another use, usually against another virus, in people infected with SARS-CoV-2 in the hope that it might save their lives. In the early days of the COVID-19 pandemic, Kaletra was widely used in Chinese hospitals for this purpose. As the analysis from Shanghai is retrospective in nature, it is not possible to be certain if the elevated levels of liver enzymes were caused by Kaletra exposure or were simply a natural part of the evolution of SARS-CoV-2 disease process. However, the Shanghai doctors urge caution when prescribing Kaletra for use as a potential treatment for COVID-19.

## Diarrhea and other symptoms

Doctors in Guangdong, China, reported details on 95 people with acute SARS-CoV-2 and gastrointestinal issues. Sixty-five percent of these people developed GI symptoms, most of which occurred after hospitalization. Symptoms included the following:

- diarrhea
- loss of appetite
- nausea

It is noteworthy that 12% of patients also had gastrointestinal symptoms prior to hospitalization.

The doctors suspect that diarrhea that occurred during hospitalization was likely due to the use of antibiotics (prescribed to treat lung infection).

Analysis of stool samples found that SARS-CoV-2 could be detected in 22 out of 42 people with gastrointestinal symptoms and in nine out of 23 people without gastrointestinal symptoms.

Additional investigation found that SARS-CoV-2 was detected in swabs or fluid samples from the throat, stomach, duodenum and rectum from two people with severe symptoms. In only one person with non-severe symptoms was SARS-CoV-2 found and only in the duodenum.

The doctors found that the presence of gastrointestinal symptoms did not seem to affect survival with COVID-19.

Other scientists in China have investigated databases that have information on different types of cells. Their research has confirmed that some cells from the digestive tract have the protein ACE2

on their surface. This protein serves as a way for SARS-CoV-2 to gain entry to cells.

There are at least two theories that may explain why some people with acute SARS-CoV-2 experience gastrointestinal symptoms:

- The virus can infect cells of the gastrointestinal tract, which injures it.
- When cells of the gastrointestinal tract are infected, inflammation occurs there, which allows the passage of bacteria and fungi that may be present in the digestive tract to enter the circulation.

As with nearly all studies of SARS-CoV-2, these findings should be viewed as preliminary.

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## J. The immune system and COVID-19

Research on COVID-19 and the virus that causes it—SARS-CoV-2—is still in its infancy. As a result, study designs on COVID-19 have not been ideal and any conclusions drawn about how the virus causes injury and disease should be considered preliminary.

Before delving into what scientists have found about SARS-CoV-2 and the immune system, we first present some general and simplified information about the immune system.

The first line of defence against germs is the innate immune system. This part of the immune system recognizes patterns in the structure of germs and can activate an immune response when it senses a virus or other germ.

Another part of the immune system is called the adaptive immune system. This involves B-cells that produce antibodies and T-cells that help regulate the immune response and also fight viruses (and other germs).

The immune system is widely distributed—it's found in lymph nodes and lymphoid organs such as the spleen, thymus and bone marrow. Cells of the immune system are also present in different organs and tissues, where they are on guard for invading germs.

### The immune response

The immunological response to an invading germ involves first sensing the germ and then releasing chemical signals to attract other cells of the immune system to the site of infection or accumulation of the germ, such as in a lymph node or infected organ. These chemical signals can cause the production of interferon, which can protect cells against infection.

Organs such as the spleen and tissues such as lymph nodes can become swollen as they cause a massive expansion in the number of the immune system's cells. Some cells that specialize in capturing invading germs bring the germs to lymph nodes and lymphoid organs, where other cells of the immune system can be educated about what to attack.

To increase the body's ability to resist the invading germ, the immune system triggers a fever. The raised temperature helps to slow the growth of infected cells. However, the steps taken by the immune system to fight an infection can cause the symptoms of what many people associate with the flu or a severe cold—fatigue, bone and muscle pain, swollen lymph nodes and so on.

It is possible that, in some cases, the immune system may overreact to an invading germ and its ability to regulate itself becomes weakened. This could lead to the immune system inadvertently attacking itself or parts of the body. Some of the severe lung injury found in people who died from COVID-19 may be immunological in origin.

## Findings in COVID-19

Scientists in China have been exploring the impact of SARS-CoV-2 on the immune system. Their findings should be treated as preliminary, as the studies generally have small numbers of people. However, they are what is available as this issue of *TreatmentUpdate* goes to press.

A study at Tongji Hospital in Wuhan, China, analyzed blood samples from 21 people (17 men, 4 women), all of whom had either severe (11 people) or moderate (10 people) symptoms of COVID-19.

People who had severe symptoms tended to be old and had elevated levels of many chemical messengers (cytokines), such as the following:

- IL-6 (interleukin-6)
- Il-10 (interleukin-10)
- TNF-alpha (tumour necrosis factor-alpha)

They also had elevated levels of high-sensitivity C-reactive protein (hsCRP) and D-dimer. All of these are suggestive of inflammation.

