Beth Israel Lahey Health

Beth Israel Deaconess Medical Center

Development of a living guidance document for the therapeutic evaluation and treatment of patients with CoVID-19

Christopher McCoy, Roger Shapiro, Katy Stephenson, Ryan Chapin, Sabrina Tan, Margaret Hayes, Howard Seth Gold.
Department of Pharmacy, Division of Infectious Diseases, Division of Health Care Quality, Beth Israel Deaconess Medical Center

Introduction/Problem

With the impending pandemic and its unclear impact, we convened a multidisciplinary workgroup across Pharmacy, Infectious Diseases, Research, Transplant, Hematologic Malignancy, Critical Care and Health Care Quality and others to begin to plot out a treatment guideline for CoVID-19.

The unknowns were many given the lack of approved treatments, the lack of peer reviewed published literature and unclear trajectory for the breadth and depth of care at our institution.

The need for a rapid response and clear guidance became increasingly pressured during the first surge as our census for those infected went from 3 to 192 from March to April 2020 with a high percentage of patients requiring ICU level care and many remaining here for weeks.

Sources of data were limited to a World Health Organization outline, preprints from China and Italy and basic science reviews of agents thought to have antiviral activity.

Early guidance were often completely refuted by well controlled trials, e.g. recommendation to given empiric antibiotics to all patients with SARI, avoidance of systemic corticosteroids.

Over 273 medication shortages were making broad treatment recommendations difficult.

Active research protocols had to be introduced to promote systematic exploration

Aim/Goal

To provide a central and locally balanced resource for clinicians for the treatment of CoVID-19 bifurcated by disease severity and predictors for advanced disease based on an ever evolving evidence base.

To grade therapeutic modalities and frame experimental therapies with risk considerations and newly launched local research.

The Team

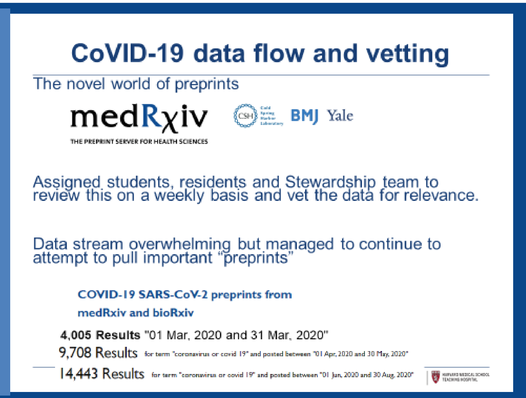
Roger Shapiro, MD	Attending Physician-HIV researcher	Infectious Diseases
Katy Stephenson, MD	Attending Physician-Viral Vaccine researcher	Infectious Diseases
Ryan Chapin, PharmD	Clinical Specialist- Infectious Diseases	Pharmacy
Sabrina Tan, MD	Attending Physician- Viral Researcher	Infectious Diseases
Margaret Hayes, MD	Attending Physician- Critical Care Director	Critical Care Medicine
Howard Seth Gold, MD	Medical Director-Antimicrobial Stewardship	Health Care Quality, Infectious Diseases
Christopher McCoy, PharmD	Clinical Manager- Infectious Diseases	Pharmacy
CoVID 19 Treatment Collaborative		

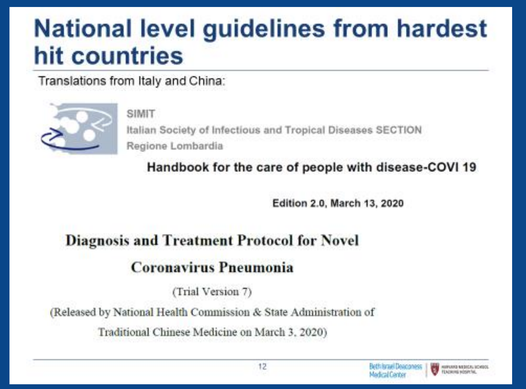
The Interventions

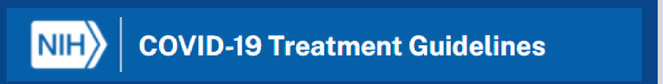
- Built a multidisciplinary team with incorporation of the network and representation from key clinical areas
- Developed a review process for preprints through MedrxIV, national guidelines (NIH, IDSA)
- Scribed a treatment algorithm by severity of disease presentation.
- Continuously evaluated and incorporated best practice for collection and interpretation of biomarkers and laboratory values as well as comorbidities for risk stratification
- Reviewed investigational therapeutics for linkage to local research studies (e.g., remdesivir, favipiravir)
- Researched and provided dosing, drug interaction, screening and place in therapy guidance for all agents
- Facilitated weekly data/literature summary meetings across a BILH network collaborative to build consensus for guideline changes.
- Reviewed drug shortage updates to alter treatment guidance toward a prioritization scheme
- Directed restrictive criteria/clinical provider order entry guidance for therapeutic agents to promote safe and evidence based utilization of scarce resources

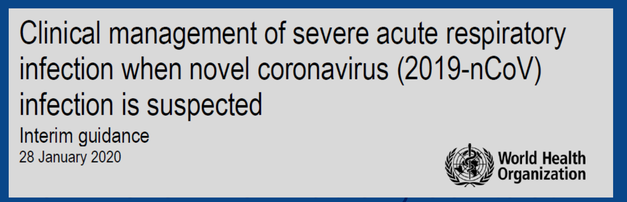
Results: Data Review

Early but continuous review of pre-published, published and guideline data.









Christopher McCoy, PharmD cmccoy@bidmc.Harvard.edu Clinical Manager, Infectious Diseases Pharmacy, Antimicrobial Stewardship

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Results and Progress

Most basic outline created Feb 2020
Basic tenets from WHO and CDC
Ongoing trial of remdesivir

Version 1: Feb 12/2020

23–32% of hospitalized patients with COVID-19 and pneumonia required intensive care for respiratory support.

- 11% received high-flow oxygen therapy, 42% received noninvasive ventilation, and 47% received mechanical ventilation.
- Among hospitalized patients with pneumonia, the case fatality proportion has been reported as 4–15%.

Severe Acute respiratory infection

- Avoid corticosteroids relative to experience from MERS-COV
- Empiric antibiotic treatment should be based on the clinical diagnosis (community-acquired pneumonia, health care-associated pneumonia
- Fluid resuscitation as per sepsis guidelines

There is no current evidence from RCTs to recommend any specific anti-nCoV treatment for patients with suspected or confirmed 2019-nCoV infection.

No specific treatment for COVID-19 is currently available. Clinical management includes prompt implementation of recommended infection prevention and control measures and supportive management of complications, including advanced organ support if indicated.

