PeerVoice

Therapy for COVID-19: Management Strategies and Clinical Rationale

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Determining Benefit of Therapies for Patients With COVID-19: Collation of the Evidence

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High-Risk Patient Presenting With Mild COVID-19 Infection

Patient With COVID-19 Experiencing Worsening Symptoms in Week 2

Patient With COVID-19 Infection After Two Doses of Vaccine

Case Report: COVID-19 Infection in a Patient Who Is Immunocompromised

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Learning Objectives

- Explain the importance of timing of antiviral initiation in patients with COVID-19
- Describe key factors that need to be considered when making a decision to initiate therapy in patients with COVID-19
- Identify patients with COVID-19 who are most likely to benefit from antiviral therapy

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Determining Benefit of Therapies for Patients With COVID-19: Collation of the Evidence

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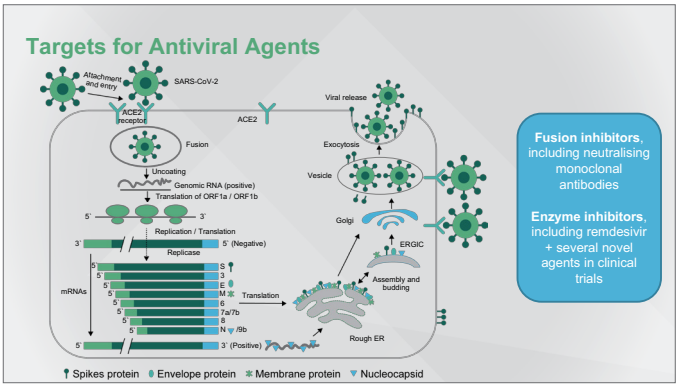
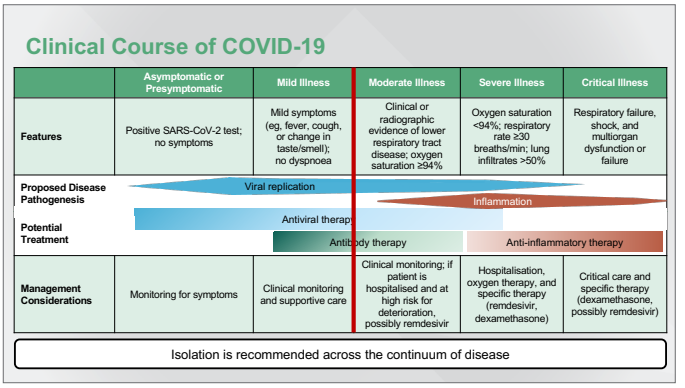


Reference(s): Shereen MA et al. *J Adv Res*. 2020;24:91-98. doi:10.1016/j.jare.2020.03.005.

Jens Dilling Lundgren, MD, DMSc: Hi, my name is Professor Jens Lundgren from Rigshospitalet, University of Copenhagen in Denmark, and welcome to this activity on therapy for COVID-19. As you know, after the first outbreak of the novel severe acute respiratory syndrome coronavirus 2 (abbreviated SARS-CoV-2) in China in the end of 2019, the virus has caused widespread global epidemics causing millions of lives lost and has significantly interfered with normal hospital practice and societal disruption due to the introduction of significant mitigation strategies. In response to this major public health threat, the research community have advanced effective vaccines. Here we'll be focusing on advancement in treatments.

Two principal mechanisms of action have been identified to lead to better outcome—namely, drugs that reduce replication of the virus itself and immunomodulatory agents able to reduce the body's immune response to the infection. We have learned that the application of these medications should be done depending on the stage of the infection.

Let me just for a few minutes introduce you to the life cycle of the virus. As you know, the virus binds to ACE2 receptors on the surface of cells and, therefore, allows for the fusion between the virus and the cell membrane. There are a number of fusion inhibitors that have been developed that prevent this from happening. The most notable are the neutralising monoclonal antibodies that all work in this way. There's also a number of enzymes that the virus is using for its replication within the cytoplasm, and there's a growing number of small molecules able to inhibit each one of those enzymes. One of them we're already using—namely, remdesivir.

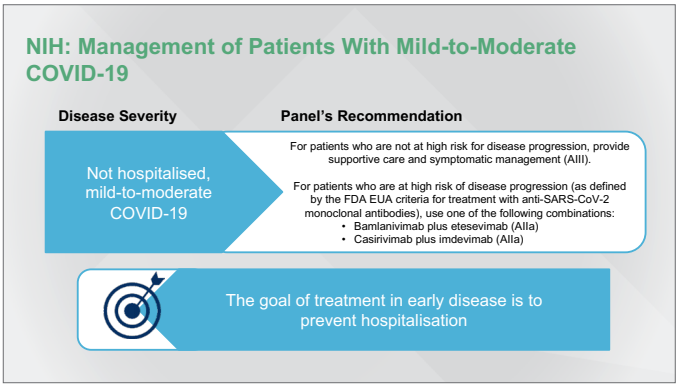


Reference(s): Gandhi RT et al. *N Engl J Med*. 2020;383:1757-1766.

The clinical course of COVID-19 is very diverse. Some people do not develop symptoms; others develop mild disease typically lasting for a week. At some point in some of them, they experience disease progression to moderate illness typically manifesting with COVID pneumonia, which then, in an even smaller subset, may progress to more advanced severe illness and critical illness characterised phenotypically as ARDS.

We know that viral replication is the major culprit to begin with and in early stage of the disease, whereas the hyperinflammatory response is the dominant cause of disease later on. Therefore, if you want to use antiviral medications, the best position to use them would be relatively early on in disease, whereas immunomodulatory agents should be restricted to people with more severe disease.

Critically important, demarked by this line here, is that most people with mild disease are not yet hospitalised—whereas clearly, for people with COVID pneumonia, they need to be in the hospital. And therefore, we separate the discussion about treatment according to whether people are still outpatients or have been hospitalised.



