IVERMECTIN AS A POSSIBLE COVID-19 TREATMENT

By Austin Krebs

Summary:

Ivermectin has demonstrated in vitro efficacy against RNA viruses such as influenza and dengue. A recent study has demonstrated in vitro effectiveness of ivermectin against SARS-CoV-2, with an effective loss of nearly all viral material noted after 48 hours in treated cells. Clinical trials are needed to further explore this potential therapy.

Evidence to Date:

Several antiviral agents have been explored as possible therapeutic options to address the COVID-19 pandemic. One option among them is ivermectin, an antiparasitic medication that has been shown to display antiviral properties against a number of different pathogens in vitro. Ivermectin was identified to inhibit the nuclear import of the HIV-1 integrase protein by interfering with its interaction with the nuclear α/β1 importin. Additionally, ivermectin has been demonstrated to limit infection by other RNA viruses such as Dengue virus, West Nile Virus, and influenza through a similar mechanism affecting this same importin. Studies have implicated a role for the α/β1 importin in SARS-CoV infection.

Given these effects, ivermectin makes sense as an investigation for an effective COVID-19 drug. One in vitro study examined the effects of serial dilutions of ivermectin on Vero/hSLAM cells infected with SARS-CoV-2. After 24 hours, there was a 93% reduction in supernatant viral RNA (indicative of released virions). A 99.8% reduction of cell-associated viral RNA (indicative of unreleased virions) was seen in the same time frame. At 48 hours, there was an observed 5000 fold decrease in viral RNA in the ivermectin-treated cells compared to controls, which represented an effective loss of nearly all viral material. This was demonstrated by no further decrease in viral RNA in the ivermectin-treated cells compared to controls, which represented an effective loss of nearly all viral material. This was demonstrated by no further decrease in viral RNA in the ivermectin-treated cells compared to controls, which represented an effective loss of nearly all viral material. 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Seasonality of COVID-19: Will the Warm Weather Stop the Pandemic?

By Candace Pallitto

Overview and Background

As summer approaches the United States, many people are wondering the effect that this change in weather will have on the spread of COVID-19. Seasonal cycling of respiratory viruses like coronaviruses and influenza has been observed, particularly with peaks during winter months in temperate climates. While the reason for this seasonal cycling is integrated and multifactorial, it is easier to understand when broken down into two main factors: environmental effects and human components. [1] These factors are not mutually exclusive and most heavily intersect at the level of human immunity where environmental effects like temperature and humidity can play a direct role on the ability to fight infections. The environmental factor can be further divided into temperature, humidity, and sunlight exposure, but most current literature about climate effect on COVID-19 focuses on temperature and humidity. Human factors include behavioral changes, such as travel, school, and amount of time spent indoors, and immunity.

Previous data shows that other viruses in the coronavirus family and influenza prefer cooler temperatures and lower humidity in temperate climates, which possibly contributes to their resurgences every fall and winter. [1] In addition, COVID-19 is most structurally similar to SARS-CoV-2 (SARS), which occurred during winter months and is found to be able to survive up to 5 days at 22-25°Celsius and relative humidity of 40-50%, which are indoor conditions. SARS also has shown to have infectivity that lasts for 2 weeks at slightly lower temperatures and lower humidities. [2] In regards to influenza, seasonality of the virus with increased transmission at cool temperatures and low humidity only explains its role in temperate climates. However, there is evidence that seasonal outbreaks of influenza also occur in tropical areas and transmission seems to be highest during rainy seasons with greatest levels of humidity. In addition, many tropical areas see significant influenza activity year round, which indicates that temperature and humidity may not be the strongest predicting factor of the seasonality of the virus. [3] There are other factors, most likely human factors, including increased time spent indoors and changes in immunity that can play a significant role in the transmission of the virus.

Environmental Factors: Temperature, Latitude, and Humidity

Most of the current literature to date is pointing to a likely climate related aspect to the spread of COVID-19, but many of these studies do not incorporate human components, such as
containment strategies or behavioral aspects. Preliminary data from a pre-print study that reviewed transmission until February 29th, suggested that temperature may play a role, but resulted a pseudo R² value of 0.44 with temperature and 0.39 without temperature, which shows minimal effect of temperature from this data.[4] Some pre-print studies have indicated that there is association between latitude and the spread of the virus, particularly that areas above 30°N were initial epicenters of the disease. It also suggests that as the pandemic progresses, there may be a trend of increased cases south of 30° latitude to areas such as Brazil and South Africa, which have begun to show a higher case rate as of March 27th.[5,6] A study released March 9, 2020 found that the initial epicenters of the disease were found along 30- 50°N zone; from Wuhan, China to South Korea, Japan, Iran, Northern Italy, and Seattle as the initial epicenter in the United States with average temperatures of 5-11°C and relative humidity between 44-84%.[7] Furthermore, since that research was conducted there were significant outbreaks in parts of England and Germany with average temperatures of 5-11°C in February 2020. There were also predictions for New York City to have significant COVID-19 outbreaks based on this data. This temperature, humidity, and latitude data was re-iterated in a pre-print report that compared daily spread of the virus in geographic and climatic spaces, with stronger association to climatic space.[8] This report also found an average environmental temperature associated with positive cases to be 5.81°C. Furthermore, this study states that “China is well-connected to the world” and assumes equal probability of transmission without providing specific evidence for this statement.[8]

The studies above mainly focus only on environmental parameters and do not take into account a significant aspect of disease transmission- the role that human immunity and behavior plays. Furthermore, a majority of the information about COVID-19 and how it behaves in temperature and humid settings are extrapolated from SARS, which also did not seem to persist in higher temperature with higher humidities. A pre-print study that analyzed absolute humidity relationship to the spread of COVID-19 by analyzing cold and dry provinces of China indicates no clear association between disease transmission and absolute humidity.[9] It also mentions the importance of recognizing that weather alone will not mitigate the spread of this disease.

**Human Factors**

**Behavior**

Seasonality of viruses, such as coronaviruses that cause the common cold and influenza, are thought to be also related to changes in human behavior, specifically school closures and overall less time spent indoors where respiratory droplets are easily transmitted. School-aged children are often popular targets for these diseases due to their relatively poor hand hygiene and close proximity.[3] While COVID-19 does not seem to have the same impact on school-age children in terms of severity and overall prevalence as other coronaviruses or the flu, it is known that asymptomatic carriers are likely agents for propagating the disease, which offers an important outlet for human-behavior related containment strategies.[10]

To further understand the global spread of COVID-19, human behavior, specifically travel patterns are important to consider. One of the pre-prints mentioned above assumed that China had equal probability of transmission globally given that it is well-connected to the rest of the world. A different pre-print from Brazil challenges this statement and the role of climate in the global progression of this pandemic. The study analyzed climate, socioeconomic, and air transportation factors and found that global transportation networks as measured by Eigenvector Centrality¹ was the only significant factor in their model (p < 0.004).[11] They specifically analyzed the spatial pattern of air travel in 44 countries that had over 100 cases of COVID-19 and the data for time included at least 10 days after the 100th case. This study shows similar results to the climate studies in terms of areas that became epicenters and areas where the disease spread, but shows the implications of human factors on the disease progression. It specifically points out Brazil, which is considered a well-connected country with varying tropical climate patterns and is currently experiencing one of the highest rates of increase of COVID-19 in its exponential phase. Furthermore, relying too heavily on climate data may delay responses in more tropical regions with lower socioeconomic status that could see a worse progression of the pandemic.

**Immunity**

Another seasonal factor that is related to humans, but is also heavily integrated with temperature is human immunity. Research has shown that colder temperatures and lower humidity decrease the ability to fight respiratory infections. Some of the reasons include vasoconstriction in the respiratory tract, leading to decreased blood flow and consequently less leukocytic and phagocytic activity in these areas. There is also decreased mucociliary clearance in the nasal and lower respiratory tracts, making it easier for infections to invade the mucosa.[3,12,13]

Immunity also plays a role in pandemic vs. epidemic infections. Epidemic influenza variations seem to follow a seasonal pattern in temperate climates, but pandemic influenza infections, such as 2009 A/H1N1 did not follow the usual seasonal pattern and it was found among the more humid months of spring, summer, and fall.[14] A likely reason for this overall spread of the pandemic was lower immunity to this strain of influenza. The fact that COVID-19 is a new strain plays a large role in its worldwide spread and it is possible that there could be future cyclical epidemics if it is

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¹ Eigenvector Centrality analyzes the level of influence that a node has on a network. A high Eigenvector Centrality refers to a node pointing to many other nodes, meaning it has high influence on that network.
found that there is lasting immunity in some people, but more information is still needed.

Conclusion

Current data of the spread of COVID-19 and information about the seasonal natures of upper respiratory viruses indicate COVID-19 could become a seasonal epidemic like influenza. There is also some support, although not peer-reviewed or validated, that as temperatures and humidity increase, the transmission of the disease may be reduced. However, these environmental factors will not be enough to mitigate the full potential effects of the pandemic and if relied on too heavily, could produce delayed responses in areas thought to be less susceptible or cause a relapse in areas where the weather is changing. Interventions on human behavior should continue, particularly social distancing.[15] Furthermore, it is possible that the United States, particularly the New York and New Jersey area may see a decline in the pandemic that is more likely related to human behavior interventions such as travel restrictions and continued social distancing measures, rather than warmer weather and higher humidity alone.

