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Yale New Haven Children's Hospital

CONSIDERATIONS FOR PHARMACOLOGIC TREATMENTS OF PATIENTS WITH CONFIRMED COVID-19 TESTING FOR THE PICU & GENERAL INPATIENT UNIT (GIU)

(This pathway will be reassessed & updated regularly based on experience & emerging data)

Pediatric Patient With Confirmed + COVID-19 Testing

Provide supportive care w acetaminophen/NSAIDs prn clinician's discretion & consider COVID-19 pharmacologic treatment criteria listed below for the GIU & PICU

GIU Criteria

- **Requiring:** ≥ 1 L/min NC O_2 for 24 hrs without being able to wean **OR**
- **Worsening clinical trajectory** with increasing oxygen support within 24 hrs of starting O_2

PICU Criteria

- **Requiring**:
  - Non-invasive vent support
  - Mechanical ventilation OR
  - ECMO

For Both PICU & GIU:

May also consider treatment for patients with no oxygen requirement (or lesser degree of resp. support) who have fever and respiratory distress AND a history of:

- Congenital cardiac disease, chronic lung disease, immmunosuppression and/or other concerning illness

Contact Pediatric COVID-19 Treatment Team (PCTT) if Considering Treatment

(Place EPIC consult order to PCTT - Available from 8am-5pm, ID fellow available for overnight consults & weekends)

PCTT to review case and determine risks/benefits of investigational treatment on a case-by-case basis

Informed verbal or written consent is required for all investigational therapies and should be obtained by either PCTT or by the primary team.

If caregiver & team agree to therapy

Obtain Baseline EKG & Labwork:

CBC*, CRP*, Procalcitonin*, Ferritin*, LDH, Troponin, D-Dimer, Fibrinogen, ESR, PT/PTT, cytokine panel

For PICU, add quantiferon gold, may start tx before get result

*Priority tests if there is limited blood volume

Provide Recommended Pharmacologic Treatment

- **For GIU**: Repeat labs q 24-hrs if patient not clinically improving
- **For PICU**: Repeat labs q 24-hrs if continues to require PICU support
- **For Both Units:**
  - Obtain q 48-hour cytokine panel if meets criteria for q-24 hr labs listed above
  - Other monitoring with medications (EKGs, additional labwork, etc.)

- Return to Inpatient Pathway when ready for discharge for guidance on home care
- Complete treatment course for outpatients as guided by PCTT

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MORE INFORMATION ON PHARMACOLOGIC AGENTS FOR SUPPORTIVE CARE

- For supportive care, it should be safe to use both acetaminophen and NSAIDs on a prn basis per clinician discretion

- There is no firm data to show that NSAIDs worsen the course of COVID-19
  - There is a theoretical risk given the fact that COVID-19 virus uses ACE2 to enter cells and NSAIDs (and ACE inhibitors) may increase ACE2 circulation.
  - However, there is some data to show other coronaviruses that also use ACE2, like SARS, have reduced viral replication with NSAIDs (indomethacin).
  - The **WHO** and **FDA** do not recommend against the use of NSAIDs for COVID-19 infections, but will be further investigating the issue - we will update our recs accordingly

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THE PEDIATRIC COVID-19 TREATMENT TEAM

- The Pediatric COVID-19 Treatment Team (PCTT) is a multidisciplinary team that will meet to review use of pharmacologic treatment on a case-by-case basis. Members will meet with caregivers and patients/families to review the risks/benefits, review existing evidence and obtain informed consent for use if the decision is reached to pursue pharmacologic therapy.

- PCTT Members:
  - Carlos Oliveira (ID, Chair)
  - Michelle Rychalsky (Pharmacy, Co-Chair)
  - Jaspreet Loyal (Hospitalist Service, member)
  - Adam Berkwitt (Hospitalist Service, memberI
  - an Ferguson (Rheumatology, member)
  - Josep Panisello (PICU, member)
  - Tom Murray (ID, member)
  - Elissa Zirinsky (ID, member)
  - ID service team (Fellow and Attending, revolving members)
  - Elijah Paintsil (ID, member)
  - Rebecca Ciaburri (Quality/Safety, member)
  - Matthew Grossman (Quality/Safety, member)

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RECOMMENDED 1st LINE PHARMACOLOGIC TREATMENT FOR COVID-19

1st LINE AGENT	DOSING	EXCLUSION CRITERIA	MONITORING	SIDE EFFECTS
Hydroxychloroquine (HCQ)	• 6.5mg/kg/dose q 12 hrs x 1 day (Max 400mg/dose) • Then 3.25-3.5mg/kg/dose q 12 hrs x 4 days* (Max 200mg/dose) • Use ideal body weight for dosing to reduce side effects	• QTc interval > 500 • Use with caution in infants < 6 months - consider 2nd line agent if not critically ill	• EKG monitoring every 2-3 days while receiving HCQ in conjunction with an interacting medication that prolongs QTc (e.g, Azithromycin) • CBC and CMP at least every 3 days while on treatment (daily if G6PD deficient)	• Risk of cardiotoxicity (QTc prolongation) • Hypoglycemia • Hemolysis in patients with G6PD (very low risk) • Retinopathy and marrow suppression (low risk with 5-days) • Hepatotoxicity: caution in patients with underlying liver disease or if using other hepatotoxic drugs • May increase levels of cyclosporine & digoxin

*Duration may be extended for up to 10 days on a case-by case basis depending on response and severity of illness.