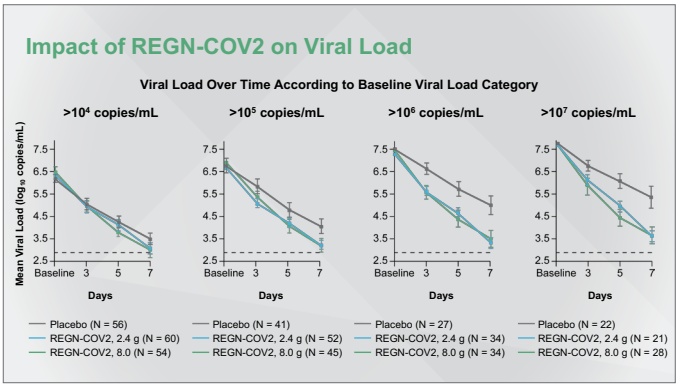
Abbreviation(s): FDA EUA: Food and Drug Administration Emergency Use Authorization; NIH: National Institutes of Health.

Reference(s): National Institutes of Health. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/management/therapeutic-management/. Accessed 2 July 2021.

There have been an impressive number of randomised trials conducted to date. Initially, of course, the focus was to use repurposed drugs, including, for example, remdesivir and dexamethasone. However, quickly a number of high affinity neutralising antibodies against the spike protein entered trials during the middle of last year. And, we are now entering into another exciting era as small molecules inhibiting viral enzymes essential for the virus to complete its life cycles are in clinical development.

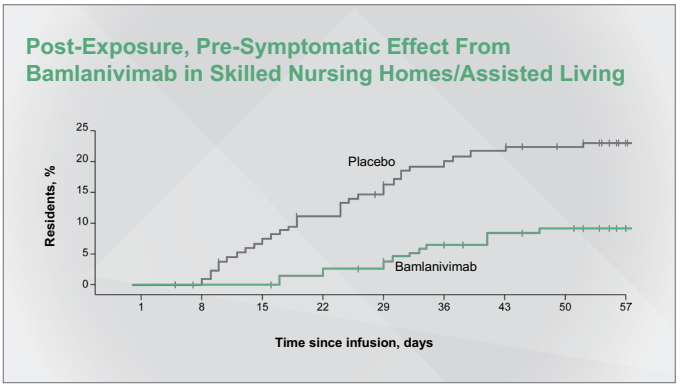
These recommendations are taken from NIH and focus on people with mild to moderate disease not yet in hospital. For those patients, viral replication is at its peak, and neutralising monoclonal antibodies should be considered, in particular, for people at high risk of disease progression because the purpose of treatment in early disease is to prevent hospitalisation.

Importantly, a number of studies recently presented also indicate that these neutralising monoclonal antibodies can be used as post-exposure prophylaxis to prevent COVID from developing to begin with. And therefore, these medications may also be helpful and potentially be used, in particular, in those patients unable to respond to the vaccination because of impaired immune function.



Reference(s): Weinrich DM et al. *N Engl J Med*. 2021;384:238-251. doi:10.1056/NEJMoa2035002.

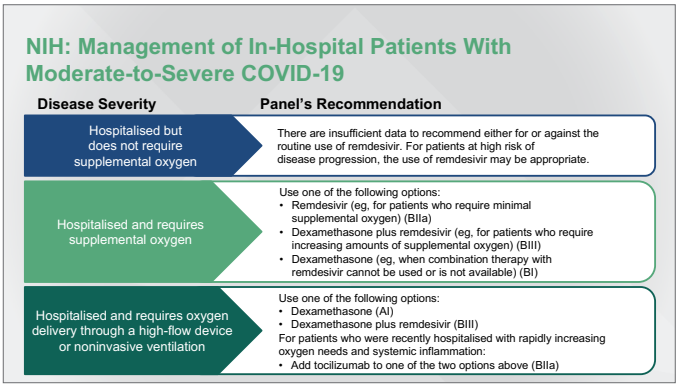
We know that these neutralising monoclonal antibodies are reducing viral replication, as intended. The location of replication is mostly in the nasal cavity, and that's where several studies have been able to demonstrate that the kinetic decline of the virus load is accelerated if you provide patients with these neutralising monoclonal antibodies.



Reference(s): Cohen MS et al. *JAMA*. 2021. Jun 3. doi:10.1001/jama.2021.8828. Online ahead of print.

Of course, in the end, we really want to see clinical data. A recent phase 3 trial demonstrated that even in people that have been exposed to the virus but had still not developed symptoms, one of these neutralising monoclonal antibodies was markedly able to reduce the risk to progress to COVID-19 compared to those who received placebo. This is very useful, in particular, in people who are unable or did not have access to vaccines—in this setting, people living in skilled nursing homes or assisted living.

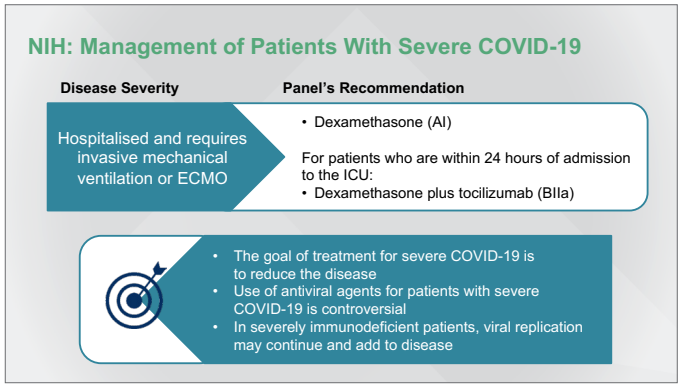
The neutralising monoclonal antibody, although it reduced the risk of disease, did not totally prevent it. But, it really gives a proof of concept that application of neutralising monoclonal antibody very early on is clinically effective.



