April 22, 2020 COVID-19 Update

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- Pandemic effects on patients without Covid-19

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- Compassionate Use of Remdesivir for Patients with Severe Covid-19

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Universal masking in hospitals in the Covid-19 era

- Wearing a mask in public does little to decrease risk of becoming infected
- In hospitals, 2 situations exist where universal masking is beneficial:
    - When caring for a patient with undiagnosed Covid-19
    - When a healthcare worker is asymptomatic of minimally symptomatic with undiagnosed Covid-19
- BUT – masking alone will not stop spread: must be paired with hand hygiene, eye protection when appropriate, gloves, and gowns when appropriate
- May paradoxically preserve PPE supply if staff have a single mask to use for the day – not using/discarding intermittently for patient encounters
- Universal masking may worsen the situation IF it detracts from other appropriate precautions such as rigorous screening of outpatients and visitors, rescreening of inpatients for new symptoms, screening employees, restricting visitors, and increasing frequency/reliability of hand hygiene
- Masks may remind people of Covid-19 and encourage social distancing and other infection-control measures for both patients/families and employees
- "Expanded masking protocols' greatest contribution may be to reduce the transmission of anxiety"
- Perspective: This is a thoughtful article about the (lack of) evidence for universal masking, but for the likely widespread benefits above and beyond the physical viral droplet mitigation.
- Reference: Klompas M, Morris CA, Sinclair J, Pearson M, and Shenoy ES. (2020). Universal Masking in Hospitals in the Covid-19 Era. *New Eng J Med*. Available online 1 April 2020 at www.nejm.org. DOI: 10.1056/NEJMp2006372

Pandemic effects on patients without Covid-19

- Modifications in standard patient care are widespread during Covid-19 outbreak due to risks to patients with being exposed to healthcare system, need to preserve PPE and minimize healthcare team exposure, and change in availability of resources as Covid-19 patient care continues high utilization
- Clinical trials are nearly all on hold – research in cancer and multiple other fields will be set back by at least a year, sometimes more depending on the type of interruption created by the pandemic
- Another key trade-off: need for non-emergent procedures vs need to protect caregivers, PPE supply, and hospital capacity
    - Often elective vs urgent can only be made in hindsight
- Patients who may have been admitted for chronic disease exacerbations are more likely to be managed at home – sometimes less effectively
- Concerns about Covid status affects other clinical care - see recent data on delayed STEMI care
- Social distancing and the need for isolation results in many patients who NEED care being afraid to seek it
- Key moving forward is to prove to patients that medicine is here to care for everyone, Covid or not
- Perspective: Many individual patient and physician stories are provided to illustrate the tolls on individuals that sometimes are missed as we focus so constantly on overall Covid numbers and spread. A reminder that humanity is a needed component of medicine is important, as it is often more challenging to relay by phone or video or through PPE.
- Reference: Rosenbaum L. (2020). The Untold Toll – The Pandemic's Effects on Patients without Covid-19. *New Eng J Med*. Available online 17 April 2020 at www.nejm.org. DOI: 10.1056/NEJMms2009984

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| Article Title: | Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases |
| Authors: | Magro C, Mulvey JJ, Berlin D et al |
| Full Citation: | Magro C, Mulvey JJ, Berlin D et al (2020). Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Transl Res.* Available online 15 Apr 2020. doi: https://doi.org/10.1016/j.trsl.2020.04.007 |

Study Question:

Many patients with COVID-19 have typical ARDS with autopsies showing typical ARDS findings. However, given different ventilatory requirements for some COVID-19 patients, with delayed respiratory distress and marked hypoxemia despite relatively normal lung mechanics, how might complement activation and microvascular thrombosis be contributing to severe illness?

Methods:

Skin and lung tissue samples were analyzed during autopsy for 5 patients who died of severe COVID-19 illness in the setting of respiratory failure – the first two COVID-19 patients where consent was obtained for autopsy and the first three who had skin findings concerning for microthrombotic disease.

Results:

- SARS-CoV-2 spike glycoproteins were isolated with complement components from lung and skin samples
- Histologic, immunohistochemical studies showed microvascular injury and thrombosis consistent with complement activation via alternative and lectin pathways
- Capillary injury due to terminal complement complexes (C5b-9, C4d, MASP2) deposits were found in damaged lung tissue (septal microvascular), skin area with rash, AND normal-appearing skin
- Authors note that mouse models have shown high levels of circulating complement levels, although these labs were not routinely checked in the patients in the study – they hypothesize they would be unhelpful as they could be reciprocally depressed if all complement is utilized in microvascular loci
- Many areas of damage were pauci-inflammatory but with prominent neutrophilia
- 3/5 patients had D-dimer checked prior to death – it was markedly elevated in all 3
- Interesting Q – why aren't platelets low if microvascular clots are forming? (This also happens in some atypical HUS)
- Interesting Q – why is there more of a delay in severe illness in these patients (day 5-9 of sx was average for respiratory failure)
- Hypothesis: spike protein has binding sites which are sites for direct complement binding

