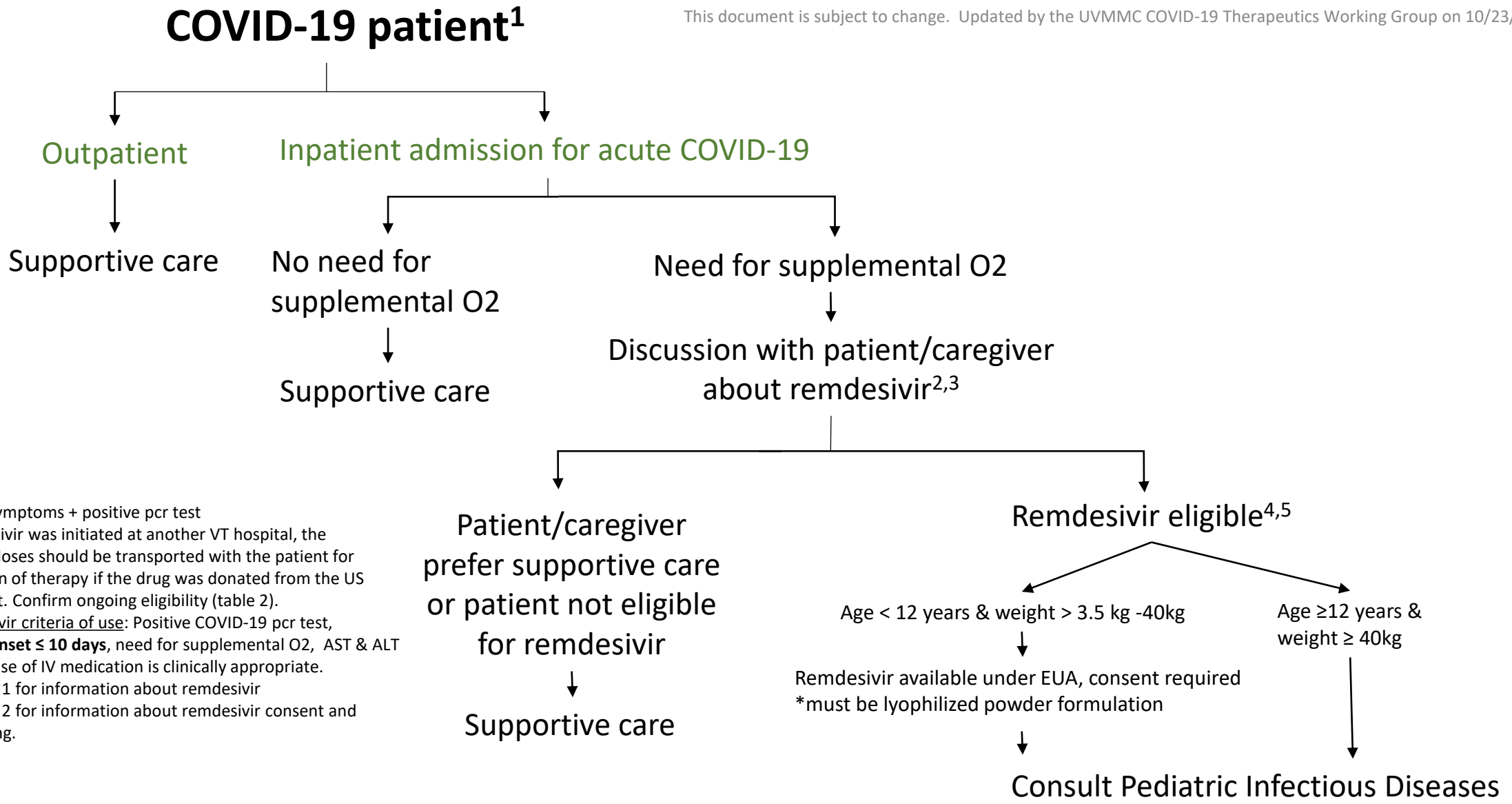
UVMMC COVID-19 PEDIATRIC Therapeutic Algorithm

