Alaska Early Treatment Summit

Alaska Covid Alliance

www.alaskacovidalliance.com

Anchorage, Alaska

Dear Fellow Physicians, December 14, 2021

We recently heard that you signed a letter addressed to the Alaska State Medical Board regarding a conference that was held in Anchorage in October called the Alaska Early Treatment Summit. We have been personally practicing early treatment for Covid for the past 20 months. These treatment protocols were developed and are being utilized very successfully in our practices. The same protocols are also being used in other parts of the United States and in many countries around the world including: Japan, India, Bangladesh, Africa, China, Brazil, and multiple others. The studies done in the United States on the successful antiviral properties of some of these medications date back to the early 2000's with the original SARS virus.

We are following protocols endorsed by the American Association of Physicians and Surgeons, Dr. McCullough, Dr. Zelenko, and the FLCCC. Over 150,000 patients have been successfully treated with these protocols and over 1,193 studies have shown efficacy for EARLY treatment of COVID-19. We realize that the majority of you are treating the secondary inflammatory and third cytokine storm stages of this disease which respond much differently. We have used these FDA-approved medications on ourselves, our loved ones, and hundreds of patients successfully, saving hundreds of lives and keeping 99 percent of the people we treat out of our hospitals.

The medications we are using are some of the safest medications available with fewer side effects than aspirin, Tylenol, and penicillin. With billions of doses used in humans all over the world, these medications are inexpensive, generic, over the counter in most countries, and have been FDA approved for over 26 years. There are over 50 medications in various combinations that are currently being studied not only for early outpatient treatment but for all stages of the disease including post-Covid syndrome. Even the NIH has listed Ivermectin as a useful medication under investigation against Covid as of July 8, 2021.

It seems this coronavirus disease has now become endemic and will likely be with us forever. The main goal we had hoped to achieve by putting on the Alaska Early Treatment Summit was to encourage other providers to consider using these safe protocols in order to save more Alaskans.

We have people contacting us from rural Alaska, other states, and even other countries thanking us for our over-the-counter supplement list. They are also thanking us for how information from this conference helped save their lives and those of their loved ones. We are committed to treating both vaccinated and unvaccinated Alaskans and are not anti-vaccine. We recognize how important vaccination is in preventing disease and lessening complications, but we also recognize that to conquer Covid both prevention and treatment are needed. It is vitally important that we continue to use these lifesaving early outpatient treatments.

Enclosed are some of our data sources for why we treat patients with these medications. We have all been working tirelessly throughout this crisis with the singular unified goal of saving lives. If we do not work together, we do a disservice not only to ourselves and our colleagues, but most importantly to the many patients that will die needlessly if early treatment and the ability to fight this disease from the moment it starts is not allowed. Please recognize that there are no ulterior motives or financial incentives at play, and that we have risked much to simply try to save lives. Please take a look at the information provided regarding early treatment.

We hope that you have a wonderful holiday season and that we can continue united against Covid into the New Year.

Happy Holidays from the Alaska Covid Alliance

PDF of this booklet here:

www.alaskacovidalliance.com/4docs

Use it to easily access the hundreds of web links in this booklet leading you to vast research resources and practitioner experience, treatment protocols that have been used successfully to treat hundreds of thousands of COVID victims and save lives.

On Line Videos from the 10/30/21 - Alaska Early Treatment Medical Summit Held in Anchorage

ESPECIALLY FOR MEDICAL PROFESSIONALS

Alaska's own Dr. Ilona Farr, primary care physician, presents on her own personal journey contracting COVID herself (twice!) while she treated over 700 COVID patients. She lost only one (who could not get her Ivermectin prescription filled by an Anchorage pharmacy) and less than 20 needed to be hospitalized.