References

Use of N95, Surgical, and Homemade Masks

By Candace Pallitto

Overview

While COVID-19 is thought to be primarily transmitted through respiratory droplets, there is concern about aerosolization of the virus and this has sparked growing concern about the supply of N95 masks in healthcare settings. COVID-19 was found to be 0.125 microns (125nm) in spherical diameter. N95 masks filter 95% of particles that are 0.1-0.3 microns in size and aerosols are considered less than 5 microns in diameter.[1] Because of the tight fit and high filtration efficiency of N95 masks, the Center for Disease Control and Prevention (CDC) recommends their use in airborne precautions and are listed as the “preferred” mask for personal protective equipment (PPE) against COVID-19.[2] In order to preserve the supply of N95 and medical/surgical masks for healthcare workers while also reducing the transmission of COVID-19 in the community, the CDC provides instructions on how to construct homemade cloth facemasks to protect individuals.[3] However, many hospitals are allowing healthcare workers to wear homemade masks due to the shortage of surgical and N95 masks, but these homemade masks are made of varying fabrics and their effectiveness has not been rigorously analyzed.[4] This report summarizes alternatives to N95 masks, use of surgical vs. N95 masks, information about materials for homemade masks, and new approaches for addressing the mask shortage.

N95 masks: The CDC notes that use of a N95 or higher respirator is “preferred,” but that medical/surgical facemasks are an alternative for general PPE for healthcare workers taking care of COVID-19 patients.[2] This is in addition to a face shield or goggles, isolation gown, and one pair of clean, non-sterile gloves. [Link to pdf]

- Surgical N95 respirators are only recommended when there are airborne and fluid hazards, such as splashes or sprays of bodily fluids. Otherwise standard N95 respirators, such as industrial N95 masks, can be used. If surgical N95 respirators are not available, but there is increased risk for splashes, sprays, or splatters of bodily fluids, then a facesheild should be worn over the standard N95.
- Expired N95 masks: N95 masks that have exceeded their shelf life have been tested and found to operate in accordance with National Institute for Occupational Safety and Health (NIOSHA). These are the models that are recommended on CDC website: 3M 1860, 3M 1870, 3M 8210, 3M 9010, 3M 8000, Gerson 1730, Medline/Alpha Protech NON27501, Moldex 1512, Moldex 2201
- CDC recommends to assess the masks for any damage and perform User Seal Check each time a N95 is worn, especially when using a mask that has exceeded its shelf life. Here is the [link] to the video they provide.

Alternatives to N95s: The CDC mentions that when N95 masks are not available, alternatives to N95s approved by NIOSHA can be used and include[5]:

- Filtering facepiece (FFP) respirators that are at least as protective as N95 (N99, N100, P95, P99, P100, R95, R99, and R100). However, if these filtering facepiece respirators have exhalation valves, they should not be used in surgical settings.
- Elastomeric half-mask and full facepiece air purifying respirators use replaceable filter cartridges and are generally made of a synthetic or rubber material so they can be cleaned and re-used. Again, many of these have exhalation valves and should not be used in surgical settings.
- Powered air purifying respirators- These use battery-powered air blower that pulls air through attached filters or cartridges that are generally made of high-efficiency particulate air (HEPA) filters. These should also not be used in surgical settings for potential contamination with blower exhaust or exhalation.
- Non- NIOSHA approved respirators which include those from other countries that have to gain approval similar to NIOSHA criteria. Examples of these include KN95 masks from China. The full list can be found on the CDC website [here] under “When N95 Supplies are Running Low.”

Surgical/Medical Masks vs. N95: The CDC lists surgical masks as an alternative to N95 as part of full PPE, but does not consider them to be adequate respiratory protection for protection from smaller airborne particles. The confusion surrounding the aerosolized nature of COVID-19 has made it difficult to appropriately determine which clinical settings or procedures should have N95 masks.

- While the CDC guidelines prefer healthcare workers to wear N95 masks while taking care of COVID-19 patients, they specify when to choose N95 masks or surgical/medical facemasks based on symptoms of the patient and distance from the patient positive or suspected of COVID-19:[5]:
  - A surgical/medical facemask can be used when the patient is masked and the healthcare provider has to be within 6ft of the patient.
  - No mask or respirator is needed when the patient is masked and the healthcare provider will remain greater than 6ft away
  - A NIOSHA-approved N95 respirator, elastomeric, or PAPR should be used when the patient is unmasked or the mask needs to be removed and during aerosol generating procedures (AGPs).

- The London Health Sciences Centre more specifically states settings and procedures that require N95 masks in setting of COVID-19. They note outside critical care
settings a fluid resistant mask with eye shield can be worn (i.e. N95 masks are not required). These are the settings and procedures they list where N95 mask should be worn (including other full PPE, such as face shield)[6]:
  o Settings:
    ▪ Critical Care
    ▪ Operating Room
    ▪ Emergency Department
  o Procedures: Aerosol Generating Medical Procedures (AGMP)
    ▪ *Intubation
    ▪ *Bronchoscopy (including insertion of percutaneous tracheostomy)
    ▪ *CPR
    ▪ *Extubation
    ▪ *2Endoscopy
    ▪ Bag-mask-valve ventilation (with a filter)
    ▪ CPAP or Non-Invasive Ventilation (until COVID-19 negative result)
    ▪ High flow or humidified oxygen
    ▪ Non-humidified oxygen at > 50%
    ▪ Tracheostomy insertion/tube change/decannulation
    ▪ Use of cough-assist device
    ▪ Open suctioning
    ▪ Any procedure that may cause a breach in ventilator circuit
    ▪ Ventilator circuit change (clamp the ETT momentarily when changing circuit or switching from manual ventilation to mechanical ventilation)
    ▪ Inhaled anaesthetic

- **Key Takeaway:** In order to ensure adequate protection of our healthcare workers and further conserve the supply of PPE equipment, it is important that surgical N95 masks are allocated to appropriate and high-risk settings as well as that surgical masks are used when appropriate.

**Homemade Masks**
The CDC does not consider homemade masks as PPE and should be used by community members in order to preserve the supply of N95 and surgical/medical masks for healthcare professionals. The CDC mentions using cotton, T-shirts, bandanas, and coffee filters. However, there are many articles on the internet that discuss the use of other materials, such as HEPA vacuum filters. Here is the summary of evidence surrounding these practices and safety considerations:

**Cloth Facemasks:** The CDC recommends use of cloth facemasks for the general public in order to preserve the supply of N95 masks and medical/surgical masks for healthcare workers. Review of the literature yields the following in regards to evidence for cloth masks:

- Cloth masks have been used in healthcare settings during previous pandemics and in other countries so there is some data on their effectiveness. No studies have demonstrated equal or superior protection to N95 masks. While there is some data on this subject, it is very limited and it is difficult to obtain evidence from well-designed randomized controlled trials because compliance is often an issue.[7]
- One study cited by most articles on this topic analyzed the filtration effectiveness of different fabrics. They found that cloth facemasks that consisted of 2 layers of pure cotton, pure polyester, or cotton/polyester blends did not sufficiently filter out particles 100-300nm.[8] These mixtures of fabrics were examined in cloth masks, sweatshirts, T-shirts, towels, and scarves. They used polydisperse aerosol penetration because this is the method to test penetration of masks like N95 masks as well as monodisperse aerosol penetration, which more specifically assess how the masks filter particles <400nm in size. They found that the polydispersion and monodispersion penetration results were similar to that of some FDA-approved surgical masks studied in previously, but they did not analyze droplet protection or splash protection in those studies. The Hanes sweatshirt made of 70% cotton and 30% polyester was found to have least polydisperion and monodispersion penetration for particles <60nm, but found to be similar to other sweatshirts for particles >60nm. This study did not look at fit either.[7]
- One pre-print study found that homemade masks made of cloth and 4 layers of paper towels was able to filter 95.15% of avian influenza virus from aerosols, which was used to replicate COVID-19.[9] The methods of this study were not clearly defined, but it indicates the importance of adding layers to increase protection.
- CDC recommends that when using a bandana to make a mask that a coffee filter should be added. Coffee filters generally filter particle sizes about 10-20 microns so more than one should be used and they should be used in addition to other materials. Cloth masks with better fit are preferable.
- Analysis of fit: N95 masks have a fit factor of 100. Most studies of cloth masks do not assess fit, but one prototype that consisted of 8 layers with alternating thread directions and 3 ties around the head had a fit factor of 67. The original prototype consisted of 4 layers, but inadequate results from previous prototypes lead to an additional 4 layers to be added. This was made from a Hanes Heavyweight 100% preshrunk cotton Tshirt.[10]
- **Key takeaway and tips**
  o Multiple layers should be used (A flashlight can be used to assess thickness of the mask by seeing if you can shine a light through the mask. There is no evidence for this

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2 High-risk AGMP
method as a method of adequate filtration, but it can be helpful.)
- Different materials should be used if possible, but cotton should be the primary material.
- Try to get the mask to fit as closely as possible.
- These masks do not replace the importance of social distancing, but instead offer additional protection when individuals have to enter public areas for necessities, such as food shopping.

