CLINICAL PATHWAYS – INTRODUCTION

Clinical Pathways are guidelines used to assist in the delivery of high-value, effective, efficient, safe, and family-centered care. Pathways have been shown to improve the quality of care for hospitalized children with many conditions and in different settings (1)

A definition of a clinical 'pathway' needs to satisfy four criteria (2)

(1) It is a structured multidisciplinary plan of care.
(2) It is used to translate guidelines or evidence into local practices.
(3) It details the steps in a course of treatment or care in a plan, pathway, algorithm,guideline, protocol, or other "inventory of actions."
(4) It is aimed to assist in standardizingcare or a specific population.

These Clinical Decision-Support (CDS) tools are aimed to assist clinicians at the bedside to deliver evidence-based care. The **Algorithm (SECTION 2**) is a visual aid that helps guide clinicians, step-by-step through the timing, indications, and details of recommended tests and treatments for managing specific conditions.In this case, **COVID-19 Testing and Treatment** is being addressed.

These PATHWAYS and their specific SECTIONS were developed by a consensus of a subject-matter-expert (SME) team, organized by the Clinical Effectiveness and Pathways (CEP) program at Nicklaus Children's Health System (NCHS). The SME team included clinicians from multiple disciplines and pediatric sub-specialties (see SECTION 7).

These clinical pathways are intended to be used as acompilation of best practice recommendations for practitioners. The practice of evidence-based pediatric medicine involves the use of pathways, the clinicians' experiences and judgment, and finally the patient's perspectives and values.
However, these clinical pathways are not intended to constitute specific medical recommendations for treatment. The practitioners must exercise their own independent judgment in applying these tools.These clinical pathways are not a script or 'cookbook' applicable to allpatients. NCHS cannot certify that CDS documents are accurate or complete in every aspect. NCHS is not responsible for any errors or omissions in the use of clinical pathways or for any outcomes a patient mightexperience where a clinician consulted or followed these CDS in providing clinical care.

1-Rising utilization of inpatient pediatric asthma pathways.Kaiser SV, et al. J Asthma. 2017.
2-Lawal AK RT, Kinsman L, Machotta A, Ronellenfitsch U, Scott SD, Goodridge D, et al. What is a clinical pathway? Refinement of an operational definition to identify clinical pathway studies for a Cochrane systematic review. BMC Med 2016;14)

COVID-19 Testing and Treatment

UCC Phase

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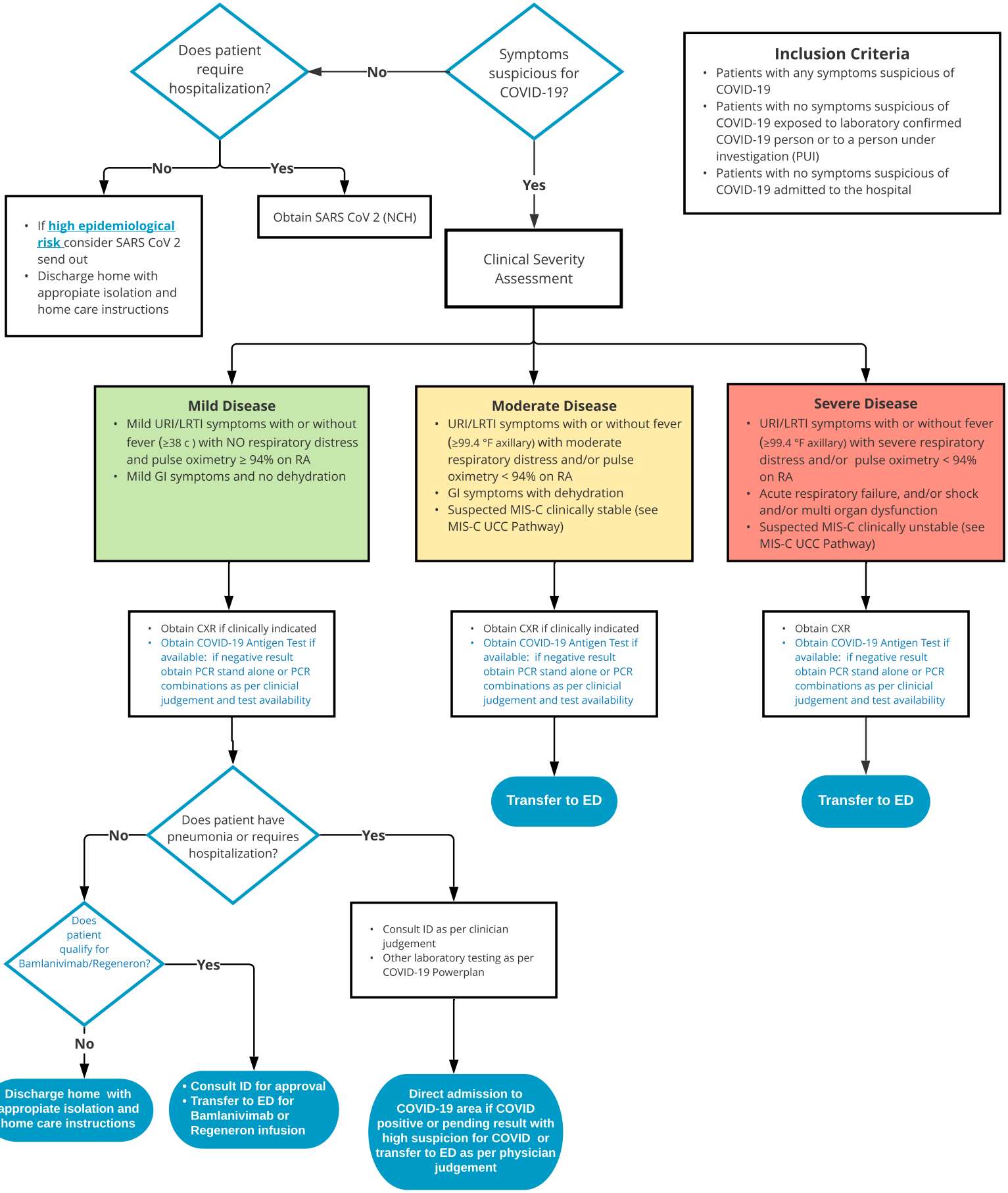