Nearly all patients had reduced levels of T-cells, including CD4+ and CD8+ cells. The normal range for CD4+ cell counts at the hospital's laboratory is between 550 and 1400 cells/mm$^3$ and the normal range for CD8+ cells is between 320 and 1250 cells/mm$^3$. Here are the cell counts in two sub-groups of patients with COVID-19:

Moderate symptoms
- CD4+ count – 328 cells/mm$^3$
- CD8+ count – 254 cells/mm$^3$

Severe symptoms
- CD4+ count – 178 cells/mm$^3$
- CD8+ count – 89 cells/mm$^3$

These values are well below the normal range.

When researchers assessed the functional capacity of cells of the immune system to produce an antiviral response (by producing interferon-gamma), this ability was generally weakened in CD4+ cells, particularly in people with severe symptoms. Immunological weakness was present but less pronounced in people with moderate symptoms.

About 27% of patients in this analysis had bacterial infections of the lungs and respiratory tract.

Doctors gave patients intravenous fluid to maintain hydration, the antibiotic moxifloxacin to treat respiratory tract infections, broad-spectrum antiviral drugs to treat any presumptive viral infections and the steroid methylprednisolone to try to reduce inflammation. Four people died, all of whom had severe symptoms.

## Limitations

There are many limitations to this and similar studies. It had a small number of people. Data were captured for one purpose and then reanalyzed at a later date for another purpose. Another limitation was that lymphocytes (T-cells) were analyzed from only blood samples. Most lymphocytes are in lymphoid organs and tissues such as lymph nodes. In the future, when conducting immunological research on SARS-CoV-2 infection, it may be more useful to extract cells from lymphoid organs and related tissues.

Another limitation is that data were captured at one point in time and assumed to be relevant to the whole course of illness with COVID-19. The immune system is dynamic; there are changes that occur over the course of an infection and these need to be documented and studied.

However, the doctors in China were dealing with a health emergency and the fact that any information was captured on the immune systems of patients is remarkable.

## Immunological issues

Why were there decreased numbers of immune cells and functional capacity? Some scientists have speculated on these findings and advanced the following theories:

- SARS-CoV-2 could have directly infected T-cells. These cells have a receptor called ACE2 on their surface. The virus uses this receptor to gain entry to other cells, so it is plausible that the virus could have used the same receptor to enter cells of the immune system.
- SARS-CoV-2 could attack important organs of the immune system, such as the bone marrow, spleen and thymus gland.

- Excessive levels of cytokines, such as TNF-alpha, could cause cells of the immune system to invoke a self-destruct mechanism (apoptosis). This mechanism is commonly triggered by many viral infections and helps to destroy infected cells. However, apoptosis can also be triggered in uninfected cells during major infections.

Similar immunological dysfunction—excessive immune activation and inflammation, apoptosis—occurs in untreated HIV infection. The number of documented cases of SARS-CoV-2 in HIV-positive people is very small. As a result, at this time, there are no extensive reports of what happens to the immune systems of people with HIV who become co-infected with SARS-CoV-2.

## Reviews and other studies

In reviewing the findings from Wuhan, scientists at Yale University stated that in some people with severe COVID-19, infection with SARS-CoV-2 appears to deplete the immune system of CD4+ and CD8+ cells in the blood. Furthermore, there was excessive production of cytokines. The Yale scientists stated that these cytokines are likely produced by cells of the immune system called macrophages. Not much research has been reported on macrophages from people with COVID-19.

Another team of scientists at Anhui Medical University in China compared blood samples from three groups of people:

- healthy controls – 25 people
- those with mild symptoms of COVID-19 – 55 people
- those with severe symptoms of COVID-19 – 13 people

They found broadly similar immunological issues as the scientists in Wuhan. In addition to low CD4+ and CD8+ cell counts, the Anhui scientists found that levels of a group of cells that can fight viruses, natural killer (NK+) cells, were less than normal.

The Anhui scientists also found that CD8+ and NK+ cells seemed less capable of carrying out antiviral functions in people with SARS-CoV-2, regardless of the degree of their symptoms. Analysis of blood samples from people who recovered from COVID-19 suggested that levels of T-cells and NK+ cells eventually returned to normal.

Another team of scientists at the Kunming Institute of Zoology, also in China, analyzed blood samples from 16 people with COVID-19. Ten of the people had mild symptoms and six had severe symptoms. For comparison, blood samples were taken from six healthy people.

In general, the scientists found a higher level of activated CD8+ cells in people with severe disease compared to people with mild disease or healthy people. What's more, the CD8+ cells from people with severe COVID-19 seemed immunologically exhausted.

## In summary

All of the teams of scientists have uncovered that infection with SARS-CoV-2 can harm the immune system. Perhaps the harm arises from excessive immunological activation, excessive inflammation, and exhaustion of CD8+, NK+ and CD4+ cells. However, it is important to note that many people who become infected with SARS-CoV-2 have mild symptoms or even no symptoms. Studying the immune systems of such people will become important to find clues about how they resist severe immunological injury.