Conclusions:

- In at least a subset of patients, severe COVID-19 may be a result of catastrophic microvascular injury via complement pathway activation leading to a procoagulant state
- This mechanism may help explain the higher-than-expected dead-space fraction, preserved lung compliance, and profound hypoxemia seen in some COVID-19 patients as well as why such prolonged ventilation is sometimes needed
- Skin biopsy (rash or not) might be of diagnostic significance
- In addition to D-dimer, other biomarkers including IL-1, IL-6, C3, C4, C5b-9 may be useful in determining which patients seem to be suffering from this type of exaggerated complement activation
- Trial of complement inhibitors such as marsoplimab, eculizumab may be reasonable in severe COVID-19 without typical ARDS findings
- The critical role of complement should be considered in ongoing therapies and in development of targets for specific interventions (ie anti-complement therapies used for atypical HUS, antiphospholipid Ab syndrome, etc)

Perspective:

By studying autopsies of 5 patients of varying ages and baseline immune-suppression, the authors were able to identify a potential mechanism explaining why a subset of COVID-19 patients develop severe respiratory failure without typical ARDS characteristics. This work could have broad implications by transforming common lab tests like D-dimer from purely prognostic tools to potential therapy-guiding indicators. The potential for anticoagulation and complement-mediating therapies – drugs which already exist – to help this subset of patients is intriguing.

Summary written by: Katherine B. Salciccioli MD

Topic Areas: COVID-19, complement activation, microvascular thrombosis, ARDS

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| Article Title: | Compassionate Use of Remdesivir for Patients with Severe Covid-19 |
| Authors: | Grein J, Ohmagari M, Shin D et al |
| Full Citation: | Grein J, Ohmagari M, Shin D et al (2020). Compassionate Use of Remdesivir for Patients with Severe Covid-19. *New Eng J Med*. Available online 10 April 2020 at www.nejm.org. DOI: 10.1056/NEJMoa2007016 |

Study Question:

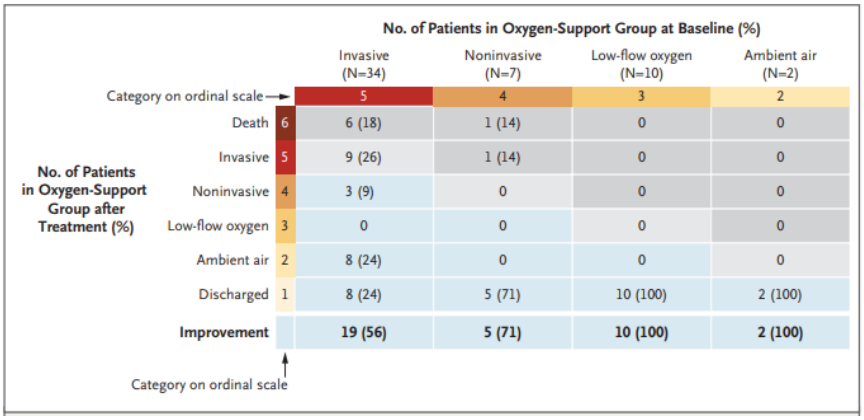
Remdesivir inhibits viral RNA polymerase and has been shown *in vitro* to be active against SARS-CoV-2. Is it clinically effective in patients with COVID-19?

Methods:

- Remdesivir was given on a compassionate-use basis to patients hospitalized with COVID-19 with O2 sat <94%, CrCl >30, LFTs <5xULN, and not on other investigational therapy
- 10 day course (200mg IV day 1, 100mg IV days 2-10) was given to patients in US, Canada, Europe, Japan 1/25/20-3/7/20