Inclusion Criteria

- Patients with any symptoms suspicious of COVID-19
- Patients with no symptoms suspicious of COVID-19 exposed to laboratory confirmed COVID-19 person or to a person under investigation (PUI)
- Patients with no symptoms suspicious of COVID-19 admitted to the hospital

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COVID-19 Testing and Treatment

ED/Inpatient Phase

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Does patient require hospitalization?

No

Symptoms suspicious for COVID-19?

No

- If high epidemiological risk consider SARS CoV 2 send out
- Discharge home with appropiate isolation and home care instructions

Yes

Obtain SARS CoV 2 (NCH)

Positive test and/or exposed to laboratory confirmed COVID-19 person or PUI?

No

If result negative or pending admit to Med-Surg floor

Yes

Admit to COVID area

Yes

Clinical Severity Assessment

Inclusion Criteria

- Patients with any symptoms suspicious for COVID-19
- Patients with no symptoms suspicious of COVID-19 exposed to laboratory confirmed COVID-19 person or to a person under investigation (PUI)
- Patients with no symptoms suspicious of COVID-19 admitted to the hospital

Mild Disease

- Mild URI/LRTI symptoms with or without fever (≥99.4 °F axillary) with NO respiratory distress and pulse oximetry ≥94% on RA
- Mild GI symptoms and no dehydration

- Obtain CXR if clinically indicated
- Obtain COVID-19 Antigen Test if available: if negative result obtain PCR stand alone or PCR combinations as per clinicial judgement and test availability

Does patient have pneumonia or requires hospitalization?

Yes

- Contact ID as per clinician judgement
- Place in negative room if available
- Other laboratory testing per COVID-19 Power Plan
- Contact Infectious Prevention Control (IPC) if needed

COVID test positive and/or patient exposed to laboratory confirmed COVID-19 person or to a PUI?

No

Admit to Med-Surg floor

Yes

- Admit to COVID area
- Consider ICU admission for selected moderate cases at risk of clinical deterioration

Management as per COVID-19 treatment guidance:

- Supportive Treatment
- **Consider Remdesivir** in consultation with ID if patient is at high risk of disease progression
- **Consider Baricitinib**
- **Consider Dexamethasone** if patient requires Supplemental Oxygen
- **Consider Anticoagulation**

No

Does patient qualify for Bamlanivimab/ Regeneron?