HEPA Filters: There is a lot of talk about how to convert high-efficiency particular air (HEPA) filters found in household vacuum filters into facemasks since these are the filters found in PAPRs. HEPA filters are designed to filter aerosols with particles 0.3 microns in diameter with a minimum efficiency of 99.97%[11] There are many websites showing people how to make these filters into facemasks and claiming they offer ultimate protection. While they most likely are highly effective at filtering particles, there are no studies that assess homemade facemasks using HEPA filters compared to medical masks or N95 masks. The safety considerations of this material as a face-mask are also not known. Here are some aspects to take into consideration before using this material:
- If you want to use a HEPA filter to make homemade mask, it is important to note that most HEPA filters contain fiberglass, which can shed and become an irritant to the respiratory tract.[12] This risk is increased when cutting the material. Therefore, HEPA filters should not have direct contact to the face if you are to make a mask with this material.
- This theoretically could provide added protection if inserted into home-made cotton masks, but the filter paper should be easily removable and replaceable for when the mask needs to be washed. However, there is no evidence on effectiveness or safety of this practice.
- **Key takeaway:**
  - This seems like a great idea, but be careful doing using the material, particularly directly on the face.
  - There is no evidence that this is safe or effective.

Other ways to address the mask supply issue:

Other new ideas:
- **BioAid** is a company that has produced a patent-pending re-usable N95 mask. Some of the features of these masks are that they use a replaceable cartridge with a HEPA or MERV13 filter and can be sterilized in clinical or home-based methods. The mask is within NIOSH requirements.
- This could prevent reliance on having masks shipped from overseas.

References

Clinical Presentation of COVID-19 in Children

By Catherine Hahn

Summary

The majority of cases of COVID-19 in children are asymptomatic, mild, or moderate in severity. Preliminary data shows that 13% of children with infection are asymptomatic, though this number is likely to be much higher as asymptomatic children are less likely to be tested. Children who are symptomatic typically will experience symptoms of an upper respiratory infection, including cough, pharyngeal erythema, and fever. Most cases do not progress to lower respiratory tract infections. There is a small subset of pediatric cases that have shown gastrointestinal symptoms including nausea, vomiting, and diarrhea. Unlike the adult population, there does not appear to be a reliable set of laboratory findings consistent with coronavirus infection in children. However, an isolated case in an infant showed elevated IL-6 levels associated with severe infection, which is in accordance with data from the adult population. Most children will not show any CT findings, suggesting mild infection. In those with CT findings, the most common abnormality is ground-glass opacities. The presence of consolidation with halo sign on CT appears to more prevalent in children with coronavirus compared to adults.

Incidence and Epidemiology

It appears that children are less susceptible to COVID-19 infection compared to adults. An analysis by the Chinese Center for Disease Control and Prevention examined epidemiological patterns in 72,314 cases of patients with SARS-CoV-2. Of these, 965 patients (1.3%) were between the ages of 0 and 19 years old, showing that children account for a minority of these infections. Most of the pediatric cases have arisen from family clusters, with data showing between 56-76% of children have a family member with confirmed infection. In a retrospective analysis of 2143 pediatric patients by Dong et al., the vast majority of cases were mild to moderate in severity with a small group of severe and critical cases. Approximately 5.9% of cases were severe or critical compared to 18.5% of adult cases. The median age of diagnosis was seven years old and there was no significant difference in incidence between males and females. Infants and younger children appeared to be more vulnerable to severe and critical infection. Infants less than 1 year old made up 53.8% of critical cases and children under the age of 6 years old contributed to almost 60% of severe infections. The mortality rate appears to be very low in children. In this study, there was one confirmed death of a 14-year-old boy out of 2143 cases.

Clinical Symptoms

Most children with COVID-19 infection are asymptomatic or have mild infection. However, there appear to be distinct

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patterns in the pediatric population for children with symptomatic infection. A study from Wuhan Children’s Hospital assessed the frequency of different clinical features in 171 pediatric cases. The most common symptoms were cough (48.5%), pharyngeal erythema (46.2%), and fever of at least 37.5°C (41.5%). There were also cases that showed gastrointestinal symptoms, including diarrhea (8.8%) and vomiting (6.4%). Other less common symptoms included fatigue (7.6%), rhinorrhea (7.6%), and nasal congestion (5.3%). The majority of children will temporarily have upper respiratory infections and very few progress to pneumonia. Another study from Wuhan Children’s Hospital examined the characteristics of 8 children with severe infection. In this cohort of patients, all of the patients presented with tachypnea (8/8), and other common presenting features included cough (6/8), fever (6/8), expectoration (4/8), nausea/vomiting (4/8), diarrhea (3/8), fatigue/myalgia (1/8), headache (1/8), and constipation (1/8).

Laboratory Findings

Compared to adults, there does not seem to be a consistent pattern of laboratory markers that coincide with coronavirus infection in children. Preliminary studies in adults have shown recurring patterns of elevated liver enzymes, anemia, increased inflammatory markers, and sometimes hyperglycemia. This does not appear to be the case in children. A retrospective analysis by Henry et al. examined laboratory findings in 66 pediatric cases. There was a wide array of leukocyte indices, as 69.6% had a normal leukocyte count, 15.2% had an increased leukocyte count, and 15.2% had a decreased leukocyte count. Most children had normal neutrophil counts with 4.6% above the normal range and 6% below the normal range. This contrasts with what is typically seen in the adult population. In adults, both increased leukocyte and neutrophil counts have been associated with progression of infection. Regarding inflammatory markers, only 13.6% of cases had elevated C-reactive protein and 10.6% had elevated procalcitonin. In the adult population, elevation of both of these markers has been associated with infection. An isolated case report in an infant suggests that elevated IL-6 is associated with increased severity of infection. This is consistent with preliminary data showing that elevated levels of IL-6 are strongly associated with the need for mechanical ventilation in the adult population. Further research needs to be done on the association between IL-6 and prognosis and using IL-6 as a possible therapeutic target.

CT Findings

The most common finding on CT in children is ground-glass opacities. In the retrospective analysis by Lu et al. examining 171 patients at Wuhan Children’s Hospital 32.7% of patients had ground-glass opacities on CT. Other findings included local patchy shadowing (18.7%), bilateral patchy shadowing (12.3%), and interstitial abnormalities (1.2%). In a smaller study by Xia et al. examining 20 pediatric patients with COVID-19 viral pneumonia, all patients had subpleural lesions. Findings included ground-glass opacities (12/20), consolidation with halo sign (10/20), fine mesh shadow (4/20), and tiny nodules (3/20). There were no cases of pleural effusion or lymphadenopathy. The presence of halo sign on CT appears to be somewhat typical in the pediatric population while it is relatively uncommon in adults. Resolution of infection defined as negative nucleic acid testing was associated with complete absorption of lesions in some cases and a decrease in consolidations in other cases with the persistence of ground-glass opacities. Thus, due to common imaging findings among children, CT can be a powerful tool to aid in diagnosis when testing is delayed and to follow progression and resolution of infection.

References

Effects of COVID-19 on Pregnancy: Is Vertical Transmission Possible?

By Catherine Hahn

Summary

The effects of COVID-19 on pregnancy appear to be less severe and have better clinical outcomes compared to SARS and MERS. As the pandemic evolves, there is still uncertainty regarding the effects of COVID-19 in utero. From limited data that is currently available, there have been no confirmed cases of vertical transmission. There have been a few neonatal cases of COVID-19, but it is unclear as to whether this was from intrauterine exposure or as a result of environmental exposure after delivery. Therefore, it appears that the risk of intrauterine transmission of COVID-19 is low, but cannot be ruled out.

Effects of SARS and MERS on Pregnancy

As a way to anticipate potential obstetric outcomes at a time when data is limited, it is helpful to turn to knowledge from past outbreaks. In a recent retrospective analysis examining the effects of SARS and MERS on pregnancy, there were no reported cases of maternal-fetal transmission of the viruses.\(^1\) However, it is critical to note that there were reported adverse effects on pregnancy due to infection from these viruses. In a study of 12 mothers with SARS, four out of seven women who presented in the first trimester had spontaneous miscarriages. Further, of the five women who presented after 24 weeks gestation, four had preterm deliveries.\(^1\) Another study examining the effects of SARS on placental pathology reported two instances of placental anomalies in mothers who acquired the virus in the third trimester. The placentas showed fetal thrombotic vasculopathy and areas of avascular chorionic villi, resulting in oligohydramnios and intrauterine growth restriction.\(^1\) Turning to MERS, there are 11 documented cases of MERS in pregnancy, and 91% had adverse outcomes. There were two instances of maternal death, one stillbirth, and one neonatal death.\(^1\) Therefore, while both SARS and MERS have been associated with adverse outcomes, there have been no documented cases of intrauterine transmission.