From the Morning (Medical Personnel) Session [38 min]

www.alaskacovidalliance.com/morning-session

Farr covers: Beginnings of COVID | Spring 2020 | Fall 2020 | Spring 2021/Summer 2021 | Her Own Covid Experience | COVID Protocols - McCullough | Supplements | Additional Treatments | Misinformation from Medical Community | Treatment Costs | Vaccine Mandates | Vaccine Efficacy | Alaska is an "Opt in State" | Problems to Solve in Alaska | Additional Research Needed

The rest of the Summit's presentations by national experts that came to Anchorage:

www.alaskacovidalliance.com

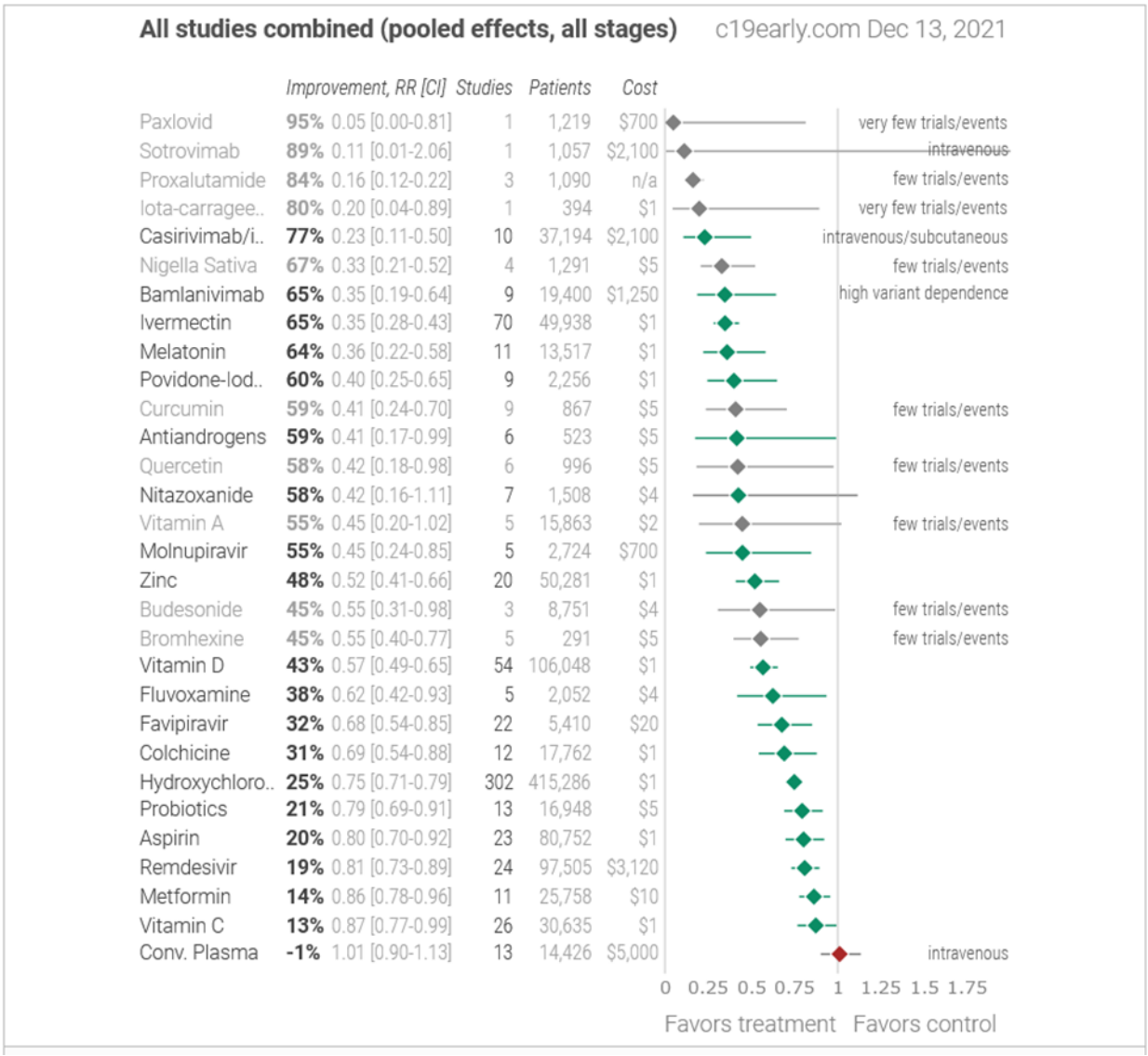
Dr. Robert Malone, Dr. Richard Urso, Dr. Meryl Nass, Dr. Ryan Cole, Dr. Li-Meng Yan, Attorney Colton Boyles.