WHO randomized double blind placebo controlled clinical trial safety and efficacy of investigational therapeutics:

- Remdesivir 200 mg once , then 100 mg iv daily (10 days)
- Kaletra + IFNbeta 1b

Remdesivir (GS-5734) nucleotide prodrug

Inhibits RNA-dependent RNA polymerase activity among a diverse group of RNA viruses including filoviruses (e.g. Ebola, Sudan, Marburg), paramyxoviruses (e.g. RSV, Nipah, Hendra) and pathogenic coronaviruses

nonhuman primate studies therapeutic efficacy of Remdesivir against Ebola virus, supporting the development of Phase 2 clinical trials in Africa

Studies in human airway epithelial cell assays demonstrated that Remdesivir inhibits replication of coronaviruses, including MERS-CoV

Weblink guidance for early therapeutics
From basic science to WHO guidance to National guidelines

COVID-19 weblinks: therapeutics

Remdesivir

NEJM First US case remdesivir experience

Gilead CoVID-19 (remdesivir)

MERS CoV remdesivir, LPV/r interferon Nature 2015

NEJM Ebola antiviral comparative trial 12/19

WHO overview

WHO landscape analysis of therapeutics (2/17/20)

WHO R&D Blueprint for candidate therapies COVID-19

WHO COVID-19 research roadmap

Lopinavir/ritonavir

JID 2015 LPV/r interferon nonhumane primate MERS

MERS CoV remdesivir, LPV/r interferon Nature 2015

MIRACLE (LPV/r interferon) MERS trial design

CDC clinical therapy guidance

CDC Interim Clinical Guidance COVID-19

Chinese guidelines/trials

Chinese Emergency Medicine guideline COVID-19

SARS 1 LPV/r multicenter China cohort 2003

US Clinical trial development and linkage

Sponsor: US	Design and link:	Primary outcome:
NIAID: **Recruiting**	Adaptive treatment trial Hospitalized only (any severity) Randomized double blind placebo controlled	Day 15 disposition
Gilead **Not yet recruiting**	Phase 3 treatment trial Severe Disease Hospitalized only with pulmonary infiltrates, altered oxygen saturation and fever Randomized duration trial (5 versus 10 days)	Day 14 Clinical recovery (sx)
Gilead **Not yet recruiting**	Phase 3 treatment trial Moderate Disease Hospitalized only with pulmonary infiltrates, altered oxygen saturation and fever Randomized duration trial (5 versus 10 days) vs. Standard of care (supportive)	Day 14 disposition

HIV Antiviral adaptive research

Lopinavir/r +/- IFN beta1b

MIRACLE TRIAL (MERS COV) Saudi Arabia	
Primary	Mortality at day 90
	Lopinavir /Ritonavir 400mg +100 mg / ml twice daily for 14 days and Interferon beta-1b 0.25 mg subcutaneous every alternate day for 14 days

LPV/r monotherapy COVID-19 China	
Primary	Clinical improvement at day 28
	None reported

LPV/r triple arm study COVID-19 China	
Primary	Clinical improvement at day 28
	A: Ribavirin + Interferon alpha-1b B: lopinavir / ritonavir + interferon alpha-1b C: Ribavirin + LPV/r+Interferon alpha-1b

Early investigational

Alternative early investigative therapies

Methylprednisolone 40 mg q12h	Emtricitabine + tenofovir (Truvada)
Hydroxychloroquine 400 mg daily	Ruxolitinib
Darunavir 800 mg/Cobicistat 150 mg daily	Pegylated interferon alfa 2b (PEG-Intron): 1.5mcg/kg subcutaneously once per week x 2
Chloroquine vs. LPV/r vs. combo	Penciclovir
Gemcitabine	Nitazoxanide
Disulfiram	Loperamide
Cyclosporine	Oseltamivir
Imatinib	Dasatinib

Earliest treatment algorithm incorporating a single experimental agent

Inpatient Coronavirus 2019 (COVID-19) Treatment Algorithm

This guideline has been designed to assist the clinician in the potential treatment of confirmed COVID-19 infection in hospitalized patients. No standard treatment has been proven or endorsed currently by the CDC or WHO. All therapies are experimental at this time but based on published case and early trial results from outside the US. Supportive care remains the cornerstone of therapy.

An Infectious Diseases consult is strongly recommended for confirmed cases as many therapies require compassionate use sign off or potential trial enrollment.

Hospitalized and confirmed SARS-2 by PCR testing

Illness of any duration and one of the following
- ❑ Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.)
- ❑ Clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air
- ❑ Requiring mechanical ventilation and/or supplemental oxygen

Contraindications
- ❑ (ALT/AST) > 5 times the upper limit of normal
- ❑ Stage 4 severe chronic kidney disease or requiring dialysis (i.e. estimated glomerular filtration rate (eGFR) < 30)
- ❑ On another study agent

Consider Remdesivir

First iterative multidisciplinary multisite algorithm: March 20

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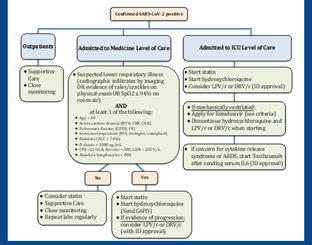
COVID-19 Treatment Guideline Version 0.2 LAST UPDATED: 18 March 2020

- This document is designed to assist clinicians in the treatment of confirmed COVID-19 infection in hospitalized patients.
- **No standard treatment has been proven or endorsed currently by the CDC or WHO.**[1]
- All therapies are deemed experimental at this time based on published cases and early trial results from outside the US.[2,3]
- Supportive care remains the cornerstone of therapy.
- An Infectious Diseases consult is strongly recommended for confirmed COVID-19 cases as many therapies require compassionate use sign off or trial enrollment.
- This document does NOT cover recommendations for management of hypoxemia, fluid resuscitation or complications in patients with COVID-19
- Please note when this document was last updated. Updates will occur in real time as data emerge.

Figure 1: Summary Flow Chart of Treatment



Lab and Imaging guidance

Laboratory Testing and Radiology

*Note: Given limited drug supplies, specific guidance in this document is intended only for **COVID-19 confirmed patients**. If the patient has not yet been tested for SARS-CoV-2,* approval for testing may be obtained through the BIDMC HID Pager (33860)

Table 1: Tests for Hospitalized Patients with Confirmed COVID-19

Daily: Laboratory Testing
- CBC with diff (trend total lymphocyte count)
- Complete metabolic panel
- Liver function tests (ALT/AST/tbili)

For risk stratification (may be repeated if abnormal or with clinical deterioration):
- CPK (creatine kinase)
- D-dimer
- Ferritin
- LDH
- Troponin[1]
- IL-6 for ICU patients

Viral serologies[2]
- HBV serologies (sAb, cAb, and sAg)
- HCV antibody, unless positive in past
- HIV 1/2 Ab/Ag

G6PD testing (in case hydroxychloroquine is required)

Immunocompromised patients:
If clinically indicated, consider serum beta-d-glucan to evaluate for *Pneumocystis*. (Do not routinely induce sputum given risk of aerosolization; yield from non-induced sputum is low).

Radiology:
- Portable CXR at admission.
- PA/lateral in ambulatory patients only if low suspicion for COVID-19 and result would change management or affect PUI status.

Baseline ECG[3]
- If starting QTc prolonging drug, can repeat ECG in 24-48 hours to monitor QTc. If baseline QTc > 500, repeat within 24 hours and consider stopping QTc prolonging drugs.

If clinically indicated:
- Routine blood cultures (2 sets)
- For acute kidney injury (i.e. serum creatinine >0.3 above baseline), send urinalysis and spot urine protein:creatinine

[1]Viral serologies assist for interpretation of ALT elevations, present in ~25% of presentations.
[2]Elevated troponin (> 2 times upper limit of normal) without hemodynamic compromise, can repeat troponin in 24 hours and echocardiogram not necessary. Uptrending troponin with hemodynamic compromise or other concerning cardiovascular symptoms /signs should prompt consideration of obtaining an echocardiogram.