COVID-19 & Vertical Transmission

An analysis of 37 pregnant mothers from China with COVID-19 revealed no evidence of vertical transmission of infection.\(^2\) All samples of neonatal throat swabs, umbilical cord blood, amniotic fluid, stool, neonatal blood samples, and breast milk were negative for the virus. There were six cases of preterm labor, six cases of premature rupture of membranes, two cases of abnormal amniotic fluid, and two cases of abnormal umbilical cords.\(^2\) Unlike the SARS virus, it appears that there are no pathologic changes in placenta as a result of infection.\(^3\) In this analysis, there was one documented case of neonatal death nine days after delivery. He initially developed shortness of breath and later died from refractory shock, multiple organ
failure, and disseminated intravascular coagulation. None of the mothers required mechanical ventilation after delivery and there were no reported maternal deaths.

Another study was recently published by New York-Presbyterian, and the researchers’ findings were consistent with initial data from China. Out of 18 COVID-positive mothers who presented for delivery, 4 had symptomatic infection.4 The asymptomatic patients were diagnosed after a universal screening protocol was implemented for all admissions on the Labor Unit after March 22. Ten deliveries were uncomplicated normal spontaneous vaginal deliveries. Eight patients delivered via C-section due to non-reassuring fetal heart rate (n=3), repeat C-section (n=2), arrest of descent (n=1), arrest of dilation (n=1), and failed labor induction (n=1). There was one case of preterm labor. None of the newborns showed clinical signs of infection. Fifteen newborns were negative for COVID-19 infection via nasopharyngeal swab on day of life (DOL) 0. Two infants had inconclusive initial screenings, but were negative on DOL 1-2.4 One infant had indeterminate test results and was treated as a “presumptive negative”. As of DOL 6, the baby continued to show no signs of infection. None of the infants had IgM or IgG antibody testing.4 This data in conjunction with data from China show no confirmed cases of vertical transmission, suggesting that the risk of vertical transmission is low.

There have been a few reported cases of confirmed COVID-19 in neonates, but it is difficult to determine at this time whether this was due to intrauterine exposure or as a result of environmental exposure after birth. A study published in JAMA Pediatrics examined the effects of maternal COVID-19 infection on 33 newborns at Wuhan Children’s Hospital.5 Three of the babies tested positive for COVID-19 via nasopharyngeal and anal swabs on DOL 2 and 4.5 Two of the babies tested negative on DOL 6 and the remaining baby tested negative on DOL 7.5 One baby was born at 31 weeks because of fetal distress and required resuscitation at delivery. Clinically, all three patients showed signs of pneumonia on chest x-ray and experienced a variety of symptoms including lethargy, fever, and vomiting. All samples from these cases had negative amniotic fluid, cord blood, and breast milk.5 The researchers of this paper argue that because they implemented strict infection control measures during delivery, it is likely the positive neonatal results are maternal in origin and the possibility of vertical transmission cannot be ruled out.5 There is an additional case report of an infant testing positive for COVID-19 at 36 hours of life.6 Similarly, all samples from cord blood, placenta, and breast milk were negative for the virus.6

There have been three documented cases of elevated IgM antibodies in neonates born to mothers with confirmed coronavirus infection.7,8 Upon delivery, all three of the infants tested negative for coronavirus via nasopharyngeal swab.7,8 Only IgG antibodies are able to be transmitted across the placenta, and IgM antibodies cannot cross the placenta due to their larger molecular structure. IgM testing for SARS-CoV-2 has a sensitivity of 70.2% and a specificity of 96.2%.7 It is possible that the IgM antibodies were produced by the fetus in utero as a result of intrauterine exposure to coronavirus. It is also possible that placental damage could have permitted these antibodies to cross the placenta, which could explain why nasopharyngeal swab tests were negative. This is plausible given our knowledge of placental abnormalities as a result of SARS-CoV infection. However, preliminary data has not shown any placental pathologies as a result of SARS-CoV-2.4 As such, more data is needed to determine is vertical transmission is a true possibility.

Conclusion
At this time, it appears that the risk of vertical transmission of COVID-19 is low, but it cannot be ruled out entirely. At this time, it is not known whether the cases of preterm labor were a result of coronavirus infection or due to a secondary reason. It is important to note that there remains a high risk of respiratory droplet transmission of infection to neonates, so proper infection control precautions should be taken. In addition, more research needs to be done on the effects of the fetus when the virus is contracted during the first or second trimester of pregnancy.

References
Hydroxychloroquine Update: Reanalysis of Gautret et. al. Study

By Daniel Menza

Evidence to Date:
This study is a reanalysis of the data from the Gautret et. al. open label non-randomized trial of Hydroxychloroquine and Azithromycin for the treatment of COVID-19 using a Bayesian analysis. The trial compared 26 patients receiving hydroxychloroquine with or without azithromycin to 16 control patients receiving standard treatment, all COVID-19 positive on PCR. The primary endpoint was presence or absence of virus on nasal swab at day 6. The authors made several assumptions and choices in analyzing the data that this new study seeks to examine. The original authors excluded 6 patients from the treatment group analysis, 1 who died, 3 who were transferred to the ICU, 1 who left the hospital, and 1 who stopped the drug because of nausea. There were also 5 patients in the control group who were not tested at day 6, and the authors analyzed these patients as positive. The authors of the new study were concerned that both of these assumptions bias the data towards supporting the hypothesis. In short, when reanalyzed with these assumptions changed, the results were much less strong in supporting the hypothesis that hydroxychloroquine increased viral clearance at day 6 post inclusion in the trial. This means that one of the main pieces of literature supporting the use of hydroxychloroquine and azithromycin in the treatment of COVID-19 suffers from serious flaws in the way it analyzes the data.

Details
The paper reanalyzed the data in many different ways, using a Bayesian analysis. The nomenclature they used to define the different data sets are defined as follows:

- **HCQ**<sub>group</sub>: Those treated with hydroxychloroquine (HCQ) and those treated with HCQ and azithromycin (AZ)
- **HCQ**<sub>Mono</sub>: Those treated only with HCQ
- **HCQ**<sub>+AZ</sub>: Those treated with HCQ and AZ
- **Data**<sub>original</sub>: The data as it was presented in the paper
- **Data**<sub>det</sub>: The data including the 4 patients who deteriorated (1 who died, 3 who went to the ICU) in the treatment group and counting them as tested positive in the day 6 endpoint
- **Data**<sub>xcon</sub>: The data including the 4 patients who deteriorated and excluding the 5 patients who were not tested in the comparison group at the day 6 endpoint
- **Data**<sub>negcon</sub>: The data including the 4 patients who deteriorated and counting the 5 patients who were not tested in the comparison group at day 6 as testing negative
They performed a Bayesian analysis which outputs a Bayes Factor as a result. The Bayes Factor is a measure of how strongly the data supports the alternate hypothesis (that HCQ and AZ improved viral clearance at day 6) over the null hypothesis (that there was no difference in viral clearance between the treatment and the comparison group). A Bayes Factor of 1-3 is classified as anecdotal evidence, 3-10 is classified as moderate evidence, 10-30 is strong evidence and 30-100 is very strong evidence. A Bayes Factor of less than 1 indicates evidence that the treatment inhibited viral clearance compared to the comparison group. This is the standard way of interpreting Bayes Factors. The results are included in this table.

As you can see, the evidence supporting the use of HCQ and AZ was much stronger under the assumptions the authors operated under than when the deteriorated patients were included and the untested patients were excluded, which is a more intuitive way of looking at the data. This analysis shows that this data is not as strong in supporting the use of HCQ and AZ as the authors may have presented it.

References

Use of Helmet Ventilators for Covid-19 Patients
*By Eric Stanton*

**Summary**

Helmet non-invasive ventilation (NIV) is growing in popularity during the Covid-19 pandemic as a way to decrease the need for invasive ventilation. When compared to mask NIV, helmets appear to decrease mortality and intubation rate in patients with acute respiratory failure. With regards to infection transmission, there is no consensus on whether helmet NIV decreases transmission when compared to mask, but it does appear to decrease the dispersion of exhaled air.

**Details**

Non-invasive ventilation (NIV) through either face mask or helmet is a way to maintain positive end expiratory pressure with the goal of reducing risks associated with invasive ventilation such as complications from sedation, use of paralytics, pneumonia, and ICU acquired weakness.1 The current consensus is mixed when comparing outcomes of ARDS patients on NIV vs. high flow nasal canula (HFNC) but it leans towards HFNC as having better outcomes when compared to NIV. However, these studies focused on the comparison of mask NIV, rather than helmet, to HFNC.2 To date, the evidence comparing HFNC to helmet NIV is limited, hopefully prompting future investigation in the outcomes between the two methods.

There is however, numerous studies comparing the outcomes of mask NIV to helmet NIV in patients with acute respiratory failure. In a meta-analysis published in 2016, it was shown that helmet NIV was associated with lower hospital mortality (OR 0.43, 95 % CI 0.26 to 0.69), and decreased intubation rate (OR 0.32, 95 % CI 0.21 to 0.47).3 These advantages have thought to been attributed to the superior seal offered by the helmet when compared to the facemask allowing for higher PEEP.1 Other benefits cited were increased communication ability and increased cough/sputum clearing as a result of not having a mask tightly fitted to the patients face.

