The following reports were written by second year students from the Hackensack Meridian School of Medicine at Seton Hall University for the COVID-19 Best Practices elective. These reports have been reviewed by Jeffrey R. Boscamp, MD, Vice Dean and Professor of Pediatrics. Individual reports can be found via https://library.shu.edu/COVID19_elective/BestPractice

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REMDESIVIR AS A POSSIBLE TREATMENT FOR COVID-19
By Kevin Brandecker

Summary
There have been several in vitro studies that have shown Remdesivir is effective at treating SARS-Covid, MERS-Covid, and other common community strains of coronavirus which all belong to the betacoronavirus family which also contains Covid-19. Prophylactic administration and treatment with Remdesivir in nonhuman primates infected with MERS-Covid showed prevention of lung abscess in the prophylactically treated group and reduction in clinical signs of infection, reduced viral replication in the lungs, and decreased presence and severity of lung lesions in the therapeutic group. In vitro testing has shown that Remdesivir can inhibit Covid-19 in doses achievable in nonhuman primates and clinical trials are currently underway with one case report from Washington about a patient successfully treated with Remdesivir without complications. An additional consideration with Remdesivir is at which time point it would need to be started in a patient in order to maximize effectiveness.

Details
There have been several attempts to design a drug that is effective at treating coronaviruses given the lack of current treatment options. Coronaviruses contain a unique CoV proofreading 3’-5’ exonuclease that has hampered the effectiveness of previous nucleoside analogies (1). Remdesivir, also known as GS-5734, is a prodrug that is converted by the host cell from a monophosphate to a biologically active triphosphate which can then be incorporated into viral replication and has been able to avoid the exonuclease activity (2,3). The active form is then incorporated into the growing RNA strand and is believed to cause early termination. Given its interference with viral replication, it has been hypothesized that Remdesivir plays a role early in the infection process when the virus is replicating.
its RNA (3). Initial trials of Remdesivir where performed looking at its effectiveness in treating patients infected with Ebola zaire. It was then investigated as a treatment option for SARS-CoV and MERS-CoV given the lack of available treatment options (1).

There have been several studies that have looked at the use of Remdesivir to treat SARS-CoV and MERS-CoV in both in vitro and non-human primates (NHP). Human airway epithelial (HAE) cultures have been used due to their high degree of similarity to lung tissue allowing a study to mimic the cellular complexity and physiology that is found in the lungs. It was found that both prophylactic and therapeutic dosing 1-day post-infection were associated with a reduction in viral replication to a level below the disease-causing threshold (2).

This work was then expanded to look at the effectiveness of using Remdesivir to treat rhesus macaque monkeys that were infected with MERS-CoV. Rhesus macaques were either given Remdesivir 24 hours prior to or 12 hours after infection. Over the next 6 days they underwent clinical symptoms scoring, measurement of respiratory rate, and repeat chest x-rays. With the prophylactically and therapeutic group having lower clinical scores, respiratory rates, and x-rays score which were all considered to be positive prognostic factors. On day 6 all subjects were euthanized, and lung viral loads were found to be significantly lower in the therapeutic group when compared to the control. Necropsy was then performed with gross and microscopic examination of lung tissue which showed that prophylactic administration resulted in essentially normal lung tissue without any sign of infection. In the therapeutic group, it was found that 2 had no sign of infection, 3 had minimal to moderate interstitial pneumonia with less severe lesions and were not as widely distributed as compared to the control group. One did have findings similar to the control group.

SARS-CoV and MERS-CoV are classified as betacoronavirus which also contains Covid-19 and several other Bat-Cov. It was hypothesized that Remdesivir may be effective in treating Covid-19 given this previous research. In vitro studies have been performed showing an EC50 value of Remdesivir against Covid-19 in Vero E6 cell to be 1.76 μM which is suggestive that Remdesivir will be able to reach appropriate concentration in nonhuman primates (4).

There is one published case report discussing the use of Remdesivir to treat Covid-19 in humans. The patient had traveled to Wuhan, China and upon returning to the US developed a subjective fever and cough. Given his symptoms and travel history, he was screened for and found to be positive for Covid-19. He was hospitalized on day 4 of his illness due to fatigue and on day 5 was found to have left lower lobe pneumonia. On day 6 he was found to have bilateral infiltrates suggestive of atypical pneumonia and was hypoxic in the low 90’s on room air and was started on 2 L oxygen nasal cannula. Given worsening of the clinical pictures on day 7, he was started on Remdesivir that night. The following day the patient no longer needed supplemental oxygen and was statting at 94-96 % on room air. His chest x-rays had improved and no longer showed bilateral infiltrates. Nasopharyngeal and oropharyngeal specimens obtained on illness days 11 and 12 showed a trend toward decreasing levels of virus, but as of January 30, 2020 the patient was still hospitalized with only a dry cough that was improving (5).

There are currently several clinical trials being performed all over the world to look at the effectiveness of Remdesivir in varying severity of patient populations. An additional question that will have to followed as the trail data comes out is, what is the time for when treatment need to be initiated. Many paper discus that given Remdesivir method of action it would likely need to be started early in the clinical course to have the most effect, similar to the use of Tamiflu in the treatment of Influenza.

References


What PPE Should Be Worn While Transporting Patients with COVID-19?

By Katherine Veltrici

Guidelines for Transportation Within a Healthcare Facility:

- **Patients**
  - Patients should only be transported within the hospital for medically essential reasons, such as going to radiology.
  - Patients should wear a facemask and be covered in a clean sheet.

- **Healthcare Workers**
  - If assisting patient, for example helping them into a wheelchair or gurney, healthcare workers should wear gloves, a gown, goggles and respiratory protection.
  - If transporting without assisting the patient, healthcare workers should use a facemask. Additional PPE is only required if the transporter anticipates providing medical assistance to the patient during the transport.

Guidelines for EMS

- Family members or other close contacts of the patient should not ride in the ambulance.
- When possible, use vehicles with isolated driver and patient compartments.
  - If the driver participates in patient care, he or she should remove all PPE and perform hand hygiene before entering the driver’s compartment.
  - Limit the number of providers in the patient compartment.
- Patients should wear facemasks for source control. Facemasks can be placed over a nasal cannula, or an oxygen mask can be used if clinically indicated.
- EMS clinicians who directly care for the patient with known or suspected COVID-19 should wear the following PPE:
  - N-95 or higher-level respirator
  - Eye protection
  - Single pair of disposable gloves
  - Gown
- Follow cleaning protocols for the vehicle and equipment after the patient is transported.

References:

What is the Mortality of Covid-19 patients on Ventilators?

By Helen Pozdniakova

Summary of Findings
Once a Covid-19 patient is placed in an ICU and requires invasive mechanical ventilation, the chance for mortality increases substantially.

Evidence to Date
Data about Covid-19 mortality has been readily coming in from all over the world and is of special interest to critical care teams. It would be beneficial to know if certain variables predispose a patient to increased mortality compared to other patients. This review is focused on mortality associated with ventilator use in hospitalized Covid-19 patients.

An estimate from The Lancet Infectious disease estimates an overall case fatality ratio from Covid-19 in China of 1.38%. [1] Furthermore, patients who become hospitalized with Covid-19 have a mortality rate from 1.4 – 11%. [2][3][4] Of those patients hospitalized, 5 - 26% will likely need to be admitted to the ICU, echoing similar data from Italy that reported 16% of their hospitalized patients required ICU admission. [8]

Once a patient is in the ICU, their outcome changes dramatically. 42-75% of these patients required invasive ventilation with data reflecting a mortality rate of 50-67%. [5][6][7][8] One retrospective study demonstrated that ICU patients who did not survive were more likely to receive mechanical ventilation than patients who did survive (94% vs 35% respectively). [5] The mean duration of ICU stay was around 1-2 weeks, with discharge from the ICU only ranging from 9.5% to 21%. %. [5][6][7][8]

Limitations of these studies are important to recognize. Many acknowledge that their patients continued to remain in the ICU after their study’s end date, leaving their outcome unknown. Additionally, because treatment is not consistent between sites, the implication of these experimental drugs on long term outcome is still to be determined.

References:
Is there a difference in Covid-19 mortality due to age or biological sex?

By Helen Pozdniakova

Summary

There is an association with increased age and increased mortality from Covid-19. Differences in rates of mortality due to biological sex are yet to be determined but data from MERS suggests a male predilection.

Evidence to Date

Data about Covid-19 mortality has been readily coming in from all over the world and is of special interest to critical care teams. It would be beneficial to know if certain variables predispose a patient to increased mortality compared to other patients. This review is focused on mortality associated with gender or age in Covid-19 patients.

