IMAC Recommendations on Antiviral Therapies for COVID-19

SUMMARY

This summary highlights recommendations made by the Infection Management Advisory Committee on the antiviral treatment of COVID-19. These recommendations follow from an extensive literature review and multiple conversations among various experts and clinicians. The full document follows this page.

IMAC will be monitoring new evidence as it emerges and updating the recommendations as needed.

The full document also provides recommendations on management of bacterial infections and addresses recent controversies related to the use of NSAIDs and ACE Inhibitors in the context of COVID-19 (Pg 15-16).

1. We recommend against the routine use of lopinavir/ritonavir outside a randomized-controlled trial (CATCO).
2. In light of insufficient evidence and potential adverse-effects, we advise against the use of ribavirin.
3. While treatment with remdesivir remains promising, obtaining the drug in a pandemic situation may not produce the drug in a timely manner. As exclusion criteria from the manufacturer are extensive and supply is limited, we recommend reserving applying for compassionate use for remdesivir to exceptional cases in consultation with Infectious Diseases Specialist and Pharmacy. We recommend enrollment in a randomized-controlled trial of remdesivir if it becomes an option at VIHA.
4. Based on the lack of clinically convincing outcomes and the fragility of the supply chain, we recommend against routine use of chloroquine or hydroxychloroquine. Use would be supported if further positive data become available and IMAC is committed to evaluating this particular therapy very closely. IMAC members are not in a position to police or restrict prescribing should it occur.
5. We were unable to evaluate any convincing evidence published in English that supports the use of tocilizumab. Although limited Chinese literature uses promising language, we currently cannot recommend routine its administration for COVID-19.
6. We acknowledge that there will be some patients in whom salvage efforts may be appropriate. We leave those decisions to individual prescribers and encourage them to contact Infectious Disease Specialists, Medical Microbiologists and/or ID&AMS pharmacist for discussion about appropriateness, safety and operational details.
7. We recommend against treatment with any other investigational agent, including ASC09, azvudine, baloxavir marboxil/favipiravir, camostat mesylate, darunavir/cobicistat, camrelizumab and thymosin due to lack of data, lack of availability, or both.

IMAC Recommendations on Antiviral Therapies for COVID-19

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PREPARED FOR:	Emergency Operations Center (EOC)
TOPIC:	Therapies for COVID-19
Prepared by:	Jolanta Piszczek, Clinical Pharmacy Specialist, Infectious Diseases and Antimicrobial Stewardship on behalf of the Infection Management Advisory Committee (IMAC)

Situation

SARS-CoV-2 (aka 2019-nCoV), the virus that causes the clinical illness COVID-19, is a novel RNA virus belonging to the coronavirus family. With well over one-hundred thousand cases worldwide, various treatments are being used clinically or undergoing evaluation. In preparation for in-patient treatment of COVID-19 at Island Health facilities, the Infection Management Advisory Committee (IMAC) has reviewed the evidence for these therapies and made recommendations concerning their use in consultation with various VIHA groups such as Intensive Care, Internal Medicine, Hospitalists and Pharmacy. IMAC has also provided general treatment guidelines for anti-infective use in the setting of viral pneumonia in in-patients. As this is an evolving situation, as emerging information becomes available IMAC will make the necessary amendments to this SBAR along with up-to-date recommendations weekly, and as needed.

Background

Coronaviruses (CoV) are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV-1). SARS-CoV-2, the virus responsible for the COVID-19 pandemic is a non-segmented, positive sense RNA virus most closely related to SARS-CoV-1, with 82% nucleotide identity. There are currently no approved therapies for COVID-19, and no therapies have been robustly evaluated. The majority of published evidence that suggests treatments for COVID-19 is extrapolated from experience with SARS, MERS or limited to case-series. Randomized-controlled trials are ongoing, most notably with two agents, an antiretroviral lopinavir/ritonavir (Kaletra) used for treatment of HIV, and a novel investigational antiviral remdesivir. Non-randomized smaller studies, mainly from China, have included a variety of drugs, with Chinese Medicine research comprising over half of the studies. One larger RCT of lopinavir/ritonavir in 199 patients in China was published on March 18, 2020 (Cao et al.