The other concern with regards to choosing helmet or facemask NIV, especially amidst the Covid-19 pandemic, is the risk of aerosolization and infection transmission. There is concern about the potential aerosolization and transmission of the Covid-19 virus with use and adjustment of BiPAP masks. A systematic review about the transmission of the SARS-CoV-1 virus during aerosol generating procedures suggested that there is an increased risk of transmission from patients on BiPAP however, it cited wide confidence intervals that were not statistically significant.4 Regardless of this evidence, efforts should be taken to minimize transmission from patients to healthcare workers. It is unclear if helmet ventilators reduce the potential risk of Covid-19 virus transmission when compared to BiPAP masks, but it does appear to reduce the dispersion of exhaled air. In a study that used a human patient
simulator, the dispersion distance of exhaled air for two different types of helmets and a facemask were measured. The results are summarized below:

- StarMed CaStar R Helmet: negligible air leak noted.
- Sea-Long Oxygen Head Tent: radial dispersion through the neck interface of 170 mm with inspiratory positive airway pressure (IPAP) of 12 cm H2O, and 270 mm with IPAP of 20 cm H2O.
- Respiration Total Facemask: dispersion distance through exhalation port of 693 mm with IPAP of 10 cm H2O and distances exceeding 916 mm with IPAP of 18 cm H2O. These findings are limited by the use of a simulation and do not describe actual transmission rates between the different methods of NIV, but it does demonstrate a difference in dispersion of exhaled air which could lead to differences in transmission.

**Bottom Line**

Helmet NIV likely decreases mortality and intubation rates in patients with acute respiratory failure when compared to mask NIV due to increased integrity of seal maintaining adequate PEEP. There is no current consensus regarding the differences in outcomes of patients on HFNC versus helmet NIV. There is limited data on differences in transmissibility of the Covid-19 virus between helmet and mask NIV but dispersion of exhaled air appears to be much lower in the helmet NIV.

**References**


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**D-Dimer Level as a Prognostic Indicator and Therapeutic Value of Prophylactic Heparin**

*By Eric Stanton*

**Summary**

Elevated d-dimer levels in Covid-19 patients appears to be a poor prognostic factor. Prophylactic heparin use, especially in patients with elevated d-dimer levels and SIC score, has a potential therapeutic value.

**Coagulation in Covid-19 Patients**

Covid-19 patients are thought to be in a hypercoagulable state due to both the endothelial cell dysfunction induced directly by the virus as well as the hypoxemic state of some patients. This has led to the potential value of the d-dimer level as a prognostic factor as well as the use of heparin in patients demonstrating a coagulopathy.

**Prognostic Value**

In three studies that looked at d-dimers as a prognostic value, it was found that a level greater than 1.0-2.0 mg/L was considered a poor prognostic factor. The findings of these studies are summarized below:

- In a retrospective cohort study that looked at 191 Covid-19 patients, a d-dimer level greater than 1.0 mg/L conferred an odds ratio of 20.04 (95% CI 6.52-61.56) for in-hospital death. 2
- In a retrospective cohort study with 183 Covid-19 patients, there was a mean d-dimer level of 0.61 mg/L in the survival group upon admission compared to a d-dimer level of 2.12 mg/L in the non-survivor group (p < 0.001). 3
- In a retrospective cohort study with 41 Covid-19 patients, there was a mean d-dimer level of 2.4 mg/L in patients requiring critical care compared to a d-dimer level of 0.5 mg/L in those who did not (p < 0.0042). 4

**Use of Anticoagulation**

One retrospective study of 449 patients that looked at the use of heparin in severe Covid-19 patients showed a reduction in 28-day mortality when the patient had a sepsis induced coagulopathy score greater than 4 (OR 0.372, 95% CI 0.154-0.901), or d-dimer greater than 3.0 mg/L (OR 0.412, 95% CI 0.207-0.817). There was no significant difference in 28-day mortality for patients below these parameters. Of the 99 patients that were in the heparin group, 94 received LMWH (40-60 mg enoxaparin/day) and 5 received unfractionated heparin (10000-15000 U/day).
Another retrospective study that looked at the use LMWH in non-severe Covid-19 patients an effect on normalizing select lab values. This study, which included 41 patients, found that the LMWH group (N = 21) had significantly lower IL-6 levels compared to the control group after treatment (15.76 ± 25.71 vs. 78.24 ± 142.41 p = 0.000) as well as significantly lower IL-6 levels within the LMWH group after treatment as compared to before (47.47 ± 58.86 vs. 15.76 ± 25.71 p = 0.006). Additionally, this study found significant differences in the percent increase in lymphocytes between the heparin and control groups (but not overall lymphocyte percentage) as well d-dimer reduction within the heparin group before and after treatment. However, this study did not contribute to improvement in mortality due to anticoagulation treatment as all the patients in the study survived.

Heparin Guidance

Currently, the interim guidance from the International Society of Thrombosis and Hemostasis recommends considering a prophylactic dose of LMWH in all patients who require hospital admission for Covid-19 in the absence of:

- Active bleeding
- Platelet count less than 25 X 109/L

Monitoring is advised in severe renal impairment and abnormal PT or APTT are not considered contraindications.

Heparin’s Biologic Effect

It is speculated that the potential therapeutic effect of heparin in Covid-19 patients extends beyond its traditional role as an anticoagulant. It was proven in-vitro that heparin is capable of binding IL-6, possibly reducing its biological activity. Additionally, heparin has been shown to induce a conformational change of the SARS-CoV-2 surface spike protein in vitro. While this seems like promising information, further investigation in-vivo must be conducted to quantify heparin’s therapeutic value.

References

Possible Therapies for Convalescent Pulmonary Management of COVID-19

By Austin Krebs

Summary
Current convalescent pulmonary management for COVID-19 patients is sparse. Melatonin is one possible option given its anti-inflammatory, anti-oxidant, and anti-fibrotic effects. These mechanisms could attenuate lung injury in COVID-19 patients. Another option is pirfenidone, an anti-fibrotic medication that has shown efficacy in models of ARDS as well as advanced idiopathic pulmonary fibrosis. Clinical trials investigating pirfenidone are currently being conducted. A final option is that of mesenchymal stem cells (MSCs). MSCs have been shown to home to damaged tissues and facilitate their repair, and have been used in small samples of COVID-19 patients with good outcomes. Clinical trials in China are ongoing. These options are some of the current therapies being explored to address COVID-19 lung injury.

Evidence to Date
Persistent hypoxemia is a problem in COVID-19 patients, sometimes requiring prolonged non-rebreather oxygenation. The current literature is sparse regarding convalescent pulmonary management of COVID-19 patients. Several potentially beneficial medications have been proposed thus far. The purpose of this review is to examine these proposals and attempt to extrapolate existing clinical data and apply it to the treatment of COVID-19.

One potential therapy that has been proposed to treat COVID-19 is melatonin. Melatonin exerts an anti-inflammatory effect through Sirtuin-1 (SIRT1), which has been shown to attenuate lung injury and inflammation in sepsis-induced acute lung injury.[1] Additionally, the anti-inflammatory effects of melatonin involve down-regulating NF-kB activation. It also stimulates NF-E2 related factor (Nrf2) which is an important component in protecting the lungs from injury.[2] An anti-oxidant effect has also been demonstrated in melatonin, which might be helpful in countering the production of oxidized products of viral infections. SARS models of lung injury demonstrated that oxidized low density lipoprotein activates innate immune responses that lead to over-production of IL-6 via toll like receptor 4 (TLR4) and subsequent lung damage.[3] Melatonin also protects against lung fibrosis, and has been shown to attenuate bleomycin-induced lung fibrosis in mice.[4] Post-ARDS fibrosis has been noted in SARS as well, and preventing progression to fibrosis could help improve patient outcomes and pulmonary function.[5] Melatonin has been studied extensively in animal models of acute lung injury, and its safety in humans has been demonstrated consistently, making it a potentially beneficial treatment for COVID-19.

ARDS can also trigger persistent lung inflammation and fibrosis through activation of the NLRP3 inflammasome and secretion of IL-1B. Pirfenidone, a federally approved anti-fibrotic medication, has been shown to reduce LPS-induced lung inflammation and fibrosis by down-regulating NLRP3 activity.[6] Pirfenidone has been shown to be efficacious even in advanced idiopathic pulmonary fibrosis, and could serve as a potential adjunct in the treatment of lung injury in COVID-19 patients.[7] A clinical trial examining the effects of pirfenidone in COVID-19 patients is currently recruiting.