The treatment algorithm presented here is based on a review of currently available literature and the NIH and IDSA/PIDS published treatment guidelines. On May 1, 2020 the FDA issued an Emergency Use Authorization (EUA) for use of Remdesivir for the treatment of hospitalized COVID-19 patients. The EUA was revised August 2020. On October 22, 2020 the FDA approved remdesivir for hospitalized patients > 12 years of age and > 40kg with COVID-19. The treatment algorithm will be updated to reflect new data as it becomes available.

This document is subject to change. Updated by the UVMMC COVID-19 Therapeutics Working Group on 10/23/2020.



1. Clinical symptoms + positive pcr test
2. If remdesivir was initiated at another VT hospital, the remaining doses should be transported with the patient for continuation of therapy if the drug was donated from the US government. Confirm ongoing eligibility (table 2).
3. Remdesivir criteria of use: Positive COVID-19 pcr test, **symptom onset ≤ 10 days**, need for supplemental O2, AST & ALT < 5x ULN, use of IV medication is clinically appropriate.
4. See table 1 for information about remdesivir
5. See table 2 for information about remdesivir consent and monitoring.

Table 1. Remdesivir

Remdesivir is a nucleotide analog with antiviral activity. It is infused as an adenosine nucleotide prodrug, then metabolized to its pharmacologically active form of nucleoside triphosphate metabolite. It acts as an analog of adenosine triphosphate (ATP) to compete with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, resulting in delayed chain termination during replication of viral RNA[1]. **Remdesivir was approved by the FDA for treatment of SARS-COV-2 infection in patients > 12 years of age and > 40kg on October 22, 2020. For patients < 12 years of age and weighing 3.5kg - 40kg, remdesivir remains available through the Emergency Use Authorization.**

Supply Source & Formulation	Dosing	Notes
Donated supply from US Government Solution: children weighing > 40kg. Lyophilized powder: children weighing 3.5 kg – ≤40kg There is currently a limited supply of donated remdesivir for use in Vermont hospitals. UVMMC will evaluate the need for purchasing when the state supply is < 40 patient treatment courses (ie, < 240 vials).	Children weighing > 40kg: 200 mg IV on day 1, then 100 mg IV daily for up to 4 days, or hospital discharge, whichever comes first. Children 3.5kg - ≤ 40kg: 5mg/kg IV on day 1, then 2.5mg/kg IV daily for up to 4 days, or hospital discharge, whichever comes first. 5 days of therapy is recommended for patients not requiring invasive mechanical ventilation or ECMO, but can be extended up to 10 days of no substantial clinical improvement is seen at day 5.	Infectious Diseases consult is required prior to prescribing. Remdesivir was approved for the treatment of hospitalized patients >age 12 with COVID-19 on October 22, 2020. This decision was based on the following studies: • ACCT-1 clinical trial conducted by National Institute of Allergy and Infectious Diseases compared 541 patients who received remdesivir to 521 patients who received placebo + standard of care. The median time to recovery was 10 days in the remdesivir group compared to 15 days in the placebo group, which was statistically significant. • JAMA published a randomized, open-label multi-center clinical trial of hospitalized adults with moderate COVID-19. The study concludes that patients who received 5 days of remdesivir had a statistically significant difference in clinical status (favorable) compared to standard of care or 10 days of remdesivir at 11 days of care. • NEJM published a randomized, open-label multi-center clinical trial of adults comparing 5 days of remdesivir to 10 days of remdesivir at day 14. Researchers found that the odds of a patient's COVID-19 symptoms improving were the same in both groups and there were no statistically significant differences in recovery rates or mortality rates between the two groups. Notably, there is no placebo group in this study. **Remdesivir should not be co-administered with strong inducers of CYP450, such as rifampin. Check for drug-drug interactions prior to prescribing. Concomitant use of hydroxychloroquine, chloroquine, and remdesivir is not recommended.** **There have been reports of infusion-related reactions and anaphylaxis with symptoms including changes in BP and HR, hypoxia, fever, shortness of breath, wheezing, swelling, rash, nausea, sweating, and shivering.**