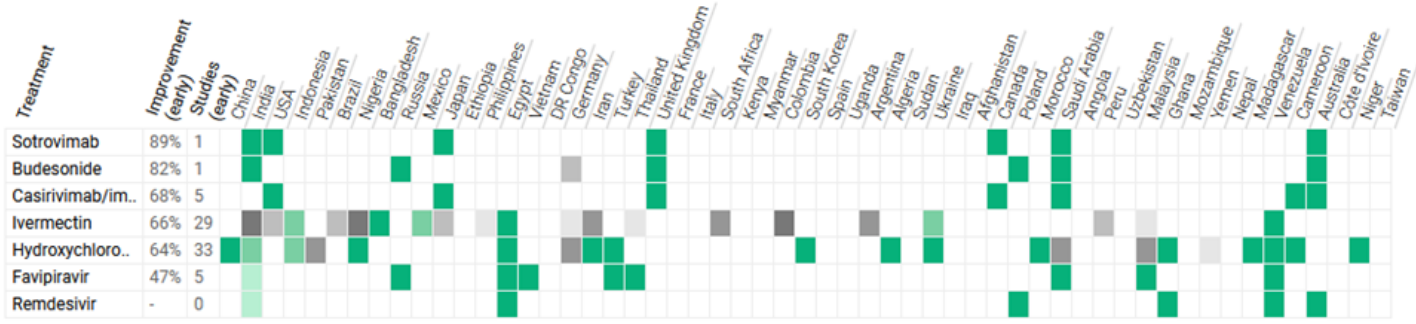
Also comments by Anchorage Mayor Dave Bronson and Dr. John Nolte.

