RESUMPTION OF ELECTIVE PROCEDURES FOLLOWING COVID-19

By Austin Krebs

Summary
At the rise of the COVID-19 pandemic, elective procedures were severely scaled down. As COVID-19 burden begins to lighten, the White House has released the Gating Criteria for reopening America in phases, which includes resuming outpatient elective surgeries with inpatient to follow if COVID-19 incidence remains low. Strategies to address the backlog of surgical cases are extremely important in the face of resuming some normal healthcare activities. The American College of Surgeons has released guidelines to help prepare facilities for resuming elective cases. These include diligent patient testing, acquiring PPE and establishing testing protocols for healthcare workers, and the use of ambulatory surgery centers to compensate for increased caseload.

Evidence to Date
As time continues to pass while following social distancing and isolation recommendations, the question everybody is asking is ‘when can we get back to normal?’ Specific to healthcare, this consideration has been asked by many surgeons who postponed elective surgeries in light of the COVID-19 pandemic. Now, however, we’re approaching what seems to be an inflection point in the trajectory of this disease. The White House has released guidelines dubbed the “Gating Criteria” which address “Opening Up America Again.” These criteria outline their recommendations for resuming some normal activities in phases. For phase one, proposed requirements include a downward trajectory of documented COVID-19 cases for at least 14 days, as well as the ability for hospitals to treat all patients without crisis care. They also recommend a robust testing program for at-risk healthcare workers, which specifically includes emerging antibody testing. So long as these conditions are met, elective outpatient surgeries may resume as clinically appropriate at facilities that adhere to CMS guidelines. Inpatient surgeries may resume in phase two, slated to begin if another 14-day reduction in COVID-19 is observed during phase one.[1]

Given the significant case backlog due to COVID-19, considerable focus has been placed on helping facilities “ramp up” to prepare for the resumption of elective cases. To help address this, the American College of Surgeons (ACS) has released a document offering some recommendations.[2] They align with the White House’s recommendation to document a decrease in local COVID-19 incidence over 14 days before resuming elective cases. They also suggest defining a threshold for COVID-19 incidence that would prompt re-entering a mitigation phase at specific facilities to ensure local resurgence does not occur.

The ACS guidelines have recommendations for COVID-19 testing protocols in pre-operative patients, as well as healthcare workers once physical distancing is reversed. They also recommend a stored inventory or a reliable supply chain of PPE for 30 days’ worth of airborne/aerosol and droplet/contact precautions. The document also suggests ensuring multidisciplinary staffing coverage for routine and expanded operating hours as well as contingency plans if healthcare workers test positive for COVID-19. A multitude of other topics are covered within the full set of guidelines. Several suggestions for addressing the backlog of surgical cases have been made, including performing operations at night as well as on weekends. As stated above, phase one of “Opening Up America Again” allows for outpatient services only. The role of the ambulatory surgery center cannot be overlooked during this time, as the existence of these facilities may help to compensate for increased case volume while reducing the burden on facilities still treating COVID-19 patients. This also helps to minimize the exposure of...
asymptomatic individuals during this transition period. Some surgeons have previously proposed using these centers for surgically necessary or time-sensitive orthopedics procedures.[3] Utilizing ambulatory surgery centers during this period of surgical backlog could help to alleviate hospital burden and more efficiently address the case backlog. As we attempt to return to some semblance of normal, surgical volume will increase considerably to address the many elective cases that have been postponed. Considerations must be taken to address this increased volume, and vigilance must be maintained to prevent unnecessary resurgence of COVID-19 while the country attempts to reopen.

Limitations

The above report is mostly based off of guidelines released by the White House and American College of Surgeons. The literature search performed did not yield much as far as the effects that resuming elective cases may have on COVID-19 incidence. Similarly, no clear strategies to address ramping up for elective procedures were found aside from the ACS guidelines. Maintaining proper treatment and operating room protocol, as well as keeping a close eye on COVID-19 incidence, will be necessary to ensure no ill effects come from the resumption of elective cases.

References


ACE Inhibitors and ARBs May Reduce COVID-19 Mortality

By Austin Krebs

Summary

Several hypotheses regarding the effects of ACEi and ARB therapy on the severity of COVID-19 have circulated based on ACE2 and its role in viral entry and attenuating lung injury. ACEi/ARB therapy has been shown to be protective in viral pneumonia. Early studies with small samples suggested that ACEi/ARB therapy might be protective in COVID-19. A recent retrospective analysis of 1128 patients in Hubei Province, China showed significantly decreased all-cause mortality in COVID-19 patients on ACEi/ARB therapy compared to patients not on these medications, with an adjusted hazard ratio of 0.42. Further research is necessary, but it appears ACEi/ARB therapy does not increase mortality and may decrease it.