2020) showing no benefit; however, experts speculate that this trial will not put an end to other RCTs as it may be underpowered for mortality and included patients who were too sick (Cao et al. 2020). In vitro data and animal studies of various agents, mainly for the treatment of SARS, have also been published. A large proportion of the discussion regarding potential treatment for COVID-19 within the medical community has been occurring through non-academic channels such as social media, blogs or the news.

A scientific literature search of potential non-vaccine therapies for COVID-19 and other coronaviruses (search strategy below) resulted in over 200 publications citing the following potential pharmaceutical agents in order of frequency of appearance:

- lopinavir/ritonavir
- chloroquine/hydroxychloroquine
- ribavirin
- remdesivir
- oseltamivir and other neuraminidase inhibitors
- tocilizumab
- steroids

Non-medical sources have also listed a dozen of other agents, including ASC09, azvudine baloxavir marboxil/favipiravir, camostat mesylate, darunavir/cobicistat, camrelizumab and thymosin, among others. These agents were not found using a search of PubMed, Medline or Embase for the treatment of coronaviruses, but limited information was available online through, for example, study protocols.

Articles commenting on safety of other agents, for example ACE-inhibitors and NSAIDs in the context of COVID-19 have also been published.

Expert bodies such as the World Health Organization (WHO) and the Center for Disease Control (CDC) have made recommendations for treatment of COVID-19 but they are limited to supportive care. Both support the enrollment of patients in clinical trials for currently unproven therapies. The WHO updated

their guideline document regarding clinical management of severe COVID-19 on March 13, 2020, with a main recommendation of ***"Investigational anti-COVID-19 therapeutics should be used only in approved, randomized, controlled trials."***.

Locally, in British Columbia, while there is no formal consensus between clinician groups regarding treatment of COVID-19 with unapproved therapies, an informal agreement has been made between the clinicians at Vancouver Coastal and Providence Health that no treatment will be employed unless part of a randomized controlled trial. All proposed treatment approaches across the province have been obtained through personal communication. Many Health Authorities have committed to enrolling in an RCT of lopinavir/ritonavir (Kaletra) called CATCO - A Multi-centre, Adaptive, Randomized, Open-label, Controlled Clinical Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Patients. This RCT, led by Shrin Murthy from BC Women's and Children's and funded through the Canadian Institutes of Health Research, is currently undergoing Operational Approval after Harmonized Ethics Approval in the province was granted. Currently, Abbvie, the maker of Kaletra would be supplying the study medication. Coastal Health and Providence have informally stated that no treatment would be employed for inpatients with COVID-19 outside of this trial. At VIHA, Dr. Daniel Ovakim (Intensivist; VIHA PI), Dr. Gordon Wood (Intensivist, co-investigator) and Dr. Eric Partlow, (Infectious Disease Physician; co-investigator) have volunteered to be the local investigators for CATCO. The clinical trials support team from Intensive Care has been engaged and is awaiting approval from ethics as the protocol is in the revision stages. Enrolling patients at other sites across the Island is being explored and based on operational ability (e.g. having enough clinicians with necessary training to give consent), but is unlikely to occur at this time.

Assessment

Lopinavir/Ritonavir (Kaletra) with/without Ribavirin

Lopinavir/ritonavir is a combination of antiviral agents used in treatment of HIV. Lopinavir is the effective agent that inhibits the protease activity of coronavirus; ritonavir increases the half-life of lopinavir. Lopinavir/ritonavir has the advantage that it is available in Canada, and has an established toxicity profile.

In BC, the agent is non-formulary and mostly obtained through the Centre for Excellence for the treatment of HIV. At this time, it is listed as a "No Stock Available" item from wholesale due to countrywide allocation, but it could potentially be obtained through other channels. Ribavirin may be synergistic when added to lopinavir/ritonavir, especially in other coronaviruses. However, most clinical data for COVID-19 does not support the routine addition of ribavirin. Oral ribavirin is available in Canada, and is currently non-formulary. Inhaled ribavirin is restricted to the treatment of RSV, but has not been evaluated for the treatment of coronaviruses.