COVID-19 early treatment: real-time analysis of 1,194 studies

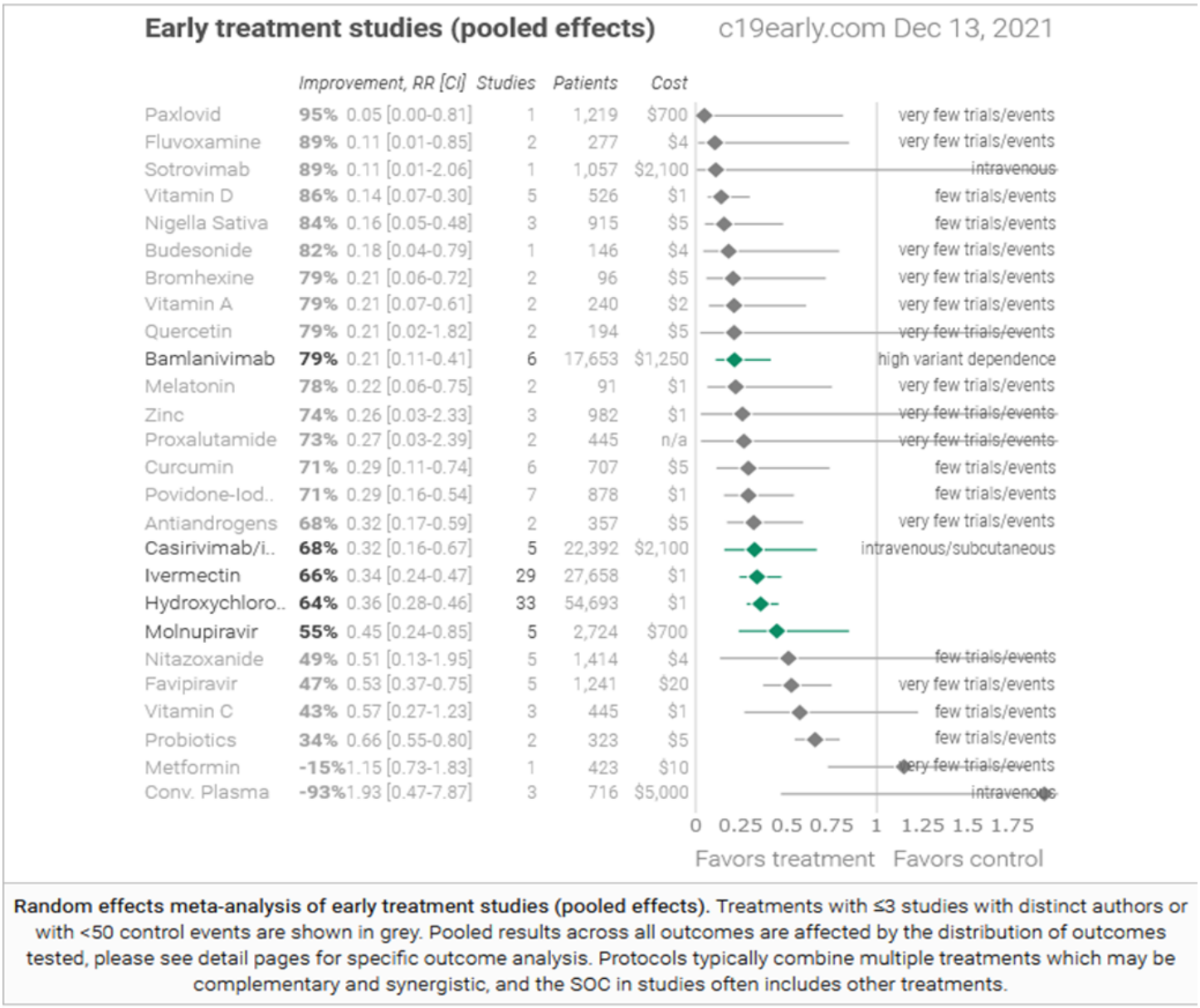
source: https://c19early.com/

Analysis of 30 COVID-19 early treatments, and database of 248 other potential treatments. 68 countries have approved early treatments. *Treatments do not replace vaccines and other measures. All practical, effective, and safe means should be used. Elimination is a race against viral evolution. No treatment, vaccine, or intervention is 100% available and effective for all variants. Denying efficacy increases the risk of COVID-19 becoming endemic; and increases mortality, morbidity, and collateral damage.*



