Pathophysiological Basis and Rationale for Early Outpatient Treatment of SARS-CoV-2 (COVID-19) Infection

Peter A. McCullough, MD, MPH,a,b,c Ronan J. Kelly, MD,a Gaetano Ruocco, MD,d Edgar Lerma, MD,e James Tumlin, MD,f Kevin R. Wheelan, MD,a,b,c Nevin Katz, MD,g Norman E. Lepor, MD,h Kris Vijay, MD,i Harvey Carter, MD,j Bhupinder Singh, MD, k Sean P. McCullough, BS, l Brijesh K. Bhami, MD,m o Alberto Palazzuoli, MD, PhD,n Gaetano M. De Ferrari, MD, PhD,o Gregory P. Milligan, MD, MPH,a Taimur Safder, MD, MPH,a Kristen M. Tecson, PhD,b Dee Dee Wang, MD,p John E. McKinnon, MD,q William W. O’Neill, MD,r Marcus Zervos, MD,s Harvey A. Risch, MD, PhDq

aBaylor University Medical Center, Dallas, Tex; bBaylor Heart and Vascular Institute, Dallas, Tex; cBaylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, Tex; dCardiology Division, Regina Montis Regalis Hospital, Mondovi, Cuneo, Italy; eChrist Advocate Medical Center, Chicago, Ill; fEmory University School of Medicine, Atlanta, Ga; gJohns Hopkins School of Medicine, Baltimore, Md; hCedars Sinai Medical Center, Los Angeles, Calif; iAbrazo Arizona Heart Hospital, Abrazo Health System, Phoenix, Ariz; jCarter Eye Center, Dallas, Tex; kCardiorenal Society of America, Phoenix, Ariz; lUniversity of Texas McGovern Medical School, Houston, Tex; mBakersfield Heart Hospital, Bakersfield, Calif; nUniversity of Siena, Le Scorte Hospital Viale Bracci, Siena, Italy; oUniversity of Torino, Torino, Italy; pHenry Ford Hospital, Detroit, Mich; qYale University School of Public Health, New Haven, Conn.

ABSTRACT

Approximately 9 months of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2 [COVID-19]) spreading across the globe has led to widespread COVID-19 acute hospitalizations and death. The rapidity and highly communicable nature of the SARS-CoV-2 outbreak has hampered the design and execution of definitive randomized, controlled trials of therapy outside of the clinic or hospital. In the absence of clinical trial results, physicians must use what has been learned about the pathophysiology of SARS-CoV-2 infection in determining early outpatient treatment of the illness with the aim of preventing hospitalization or death. This article outlines key pathophysiological principles that relate to the patient with early infection treated at home. Therapeutic approaches based on these principles include 1) reduction of reinoculation, 2) combination antiviral therapy, 3) immunomodulation, 4) antiplatelet/antithrombotic therapy, and 5) administration of oxygen, monitoring, and telemedicine. Future randomized trials testing the principles and agents discussed will undoubtedly refine and clarify their individual roles; however, we emphasize the immediate need for management guidance in the setting of widespread hospital resource consumption, morbidity, and mortality.

© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. (http://creativecommons.org/licenses/by-nc-nd/4.0/) • The American Journal of Medicine (2020) 000:1–7

KEYWORDS: Ambulatory treatment; Anticoagulant; Anti-inflammatory; Antiviral; COVID-19; Critical care; Epidemiology; Hospitalization; Mortality; SARS-CoV-2
Day 0 Symptom Onset     7 days                14 days                21 days                30 days

- Cough
- Difficulty Breathing
- Fever
- Sore Throat
- Malaise
- Body Aches
- Nasal Stuffiness
- Loss of taste
- Anorexia
- Nausea
- Diarrhea
- Chest Heaviness/Pain
- Dyspnea
- Desaturation
- Systemic Thromboembolism

Off-Target Antivirals

Corticosteroids

Antiplatelet Drugs/Antithrombotics

Cytokine Storm

Microthrombosis

Viral Replication

Unprocessed Mortality Risk

SARS-CoV-2
Nasal PCR+
Oral PCR/Ag+
D-dimer
Hs-CRP
Lymphocytes

Ambulatory Phase                                            Hospitalization Phase

Death

McCullough PA, Fourth-Quarter 2020 COVID-19 Drug and Diagnostic Developments A Virtual Conference Monday, November 2nd 2020, 9:00am - 6:00pm CET McCullough PA Proc (Bayl Univ Med Cent). 2020 (in press)
COVID-19-like or COVID-19-confirmed illness
Self-quarantine at home, Contagion Control

Age < 50 yr. Healthy

Watchful Waiting

If Symptoms Worsen

Complete Self-quarantine

Age ≥ 50 yr. or a Single Comorbidity
BMI > 30 kg/m², Pulmonary Dz, DM, CVD, CKD, Cancer

Immediately: Fresh air/reduce reinoculation, zinc sulfate 220 mg po qd (5-30 days)

Immediately ≥ 2 Antiviral Agents (5-30 days)

HCQ 200 mg po bid
+ AZM 250 mg po bid or
+ Doxy 100 mg po bid

IVM 6-12 mg po qd x 1-3 days
+ AZM 250 mg po bid or
+ Doxy 100 mg po bid

Favipiravir 600 mg po bid
+ AZM 250 mg po bid or
+ Doxy 100 mg po bid

Respiratory Symptoms Develop or Day 5 of illness

Prednisone 1 mg/kg qd x 5 days ± taper ± Colchicine 0.6 mg po bid

Underlying Serious Medical Condition, ↑VTE Risk, Suspect micro- or overt thrombosis

Aspirin 325 mg po qd ± Low-molecular weight heparin or Apixaban, Rivaroxaban, Dabigatran, Edoxaban in Standard doses (5-30 days)

BMI=body mass index, Dz=disease, DM=diabetes mellitus, CVD=cardiovascular disease, CKD=chronic kidney disease, yr=years, HCQ=hydroxychloroquine, AZM=azithromycin, Doxy=doxycycline, IVM=ivermectin, VTE=venous thrombo-embolic