Reference(s): National Institutes of Health. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/management/therapeutic-management/. Accessed 2 July 2021.

Once patients come into the hospital, the treatment paradigm shifts. In people who are hospitalised but not requiring supplementary oxygen, there is a big debate of what medication is indicated for them. Conversely, once patients start to become in need of supplementary oxygen, remdesivir and possibly in combination with dexamethasone are the cornerstone of treatment. In some clinics, they do not use an antiviral and totally focus on dexamethasone.

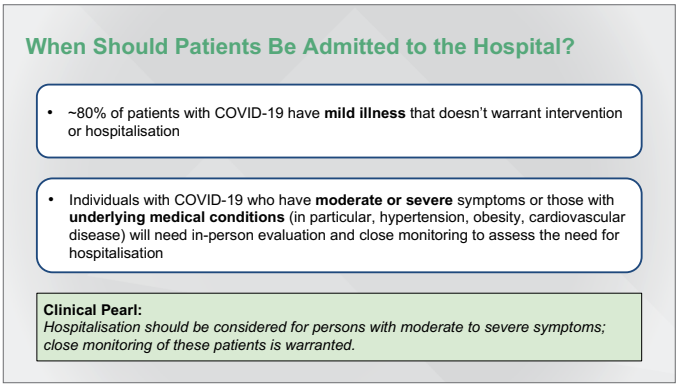
When we see even more need of supplementary oxygen—so, people who are receiving oxygen by high-flow nasal cannula or noninvasive ventilation—dexamethasone becomes more and more the key focus. Of course, the goal of treatment in this phase of the disease is two-fold. The one is to reduce the chance of further progression to severe COVID-19 but also to accelerate recovery and therefore discharge of patients. It's really important to emphasise that in this stage of the disease—compared to mild disease—the anatomic compartment of viral replication resides in the pulmonary and probably also the vascular compartment, whereas the nasal compartment does not contribute to disease anymore. Therefore, if you want to monitor viral replication, you should do that for the lower respiratory tract, as opposed to from the nose.



Abbreviation(s): ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit.
Reference(s): National Institutes of Health. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/management/therapeutic-management/. Accessed 2 July 2021.

In patients with severe COVID-19, we are now exclusively focusing on providing an immunomodulatory agent—for example, dexamethasone. There is also growing evidence, in particular, for people who are progressing very quickly that it is of clinical benefit to combine dexamethasone with tocilizumab. Of course, the goal of treatments for severe COVID-19 is to reduce the disease intensity. Use of antiviral agents for patients with severe COVID-19 is controversial. It appears that, for most patients, the immunomodulatory overreaction is the main culprit causing disease, and therefore use of these immunomodulatory agents is the key.

However, in severely immune deficient patients, viral replications may continue even in severe COVID-19 and add to disease burden. Therefore, if there is microbiological evidence of ongoing robust viral replication in the lung tissue, some clinicians may use remdesivir in patients with also severe COVID-19.



Reference(s): National Institutes of Health. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/management/therapeutic-management/. Accessed 2 July 2021.
Wang C et al. *Sig Transduct Target Ther.* 2021;6:114. https://doi.org/10.1038/s41392-021-00527-1.
Centers for Disease Control and Prevention. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). 2021. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. Accessed 18 June 2021.
Centers for Disease Control and Prevention. Coronavirus self-checker. 2021. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/coronavirus-self-checker.html. Accessed 18 June 2021.

So, in summary, which patients should be treated with medication, and when should they be treated with which medications? Again, in people with mild COVID-19 and those who have been exposed to the virus but still have not developed symptoms but who are at high risk of disease progression, serious considerations should be made to use one of the fusion inhibitors. Once people are hospitalised with moderate COVID-19 typical pneumonia, remdesivir is the standard in many clinics. For patients with severe COVID-19, focus of treatment is no longer antivirals but immune modulatory agents—except for those who are severely immune deficient, where antivirals may still be of use.

Let me end up with a public health note. As you know, most people with COVID-19 only develop mild symptoms and never progress to hospitalisation. On the other hand, it is sometimes difficult to identify those who are actually progressing to COVID-19 pneumonia. But, as early as possible after people develop COVID pneumonia, they should be started on an antiviral. And, it is therefore upon us to try to do our utmost to educate the population to understand that if you start to have symptoms of pneumonia, you need to seek medical care.

I'm now happy to introduce Dr. Jason Goldman from the Swedish Medical Center in Seattle, Washington, who will share insights on common situations and challenges. Thank you.

High-Risk Patient Presenting With Mild COVID-19 Infection

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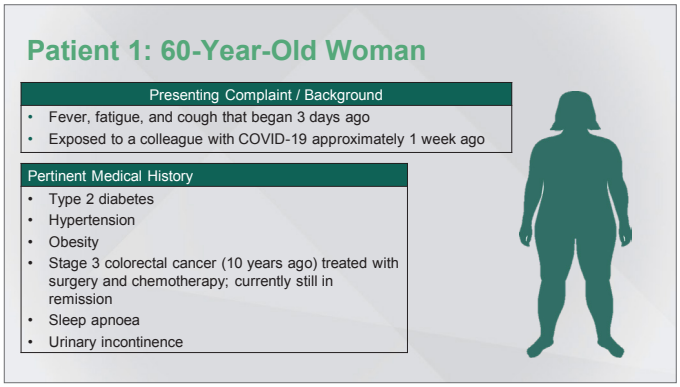
Seattle, Washington



Jason D. Goldman, MD, MPH: Hi, my name's Jason Goldman. I'm an infectious disease clinician and researcher in Seattle, Washington. I practice at Swedish Medical Center, and I have an academic affiliate appointment at University of Washington. My colleague, Dr Jens Lundgren, has reviewed some of the latest research on COVID-19 infection and management.