Evidence to Date

Previous reviews in this series have examined the potential effect that angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) may have on the disease course of COVID-19. Several hypotheses were formulated when the mechanism of viral entry was identified as angiotensin converting enzyme 2 (ACE2). One camp thought it would lead to higher viral load and more severe disease, the other that it would ameliorate lung injury induced by the virus and decrease severity. The purpose of this review is to reexamine the evidence in light of new research. Early research with a limited sample size suggested a less severe disease course in patients on ACEi or ARB therapy.[1] This mechanism might be explained by a few mechanisms. ACE2 has been associated with attenuation of acute lung injury in animal models.[2] This effect has been attributed to the conversion of angiotensin II, a vasoconstrictor, to angiotensin 1-7, a vasodilator. Other studies have shown that ACE2 can have effects on the inflammatory milieu present in acute lung injury, as it is associated with reduced levels of IL-6 and TNF-α.[3]

One retrospective study of 539 patients with viral pneumonia showed a decreased risk of death in patients on ACEi/ARB therapy, with respective odds ratios of 0.25 and 0.75 for ACEi and ARBs compared to patients not on either of these medications.[4] This research served as a basis for the possible benefits of ACEi/ARB therapy in COVID-19, but targeted research had not yet been conducted.

Recently, a large retrospective study directly examining the effects of ACEi/ARB therapy on COVID-19 has been performed. Peng et al performed a retrospective analysis of 1128 adult patients with COVID-19. Of these patients, 188 were taking an ACEi or ARB and 940 were not. This group observed a decreased risk for all-cause mortality after adjusting for age, gender, comorbidities, and in-hospital medications with an adjusted hazard ratio of 0.42. A
propensity score-matched analysis also showed a mortality benefit when compared to other hypertension medications, with an adjusted hazard ratio of 0.30 when taking an ACEi/ARB compared to other antihypertensive agents.[5]

This study had limitations, including insufficient power to differentiate between the effects of ACEi and ARBs individually. Additionally, it was a retrospective study, and warrants future confirmation with prospective trials. However, Peng et al state that based on their results, it is unlikely that ACEi/ARB therapy increases mortality and recommend continuing these therapies in patients already receiving them. This study appears to be the first to directly address the debate about the potential effects of ACEi/ARB therapy with a large enough sample to speak with confidence. More targeted, robust data are necessary to further examine the relationship between these medications and COVID-19, but this lends support to continuation of ACEi and ARBs in a time of relative uncertainty.

Limitations

The Peng et al paper highlighted in this review highlights patient-oriented outcomes, as its main aim was to examine mortality in subsets of patients. It is a retrospective cohort study which makes it a Level 2 based on the Strength of Recommendation Taxonomy (SORT). The authors themselves acknowledge the need for future research to determine the nature of the relationship between ACEi/ARBS and COVID-19. Their cohort included 1128 patients, however only 188 of them were on ACEi/ARB therapy, leaving insufficient power to differentiate between the two individual therapies in their analysis. This paper appears to be one of the first directly examining the relationship between ACEi/ARBS and COVID-19 with a large sample size. Other retrospective studies are expected in the future for comparison, and prospective cohort or RCTs are necessary to further elucidate the effect of these medications on COVID-19 disease course.

References

COVID-19 Antibody Response and Testing
By Candace Pallitto

Summary:
Most studies currently indicate that seroconversion of IgG occurs within two weeks after symptom onset. Understanding the timing of seroconversion can guide when to use antibody tests to yield the best results. Creating effective and accurate antibody tests will serve many purposes, including contact-tracing of asymptomatic individuals, providing information about future vaccine efficacy, and determining if healthcare and other workers have immunity when returning to work. Targets of antibody testing include the nucleocapsid protein (N protein) and spike protein (S protein) of COVID-19, which can be more specifically broken down into two domains: S1 and receptor binding domain (RBD). The S protein is the most specific protein on the surface of the virus, but the nucleocapsid protein (N protein) is one of the most abundant.[1] At this time, most antibody tests evaluated have shown minimal cross-reactivity to common pathogens, including other human coronaviruses. In the United States, there are only two FDA approved assays for COVID-19 under Emergency Use Authorization: a lateral flow assay by Cellex Inc. and Mount Sinai Laboratory’s ELISA IgG.

Antibody Response to COVID-19
Understanding the timing and duration of seroconversion in patients with COVID-19 could provide insight into disease progression and future protection from COVID-19. Previous data about SARS-CoV shows that it induces seroconversion by about day 4 of illness and in most patients by 14 days, while MERS-CoV demonstrated seroconversion in the second and third week of illness.[2] Current research about COVID-19 antibody response is limited, but most studies are showing full IgG response by two weeks. One study by Guo et al. with 208 blood samples from 140 patients with varying severity found that IgM and IgA were detected an average of 5 days after symptom onset (IQR, 3-6) while IgG was detected around 14 days (IQR, 10-18).[3] One advantage to this study was that they found no cross-reactivity with antibodies for other coronaviruses. Another study with 173 patients and 535 serial plasma samples found that the median time to antibody detection was 12 days for IgM and 14 days for IgG.[4] This study also showed that higher titer of total antibody was independently associated with more severe disease. However, the overall data on association between disease severity and immunoglobulin response is inconclusive as other studies have not demonstrated the same association. In addition, a different analysis found that either IgG or IgM for recombinant N protein and RBD were present after 10 days for the majority of patients with seropositivity rate of 94% for anti-NP IgG and 100% for anti-RBD IgG at 14 days after symptom onset for 16 patients.[5] Furthermore, a few studies have shown that IgG responses were detected sooner than IgM and IgA responses for COVID-19, which could indicate an unexplained immune evasion mechanism, but could also be due to greater sensitivity of the assay for IgG and the fact that some studies classified their duration from when the sample was obtained and not from symptom onset.[4,6,7]