No

- Discharge home with appropiate isolation and home care instructions

Yes

- Consult ID for approval
- Follow up instructions for infusion administration

Moderate Disease

- URI/LRTI symptoms with or without fever (≥99.4 °F axillary) with moderate respiratory distress and/or pulse oximetry <94% on RA
- GI symptoms with dehydration
- Suspected MIS-C clinically stable (see MIS-C ED Pathway)

- Obtain CXR if clinically indicated
- Obtain COVID-19 Antigen Test if available: if negative result obtain PCR stand alone or PCR combinations as per clinicial judgement and test availability

Severe Disease

- URI/LRTI symptoms with or without fever (≥99.4 °F axillary) with severe respiratory distress and/or pulse oximetry <94% on RA
- Acute respiratory failure, and/or shock and/or multi organ dysfunction
- Suspected MIS-C clinically unstable (see MIS-C ED Pathway)

- Obtain CXR
- Obtain COVID-19 Antigen Test if available: if negative result obtain PCR stand alone or PCR combinations as per clinicial judgement and test availability

- Consult ID
- Place in negative room if available

- Other laboratory testing per COVID-19 Power Plan
- Contact Infectious Prevention Control (IPC) if needed

Admit to PICU

Management as per COVID-19 treatment guidance:

- Supportive Treatment
- **Remdesivir** plus **Dexamethasone**
- **Consider Baricitinib**
- **Anticoagulation**

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High Epidemiological Risk
Any of the following:

- Close contact (more than 15 min and less than 6 feet distance) with a laboratory confirmed COVID-19 person (see cdc.gov)
- Close contact (more than 15 min and less than 6 feet distance) with person under investigation (PUI) (see cdc.gov)

Return to UCC Phase

Return to ED Phase

Approval and Citation

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COVID 19 TESTING: Current availability and resources for Clinicians

PCR based testing:

Stand Alone Tests:

SARS CoV 2 (NCH) In-house PCR available to all units

CORONAVIRUS SARS-CoV 2 RT-PCR Send-out PCR available to ED

SARS Coronavirus 2 RNA detection, V Send-out PCR available to UCC

Combined Tests:

RPP 2.1 - SARS CoV2 PCR with other respiratory pathogens available to all units

SARS-CoV 2-FLU A/B-RSV-PCR

Antigen Test:

SARS CoV 2 Ag EIA POCT - Antigen test (available to ED)

SARS CoV 2 Ag FIA - Antigen test (available to UCC)

Serology:

SARS CoV 2 IgG (NCH) – Covid serology available to all units

Considerations for test results interpretation. Clinical decision making and proper communication with patients/families is based on:

a) Pre-test probability: depends on the prevalence of COVID 19 in Miami –Dade County. Please check out the latest data and information as.
https://floridahealthcovid19.gov/#latest-stats

b) Test performance / accuracy. Determined by **SENSITIVITY and SPECIFICITY: SARS CoV 2 RT-PCR tests:**

SENSITIVITY = 95% (0.950); very high SPECIFICITY ~ 100% (0.999).

SARS CoV2 Antigen-based test:

SENSITIVITY = 85% (0.850); very high SPECIFICITY ~ 100% (0.999)

Return to UCC Phase

Return to ED Phase

Approval and Citation

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Agents under Investigation for Treatment of COVID-19