A recent CDC report of 7,000+ Covid-19 cases in the US showed that the percentage of cases that resulted in an ICU admission were higher in older people and in those with at least one underlying health condition. We know from many studies that there is a high mortality in older Covid-19 patients who are in the ICU. One study showed a 62% mortality in those over 65 compared to a 37% mortality in those under 65.[6] In the US, 94% of Covid-19 deaths were in patients with at least one underlying medical condition, something that is more common as we age. A similar finding was reported by the Chinese CDC who demonstrated a case fatality ratio that scales with age: from 0.2% for people 11-19 years old to 14.6% for people over 80. [10] However, it is important to acknowledge that even for young patients (20-29 years old), the mortality rate of Covid-19 is 33x higher than that of seasonal influenza.[10]

The impact of biological sex on Covid-19 susceptibility still needs more research. The reason this is a question is because a relative of Covid-19, MERS, is thought to have shown favoritism for men. Likewise, we know that the binding site for Covid-19, ACE2, has high mRNA expression in the testis.[14] Currently, we do not know if being male has an impact in the pathogenicity or severity of Covid-19. The studies I looked at regarding ICU mortality in Covid-19 patients all reported a patient pool of over 52% male but it is unknown if this is statically significant. It is worth noting that the highest % of male patients enrolled were in two studies that included ICU patients only (63% and 67% male).

Comparing Covid-19 to MERS may be the best starting point. In studying MERS, many have cited a male predilection for infectivity. Epidemiology showed a majority of MERS patients are male and comprised a higher % of those who died.[13] In a study from South Korea where 59% of the cases were men, being male seemed to increase the odds of death, but the relationship was not significant (odds ratio of 2.85, p value 0.052). [12] A similar study in the Middle East found MERS infection had a male to female ratio of 2.03. Interestingly, both sexes exhibited similar symptomatology on presentation.[11]

Still, more information on biological sex and Covid-19 is needed at this time.

References


How Should Resources Be Allocated in the Covid-19 Pandemic?
By Helen Pozdniakova

Contingency planning must be started early in the face of a possible Covid-19 surge. Though our country is already experiencing shortages of PPE and various medications, the major concern for the future is the availability of mechanical ventilators. Based on data from Italy, we can expect 10–25% of hospitalized Covid-19 patients to require ventilation. Nationally, we currently have around 62,000 full functioning ventilators with 98,000 basic ventilators. [2] We know that in Covid-19 respiratory failure, that a ventilator is a lifesaving therapy and if it is needed, it must be started right away. The real question is: If we had a shortage, how can we decide who gets this life saving treatment?

We can look to other guidelines for comparison. Professional society guidelines often exclude patients with “severe” conditions from ICU care, citing poor long-term prognosis or functional status even with treatment. [3] The kidney transplant list uses a “first-come, first-served” basis for determining eligibility given that patients can still survive without this resource. When looking at recommendations from several sources, it is clear that neither of these criteria are good enough for the Covid-19 pandemic - we need a new framework.

In the literature I reviewed, there are some common tenants of a good triage system for fair allocation of scarce lifesaving resources in the event of a Covid-19 surge. They are:

1. **Discuss these issues with the patients before they deteriorate**
   a. Clinicians should proactively engage discussions with patients and their families regarding their end-of-life wishes
   b. One study suggested clinicians should frame ventilation as a time limited therapeutic trial, not an unlimited promise, to appropriately set expectations [3]

2. **Maximize benefits**
   a. All authors prioritize saving the most amount of people, and the people with the most time left to live.
      i. A core tenant is that all people should be able to enjoy all the phases of life, ranging from childhood to old age.
   b. All authors prioritize saving healthcare workers/first responders so they can continue to save others

3. **Allocate based on some type of prognosis**
   a. Do not use a first-come, first-served system
      i. Do not exclude categories of patients just because they are labeled with a certain disease that is associated with poor functional status – do it on a case by case basis [3]
   b. Patients should not feel as if they are cut out completely from getting treatment based on some kind of exclusion criteria. We know the numbers of ventilators will change and some patients may
become eligible for treatment later on. This kind of system gives patients hope.

c. One study recommends allocating by assigning all patients to a priority score based on several factors (likelihood to surviving to hospital discharge, likelihood of achieving longer term survival, objective measures of illness severity etc.) [3]

4. **Be ready for dynamic changes**
   a. The quantity of ventilators will change in ways we cannot predict, and we must be ready for that

5. **The use of a triage team**
   a. A triage team is vitally important to this scenario if there needs to be a decision made about reallocating resources. A triage team makes decisions separately from the healthcare team and is not involved in the care of the patient. This allows the healthcare team to continue being an advocate for the patient while also not placing the burden on them if the patient’s care must be withdrawn. [2]

6. **If withdrawing ventilation, use a separate team, and palliative care is imperative** [2]
   a. A team can be assigned to delegate the task of withdrawing ventilation and communicating with the family members as to not place the burden on the attending physician.
   b. All authors agree that a palliative care team is vital in this situation

7. **Criteria for ventilation should apply the same principles for Covid-19 patients and non-Covid-19 patients.** [1]

References


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**Lung Ultrasound in Covid-19 Patients**
*By Eric Stanton*

**Summary**

Lung ultrasound is emerging as a quick way to triage and assess Covid-19 patients while reducing exposures to healthcare workers. Vertical artifact (B lines) seems to be the main finding especially earlier in the course of the disease. Its use is currently limited by lack of data and inability to visualize deeper pathologies. Despite these shortcomings, hospitals should begin familiarizing themselves with lung ultrasound use in Covid-19 patients in the event that CT scans fail to meet the needs of healthcare workers.

**Why is it important to use?**

CT scans are currently an important tool in the diagnosis and evaluation of Covid-19 patients. However, due to the danger of spreading to healthcare workers and contamination of CT scanners, lung ultrasound is beginning to look like a more attractive imaging alternative. Using lung ultrasound has the potential to reduce the number of healthcare workers exposed to Covid-19 patients due to the ability to be performed at the bedside, provide an imaging alternative when ionizing radiation cannot be used, and provide a potential use for triage or monitoring of lung function that is quicker than CT.

**What are the findings?**

The findings on lung ultrasound vary depending on the severity and course of the disease. A study by the Chinese Critical Care Ultrasonography Group summarized common findings as:¹

1. thickening of the pleura, (which correlate with pleural thickening on CT)
2. B lines that can either be focal, multifocal, or confluent (which correlate with ground glass opacities on CT).
3. Small consolidations (which correlate to subpleural consolidations on CT).
4. Trans lobar consolidations (which correlate to trans lobar consolidations on CT)

Vertical, bilateral artifact (B lines) are usually observed first earlier in the course of the pneumonia with consolidations occurring later in more advanced disease.² Ultrasound findings are most commonly observed in the posterior lung fields with B lines seeming to be the most common pathology observed. One study found B lines in 91 lung areas out of the 240 lung areas imaged. These B lines also tended to be fused when
compared to the findings in patients with cardiogenic pulmonary edema which can help distinguish between these two diseases.\(^3\)

Despite the promise in these findings, lung ultrasound has the drawback of only being able to see pathology that extends to the periphery of the lungs. With this in mind, the question arises of: in what settings should lung ultrasound be used? One study suggests that due to the lack of data and inability to see deeper pathologies, that lung ultrasound should not replace CT and should only be used as an adjunct.\(^3\) This differs from other studies where the recommendations range from use in early screening/triage, to serial imaging to assess more critically ill patients.\(^4\) There also appears to be application in pregnant patients where the use of ionizing radiation is contraindicated.\(^5\)

**How to use**

There appears to be no consensus on the specific type of probe to be used during the procedure. Here is a list of probes and settings used in select studies.

1. Convex array probe or linear array probe with frequencies of 1-8 MHz and 3-17 MHz respectively.\(^3\)
2. Portable convex probe with frequency of 3.5 MHz.\(^6\)
3. Convex or linear probe with linear being preferable due to increased detail.\(^2\)

Careful measures should be taken to prevent probe contamination. This includes using sterile plastic coverings and disinfection with alcohol.\(^6\) There has been variation with the number of lung areas that should be imaged. One study suggests that 12 total areas should be imaged bilaterally in the following pattern:\(^3\)

- Anterior upper and lower
- Axillary upper and lower
- Posterior upper and lower

**Bottom line**

While the current data on lung ultrasound for Covid-19 patients is limited, the growing number of cases and need for reducing exposures to healthcare workers could further the need for quicker bedside imaging. The applications could include triage for ED patients and new admits, and monitoring lung function in critically ill patients. Hospitals should consider using lung ultrasound in adjunct with CT in order to familiarize staff with the associated findings so that it can be easier to implement if the need for a replacement to CT scans arises.