Agents not recommended

Not recommended

- **Systemic steroids** should in general be avoided given potential harm. Steroids may be considered if indicated for another reason. A randomized controlled trial is testing the safety/efficacy of steroids for COVID-19 (NCT04273321). Until results are available, broad use of steroids, especially in milder forms of the disease, is discouraged.
- **Ribavirin** is not recommended at this time.

Unknown or Neutral

- **ACE-Inhibitors (ACEi) / Angiotensin Receptor Blockers (ARBs):**
  - SARS-CoV-2 virus binds to the ACE2 receptor for cellular entry. It is unknown if these agents either help or worsen COVID-19 disease.
  - Currently there are no data to support either starting or stopping ACEi/ARBs on any patients with COVID-19. However, if acute kidney injury, hypotension or other contraindication develops, we recommend stopping them at that time.
- **Inhaled steroids:**
  - May theoretically reduce local immunity and promote viral replication, but this consideration must be balanced by potential benefits for management of reactive airways. There is no current evidence that inhaled steroids worsen the course of COVID-19
- **NSAIDs:**
  - NSAID use has been reported preceding clinical deterioration in some patients with severe COVID-19 disease, but the association remains uncertain. Until more information is available, providers may wish to consider avoiding use of NSAIDs while patients are admitted if alternatives such as acetaminophen are available.

Agents with unknown utility

Unknown or Neutral

- **ACE-Inhibitors (ACEi) / Angiotensin Receptor Blockers (ARBs):**
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Severity graded guidance

Step 2: Treat Based on Severity

Table 3: Suggested Treatment Algorithm Based on Clinical Severity

Clinical Situation	*Recommendation*	*Notes / Considerations*
All hospitalized patients (regardless of severity)	May consider use of a statin (see below)	Close monitoring for progression
Patients requiring floor-level admission with suspected lower respiratory disease (radiographic infiltrates by imaging OR evidence of rales/crackles on physical exam OR SpO2 ≤ 94% on room air) AND at least one additional risk factor (see Table 2)	Start statin atorvastatin 40 mg daily Start hydroxychloroquine 400 mg BID x2 followed by 400 mg daily while hospitalized for up to 5-10 days. Note chloroquine has activity but limited supply so hydroxychloroquine preferred If evidence for progression: With ID approval, consider: lopinavir/ritonavir (LPV/r or Kaletra) 400/100 mg BID for 10 days If LPV/r not available, consider using darunavir/cobicistat (DRV/c) 800/150 mg daily	Avoid statins if elevated CPK (>2x ULN) or ALT (>3x ULN). Monitor LFTs (discontinue if >5x ULN) Check ECG prior to HCQ initiation given risk of QT prolongation. Risk is increased in patients on other QT-prolonging agents. Do not use if QT > 500 msec. Avoid in myasthenia gravis, porphyria, retinal pathology, epilepsy. Pregnancy is not a contra-indication. Assess for drug-drug interactions before starting. Main HCQ side effect is gastrointestinal intolerance. Monitor liver function tests while on therapy.
Patients requiring ICU-level admission	Manage as above. If mechanically ventilated: obtain remdesivir (RDV) through compassionate use Current dosing of RDV is 200 mg IV loading dose following by 100 mg IV daily for up to 10 days. Discontinue hydroxychloroquine and any other other antiviral agent when starting remdesivir	For compassionate use, apply through portal here: https://rdvu.gilead.com Exclusion criteria: Evidence of multiorgan failure, on pressors, creatinine clearance < 30, transaminases > 5X ULN, concomitant use of other antivirals

Risk analysis for progression

Step 1: Identify Risk Factors

Table 2: Risk Factors for Severe COVID-19 Disease

Demographic	*Labs*
-Age > 60 -Pre-existing pulmonary disease -Chronic kidney disease -Diabetes with A1c > 7.6% -History of hypertension -History of cardiovascular disease -Use of biologics -History of transplant or other immunosuppression -All patients with HIV (regardless of CD4 count)	-D-dimer > 1000 ng/mL -CPK > twice upper limit of normal -CRP > 100 -LDH > 245 U/L -Elevated troponin -Absolute lymphocyte count < 800 -Ferritin > 300 ug/L

Special Populations

Table 4: Special Populations

	Recommendation	Notes
Solid organ and BMT recipients	Guided by transplant and transplant ID teams – please call/consult Request bronchoscopy only if significant decompensation, versus lung biopsy as may be lower risk for aerosolization and exposure to staff Reduction of immunosuppressants need to be considered with guidance by transplant and transplant ID teams.	Screen for drug-drug interactions with anti-viral agents, if they are being used
If IgG <400	Consider IVIG at standard dose of 1 gm/kg daily x 2 doses	

For more information, contact:

Christopher McCoy, PharmD cmccoy@bidmc.Harvard.edu Clinical Manager, Infectious Diseases Pharmacy, Antimicrobial Stewardship

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Results and Progress

Milestones

Late March 2020

Invited content experts and leaders across the BILH network to build the first Network treatment algorithm

Institution	Pharmacy	Infectious Diseases	Critical Care	Research
BIDMC Boston	Chris McCoy Nick Mercuro Ryan Chapin	Howard Gold Roger Shapiro Sabrina Tan Rebecca Zash Carolyn Alonso Chris Rowley Mary Lasalvia	Margaret Hayes Danny Talmor Todd Sarge Shahzad Shaefi	Katy Stephenson
Lahey Health Medical Center Burlington	Elizabeth O'Gara	Robert Duncan Ken Wexler Julie M. Freiman	Fraser MacKay	Kimberly Christ Deborah Perry
Mount Auburn Hospital	Patricia Masters	Diana Sullivan Dan Bourque Robin Colgrove Shiv Sehra	Pete Clardy Jess McCannon	Lin Chen
Ana Jacques Hospital	Yinka Ojutalayo	Peter Sebeny Patricia Lawrence	Sandra Levin	
BI Needham	Joseph Giovangello	Natasha Glushko Constance Crowleyganser Ghania El Akiki	William Durbin	
BI Plymouth	James Berghelli Timothy Winders	Kimberly Teves Stefanie Marglin		
New England Baptist Hospital	Tim Fouche	Brian Hollenbeck		
Lahey Health Medical Center Beverly	Hope Violette	Ilona Breiterene Peter Short Joseph Gross Humera Kauser	Michael Colancecco	Karin Lepannen Shakeeb Yunus
Lahey Health Medical Center Winchester	Mike Dupuis	Andrew Lubin		
Cambridge Health Alliance	Amanda Barner	Lou Ann Bruno-Murtha Mary Regan	Alex White	Melisa Lai-Becker

Introduced Nephrology research on niacinamide and conditional framework

Did quality review of local tocilizumab utilization and infectious complications

Added more evidence based guidance for patients who may benefit from IL-6 modulation