Human Clinical Data

Cao at al. 2020: Randomized Controlled Trial of 199 patients with COVID-19 treated in Wubei, China at the peak of the outbreak

- 100 patients were randomized to receive lopinavir/ritonavir for 14 days and 99 to receive standard of care
- Patients included were those who had difficulty maintaining O2 saturations of >94% on room air; many patients were severely ill and received treatment late as evidenced by the nearly 25% mortality.
- The primary outcome was clinical improvement by 2 points measured by a 7-point ordinal scale, or discharge from hospital, whichever came first.
- The trial did not find a difference between the two groups in the primary outcome. Viral shedding was no different between groups. Mortality was slightly lower in the treatment arm but was not clinically or statistically significant.
- 13.8% of patients in the treatment arm had to stop the drug because of adverse-effects such as gastrointestinal intolerance and laboratory abnormailities.

Chu et al. 2004: Open-label before/after study on SARS

- 41 patients treated with lopinavir/ritonavir plus ribavirin were compared to 111 historical control patients treated with ribavirin alone. Poor clinical outcomes (ARDS or death) were lower in treatment group (2.4% vs. 29%). These differences persisted in multivariable models, which attempted to correct for baseline imbalances between the groups.

- Use of lopinavir/ritonavir use correlated with a dramatic reduction in viral load.
- All patients received concomitant ribavirin.
- One patient discontinued the medications due to doubling of liver enzymes

Chan et al. 2003: Retrospective matched multi-center cohort study on SARS

- 75 patients treated with lopinavir/ritonavir were compared with matched controls.
- Up-front treatment with lopinavir/ritonavir combined with ribavirin correlated with reduced mortality (2.3% versus 16%). However, rescue therapy with lopinavir/ritonavir (often without concomitant ribavirin) showed no effect.
- Study reported that the drug was "well tolerated" and side effects were minimal.

Park et al. 2019: Retrospective cohort study on post-exposure prophylaxis against MERS

- This is a retrospective cohort study involving 22 patients with high-risk exposure to a single MERS patient). As a control group, four hospitals with outbreaks of MERS were selected. Post-exposure prophylaxis consisted of a combination of lopinavir/ritonavir (400 mg / 100 mg BID for 11-13 days) plus ribavirin (2000 mg loading dose, then 1200 mg q8hr for four days, then 600 mg q8hr for 6-8 days).
- MERS infections did not occur in anyone treated with post-exposure prophylaxis. However, the manner in which the control group was selected likely biased the study in favor of showing a benefit of post-exposure prophylaxis.
- Post-exposure therapy was generally well tolerated, although most patients reported some side effects (most commonly nausea, diarrhea, stomatitis, or fever). Laboratory evaluation shows frequent occurrence of anemia (45%), leukopenia (40%), and hyperbilirubinemia (100%).

Young et al. 2020 Cohort study describing 16 COVID-19 patients in Singapore.

- Among 6 patients with hypoxemia, five were treated with lopinavir/ritonavir (200 mg/100 mg BID, which is half of the usual dose of lopinavir).
- Among the 5 patients, 2 patients deteriorated and had persistent nasopharyngeal virus carriage.
- The authors of the study suggested that perhaps ribavirin should have been used in addition

Lopinavir/ritonavir has been used to successfully treat one patient with COVID-19 (Kim 2020).

Small Case-series for COVID-19 (Wang 2020)

- Four patients with COVID-19 were given antiviral treatment including lopinavir/ritonavir.
- After treatment, three patients showed significant improvement in pneumonia-associated symptoms, two of whom were confirmed to be COVID-19 negative and discharged, and one of whom was negative for the virus at the first test.

Larger Retrospective Study for COVID-19 (Chen 2020)

- A retrospective study enrolled 134 patients revealed that there is no significant difference between LPV/r-treated group (n=52), Abidol-treated group (n=34), and control group (n=48) in improving symptom or in reducing viral loads.
- The negative rate of COVID-19 nucleic acid on the 7 day was 71.8%, 82.6%, and 77.1%, respectively (P=.79).