Another possible option is mesenchymal stem cells (MSCs). MSCs have demonstrated immunosuppresive effects, but only when induced by inflammatory cytokines and nitric oxide.[8] These stem cells have been shown to home to damaged tissue and integrate into the microenvironment, preparing it to facilitate tissue repair.[9] In fact, MSCs have already been used in COVID-19 patients. Seven patients in Wuhan with COVID-19 were treated with MSCs and within 2–4 days after treatment, showed resolution of symptoms, increase in O2 saturation, significant reduction in the pro-inflammatory TNF-α, and significant increase in the anti-inflammatory IL-10.[10] Clinical trials are currently enrolling in China to investigate the effects of MSCs in the treatment of COVID-19 lung disease.

The current literature regarding convalescent pulmonary management is thin, but the above therapies are some of the options currently being investigated to ameliorate lung disease due to COVID-19.

References


Can Nitric Oxide be used to treat Covid-19?
By Helen Pozdniakova

Summary
There is data that nitric oxide can inhibit viral replication of similar viruses (SARS) while also improving pulmonary hypertension. If the respiratory illness caused by Covid-19 is similar to HAPE, agents that increase nitric oxide such as PDE5 inhibitors may show promise in treating severe disease.

Evidence to Date
Guidelines for severe illness in Covid-19 recommend treatment based on ARDS protocol. ARDS is defined by the Berlin Criteria. Despite using ARDS protocol, 50+% of patients who require invasive ventilation die. Dr. Gattinoni, an anesthesiologist working in the epicenter in Italy, recently proposed that we think of Covid-19’s respiratory illness as an “atypical ARDS” and look at patients as having a biphasic disease.[1] Initially, the hypoxemia begins with a dysregulation of pulmonary perfusion. Patients in this phase are described as Type L and are characterized by:
- Low elastance (i.e., high compliance)
- Low V/Q ratio
- Low lung weight
- Low recruitability
- Limited “PEEP response”

Later, patients go into pulmonary edema collapse or an “ARDS” like state. These patients exhibit a phenotype described as type H and are characterized by:
- High elastance
- High right-to-left shunt
- High lung weight
- Higher “PEEP response”
- High recruitability.

He cautions physicians that type L patients can progress to being type H depending on disease progression and our management. Because of this, many physicians compare the symptomatology of Covid-19 to high altitude pulmonary edema (HAPE) which is a pure hypoxemic disease leading to pulmonary hypertension. HAPE shares some similarities with Covid-19 such as:
- A low PaO2/FiO2 ratio
- Hypoxia/tachypnea
- Hypocarbia
- Ground glass opacities on chest CT or patchy infiltrates on chest x-ray
- High levels of fibrin
- ARDS in severe disease[10]
This begs the question: if this theory is true, can we use HAPE treatments for severe Covid-19? Treatment options for HAPE includes supplemental oxygen, nifedipine, phosphodiesterase type 5 inhibitors (PDE5-i), and dexamethasone. Relieving hypoxemia is the most effective method of reducing pulmonary artery pressure and protecting other organs. Preliminary treatment for hospitalized Covid-19 patients currently is noninvasive ventilation with high oxygen settings. Out of the above choices, there may be a role for adjunct PDE5 inhibitors. In SARS, the literature shows that nitric oxide inhibits the replication cycle of the virus in-vitro in a dose dependent fashion. Induction of iNOS reduced the yield of virus by about 82%.[3] In a separate study with the same methodology, they found the survival rate of SARS infected cells was greatly increased with treatment with NO. [7] Because SARS shares a lot of similarities to Covid-19, these results may be applicable in the current pandemic.

In the context of acute lung injury, a study using a rabbit model demonstrated reduced markers of lung inflammation using 1mg/kg IBW of IV sildenafil. Markers that were reduced included release of TNF-alpha/IL-8/IL-6, lung edema formation, protein content in bronchoalveolar lavage, and apoptosis of epithelial cells with an improvement in respiratory parameters. [6]

Clinically, studies have shown that nitric oxide production is impaired in patients with HAPE which is probably the underlying mechanism for the elevated pulmonary artery pressures. [8] Likewise, studies have shown a correlation between hypertension and depletion of nitric oxide, likely due to endothelial dysfunction. [4] Some authors postulate that the depletion of nitric oxide may be the reason that we are seeing Covid-19 patients having a higher susceptibility to than healthy patients. [9] One benefit of using PDE5 inhibitors is that they are primarily a pulmonary vasodilator and not systemic like nifedipine. The current treatment of HAPE is 20-50mg q8 of sildenafil or 10mg q12 of tadalafil. [8]

Given this information, the data looks promising. However, we know that nitric oxide can be a double-edged sword and actually be detrimental in high quantities. Some postulate increased nitric oxide may be an early marker of lung inflammation. Therefore, studies done on this topic should pay attention to dosages and effect on nitric oxide levels in vivo.

References
Does O2 Saturation Speak to the Severity of Covid-19?

By Helen Pozdniakova

Summary

Anecdotal evidence and recent literature may suggest the ARDS protocol for treating Covid-19 may be inappropriate. Oxygen saturation may not be a reliable indicator of respiratory status in Covid-19 patients.

Evidence to Date

Patients triaged in the emergency room are monitored by their vital signs. A decrease in oxygen saturation measured by pulse oximetry is used as an indication of worsening respiratory function in Covid-19 patients and an indication for endotracheal intubation. With the growing concern over the shortage of ventilators, we are trying to prevent or delay intubation in as many patients as possible. However, we also know that Covid-19 patients on invasive ventilation have a mortality between 50-80% despite using the acute respiratory distress syndrome (ARDS) protocol. This report discusses the efficacy of the current management of Covid-19 as ARDS.

On March 30th, 2020 Dr. Luciano Gattinoni, an anesthesiologist on the front lines in Italy, wrote his viewpoint discussing that patients with severe Covid-19 exhibit an atypical form of ARDS. This has since gained support by many physicians, especially those working in NYC. These physicians speculate Covid-19 patients behave more like people with high altitude pulmonary edema (HAPE) rather than your typical ARDS patient. This is because many patients seem to exhibit a lower-than-tolerable O2 saturation but without all the symptoms one would expect with hypoxia such as altered mental status or lethargy. In HAPE, high altitudes cause an increase in pulmonary artery pressure leading to pulmonary artery vasoconstriction in a patchy and diffuse pattern, similar to Covid-19. HAPE patients initially compensate for the low oxygen in high altitudes by tachycardia in the presence of a low oxygen saturation. As the disease worsens, Dr. Gattinoni reports these patients seem to have a dissociation between well-preserved lung mechanics and the severity of hypoxemia shown by a large discrepancy in compliance vs shunt fraction.

Given this evidence it seems that Covid-19 is primarily a hypoxemic disease, unlike ARDS, which involves alveolar collapse and exhaustion of respiratory muscles. The reason for the hypoxemia is proposed in a pre-print article showing in vivo that Covid-19 proteins exhibit binding to the 1-beta chain of hemoglobin leading to dissociation of the iron from the protoporphyrin. This may explain severe hypoxemia out of proportion to lung pathology. Since it is likely that this is a vascular issue, this may explain why ARDS protocol ventilation may lead to high mortality in ventilated patients; it involves high PEEP pressures to keep the alveoli open at the expense of compressing the pulmonary vasculature. High enough PEEP pressures can also lead to hypotension.

Perhaps it is time for a change in the way we are treating these high-risk patients. The physicians who spoke in the podcasts used in this study recommend using the O2 saturation in addition to the patient’s appearance to decide when to intubate. They recommend starting conservatively with high flow nasal cannula in combination with self-pronation and restriction of maintenance fluids. High flow nasal cannula has been shown to improve outcomes in ARDS and may contribute a small amount of PEEP to maintain lung inflation which may be all these patients need. The ROTH score, which involves asking a patient to count from 1 to 30 using one signal breath, may be useful as a screening tool (sensitivity 91% and specificity 93% for pulse ox < 95%). Some physicians have even asked their patients to walk to sit up and down in their chair as a measurement of hypoxia.

It is important to remember that we cannot become too lax in our criteria to intubate. In a study from California with 54 Covid-19 patients showed that low oxygen saturation at initial examination were significantly associated with admission to the ICU, diagnosis of pneumonia, and progression to ARDS. For now, we do not know at what oxygen saturation someone will decompensate, but it likely depends on the patient. Because of the high mortality of ventilation, maybe it is time for us to use other measures including respiratory effort and mental status to determine treatment, focusing on delaying intubation. This differs from the current dogma of early intubation is best, so the sources used in this paper argue more information is needed on proper ventilation protocol in these patients.

References

What is the Role of ECMO for Severe Covid-19?

By Helen Pozdniakova

Summary

ECMO is a limited resource that seems to have a high mortality in Covid-19 but Japan is seeing good results. Right now, there is no Covid-19 specific inclusion criteria for ECMO. There is a theoretical risk of bloodborne Covid-19 transmission on ECMO but it is probably more of a concern during long runs. We are unsure about how to address the coagulopathies of Covid-19 for patients on ECMO.

Evidence to Date

Extracorporeal membrane oxygenation (ECMO) is a form of last resort support for critically ill patients whose heart or lungs cannot provide adequate perfusion for the body. In dedicated ECMO centers, it has been an invaluable resource for those critically ill who meet criteria. It has also been used successful in the past during the H1N1 to improve survival.