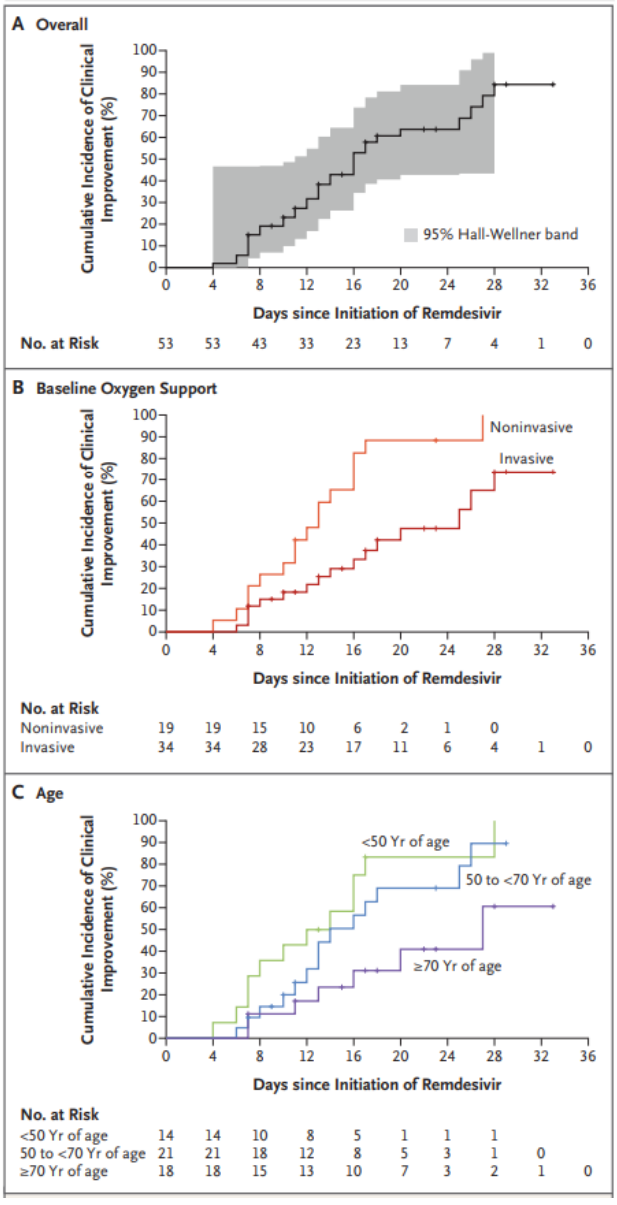
Results:

- 53/61 enrolled patients had data analyzed – other had missing post-baseline data
- N=40 (75%) completed 10 day course, N=10 (19%) had 5-9 days treatment, N=3 (6%) had <5 days treatment
- N=34 were mechanically ventilated at baseline vs N=19 had noninvasive O2 support
- N=7 (13%) died including 6/34 (18%) who were mechanically ventilated at time of therapy initiation
    - Older age, higher Cr, mechanical ventilation at baseline were associated with mortality
- Clinical improvement seen in 36/53 patients (68%), with 17/30 intubated patients successfully extubated and 3/4 patients on ECMO successfully decannulated
- At the end of the study period, 47% (n=25) were discharged from the hospital (8/34 who were on ventilators to start, 17/19 who were on noninvasive O2 support to start)
- Four patients stopped medication – worsened renal failure, multisystem organ failure, elevated LFTs, rash



| No. of Patients in Oxygen-Support Group after Treatment (%) | Category on ordinal scale | No. of Patients in Oxygen-Support Group at Baseline (%) | | | |
|---|---|---|---|---|---|
| | | Invasive (N=34) | Noninvasive (N=7) | Low-flow oxygen (N=10) | Ambient air (N=2) |
| | 5 | 5 | 4 | 3 | 2 |
| Death | 6 | 6 (18) | 1 (14) | 0 | 0 |
| Invasive | 5 | 9 (26) | 1 (14) | 0 | 0 |
| Noninvasive | 4 | 3 (9) | 0 | 0 | 0 |
| Low-flow oxygen | 3 | 0 | 0 | 0 | 0 |
| Ambient air | 2 | 8 (24) | 0 | 0 | 0 |
| Discharged | 1 | 8 (24) | 5 (71) | 10 (100) | 2 (100) |
| **Improvement** | | **19 (56)** | **5 (71)** | **10 (100)** | **2 (100)** |

Category on ordinal scale



Conclusions:

- Overall, clinical improvement was seen in 68% of patients who received remdesivir
- While study population not directly comparable with other cohort studies, remdesivir may have clinical benefit
- Safety profile seems acceptable – difficult to know if organ dysfunction was due to medication or Covid-19
- Key weakness of this study – viral loads were not collected
- Randomized, placebo-controlled trials are needed

Perspective:

While this study suffers from the lack of control-matching, blinding, and placebo-control, it gives a signal that remdesivir may be clinically useful in treating COVID-19. As the authors note, further study is needed to determine its true utility. As with many diseases and therapies, outcomes are better when it is initiated earlier in the disease course and/or in less severe disease, but without matching and placebo-control it is difficult to know how much change from natural history was a result of the medication.

Summary written by: Katherine B. Salciccioli MD

Topic Areas: COVID-19, remdesivir