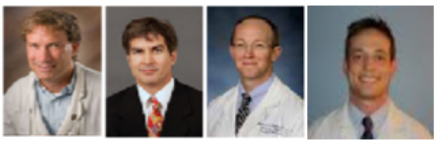
critical care perspectives in emergency medicine



COVID19 Updates – March, 2021

Key Articles

Alhazzani W, Evans L, Alshamsi F, et al. Surviving sepsis campaign guidelines on the management of adults with coronavirus disease 2019 (COVID-19) in the ICU: first update. Critical Care Medicine. 2021;49(3):e219-e234.

Background

- The COVID19 literature base continues to rapidly evolve as the rigorous evaluation of therapies comes to publication.
- The RECOVERY trial group, REMAP CAP trial group, and SIREN network continue to guide our evidence-based approach to COVID19 care in and outside of the Emergency Department.
- Our goal today will be to review the first update from the Surviving Sepsis Campaign, who just published an update to their guidelines for the care of critically ill patients with COVID19.
- In addition to a narrative review, the SSC performed a random-effects meta-analyses to summarize treatment effects when able. While there are a number of recommendations, we will be specifically discussing o recommendations that have changed since the initial SSC COVID19 guideline publication.
- Recommendations were made using the GRADE approach to generate recommendations based on the balance between benefit and harm, resource and cost implications, equity, and feasibility.

Awake Prone Positioning

- **Rationale:** Awake prone positioning has been under investigation as an intervention that may increase secretion drainage, improve aeration to atelectatic lung bases, reduce V/Q mismatch, and decrease the need for invasive mechanical ventilation.
- **Evidence**: Recommendation update using one systematic review using 35 observational studies, 12 prospective cohort studies, 18 retrospective cohort studies, and 5 case reports in ICU and non-ICU settings.
    - All reports showed a *transient* improvement in oxygenation while in the prone position, but a large amount of uncertainty remains about its effect on clinical outcomes.
    - There are 7 ongoing clinical trials investigating this practice, but until those results are published….

- **SSC Recommendation:** There is insufficient evidence to issue a recommendation on the use of awake prone positioning in nonintubated adults with severe COVID-19.

Corticosteroids

- **Rationale:** Systemic corticosteroids have the potential to reduce the severity of ARDS, systemic inflammation, and hypoxia due to pulmonary interstitial edema.
- **Evidence**: Recommendation update based on 7 randomized control trials, including the RECOVERY Trial, that have been published since the first SSC guidelines 6 months ago. Three trials used dexamethasone, 3 used methylprednisolone.
- **SSC Recommendations**
    - The use of corticosteroids reduces the risk of 28-day mortality in hypoxic patients with COVID19 compared to no steroids or placebo **(STRONG recommendation)**.
    - A firm recommendation on type of steroids and dosing regimen could not be made until further trials are published, but the SSC prefers using the RECOVERY trial regimen of dexamethasone, which was 6mg/day for 10 days.

Antivirals

- **Hydroxychloroquine**
    - **Rationale:** In vitro studies suggest that chloroquine and HCQ may inhibit SARS-CoV replication, but clinical trials have failed to demonstrate clinical benefit in hospitalized patients with COVID19. In the first guideline, SSC was not able to issue a recommendation on HCQ use.
    - **Evidence:** Updated search identified 5 new RCTs since the first set of guidelines. The results of these trials found that HCQ use did not reduce 28-day mortality or the need for mechanical ventilation but *increased* the risk of adverse events.
        - An updated systematic review that included 26 RCTs with over 10,000 showed HCQ use was associated with an *increased* risk of death.
    - **SSC Recommendations**
        - HCQ does not reduce the risk of death in hospitalized patients with COVID19 and may cause increased harm.
        - The SSC has now made a STRONG recommendation against the use of HCQ for the treatment of severe or critical COVID19.
- **Convalescent Plasma**
    - **Rationale:** Convalescent plasma may provide passive immunity by the transfer of SARS-CoV2 antibody to infected patients from patients who have previously recovered from a COVID19 infection.
    - **Evidence:** Four new RCTs have since been published evaluating the use of convalescent plasma, including the PLACID trial which included over 450 noncritical, but hospitalized patients with COVID19.
        - The SSC performed a meta-analysis of the 4 RCTs published and found that convalescent plasma did not reduce hospital mortality compared to usual care.

- **SSC recommendations**
  - There appears to be a lack of benefit toward improved outcomes, increased cost, and as a result, the SCC issued a **WEAK** recommendation against the use of convalescent plasma in patients with severe or critical COVID19.
  - ***Worth noting:*** The SIREN network recently performed an interim analysis of its C3PO trial being performed in 47 EDs across the US and found that convalescent plasma did not appear to cause harm, but that it was unlikely to benefit patients with mild to moderate COVID19. As a result, the DSMB recommended that the NHLBI stop enrolling new patients and halt the study.