**References**

Addendum to Chloroquine and hydroxychloroquine in the treatment of COVID-19
By Daniel Menza

A new preprint manuscript from China recently made publicly available found that hydroxychloroquine was effective in treating COVID-19. 62 patients were randomized to either standard care or standard care plus a 5 day course of 400mg/d of hydroxychloroquine. The hydroxychloroquine group had significantly shorter duration of fever and cough and reduced progression to severe disease. The hydroxychloroquine group also showed a greater proportion of patients with resolution of pneumonia on day 6 compared with the standard care group. While this study has a small sample size, it is larger than the previously available studies, and is randomized which some of the other studies are not. This study adds to the body of evidence showing effectiveness of hydroxychloroquine in treating COVID-19, although more studies are still needed to definitively show a benefit.

Reference

NSAIDs and COVID-19
By Daniel Menza

Evidence to Date
Currently there is no evidence that using NSAIDS in treating COVID-19 is harmful. The thinking that this was the case appears to stem from two sources. The first is the suggestion that Ibuprofen may upregulate ACE2 in the lungs, which is most likely the receptor that SARS-CoV-2 uses to enter the lungs. This is based on a single study in rats and has never been shown in humans, and it has not been established that upregulation of ACE2 in the lungs is harmful in COVID-19. The second is an article in the BMJ which mentioned 4 young healthy patients in France who had bad outcomes from COVID-19 after being treated with NSAIDs. No case series describing this was ever published and this report has not been verified. The WHO originally recommended against the use of NSAIDs in COVID-19 following these claims but has since retracted their statement. Currently their stance on NSAIDs is: “Based on currently available information, WHO does not recommend against the use of ibuprofen.”

Details
A report published 3/11/2020 hypothesized that one reason that those with diabetes and hypertension were at increased risk for COVID-19 infection and poor outcomes was because they were often treated with ACE inhibitors and ARBs, leading to higher levels of ACE2 expression [1]. ACE2 is thought to be the receptor that SARS-CoV-2 uses to enter cells, and so higher expression may give the virus more opportunities to enter cells. This hypothesis was entirely theoretical and there was no evidence presented to support it. Besides ACEI and ARBs, they also mentioned Ibuprofen being a drug that might increase expression of ACE2. This was based on a single Chinese study on rats which has not been replicated [2]. It is therefore not a sure association, and neither is the association between higher ACE2 expression and increased COVID-19 infection.

Another source of concern regarding NSAIDs and COVID-19 came from a report in the BMJ from French officials. They said that NSAIDs should not be used in managing COVID-19, and their statement seemed to stem from reports in France regarding four young patients without comorbidities that had poor outcomes from COVID-19 after being treated with NSAIDs [3]. No case studies or any other reports of this are available.

Following these reports, the WHO recommended avoiding NSAIDs in COVID-19 patients and instead using paracetamol.
However, a few days later they amended this statement and their official position now is that they “do not recommend against the use of ibuprofen.”

References
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Vitamin C, D and Zinc for COVID-19
By Daniel Menza

Evidence to Date
Currently there is no evidence for Vitamin C, D and Zinc in the treatment of COVID-19. However, these treatments have received attention due to evidence of their ability to help fight other diseases, some of which are related to COVID-19. Zinc has shown in vitro activity against many coronaviruses including SARS, creating speculation that it may be successful in fighting COVID-19. High doses of IV Vitamin C have been shown to have some effectiveness in treating severe illness like sepsis and ARDS, causing some providers to attempt using this to treat critically ill COVID-19 patients. Zinc and Vitamin C have both received attention as treatments for the common cold, which is caused by coronaviruses among other viruses. Lastly, deficiency of Vitamin D has been shown to reduce the ability to fight infection, and the fact that many American adults are Vitamin D deficient has prompted interest in using this to help treat COVID-19 patients.

Details
There have been no studies examining zinc in the treatment of COVID-19. The best evidence regarding this subject comes from in vitro studies on SARS-CoV. One study found that zinc inhibited binding of the replication and transcription complex of SARS-CoV to RNA, suggesting that it was able to inhibit the virus’ replication [1]. The relevance of these results to SARS-CoV-2 is not known, but due to the relatedness of the viruses it is possible zinc would also inhibit replication of SARS-CoV-2.

Vitamin C is currently being investigated for the treatment of COVID-19 in a randomized controlled trial in China, but the results will not be available until the fall. Current interest in the drug is mainly based off of the CITRIS-ALI trial, which was a randomized clinical trial of high dose IV vitamin C in patients with sepsis and ARDS. It did not show any effect on the primary endpoints of organ dysfunction scores and markers of inflammation, but the vitamin C group did have significantly lower 28 day mortality (29.8% vs 46.3%) [2]. The trial was small (167 patients) and so the conclusions are limited but it has sparked interest in further studies. Because many COVID-19 patients develop ARDS, Vitamin C has been used as a treatment for severely ill patients.

Zinc and Vitamin C have long been examined as a treatment for the common cold, which are caused by coronaviruses among other viruses. A Cochrane Systematic Review of using
zinc to prevent or treat the common cold was published in 2013 and found that zinc significantly reduced the duration of cold symptoms. Zinc supplementation greater than or equal to 75mg a day for the duration of the cold reduced symptoms by one day. They cautioned, however that the data was heterogeneous and the evidence was not strong. They were unable to draw a conclusion on the prophylactic effect of zinc due to insufficient data [3]. A large meta-analysis of many studies on Vitamin C found no prophylactic benefit and a minimal reduction in length of symptoms. There was a significant prophylactic effect in those subjected to extreme physical stress and cold, raising the idea that there may be true biological mechanism at work, and the authors called for more research, especially on higher doses [4]. While there is temptation to apply these results to SARS-CoV-2 because they are in the same family, there is a wide variety among the Coronavirus and caution must be taken when trying to extrapolate results.

Like Zinc and Vitamin C, there is no direct evidence regarding COVID-19 and Vitamin D, but results from prior studies have sparked interest in its possible application to this virus. Vitamin D plays an important role in the immune system, and studies have found that as many as 40% of Americans are Vitamin D deficient. A systematic review and meta-analysis from 2012 found a significantly lower rate of respiratory infections in those given Vitamin D supplements compared to placebo groups, with an odds ratio of .589 [5]. It has also been suggested that Vitamin D may be able to modulate the immune system and control the cytokine storm involved in the pathogenesis of COVID-19. Vitamin D deficiency has been associated with autoimmunity and has been shown to reduce production of inflammatory cytokines, increase production of anti-inflammatory cytokines, and shift T cell differentiation away from the Th17 phenotype to the Treg phenotype [6]. The application of these effects to COVID-19 is theoretical at this point, but there is certainly the possibility that Vitamin D could be beneficial in this disease.

References
Lopinavir for the treatment of COVID-19

By Daniel Menza

Evidence to Date

Lopinavir, usually combined with Ritonavir for pharmacokinetic reasons, has attracted attention as a possible treatment for COVID-19 since it was found to be effective against SARS and MERS. Several studies showed that Lopinavir improved clinical outcomes in patients with SARS and MERS[1]. A randomized controlled trial from China found that Lopinavir/Ritonavir was no more effective than standard of care in treating COVID-19 patients (linked below). They randomized 199 COVID-19 patients to receive standard treatment or standard treatment and Lopinavir/Ritonavir and saw no significant difference in their primary endpoints of 28-day mortality or time to clinical improvement [2]. There have been other reports of treating COVID-19 patients with Lopinavir, but since they were not placebo controlled, they are not very useful in determining its effectiveness.

References


Breastfeeding and COVID-19

By Catherine Hahn

Summary

Due to respiratory droplet transmission of COVID-19, mothers need to take proper precautions for breastfeeding. Both the CDC and the American College of Obstetricians and Gynecologists (ACOG) recommend that a mother with confirmed infection perform proper hand hygiene, clean her breast, and wear a face mask while breastfeeding her newborn until she is confirmed to no longer have the infection.1,2,3 It is currently recommended that newborns of mothers with confirmed infection should remain isolated for 14 days.4 If mother and baby are not in-room, the mother should pump in order to maintain lactation. She should follow proper hand hygiene before and after pumping, clean her breast before and after pumping, and disinfect equipment in accordance with the manufacturer’s guidelines.3

Details

In accordance with CDC and ACOG guidelines, it is recommended that mothers with confirmed or suspected infection continue to breastfeed due to the strong nutritional benefits of breast milk for newborns.1 At this time, it appears the vertical transmission of SARS-CoV-2 is unlikely and the virus is unlikely to be transmitted through breast milk. Chen et al. sampled the breast milk of first lactation of six mothers with confirmed COVID-19. All samples tested negative for the virus.5 There is a case report of a mother who was infected with SARS during the 2002 outbreak at 19 weeks gestation. Breast milk produced 130 days after symptom onset had positive antibodies to SARS-CoV, which raises the possibility of passive immunity through breast milk.6 However, because COVID-19 has confirmed respiratory droplet transmission, mothers with confirmed or suspected infection need to take proper precautions to protect their newborn, including during breastfeeding. It is currently recommended that infants born to mothers with confirmed or suspected COVID-19 should be isolated for 14 days following birth.4 Those mothers who are separated from their newborns should continue to express milk in order to sustain lactation.2 The mother should perform proper hand hygiene and clean her breast before and after pumping. After pumping, all pumping equipment should be properly disinfected in accordance with the manufacturer’s guidelines.2 A healthy caregiver should feed the expressed breast milk to the newborn. If the mother and newborn room-in, the mother should follow proper hand hygiene before and after touching the child, clean her breast