Medication	Comments
Bamlanivimab (Evidence:Bamlanivimab) *Recommended therapy for patients who meet criteria for use.* **Pediatric and Adult dosing*:** Age ≥12 years AND ≥ 40 kg: 700 mg IV one time infusion given over at least 1 hour **Duration:**one time dose **Renal or Hepatic dosing:** No dosage adjustment recommended **Adverse reactions:** • Pruritus (2%) • Hypersensitivity reaction (2%; including type 1 hypersensitivity reaction, flushing and facial swelling) • Dizziness (3%) • Headache (3%) • Infusion related reactions (including anaphylaxis and severe infusion related reaction) **Regeneron** (Casirivimab/Imdevimab) (Evidence:Regeneron) *Recommended therapy for patients who meet criteria for use.* **Pediatric and Adult dosing*:** Age ≥12 years AND ≥ 40 kg: 1200 mg Casirivimab/1200 mg Imdevimab IV one time infusion given over at least over 1 hour **Duration:**one time dose **Renal or Hepatic dosing**: No dosage adjustment recommended **Adverse reactions**: • There are limited clinical data available for casirivimab and imdevimab. Serious and unexpected adverse events may occur that have not been previously reported with use. • Infusion related reactions (including anaphylaxis and severe infusion related reaction) - if reaction occurs, consider slowing or stopping the infusion and administering appropriate medications and/or supportive care * The authorized dosage may be updated as additional data from clinical trials becomes available.	**Requires ID approval** Only available as an investigational agent under emergency use authorization by the FDA. **How to Order:** 1. To start the request for Bamlanivimab or Regeneron, please send an email to RegulatoryAffairs@nicklaushealth.org 2. Use PowerPlan to place order for Bamlanivimab or Regeneron. 3. Obtain Consent and scan into medical record. 4. Give the Fact Sheet for Patients and Parents/Caregivers. **Inclusion Criteria:** • Patient age ≥ 12 years **AND** weight ≥ 40 kg • Positive SARS-CoV-2 test (antigen or PCR) • Experiencing symptoms of COVID-19 within the last 10 days • With one or more of the following risk factors: **• BMI ≥ 85th percentile for their age and gender based on CDC growth charges: https://www.cdc.gov/growthcharts/clinical_charts.htm** **• Chronic kidney disease (CKD)** **• Diabetes mellitus (T1DM or T2DM)** **• Immunosuppressed due to a disease** **• Immunosuppressed due to a medication** **• Sickle Cell Disease** **• Neurodevelopmental disorders (i.e., cerebral palsy, etc)** **• Hemodynamically significant congenital heart disease (cyanotic heart disease, severe pulmonary hypertension, acyanotic heart disease receiving medications to control heart failure)** **• Asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control** **• Medical-related technological dependence (i.e., tracheostomy, gastrostomy, positive pressure ventilation not related to COVID-19)** **Exclusion Criteria:** • Patient age < 12 years of age OR weight ≤ 40 kg • Patient ≥ 12 years of age AND weight ≤ 40 kg and requiring oxygen supplementation above baseline

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Agents under investigation for treatment of COVID-19	Comments
Remdesivir (Evidence: Remdesivir) *Preferred therapy for patients hospitalized due to COVID-19 if criteria are met for obtaining product from manufacturer (see comments)* **Pediatric dosing*:** < 40 kg: 5 mg/kg IV load (infused over 30 min), then 2.5 mg/kg IV q24h ≥ 40 kg: 200 mg IV load, then 100 mg IV q24h **Adult dosing:** 200 mg IV load, then 100 mg IV q24h **Duration:** 5-10 days. May extend to 10 days if inadequate response at 5 days.	**Requires ID approval** **FDA approved for ≥12 yo and ≥40kg** **If patient <12 yo and/or <40kg available under expanded use access(EUA).** **Inclusion Criteria:** • Hospitalization • SARS-CoV-2 positive by PCR or Ag • Oxygen saturation less than 94 % on RA **Exclusion Criteria:** • ALT > 5x ULN • Use caution in patients with CrCl < 30 mL/min, dialysis, or CVVH **How to order:** 1- Make sure patient meets criteria and ID has approved use. 2- If patient is ≥12 yo a consent is not needed. If patient is <12 yo obtain consent and scan into medical records. 3- Place order for Remdesivir. 4-Provide fact sheet to patient/caregiver. **A/E:** increased liver enzymes. Also potential to have drug-drug interactions with medications metabolized through the cytochrome system. **Monitor**: Renal and Hepatic function daily
Dexamethasone (Evidence: Steroids) *To be used for patients requiring oxygen support* **Adult & Pediatric dosing:** 0.15 mg/kg/dose IV/PO Q24H (max dose: 6 mg) **Duration**: 5-10 days **Alternatives**: other glucocorticoid at equivalent doses (Equivalent dose of Dexamethasone 6 mg = Methylprednisolone 32 mg or Prednisone 40 mg)	**Contraindications:** • None **A/E:** • Hypertension • Hyperglycemia • Gastritis/Abdominal Pain • Behavioral irritability • Hallucinations hallucinations **Monitor:** • Blood pressure • Blood glucose • CBC • Clinical response