Nine randomized controlled trials of lopinovir/ritonavir in patients with COVID-19 have been registered in China up to February 22, 2020, and two trials in North America, including the Canadian CATCO trial in which VIHA is participating. Currently, the combination of lopinavir/ritonavir is a recommended antiviral regimen in the latest version of the Diagnosis and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China.

In-vitro Data

In-vitro activity against SARS

- Lopinavir showed in vitro antiviral activity against SARS at concentration of 4 ug/ml. However, when combined with ribavirin, lopinavir appears considerably more effective (with an inhibitory concentration of 1 ug/mL) (Chu et al. 2004).
- For reference, the peak and trough serum concentrations of lopinavir are 10 and 5.5 ug/ml
- An analysis of molecular dynamics simulations showed that the SARS-CoV 3CLpro enzyme could be inhibited by the combination of lopinavir and ritonavir. (Nukoolkarn 2008).

- A binding analysis of the main coronavirus proteinase with lopinovir showed that half of lopinavir is left outside the catalytic site, and the efficacy of lopinavir may be poor (Zhang 2004).
- Another study showed that neither lopinavir nor ritonavir has an effect on the replication of SARS-CoV (Yamamoto 2004).

There are no reported in vitro studies of COVID-19.

Animal Data

Lopinavir/ritonavir was effective against MERS-CoV in a primate animal model (Chan 2015).

Safety

Diarrhea, nausea, and asthenia are the most frequently reported reactions in patients receiving lopinavir therapy for treatment of coronaviruses (Hurst 2000). Elevated total bilirubin, triglyceride, and hepatic enzyme levels have also been reported. A retrospective study of MERS showed that the most common symptoms and laboratory tests of lopinavir/ritonavir were diarrhea (40.9%), nausea (40.9%), stomatitis (18.2%), fever (13.6%), anemia (45.0%), leukopenia (40.0%), and hyperbilirubinemia (100%) (Park 2019). However, the symptoms and laboratory tests returned to normal after lopinavir therapy ceased. In the 2020 RCT by Cao et al. 13.8% of patients needed to stop lopinavir/ritonavir due to adverse effects, but no ADR was considered serious. Drug interactions with protease-inhibitors are well known and limit their use somewhat. Patients receiving interacting therapies such as amiodarone, certain statins and benzodiazepines, rifampin and many others are generally not candidates for treatment with lopinavir/ritonavir.

From experience in treatment of hepatitis C, ribavirin is well known to be a poorly tolerated drug. Flu-like symptoms and nausea develop in nearly 50% of patients and lead to premature discontinuation of hepatitis C treatment. Regular monitoring of CBC for hemolytic anemia, leukopenia and dose adjustment may be required for toxicity as ribavirin causes bone marrow suppression in many after 2-4 weeks of treatment. Ribavirin may also cause liver toxicity and transaminitis.

Remdesivir

Remdesivir is an investigational nucleotide analog with broad-spectrum antiviral activity. It was initially developed and evaluated for the treatment of Ebola. It inhibits RNA-dependent RNA polymerase, which is 96% identical in sequence between MERS, SARS and COVID-19. Remdesivir has demonstrated in vitro and in vivo activity in animal models against the viral pathogens MERS and SARS (Sheahan 2020 and others).

Unfortunately, remdesivir is not commercially available and not approved by the FDA yet. Remdesivir was used on the basis of Compassionate Use for one of the first patients with COVID-19 in the United States (Holshue 2020). The patient improved rapidly with 7 days of treatment and no adverse effects. Viral PCR was negative for the virus after one day of therapy.

Remdesivir is being used in several stage 3 trials in the United States being sponsored by NIAID. Enrollment in this trial seems like a desirable approach to antiviral therapy but is not feasible in Canada at this time. There are four other trials registered world-wide.