References


before and after breastfeeding, and should wear a mask while breastfeeding.\textsuperscript{1}

Due to the recommended reduced contact between mother and baby, it is important to consider the stress on mothers. This can have a great impact on early bonding and inducing lactation. The mother’s care team should provide support and treatment when necessary to promote the mother’s mental health and well-being.\textsuperscript{7}

With the emergence of the use of antiviral therapy to treat COVID-19, there is a question of whether these antivirals are present in breast milk. The combination of lopinavir/ritonavir has not been associated with teratogenicity and is found in very low amounts in breast milk. It has not been detected in breastfed infants.\textsuperscript{8} At this time, it is not known if remdesivir can be transmitted to breast milk. However, it has been used previously to treat an infant with Ebola with no adverse effects.\textsuperscript{9}

Mothers can also consider using donor breast milk during this time. However, milk banks across the globe are facing their own unique challenges. At this time, there is no evidence that coronavirus is transmitted through breast milk and any virus present would very likely be inactivated during pasteurization.\textsuperscript{10} In spite of this, there is heightened anxiety for donors and recipients alike. China has seen a decrease in both supply and demand of donor break milk as both donors and potential recipients are reluctant to go outside to hospitals and milk banks.\textsuperscript{10} There are rigorous screening procedures in place, and all donors are required to go to the hospital for in-person donation. As of March 16 in the United States, there have not been changes in either supply or demand of breast milk.\textsuperscript{10} However, it is anticipated that the United States milk banks will soon follow similar patterns to those seen in China. In the high likelihood that this will happen, there is great concern that there will be a sharp decline in donations that could be of great benefit to some of the most vulnerable in our population.

References

Delivery and Neonatal Infection Control Guidelines for Confirmed COVID-19 Pregnancies
By Catherine Hahn

Summary

COVID-19 has been associated with high rates of infectivity. This poses many challenges during delivery of mothers with confirmed COVID-19 due to the potential for transmission. In addition, while preliminary evidence suggests that vertical transmission is unlikely, it cannot be ruled out. The following procedures are essential to protect the newborn and to prevent nosocomial transmission during delivery. During delivery, all personnel should wear disposable hats and protective clothing, shoe covers, N95 masks, goggles or face shields, and two-layer gloves. Both epidural and generalized anesthesia have been proven to be safe during delivery for mothers with confirmed COVID-19. The anesthesiologist should follow airborne precautions for generalized anesthesia. The newborn should remain in isolation in the Neonatal Intensive Care Unit for at least 14 days in cases of confirmed maternal infection. Full airborne precautions should take place during aerosol-generating procedures for the newborn, including cardiopulmonary resuscitation, endotracheal intubation, non-invasive ventilation, manual ventilation prior to intubation, bronchoscopy.

Delivery Room Precautions

The following are recommended guidelines for safe delivery for confirmed or suspected COVID-19 pregnancies1:

- Whenever possible, deliveries should take place in a negative pressure isolation room. If not available, an infection isolation ward or surgery room should be used for delivery.
- There is no clear consensus regarding route of delivery with regards to infection prevention. Mode of delivery should be determined based on obstetric indications.
- The number of personnel in the delivery room should be minimized. Two to three obstetricians and midwives/nurses are recommended.
- All personnel should wear proper personal protective equipment throughout the duration of the delivery. This includes disposable hats and protective clothing, shoe covers, N95 masks, goggles or face shields, and two-layer gloves that cover the sleeves of protective clothing.
- Hands should be washed thoroughly with soap prior to donning PPE. Hands should be disinfected after delivery with alcohol or hydrogen peroxide disinfection liquid.
- Patients who are not under general anesthesia should wear surgical masks throughout the duration of the delivery.
- All surgical instruments should be labeled “COVID-19” and stored, transported, and sterilized in processes separate from other instruments.
- Biospecimens including vaginal secretions, umbilical blood, amniotic fluid, and neonatal throat swab should be collected and tested to ascertain potential vertical transmission.
- All staff who participate in deliveries of confirmed COVID-19 patients should undergo regular fever monitoring and self-assess for symptoms of infection.

Anesthesia Guidelines During Delivery

- Epidural or general anesthesia have been shown to safe methods of anesthesia during delivery of COVID-19 patients. Neither have been associated with maternal deaths, neonatal deaths, or serious neonatal asphyxia events. However, general anesthesia has the increased possibility of aerosolization, and epidural anesthesia has been associated with a higher incidence of hypotension.2
- Airborne precautions should be used during tracheal intubation.
- If the mother is in stable respiratory status, epidural anesthesia is recommended when possible in pregnant women with pneumonia secondary to COVID-19 to decrease chances of aerosolization and to prevent side effects of general anesthesia on the newborn, including respiratory compromise decreased muscle tone.
- If the mother is intubated prior to delivery due to respiratory complications from COVID-19, general endotracheal anesthesia should be used for cesarean delivery.1

Neonatal Infection Control

Following delivery, the newborn should be cleaned immediately and taken to the Neonatal Intensive Care Unit (NICU) to be closely monitored for signs of infection. Delayed cord clamping is not recommended at this time due to the uncertainty surrounding vertical transmission.3 The newborn should immediately be placed in an incubator rather than an open rescue table to prevent transmission of the virus.4

Medical masks, eye protection, long-sleeved protective suits, and gloves should be available for all personnel involved in care of the newborn.5 Proper hand hygiene should occur before and after donning PPE. During procedures that may induce aerosolization (cardiopulmonary resuscitation, endotracheal intubation, non-invasive ventilation, manual ventilation prior to intubation, bronchoscopy), airborne precautions should be followed. Personnel should wear N95 masks, eye protection, long-sleeved protective suits, and gloves.4 Procedures should take place in a well-ventilated
Pediatric Immunocompromised Patients and COVID-19

By Catherine Hahn

Summary

Immunocompromised children have been shown to have increased susceptibility to various respiratory viral pathogens. In addition, previous studies have shown that this group may be more at risk for severe infections from coronavirus. Yet, preliminary data suggests that this may not be the case for the SARS-CoV-2 pandemic. Recent data from Bergamo, Italy shows that out of 200 pediatric transplant patients, none developed pulmonary symptoms even though 3 tested positive for the virus and many more who were not tested could have been asymptomatic carriers. Still, in these early stages when there is a paucity of data available, it is important to consider this information in the context of previous coronavirus outbreaks. Successful treatment of immunosuppressed adult transplant recipients with confirmed COVID-19 has included withdrawing baseline immune-suppressing therapy and initiating high-dose corticosteroids, broad-spectrum antibiotics, and intravenous immunoglobulin. With regards to the continuation of immune-suppressing therapy, each patient must be evaluated on a case-by-case basis. If patients do not show signs of infection, it is recommended at this time that they continue with necessary chemotherapy and radiation treatments, though perhaps at increased intervals between treatments or decreased dosages if possible.

Background: What We Know from Past Outbreaks

Currently, it appears that pediatric patients generally have less severe presentations of COVID-19 infection compared to adults. However, there is limited information available that elucidates whether this includes pediatric patients who are immunocompromised. Traditionally, immunocompromised patients are thought of as a high-risk group because they are at increased risk for severe infections by viruses, including adenovirus, influenza, norovirus, respiratory syncytial virus, and rhinovirus. The concern now is whether this applies to the current COVID-19 epidemic. If so, should immunocompromised patients continue to receive immune-suppressing therapy, and how should physicians treat immunocompromised patients with confirmed COVID-19?

Given the limited amount of data available for SARS-CoV-2, it is necessary to examine how coronavirus has presented in immunocompromised children prior to this current outbreak. A large retrospective analysis compared coronavirus incidence and severity in 85 immunocompromised and 1152 non-immunocompromised children over the course of three years. Initially, it appeared that there was no statistically significant
difference in incidence or severity of coronavirus infection between non-immunocompromised or immunocompromised children. However, after adjusting for demographics and clinical variants, immunocompromised children were more likely to have severe lower respiratory tract disease, which was defined as requiring supplemental oxygen. This suggests that while immunocompromised children may not be more susceptible to acquiring coronavirus infections, they may have more severe presentations.

