Brigham & Women’s Hospital Inpatient COVID-19 Infectious Diseases Treatment Guidelines

Appendix A: Tocilizumab Criteria for Use

COVID-19 Acute Respiratory Distress Syndrome (ARDS). COVID-19 ARDS is associated with systemic inflammation and elevated inflammatory biomarkers (e.g., C-reactive protein [CRP], ferritin, D-dimer).

Immunomodulation in COVID-19 ARDS. In response to the mortality benefit demonstrated in the RECOVERY trial, glucocorticoid steroids are recommended for all hospitalized COVID-19 patients requiring supplemental oxygen. Tocilizumab is a monoclonal antibody against the IL-6 receptor. One dose of tocilizumab has been shown to significantly reduce CRP levels in COVID-19 patients. See BWH covidprotocols for a discussion of RCT literature. In one of the RCTs to assess tocilizumab exclusively in ICU patients (REMAP-CAP, n=803), the tocilizumab group met the primary endpoint of a greater number of organ support-free days compared to placebo. Moreover, hospital mortality was lower in the tocilizumab arm (28.0%) compared to the control arm (35.8%). In response, tocilizumab may potentially be used in addition to steroids in certain patients with COVID-19 ARDS.

Tocilizumab (+ steroids) may be considered in select patients via a multidisciplinary discussion

- Must meet ALL criteria and none of the absolute contraindications below:
  1. COVID-19: Confirmed SARS-CoV-2 infection
  2. Early in course: Within 4 days of initial hospital admission
     a. For example, a patient transferred to ICU from floor on hospital day 7 would NOT meet this criterion. In addition, a patient with a recent COVID-19 admission now readmitted with respiratory failure would NOT meet this criterion
     b. This early administration is driven by RCT and observational data. Further, respiratory decompensation later in the hospital course has a higher likelihood of involving super-infection or thrombosis
  3. Critical hypoxemic respiratory failure (must meet 1 of 2 criteria below):
     a. ICU admission specifically for ARDS
        i. Patients would NOT meet this criterion if admitted to ICU for asthma exacerbation without severe hypoxemia or for non-respiratory issues (e.g., GI bleed or stroke)
     b. Requirement for HFNC or NRB (regardless if patient is in ICU or on non-ICU floor)
  4. Approval by pulmonary or rheumatology attending

- Absolute contraindications to tocilizumab
  1. Neutropenia with ANC < 2,000
  2. Transaminitis with AST or ALT > 250 from presumed hepatic source
  3. Thrombocytopenia with platelet count < 50
  4. Significant active bacterial super-infection
  5. Active diverticulitis, bowel perforation, or at increased risk for bowel perforation
  6. Active fungal infection, active TB infection, or active zoster

These recommendations are based on the current state of information, which is highly fluid and will be updated regularly. Participation in clinical trials to determine the risk/benefit of unproven therapies is critical.
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- **Relative contraindications**
  1. Immunocompromised or on immunosuppressive agents
  2. Significant history of large intestinal disease, such as recent (<1 year) instance of severe diverticulitis, bowel perforation, major bowel surgery
  3. Patients with Crohn’s disease can be considered for tocilizumab, but GI consultation and discussion is **required** prior to its administration

Dosing and Adverse Effects

- **Dosing:** 8 mg/kg x1, rounded to the nearest 200 mg
  - Weight >90 kg = 800 mg; >65 to 90 kg = 600 mg; >40 to 65 kg = 400 mg; ≤40 kg = 8 mg/kg
  - Only rarely needs to be re-dosed if CRP does not decline after 24 hours
- **Potential adverse effects:** transaminitis, increased serum cholesterol, infusion-related reactions, neutropenia
  - Tocilizumab carries a **black box warning** for a risk of serious infections that may lead to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections
  - Patients should be tested for latent TB prior to hospital discharge and followed up in outpatient TB clinic if positive. TB testing does not need to be performed prior to tocilizumab administration

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*Participation in clinical trials to determine the risk/benefit of unproven therapies is critical.*
Appendix B: Supplemental guidelines on cytokine release syndrome (CRS) / cytokine storm syndrome and multisystem inflammatory syndrome in children (MIS-C):

**Cytokine release syndrome (CRS).** CRS or Cytokine storm syndrome (CSS) is an immune-mediated hyperinflammation syndrome believed to contribute to morbidity and mortality in rare patients with COVID-19. Affected patients demonstrate systemic inflammation and progressive multisystem dysfunction, including ARDS and shock. Laboratory studies show systemic inflammation (elevated CRP), DIC (D-dimer, cytopenias), elevated ferritin, and evidence of hepatic dysfunction including elevation in transaminases and LDH. Trends in these values are more important than absolute values and no absolute cutoffs are defined for COVID-19. Importantly, these markers are non-specific, making it difficult to distinguish formal CRS/CSS from other states of inflammation. **Formal CRS/CSS has proven to be rare in hospitalized COVID-19 patients.** A COVID-19 patient developing shock is more likely to have an explanation other than CRS or CSS (e.g., sepsis due to bacterial super-infection). **If CRS/CSS is suspected, multi-disciplinary discussion is recommended** (e.g., with pulmonary, rheumatology, infectious diseases, pharmacy resources recommended above). The treatment for CRS/CSS is debated, and options include higher dose steroids, tocilizumab, anakinra (IL-1 pathway antagonist), or baricitinib (JAK inhibitor).

**Multisystem inflammatory syndrome in children (MIS-C):** MIS-C is a post-infectious inflammatory syndrome seen in children and young adults after COVID-19 infection. This syndrome shares several features with Kawasaki disease, a medium-vessel vasculitis that occurs in young children. Young adults with MIS-C typically present with fever, GI symptoms (belly pain, diarrhea), and shock due to heart failure (see covidprotocols for further information). Management of this condition differs from the treatment of acute COVID-19 disease in several respects, with the goal of preventing complications such as coronary artery aneurysms. **All patients suspected of having MIS-C should be urgently evaluated by rheumatology.**