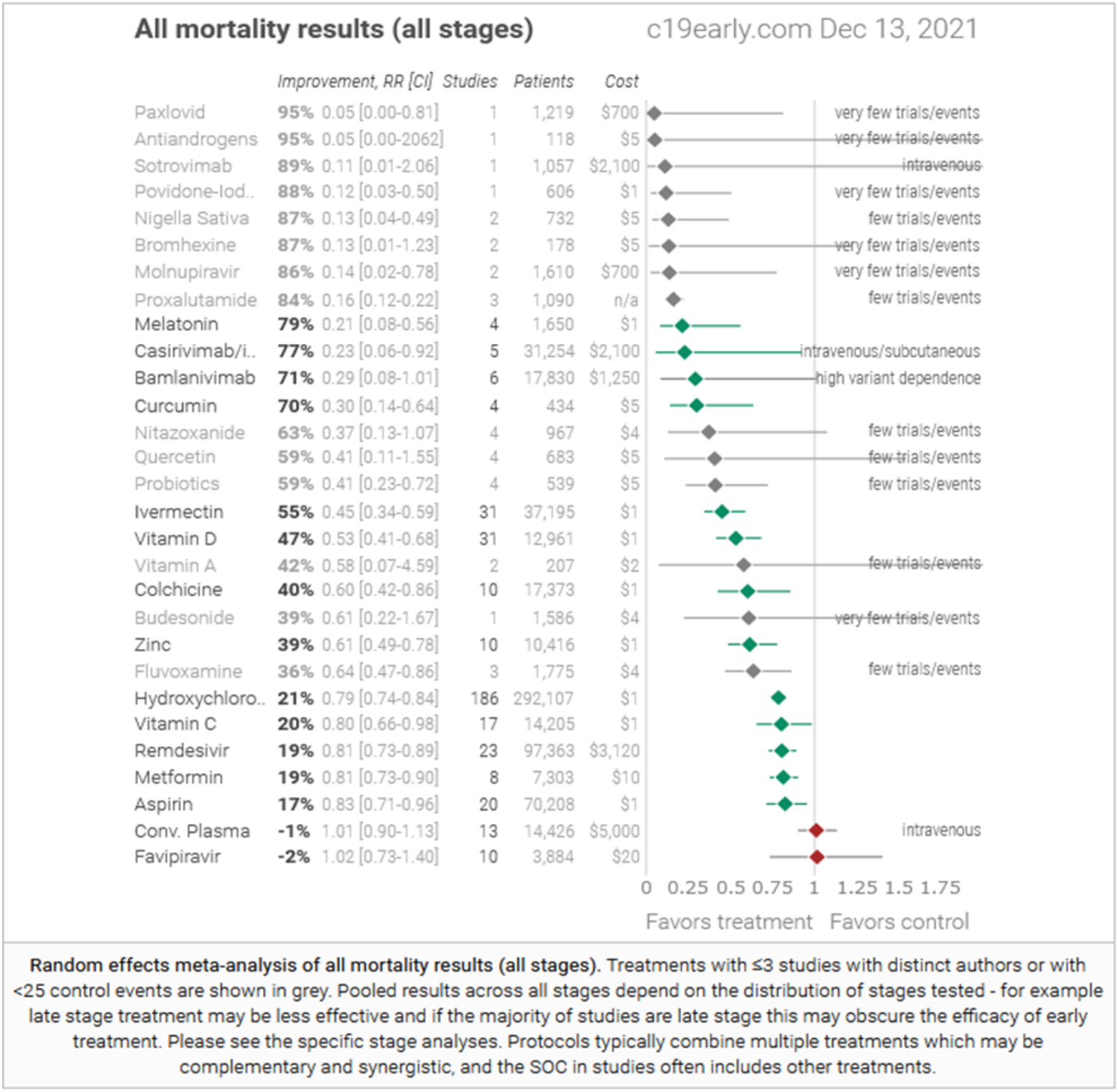


Early treatments approved by >2 countries. 68 countries have officially approved treatments. Details.



Random effects meta-analysis of early treatment studies (pooled effects). Treatments with ≤3 studies with distinct authors or with <50 control events are shown in grey. Pooled results across all outcomes are affected by the distribution of outcomes tested, please see detail pages for specific outcome analysis. Protocols typically combine multiple treatments which may be complementary and synergistic, and the SOC in studies often includes other treatments.

source: https://c19early.com/



Random effects meta-analysis of all mortality results (all stages). Treatments with ≤3 studies with distinct authors or with <25 control events are shown in grey. Pooled results across all stages depend on the distribution of stages tested - for example late stage treatment may be less effective and if the majority of studies are late stage this may obscure the efficacy of early treatment. Please see the specific stage analyses. Protocols typically combine multiple treatments which may be complementary and synergistic, and the SOC in studies often includes other treatments.