In regard to how long immunity for COVID-19 will persist, there is not much data on this topic. Previous studies of SARS found that immunity could last for 2-3 years.[1,4] One report of convalescent COVID-19 patients found that all 60 patients tested positive for IgG 6-7 weeks after infection with levels of IgG higher than IgM at this time. They tested one group of 10 patients twice at one week apart and found that both levels of IgG and IgM decreased with the second testing.[8] The authors concluded that antibody levels could help determine the stage of disease, but that more information is needed about duration of protection.

Antibody Testing
Targets and Cross-Reactivity
One study listed by the Center for Disease Control and Prevention used 3 patient samples to examine COVID-19 antibodies to the N protein as well as the S1 and receptor-binding domains of the S protein using an the EUROIMMUN ELISA from Germany.[9] Current studies of ELISA have consistently shown very little or no cross reactivity with antibodies to other human coronaviruses, including SARS-CoV. This study did show mild cross-reactivity of COVID-19 S protein with MERS-CoV S protein, but not with the S1 protein domain, indicating that this portion is more specific to COVID-19. There was also some cross-reactivity with the S1 domain and RBD of COVID-19 with SARS-CoV, but the authors suggest that since SARS has not circulated in humans since 2003 and that the immunity is most likely limited to a few years, this cross-reactivity will not pose a problem when testing patients for COVID-19. This idea also applies to the N protein, which is 90% similar to SARS. Furthermore, this study also found that RBD and N were more sensitive targets for antibody detection in mild infections.

Types of Tests
Two popular types of antibody tests are enzyme-linked immunosorbert assay (ELISA) and chemiluminescence immunoassay (CLIA). One specific test for COVID-19 is the MAGLUMI 2019-nCoV IgG and IgM which are indirect CLIA’s that assess for anti-COVID-19 IgG and IgM. A preprint study compared the results of the MAGLUMI IgG and IgM to the EUROIMMUN ELISA IgG and IgA and found a 90% concordance between the two tests. Another preprint study aimed to assess the analytical performance of MAGLUMI™ 2000 Plus CLIA found that it was a reliable test with high precision, despite lacking a validated method for comparison studies and information about the cross-reactivities of the assays.[10] There are other tests being developed, but the Euroimmun and MAGLUMI currently have the most data, comparison studies, and seem to be the more popular assays in Europe at this time.
Another type of test to detect COVID-19 antibodies are lateral flow immunoassays. The Federal Drug Administration (FDA) under Emergency Use Authorization (EUA) has approved a lateral flow assay from Cellex Inc. that qualitatively detects IgG and IgM of COVID-19. This test was found to have a positive percent agreement (PPA) of 93.8% and a negative percent agreement (NPA) of 96% compared to RT-PCR positive specimens as well as no cross-reactivity to a panel of common pathogens, including other human coronaviruses.[11] Two weeks later an ELISA IgG test to the recombinant S and RBD domains created by Mount Sinai was approved under EUA too. The PPA and NPA for this test was 92% (95% CI: 79%, 98%) and 100% (95% CI: 94%, 100%) respectively with no cross-reactivity.[12] This group of researchers has also released a pre-print study analyzing a high-throughput method of evaluating antibody results using the Luminex bead binding antibody assay that can run in 2.5 hours, analyze about 1,000 samples per day, and required less antigen.[13]

Further analysis and development of high-throughput methods and increased amount of accurate serological tests are needed at this time. Currently, there are over 70 other serological tests for COVID-19 on the market without FDA approval, but the lateral flow assay from Cellex and ELISA IgG developed at Mount Sinai Laboratory are the only two tests approved under EUA.

**Conclusion**

Review of the recent literature reveals that IgG seroconversion occurs by 14 days with varying results in terms of persistence of immunity as well as IgM and IgA levels. Some studies have also shown that disease severity may be related to amount of IgG. More data is needed to assess how long this immunity will persist. In terms of application, understanding the timing of antibody response can inform when antibody testing may work best. Antibody testing can be used to enhance diagnoses of COVID-19 when used with other tests, such as RT-PCR, but it should primarily be used for contact-tracing of asymptomatic individuals, assessing immunity of individuals with decreased social distancing, and evaluating future vaccine efficacy data. Current research is showing that cross-reactivity does not seem to be an issue with COVID-19 serological assays and that target proteins can include the S1 and RBD of the S protein as well as the N protein. The main antibody tests for COVID-19 are ELISA, CLIA, and lateral flow assays with the Cellex lateral flow assay and Mount Sinai Laboratory ELISA IgG being the only two FDA emergency use authorized tests at this time. Understanding the timing of antibody response as well as the development of better serological tests will be an important step in the eventual relaxation of social distancing measures.