The process of obtaining remdesivir in Canada for Compassionate Use (CU) outside of the abovementioned RCT has been verified with the company (Gilead) and Health Canada. It consists of a multi-step process that includes an application on the Gilead website, as well as a Special Access Program (SAP) application to Health Canada. Our estimates are that obtaining the drug would take days and is not guaranteed. Personal communication confirmed that one group in Edmonton attempted to get remdesivir for compassionate use; the outcome of this is not known. The inclusion criteria for the use of remdesivir seem prohibitive; patients need to be diagnosed with severe, virologically confirmed disease failing supportive case, on ventilator support but not receiving vasopressor support or experiencing organ failure. Application for SAP and CU may be considered if the eligibility criteria are met. Gilead states on their website that stock is limited and we were unable to verify if the drug would be provided free of charge.

Chloroquine/Hydroxychloroquine

Chloroquine/hydroxychloroquine are generally used for treatment of malaria, amebiasis and certain inflammatory conditions like rheumatoid arthritis. It has anti-viral activity in vitro, but no established clinical efficacy in treatment of viral disease. Chloroquine/hydroxychloroquine appear to work via multiple mechanisms, including interference with cellular receptor ACE2 (potentially making it particularly effective against SARS and COVID-19) and impairment of acidification of endosomes, which interferes with virus trafficking within cells. Both drugs also have immunosuppressive activities. It is unknown whether such immunosuppressive action could be beneficial or harmful (analogous to steroid therapy).

Human Data

One small case series of 22 hospitalized patients in France (Gautret et al. 2020) received 200mg of hydroxychloroquine three times per day for 10 days; 6 patients received azithromycin. The primary endpoint was virological clearance on day 6. The trial compared the primary outcome to 16 controls who refused to participate or were treated at another center. Some patients were asymptomatic. The study reported that COVID-19 PCR was negative on 100% of patients on day 6 who took both drugs, 57.1% in those who received hydroxychloroquine alone and 12.5% of those who did not receive treatment. No clinical endpoints were reported. This study has not been published by any scientific journal; the manuscript was available on line as a pdf from a news website.

There are two citations whose abstracts read that chloroquine could reduce the length of hospital stay and improve the evolution of COVID-19 pneumonia, apparently assessed through a multi-center trial (Gao 2020; Zhonghua 2020). The drug is recommended to be included in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China for treatment of COVID-19 infection in larger populations in the future. However, both the articles are not available in English and this data could not be assessed. A news report stated that one study investigator cited that “120 patients treated with chloroquine phosphate developed critical illness, and 81 patients have been discharged so far.”

In-vitro Data

In vitro data using cell lines shows that chloroquine can inhibit COVID-19 with a 50% inhibitory concentration of 1 µM, implying that therapeutic levels could be achieved in humans (Wang 2020). The 50% inhibitory concentration of chloroquine for SARS is closer to 9 µM, suggesting that chloroquine could be more effective against COVID-19 than SARS (Al-Bari 2017).

A study published in Clinical Infectious Diseases suggested that hydroxychloroquine might be more potent for COVID-19 than chloroquine. The EC50=0.72 µM for hydroxychloroquine was found to be more potent than chloroquine (EC50=5.47 µM) in vitro. The study cited that "based on PK models results, a loading dose of 400 mg twice daily of hydroxychloroquine sulfate given orally, followed by a maintenance dose of 200 mg given twice daily for 4 days is recommended for SARS-CoV-2 infection, as it reached three times the potency of chloroquine phosphate when given 500 mg twice daily 5 days in advance" (Yao 2020).

Animal Data

Chloroquine failed to work in mice infected with SARS (Bernard 2006).

The safety of cholorquine or hydroxychloroquine has not been assessed in the treatment of coronavirus infections. However, toxicity profile seems to be acceptable from experience in use in malaria and rheumatoid arthritis.

Hydroxychloroquine is currently available in Canada and is on the BC Provincial Hospital Formulary. There are no known supply issues. On March 19th, 2020 President Donald Trump announced at a Press Conference that choloroquine and hydroxycholorquine are "game-changers" as a "vaccine" against the virus and that he plans to "make the drug available immediately" to Americans. Supply issues should be therefore regarded as extremely unstable. (The FDA quickly replied that these drugs are not approved for COVID-19 and no such approval is in process).