1. https://www.gilead.com/-/media/files/pdfs/remdesivir/eua-fact-sheet-for-hcps_01may2020.pdf

Table 2. Consent and Monitoring of Remdesivir

Criteria of Use and Consent

Current criteria for consideration of use as decided by the State of Vermont:
Positive COVID-19 pcr test
O_2 sat ≤ 94%, or the need for supplemental O_2, mechanical ventilation, or ECMO
CrCl ≥ 30ml/min
AST & ALT ≤ 5x upper limit of normal
The use of IV medication is appropriate

Consent needed for patients <12 years of age and <40kg
Prior to administration:

1. It must be documented that the patient (or caregiver) received the EUA patient fact sheet and fact sheet has been explained to the patient. The patient fact sheet has been translated into eight languages as all are available on the UVMMC COVID-19 website.
2. Physician must document that he/she has read the EUA physician fact sheet.
3. It must be documented that the patient has been informed about alternative treatments.
4. It must be documented that the patient has been informed that remdesivir is not an FDA approved medication.

Use dotphrase ".remdesivirconsent" in H&P or progress note to document patient consent.

Monitoring

Daily laboratory monitoring:
Creatinine and creatinine clearance
AST, ALT
CBC
Electrolytes

Risk of Infusion related reaction
Infusion-related reactions have been observed during, and/or been temporally associated with, administration of remdesivir. Signs and symptoms may include hypotension, nausea, vomiting, diaphoresis, and shivering. If signs and symptoms of a clinically significant infusion reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment. The use of remdesivir is contraindicated in patients with known hypersensitive to remdesivir.

Hepatotoxicity
Discontinue remdesivir if ALT ≥ 5x upper limit of normal. Remdesivir may be restarted when ALT ≤ 5x upper limit of normal. Discontinue remdesivir if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

For patients receiving remdesivir under the EUA (age <12, weight <40kg), adverse events or death must be reported to FDA Medwatch within 7 days of event.
www.fda.gov/medwatch/report.htm and copied to Gilead at Safety_fc@gilead.com
Serious adverse events are defined in the EUA are:

- Death
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly

Multisystem Inflammatory Syndrome in Children (MIS-C)

MIS-C Case Definition

Patient <21 years old with fever, laboratory evidence of inflammation[1], and clinically severe illness requiring hospitalization with multisystem (≥2) organ involvement[2]

AND

No alternative plausible diagnosis

AND

Recent or current +COVID-19 pcr or +SARS-CoV-2 Ab
or
Confirmed exposure to COVID-19 within 4 weeks prior to the onset of symptoms

1. Elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid, LDH, IL-6, neutrophils; or reduced lymphocytes and albumin.
2. Organ systems include cardiac, renal , respiratory, hematologic, gastrointestinal, dermatologic, or neurologic.

Per the CDC, MIS-C presents with persistent fever, abdominal pain, vomiting, diarrhea, skin rash, mucocutaneous lesions, and in severe cases, with hypotension and shock. Patients have elevated laboratory markers of inflammation and laboratory markers of damage to the heart. Some patients develop myocarditis, cardiac dysfunction, and acute kidney injury.

It is strongly encouraged to consult pediatric infectious disease and rheumatology teams if this diagnosis is suspected.

Healthcare providers should report suspected cases to the Vermont Department of Health.

References:
Henderson LA, *et al.* American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated with SARS-CoV-2 and Hyperinflammation in Piatric COVID-19: Version 1. Arthritis & Rheumatology. Vol 0, No 0, 2020, pp1-15.
Riphagen, S, *et al.* Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet. 2020:395(10237); p1607-1608.