**Limitations**

Limitations of the antibody response time studies include lack of a gold-standard for detection of antibodies, varying definitions of symptom onset (i.e. presence of fever or not), small samples, and fact that not all of the studies included cross-reactivities. The main limitations of the antibody testing studies are that there is no adequate reference test for comparison, lack of a gold-standard diagnostic test for COVID-19, small sample sizes, lack of repeated trials, and overall abundance of tests on the market with limited evaluation or validation. Many of the studies at this time are also not peer reviewed.

**References**

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Rheumatologic Considerations During the COVID-19 Pandemic
By Catherine Hahn

Summary
Rheumatologic treatments are at the center of a paradoxical debate with regards to COVID-19: are they putting patients at increased risk for infection from immunosuppression, or are they the source of a possible life-saving treatment for patients with COVID-19? Current data suggests that there is no evidence that patients on immunosuppressants are at increased risk for COVID-19 complications compared to the general population. Preliminary data of COVID-19 in a small group of rheumatic disease patients revealed that these patients did not suffer from severe respiratory disease and had good outcomes. While immunosuppressants and biology disease-modifying agents confer a potentially increased risk of infection, uncontrolled rheumatic disease is an even greater risk factor for infection. As such, it is recommended that all patients with rheumaticologic diseases continue their immunosuppressant therapies at this time.

Are Patients with Rheumatic Disease on Immunosuppressants at Increased Risk of COVID-19?
In general, patients with rheumatic diseases are at increased risk of infection due to the disease process itself, immune-modifying therapies, and comorbidities. Available data suggests that immunosuppressants and biologic disease-modifying agents used to treat rheumatic disease potentially increase the risk of infection. Previous randomized control trials of patients with rheumatoid arthritis on corticosteroids show that these patients are not more susceptible to viral infection. However, case-control and cohort studies have shown an increased susceptibility to viral infection in rheumatoid arthritis patients treated with corticosteroids in a dose-dependent manner. There is a limited amount of data on respiratory viral infections and biological disease-modifying antirheumatic drugs (bDMARDs). One study of 159 patients on bDMARDs showed that these patients had an increased incidence of influenza compared to the generally population but did not have an increased risk of serious complications. There is currently no available data on JAK inhibitor use and risk of respiratory viral infections. However, rheumatoid arthritis patients on JAK inhibitors have been shown to have to up to two times the risk of HZV infection compared to rheumatoid arthritis patients not on JAK inhibitors.

There is currently a limited amount of data on the disease course of COVID-19 in patients with rheumatic diseases. However, preliminary data from Lombardy, Italy at the heart of the outbreak shows that there is no evidence to suggest that
this population is at increased risk of infection or complications from COVID-19. A group of rheumatologists reported out of a cohort of 320 patients treated with biological disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), only four patients had confirmed COVID-19 and four patients had symptoms highly suggestive of COVID-19. Of note, five of these patients were on hydroxychloroquine treatment prior to acquiring infection. As part of the treatment course, the patients temporarily suspended their bDMARD or tsDMARD treatment. None of the patients had severe respiratory disease and only one patient, who was 65 years old, required hospital admission and low-flow oxygen prior to being discharged. This data is in accordance with other available data on COVID-19 and immunosuppressed patients. A recent paper documenting cases of COVID-19 among liver transplant patients in Bergamo, Italy showed that out of 200 patients, only 3 tested positive for COVID-19 and none developed symptoms. Thus, both of these samples illustrate that patients on immune-modifying therapy, including those with rheumatic diseases, do not seem to be at increased risk of respiratory complications due to COVID-19 or have increased mortality.

Management of Rheumatic Disease Patients During the COVID-19 Pandemic

The discontinuation of immune-suppressing therapy is not justified based on the data that is available at this time. It is recommended that patients continue their immune-suppressing therapies in order to keep their rheumatic diseases under control. In addition, poor control of inflammatory diseases such as rheumatoid arthritis is a known risk factor for infection, so it is critical that patients maintain their current medication regimens to minimize infection susceptibility.

Data suggests that viral infections, including coronaviruses, can precipitate flares of rheumatic diseases. This includes triggering new onset rheumatoid arthritis and reactivating arthritis in patients previously in remission. The posited mechanisms behind this phenomenon include the virus inducing cross-reactivity of T cells via molecular mimicry or direct damage from the virus leading to autoreactive T-cell activation. As such, these patients should continue to follow best hygiene practices and continue with their disease-controlling treatments to minimize risk of infection and disease flares.