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Agents under investigation for treatment of COVID-19	Comments
Baricitinib (Evidence: Baricitinib**)** *Reserved therapy for patients hospitalized due to COVID-19 requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) and who are receiving Remdesivir* **Adult dosing:** 4 mg PO, GT, NG Q24H **Pediatric dosing:** 2 to < 9 years: 2 mg PO, GT, NG Q24H ≥ 9 years and adolescents: 4 mg PO, GT, NG Q24H **Duration:**14 days or until hospital discharge, whichever is first **Dosage adjustment for toxicity:** *Evaluate baseline eGFR, liver enzymes, and CBC to determine treatment suitability and dose. Monitor closely patients with abnormal baseline and post-baseline laboratory values.* ·Absolute lymphocyte count (ALC) < 200 cells/mm3: considerinterruption until ALC ≥ 200 cells/mm3 ·Absolute neutrophil count (ANC) < 500 cells/mm3: consider interruption until ANC ≥ 500 cells/mm3 ·Renal dysfunction: requires dose adjustment ·Liver dysfunction: if hepatotoxicity occurs during therapy, discontinue Baricitinib until drug-induced liver injury is excluded **Adverse Events:**infection, increased liver enzymes, thrombosis, anemia, lymphocytopenia and neutropenia. Also potential to have drug-drug interactions with medications metabolized through the cytochrome system. **Monitor:**Renal function, Hepatic function and CBC with differential daily	**Requires ID approval** **Available under Expanded Use Access (EUA) if ≥ 2 years of age** **Inclusion Criteria:** ·Hospitalization ·SARS-CoV-2 by PCR ·Receiving Remdesivir treatment ·Requiring supplemental oxygen, invasive mechanical ventilation or ECMO **Exclusion Criteria:** ·Not recommended in patients with who are on dialysis, have end-stage renal disease (ESRD, EGFR < 15 mL/min/1.73 m2), or have acute kidney injury ·Patients with known active tuberculosis **Warnings:** ·Chronic infections - Consider if the potential benefits outweigh the potential risks of Baricitinib treatment in patients with active serious infections other than COVID-19 or chronic/recurrent infections. ·Thrombosis – Prophylaxis for VTE is recommended unless contraindicated. • **How to Order:** • 1.To start the request for Baricitinib, please send an email toRegulatoryAffairs@nicklaushealth.org • 2.Discuss use of Baricitinib with your patient if via EUA and obtain Consent. • 3.Place order for Baricitinib. • 4.Scan Consent into medical record.Give the Fact Sheet for Patients and Parents/Caregivers.

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Summary of Evidence

BAMLANIVIMAB

Mechanism of action: Bamlanivimab is a neutralizing IgG1 monoclonal antibody that binds to the receptor binding domain of the spike protein of SARS-CoV-2. It is an investigational drug and is not currently approved for any indication.

Evidence Summary:
Based on review of the topline data from the planned interim analysis of TrialJ2W-MC-PYAB, also called BLAZE-1 (NCT04427501), an ongoing randomized, double-blind, placebo-controlled, Phase 2 dose finding trial of Bamlanivimab monotherapy in outpatients with mild to moderate COVID-19, it is reasonable to believe that bamlanivimab may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older, weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization, and that, when used under the conditions described in this authorization, the known and potential benefits of Bamlanivimab outweigh the known and potential risks of such product.

REGENERON (CASIRIVIMAB/IMDEVIMAB)

Mechanism of action: Casirivimab (igG1κ) and imdevimab (IgG1λ) are two recombinant human mAbs which are unmodified in the Fc regions. Casirivimab and imdevimab bind to non-overlapping epitops of the spike protein receptor binding domain (RBD) of SARS-CoV-2 with dissociation constants K_D = 45.8 pM and 46.7 pM, respectively. Casirivimab, imdevimab and the casirivimab + imdevimab combination blocked RBD binding to the human ACE2 receptor with IC_{50} values of 56.4 pM, 165 pM, and 81.8 pM, respectively.

Evidence Summary: The data supporting this EUA are based on the analysis of Phase 1/2 from trial R10933-10987-COV-2067, that occurred after 799 enrolled subjects had completed at least 28 days of study duration. R10933-10987-COV-2067 is a randomized, double-blinded, placebo-controlled clinical trial studying casirivimab and imdevimab for the treatment of adult subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). The trial enrolled adult subjects who were not hospitalized and had at least 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining a positive SARS-CoV-2 viral infection determination. Subjects were randomized in a 1:1:1 manner to receive a single intravenous (IV) infusion of 2,400 mg of casirivimab and imdevimab (1,200 mg of each) (n=266), or 8,000 mg of casirivimab and imdevimab (4,000 mg of each) (n-267), or placebo (n=266).