In the literature, there are case reports of fatalities in immunocompromised children as a result of coronavirus infection. Szczawinska-Popłonyk et al. published a case report in 2013 of a 15-month-old girl who died as a result of complications from coronavirus HKU1-related pneumonia. Prior to infection, the child had been thriving and had no history of respiratory compromise. In February 2020, Nilsson et al. published a case of fatal encephalitis due to coronavirus OC43 as confirmed with brain biopsy in a 17-month-old child who was undergoing chemotherapy treatment for acute lymphoblastic leukemia. The child initially presented with upper respiratory symptoms which later progressed to myoclonic seizures after persistent infection for a few months. Both cases illustrate the potential consequences of coronavirus infection in immunocompromised children, particularly in immunocompromised infants.

The COVID-19 Pandemic and Immunocompromised Patients

Despite previous patterns we have seen, recent data from Italy suggests that immunocompromised children are not at increased risk for COVID-19 or more severe complications from the virus. D’Antiga reports that at his liver transplant center, no pediatric transplant patients out of 200 patients developed pulmonary symptoms even though 3 patients tested positive for SARS-CoV-2. It is important to note that not all of the 200 patients were tested, and many more could have been asymptomatic carriers. The three patients who tested positive were tested due to febrile neutropenia during chemotherapy for solid tumors. They showed no other signs or symptoms and did not develop pneumonia.

A proposed mechanism is that the host innate immune response mediates lung damage in infection with COVID-19, suggesting that an immunocompromised patient’s weakened immune system may be protective with respect to coronavirus. This is consistent with an analysis of the pathogenesis of the SARS and MERS viruses. Li et al. illustrate that coronaviruses infection results in activation of the innate immune system to clear the virus, inhibit viral replication, and initiate an adaptive immune response. However, an unregulated and overactive immune response including increased cytokine production induces damage to the pulmonary interstitial arteriolar walls and decreases lung capacity. As such, D’Antiga suggests that life-saving chemotherapy and transplantation should not be delayed at this time.

Treating Immunosuppressed Patients with Confirmed COVID-19 Infection

There are four case reports of adult solid organ transplant recipients on long-term immunosuppressive therapy with symptomatic COVID-19 infection. They include two heart transplant patients from China, one kidney transplant patient from China, and one kidney transplant patient from Spain. One patient recovered after a few days of supportive therapy. Three out of four of these cases became severe. The treatment for all three of these patients included withdrawing their baseline immunosuppressive therapy. All three patients were treated with high dose corticosteroids and broad-spectrum antibiotics. Two of these patients were additionally treated with intravenous immunoglobulin and have both recovered.

At the time of publication, the remaining patient was intubated and hemodynamically stable on a treatment regimen of lopinavir/ritonavir, interferon beta, and hydroxychloroquine. These reports provide insight into COVID-19 treatment for immunosuppressed patients, and their modalities could be extrapolated to pediatric transplant patients and perhaps other pediatric patients on immune-suppressing therapy.

Guidelines for Administering Immune-Suppressing Therapy During the COVID-19 Outbreak

Due to patterns from previous viral epidemics suggesting that immunocompromised children could be more susceptible to coronavirus infection or be at increased risk of complications, it is necessary to examine whether physicians should continue to administer treatments to children that may further compromise their immune systems. Yang et al. published a series of guidelines in Pediatric Blood and Cancer that details the approach to cancer treatment in pediatric patients during the COVID-19 pandemic. This includes:

- **Pre-admission screening** – All patients, family members, and caregivers should be screened for COVID-19 symptoms. Those with fever defined as greater than 37.3°C for three days should be referred for screening, including lung CT and nucleic acid testing. Those with suspected or confirmed infection should be placed in isolation and receive appropriate treatment. Cancer therapy can be continued once patients are excluded from having COVID-19.

- **Chemotherapy** – Chemotherapy should be continued in children with no symptoms and “normal physical status” following a detailed risk assessment for chemotherapy. Consider moderate reduction of chemotherapy or increasing the intervals between chemotherapy treatments for children with stable disease.
• **Radiotherapy** – Radiotherapy can be continued as scheduled since radiotherapy has relatively less effects on the immune system compared to chemotherapy. Consider a moderate delay in treatment for children who are starting radiotherapy.

• **Surgery** – All necessary or emergency surgeries for treating cancer in patients with confirmed or suspected COVID-19 should be performed with appropriate infection prevention and control measures during the procedure, and the operating room should be thoroughly disinfected following the procedure.

• **Follow-up** – Telemedicine should take place whenever possible for non-critical outpatient visits to limit potential exposure.\(^1\)\(^2\)

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**References**


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Should We Perform Serial Tests on COVID-19 Positive Neonates to Assess for Resolution of Infection?
By Candace Pallitto

Summary
At this time, neonates are considered a high-risk group for COVID-19 infection due to their immature immune systems and lack of sufficient data about how the virus affects this group.1 While the United States does not have neonatal-specific guidelines, the Centers for Disease Control and Prevention (CDC) delineates 3 required components for their test-based strategy for discontinuation of transmission-based precautions for hospitalized individuals: 1) resolution of fever without the use of anti-pyretics, 2) respiratory symptom improvement, and 3) at least 2 negative consecutive nasopharyngeal swab specimens that are collected ≥24 hours apart.2 This test-based strategy correlates with the 2 negative consecutive upper airway (nasopharyngeal and pharyngeal swabs) collected at least 24 hours apart described by expert consensus released from China in February in regards to discharge criteria for COVID-positive neonates.3 These discharge criteria are overall more specific than the discontinuation of transmission-based precautions, but show support for serial testing in neonates for resolution of infection. Review of the literature to date does not reveal further updates to these criteria, neonatal-specific guidelines in this area from other groups, or specific testing of the efficacy of these procedures in neonates. Based on this information, it seems that serial testing COVID-19 positive neonates should be performed under the guidelines of the CDC’s test-based strategy for discontinuation of transmission-based precautions for hospitalized individuals until further evidence is released.

Evidence to Date
Due to their immature immune systems and lack of sufficient information on how the virus affects neonates, they are considered a high-risk group for COVID-19 infection.1 Currently, there does not appear to be specific guidelines in the United States in regards to discontinuation of transmission-based precautions specifically in neonates. The CDC outlines 3 required components for the test-based strategy of discontinuation of transmission-based precautions for hospitalized individuals: 1) resolution of fever without the use of anti-pyretics, 2) improvement in respiratory symptoms, 3) at least 2 negative consecutive nasopharyngeal swab specimens that are collected ≥24 hours apart and are analyzed using an FDA Emergency Use Authorized COVID-19 molecular assay for detection of COVID-19.2 While these guidelines do not specify a population other than “hospitalized individuals,” they closely correlate with expert opinion from China about perinatal and neonatal COVID-19 infection control and prevention.

An expert consensus report released in February 2020 from Wang et. al in China discusses criteria for discharge of COVID-positive neonates. These criteria are similar to the test-based strategies of the CDC’s test-based discontinuation of transmission-based precautions in terms of a patient needing 2 consecutive negative tests results collected at least 24 hours apart.3 They also specify that nasopharyngeal and pharyngeal swabs should be used for this test, but that stool specimens could also be used. While there has been recent evidence that fecal specimens are comparable to nasopharyngeal specimens for RT-PCR, the CDC at this time specifies obtaining nasopharyngeal samples.2,3,4 Furthermore, the expert opinion from China about discharge of COVID-positive neonates further categorizes the criteria based on severity of infection. This increased categorization are could be due to the fact that these criteria are for discharge of a neonate and not only for discontinuation of transmission-based protocols. The chart below summarizes the criteria for discharge of a COVID-positive neonate outlined by the Expert Group on Prevention and Control of 2019-nCoV Infection in the Perinatal Period:3

<table>
<thead>
<tr>
<th>Asymptomatic</th>
<th>Mild</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing</td>
<td>2 negative consecutive upper airway (nasopharyngeal and pharyngeal swabs) collected at least 24 hours apart*</td>
<td>2 negative consecutive upper airway (nasopharyngeal and pharyngeal swabs) collected at least 24 hours apart*</td>
</tr>
<tr>
<td>Temp.</td>
<td>N/A</td>
<td>Normal for more than 3 days</td>
</tr>
<tr>
<td>Symptoms</td>
<td>N/A</td>
<td>Improvement</td>
</tr>
<tr>
<td>Imaging</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*The report also writes: “Stool samples may be collected and tested every 2 days until 2 consecutive results show negative”

According to review of the literature to date, these criteria have not been updated since February and no other neonatal-specific guidelines have been described. While these guidelines are more specific to neonates, they are expert consensus and have not been specifically tested. Given the limited information about COVID-19 testing in the neonatal population and the similarities in testing recommendation between current CDC guidelines and Chinese expert consensus, it appears that serial testing COVID-19 positive neonates should be performed under the guidelines of the CDC’s test-based strategy for discontinuation of transmission-based precautions for hospitalized individuals until further evidence is released.