Addressing the Hydroxychloroquine Shortage

Hydroxychloroquine attracted attention as a possible treatment for COVID-19 as a result of early in vitro studies. Even in the absence of a significant amount of data showing possible benefit, pharmacies quickly began to run out of stock of hydroxychloroquine due to increased demand from hospitals, physicians, and individuals. This poses a challenge for rheumatologists whose patients require hydroxychloroquine to control flares of their diseases and now have trouble filling their prescriptions. Hydroxychloroquine plays a crucial role in lupus management. In lupus patients, hydroxychloroquine has been shown to decrease flare-ups, prevent the need for extended use of glucocorticoids, minimize organ damage, prevent thromboembolism, and increase life expectancy. Hydroxychloroquine is also used for a host of other rheumatologic diseases, including rheumatoid arthritis, Sjogren syndrome, and antiphospholipid syndrome. It is low cost, efficacious, safe in pregnancy, and generally well-tolerated, making it an ideal option for disease management for many patients. As such, there are many concerns in the rheumatology community surrounding this shortage. There is a known risk of flares following withdrawal of hydroxychloroquine. There has been heightened anxiety among patients who are concerned that they will not be able to fulfill their prescriptions, and psychological stress has been associated with worse disease outcomes in lupus patients. If the shortage continues, rheumatologists may need to prioritize which of their patients require hydroxychloroquine and which patients may benefit from alternate treatment options while continuing to prevent disease flares. In addition, off-label use in patients who do not have COVID-19 and wish to use hydroxychloroquine as a preventative measure should be deterred as it does not have evidence-based benefit for SARS-CoV-2 prevention at this time.

Conclusions and Limitations

The information available regarding the susceptibility of COVID-19 infection in patients with rheumatic diseases is based on small samples sizes and a limited number of case reports. There is currently not enough data available to definitively conclude that patients with rheumatic diseases on immunosuppressants are at increased risk of COVID-19 infection. However, there is no available data to support that these patients are at increased risk. Further, it is reassuring that this population does not appear to be at increased risk of severe complications from COVID-19 infection. The data available for repurposing rheumatologic therapies for COVID-19 treatment are in very early stages, and randomized control trials are necessary to determine the true efficacy of these drugs in treating the novel coronavirus.

References


Update: New study on Hydroxychloroquine in COVID-19
By Daniel Menza

A new preprint manuscript was recently released describing a retrospective observational study of hydroxychloroquine and azithromycin for COVID-19 patients [1]. They did a chart review of all COVID patients in all US Veterans Health Administration hospitals up to April 11th, and compared patients who received hydroxychloroquine (HC), hydroxychloroquine and azithromycin (HC+AZ) and those who did not receive hydroxychloroquine (no HC). They included 97 patients in the HC group, 113 patients in the HC+AZ group and 158 patients in the no HC group, making it the largest study available thus far on the drug. They found that the HC group had a higher risk of death than the other two groups, and there was no significant difference between the three groups among rates of mechanical ventilation. Figures are included below. Because this study was non-randomized and sicker patients were likely to get these drugs, they adjusted for this by calculating propensity scores for the groups based on baseline characteristics. These differences between the groups persisted after adjustment. The researchers suggested that since there was no increase in ventilation in the hydroxychloroquine group that this difference may be attributable to drug or disease related effects on non-respiratory organs, perhaps the heart given concerns about hydroxychloroquine’s cardiac toxicity. The authors cited a study on related compound chloroquine in COVID-19 that was stopped early due to cardiac toxicity and increased mortality in the group treated with high dose chloroquine [2].

The major limitation of this study is the fact that it is not randomized. Although they attempted to adjust for this with propensity scores, there is always the possibility of cofounders which are not identified and adjusted for. Despite these flaws, the large sample size makes this one of the best pieces of evidence currently available on the efficacy of hydroxychloroquine, and it raises serious doubts to the widespread use of hydroxychloroquine for COVID-19.

Adjusted Hazard Ratios for ventilation and death

| Subdistribution hazard of ventilation, death and death after ventilation. |
|-----------------|--------|-----------------|-----------------|
|                   | Ventilation | Death | Death after ventilation |
| HC vs. No HC     | 1.43 (0.53-3.79) | 2.61 (1.10-6.17) | 4.98 (0.77-21.70) |
| HC+AZ vs. HC     | 0.43 (0.16-1.12) | 1.14 (0.56-2.32) | 1.20 (0.25-5.77) |
Unadjusted death rates for each of the 3 groups.

Table 3. Outcomes based on treatment exposure.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HC</th>
<th>HC+AZ</th>
<th>No HC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=97</td>
<td>N=113</td>
<td>N=158</td>
<td></td>
</tr>
<tr>
<td>Death – no. (%)</td>
<td>27 (27.8)</td>
<td>25 (22.1)</td>
<td>18 (11.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Discharge – no. (%)</td>
<td>70 (72.2)</td>
<td>88 (77.9)</td>
<td>140 (88.6)</td>
<td></td>
</tr>
</tbody>
</table>

HC: hydroxychloroquine-treated
HC+AZ: hydroxychloroquine and azithromycin-treated
No HC: not treated with hydroxychloroquine