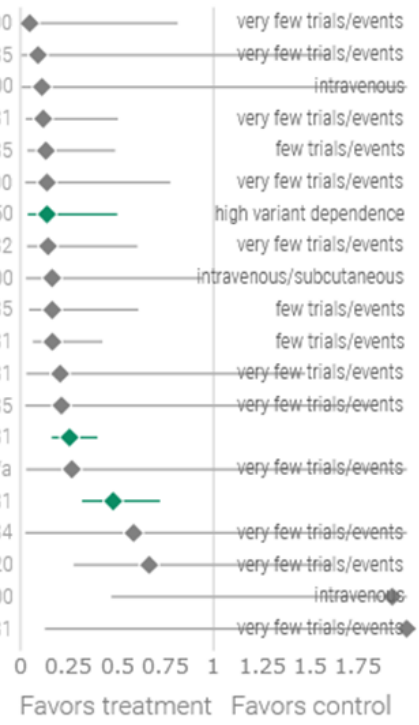
source: https://c19early.com/

source: https://c19early.com/

Early treatment mortality results

c19early.com Dec 13, 2021

	Improvement, RR [CI]	Studies	Patients	Cost	
Paxlovid	**95%** 0.05 [0.00-0.81]	1	1,219	$700	very few trials/events
Bromhexine	**91%** 0.09 [0.01-1.59]	1	78	$5	very few trials/events
Sotrovimab	**89%** 0.11 [0.01-2.06]	1	1,057	$2,100	intravenous
Povidone-Iod..	**88%** 0.12 [0.03-0.50]	1	606	$1	very few trials/events
Nigella Sativa	**87%** 0.13 [0.04-0.49]	2	732	$5	few trials/events
Molnupiravir	**86%** 0.14 [0.02-0.78]	2	1,610	$700	very few trials/events
Bamlanivimab	**86%** 0.14 [0.04-0.50]	4	17,048	$1,250	high variant dependence
Vitamin A	**86%** 0.14 [0.03-0.61]	1	140	$2	very few trials/events
Casirivimab/i..	**84%** 0.16 [0.03-0.95]	3	19,513	$2,100	intravenous/subcutaneous
Curcumin	**84%** 0.16 [0.04-0.61]	2	314	$5	few trials/events
Vitamin D	**83%** 0.17 [0.06-0.42]	3	128	$1	few trials/events
Zinc	**79%** 0.21 [0.03-1.47]	1	518	$1	very few trials/events
Quercetin	**79%** 0.21 [0.02-1.82]	2	194	$5	very few trials/events
Hydroxychloro..	**75%** 0.25 [0.16-0.40]	13	50,628	$1	
Proxalutamide	**73%** 0.27 [0.03-2.39]	2	445	n/a	very few trials/events
Ivermectin	**52%** 0.48 [0.32-0.72]	10	25,482	$1	
Nitazoxanide	**41%** 0.59 [0.02-13.8]	2	873	$4	very few trials/events
Favipiravir	**33%** 0.67 [0.28-1.61]	1	774	$20	very few trials/events
Conv. Plasma	**-93%** 1.93 [0.47-7.87]	3	716	$5,000	intravenous
Vitamin C	**-204%** 3.04 [0.13-72.9]	1	98	$1	very few trials/events



Random effects meta-analysis of early treatment mortality results. Treatments with ≤3 studies with distinct authors or with <25 control events are shown in grey. Protocols typically combine multiple treatments which may be complementary and synergistic, and the SOC in studies often includes other treatments.

Global adoption of COVID-19 early treatments

Home | Share | Tweet | Submit Feedback

Treatment	Improvement (early)	Studies (early)
Paxlovid	95%	1
Fluvoxamine	89%	2
Sotrovimab	89%	1
Vitamin D	86%	5
Nigella Sativa	84%	3
Budesonide	82%	1
Bromhexine	79%	2
Vitamin A	79%	2
Quercetin	79%	2
Bamlanivimab	79%	6
Melatonin	78%	2
Zinc	74%	3
Proxalutamide	73%	2
Curcumin	71%	6
Povidone-Iodine	71%	7
Antiandrogen	68%	2
Casirivimab/im..	68%	5
Ivermectin	66%	29
Hydroxychloro..	64%	33
Molnupiravir	55%	5
Nitazoxanide	49%	5
Favipiravir	47%	5
Vitamin C	43%	3
Probiotics	34%	2
Remdesivir	-	0
Colchicine	-	0

Global adoption of early treatments. Studies, improvement, and adoption refer to early treatment only. Countries ordered by population. Official: ■ Unofficial: ■

Ivermectin Study #135, Meta Analysis

Kerr et al., Research Gate - Source: https://c19ivermectin.com/kerr.html

Ivermectin prophylaxis used for COVID-19 reduces COVID-19 infection and mortality rates: A 220,517-subject, populational-level retrospective citywide

PSM retrospective 220,517 patients in Brazil,133,051 taking ivermectin as part of a citywide prophylaxis program, showing significantly lower hospitalization and mortality with treatment. CAAE:47124221.2.0000.5485. risk of death, 48.0% lower, RR 0.52, $p < 0.001$, treatment 62 of 133,051 (0.0%), control 79 of 87,466 (0.1%), adjusted per study, risk of COVID-19 death, propensity score matching.

risk of death, 45.0% lower, RR 0.55, $p < 0.001$, treatment 62 of 4,311 (1.4%), control 79 of 3,034 (2.6%), adjusted per study, mortality rate for cases, propensity score matching.

risk of hospitalization, 46.0% lower, RR 0.54, $p < 0.001$, treatment 105 of 133,051 (0.1%), control 127 of 87,466 (0.1%), adjusted per study, risk of COVID-19 hospitalization, propensity score matching.

risk of hospitalization, 42.0% lower, RR 0.58, $p < 0.001$, treatment 105 of 4,311 (2.4%), control 127 of 3,034 (4.2%), adjusted per study, hospitalization rate for cases, propensity score matching.

risk of case, 7.0% lower, RR 0.93, $p = 0.003$, treatment 4,311 of 133,051 (3.2%), control 3,034 of 87,466 (3.5%), adjusted per study, propensity score matching.

