Memorandum

Date: April 19, 2021
To: BC Physicians, Family Medicine Specialists, & Pharmacists
From: BC COVID-19 Therapeutics Committee
Re: Treatments for Non-Hospitalized COVID-19 Patients

A third wave of COVID-19 infections is leading to record daily case counts and rapid surge in hospitalizations in BC. A number of therapies have been investigated for management of non-hospitalized COVID-19 patients. While the current evidence remains limited, the BC COVID-19 Therapeutics Committee (CTC) is providing the following guidance to clinicians.

RECOMMENDATIONS FOR TREATMENT OF NON-HOSPITALIZED COVID-19 PATIENTS

INHALED BUDESONIDE

Inhaled budesonide 800 µg BID x 7-14 days may be considered on a case by case basis for adults with mild COVID-19 within 14 days of symptom onset who are aged 65 or over **OR** aged 50 or over with underlying health conditions[1].

Possible Benefit = Inhaled budesonide reduces time to symptomatic recovery by 1-3 days. COVID-19-related hospitalization may be reduced, but this remains uncertain in the literature at this time.

Possible Harm = Adverse effects associated with short course inhaled budesonide include oral thrush and dysphonia.

Cost = Budesonide Turbuhaler® 200 mcg/dose (200 doses/inhaler) is ~$75 and 400 mcg/dose (200 doses/inhaler) is ~$110, plus professional dispensing fee**.**

COLCHICINE

Colchicine 0.6 mg PO BID x 3 days, then 0.6 mg PO daily x 27 days may be considered on a case by case basis for adults aged 40 years or over with mild COVID-19 with at one risk factor[2] and no contraindications[3] to colchicine.

Possible Benefit = Colchicine may reduce hospitalization in 1 out of 71 patients (4.5% colchicine vs. 5.9% placebo).

Possible Harm = Side-effects include diarrhea (14% colchicine vs. 7% placebo) and nausea (2% colchicine vs. 2% placebo), and pulmonary embolism (0.5% colchicine vs. 0.1% placebo).

Cost = Course of colchicine treatment is ~$15, plus professional dispensing fee.

1. Inhaled budesonide – underlying health conditions: weakened immune system due to illness or medication, heart disease and/or hypertension, chronic lung disease, diabetes mellitus, hepatic impairment, stroke or other neurological condition, obesity or BMI above 35.
2. Colchicine – risk factors: age >70 years, obesity (BMI >30 kg/m2), diabetes, hypertension (systolic >150 mmHg), respiratory or coronary disease, heart failure, fever >38.4□C, or dyspnea.
3. Colchicine – contraindications: GFR <30 mL/min, inflammatory bowel disease, chronic diarrhea or malabsorption, neuromuscular disease, severe liver disease, chemotherapy, current colchicine treatment, hypersensitivity to colchicine, or concurrent medications that interact with colchicine (e.g. amiodarone, azoles, carvedilol, cyclosporine, estradiol, macrolides, propafenone, protease inhibitors, quinidine, quinine, verapamil).

Evidence used for these recommendations:

Inhaled Budesonide

In the PRINCIPLE multi-centre, open-label, randomized controlled trial (n=2617), non-hospitalized COVID-19 patients aged ≥65 years or ≥50 years with comorbidities (immunosuppression, heart or lung disease, hypertension, diabetes, mild hepatic impairment, stroke or neurological disease, obesity), who had symptoms for 14 days or less were randomized to usual care (n=1028), usual care plus inhaled budesonide 800 µg BID for 14 days (n=751), or usual care plus other interventions (n=643). The co-primary endpoints were time to first self-reported recovery and COVID-19-related hospitalization or death at 28-days follow-up. There was a 3-day improvement in time to self-reported recovery in those who received inhaled budesonide compared to usual care **(11 days budesonide vs. 14 days usual care [hazard ratio 1.208, (95% BCI 1.076-1.356)])**. The composite 28-day hospitalization or death was numerically lower with inhaled budesonide (8.5% vs. 10.3% usual care), however, this did not reach statistical significance. These results have only been reported as an interim analysis in preprint. Final analysis and peer review are pending.

STOIC is a Phase 2, open-label, randomized controlled trial (n=146) in non-hospitalized COVID-19 patients aged 18 years or older who developed mild symptoms within 7 days. Participants were randomized to usual care (n=73), or usual care plus inhaled budesonide 800 µg BID (n=73) until symptom resolution. Primary endpoint was COVID-19-related urgent care visit (including emergency department visit or hospitalization). Inhaled budesonide was given for a median of 7 days. The STOIC trial was stopped early after interim analysis concluded the outcome would not change with further enrolment. Patients who received inhaled budesonide had significantly fewer COVID-19-related urgent care visits **(3% budesonide vs. 15% usual care, difference in proportions 0.123, 95% CI 0.033-0.213, p=0.009)**. Clinical recovery was reduced by 1 day (7 days budesonide vs. 8 days usual care). Limitations include the open-label design, relatively small sample size, and the early discontinuation of the study.

Colchicine

In the COLCORONA randomized, double-blind, placebo-controlled trial of non-hospitalized patients with probable or proven COVID-19, colchicine 0.5 mg PO BID x 3 days, then 0.5 mg daily x 27 days trended towards reduction in a composite primary endpoint of hospitalization or mortality at 30 days when compared to placebo **(4.7% colchicine [n=2235] vs. 5.8% placebo [n=2253]; OR 0.79; 95% CI 0.61 to 1.03; p<0.08)**. However, when only COVID-19-confirmed patients were included, results were statistically significant **(4.6% colchicine [n=2075] vs. 6.0% placebo [n=2084]; OR 0.75; 95% CI 0.57 to 0.99; p<0.04)**. Of these patients, the odds ratio was statistically significant for reduction in hospitalization 0.75 (95%CI, 0.57 to 0.99), but not for mechanical ventilation 0.50 (95%CI, 0.23 to 1.07) and death 0.56 (95%CI, 0.19 to 1.66). Serious adverse events were 4.9% in colchicine vs. 6.3% in placebo groups (p=0.05), pneumonia 2.9% vs. 4.1% (p=0.02), pulmonary embolism 0.5% vs. 0.1% (p=0.01), and diarrhea 13.7% vs. 7.3% (p<0.0001).

Several limitations exist. The intent-to-treat analysis did not show statistical significance in the primary endpoint, yet after removal of 329 patients without PCR-confirmed COVID-19 significance was observed. The absolute difference of 1.4% for the primary endpoint provides a relatively minor benefit corresponding to a number-needed-to-treat of 71, and odds ratios had wide confidence intervals. Median age was young at 54.7 years with only 9.9% who were 70 years or older. Additionally, the trial was terminated early due to logistical issues and intent for early publication, attaining 4506 out of the intended sample of 6000 patients.

The CTC will continue to update the “Clinical Practice Guidance for Antimicrobial and Immunomodulatory Therapy in Adult Patients with COVID-19” document based on any new studies and relevant data. Please refer to the BCCDC website for the most updated information:

http://www.bccdc.ca/health-professionals/clinical-resources/covid-19-care/clinical-care/treatments