Unadjusted mechanical ventilation rates for each of the 3 groups

Table 4. Outcomes based on pre-ventilation treatment.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HC</th>
<th>HC+AZ</th>
<th>No HC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=90</td>
<td>N=101</td>
<td>N=177</td>
<td></td>
</tr>
<tr>
<td>Ventilation – no. (%)</td>
<td>12 (13.3)</td>
<td>7 (6.9)</td>
<td>25 (14.1)</td>
<td>0.547</td>
</tr>
<tr>
<td>Death without ventilation – no. (%)</td>
<td>9 (10)</td>
<td>11 (10.9)</td>
<td>15 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Discharge without ventilation – no. (%)</td>
<td>69 (76.7)</td>
<td>83 (82.2)</td>
<td>137 (77.4)</td>
<td></td>
</tr>
</tbody>
</table>

HC: hydroxychloroquine-treated
HC+AZ: hydroxychloroquine and azithromycin-treated
No HC: not treated with hydroxychloroquine

References


Update on N95 Mask Decontamination

By Daniel Menza

A new study was recently released as a pre-print that directly examines 4 methods of decontaminating N95 masks using the SARS-CoV-2 virus. They examined dry heat, UV light, vaporized hydrogen peroxide and 70% ethanol as methods for decontamination. They found that UV light was effective but took longer to decontaminate than other methods. However, UV light resulted in less degradation compared to most other methods. Of note, another method examined in this study, treatment with vaporized hydrogen peroxide, resulted in faster times to decontamination and less degradation of the mask. Ethanol and Heat both resulted in too much mask degradation to be considered useful. Overall this study shows that UV light is an effective means to decontaminate masks without significant degradation, but that treatment with vaporized hydrogen peroxide may be better. One limitation of this study is that they tested the decontamination method on pieces of masks, rather than whole masks which may impact the results. The figure they produced is below.

Details

This study was conducted by first inoculating 15mm disks of N95 mask material and 15mm steel discs with solution containing SARS-CoV-2 virus. Each disk was exposed to the respective methods of decontamination and virus present on the disks after decontamination was quantified. This was the data used to calculate the ability of each method to kill virus. To assess respirator integrity, masks were worn for 2 hours and then fit tested after each round of decontamination. This was done by generating aerosol outside the masks and comparing the amount of aerosol outside the mask to the amount inside the mask while the wearer is asked to talk, turn their head and move around. A score of 100 was used as a passing score, which is the standard passing score when this method is used to fit test masks.

The methods for each decontamination strategy were as follows:

UV Light: Disks were placed 15mm from a high power UV germicidal lamp for a calculated energy delivery of 50 microwatts/cm². Plates were removed at 10 minutes, 30 minutes and 60 minutes and live virus was measured.

Vaporized hydrogen peroxide (VHP): The disks were placed in a Panasonic MCO-19AIC-PT incubator and exposed to VHP for 10 minutes, after which they were removed and live virus was measured.

Heat: Disks were placed in a 70 degrees Celsius oven and removed at 10, 20, 30 and 60 minutes and live virus was measured.
Ethanol: Disks were sprayed to saturation with 70% ethanol and at 10 minutes live virus was measured.

The first line of figures shows titer of live virus recovered on the Y axis and time on the X axis. They tested each decontamination method on N95 mask material and steel. The second line of figures shows the mask integrity on the Y axis and number of decontaminations on the X axis. The last line compares the rate of virus decontamination on the Y axis and the mask integrity on the X axis.

Reference

Therapeutic Use of Type I Interferons in Covid-19 Patients
By Eric Stanton

Type I interferons (also referred to as interferon alpha/beta) are cytokines that are produced in response to viral infection that modify certain cell functions along with enacting pro/anti-inflammatory measures to help limit viral replication. Type I IFN expression is induced when certain patterns, such as viral nucleic acids, interact with toll like receptors found in monocytes, macrophages, and dendritic cells along with RIG-like receptors found in a wider variety of cells. One of the antiviral mechanisms of type I IFNs is through the suppression of host translation. This is achieved through the induction of interferon stimulated genes that universally suppress translation, and induction of miRNAs which target both viral and host transcripts for degradation.

Viral Evasion and Delayed Interferon Responses
Viruses, unfortunately, have adapted ways to mitigate the defensive properties of type I IFNs and in some cases, potentially cause a dysregulation that causes further damage to the host. For example, in the SARS-CoV-1 virus, it was demonstrated in one in vitro study that the viral nucleocapsid proteins interfered with the host’s RIG-like receptor signaling cascade thus decreasing type I IFN production.

The timing of interferon production also appears to have significance in the course of viral illnesses. In one study that investigated the effects of interferon in mice infected with SARS-CoV-1, it was found that a delayed surge of type I interferon activity increased mortality. This study used two subsets of mice: one wild type control and one interferon receptor gene knockout. The knockout group had decreased mortality, increased lung function, as well as decreased levels of TNF and IL-6 when compared to the wild type. However, when exogenous type I IFN was introduced 6 hours post infection, there was no observed clinical disease. When administered at 12 hours post infection, exogenous IFN had a moderate effect on reduction of mortality and disease symptoms. Administration at 24 hours post infection had no effect on these measures compared to control. This study highlights two key points:

1. Type I IFNs most likely exert their greatest protective effect earlier in the course of the infection, especially before viral replication is at its maximum
2. Type I IFNs can possibly be harmful to the host through dysregulation later in the course of the disease.
Use of Type I Interferons In MERS

In a review that investigated treatment options for MERS, type I IFNs were not found to have a significant effect on overall mortality despite showing positive results in-vitro. However, many of these studies included were retrospective with small sample sizes. Of note, one retrospective study with 44 patients (20 treatment, 24 control) that looked at the effect of early intervention with a combination of type I IFN and ribavirin saw significantly improved survival at 14 days (70% survival for treatment vs. 29% for control, p = 0.004). However, there was no significant difference in survival at 28 days.