With the high mortality of Covid-19 and the surge of cases worldwide, does ECMO has a role now?

Is ECMO available?

WHO interim guidelines recommend offering ECMO to eligible patients with ARDS due to Covid-19. Right now, we do not know how many patients with Covid-19 will develop ARDS that is refractory to maximal medical management. The use of ECMO globally is overall low and generally restricted to specialized centers. Therefore, the ELSO (the foundation overseeing ECMO) acknowledges that widespread ECMO use in this pandemic may be unrealistic. ECMO is resource intensive and limited in availability. The need for specially trained staff and transportation to specific facilities may not be feasible during a severe surge.

Is ECMO indicated?

ECMO has been used already for severe Covid-19 ARDS. The ECMO registry has 122 patients who received ECMO for Covid-19. Of those, 34 have completed their ECMO run but only 1 was discharged alive. Similarly, recommendations from China cite high mortality of patients on ECMO, with a 50% mortality in a study of 28 patients. Because of this, ELSO recommends judicious selection of patients for ECMO therapy. Hospitals continue to use conventional inclusion/exclusion criteria and they do not provide specific guidelines for Covid-19.

REFERENCES


considerably high. We know that Covid-19 infection is deadlier in those who are older, so many favor ECMO use only in young patients. Another common exclusion criteria is multi-organ dysfunction which is a common complication of those critically ill with Covid-19. We need more data before we can identify Covid-19 patients who are older or with multi-organ dysfunction that will benefit from ECMO.

However, data from Japan seems to be different. Statistics as of March 30th, 2020 from the Japanese Society of Intensive Care Medicine show a total of 40 patients on ECMO, of which 14 recovered (35%) and 6 died (15%). We also know that ECMO is being utilized at a higher rate in Japan compared to the US. More information is needed but we may be seeing a large difference in ECMO mortality between the US and Japan.

Can ECMO spread Covid-19?

Due to limited information, ELSO recommends proper PPE during any ECMO related procedures. In addition to PPE, sterile attire must be worn when performing cannulation and decannulation. Because of all these layers, performing a proper procedure may be challenging and therefore extensive training must be done beforehand to decrease risk of contamination and procedural error.

In regard to blood transmission, the diameter of an ECMO membrane is 0.04 – 0.10 μm and the diameter of Covid-19 is 0.06 – 0.14 μm. It is theoretically possible that Covid-19 could pass through. However, it is thought that the charge created by the coating material of the membrane is likely enough to block Covid-19 transmission and that the risk of transmission is likely lower than the risk of respiratory tract transmission through mechanical ventilation. There is one caveat: with long ECMO runs the membrane can deteriorate causing a plasma leak. A hospital in Japan had a positive PCR swab from the exhalation port from an ECMO machine during a plasma leak. [2][4]

What is the concern for coagulopathy on ECMO?

Patients on ECMO for any reason are given unfractionated heparin at the time of cannulation and by continuous infusion during the course of treatment. This is to prevent thrombosis within the system so a target aPTT of 40-60 is recommended. This may be beneficial for Covid-19 patients who are thought to be in a hypercoagulable state, evidenced by the increased reports of VTE and elevated d-dimer levels. However, we have seen that patients who exhibit coagulopathy (elevation of PT or aPTT) are at higher risk for severe illness and may be a late complication of Covid-19. [6] Based on experience in Japan, they believe bleeding is actually a more common complication of severe Covid-19 than thrombosis. However, they did not make any specific recommendations on changing the anticoagulant protocol for Covid-19 ECMO patients. Instead, they suggested monitoring the PT/aPTT every 6 hours for bleeding risk. [2]
Convalescent Plasma as a Treatment Option for Patients with COVID-19

By Katherine Veltri

Summary

Convalescent plasma provides passive immunization to critically ill patients with COVID-19. Studies assessing the benefit of convalescent plasma treatment in patients with SARS-CoV, influenza, and COVID-19 show improvement of clinical status, decreased mortality and decreased viral load. While these results seem promising, high-quality control trials are needed to truly assess the benefits of convalescent plasma.

Background

Plasma is a component of blood composed of many proteins, including antibodies. Treatment with convalescent plasma provides immediate, passive immunization to different diseases. It is especially helpful when there are no immunization for a disease, or when a disease carries significant morbidity and mortality [5]. Convalescent plasma has been used in the past to treat SARS-CoV, H1N1, and other viral infections with promising results [4] and it is currently being investigated as a treatment option for patients with COVID-19.

Evidence to Date

Due to the possibility of adverse outcomes and the lack of consistent, high-quality research, convalescent plasma is being used as a last resort option for patients who are critically ill [6]. Possible adverse reactions to convalescent plasma include a small but nonzero risk of infectious disease transmission, fever, life threatening bronchospasm, and transfusion related acute lung injury (TRALI) [2].

In 2014, a systemic review and exploratory meta-analysis assessed 32 studies that administered convalescent plasma to critically ill patients with SARS-CoV and influenza. They found consistent evidence for reduction in mortality, especially when given early on in the disease. Some of the studies in the review also showed significant decrease in viral load in the respiratory tracts of patients with both SARS-CoV and influenza. None of the studies reported adverse effects from treatment. The overall significance of the results found in this review is limited by the lack of high-quality studies and risk of bias. [1]

Treatment with convalescent plasma is currently being investigated in critically ill patients with COVID-19. In an uncontrolled case series from China, convalescent plasma containing neutralizing antibody was administered to 5 critically ill patients with COVID-19 and acute respiratory distress syndrome (ARDS) [3]. The patients, 2 women and 3 men aged 36-65, were receiving mechanical ventilation at the time of transfusion, and had received antiviral agents and methylprednisolone. Following the transfusion with convalescent plasma, all of the patients showed improvement in clinical status approximately one week after transfusion [2]. Additionally, ARDS resolved in 4 of the patients within 12 days and viral loads became zero in all 5 patients within 12 days of transfusion [3]. This study was limited by a lack of a control group [2].

Another study assessed four case reports of critically ill patients with COVID-19 who were treated with supportive care and convalescent plasma. In the first case, the viral load dropped from $55 \times 10^5$ to $3.9 \times 10^4$ to 180 copies per milliliter after the administration of convalescent plasma. The time from transfusion to negative RT-PCT testing in all four patients ranged from 3-22 days. They reported no serious adverse reactions. Three out of the four patients were discharged from the hospital and are recovering, one remained in the ICU. The limitations of this study are that the contributions of convalescent plasma versus supportive care and the patient’s immune-response cannot be determined. [6]

Conclusion

We need well-designed clinical trials to truly assess the benefit of convalescent plasma as a treatment option for COVID-19. However the improvement in clinical status seen in these studies is compelling and we should continue investigating this treatment option in critically ill patients with COVID-19.

References


Who Can Receive or Donate Convalescent Plasma?

By Katherine Veltri

Background

Convalescent plasma treatment is a way to provide critically ill patients with antibodies to fight COVID-19. People who recovered from the disease may be eligible to donate their plasma to patients with severe or life-threatening illness.

Criteria

Patient Eligibility: [4]
- Patients with laboratory confirmed, severe or immediately life-threatening COVID-19 infection are eligible for treatment.
  - Criteria for severe disease:
    - Dyspnea
    - Respiratory rate >30 BPM
    - SpO₂ less than or equal to 93%
    - PaO₂/FiO₂ ratio of <300 and/or
    - Lung infiltrates >50% within 24-48 hours
  - Criteria for life-threatening disease:
    - Respiratory failure
    - Septic shock and/or
    - Multiple organ dysfunction or failure

Donor Eligibility: [4]
- Who:
  - Males, females who have not been pregnant, or females who have been pregnant but who have negative HLA antibodies who have been infected with COVID-19.
  - Infection must be confirmed with a diagnostic test at time of illness or with positive antibodies after recovery.
- When:
  - Complete resolution of symptoms for 28 days prior to donation or complete resolution of symptoms for 14 days with a negative test (e.g. nasopharyngeal swab)

Details of Donating Plasma [1], [2]

Whole blood has four components: red blood cells, white blood cells, platelets, and plasma. Plasmapheresis is the process of separating plasma from the rest of the blood and can be performed by two different techniques. Centrifugation spins whole blood so that the components are separated based on density. Filtration is when whole blood passes through a filter that separates plasma from the other components. Most blood centers use the centrifugation technique: blood gets drawn from the body and spun in a machine, plasma is separated, and the rest of the blood is returned to the body. Donated plasma must have COVID-19 neutralizing antibody titers > 1:80 to be used in treatment. Donors should weigh more than 110lbs and be in general good health.

Possible Adverse Reactions

Although serious adverse reactions are not reported in many studies assessing the benefits of convalescent plasma treatment, there still is risk associated with the transfusion. Possible adverse reactions include mild fever, allergic reactions, life threatening bronchospasm, transfusion related acute lung injury (TRALI), and circulatory overload [5].