- **Remdesivir**
  - **Rationale:** Remdesivir is a prodrug that has been found to inhibit replication of coronaviruses during in vitro studies.
  - **Evidence:** Four RCTs have been published that examine the efficacy and safety of remdesivir in COVID19.
    - The ACTT-1 trial randomized over 1,000 hospitalized adults within 72 hours of positive testing, and found an increased time to recovery with the use of remdesivir leading to a reduced hospital stay and decreased need for invasive mechanical ventilation.
    - Remdesivir did not reduce the risk of death at 28 days in the SOLIDARITY trial, which included over 2,750 hospitalized adults with COVID19.
    - A recently updated meta-analysis of over 7,500 patients also found that remdesivir did not reduce 28-day mortality.
  - **SSC Recommendation:** Mixed recommendation **(READ THIS CAREFULLY)**
    - A WEAK recommendation in favor of the use of IV remdesivir that should be *ideally* started within 72 hours of admission in patients with severe COVID19 who DO NOT REQUIRE mechanical ventilation
    - A Weak recommendation against the use of IV remdesivir in patients with severe COVID19 who REQUIRE mechanical ventilation:

Anticoagulation

- **Rationale:** Recent studies have found an increased incidence of endothelial injury, microvascular thrombosis, and a high rate of VTE in hospitalized patients with severe COVID19.
- **Evidence:** A systematic review and meta-analysis of four RCTs that compared chemical VTE prophylaxis vs. no prophylaxis found there was a reduced risk of DVT and PE with the use of heparin therapy.
- **SSC Recommendation:** STRONG recommendation to use pharmacologic VTE prophylaxis in hospitalized patients with COVID-19.
  - **Worth Noting (not discussed in these guidelines):** 2 large RCTs produced by the REMAP CAP and ACTIV-4 trial groups were published their data after these guideline updates were published, which found therapeutic anticoagulation did

not reduce mortality o in critically ill adults with COVID19, but decreased the need for invasive mechanical ventilation and organ failure in non-critically ill patients. It will be interesting to see if these results affect the strength of SSC recommendations in the next revision.

Bottom line: The evidence for therapies and interventions for patients with COVID19 presenting to the emergency department continue to evolve. As we continue to monitor the evidence and guideline revisions, we will definitely continue to bring these findings to CCPEM audience.

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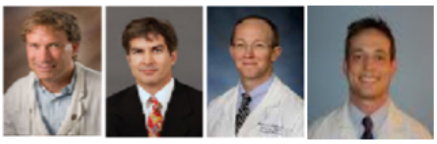

Convalescent Plasma in COVID-19

Key Article

Janiaud P, et al. Association of convalescent plasma treatment with clinical outcomes in patients with COVID-19. JAMA 2021. Published online February 26, 2021.

Background

- Patients with COVID-19 have frequently been treated with convalescent plasma – plasma from persons who have recovered from COVID-19.
- Preliminary reports from early in the pandemic indicated that the treatment was well tolerated with low risk of adverse events.
- Convalescent plasma was given EUA in the United States in August 2020.
- The clinical benefits, however, remain uncertain

Objective

- To assess clinical outcomes with convalescent plasma treatment vs placebo or standard care in peer-reviewed and preprint publications or press releases of RCTs.

Study

- Systematic review and meta-analysis of all published RCTs assessing the benefits and risks of convalescent plasma in patients with COVID-19.
- Inclusion:
    - Peer-reviewed publications
    - Preprints
    - Press releases
    - Patients with suspected or confirmed SARS-CoV-2
- Outcomes
    - All-cause mortality at any point in time
    - Length of hospital stay
    - Clinical improvement or deterioration
    - Number of patients requiring mechanical ventilation
    - Serious adverse events

Results

- Included 10 RCTs
    - 4 published in peer-review journals – 1060 patients
    - 5 published as preprints – 316 patients
    - 1 press release (RECOVERY Trial) – 10,406 patients

    - 3 conducted in India, 2 in Argentina, 1 in the UK, China, Netherlands, Spain, Bahrain
    - 5 were terminated early (2 for futility and 3 for slow recruitment)
    - In 5 of the RCTs, patients received a single convalescent plasma transfusion, whereas in the remaining 5 RCTs they received 2 plasma transfusions 24 hours apart.
- Risk of bias deemed low for 7 of the 10 RCTs
- Clinical Outcomes
    - All-cause mortality across all 10 RCTs
        - RR was 1.02
        - 95% CI 0.92 to 1.12
        - P=0.68
    - Reductions in hospital LOS or mechanical ventilation use across all RCTs
        - No significant association between convalescent plasma compared with the control group.
    - Clinical improvement or clinical deterioration across 5 RCTs that reported data
        - No significant difference between patients who received convalescent plasma compared with the control group.
- No meta-analysis could be performed on serious adverse events due to inconsistencies in reporting among the RCTS.