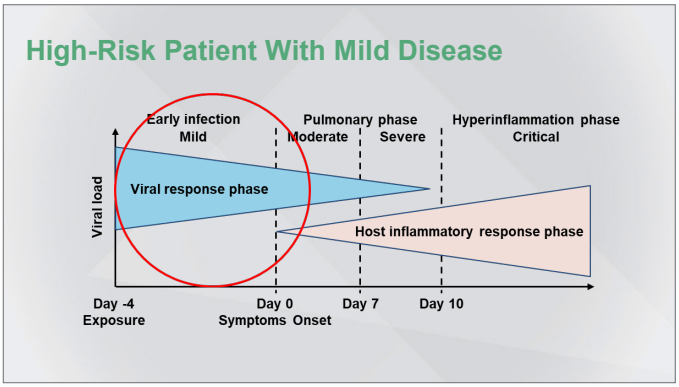
In the next four episodes, we'll explore the implication of these data in specific patient scenarios. We'll consider the trajectory of disease for each patient, and whether or not we can change it with interventions, including disease management strategies.

In this first episode, we'll focus on a high-risk patient with early infection.

Patient 1 is a 60-year-old woman who presents with fever, fatigue, and cough that began 3 days ago. She was exposed to a colleague at work with COVID-19 approximately 1 week ago.

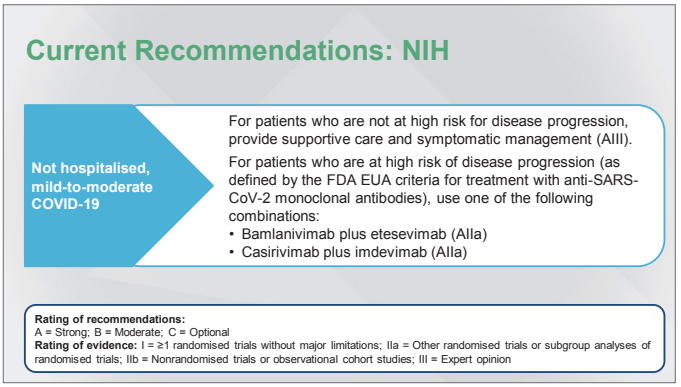
Her past medical history includes type 2 diabetes, hypertension, obesity, and she has a history of Stage 3 colorectal cancer 10 years ago for which she received surgery followed by chemotherapy and is now in remission. She also has sleep apnoea and urinary incontinence.

When she presents to the emergency room, she has a nasal swab, which is positive for SARS-CoV-2 by RT-PCR. Her vital signs are 38.3° for the temperature, blood pressure is 153/95, pulse is 81, and respiratory rate is 20. She's saturating 96% on room air, and her chest x-ray shows no evidence of COVID-19 pneumonia. She had laboratory work-up to include chemistry, CRP, procalcitonin, and a CBC with differential—all of which are within normal limits.



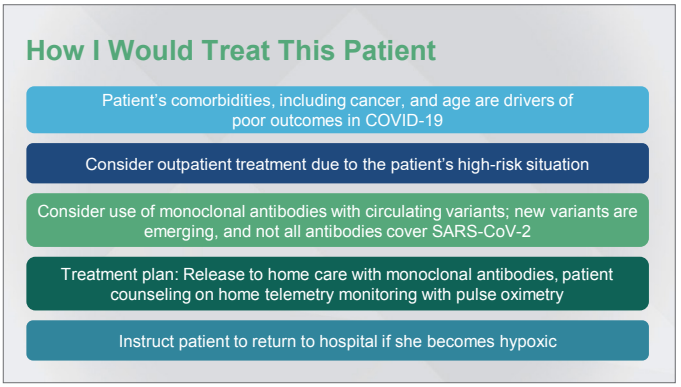
Reference(s): Siddiqi HK and Mehra MR. *J Heart Lung Transplant*. 2020;39:405-407. doi:10.1016/j.healun.2020.03.012.
Gandhi RT et al. *N Engl J Med*. 2020;383:1757-1766. doi:10.1056/NEJMcp2009249.

COVID-19 is a bimodal disease process that starts with a viral response phase early in the disease course, characterised by typical symptoms that are nonspecific to viral disease, and is later followed by progression of respiratory illness and hyperinflammation that might affect other organs as well. This patient is at high risk for progression to these more severe forms of COVID but is currently early in the disease when an antiviral therapy might be efficacious.



Abbreviation(s): FDA EUA: Food and Drug Administration Emergency Use Authorization.
Reference(s): National Institutes of Health. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/. Accessed 28 June 2021.

As we see from the NIH guidelines, this is the key target population for monoclonal antibody treatments. There's a number of available monoclonal antibodies at this time, including bam[lanivumab]/ete[sevimab] and cas[irivimab]/imdev[imab], both of which are combination monoclonal antibody products which can be used to halt disease progression and prevent further medical visits at the ER, hospitalisation, or death.



Reference(s): Personal communication: Jason D. Goldman, MD, MPH.

Given this patient's high-risk comorbidities, including the history of cancer, diabetes, and hypertension, I'm going to refer her for an outpatient treatment with a monoclonal antibody infusion. We're going to have to consider the circulating variants in the region where this patient's presenting to care as we select the monoclonal antibody. Not all antibodies are going to be covering all SARS-CoV-2 variants, and this is a rapidly changing area where new variants are emergent.

After referral for a monoclonal antibody, I'll counsel the patient on how to monitor herself at home. In certain circumstances, I might prescribe a home oxygen saturation monitor where a patient can self-monitor the oxygen, and she'll be instructed to return to the hospital if she develops hypoxia or she develops severe dyspnoea that becomes debilitating.

So, in summary, we have a patient who has comorbidities that might suggest progression to more severe forms of COVID pneumonia but currently has mild infection in the earliest stages of the disease. This is where a monoclonal antibody therapy might be helpful to prevent progression, and we'll do further monitoring in the outpatient setting. Thank you, and we'll see you next episode.