Linked ICU teams with ongoing IL6 modulation trial-sarilumab

Identified hydroxychloroquine and azithromycin utilization as concerning

Removed darunavir-cobicistat from therapeutic recommendations

Began populating an ever growing annotated citation list

Annotated References

1. Centers for Disease Control and Prevention. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). Coronavirus Disease 2019. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
   - **Consensus statement**: CDC statements on clinical presentation, course, laboratory findings, diagnostic testing and management. Currently, no specific available antiviral treatment is recommended. Routine use of corticosteroids is not recommended. Remdesivir is an investigational therapeutic with ongoing trials in the US.
2. Wang M, Cao R, Zhang L, Yang X, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research. 2020 https://doi.org/10.1038/s41422-020-0282-0
   - **In-vitro**: Remdesivir, chloroquine, nitazoxanide, and other antivirals were tested against COVID-19 in a virus-cell model. The two antivirals that blocked virus infection at the lowest (and clinically achievable) concentrations were remdesivir (EC_{50}= 0.77 uM) and chloroquine (EC_{50}= 1.13 uM). The half maximal effective concentration for investigational favipravir was higher (EC_{50}= 61.88 uM).
3. Study to evaluate the safety and antiviral activity of remdesivir (GS-5734) in participants with severe coronavirus disease (COVID-19). NCT04292899. https://clinicaltrials.gov/ct2/show/record/NCT04292899
   - **Ongoing open-label trial** in US evaluating 5 and 10 days of remdesivir against standard of care in hospitalized adults with positive COVID-19 test ≤4 days before randomization, fever, **SpO_2 ≤ 94%** on room air, and radiographic evidence of pulmonary infiltrate. Key exclusion criteria are: participation in other experimental trials, concurrent active antiviral targeted towards COVID-19, multi-organ failure, mechanical ventilation, ALT/AST >5x ULN, CrCl <50 mL/min.
4. Study to evaluate the safety and antiviral activity of remdesivir (GS-5734) in participants with moderate coronavirus disease (COVID-19). NCT04292730 https://clinicaltrials.gov/ct2/show/NCT04292730?term=Study+to+Evaluate+the+Safety+and+Antiviral+Activity+of+Remdesivir&draw=2&rank=2
   - **Ongoing open-label trial** in US evaluating 5 and 10 days of remdesivir against standard of care in hospitalized adults with positive COVID-19 test ≤4 days before randomization, fever, **SpO_2 >94%** on room air, and radiographic evidence of pulmonary infiltrate. Key exclusion criteria are: participation in other experimental trials, concurrent active antiviral targeted towards COVID-19, ALT/AST >5x ULN, CrCl <50 mL/min.
5. Yao X, Ye Fei, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). Clin Inf Dis. 2020. Ahead of press. doi: 10.1093/cid/ciaa237
   - **In-vitro, pharmacokinetic modeling**: comparing potency and predicted exposures of different hydroxychloroquine (HCQ) regimens compared to chloroquine (CLQ). Authors concluded that regimen of HCQ 400mg BID x1 day then 400mg/day x4 days is appropriate given the levels achieve in serum and pulmonary tissue, which persist even five days after the

Tocilizumab guidance

Criteria suggestive of COVID-19 CRS:

1. **COVID-19 confirmed positive by molecular diagnostic testing.**
   AND
2. **Evidence of acute host inflammatory response and/ or multi-organ failure (≥2 of the following):**
   - **Fever >38C**
   - **Hypotension (MAP <65) requiring vasopressors**
   - **ARDS type pulmonary infiltrates and P/F ratio <300**
   - **Acute kidney injury**
   - **Worsening encephalopathy**

   AND
3. **Patients displays elevated ferritin levels >700 ng/dL**
   AND
4. **Patient displays any 2 of the following:**
   - **Thrombocytopenia (<130,000), elevated D-dimer >250, or depleted fibrinogen (<150)**
   - **Leukopenia (<3500/mm3) or lymphopenia (<1000/mm3)**
   - **AST or ALT elevated >2x upper limit of normal**
   - **LDH elevated >2x upper limit of normal or CRP >100**

Patients may also benefit from risk stratification for COVID-19 CSS with the use of the Hscore, commonly used for the diagnosis of HLH]

Treatment of COVID-19 Patients

1. **COVID-19 with ARDS (moderate to severe by Berlin Criteria) *without* shock**
   - **Dexamethasone 10-20 mg per day for at least 5 days (5)**
   - **If no improvement by Day 3, add one dose of tocilizumab**
2. **COVID-19 with ARDS (moderate to severe) *with* shock**
   - **Hydrocortisone 100 mg every 8 hours for duration of shock**
   - **If no improvement by Day 3, add one dose tocizilimab**

Expanded sections on Immunomodulators

- **IL-6 inhibitors (may be available within clinical trials):**
  - Tocilizumab (IL-6 inhibitor) – May be helpful in cytokine release syndrome, characterized by elevated IL-6 (>40 pg/mL), and supported by D-dimer > 1000 ng/mL, CRP > 100.
  - Sarilumab (IL-6 inhibitor) – As above. May be available as part of clinical trial.

Built links to ongoing trials to boost enrollment

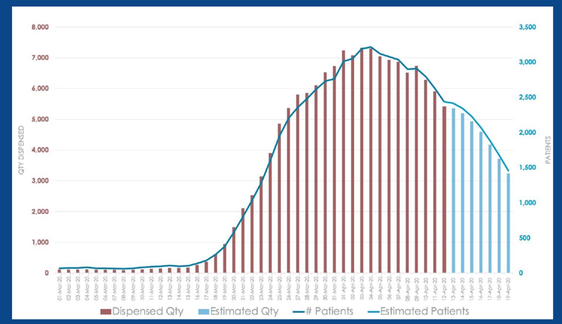
BIDMC Clinical Trial List

Created by Stephenson, Kathryn Elaine, last modified on Apr 06, 2020

- **(Updated 4/6/20)**

	Investigational Product	Protocol	Site PI	Study Coordinator	Major Inclusion	Co-Enrollment	Contact
1	Remdesivir - Protocol Details Link	RDV-73 - Severe	Kathryn Stephenson	Diane Kanjilal	Hospitalized, Intubated OK	No	Diane Kanjilal, b31392
2	Remdesivir - Protocol Details Link	RDV-74 - Moderate	Kathryn Stephenson	Diane Kanjilal	Hospitalized, Room Air >95%	No	Diane Kanjilal b31392
3	Remdesivir - Protocol Details Link	Compassionate Use	Kathryn Stephenson	Jessica Ansel	Pregnant and Intubated	No	Jessica Ansel, b30833
4	DAS181 - Protocol Details Link	Compassionate Use	Sabrina Tan	n/a	Critically ill		Sabrina Tan, b38938
5	Convalescent Plasma - Protocol Details Link	Compassionate Use	Ruvandhi Nathavitharana	n/a	Critically ill		Ruvandhi Nathavitharana, b37508
6	Tissue Plasminogen Activator (tPA) - Protocol Details Link	tPA-COVID-19	Daniel Talmor / Michael Yaffe	TBD	ARDS, Intubated		Valerie Banner-Goodspeed Michael Yaffe, b92028
7	Sarilumab	6R88-COV-2040	Robert Hallowell		Hospitalized, Intubated OK		Robert Hallowell, b92779

Hydroxychloroquine utilization



Held first in a series of Network Meetings

April 2020

Agenda

Review notable updates to discuss from the 3/25 document last presented:

- Additional wording on supply and restrictions in the algorithm for treatment agents
- Clinical trial eligibility link
- Rewording o outpatient trial consideration
- Addition of troponin elevations to risk factor list
- Softening of wording regarding "transfer to a facility with remdesivir trial" under all inpatient arms
- Change nonICU language regarding HCQ to consider with unknown efficacy
- Removal of statin consideration for additional therapy for all arms
- Removal of mechanical ventilation as an exclusion for remdesivir trial
- Moving IL6 inhibitors to Unknown Benefit from not recommended
- Moving statins to unknown benefit with removal from algorithm/table 3
- Table 3 details the current remdesivir trial inclusion/exclusion (moving target)
- Clarifying HCQ dosing as bid x 2, then daily for total 5 days
- Removal of statins from table 3
- Addition of tocilizumab to table 3 for ICU care with inclusion and exclusion
- Table 5 revisions: statin removed, tocilizumab removed not recommended
- Added all your names (please email Shirley Lo and cc me for any changes)
- Removed table 6 and replaced with study hyperlink
- Updated reference list to include Gautret/Raoult 80 patient series for azi/HCQ, Chen HCQ TTCR RCT (not peer reviewed)

Review customization:
Things you should take out

- Our HID pager won't apply for lab test approval

Review things to work on/discuss (open):

- How to update the clinical research trial availability for the network
- G6pd lab testing
- Place of IL6 inhibitors
- Role of steroids

Review Local experience sharing (open):

- BIDMC have a therapeutic substitution for doxy in place of azi for nonCOVID CAP

Review BILH HCQ supplies

- More than 57K across the network

COVID status across network

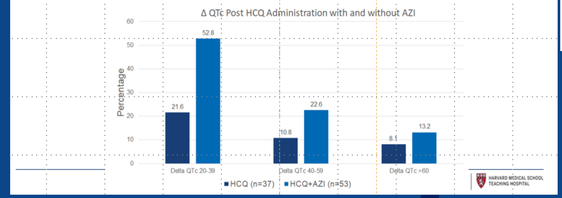
- Updated daily re: positives/ pending and staff

Hydroxychloroquine +/- Azithromycin Adverse Event Investigation

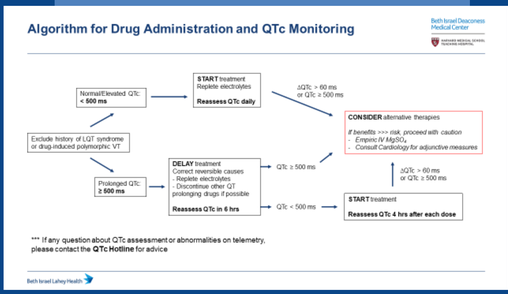
N= 90 patients,
53 received HCQ/AZI, 37 received HCQ alone

median baseline QTc was 455 ms and became prolonged to ≥500 ms in **18 (20%)** subjects.

prolonged QTc ≥500 ms was greater in those receiving concomitant loop diuretics (30.8 vs 11.8%, p=0.026), and baseline QTc ≥450 ms (30 vs 7.5%, p=0.008)



Worked with EP/Cardiology to enhance guidance evaluation of therapeutic agents with QT prolongation concern



JAMA Cardiology Publication

Tolerability and safety of hydroxychloroquine and impact on QTc interval with and without azithromycin for hospitalized COVID-19 patients

Nicholas J Mercuro PharmD, BCIDP[*1], Christina F Yen MD[*2], David J Shim MD, PhD[3], Timothy R Maher MD[4], Christopher M McCoy PharmD, BCPS AQ-ID, BCIDP[1], Peter J Zimetbaum MD[3,4], Howard S Gold MD[2]

[1]Department of Pharmacy, Beth Israel Deaconess Medical Center
[2]Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Harvard Medical School
[3]Division of Cardiovascular Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School
[4]Harvard-Thorndike Electrophysiology Institute, Division of Cardiovascular Medicine, Beth Israel Deaconess Medical

For more information, contact:

Christopher McCoy, PharmD cmccoy@bidmc.Harvard.edu Clinical Manager, Infectious Diseases Pharmacy, Antimicrobial Stewardship

Beth Israel Lahey Health

Beth Israel Deaconess Medical Center

Development of a living guidance document for the therapeutic evaluation and treatment of patients with CoVID-19

Christopher McCoy, Roger Shapiro, Katy Stephenson, Ryan Chapin, Sabrina Tan, Margaret Hayes, Howard Seth Gold.

Department of Pharmacy, Division of Infectious Diseases, Division of Health Care Quality, Beth Israel Deaconess Medical Center

Results and Progress

Milestones

April 2020

Anticoagulation Prophylaxis and Treatment Guidelines

BIDMC Guidelines for Prophylactic and Therapeutic Anticoagulation in ICU Patients with Confirmed or Suspected COVID-19

The purpose of this document is to offer guidance to providers on prophylactic and therapeutic anticoagulation in ICU patients with confirmed or suspected COVID-19. These guidelines will not cover all potential clinical scenarios and clinical judgment is required for optimal application. Updated 4/10/20

Venous Thromboembolism Prophylaxis

- Indicated for all confirmed or suspected COVID-19 patients*
- Recommendation: Enoxaparin 40 mg SQ BID** or Heparin 7500 units SQ TID (for CrCl <30 mL/min or increase in Scr by 0.5 from baseline)

Therapeutic Anticoagulation

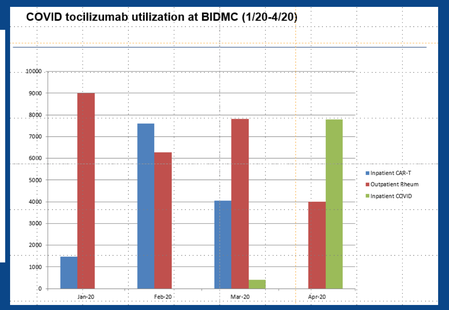
- Considered for patients with D-dimer >1500 ng/ml, thromboelastography (TEG) consistent with hypercoagulability or high clinical suspicion of thromboembolism
- Recommendation: Therapeutic unfractionated heparin infusion[a] (goal aPTT 60 to 100 or anti-factor Xa level 0.3-0.7), Enoxaparin 1 mg/kg SQ BID[b], or direct oral anticoagulants (DOACs)[c]

Fibrinolytic Therapy

- Considered as potential salvage therapy outside of the IRB-approved protocol for patients with a P:F ratio<100, with no further options for escalation of care. There must be documentation of healthcare proxy consent of risks vs. benefits, attending note describing clinical rational, and note of approval from either the medical or surgical critical care director.
- Recommendation: Alteplase 50 mg IV over 2 hours. If pt is on heparin prior to alteplase and has a supratherapeutic aPTT, consider holding heparin until aPTT is in the therapeutic range.

Convalescent Plasma considerations added

Tocilizumab shortage management



Tocilizumab Plan

Suggested ACTIONs:

Bolster enrollment in Sarilumab trial (identify barriers/need for resources)
How is this progressing (supply of drug, research staff)

Continue with restrictive criteria for ICU patients (outlined)

- Expand to *high risk* non ICU patients w/ elevated inflammatory markers
  - Not ready
- Define "high risk" as immunocompromised, additional criteria?
  - Unclear
- Consider an approval process by review group of ID/AST/Crit Care

Remdesivir approved for EUA utilization: need for local guidance and separation from clinical trials

May 2020

Remdesivir Emergency Use Authorization

(Note: Remdesivir is only available for use in a clinical trial or under FDA Emergency Use Authorization)

This document will describe the prioritization of the first release of remdesivir from the FDA, and the unique regulatory requirements for use.