At baseline, the median age was 42 years (with 7% of subjects ages 65 years or older), 53% of the subjects were female, 85% were White, 50% were Hispanic or Latino, and 9% were Black; 34% were considered high risk (as defined in Section 2). Approximately 31% of subjects reported at least 1 severe symptoms at baseline, 36% reported at least 1 moderate symptom and no severe symptoms, and 13% reported only mild symptoms. The median duration of symptoms was 3 days; mean viral load was 5.8 $\log_{10}$ copies/mL at baseline. The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.
A lower proportion of subjects treated with casirivimab and imdevimab had COVID-19 related MAVs (2.8% for combined treatment arms vs 6.5% placebo). In post-hoc analyses, a lower proportion of subjects treated with casirivimab and imdevimab had COVID-19-related hospitalizations or emergency room visits compared to placebo (see table 4). Results for this endpoint were suggestive of a relatively flat dose-response relationship. The absolute risk reduction for casirivimab and imdevimab compared to placebo was greater in subjects at high risk for progression to severe COVID-19 and/or hospitalization

Summary of Evidence

REMDESIVIR

Mechanism of action: nucleotide analogue, initially developed for treatment of Ebola. Works by inhibiting RNA-dependent RNA polymerase

Evidence Summary:
In-vitro activity against MERS and SARS, and has shown efficacy in animal models. (Gordon et al, 2020, de Wit et al 2020, Sheahan et al 2017)[9-11]. It has been shown to exhibit SARS-CoV-2 *in vitro*. (Wang et al, 2020)[12]
A double-blind, randomized, placebo-controlled study[2] was published in October 2020, that showed that remdesivir was superior to placebo in shortening the timie to recovery in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection. The primary outcome was the time to recovery. A total of 1062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo). Those who received remdesivir had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), as compared with 15 days (95% CI, 13 to 18) among those who received placebo (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P< 0.001, by a log-rank test). In an analysis that used a proportional-odds model with an eight-category ordinal scale, the patients who received remdesivir were found to be more likely than those who received placebo to have clinical improvement at day 15 (odds ratio, 1.5; 95% CI, 1.2 to 1.9, after adjustment for actual disease severity). The Kaplan–Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%).

STEROIDS (DEXAMETHASONE)

Mechanism of action: Dexamethasone is a long acting corticosteroid with minimal sodium-retaining potential. It decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability, suppresses normal immune response.

Rationale for use: Patients with severe COVID-19 develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these harmful effects.

Evidence Summary: The Randomised Evaluation of COVID-19 Therapy (RECOVERY) study, published in July 2020, showed that in patients hospitalized with COVID-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P< 0.001). The proportional and absolute between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).

Summary of Evidence

BARICITINIB

Mechanism of action:inhibits the intracellular signaling pathway of cytokines known to be elevated in severe Covid-19, including interleukin-2, interleukin-6, interleukin-10, interferon-λ, and granulocyte-macrophage colony-stimulating factor; acts against SARS-CoV-2 through the impairment of AP2-associated protein kinase 1 and the prevention of SARS-CoV-2 cellular entry and infectivity.

Evidence Summary:A randomized, double-blind, placebo-controlled clinical trial (ACTT-2, NCT04401579) of hospitalized adults with confirmed SARS-CoV-2 infection compared treatment with Baricitinib, a JAK inhibitor, plus remdesivir, an anti-viral (combination group; n=515) with placebo plus remdesivir (placebo group; n=518). Patients had to have laboratory-confirmed SARS-CoV-2 infection as well as at least one of the following to be enrolled in the trial: radiographic infiltrates by imaging, SpO2 ≤ 94% on room air, a requirement for supplemental oxygen, or a requirement for mechanical ventilation. Patients treated with the combination received the following regimen:
·Baricitinib 4 mg once daily (orally) for 14 days or until hospital discharge
·Remdesivir 200 mg on Day 1 and 100 mg once daily (via intravenous infusion) on subsequent days for a total treatment duration of 10 days or until hospital discharge
For the overall population (N=1033 patients) at randomization, mean age was 55 years (with 30% of patients aged 65 or older); 63% of patients were male, 51% were Hispanic or Latino, 48% were White, 15% were Black or African American, and 10% were Asian; 14% did not require supplemental oxygen, 55% required supplemental oxygen, 21% required noninvasive ventilation or high-flow oxygen, and 11% required invasive mechanical ventilation or ECMO. The most common comorbidities were obesity (56%), hypertension (52%), and type 2 diabetes (37%). Demographics and disease characteristics were balanced across the combination group and the placebo group.
The primary endpoint, for the intent to treat population, was time to recovery within 29 days after randomization. Recovery was defined as being discharged from the hospital without limitations on activities, being discharged from the hospital with limitations on activities and/or requiring home oxygen or hospitalized but not requiring supplemental oxygen and no longer requiring medical care.
For the overall population, the median time to recovery (defined as discharged from hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care) was 7 days for Baricitinib + remdesivir compared to 8 days for placebo + remdesivir [hazard ratio: 1.15 (95% CI 1.00, 1.31); p=0.047].
Patients assigned to Baricitinib + remdesivir were more likely to have a better clinical status (according to an 8-point ordinal scale) at Day 15 compared to patients assigned to placebo + remdesivir [odds ratio: 1.26 (95% CI 1.01, 1.57); p=0.044].
The proportion of patients who died or progressed to noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation by Day 29 was lower in baricitinib + remdesivir (23%) compared to placebo + remdesivir (28%) [odds ratio: 0.74 (95% CI 0.56, 0.99); p=0.039]. Patients who required noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) at baseline needed to worsen by at least 1 point on an 8-point ordinal scale to progress.
The proportion of patients who died by Day 29 was 4.7% (24/515) for Baricitinib + remdesivir vs. 7.1% (37/518) for placebo + remdesivir [Kaplan Meier estimated difference in Day 29 probability of mortality: -2.6% (95% CI -5.8%, 0.5%)].