Review potential medication interactions with clinical pharmacist prior to initiation

CLICK HERE FOR INFORMATION ON:
- **2nd line agents for COVID-19 AND**
- **Managing critically ill patients not responding to therapy**

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All of these medications have multiple drug interactions - review with clinical pharmacist prior to initiation

Click on this link for further information on protease inhibitor drug-drug interactions

RECOMMENDED 2nd LINE PHARMACOLOGIC TREATMENTS FOR COVID-19 & PATIENTS CRITICALLY ILL

CONSIDER 2ND LINE AGENTS IF CANNOT TOLERATE OR MEETS EXCLUSION CRITERIA FOR HCQ

2ND LINE AGENTS	DOSING	EXCLUSION CRITERIA	MONITORING	SIDE EFFECTS
Lopinavir/ritonavir	• **Age 14 days - 12 months**: 16mg/kg/dose of lopinavir twice daily x 7 days** • **Age ≥ 12 months:** 300mg/m^2/dose of lopinavir twice daily (max 400mg of lopinavir twice daily) x 7 days**	• Coadministration with drugs that are highly dependent on CYP3A for clearance • Avoid use in combination with QTc/PR prolonging drugs • Avoid use in neonates <14 days of age	• Daily Glucose testing • CBC and CMP at least every 3 days while on treatment. • Daily LFTs in patients with underlying hepatic disease • EKG monitoring every 2-3 days if receiving other drugs that prolong QTc • Amylase and Lipase every 3 days if using Lopinavir/ritonavir	• Rash • Hyperglycemia • Nausea, vomiting, diarrhea • May cause hepatitis and/or exacerbate pre-existing hepatic dysfunction • Use Lopinavir/ritonavir with caution in patients with increased triglycerides; pancreatitis has been observed.
Atazanavir*	• **Age 13 to <18 years**: Oral capsule: 620 mg/m2 divided twice daily (round to nearest 150 mg to accommodate capsule size) for 7 days** • **Adolescents ≥18 years**: Oral capsule: 400mg daily (to align with adult recommendations) for 7 days**	• Do not use in infants <3 months-old due to kernicterus risk • Coadministration with drugs that are highly dependent on CYP3A for clearance • Avoid use in combination with QTc/PR prolonging drugs • Avoid using unboosted Atazanavir in children <13 years old • Use with caution in patients with sulfa allergy		

*Atazanavir requires acidic gastric pH for absorption. Avoid antacids, H2 receptor antagonists, and PPIs. If an agent must be administered: Atazanavir should be administered 2 hours before or 1 hour after antacids.
- For twice daily dosing of atazanavir: Avoid PPIs and H2 receptor antagonists. For daily dosing of atazanavir: Avoid PPIs. An H2 receptor antagonist may be administered at the same time as atazanavir.

**Duration may be extended for up to 14 days on a case-by case basis depending on response and severity of illness.

CONSIDER FOR CRITICALLY ILL PATIENTS NOT RESPONDING TO 1st or 2ND LINE MONOTHERAPY

1) Dual Therapy Using HCQ + (Lopinavir/ritonavir or Atazanivir)
Check above recs on dosing, exclusion criteria, interactions, monitoring and side effects for individual treatments in addition to interaction noted to right to determine safety for use

INTERACTION & MONITORING HCQ & (Lopinavir/ritonavir or Atazanivir)
- The combination of HCQ + (Lopinavir/ritonavir or Atazanivir) increases chance of prolonged QTc
  - Pts should have daily EKGs for 72 hours and be on telemetry during combination therapy
  - If EKG normal after 72 hours, may discontinue further EKGs
  - If EKG with prolonged QTc >500, discontinue medications - avoid other QTc prolonging agents

AND/OR	DOSING	EXCLUSION CRITERIA	MONITORING	SIDE EFFECTS
2) Remdesivir - via Emergency IND	• <40 kg: loading dose: 5 mg/kg (max 200 mg) once; followed by maintenance dose (starting 24 hours after loading dose) of 2.5 mg/kg (max 100 mg) every 24 hours x 9 days • ≥40 kg: loading dose: 200 mg once; followed by maintenance dose (starting 24 hours after loading dose) of 100 mg every 24 hours x 9 days	• Multiorgan failure • Pressor requirement • ALT > 5 X upper limit of normal • Creatinine clearance <30 ml/min • Dialysis • Cannot use with another antiviral agent	PER GILEAD PROTOCOL Check for updated exclusion criteria as well	• Not yet FDA approved • Known potential side effects include: elevated transaminases, reversible kidney injury, and hypotension during infusion.

MAY CONSIDER ADDITION OF ANAKINRA & CORTICOSTEROIDS IF CONCERN FOR CYTOKINE STORM/CLINICAL DETERIORATION - Contact Rheumatology for dosing and guidance

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