Remdesivir (RDV) is a RNA-dependent RNA polymerase inhibitor currently under investigation as a potential treatment for SARS-CoV-2, or COVID-19. Clinical trials at BIDMC are ongoing. In May 2020, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to permit use of RDV outside of clinical trials for hospitalized patients with severe disease.

BIDMC is currently (5/20) a registered site for two open-label trials of RDV for moderate and severe disease, the criteria of which are defined via link (moderate-RDV?&/severe-RDV?&). The severe trial will CLOSE in the next 10 days.

Points of uncertainty at this time:

1. Future distributions of RDV to BIDMC under EUA
2. Sponsor's (Gilead) plan for currently active RDV research trials (now in open label phase, only gathering safety data)
3. Optimal patient population of COVID-19 patients to treat with RDV based on very limited published data
4. Minimal effective duration of treatment (5 vs. 10 days)

General criteria for use provided by FDA for EUA are broad

- Patients hospitalized with confirmed COVID-19
- Patients with severe disease defined as
  - **Oxygen saturation (SpO2) ≤94% on room air**
  - Requiring supplemental oxygen
  - Requiring mechanical ventilation
  - Requiring extracorporeal membrane oxygenation (ECMO)

Precautions/warnings

- Renal impairment - estimated glomerular filtration rate <30 mL/min
  - CRRT may be an exception (use can be considered at standard dosage)
- Hepatic impairment - assess risk/benefit (limited data in this population)
  - ALT > 5x upper limit of normal is a contraindication for initiation
- Pregnancy assess risk/benefit to mother and fetus (no adequate and well-controlled studies of remdesivir use in pregnant women have been conducted)

BIDMC and resource considerations for exclusion

- Current of previous enrollment in a remdesivir clinical trial
- Goals of care not aligned with experimental intervention

Inclusion Criteria:

1. COVID PCR+ result within 14 days of intended first RDV dose
2. Documented consent for treatment after education of risks/benefits, as described here

Exclusion Criteria:

1. Mechanical ventilation > 10 days
2. eGFR < 30, unless on CRRT
3. ALT > 200
4. Non-ICU with improving clinical trajectory (e.g., decreasing oxygen requirement over time)

National allocation was small for MA hospitals requiring prioritization scheme

Remdesivir via Emergency Use Authorization guidline_v 5.0 **LAST UPDATED: 14 May 2020**

Acknowledging that there remains scientific uncertainty regarding which patients are most likely to derive benefit from remdesivir administration for treatment of COVID, an Interdisciplinary Advisory Workgroup has convened to develop a consensus guideline estimating degree of benefit for subsets of COVID patients based on collective review of available published evidence, accrued COVID management experience, and clinical judgement.

The Interdisciplinary Advisory Workgroup set forth to establish specific clinical criteria for COVID patients with varying degrees of anticipated benefit of RDV administration, as follows:

- Tier 1 allocation (highest priority objective): Survival benefit
- Tier 2 allocation: Prevention of severe morbidity, including risk of prolonged/permanent vital organ impairment or functional disability
- Tier 3 allocation (valid, but lowest priority objective): Reduction in illness burden, including shortening duration of hospitalization

Based on Workgroup review, the following interim guideline has been developed to prioritize RDV allocation for patients hospitalized due to COVID illness, with the explicit attempt to direct available supply to patients felt most likely to derive possible survival benefit (accepting that there remains substantial scientific uncertainty in how best to accomplish that objective).

Priority	Site of Care	Respiratory failure
1 (highest)	ICU	Mechanical Ventilation ≤5 days
2	ICU	Mechanical Ventilation 6 -10 days
3	Ward/ICU	Requires ≥ 4L O2 NC
4 (lowest)	Ward/ICU	O2 sat ≤ 94% RA

Communications to staff regarding remdesivir

To: BIDMC Clinicians and Managers

From: Antimicrobial Stewardship
Drug Shortage Task Force

Subject: Remdesivir Update

We are writing to update the BIDMC community on the status of the antiviral drug remdesivir (RDV) for the treatment of COVID-19. Please read the important updates below.

Overview:

- The Emergency Use Authorization (EUA) for RDV remains in effect, but with additional supplies and fewer new COVID admissions we will transition from the Drug Shortage Task Force mechanism to a more typical restricted antimicrobial drug approval process (with additional steps as required by the EUA).

New Process:

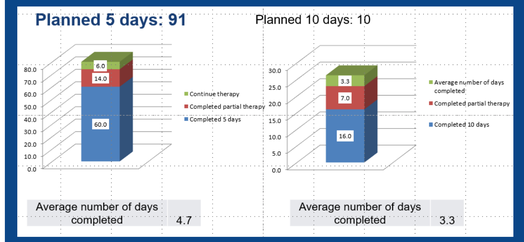
- Antimicrobial Stewardship Team (AST), and for active consult patients the Infectious Diseases (ID) consult teams will review requests for RDV and/or actively reach out to care teams for patients meeting updated criteria for RDV for treatment of COVID-19 in hospitalized patients.
- The RDV allocation guideline will remain under constant review by an interdisciplinary committee including members from Infectious Diseases, Critical Care, Hospital Medicine, Pharmacy and Health Care Quality, as new data are published and local experience is enriched.
- RDV orders in POE will require discussion with a member of the Antimicrobial Stewardship Team or Infectious Diseases team if a consult patient, much like the standard process of restricted antimicrobial authorizations prior to Pharmacy release.
- Once the prescriber is given preliminary approval for RDV, ordering physicians are required to follow the consent process guided by the EUA:
  a. Review the risks and benefits with patient and/or appropriate surrogate decision maker.
  b. Provide Fact Sheet for Patients prior to administering RDV.
  c. Document the patient's (or appropriate surrogate decision-maker's) consent in patient's record.
- When consent is completed, AST/ID approval can be granted in POE, allowing Pharmacy to release the drug for administration.
- Daily monitoring is mandated by the EUA – clinical status and labs (serum chemistries, creatinine, ALT, AST, bilirubin, and alkaline phosphatase, CBC/diff).
- The updated treatment guidelines are available on Coronavirus Central and will be continuously updated as needed.

Please review the FDA information for providers: Provider Information Sheet.

The future supply of RDV is unknown at this time, but with the decline in COVID admissions, we seek to sustain an adequate supply for a few months. Thank you for your continued adherence to this regulated protocol and for your dedicated care to our patients. Please email Antimicrobial Stewardship with any questions.