References
An Update on Surface, Fabric, and Aerosol Survivability of COVID-19

By Candace Pallitto

Summary

There are many questions about the survivability of COVID-19 on different surfaces, fabrics, and in the air. A report released on March 17th suggests that in a controlled environment, the virus is viable on plastic and stainless steel up to 3 days, copper up to 4 hours, and cardboard up to 24 hours. The results for these surfaces were similar to that of SARS with the largest difference being on cardboard. This study also showed that the virus is able to survive in aerosols for up to 3 hours. While the virus is believed to be transmitted through respiratory droplets and contact, data regarding the potential aerosol nature of the disease without aerosol generating procedures is inconclusive at this time. Furthermore, there is not specific information about the viability of COVID-19 on fabrics, such as cotton. However, previous research about SARS indicates that the infectivity of the virus is decreased when in contact with porous surfaces, such as a cotton hospital gown. Another important feature of SARS is that it survives longer under dry conditions compared to other human coronaviruses. Once this information is known about COVID-19 specifically, it could provide better understanding how the disease is spread through fomites. Overall, more information is needed about surface, fabric, and aerosol survivability of COVID-19 specifically, but the data at this point shows similarities to SARS in terms of surface and aerosol survivability. It is important to adhere to the Centers for Disease Control and Prevention (CDC) recommendations for Personal Protective Equipment for healthcare workers as well as daily cleaning of high-touch surfaces at home until more specific information is known about the surface, fabric, and aerosol survivability of COVID-19.

Surfaces

A study released in March 2020 by Doremalen et. al examined the surface and aerosol survivability of COVID-19 compared to SARS-CoV-1 (SARS) because COVID-19 is most closely related to SARS compared to other human coronaviruses. Although this study was performed in a highly controlled experimental setting, it provides more specific information about COVID-19 as and its similarities to SARS, which could be useful when trying to understand COVID-19 in other contexts. They examined aerosol, plastic, stainless steel, copper, and cardboard. Here is a summary of the results for COVID-19 as compared to SARS:1

References


• Plastic: COVID-19 was detected as viable up to 3 days after it was applied to the surface.
  o Reduction in viral titer reduced from 103.7 to 100.6 TCID50* per mL of medium in 72 hours
  o Stability of the virus was similar to SARS with viral titer reduced 103.4 to 100.7 TCID50 per mL of medium in 72 hours
• Stainless steel: Detected as viable up to 3 days
  o Reduction in viral titer reduced from 103.7 to 100.6 TCID50 per mL of medium in 48 hours
  o Similar to SARS with reduced viral titer of 103.6 to 100.6 TCID50 per mL of medium in 48 hours
• Copper: Viable is up to 4 hours
  o SARS was detected up to 8 hours
  o Similar half-lives
• Cardboard: Viable up to 24 hours
  o SARS was measured up to 8 hours

Fabrics
Current research has not revealed the viability of COVID-19 on fabrics, particularly cotton, which is found in blankets, towels, scrubs, hospital gowns, and clothing. The results from the Doremalen et al. study indicate that surface survivability of COVID-19 is similar to that of SARS. Given the similarity of COVID-19 and SARS on surfaces, it is possible that past data on SARS survivability on fabrics could be useful to understanding COVID-19 until further evidence is available. Previous research indicates that the infectivity of SARS is reduced more rapidly when the virus is placed on porous surface, such as cotton, and that this occurs in a dose-dependent fashion. A study from 2005 analyzing survivability of SARS found that at a high concentration of viral dose (105 TCID50/mL) in the droplets lost infectivity after 1 hour of being placed on a cotton gown compared to 24 hours on a disposable gown. They suggest that the droplets are absorbed more quickly on cotton, which makes it difficult for the droplets to contaminate the environment. This is compared to non-porous surfaces like the ones listed above because the droplets can exist on top of the surfaces and be easily transmitted through touch. Due to this property, the study suggests that cotton, and other porous surfaces may offer some protection against the immediate spread of small droplets.

Aerosol
The study by Doremalen et al. also examined survivability in aerosols in a highly controlled experimental setting. It found that COVID-19 could be found up to 3 hours in aerosols with a reduction in infectious titer of 103.5 to 102.7 TCID50 per liter of air and that this result was similar to SARS. One of the important features of this study is that it analyzes infectivity and not only the presence of the virus. While the virus at this time is considered to be transmitted via respiratory droplets and contact, there is conflicting evidence for airborne transmission. Airborne transmission refers to the virus existing in aerosols smaller than 5 micrometers in diameter and the concern is that these can travel further as well as persist in the air longer than droplets.

Review of the literature represents conflicting data about aerosol survivability and transmission of COVID-19 and an article in Nature posted April 2nd 2020 discusses these key findings. A couple of these studies looked for possible support for the virus being aerosolized through positive samples found on ventilation grates and air outlet fans in patient rooms. In a report from Singapore, an COVID-19 positive sample was found on an air exhaust outlet fan in a patient room, the authors told Nature that the air outlet was close enough to the patient for droplet transmission, but they write in their report that it is possible for the virus-laden droplets to be further transmitted or redirected via airflow from the fan. Another study from Nebraska that the article discusses supports airborne transmission of COVID-19 because they found positive air samples that were maintained at a distances greater than 6ft from the patient as well as that 66.7% of hallway air samples were positive. They also believe that this could be supported the fact that positive results were found on all personal air samplers worn by sampling personnel despite absence of cough by most patients while the sampler was present; however while the patient did not cough while the sampler was in the room, they did not state whether the patient had sneezed or cough at any point prior to entering the room. This would be important to know given the possibility that the virus can survive in aerosol droplets for about 3 hours. The article mentions another study that analyzed a patient who had moderate viral load in respiratory samples, but air samples from this patient were negative for RNA of COVID-19, but that they were present in environmental samples. The air samples were obtained 10cm at the level of the patient’s chin and were collected when the patients performed 4 maneuvers: normal breathing, deep breathing, speaking 1, 2 and 3 continuously, and coughing continuously all while taking a surgical mask on and off. These results indicate aerosol transmission is less likely. Overall, these studies do not look at infectivity of the COVID-19 in these samples, but simply the presence of the virus and there are many limitations including small sample sizes and that they currently are not peer reviewed. However, these results represent the most recent evidence, specifically related to COVID-19, and indicate that there is a possibility that the virus is more transmissible than
originally thought so continued evidence is needed about the infectivity of the virus from aerosols.

Conclusion

There is still much more information needed about the survivability of COVID-19 on fomites and in the air. Another possibly useful property of the virus to understand would be its response to desiccation. For instance, previous data indicates that SARS was able to survive up to 6 days on a dried surface, while other human coronaviruses, such as HCoV-229E, was only found to survive for 24 hours. Understanding this property in COVID-19 could provide insight into its transmission and further inform practices of disinfection. Furthermore, individuals at home and in healthcare settings should continue daily disinfection of high-touch surfaces as indicated by the CDC and healthcare workers should continue to apply Personal Protective Equipment according to CDC guidelines until further information is known about survivability of the virus.

References


ACE2, RAS System Modulators and COVID-19 Update

By Austin Krebs

Summary

SARS-CoV-2 enters cells through ACE2, and ACEi and ARB treatment upregulate ACE2. ARBs have been shown to be beneficial in models of acute lung injury. One study has shown that ACEi/ARB therapy is associated with decreased IL-6 and peak viral load levels, and increased CD3+ and CD8+ T cells. ACE2 has been shown to decrease IL-6 in LPS-induced lung injury. Hypokalemia is a common finding in COVID-19 patients and is thought to be due to RAS dysregulation, which can potentially be addressed with ACEi/ARBs. Further research is necessary to elucidate the effect of ACEi/ARBs in COVID-19 patients, but early evidence suggests they may be beneficial.

Evidence to Date

ACE2 is expressed in various human body tissues including lung, heart, kidney, brain, and intestines. Its primary function is to convert angiotensin II, a vasoconstrictor, to angiotensin 1-7, a vasodilator. Increased levels of angiotensin II are positively correlated with severity of acute lung injury and vascular permeability in the lungs. ARBs have been shown to downregulate the ACE-Angiotensin II axis and upregulate the ACE2-Angiotensin 1-7 axis. Based on the fact that ARBs upregulate ACE2, and despite SARS-CoV-2 using ACE2 as its entry point, ARBs might paradoxically be beneficial in COVID-19 patients.

Hypokalemia is a common finding in COVID-19 patients, and is thought to be present due to RAS dysregulation. One study showed that 61% of COVID-19 patients present with hypokalemia, primarily through urinary loss of potassium. This study suggests that the end of urinary potassium loss is a good prognostic factor for patients, signifying the end of adverse RAS effects. ACEi/ARB therapy could be beneficial in treatment of hypokalemia by preventing the downstream effects of aldosterone in the RAS.