Patient With COVID-19 Experiencing Worsening Symptoms in Week 2

Jason D. Goldman, MD, MPH
Swedish Medical Center
University of Washington
Seattle, Washington

Patient 2: 36-Year-Old Man

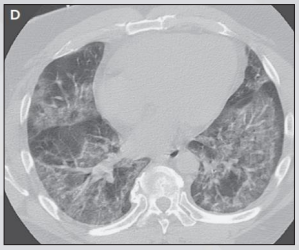
Presenting Complaint / Background

- Fatigue, fever, cough, and dyspnea
- Symptom onset 10 days ago; positive PCR same day
- Initial onset of low-grade fever, fatigue, and cough has progressed over the last few days
- Currently experiencing episodes of chest pressure

Pertinent Medical History

- Surgical repair of torn meniscus at age 28
- Otherwise healthy and active; patient plays basketball, softball, and is a marathon runner

Bilateral Ground Glass Opacification Typical of COVID-19 Pneumonia



Note: CT image shown is an example of bilateral ground glass opacification occurring ~10 days after symptom onset but is not from the patient discussed.

Abbreviation(s): CT: computed tomography.
Reference(s): Bhatraju PK et al. *N Engl J Med*. 2020;382:2012-2022.

Jason D. Goldman, MD, MPH: Hello, everyone. My name's Jason Goldman. I'm an infectious disease specialist in Seattle, Washington, and we're going to do an episode today of a patient who presents with worsening symptoms of COVID-19 pneumonia in the second week of infection.

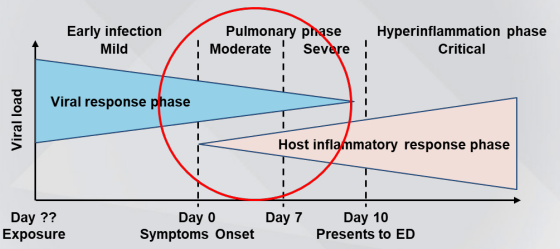
Patient 2 is a 36-year-old man who presents to the emergency department with fatigue, fever, cough, and dyspnoea. Symptoms first onset approximately 10 days ago when he was PCR positive in an outpatient testing centre. He initially had an onset of a low-grade fever, fatigue, and cough, and the fatigue, cough, and dyspnoea progressed over the last few days. He is experiencing episodes of chest pressure as well.

On past medical history, he had a surgical repair of a torn meniscus at age 28. Otherwise, he's active and healthy and plays sports, such as basketball and softball.

In the emergency room, the patient has a temperature of 38.6°, blood pressure of 140/90, pulse rate of 95 beats per minute, and a respiratory rate of 24 breaths per minute. SvO2 monitor shows that he's hypoxic, with an oxygen saturation of 91% on room air. His laboratory work-up shows severe inflammation with an elevated CRP approximately 10 times the upper limit of normal, and lymphopenia with his total white blood cell count of 3.0. Chemistries and procalcitonin are within normal limits.

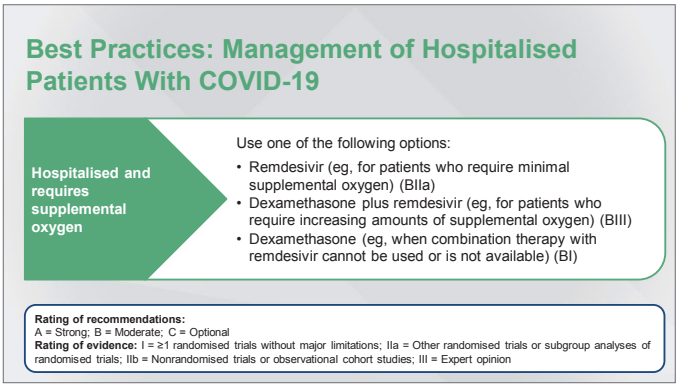
A chest CT shows evidence of severe COVID pneumonia with multifocal ground-glass opacities affecting all lobes of the lung.

Patient With Worsening COVID-19 Symptoms



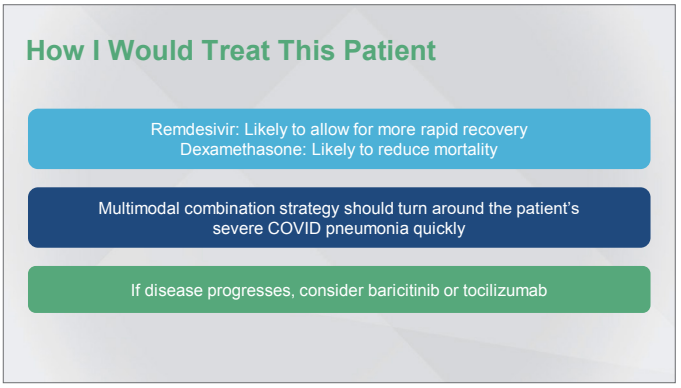
Abbreviation(s): ED: emergency department.
Reference(s): Siddiqi HK and Mehra MR. *J Heart Lung Transplant*. 2020;39:405-407. doi:10.1016/j.healun.2020.03.012.
Gandhi RT et al. *N Engl J Med*. 2020;383:1757-1766. doi:10.1056/NEJMcp2009249.

This is a patient who was previously healthy but has developed severe COVID pneumonia approximately 10 days into the illness. In the bimodal COVID-19 disease process, he's traversed beyond the viral response phase, and he's entered into the pulmonary phase, or the host inflammatory response phase.



Reference(s): National Institutes of Health. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/management/therapeutic-management/. Accessed 2 July 2021.

At this point in the illness, he needs hospitalisation and will receive treatments in the hospital, such as remdesivir and dexamethasone. In addition to antiviral treatment directed at the virus, and corticosteroid therapy directed at the host inflammatory response phase, we'll also do a multimodal treatment strategy, including anticoagulation and supportive care.