Kerr et al., 12/11/2021, retrospective, propensity score matching, population-based cohort, Brazil, South America, preprint, 11 authors, July 2020 - December 2020, dosage 200µg/kg days 1, 2, 16, 17, 0.2mg/kg/day for 2 days every 15 days.

Effect extraction follows pre-specified rules prioritizing more serious outcomes. For an individual study the most serious outcome may have a smaller number of events and lower statistical signifi-

		Overall	Ivermectin users	Non-IVM users	Relative risk ratio (95%CI) *p-value*
	Overall population (n)	220,517	133,051 (60.3%)	87,466 (39.7%)	
COVID-19 infection	Infected population (n)	7,345	4,311 (58.7%)	3,034 (41.3%)	
	Infection rate (%)	3.3%	3.2%	3.5%	0.93 (0.89-0.98) p = 0.003
COVID-19 hospitalization	Hospitalization due to COVID-19	232	105	127	
	Hospitalization rate (in case of COVID-19) (%)	3.16%	2.43%	4.18%	0.58 (0.45-0.75) p<0.0001
	Risk of hospitalization due to COVID-19	0.11%	0.08%	0.15%	0.54 (0.42-0.70) p<0.0001
COVID-19 death	COVID-19 deaths (n)	141	62	79	-
	Risk of dying from COVID-19 (%)	0.06%	0.05%	0.09%	0.52 (0.37-0.72) p = 0.0001
	Mortality rate (among infected subjects) (%)	1.9%	1.4%	2.6%	0.55 (0.40-0.77) p = 0.0004

Vitamin D for Covid-19; real-time meta analysis of 143 studies, Dec 9, 2021
Version 118 Source: https://vdmeta.com/#intro

•Statistically significant improvements are seen in treatment studies for mortality, ventilation, ICU admission, hospitalization, and cases. 28 studies from 26 independent teams in 12 different countries show statistically significant improvements in isolation (22 for the most serious outcome).
•Random effects meta-analysis with pooled effects using the most serious outcome reported shows 86% [70-93%] and 43% [35-51%] improvement for early treatment and for all studies. Results are similar after restriction to 49 peer-reviewed studies: 84% [68-92%] and 44% [35-52%], and for the 31 mortality results: 83% [58-94%] and 47% [32-59%].
•Late stage treatment with calcifediol/calcitriol shows greater improvement compared to cholecalciferol: 78% [67-85%] vs. 45% [24-60%].
•Sufficiency studies show a strong association between vitamin D sufficiency and outcomes. Meta analysis of the 93 studies using the most serious outcome reported shows 57% [51-63%] improvement.
•While many treatments have some level of efficacy, they do not replace vaccines and other measures to avoid infection. Only 11% of vitamin D treatment studies show zero events in the treatment arm.
•Elimination of COVID-19 is a race against viral evolution. No treatment, vaccine, or intervention is 100% available and effective for all current and future variants. All practical, effective, and safe means should be used. Not doing so increases the risk of COVID-19 becoming endemic; and increases mortality, morbidity, and collateral damage.
•All data to reproduce this paper and the sources are in the appendix.

	Improvement	Studies	Authors	Patients
Treatment RCTs	**53%** [23-72%]	9	84	774
Treatment studies	**43%** [35-51%]	54	545	106,048
Cholecalciferol treatment	**42%** [32-51%]	45	434	97,705
Calcifediol/calcitriol treatment	**53%** [26-71%]	9	111	8,343
Treatment mortality	**47%** [32-59%]	31	283	12,961
Sufficiency studies	**57%** [51-63%]	93	776	180,979