Other Therapies

Oseltamivir - Neuraminidase inhibitors do not seem to have activity against COVID-19 (Tan et al 2004). Initial empiric therapy with neuraminidase inhibitors could be reasonable during influenza season in critically ill patients, if there is concern that the patient might have influenza pneumonia. Such patients can have confirmatory nasopharyngeal swabs for influenza. Currently, in many locations, patients presenting with viral pneumonia are much more likely to have influenza than COVID-19. Otherwise, the role for oseltamivir specifically for COVID-19 is limited.

Steroids - Steroid use outside of the Surviving Sepsis Campaign is not recommended. Steroids have not demonstrated benefit in prior SARS or MERS epidemics. Steroids may increase viral shedding (Lee 2004) and impair immune function. However, steroids may be used if there is another clear-cut indication (e.g. coronavirus plus asthma exacerbation, refractory septic shock). WHO guidelines for the supportive treatment of COVID-19 echo this statement.

Tocilizumab – Tocilizumab is an anti-interleukin 6 monoclonal antibody used as immunotherapy for treatment of rheumatoid arthritis. While the maker of the drug, Sanofi is currently in discussion with the FDA to initiate trials for treatment of COVID-19, evidence for the use of this medication is limited to unpublished case-reports. For example, according to a blog post the IDSA website, there is anecdotal evidence that the drug has been used in cases in China. Through google-translation, the blog stated that toculizimab was used in cases of severe inflammatory response to COVID-19 with laboratory-proven high levels of IL6 (a test not done locally). The Chinese medical community appears to support the drug to "control the cytokine storm" and "purify the blood" according to the IDSA blog. No medical journal has published a case or case series as of March 13, 2020.

Antibiotic Therapies

Initial Therapy - As with any viral pneumonia, COVID-19 itself is not an indication for antibiotics. However, patients who present with respiratory symptoms and pulmonary infiltrates on imaging may meet the diagnostic criteria for pneumonia. Co-infection with a bacteria pathogen can be possible, and as per standard CAP therapy, antibiotics are indicated. At Island Health, the standard therapy for in-patient treatment for community acquired pneumonia is ceftriaxone 1-2 g IV daily with a macrolide, usually azithromycin 500mg IV x 3 days or azithromycin 500mg PO x1 day followed by 250mg PO x 4 days. While patients infected with COVID-19 may have travel history or have come in contact with travelers, extending the spectrum of antimicrobials is not warranted unless the patient has significant risk factors for drug-resistant organisms. This is generally limited to health-care exposure in an area with high rates of antibiotic resistance in the last 90 days. Such patients should obtain an Infectious Disease consult for tailored antibiotic therapy.

De-escalating antimicrobials is usually possible in confirmed COVID-19 infection. Procalcitonin is a useful marker and is usually negative. This can be combined with other clinical features like lymphopenia, normal neutrophil count and lack of positive bacterial cultures. Based on these tests, antibiotics might be discontinued in <48 hours.

Delayed Bacterial Infection – Hospital and ventilator-associated pneumonia can emerge during the hospital stay. Among patients who died from COVID-19, one series found that 11/68 (16%) had secondary infections (Ruan 2020). Hospital-acquired infection may be investigated and treated according to current VAP/HAP guidelines. At VIHA, piperacillin/tazobactam or a carbapenem is the standard of treatment, with added vancomycin if the patient has MRSA risk factors.

NSAIDs – On March 17, the World Health Organization recommended NSAIDs should be avoided for treatment of COVID-19 symptoms avoid taking ibuprofen, after French officials warned that anti-inflammatory drugs could worsen effects of the virus. The warning by French Health Minister Olivier Veran followed a recent study in The Lancet medical journal that hypothesised that an enzyme boosted

by anti-inflammatory drugs such as ibuprofen could facilitate and worsen COVID-19 infections. After two days of contemplation, the WHO reissued a statement on Twitter stating that there is no specific reason to avoid NSAIDs based on this data.