Reference(s): Personal communication: Jason D. Goldman, MD, MPH.

What we know from clinical trials is remdesivir is likely to allow for more rapid recovery compared to patients not receiving remdesivir, and dexamethasone is likely to reduce mortality. Hopefully this multimodal combination strategy will quickly turn around the patient's severe COVID pneumonia and return him to health. However, if disease progresses, there might be other options available such as baricitinib or tocilizumab if the hyperinflammation progresses.

So, to summarise, this was a previously healthy patient who developed severe COVID pneumonia approximately 10 days into the disease course. He was treated in the hospital with remdesivir and dexamethasone.

Patient With COVID-19 Infection After Two Doses of Vaccine

Jason D. Goldman, MD, MPH
Swedish Medical Center
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Patient 3: 53-Year-Old Man

Presenting Complaint / Background

- Low-grade fever, fatigue, and cough
- Onset of symptoms 3 days ago
- Positive RT-PCR 3 days ago
- Received second dose of mRNA vaccine 3 weeks ago
- Exposure to family member with SARS-CoV-2 infection

Pertinent Medical History

- Hypertension; type 2 diabetes; obesity (BMI = 32)
- Cholecystectomy at age 45
- Otherwise healthy

Abbreviation(s): BMI: body mass index; RT-PCR: reverse transcription polymerase chain reaction.

Jason D. Goldman, MD, MPH: Hello, my name's Jason Goldman. I'm an infectious disease specialist in Seattle, Washington. For Episode 3, we'll discuss a patient with SARS-CoV-2 infection after vaccination.

Despite excellent efficacy of SARS-CoV-2 vaccines, even those who are fully vaccinated might present with COVID-19 disease. Our third case is just such a presentation.

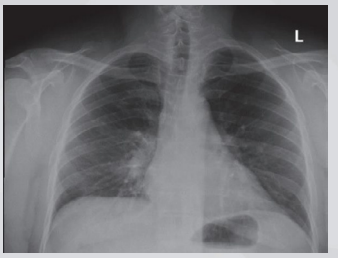
Patient 3 is a 53-year-old man who presents to the emergency room with low-grade fever, fatigue, and cough. These symptoms first onset 3 days ago, and he had a SARS-CoV-2 test by RT-PCR on that same day, which was positive. He completed a second dose of an mRNA vaccine approximately 3 weeks earlier, and he was exposed to a family member who is positive for SARS-CoV-2 by PCR.

On past medical history, this patient has hypertension, type 2 diabetes, and obesity with a BMI of 32. He also had a cholecystectomy at age 45 but is otherwise healthy.

In the emergency room, temperature was 38.3°, blood pressure was 120/70, pulse rate was 66, and respiratory rate was 20 breaths per minute. He had a nasal swab for RT-PCR of SARS-CoV-2, which was positive. On blood oxygen monitoring, he had an SvO2 of 93%; so, he was mildly hypoxic on room air, and this rapidly corrected with 2 litres of O_2 by nasal cannula.

On his laboratory evaluation, his CRP was only mildly elevated—just above the upper limit of normal of the assay. On a CBC, his white blood cell count was normal without evidence of lymphopaenia. And, chemistries and procalcitonin were within normal limits.

Mild Interstitial Infiltrates in Patient With COVID-19

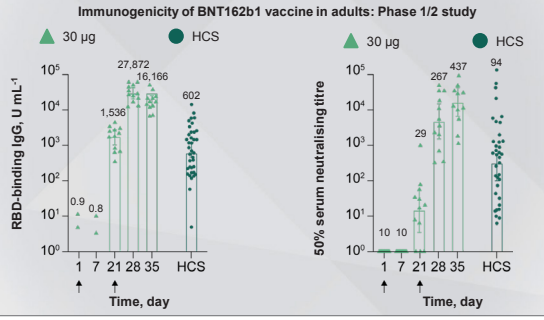


Note: Image shown is as an example only.

Reference(s): Atere M et al. *Case Rep Med*. 2020 May 24;2020:9185041. doi:10.1155/2020/9185041.

A chest x-ray showed no evidence of COVID pneumonia but perhaps some mild interstitial infiltrates.

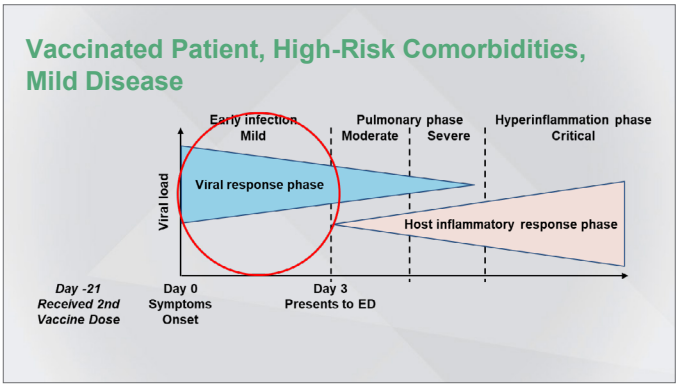
Response to COVID-19 RNA Vaccine



Abbreviation(s): HCS: human COVID-19 convalescent sera.
Reference(s): Mulligan MJ et al. *Nature*. 2020;586:589-593. doi:10.1038/s41586-020-2639-4.

