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

Appendix A: Tocilizumab & Baricitinib 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. Given the available evidence, tocilizumab or baricitinib may potentially be used in addition to steroids in certain patients with COVID-19 ARDS. See BWH covidprotocols for a discussion of the RCT literature.

Tocilizumab or baricitinib (+ steroids) may be considered in select patients with multidisciplinary discussion

- Must meet ALL criteria and none of the absolute contraindications below:
  1. Approval by pulmonary OR rheumatology attending
  2. COVID-19: Confirmed SARS-CoV-2 infection
  3. Early in acute hypoxemic respiratory failure due to COVID-19: Within 4 days of initial hospital admission for acute hypoxemic respiratory failure due to COVID-19; or within 4 days of developing acute hypoxemic respiratory failure later during an inpatient admission, if initially admitted for an unrelated diagnosis
    a. Example of a patient who meets this criterion: A patient is admitted for a gastrointestinal hemorrhage and incidentally found to be SARS-CoV-2 positive. On hospital day 7 the patient develops acute hypoxemic respiratory failure attributed to COVID-19. While past hospital day 4, the patient is physiologically similar to patients early in their inpatient admission for respiratory failure due to COVID-19 and thus WOULD meet criterion for tocilizumab or baricitinib
    b. Example of a patient who does not meet this criterion: A patient transferred to ICU from floor on hospital day 7 of an admission for acute respiratory failure due to COVID-19 would NOT meet this criterion. In addition, a patient with a recent admission for acute respiratory failure due to COVID-19 and now readmitted with worsening respiratory failure more than 4 days after their prior admission
    c. 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, thrombosis, or have other causes not directly relating to inflammation due to SARS-CoV-2
  4. Critical or rapidly progressing 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).
    c. The pulmonary or rheumatology attending can use their judgement and recommend tocilizumab or baricitinib for patients with rapidly progressing acute hypoxemic respiratory failure due to COVID-19 who are not yet on sustained HFNC or NRB
  5. EUA fact sheet provided to patient or health care proxy and verbal consent obtained

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

- **Absolute contraindications to tocilizumab and baricitinib**
  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

- **Relative contraindications**
  1. Immunocompromised or on immunosuppressive agents (the consultative services noted below can help with determining whether the degree of immunocompromise or a particular immunosuppressive medication is a contraindication)
  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 or baricitinib, but GI consultation and discussion is required prior to its administration
Assess for contra-indications (CI) to baricitinib or tocilizumab:

- ANC < 2,000 for tocilizumab, < 1,000 for baricitinib
- AST/ALT > 250 (hepatic source)
- Platelet < 50
- Significant, active bacterial infection
- Active diverticulitis, bowel perf. or increased risk for bowel perf.
- Active fungal, TB, zoster infection

If pulmonary or rheumatology attending gives verbal authorization for immunomodulation (i.e., baricitinib x14d, tocilizumab x1 dose)

- Verbally consent patient and give patient fact sheet for EUA treatment if using baricitinib or tocilizumab
- Covering pharmacist to enter order, adding Pulm/Rheum attending name as free text in EPIC order

Contact re: guidelines: Edy Kim (Pulmonary, ekim11@bwh.harvard.edu); Jeffrey Pearson (ID/Rx, jcpearson@bwh.harvard.edu); A. Helena Jonsson (Rheumatology, ajonsson@bwh.harvard.edu)
Brigham & Women’s Hospital Inpatient COVID-19 Infectious Diseases Treatment Guidelines

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) and in adults (MIS-A): MIS-C/MIS-A is a post-infectious inflammatory syndrome seen in children, young adults, and rarely in older adults after COVID-19 infection. This syndrome shares several features with Kawasaki disease, a medium-vessel vasculitis that occurs in young children. Adults with MIS-A 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 or MIS-A should be urgently evaluated by rheumatology.