ACE-I and ARBs – COVID-19 uses the ACE2 enzyme to gain entry into human cells, and some reports state that those taking ACE-inhibitors or ARBs may experience an up-regulation of these enzymes. Theoretically, patients taking these medications may have increased susceptibility to the various; however this has not been shown clinically. Various expert groups such as the Canadian Cardiovascular Society and Hypertension Canada issued statements that uncontrolled hypertension or heart failure for which these medications are used would put patients at increased risk of poor outcomes due to COVID-19 and recommended that these agents not be discontinued.

Recommendations on March 19, 2020

IMAC recommends the following regarding therapies for COVID-19 and associated infections:

8. IMAC supports practicing evidence-based medicine and recommends against exceptionalism. We encourage clinicians to obtain best-practice information from reputable sources such as medical literature of acceptable quality, World Health Organization, Centers for Disease Control and not from blogs, news articles, press interviews, social media and politicians.

9. We recommend that VIHA become a partner site for the randomized controlled trial (CATCO) that would allow ethical and appropriate evaluation of investigational use of lopinavir/ritonavir. This option is also favourable as it would not deplete the sensitive supply chain of lopinavir/ritonavir for those who require it for HIV therapy.

10. We recommend against the routine use of lopinavir/ritonavir outside a randomized-controlled trial (CATCO).

11. In light of insufficient evidence and potential adverse-effects, we advise against the use of ribavirin.

12. While treatment with remdesivir remains promising, obtaining the drug in a pandemic situation may not produce the drug in a timely manner. As exclusion criteria from the manufacturer are extensive and supply is limited, we recommend reserving applying for compassionate use for remdesivir to exceptional cases in consultation with Infectious Diseases Specialist and Pharmacy. We recommend enrollment in a randomized-controlled trial of remdesivir if it becomes an option at VIHA.

13. Based on the lack of clinically convincing outcomes and the fragility of the supply chain, we recommend against routine use of chloroquine or hydroxychloroquine. Use would be supported if further positive data become available and IMAC is committed to evaluating this particular therapy very closely. IMAC members are not in a position to police or restrict prescribing should it occur.

14. We were unable to evaluate any convincing evidence published in English that supports the use of tocilizumab. Although limited Chinese literature uses promising language, we currently cannot recommend routine its administration for COVID-19.

15. We acknowledge that there will be some patients in whom salvage efforts may be appropriate. We leave those decisions to individual prescribers and encourage them to contact Infectious Disease Specialists, Medical Microbiologists and/or ID&AMS pharmacist for discussion about appropriateness, safety and operational details.

16. We recommend against treatment with any other investigational agent, including ASC09, azvudine, baloxavir marboxil/favipiravir, camostat mesylate, darunavir/cobicistat, camrelizumab and thymosin due to lack of data, lack of availability, or both.

17. We recommend against the use of natural health products or Chinese medicines for treating COVID-19 due to lack of data or an inability to evaluate the data in English.

18. We recommend against the use of oseltamivir outside its current indication for suspected and confirmed influenza.

19. We recommend that patients with suspected or confirmed COVID-19 who meet diagnostic criteria for CAP be started on ceftriaxone and azithromycin for concomitant bacterial infection until such infection is ruled out.

20. We recommend against broad-spectrum antibiotic treatments based on travel history alone and reserve these agents for patients with significant risk factors for drug-resistant bacteria (e.g. exposure to health-care in an endemic area). Infectious Diseases Specialists should be consulted in these circumstances.

21. We recommend standard therapy of piperacillin/tazobactam or a carbapenem with or without vancomycin for the treatment of health-care associated infection such as hospital or ventilator associated pneumonia.

22. We recommend that patients on ACE-I and ARBs continue these agents as indicated and not cease therapy solely on the basis of COVID-19.

23. We recommend that acetaminophen be used preferentially for symptomatic management of COVID-19 but do not recommend against the use of NSAIDs such as ibuprofen.

24. We recommend that the summary articulating these points be posted on the VIHA COVID-19 website, the Medical Affairs website and circulated internally as a reference for best practices. Evidence would be reviewed regularly by IMAC and this reference would be regularly updated.

Search Terms: ("COVID-19"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND 2019/12[PDAT] : 2030[PDAT])) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])
Search Databases: PubMed, Medline, Ovid

Search Date: March 19, 2020

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