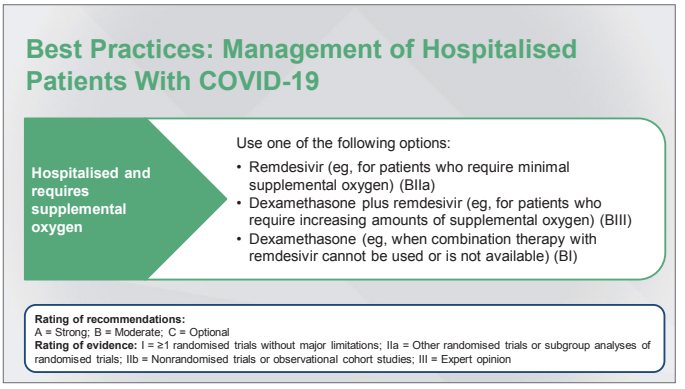
After two doses of mRNA vaccine for SARS-CoV-2, most patients will mount a very robust immune response. These can be measured with ELISA assays for the receptor-binding domain, or pseudovirus neutralisation, which were done in the phase 1/2 studies of the mRNA vaccines. All patients studied in these mounted these robust responses.

In the phase 3 trials, vaccines were shown to be approximately 95% effective at preventing SARS-CoV-2 infection that's symptomatic and nearly 100% effective at preventing severe infections. Nevertheless, as we're scaling up vaccinations for millions of people, we will see cases of vaccine breakthrough—ie, patients who develop SARS-CoV-2 infection that's symptomatic after being fully vaccinated.



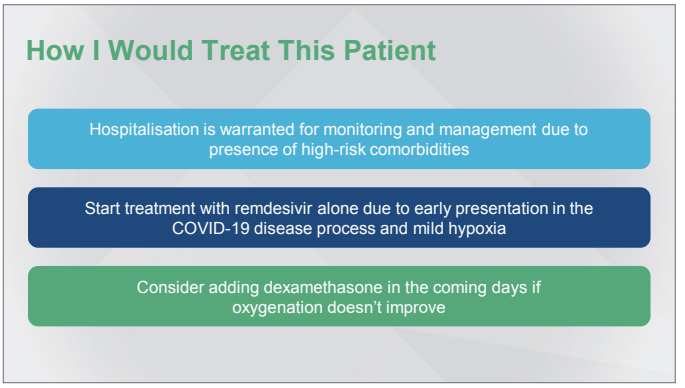
Reference(s): Siddiqi HK and Mehra MR. *J Heart Lung Transplant*. 2020;39:405-407. doi:10.1016/j.healun.2020.03.012.
Gandhi RT et al. *N Engl J Med*. 2020;383:1757-1766. doi:10.1056/NEJMcp2009249.

This patient is a vaccinated patient who has high-risk comorbidities and is presenting to the emergency room with mild disease.



Reference(s): National Institutes of Health. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/management/therapeutic-management/. Accessed 2 July 2021.

He might be someone who is on the border of being admitted to the hospital or not. He's only on a slight dose of oxygen; so, after some monitoring in the ER, he might be triaged either to outpatient management or inpatient management.



Reference(s): Personal communication: Jason D. Goldman, MD, MPH.

In this case, because of his high-risk comorbidities, I would prefer to admit him to the hospital. And, given his early presentation, only 3 days after symptoms onset, I would want to treat him with antiviral therapy. In this case, remdesivir alone would be a reasonable option due to the early presentation in the COVID-19 disease process and the mild hypoxia.

Dexamethasone is another consideration, but what we know from the RECOVERY trials, patients presenting within the first 7 days after symptoms onset didn't show any benefit from dexamethasone. Dexamethasone also might impair the beneficial host antiviral response.

Therefore, I'd want to give patients in this situation only remdesivir, and if further hypoxia develops, or after a number of more days, I'd add on dexamethasone at that time.

So, to summarise our case patient in Episode 3, this is a patient with high-risk comorbidities who presents with symptomatic COVID-19 after SARS-CoV-2 vaccination. Even though he's fully vaccinated, he's still presenting with evidence of disease. He likely has some immune response and is early in the disease course, such that he probably will do very well and has a low-risk chance of developing severe COVID-19 pneumonia.

Nevertheless, we'll treat these patients similarly to how we would treat unvaccinated patients. I'm prescribing remdesivir, given the antiviral efficacy and his presentation in the early viral response phase of the illness. Also, if he develops any more than a whiff of oxygen requirements, I'm going to also add on dexamethasone. But, I think, because of his prior vaccine status, he'll do well and will probably go home from the hospital soon.

Case Report: COVID-19 Infection in a Patient Who Is Immunocompromised

Jason D. Goldman, MD, MPH
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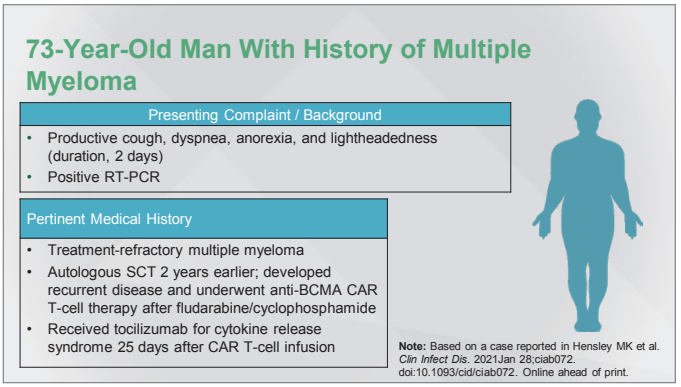


Abbreviation(s): BCMA: B-cell maturation antigen; CAR: chimeric antigen receptor; RT-PCR: reverse transcription polymerase chain reaction; SCT: stem cell transplant.
Reference(s): Hensley MK et al. *Clin Infect Dis*. 2021Jan 28;ciab072. doi:10.1093/cid/ciab072. Online ahead of print.