References:
1.Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer UpToDate, Inc.; 2020; December 8, 2020.

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ANTICOAGULATION CONSIDERATIONS FOR PATIENTS WITH ACTIVE CORONAVIRUS DISEASE 2019 (COVID-19)

• COVID-19 is associated with hypercoagulability and increased risk of venous thromboembolism (VTE) in adults.[1]
• Common laboratory findings associated with COVID-19 associated coagulopathy in hospitalized adults include mild thrombocytopenia, increased D-dimer levels, increased fibrin degradation products, and prolonged prothrombin time.Elevated D-dimer levels have also been associated with a greater risk of death.[1]
• Due to this risk, routine use of pharmacologic prophylaxis or therapeutic anticoagulation is utilized in hospitalized adult patients unless contraindicated.[2]
• There is no current published evidence specific to use of anticoagulation in pediatric patients with COVID-19. However, ASPHO has published some recommendations.

Recommendations for Anticoagulation in COVID-19 Infection:

• Low molecular weight heparin (LMWH) prophylaxis is **recommended** in all acutely ill hospitalized or critically ill **adult patients** with confirmed COVID-19 unless contraindicated1
• LMWH **prophylaxis** should be **strongly considered on a case-by-case basis** in **pediatric patients** with confirmed COVID-19 AND additional risk factors for VTE or with slightly elevated D-dimer unless contraindicated.
• LMWH **treatment** should be **strongly considered on a case-by-case basis** in **pediatric patients** with confirmed COVID-19 with elevated D-dimer and additional risk factors for VTE unless contraindicated.
• Bleeding risk and benefits should be assessed on all patients.
• Avoid anticoagulation in patients with active bleed or intracranial hemorrhage
• Use with caution in patients with intracranial mass, LP or neurosurgical procedure in previous 24 hours, or pre-existing coagulopathy
• Consider early ambulation or mechanical prophylaxis in all patients in whom pharmacologic prophylaxis is contraindicated, and all pediatric patients greater than or equal to 12 years of age if applicable.
• Refer toTable for risk factors and dosing recommendations.

Post-discharge duration of therapy:

• **Consultation with hematology is strongly recommended if patient is being considered for extended duration of anticoagulation post-discharge.**
• For patients not being discharged on LMWH, consider one baby aspirin (81 mg) daily to be continued until acute phase reactants and inflammatory markers normalize.

***For recommendations on Anticoagulation in patients with MIS-C, see MIS-C Guideline.**

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Venous Thromboembolism (VTE) Risk Factors
Review ALL risk factors prior to proceeding with anticoagulation recommendations

Acute Hospital-Related Conditions

- New immobility
- Central venous line present
- Critically ill mechanically ventilated
- Active systemic infection (i.e., sepsis or any other infection other than COVID-19)
- Major trauma or spinal cord injury
- Post-major surgery (orthopedics) within past 30 days
- Pregnancy

Chronic Medical Conditions

- Obesity (BMI > 95th percentile for age)
- Acquired or inherited thrombophilia
- Active malignancy
- Sickle cell disease
- Inflammatory disorder (SLE, IBD, JIA)
- Protein losing disorder

Historical Conditions

- Previous history of DVT or PE
- Family history of DVT/PE in first degree relative
- Active smoker
- Long distance travel in past 4 weeks
- History of oral, intramuscular, or implantable estrogen