Limitations

- Evidence largely dominated by the RECOVERY Trial – results obtained from a press release and should be interpreted with caution until full results published and analyzed
- 3 of the 10 RCTs deemed at high risk of bias
- The reporting of clinical outcomes was inconsistent due to use of different definitions
- Patients appeared to have moderate to critical COVID-19, as nearly all were hospitalized with or without supplemental oxygen

Authors Take Home Points

- There was no significant association with a decrease in all-cause mortality or any other benefit in clinical outcome in patients who received convalescent plasma compared with placebo in combination with standard care or standard care alone.

Tocilizumab in COVID-19 Pneumonia

Key Article

Rosas IO, et al. Tocilizumab in hospitalized patients with severe COVID-19 pneumonia. N Engl J Med 2021. Published online February 25, 2021.

Background

- COVID-19 begins with an initial phase of high viral replication that is followed by a second phase that may be driven by the host immune response.
- This progression can lead to a rapid increase in proinflammatory cytokines, an uncontrolled inflammatory response, ARDS, and MOF.
- Levels of IL-6 correlate with COVID-19 severity
- IL-6 promotes endothelial dysfunction and the development of vascular permeability. May also play a role in the vascular dysfunction associated with COVID-19.
- Tocilizumab is a monoclonal antibody against IL-6 receptor alpha that can be used to treat certain inflammatory diseases.
- Case reports and retrospective observational cohort studies have demonstrated rapid reduction in fever, reduced use of O2 and mechanical ventilation, and a reduction in lung manifestations of COVID-19.

Objective

- To assess the effectiveness and safety of tocilizumab in hospitalized patients with severe COVID-19 pneumonia.

Study

- Phase 3, international, randomized, double-blind, placebo-controlled trial
- 62 hospitals in 9 countries in Europe and North America
- Inclusion:
    - Adult greater than or equal to 18 years of age
    - Severe COVID-19 pneumonia
    - SpO2 93% or less or a P/F ratio less than 300 mm Hg
- Exclusion:
    - Treating physician determined death was imminent and inevitable within 24 hours
    - Active Tb
    - Bacterial or viral infection other than with SARS-CoV-2
- Standard care provided according to local practices
- Intervention

    - Patients randomly assigned in 2:1
    - Tocilizumab Group
        1. Single IV infusion at 8 mg/kg
        2. Standard care
    - Placebo Group
        1. Single IV infusion
        2. Standard care
    - Second infusion of tocilizumab or placebo could be given 8 to 24 hrs after the first for no improvement or worsening of the condition
- Evaluation
    - Assessed clinical status using an ordinal scale
        1. Discharged or ready for DC
        2. Hospitalized in a non-ICU unit w/o O2
        3. Hospitalized in a non-ICU unit with supplemental O2
        4. ICU or non-ICU hospitalization with NIV or HFNC
        5. ICU hospitalization with intubation and mechanical ventilation
        6. ICU hospitalization with ECMO, MV, and additional organ support
        7. Death
- Primary Outcome
    - Clinical status at day 28
- Secondary Outcomes
    - Clinical status at day 14
    - 28-day mortality
    - Number of ventilator free days at 28
    - Time to improvement from baseline by at least 2 categories on clinical scale
    - Time to hospital DC or ready for DC
- Statistical analysis used a modified intention-to-treat

Results

- 452 patients underwent randomization; 438 patients included in the MITT analysis
    - Tocilizumab Group – 294
    - Placebo Group – 144
    - Groups generally well balanced except for:
        - Lower percentage of patients in the tocilizumab group received steroids
    - A second dose was administered to 22.1% of patients in the tocilizumab group and in 29.2% of patients in the placebo group.
- Primary Outcome
    - Median value for clinical status on the ordinal scale at day 28
        - Tocilizumab Group: 1
        - Placebo Group: 2
        - Between group difference -1; 95% CI -2.5 to 0; P=0.31
- Secondary Outcomes
    - Median value for clinical status on the ordinal scale at day 14

        - Tocilizumab Group: 3
        - Placebo Group: 4
    - 28-day mortality
        - Tocilizumab Group: 19.7%
        - Placebo Group: 19.4%
        - Not significant
    - Ventilator free days
        - Tocilizumab Group: 22
        - Placebo Group: 16.5
    - Median time from baseline until improvement by at least 2 categories
        - Tocilizumab Group: 14
        - Placebo Group: 17
- Safety
    - Adverse events
        - Tocilizumab Group: 77.3%
        - Placebo Group: 81.1%
    - No difference in serious adverse events or fatal events
    - No patients who received tocilizumab had anaphylaxis

Limitations

- Using clinical status on an ordinal scale as the primary outcome
    - Integrates several outcomes that are important in a pandemic illness
    - Sensitive to differences in local practice
    - Lack of proportionality between categories
    - Lack of established minimum clinically important difference for therapeutic effect
- Lack of standardized treatment across sites and countries

Authors Take Home Points

- No significant difference in clinical status between patients who received tocilizumab and placebo at day 28
- No mortality benefit associated with the use of tocilizumab
- No safety concerns with tocilizumab