Several pieces have been written about the potential harm or benefit of medications that affect the RAS without much more than theoretical hypotheses. One article was published after some of these pieces to highlight that no evidence currently exists to abandon ACEi or ARB therapies despite the COVID-19 pandemic.

Another study examined patients with preexisting hypertension in 42 COVID-19 patients. Of these patients, 17 were on ACEi/ARB treatment, and 25 were on therapies from different drug classes. Within the ACEi/ARB group, there was a trend towards lower IL-6 levels when compared to the non-ACEi/ARB group. This finding was not significant, potentially due to small sample size. Additionally, the absolute number of CD3+ and CD8+ T cells was significantly higher in the ACEi/ARB group, and peak viral load was significantly lower in this group.

In a mouse model, ACE2 deletion was associated with increased levels of pro-inflammatory markers, including IL-6 and TNF-α. ACE2 treatment has been shown to decrease IL-6 levels in LPS-induced models of lung injury. Additionally, TNF-α is associated with lymphopenia, which is a common presentation of COVID-19 patients. ACE2 may be a component in a unifying theory of COVID-19 pathophysiology.

Based on the currently available data, there seems to be no reason to discontinue ACEi or ARB therapy during the COVID-19 pandemic. In fact, therapy with these agents may be beneficial, although the sample size of the one study that examined these effects was small. Further studies could confirm if there is a benefit to ACEi/ARB therapy in COVID-19 patients.

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doi:10.1161/HYPERTENSIONAHA.120.15082.

Preventing COVID-19 Transmission in Operating Rooms
By Austin Krebs

Summary

Precautions against airborne transmission of COVID-19 are prudent based on persistence of the virus in aerosol. Research regarding COVID-19 is lacking, but influenza studies have demonstrated infection can be transmitted via aerosol.

Adequate time (see: CDC Air Appendix) should be permitted to allow for removal of airborne contaminants after aerosol-generating procedures are performed. Appropriately placed HEPA filters for anesthesia machines can prevent contamination of this equipment.

Evidence to Date

Aerosol generating procedures in the context of COVID-19 have come under great scrutiny. The risk of transmission through aerosol has spurred the development of new PPE and workflow policies healthcare workers. In the realm of surgery, this has led to a workflow that recommends waiting periods after intubation and extubation before the surgical team enters to perform the case. This is to allow for adequate air exchange within operating rooms to reduce the number of airborne particles. This review aims to explore these practices and their applicability to COVID-19 based on emerging data and extrapolation from other infectious agents.

A NEJM study has found that SARS-CoV-2 can persist in aerosols for up to 3 hours.1 This ability of the virus to persist in aerosol justifies the current operating room workflow decision, as current recommendations only provide N95 respirators for the anesthesiologist and circulator present for the intubation and extubation. Airborne infectious particles have been demonstrated to spread throughout a space quickly and evenly despite the configuration of the room, highlighting the need for adequate air exchange in this scenario.2

Recommendations from Kaiser Permanente encourage a 20-minute interval to achieve a 95% reduction in airborne particles. This is not a universal time recommendation as it is dependent on the number of air changes per hour (ACH) permitted by a room’s ventilation. A CDC appendix outlining the time necessary for 99% and 99.9% efficiency based on different ACH values is available.3 For example, operating rooms are rated at 20 ACH would remove airborne contaminants with 99% efficiency after 14 minutes, and with 99.9% efficiency after 21 minutes.
Studies regarding influenza have been conducted demonstrating that more than half of viral particles detected in influenza aerosol are within the respirable fraction. Further studies have demonstrated that these particles can still be infectious and facilitate transmission of influenza. Based on these influenza studies and the persistence of SARS-CoV-2 in aerosol, taking airborne precautions seems reasonable. Further research regarding the ability of aerosolized SARS-CoV-2 to cause infection is necessary at this time.

Another important perioperative concern is the use of anesthesia machines in the COVID-19 pandemic. If the airway is handled as if it were positive for COVID-19, logic would dictate that the anesthesia machine be handled similarly to prevent contamination if a patient was found to be positive after surgery. To prevent contamination, a high efficiency particulate air (HEPA) filter should be connected to the patient end of the breathing circuit, and another between the expiratory limb and the anesthetic machine. The Anesthesia Patient Safety Foundation (APSF) recommends discarding these filters and replacing them after each patient.

Based on the above literature review, taking precautions against airborne transmission of COVID-19 is reasonable. The methods highlighted may reduce the risk of nosocomial transmission to the surgical team and other patients.

References
An Update on COVID-19 and Associated Risk to the Surgical Team

By Austin Krebs

Summary

Precautions to prevent COVID-19 transmission in aerosol have focused on aerosol generation in airway management and related procedures. Aerosol is also produced during electrocautery and laparoscopic procedures. SARS-CoV-2 has been found in nasal swabs, saliva, sputum, throat swabs, blood, bile and feces. Urine and CSF retrieval has not been documented. It is extremely difficult to gauge whether an asymptomatic carrier will be brought to the OR, however there is evidence that presence of virus outside of the respiratory tract is associated with more severe disease which could be mildly reassuring despite a paucity of evidence. These precautions are based on emerging literature and extrapolation from the behavior and study of other viruses.

Evidence to Date

Given that laboratory testing for COVID-19 is not universally and readily available, a joint statement has been issued by the AANA, ASA, APSF, and AAAA. They recommend all anesthesia professionals utilize PPE appropriate for aerosol-generating procedures for all patients when working near the airway. Ideally, this equipment includes N95 masks or powered air purifying respirators (PAPR).

However, these organizations acknowledge the likelihood of shortages of these respirators and recommend extended use and/or limited reuse of N95 masks according to CDC guidelines. These guidelines recommend healthcare professionals that will be present in the room during aerosol-generating procedures on symptomatic persons wear N95 masks or PAPRs.

This begs the question as to whether surgeons are at increased risk for transmission of COVID-19 in the operating room. The American College of Surgeons has released recommendations regarding practices before, during, and after surgery to minimize risk. These include keeping surgeons and individuals not necessary for intubation outside of the room until induction and intubation are complete. They also recommend the use of smoke evacuators when electrocautery is necessary.

SAGES guidelines include considerations for laparoscopy due to aerosolization of bloodborne viruses. They recommend the use of filtration during laparoscopic procedures, as well as evacuation of pneumoperitoneum through ports prior to trocar removal, specimen extraction, conversion to open, and closure. All escaping gas should be captured with an ultrafiltration system.

COVID-19 transmission through surgical smoke has not been documented yet. However, other viruses including hepatitis B have been isolated in surgical smoke. Additionally, the transmission of HPV through surgical smoke has been documented. SARS-CoV-2 has been detected in nasal swabs, saliva, sputum, throat swabs, blood, bile, and feces. Urine and CSF evaluations have thus far been negative. Given these sites testing positive for virus, taking precautions with respect to aerosol generation in laparoscopy and electrocautery is prudent, in addition to existing precautions surrounding intubation and other airway management.

However, this leaves a notable gap in the treatment of asymptomatic carriers who are still capable of spreading virus. Aerosolized blood is the greatest risk factor in the surgical theater. One study by Chen et al found that the presence of viral RNA outside of the respiratory tract was significantly associated with increased disease severity. This does not rule out the possibility of asymptomatic patients having virus in these tissues, however there is a paucity of evidence on this topic. The University of Kansas Health System has produced PPE recommendations most recently updated on 3/25/2020 based around level of suspicion of COVID-19 infection.

Research on this topic specific to COVID-19 is lacking, but the above recommendations are based on current operating room guidelines per the CDC and SAGES, as well as extrapolation based on the presence of virus in certain tissues as well as detection and transmission of other viruses in surgical smoke in this past.

References


Use of inhaled cortical steroids in ARDS from Covid-19

By Kevin Brandecker

Summary

The current Surviving Sepsis Guidelines for the treatment of Covid-19 gives a weak recommendation with a low quality of evidence for the use of steroids in the treatment of a mechanically ventilated patient with ARDS. This differs from previous work done in MERS-CoV and SARS-CoV which showed possible harm with the use of corticosteroids. Given that the insult in ARDS is occurring in the alveoli there has been interest in the use of inhaled corticosteroids as a way to decreased inflammation while avoiding systemic effects. One study looked at the treatment of ALI/ARDS with Budesonide and found that it increased the PaO2/FiO2 ratio after treatment. And at the end of the three-day trial led to decreased levels of TNF-alpha, IL-1B, and IL-6. One limitation of this study is its short time frame (3 days), mortality and ventilator-free days were not reported, and it excluded patients with ARDS secondary to pneumonia. Another study found that the use of inhaled budesonide/formoterol led to a significant increase in the ratio of oxygen saturation to fraction of inspired oxygen which correlates with the PaO2/FiO2 ratio and to predict the mortality in patients with ARDS. One in vitro study found that Ciclesonide was able to suppress viral replication with similar efficacy to Lopinavir. This must be balanced with the fact that a recently published trial in China demonstrated no benefit in patients treated with Lopinavir-ritonavir when compared to the standard of care.