Type I Interferons In Covid-19

Currently, there is very limited data assessing the efficacy of type I IFNs in Covid-19 patients. One pre-print study shows that SARS-CoV-2 is susceptible to type I IFNs in vitro using Vero cells. However, there are no current published clinical trials. One randomized, open-label study with 328 patients is expected to be complete in June 2020.

Conclusion/Summary

The in-vitro and mouse studies demonstrate the potential beneficial effect of early type I interferon use in Covid-19 patients. However, with limited current data as well as past data from SARS and MERS, it is difficult to assess how efficacious this treatment will be for Covid-19.

Limitations of Studies

Many of these studies either rely on non-human models or in-vitro models. The human studies were mostly retrospective with small sample sizes and involved a similar, yet different disease.

References

Obesity: A Risk Factor for Severe Disease

By Katherine Veltri

Summary

Obesity is a chronic inflammatory state that is linked to defective response of both the innate and adaptive immune systems [4]. Though younger people are thought to have low risk for serious complications from COVID-19, there is convincing evidence that obesity at any age is an epidemiological risk factor for hospital admission [3]. Moving forward, we need work to prevent this risk factor by offering weight counseling and patient education to obese patients, and by promoting lifestyle changes such as diet and exercise. Most importantly, we must take a closer look at the social determinants of health and systemic issues that lead to increased risk of obesity and infection in some populations.

Evidence to Date

At the beginning of the COVID-19 pandemic, it was commonly thought that the people who got severely sick from COVID-19 had asthma, a compromised immune system or were over the age of 65. Surprisingly, when examining the characteristics of patients hospitalized with COVID-19, Garg et al. found that among patients in age categories 18–49 years, and 50–64 years old, obesity was the most common underlying condition. Among patients ≥65 years, hypertension was most prevalent. [2]

A retrospective analysis of 3,615 COVID-19 cases in New York City suggests that obesity in patients <60 years old is risk factor for hospital admission and need for critical care. They found that patients <60 years old with a BMI between 30-34 were twice as likely to be admitted to acute care (95% CI 1.6-2.6, p<0.0001), and 1.8x as likely to be admitted to critical care (95% CI 1.2-2.7, p=0.06), compared to individuals <60 years old with a BMI <30. Likewise, patients with a BMI ≥35 and aged <60 years were 2.2 times more likely to get admitted to acute care, (95% CI 1.7-2.9, p<0.0001) and 3.6 times more likely to admitted to critical care (95% CI 2.5-5.3, p<.0001) compared to patients <60 years old who had BMI <30. [3] Similarly, a retrospective cohort study from France showed that disease severity and risk for invasive mechanical ventilation increases in proportion with BMI categories, and was greatest in patients with BMI >35. However, this study did not age stratify. [7]

Many times, people with obesity have comorbid conditions such as hypertension and diabetes which have been shown to also lead to adverse outcomes in COVID-19. This can make it challenging to distinguish if the risk factor is obesity or the comorbid conditions. Peng et al. performed a retrospective analysis in 112 patients with known cardiovascular disease and found that the BMI of the patients who required critical care was significantly higher than that of the general group. They also found that of the 17 patients who did not survive, 15 (88.24%) of them had a BMI of >25. Of the 95 patients who survived, only 18 (18.95%) had a BMI >25. [6] While this is only one study, it shows that obesity leads to increased risk of critical care even when accounting for comorbidities. Moving forward, studies should continue controlling for comorbid conditions when investigating obesity as an individual risk factor for severe disease.

Suggested Mechanism

Obesity has been linked to defective response of both innate and adaptive immune systems. Obesity is a proinflammatory state and obese patients have higher levels of leptin (a proinflammatory adipokine) and pro-inflammatory cytokines like TNF-alpha, MCP1 and IL6. This chronic inflammatory state causes reduced macrophage activation, and reduced pro-inflammatory cytokine production when macrophages are stimulated. Obese patients are also more likely to lead a sedentary lifestyle with reduced physical activity, which is another factor leading to impaired immune response. [4] Dietz et al. identified decreased expiratory reserve volume, functional capacity and respiratory system compliance as possible contributing factors that could cause obese patients to have poor outcomes. The study also proposes that abdominal obesity could make ventilation more difficult in these patients due to decreased diaphragmatic excursion in the supine position. [1]

Additional Considerations

Some studies suggest that obese patients have longer periods of viral shedding compared to nonobese patients. For example, Maier et al. found that symptomatic obese patients shed influenza A 42% longer than nonobese patients (adjusted ETR, 1.42; 95% CI, 1.06–1.89). [5] While we are lacking studies regarding this matter with COVID-19, we should consider longer isolation periods for obese patients to reduce viral transmission to others.