Clinical Presentation			Recommended Anticoagulation
Active COVID-19 Infection	All SARS-CoV-2 +	D-Dimer < 0.5 mcg/mL With No VTE risk factor above **OR** Any patient with bleeding risk factors, active bleeding, or platelets < 30,000	**Sequential compression device (SCD) and early ambulation**
		D-Dimer < 0.5 mcg/mL and pt has Any VTE risk factor above with No bleeding risk factors **OR** D-Dimer 0.5 - 1 mcg/mL Age ≥ 12 yrs with No bleeding risk factors	**Consider Enoxaparin Prophylaxis** • CrCl ≥ 30 mL/min • < 2 months: 0.75 mg/kg/dose SC every 12 hours • ≥ 2 months: 0.5 mg/kg/dose SC every 12 hours up to max 30 mg every 12 hours • Adolescents > 60 kg: 40 mg SC every 24 hours • BMI > 95% tile for age or > 40 kg/m2: 40 mg every 12 hours • No levels required • CrCl < 30 mL/min • 0.5 mg/kg SC every 24 hours up to max 40 mg every 24 hours • BMI > 95%tile for age or > 40 kg/m2: 40 mg every 24 hours • Target anti-Xa: 0.2-0.4 IU/mL • Continue enoxaparin prophylaxis while VTE risk factor present
		D-dimer > 1 to < 10 mcg/mL With 2 or more VTE risk factors above and No bleeding risk factors **OR** D-dimer > 10 mcg/mL with or without VTE risk factors and No bleeding risk factors	**Consider EnoxaparinTreatment** • CrCl ≥ 30 mL/min • < 2 months: 1.5 mg/kg/dose SC every 12 hours • ≥ 2 months: 1 mg/kg/dose SC every 12 hours • Target anti-Xa: 0.5-1 IU/mL • CrCl < 30 mL/min • 1 mg/kg SC every 24 hours • Target anti-Xa: 0.5-1 IU/mL • Use total body weight in obese patients up 150 mg per dose, and monitor anti-Xa levels • Continue enoxaparin treatment until D-dimer < 1 mcg/mL; then transition to prophylaxis while VTE risk factor is present
		Known DVT or PE	**Enoxaparin Treatment** (see above)

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References

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ICD-10 Codes

- COVID-19 virus infection U07.1
- Pneumonia due to COVID-19 U07.1
- Exposure to COVID-19 virus Z20.828
- Suspected COVID-19 virus infection R68.89
- Gastroenteritis due to COVID-19 virus U07.1

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CLINICAL EFFECTIVENESS / PATHWAYS PROGRAM

SUBJECT-MATTER EXPERTS (SME) TEAM

UCC: Richmond Darko. Sheree Mundy
ED: William Coombs, Ana Paez, Daniela Ricci, Diana Gomez
Hospital Medicine: Beatriz Ladd, Melissa Clemente, Marcos Mestre
Med - Surg Nursing: Ana Bandin, Ana Tyrkala. Natalia Lopez
PICU: Pritvi Raj Sendi Keshavamurthy, Balagangadhar Totapally
Pulmonology: Alicia Della Volpe
Infectious Diseases: Otto Ramos, Pablo Laufer
Pharmacy: Marry Vuong, Gabriella Blyumin
Infection Prevention Control: Regina Piszcz

Clinical Effectiveness & Pathways (CEP) program Lead TEAM

Mario A. Reyes - Quality
Veronica Etinger - EBM Co-Chair
Rodney Baker, ED Director
Rebeca Calderon - Pharmacy
Aileen Permuy - Systems Analyst
William Smit - Data Scientist
Brandon Korman- Behavioral Medicine
Roberto Gonzalez Jr. - Web Graphic Designer II
Danielle Altares-Sarik - Nursing Research
Maria Ramon-Cotton - UCC Director
Pritvi Raj SendiKeshavamurthy - PICU
Beatriz Cunill - Med Education Director
Jose Rosa-Olivares - CMIO
Donna Lewis - Systems Analyst
Lourdes Fernandez - CI-HIT
Rodeline Estime - Coordinator

EBM Council

Jeffry Biehler-EBM Chair-Executive Medical Director of Quality
Michael Gagnon-Manager Quality Assurance
Frederick Trent-Quality Resource Administrator

Version 1.0 Approved by Incident Command: August 28th, 2020
Version 2.0 Approved by Incident Command: December 7th, 2020.
Version 3.0 Approved by EBM : December 23, 2021
Version 4.0 Approved by P & T; January 12, 2021

Last updated: January 12, 2021

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