Background

There has been interest in the use of inhaled cortical steroids (ICS) to treat acute respiratory distress syndrome (ARDS) due to their decreased risk of negative systemic effects when compared to systemic glucocorticoids. ARDS is a critical illness resulting from increased permeability of the alveolar-capillary barrier due to an initial insult. This triggers the release of neutrophils, cytokines, and other inflammatory mediators into the area leading to congestion, atelectasis, and alveolar flooding which can impair gas exchange and respiratory mechanics. ICS would be able to reach the alveolar sites where they could help to mitigate the degree of inflammation on the alveolar side due to the small size of the particle.
Animal studies showed that pretreatment with Budesonide was able to decrease the degree of acute lung injury induced by the administration of Lipopolysaccharide in rats. This study was used as a justification to perform a randomized control study to look at the effect of nebulized budesonide on respiratory mechanics and oxygenation in acute lung injury (ALI) and ARDS. The study included 60 patients that were split into either nebulized budesonide or saline group 6-12 hours after the confirmation of ALI/ARDS per the Berlin criteria. The characteristic of the two groups was considered comparable without any significant difference. Patients had to be within 18-65 years of age and were excluded if there was any history of chronic obstructive pulmonary disease, restrictive respiratory insufficiency, pneumonia, increased intracranial pressure, bronchopleural fistula, the persistence of unstable postshock hemodynamics despite appropriate supportive therapy, liver cell failure (Child-Pugh Class B or C), end-stage chronic renal failure on hemodialysis, acute myocardial infarction, and neuromuscular disease. Before treatment patients cardio-respiratory and ventilator parameters were recorded. And levels of TNF-alpha, IL-1β, and IL-6 were measured. Patients were treated with 2 mg Budesonide or saline twice a day for 3 days in addition to the normal standard of care treatment1.

It was found that 1 hour after treatment there was a statistically significant increase in the PaO2/FiO2 of the Budesonide treatment group 239 ± 15 compared to the control 207 ± 12. At the end of day three TNF-α, IL-1β, and IL-6 were redrawn and found to have a statistically significant decrease compared to the control group1. One of the major limitations of this study is the short time frame of the study. Because the study was limited to 3 days, they were unable to focus on outcome like overall mortality or length of ventilator stay. Additionally, the exclusion of patients with pneumonia as a cause of ALI/ARDS limits how the study can be applied to patients with ARDS secondary to Covid-19 pneumonia.

Another study looked at the use of Aerosolized budesonide/formoterol vs. placebo twice daily for up to 5 days in patients who had one risk factor for ARDS, lung injury prediction score >3, and acute hypoxemia. The primary measurement was the change in oxygen saturation divided by the fraction of inspired oxygen (S/F) which had been shown to be a good predictor of the development of ARDS. The need for mechanical ventilation and the development of ARDS was also tracked. There was a statistically significant increase in the S/F ratio in the treatment group compared to the placebo with significant separation on day two. Previous work has shown that S/F correlates well with the PaO2/FiO2 ratio and to predict mortality in patients with ARDS. They note that while the study showed lower rates of ARDS, decreased need for mechanical ventilation, and earlier hospital discharge in the treatment group were at least partially confounded by baseline imbalances in covariates, particularly shock. But their work did agree with previous animal studies which show the use of inhaled corticosteroids decreased histological evidence of lung injury as well as improved oxygenation and respiratory mechanics.

One study published on March 12, 2020 screened several different inhaled steroids to look for candidates that would have anti-inflammatory properties and interfere with coronavirus replication at non-toxic doses. Ciclesonide was found to have potent suppression of viral growth at doses with low cytotoxicity in cells that were infected with MERS-CoV. The drug target was then found by conducting 11 consecutive MERS-Covid passages in the setting of Ciclesonide and mometasone before a mutant was created that could escape treatment with Ciclesonide. This mutant was sequenced and was found to have a mutation in non-structural protein 15. VeroE6/TMPRSS2 cells were infected with Covid-19 in the presence of Ciclesonide and at six hours were found to have suppressed viral replication with similar efficacy to Lopinavir. A recently published trial in China demonstrated no benefit in patients treated with Lopinavir-ritonavir when compared to the standard of care.

Current Surviving Sepsis Campaign guidelines for the management of critically ill adults with Covid-19 give a weak recommendation with a low quality of evidence for the use of systemic corticosteroids for mechanically ventilated adults with COVID-19 and ARDS. This differs from prior studies with SARS-CoV and MERS-CoV which showed possible harm with the use of corticosteroids.

References
CPR for COVID-19 Patients

By Eric Stanton

Summary

CPR is listed as a possible aerosol generating procedure which necessitates the use of respirators during the resuscitation of Covid-19 evidence. However, there is evidence showing that the fit seal of the N95 respirators can be compromised during CPR allowing for possible airborne transmission of the Covid-19 virus. The current recommendation is still to use N95 masks during CPR, but additional attention should be given to its possible shortcomings.

Evidence to Date

Currently, the WHO website lists cardiopulmonary resuscitation as a possible aerosol generating procedure that could allow for the airborne transmission of the Covid-19 virus. The solution to this has been to utilize N95 mask as well as other PPE such as powered air purifying respirators (PAPR) during CPR to decrease the likelihood of airborne transmission. However, there is a possibility that N95 masks might not be sufficient for preventing airborne transmission while performing CPR.

There have been reported cases of transmission of SARS and MERS to healthcare workers while giving CPR despite having N95 masks and proper PPE equipment. One study on the Toronto SARS outbreak reported an apparent transmission of the virus to an ICU nurse during a resuscitation despite wearing proper PPE, which included a N95 respirator. This nurse was reported to have an exposure time between 10-15 minutes. Another report of transmission during CPR was reported during the MERS outbreak where a nurse was infected despite wearing proper PPE and N95 respirator. This nurse was estimated to have an exposure time to the patient and isolation room of 3 hours. Both of these studies cited a failure of the seal of the N95 masks due to either the intense movement required during CPR or sweat as possible reasons for the transmission.

The possibility of N95 seal failure during chest compressions is a problem that has been noted and tested. One study that compared the protective performances of 3 types of N95 masks showed a decreased in the fit factor for all 3 types of respirators during chest compressions when compared to baseline. An additional study also tested fit factor of one type of N95 respirator during chest compressions with a sample size of 44 healthcare workers. A failure was considered any
decrease in FF to less than 100. Overall, there was 73% failure rate amongst participants at some point during the chest compressions. While both of these studies are simulations and do not indicate whether these reported failures are sufficient to allow for transmission of the Covid-19 virus during CPR, it is important to note that the movements associated with chest compressions are not accounted for when fit testing for N95 masks. This information emphasizes the need to ensure proper fit testing to minimize seal compromise as much as possible as well as explore other options such as PAPRs for CPR.

Unfortunately, there does not appear to be an easy solution to this problem with each possibility presenting with a unique set of drawbacks.

- One solution is to use PAPR for CPR and other aerosol generating procedures in which the N95 mask fit could be compromised. While there is no definitive evidence proving that PAPRs reduce airborne spread compared to N95 masks in the setting of CPR, PAPRs have been reported to be more comfortable to wear and do not rely on a tight seal around the wearer’s face that seems to be the issue with N95 masks. This was also mentioned as a possible solution in the aforementioned study involving the Toronto SARS outbreak. The obvious drawback to this solution is that PAPRs could be in extremely short supply in hospitals with high numbers of cases making their use for every Covid-19 patient needing CPR unfeasible.

- The alternative is to continue using N95 respirators with heightened awareness regarding their shortcomings. While there is evidence showing seal compromise during chest compressions, there is insufficient data demonstrating if this failure is enough to allow transmission of the Covid-19 virus during CPR. Regardless of this possibility, there should be greater emphasis on proper fit testing. Another possibility, although not evidence based, could be to limit the amount of time each healthcare worker is performing chest compressions to decrease the likelihood of seal failure. Overall, this solution requires the recognition of potential N95 respirator failure during CPR and making necessary adjustments to decrease the probability of transmission.

**Conclusion**

N95 respirators are an important piece of PPE when treating Covid-19 patients but their efficacy can be compromised with the movements associated with chest compressions. It is unclear if this failure is sufficient to allow for airborne transmission of the Covid-19 virus during CPR, but extra precautions should be considered.

**References**


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<td>A medical record analysis of 1099 Covid-19 patients from 552 hospitals in China [Retrospective - 12/11/2019 to 1/29/2020]</td>
<td>Median 47 years old (35-58)</td>
<td>58.1% male</td>
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<td>57.3% were male</td>
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<td>Of the patients in the ICU</td>
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<td>Mean age 70 years (43-92)</td>
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<td>71% received mechanical ventilation</td>
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References