Conclusion

The research available suggests that obesity leads to increased risk of hospital admission and critical care. With this perspective, we should promote healthy changes to modifiable lifestyle factors, such as improving diet and exercise, and offer weight loss counseling and patient education to all obese patients. We also need to consider the social determinants of health that influence the risk of obesity. People who live in food deserts- areas dense in fast food restaurants with poor access to fresh groceries- are at higher risk for obesity. These neighborhoods are typically urban areas where people live in close contact with one another, and thus are at high risk for infection with COVID-19. As we move forward, we must highlight these systemic issues that put some populations at increased risk for infection and adverse outcomes, and look to for solutions.

Limitations

General limitations in in these studies include small sample sizes and inadequate control for comorbidities. Additionally, these studies do not control for sex even though it has been shown that females are having better outcomes than males. Lastly, these studies do not account for the quality of care, or differences in care that the patients received.
References


6. Peng YD, Meng K, Guan HQ, et al. [Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV], Zhonghua Xin Xue Guan Bing Za Zhi. 2020;48(0):E004. doi:10.3760/cma.j.cn112148-20200220-00105


Update on Anticoagulation and Discharge prophylaxis in Covid-19

By Kevin Brandecker

Summary

There continues to be a debate about the dosing of anticoagulation in the treatment of Covid-19 infection as well as new discussions about the role of discharge prophylaxis. A recent article in the Journal of the American College of Cardiology recommended the use of venous thromboembolism (VTE) prophylactic dosing with either Heparin or LMWH with a minority recommending intermediate to full therapeutic dosing.1 The American Society of Hematology currently recommends pharmacologic thromboprophylaxis with LMWH or fondaparinux.2 Both groups agree that it is reasonable to consider discharge prophylaxis, but this decision needs to be made on a per-patient basis considering the thrombotic and bleeding risk.1,2

Update

An article accepted to the Journal of the American College of Cardiology on April 15, 2020, looked at the role of prevention of thromboembolism and follow up in patients infected with Covid-19. Hospitalized patients with medical illnesses are at increased risk of venous thromboembolism (VTE), and in those patients hospitalized with Covid-19 infection initial series suggest that there is an increased risk of venous thromboembolism which is further being studied. In patients hospitalized with Covid-19 infection with respiratory failure or co-morbidities (active cancer or heart failure), bedridden patients, or those requiring intensive care they recommend that they should receive pharmacological VTE prophylaxis unless there is a contraindication. They recommend that Heparin or LMWH be used with each having their benefits and drawbacks. While the majority of the panel recommends prophylactic dosing, a minority recommends the use of intermediate to therapeutic dosing to prevent microvascular events.1

The American Society of Hematology currently recommends pharmacologic thromboprophylaxis with LMWH or fondaparinux (suggested over unfractionated heparin to reduce contact) unless the risk of bleeding is judged to exceed the risk of thrombosis. In the setting of critically ill COVID-19 patients, the use of therapeutic-intensity anticoagulation in the absence of confirmed or suspected VTE is currently unknown.1

An initial study published by Tang et. al. titled, “Anticoagulation treatment is associated with decreased mortality in sever coronavirus disease 2019 coagulopathy” was described in an earlier report titled, “Anticoagulation in Covid-19” on 4/9/2020. Since then this paper has received multiple criticisms. First due to the use of the Sepsis-induced coagulopathy scoring system which uses a combination of the platelet count, SOFA score, and PT. The platelet count is thus double-counted because it is included in the SOFA score and
independently. Thrombopenia is a common finding in Covid-19 which could lead to a bias in the data. Another area of criticism was the use of the term “therapeutic dosing.” Patients were receiving enoxaparin 40-60 mg/day via an unspecified route. If patients were receiving 40 mg/day SQ this would be consistent with daily prophylactic dosing which is considered standard of care due to the increased risk of VTE in hospitalized patients. But even at a dose of 60 mg/day IV, this would only be therapeutic for a patient weighing 40 kg and there is no mention of how many patients were at each dose.

**Discharge prophylaxis in Covid-19**

To date, there has been no data collected looking at the role of continued anticoagulation in patients discharged with Covid-19. The American College of Cardiology recommends that clinicians use individual risk stratification to look at thrombotic and bleeding risk. If patients are continued on anticoagulation after discharge, they recommend the use of DOAC or LMWH due to the decreased need for lab monitoring. The American College of Hematology agrees that it is reasonable to consider extended anticoagulation using a regulatory approved regimen (e.g., betrixaban 160 mg on day 1, followed by 80 mg once daily for 35-42 days; or rivaroxaban 10 mg daily for 31-39 days). But that this decision needs to be made on a per-patient basis considering the thrombotic and bleeding risk.

**Limitations**

There is currently a lack of evidence regarding the dosing of anticoagulation in the hospital setting or the continued use of anticoagulation in the outpatient setting. Thus many professional societies recommend that providers use their clinical judgment in determining what treatments are most appropriate for their patients.

**References**