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## K. The immune response in a person with non-severe COVID-19

Scientists in Melbourne, Australia, were able to analyze the immune response of a woman with non-severe COVID-19. They found that the immunological response was both fast and dynamic. The findings from their study can help support a better understanding of SARS-CoV-2 infection and the type of responses needed from a future candidate vaccine.

### Case details

A 47-year-old woman from Wuhan, China, sought care at a Melbourne hospital because for four days she was experiencing the following: lack of energy, sharp chest pains when breathing, mild shortness of breath and fever. Eleven days prior she had visited Wuhan. She was a non-smoker and otherwise healthy and not taking medicines.

Doctors found that she had a mild fever, a rapid pulse and somewhat elevated blood pressure. These can be general reactions to an infection. The amount of oxygen in her blood was normal.

On the day of admission to the hospital, swabs from her nose and throat tested positive for SARS-CoV-2. The doctors called this day four, as she had a four-day history of symptoms. The virus continued to be detected on days five and six in samples from her nose, throat and stool. However, on day seven, no virus was detected, nor was it on any subsequent day.

Analysis of the woman's blood samples found normal levels of lymphocytes and other cells of the immune system. However, her overall level of inflammation was high.

No other respiratory germs were detected and the sounds that she made when breathing were normal. A chest X-ray on day five showed mild inflammation that resolved on day 10.

As her symptoms of COVID-19 were considered "mild-to-moderate," doctors did not prescribe antibiotics, steroids or antiviral drugs.

On day 11, the woman was sent home and told to remain in isolation. Doctors found that her symptoms entirely resolved on day 13. On day 20, the end of their observation of her, she continued to be well.

### Antibodies

Further laboratory analysis of the woman's stored blood samples revealed that antibody producing cells appeared on day seven, the same day that virus was no longer detected. Subsequent testing revealed that the level of these cells reached their peak on day eight and then declined.

Levels of antibodies (called IgG) that attacked SARS-CoV-2 were detectable on day seven and increased through day 20. Levels of another type of antibody (called IgM) that also attacked the virus became detectable on day nine and rose through day 20.

### Antiviral CD8+ cells

During acute viral infections, CD8+ T-cells are activated and deployed by the immune system to attack viruses and virus-infected cells. On day seven, the level of activated CD8+ cells rose and kept rising but had fallen by day 20. The level of

activated CD4+ T-cells also rose during the same period but not as much as CD8+ cells did.

Scientists also assessed the functioning of CD8+ cells, specifically, their ability to release enzymes that damage the genetic material of virus-infected cells and cause them to die. Activated CD8+ cells were highly functional.

No increased levels of other cells, natural killer cells or monocytes/macrophages were found.

## Signals of inflammation

Excessive levels of inflammation may play a role in some viral infections when organ injury occurs. In the present study, scientists found that levels of chemical signals that incite inflammation were "minimal" in the blood samples of the woman. This was the case even on days seven through nine when she had symptoms of COVID-19.

## Bear in mind

The present study underscores the dynamic nature of the immune response; it can wax and wane. The study also shows the need for similar studies in larger numbers of people throughout their course of COVID-19. Such studies may help do the following:

- identify components of a useful immunological response against SARS-CoV-2
- uncover the timing of such a response, which has implications for treatment (once treatments are approved)
- contribute to the development of candidate vaccines against SARS-CoV-2

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## Disclaimer

**Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.**

CATIE provides information resources to help people living with HIV and/or hepatitis C who wish to manage their own health care in partnership with their care providers. Information accessed through or published or provided by CATIE, however, is not to be considered medical advice. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. We strongly urge users to consult with a qualified medical practitioner prior to undertaking any decision, use or action of a medical nature.

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## What CATIE Does

CATIE is Canada's source for up-to-date, unbiased information about HIV and hepatitis C. We connect people living with HIV or hepatitis C, at-risk communities, healthcare providers and community organizations with the knowledge, resources and expertise to reduce transmission and improve quality of life.

For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients' needs.

CATIE provides such information through a comprehensive website (www.catie.ca), electronic and print resources, webinars and other online learning, a national reference library, regional conferences, subscriptions to e-newsletters and a confidential phone inquiry service.

## CATIE Publications

***TreatmentUpdate***
CATIE's flagship treatment digest on cutting-edge developments in HIV/AIDS and hepatitis C research and treatment. Subscribe to *TreatmentUpdate* and automatically receive an email notifying you the moment a new issue is available online or contact us at 1.800.263.1638 to receive a print subscription.

***CATIE News***
CATIE's bite-sized HIV and hepatitis C news bulletins.

***HepCInfo Updates***
CATIE's bi-weekly electronic newsletter highlighting key hepatitis C prevention, treatment and epidemiology information.

***A Practical Guide to HIV Drug Side Effects***
The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

***The Positive Side* magazine**
Holistic health information and views written by and for people living with HIV.

**Fact Sheets**
Concise overviews of conditions, symptoms, medications, side effects, complementary therapies, vitamins, herbs and other treatment issues.

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