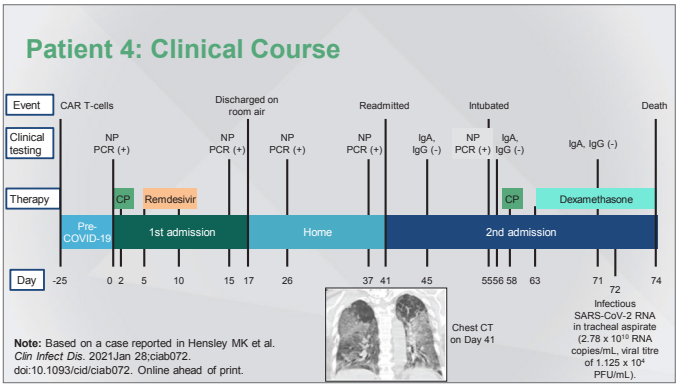
Jason D. Goldman, MD, MPH: Hello, my name's Jason Goldman. I'm an infectious disease specialist in Seattle, Washington. And, for Episode 4, we're going to discuss the case of an immunocompromised patient. This is a scenario which is becoming increasingly common, as we're seeing patients who are immunocompromised not responding to SARS-CoV-2 vaccination. These individuals may be more vulnerable to having COVID-19 disease even as the pandemic is waning for other patients who are fully vaccinated.

Patient 4 is a 73-year-old man who presents to the emergency room with 2 days of productive cough, dyspnoea, anorexia, and light-headedness. He's found to be SARS-CoV-2 positive by PCR.

Past medical history includes treatment for multiple myeloma, which has been refractory. Two years earlier, he received autologous stem cell transplant but developed recurrent disease and underwent CAR T-cell therapy after conditioning chemotherapy approximately 25 days earlier.

In the course after his CAR T-cell infusion, he developed cytokine release syndrome and received tocilizumab as treatment. He presents to the emergency room and is found to be positive for SARS-CoV-2 by PCR. His temperature was 37.1°, and his blood oxygen levels showed hypoxia with an SvO2 of 86% on room air.

Chest x-ray showed bibasilar and mid-lung zone opacities. Laboratory evaluation showed a total white blood cell count of 3.5, with an absolute lymphocyte count of 0.7, and an absolute neutrophil count of 2.6.

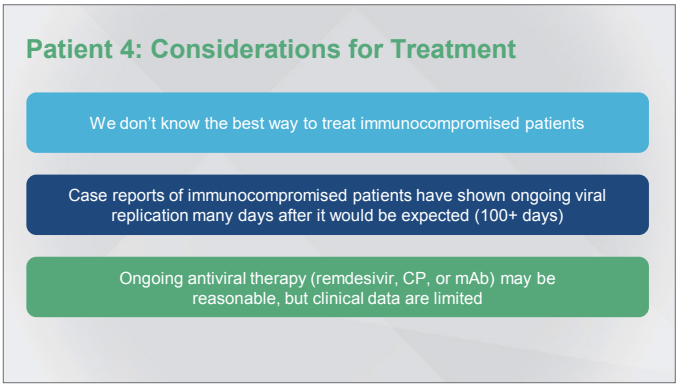


Abbreviation(s): CP: convalescent plasma; PFU: plaque-forming unit.
Reference(s): Hensley MK et al. *Clin Infect Dis*. 2021Jan 28;ciab072. doi:10.1093/cid/ciab072. Online ahead of print.

He was admitted to the hospital and received initially antiviral therapy—first with convalescent plasma on day 2 of hospitalisation and then with remdesivir on days 5 to 10 of hospitalisation. During this hospitalisation, he had escalating oxygen requirements, and he required the use of noninvasive, positive-pressure ventilation starting on day 5. He never required intubation and ultimately was discharged from the hospital on day 17, following his PCR test, with dyspnoea ongoing but not requiring supplemental oxygen.

Unfortunately, he was readmitted to the intensive care unit 41 days after the initial SARS-CoV-2 positive PCR test. At that point, he had a 1-week history of weakness and 4 days of progressively worsening dyspnoea, with a minimally productive cough and diarrhoea. A chest CT was typical for COVID pneumonia with diffuse bilateral ground-glass opacities in all lung zones.

He was subsequently intubated on day 55, received a second dose of convalescent plasma on day 58, and started on a course of dexamethasone on day 63. Ultimately, he succumbed to COVID-19 on day 74, in the context of escalating plasma SARS-CoV-2 RNA levels.



Abbreviation(s): mAb: monoclonal antibody.
Reference(s): Personal communication: Jason D. Goldman, MD, MPH.

We don't really know the correct way to treat severely immunocompromised persons. There have been a number of case reports in the literature that have shown ongoing viral replication many days after we would expect the virus to no longer be replicating. Most patients with mild disease will no longer have replicating virus approximately 10 days after symptoms onset, when they're mild-to-moderately infected and in the outpatient setting. Patients with severe disease might have replication-competent virus up to 20 days after admission.

The case report literature on immunocompromised persons, however, shows that some patients will shed replication-competent virus for up to 100 days or more. In the case we presented in Episode 4, we see a severely immunocompromised person who succumbed to infection. His treatment team utilised multiple courses of antiviral therapy, including remdesivir and convalescent plasma, and ultimately prescribed dexamethasone, but the patient succumbed to disease.

In other case reports in this emerging literature, we see other courses of repeated antiviral therapies.

We don't know the best way to treat these patients, but ongoing antiviral therapy, whether it's a small molecule inhibitor like remdesivir or an antibody therapy, such as monoclonal antibody combination, or convalescent plasma may be reasonable, but it's currently unstudied outside of these few case reports.

So, to summarise, immunocompromised persons who develop COVID-19 pneumonia are a very vulnerable population. They don't have the typical immune responses necessary to control the virus, and they might be additionally vulnerable because of a lack of response to SARS-CoV-2 vaccination. These patients will sometimes develop severe disease, and the typical course of viral shedding is not necessarily the same in these patients as those with a healthy immune system. Therefore, we need further study about the optimal treatments for immunocompromised persons. In the meantime, it may be reasonable to repeat or extend the courses of antiviral treatments.

Thank you very much for your attention as we discussed these case presentations of persons who develop SARS-CoV-2 infection and COVID-19 disease.

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