June 2020

Network Remdesivir Experience Exploration



Based on study data, limited treatment duration to 5 days

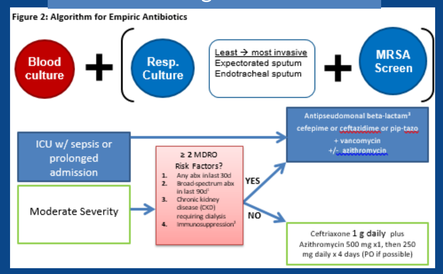
Identified population with benefit with moderate 02 requirements

July 2020

Presented and added dexamethasone to treatment guidance

Removed hydroxychloroquine and azithromycin as treatment agents

Added additional sections on culture based antibiotic utilization with rapid tailoring for negative cx



Dexamethasone

Effect of Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report

Running title: Dexamethasone for COVID-19 – Preliminary Report

RECOVERY Collaborative Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

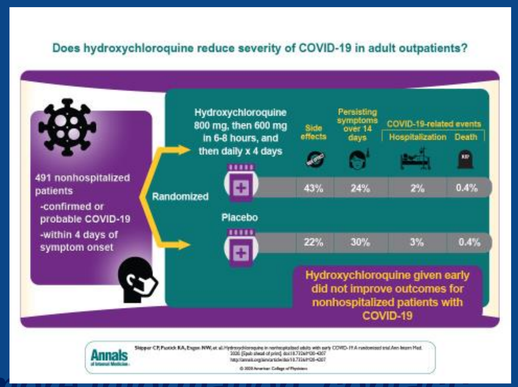
Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

"early trial discontinuation" June 2020

Based on power calculations that if 28-day mortality was 20%, then enrollment would close at 2000 patients in the dexamethasone group

Lack of HCQ benefit



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Results and Progress

Milestones

July 2020

Baicitinib initial review

JAK1- Baracitinib

Use of Baricitinib in Patients with Moderate and Severe COVID-19

Bogbuma K Titanji, MD, PhD, Monica M Farley, MD, Ashish Mehta, MD, M.Sc, Randi Connor-Schuler, MD, Abeer Moanna, MD, Sushma K Cribbs, MD, M.Sc, Jesse O'Shea, MD, M.Sc, Kathryn DeSilva, Pharm.D, Bonnie Chan, Pharm.D, Alex Edwards, MSPH ... Show more

Clinical Infectious Diseases, ciaa879, https://doi.org/10.1093/cid/ciaa879
Published: 29 June 2020 **Article history**

Non randomized descriptive review from Atlanta VA
15 patients co-treated with baracitinib and HCQ

6 patients ICU: 4 on greater than 5 days mech vent

11 of the 15 (73.3%) patients with clinical improvement
3 deaths

August 2020

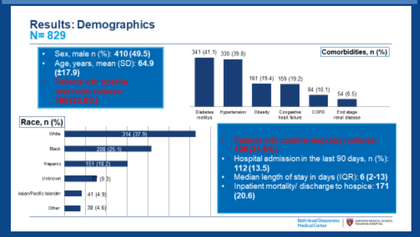
Convalescent Plasma considerations clarified given Mayo closes enrollment

FDA opens Remdesivir to all inpatients

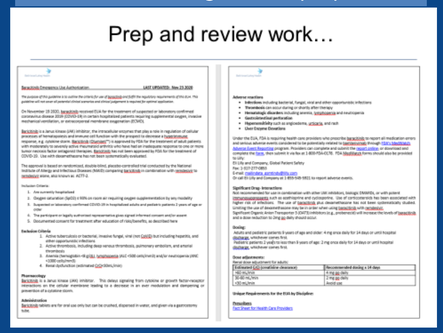
*RDV has been approved by the FDA for distribution through an emergency use authorization which details specific use, dosing, duration, preparation. New guidance allows for use in any patient hospitalized if their renal and hepatic function is normal. Our review supports use in patients requiring supplemental oxygen. More details on inventory control and individual institutional allocation. The BILH system was given access at varying supply levels depending on need. BILH EUA guidelines (network/local) are in place but may be institution specific based on acuity and resources. Allocations currently go through a wholesaler with the caveat that reporting to HHS occurs daily.

October 2020

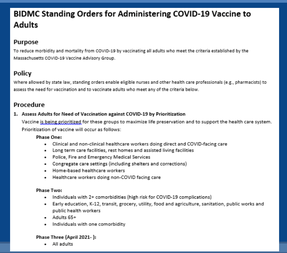
BIDMC local abx utilization and collateral damage review published



Baricitinib EUA guidance prepared



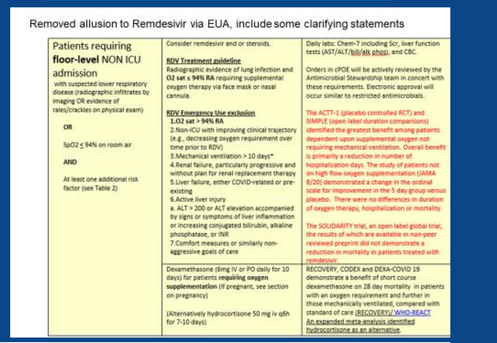
On hold for vaccine launch



Remdesivir EUA ends: FDA approved

November 2020

Removed allusion to Remdesivir via EUA, include some clarifying statements



Winter surge demand for therapeutics on the rise, primarily dexamethasone and remdesivir

Remdesivir supply will quickly be depleted leading to need for commercial buying

Data review unfurls opportunities for improved stewardship

Propose to amend guideline

EUAs for Antibody therapies released "prematurely"

Lack of supply, space for infusion, staff for administration
Data is preliminary, unvetted, minimal effect size
Consensus groups reject entry

Propose to de-emphasize in guideline/ redirect towards vaccine

Efforts now steered toward vaccine launch

Logistics
- Storage, inventory logs
- Preparation
- Waste avoidance
- Staffing centers/immunizers

Rollout
- Prioritization scheme
- Communication
- 2 dose coordination

Regulatory
- Adverse Event tracking
- Reporting to HHS

First CoVID monoclonal Ab Approved via EUA process Guidance prepared

Bamlanivimab (BAM)

Bamlanivimab via Emergency Use Authorization (EUA) guideline v 1.0 **LAST UPDATED: Nov 11 2020**

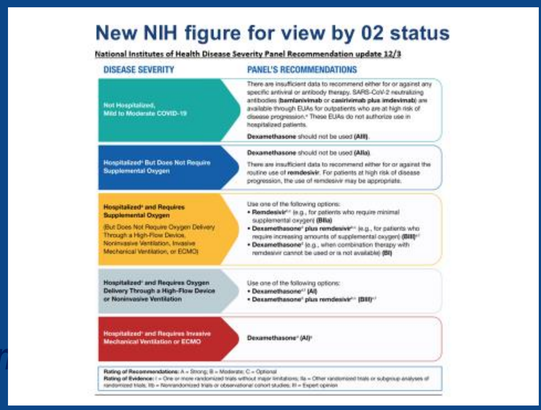
The purpose of this guideline is to reiterate the criteria for use of bamlanivimab (A.K.A. LY-CoV555, LY3819253) and fulfill the regulatory requirements of this EUA. This guideline will not cover all potential clinical scenarios and clinical judgement is required for optimal application.

US Food and Drug Administration (FDA) has recently approved the intravenous antiviral drug remdesivir for the treatment of hospitalized patients with COVID-19, but no treatment has been approved by the as safe and effective for COVID-19 in non-hospitalized patients. On November 9 2020, bamlanivimab became the first drug against SARS-CoV-2 to be approved under an EUA for the treatment of mild-moderate COVID-19 in adults and children (>40 kg) who are at high risk for progressing to severe COVID-19 and hospitalization. This neutralizing IgG1 monoclonal antibody binds to the receptor-binding domain of the spike protein of SARS-CoV-2.. The benefits of this investigational monoclonal antibody are thus far supported only by limited clinical data from a published interim analysis of an ongoing Phase 2 randomized, double-blind, placebo-controlled, single-dose trial conducted at 41 centers in the United States (BLAZE-1 trial) showing a reduction in hospitalization or emergency room visits in high-risk patients within 28 days after treatment vs. placebo. This was a secondary endpoint. The primary endpoint of viral load reduction was not met in the aggregate population receiving 3 different doses of the drug, however there was trend in improved viral clearance.