Whole Blood Donation:

Typically, when someone donates plasma, the rest of the blood components are returned to their body. This differs from whole blood donation, when all four components of blood are taken: red blood cells, white blood cells, platelets, and plasma. Currently, blood centers are being challenged to maintain their inventory due to blood drive cancellations, social distancing, and decreased number of eligible donors [6]. As we implement convalescent plasma treatment and recruit plasma donors, it could be beneficial to collect whole blood from donors since plasma can be extracted from the whole blood donation. This could help replenish the inventory of the other components of blood in blood centers and hospitals. However, the downside of whole blood donation versus plasma donation is that we get approximately 2-3 times more plasma per donation when someone solely donates plasma [3].

References:

Anticoagulation in Covid-19

By Kevin Brandecker

Summary

Elevated D-dimers have been a lab finding seen in several patients hospitalized with Covid-19. Lung dissection of a critically ill patient found the evidence of microthrombi which has raised the question of the role of anticoagulation in the treatment of Covid-19. A team out of China, citing unpublished data on DIC in Covid-19, recommends the use of LMWH, 100 U/kg every 12 hours for 3-5 days when the D-dimer is > 4 times upper limit of normal. One member of this team published his account of working in Wuhan and noted that some patients between days 7 and 14 seemed to develop a worsening of their clinical state which was associated with a hypercoagulable state and thus recommend the use of LMWH and IVIG. A retrospective study showed that in patients with sepsis-induced coagulopathy score (SIC) ≥ 4 or a D-dimer > 6 times the upper limit of normal there was decrease mortality in the group treated with LMWH or Heparin mostly given at prophylactic dosing. A commentary on this article echoed the use of LMWH citing anecdotal accounts out of Italy that showed an increased risk of venous thromboembolism in Covid-19 hospitalized patients.

Background

A team out of China reported that they have noticed Covid-19 patients with severe disease often develop DIC, citing unpublished data. Because of this, they recommend the anticoagulation of patients when their D-dimer is four times the upper limit of normal and there are no contraindications to anticoagulation. They used LMWH at a dose of 100 U/kg every 12 hours for 3-5 days. In addition to LMWH, they are also endorsing the use of high-dose IVIG at 0.3–0.5 g/kg per day for 5 days with the thought that it will disrupt the cytokine storm due to its efficacy in the treatment of patients with influenza and SARS-CoV.1

One of the authors on this paper is Taisheng Li M.D. Ph.D. who published on March 25th, 2020 his observation on Covid-19 patients since arriving in Wuhan on February 7th, 2020. He notes that often between days 7-14 of the infection some patients develop a worsening of their clinical condition which he calls the “second phase.” As part of this, they developed a hypercoagulable state and D-dimer coagulation becomes abnormal. He notes that with the elevated D-dimer there is often an increase in the PT and decrease in fibrinogen. Because of this his colleagues at the Department of Hematology, Peking Union Medical College Hospital recommend the use of LMWH as well as IVIG at this stage of the disease.2

A retrospective review of hospitalized Covid-19 patients in Wuhan, China was performed to look at the role of anticoagulation in the treatment of Covid-19 coagulopathies. The sepsis-induced coagulopathy (SIC) scoring system was used which factored in PT, platelet count, and sequential organ failure assessment (SOFA). They found that there was no difference in 28-day mortality in heparin vs non-heparin patients. But there was a decrease in 28-day mortality between heparin and non-heparin patients when both groups had a SIC ≥4 or a D-dimer > 6 times the upper limit of normal. Given the design of the study, they acknowledge that patients may have been started on Heparin for a specific symptom or past medical condition, the influence of other therapies cannot be excluded and was conducted early in the outbreak. A lung dissection of a critically ill patient found microthrombi on the exam which may have led to the use of anticoagulation after these results were released.3,4

They conclude that anticoagulation mainly with LMWH may benefit patients with a SIC ≥4 or a markedly elevated D-dimer. Regarding dosing, there is no specific dose endorsed but most patients were on prophylactic doses. They do acknowledge that there are lower rates of venous thromboembolism in the Asian population so the dose may need to be increased in non-Asian populations. Recombinant soluble thrombomodulin or antithrombin is not currently available in China and thus was not able to be used.5

A commentary on this paper also in the Journal of Thrombosis and hemostasis was written by Dr. Jecko Thachil who is the chairman of the DIC subcommittee of the International Society of Thrombosis and Hemostasis. He mentions anecdotal accounts in Italy that showed an increased risk of venous thromboembolism in patients admitted to the hospital with Covid-19. The severe lung inflammation seen in Covid-19 triggers the upregulation of pro-inflammatory cytokines which could lead to increased fibrinogen lysis. Also mentioned is a systematic review that concluded in the clinical environment heparin decreased levels of inflammatory biomarkers and a meta-analysis that showed LMWH reduced 7- and 28-day mortality and increased oxygen index among ALI/ARDS patients. The immediate question raised is determining what the dose of LMWH is effective to treat patients. Prophylactic dosing may be appropriate in most patients but may need to increase the dose in higher body mass patients.6

Reference


Update on QT monitoring in Covid-19 when treated with Hydroxychloroquine and/or Azithromycin

By Kevin Brandecker

Summary

The use of either Hydroxychloroquine alone or paired with Azithromycin has garnished much interest as a possible treatment for Covid-19. Both medications are associated with QTc prolongation which increases the risk of drug induced Torsades de pointes and sudden cardiac death. A retrospective study performed at NYU Langone medical center with 84 patients found that the average QTc increased from 435 ± 24 ms to a maximum of 463 ± 32 ms after the initiation of treatment with Hydroxychloroquine and Azithromycin. The increase QTc peaked on day 3.6 ± 1.6 of therapy. A paper in Mayo Clinical Proceeding provided guidelines about the use of QTc prolonging drug in Covid-19 by creating a “green light, yellow light, red light” system to classify patients by their pre-treatment and post-treatment QTc. This scheme was then used to create a flow chart to help guide clinical decision making. They recommend the use of repeat ECG 2-4 hours after the initiation of treatment in patients with a QTc ≥500 ms. They state that those patient with a QTc ≥ 500 ms should only be started on QTc prolonging medications if they have significant benefit compared to the risk. And then for all patients to have a repeat ECG 48-96 hours after initiation of treatment. Given the results out of NYU Langone it may be worth expanding the window recommended from the paper in Mayo Clinical Proceeding, 48-96 hours after initiation of treatment, in order to better assess the maximum QTc interval if Azithromycin is also being used.

Evidence to Date

There was a preprint paper released on April 3, 2020 out of NYU Langone medical center that looked at 84 patients that were treated with Hydroxychloroquine and Azithromycin (HY/AZ) combo therapy and its effect on the QTc interval. Prior to initiation of HY/AZ treatment the average QTc was 435 ± 24 ms which lengthen to a maximum of 463 ± 32 ms on day 3.6 ± 1.6 of therapy. During this time 11 % of patients were found to develop a QTc > 500 ms and 30 % had their QTc increase by greater than 40 ms. The development of acute renal failure was found to be a significant predictor of QTc elongation. They concluded that pretreatment QTc measurement is unable to predict QTc elongation and that repeat testing needs to be performed after the initiation of treatment.

An article out of the Mayo Clinical Preceding focused on the creation of precautions that should be taken to decrease the risk of drug induced Torsades de pointes and sudden cardiac death in those with Covid-19 being treated with QTc prolonging agents. They endorse an approach of using pre-treatment EKG or smartphone enabled mobile QTC meter to
screen patients for a prolonged QTc interval and to stratify them into varying groups.

“Green light” patients are those who are pre-puberty with QTc < 460 ms, post-puberty males QTc <470 ms, or post-puberty females < 480 ms and thus can be prescribed the Hydroxychloroquine if indicated.

“Yellow light” patients are pre-puberty with QTc ≥ 460 ms, post-puberty males QTc ≥470 ms, or post-puberty females ≥ 480 ms but less then 500 ms. These patients should have any unnecessary QTc prolonging medications stopped and their potassium and magnesium checked and then can start Hydroxychloroquine if indicated.

“Red light” is considered those with a QTc ≥ 500 ms and they recommend carefully weighing the risk and benefits of Hydroxychloroquine. If there is initiation of treatment, they recommend a repeat EKG 2-4 hours after the first dose of Hydroxychloroquine.

All patients should then have a repeat EKG 48 to 96 hours after initiation to evaluate for changes in QTc which may change management. Their decision making progress is found in figure 1 of their paper. A limitation discussed is that repeat testing is going to result in increased personal exposure, use of limited PPE, and contamination of ECG machine/wires. An alternative discussed is the use of FDA-approved consumer mobile ECG devices or telemetry systems that are equipped with real time QTc monitoring.

These two studies in combination can provide guidance on the use of QTc prolonging drugs like Hydroxychloroquine and Azithromycin in the treatment of Covid-19. Applying the data from the study performed at NYU to the guidelines released in the article from Mayo Clinical Preceding it may be worth increasing the time frame recommended from the article in Mayo Clinical Preceding, 48-96 hours, to factor in that maximum QTc found at NYU Langone was on day 3.6 ± 1.6. It’s important to note that this article did not include the use of Azithromycin in their algoerytheme.

Reference