Supplies of bamlanivimab may be limited, and the logistics of safely administering this intravenous drug to SARS-CoV-2-infected outpatients have yet to be determined.

Clinical trials to assess the benefit of this drug for hospitalized patients or those requiring oxygen therapy were stopped due to futility (National Institute of Allergy and Infectious Diseases (NIAID)-sponsored trial ACTIV-3). Moreover, per FDA, "monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation." This drug should not be used to prevent COVID-19.

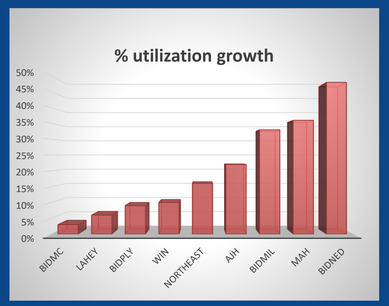
Incorporation of NIH figures



Dec 2020

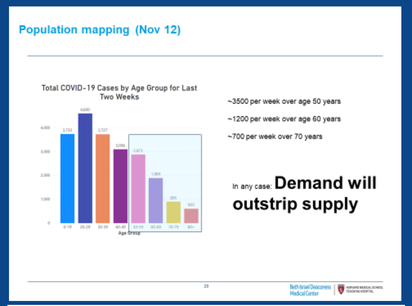
Resources turn towards vaccine approvals and EUA rollout

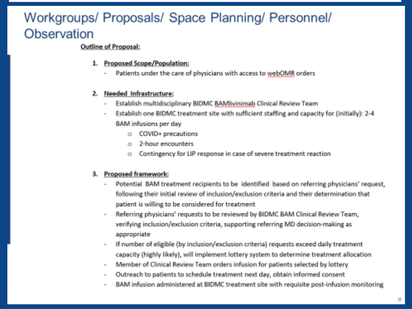
Remdesivir EUA supplies dwindle prompting network utilization review



Despite high census, BIDMC has strict control on remdesivir use

Concern about Bamlanivumab launch





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Results and progress

Milestones

Jan 2021

Continued tocilizumab evidence evaluations REMAP-CAP redirecion

Notable/Larger Observational Studies: Tocilizumab

	Martinez et al. CMI, 2020	Biran et al, Lancet Rheum 2020	Guaraldi et al (TESEO), 2020	Somers et al, Clin Inf Dis 2020	Gupta et al, JAMA (STOP-COVID) 2020	Sciasas (2020)
N	1229	764	544	154	3924	63 (single arm)
Population/ Severity	Moderate disease, non-ICU	Severe, ICU	Severe, 17% on MV at baseline	Severe, ICU + MV	Severe, ICU	SpO2 <93%+ 3 inflammatory markers
Primary outcome	Time-to-death	Time to mortality, PS matched	Composite death + ventilation	Survival after intubation	Time-to-mortality	In-hospital mortality
Safety	n/a – steroid imbalance	No diff in infxn rates	Increased risk of secondary infxn	Increased risk of secondary infxn	Not assessed	Not assessed
Conclusions	TCZ decreased time to mortality in pts w/ CRP> 150	TCZ improved mortality in pts <65 years and with >CRP	TCZ reduced risk of mechanical ventilation or death	TCZ associated with higher survival	TCZ associated with lower adjusted risk of death	No comparison arm
Mortality	Not reported- overall higher OR in TCZ arm	49% 61%	7% 20%	18% 36%	29% 41%	11%

Guideline changes (new-proposed)

Table 4. Considerations for Experimental COVID-19 Therapeutics

- **IL-6 inhibitors (based on current data, , should not be considered a standard of care therapy, however these data may be evolving):**
  - Multiple RCTs for tocilizumab and sarilumab (e.g., Salvarini, JAMA Oct 20; Stone, NEJM Dec 20; Salama, NEJM Jan 21) resulted in no mortality benefit or higher mortality versus standard of care. One recent open-label study REMAP-CAP reported preliminary data in a non-peer-reviewed pre-print that showed a mortality benefit in patients admitted to ICU (Gordon, MedRxiv Jan 21) treated with tocilizumab (primarily) or sarilumab within <24 hours of organ failure, in combination with corticosteroids. Another recent open-label study was stopped due to increased risk of mortality in the tocilizumab arm (Veiga, BMJ, Jan 21). Of note, these IL-6 inhibitors are NOT currently recommended in NIH or IDSA COVID treatment guidelines (outside of clinical trials). If use of tocilizumab is under consideration by the Critical Care team and their consultants, it should clearly delineated by the inclusion/exclusion criteria in REMAP-CAP.

Ivermectin review

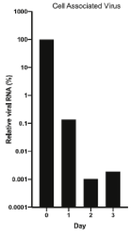
Ivermectin

The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*

Leon Caly[a], Julian D. Druce[a], Mike G. Catton[a], David A. Jans[b], Kylie M. Wagstaff[b,*]

Publish 4/20

Vero cell model: 5 microM/L instilled into infected cells and harvested for 3 days.

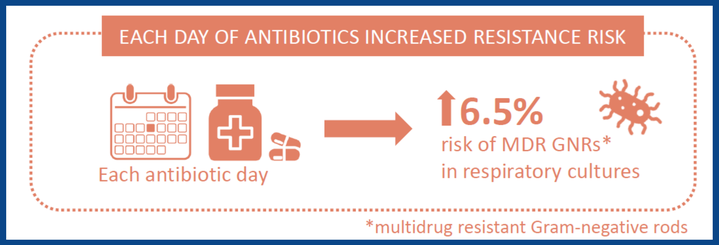


Caveat: Exposure is 50 times higher than the levels attainable after 700 µg/kg

Recommendation

- The COVID-19 Treatment Guidelines Panel (the Panel) has determined that currently there are insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin for the treatment of COVID-19.

Infographics for antibiotic overuse



February – November 2021

- Outpatient and Employee vaccine rollouts
- Vaccine recommendations for immune compromised host
- Third dose and half dose boosters launched
- Monoclonal Antibodies reviewed and infusions begun in June 2021
- Additional antibody combinations reviewed and added given variants of interest
- Regulatory reports for EUA allocation established and submitted
- Tocilizumab shortage addressed with introduction of baricitinib via EUA and other mitigation processes
- Vaccine AE warnings added to screening documents for selection

Lessons Learned

- Therapeutic review and guidance for an entity and a pandemic not seen before requires significant human resources to vet hundreds of citations and build consensus.
- A network wide guideline posted to institution specific intranet sites to accommodate resources of size and demand is an achievable goal with regularly scheduled meetings.
- Version control and edits can be daunting
- The process of review and utilization reports revealed the potential for reflexive prescribing

Next Steps

- Continue network collaborations across the CoVID 19 trajectory, vaccines and preventive therapies.
- Determine ways to communicate more broadly and efficiently

For more information, contact:

Christopher McCoy, PharmD cmccoy@bidmc.Harvard.edu Clinical Manager, Infectious Diseases Pharmacy, Antimicrobial Stewardship