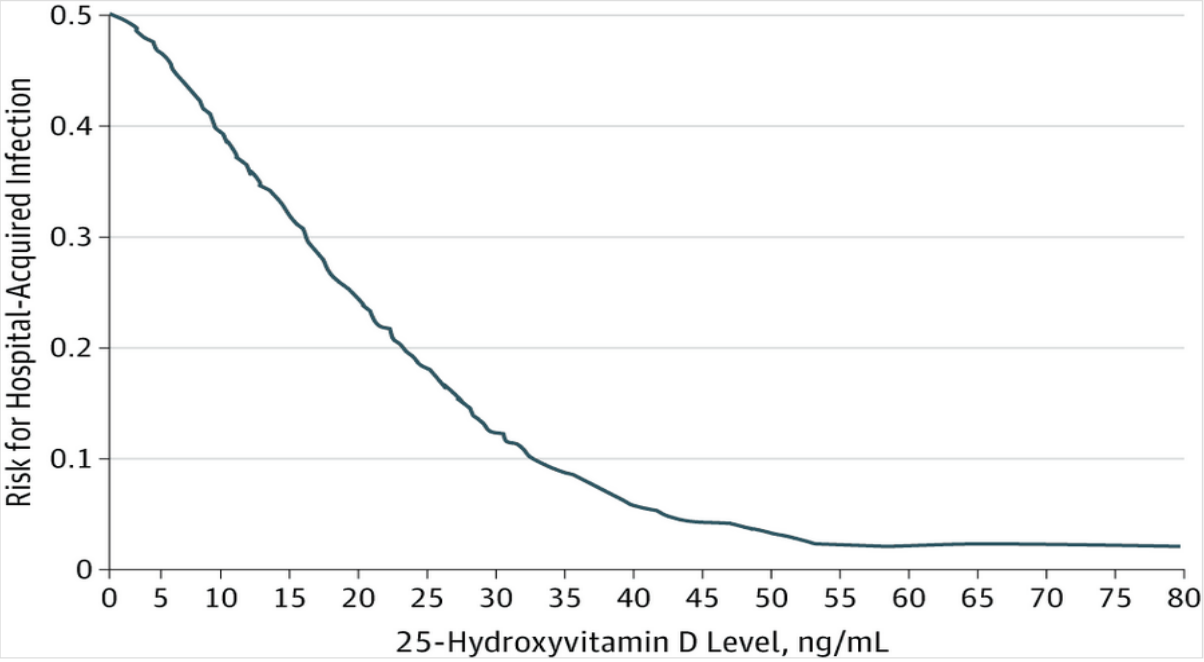


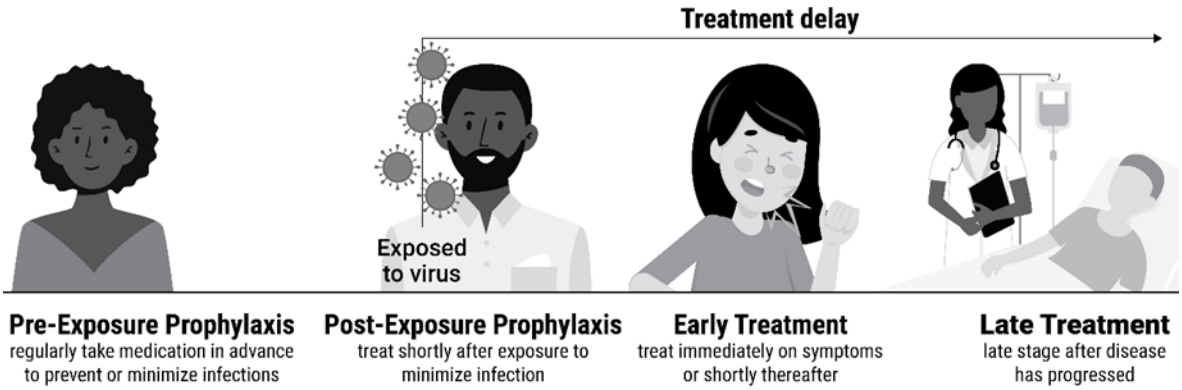
Figure 3. *Risk of hospital-acquired infections as a function of pre-operative vitamin D levels, from* ***[Quraishi]****.*

HCQ for Covid-19; Real Time Meta Analysis of 302 Studies, Dec 12, 2021 Version 166

Source: https://hcqmeta.com/

- 97% of the 33 early treatment studies report a positive effect (14 statistically significant in isolation).
- Meta analysis using the most serious outcome reported shows 64% [54-72%] improvement for the 33 early treatment studies. Results are similar after exclusion based sensitivity analysis and after restriction to peer-reviewed studies. Restricting to the 8 RCTs shows 46% [16-65%] improvement, and restricting to the 13 mortality results shows 75% [60-84%] lower mortality.
- Late treatment is less successful, with only 67% of the 203 studies reporting a positive effect. Very late stage treatment is not effective and may be harmful, especially when using excessive dosages.
- 83% of Randomized Controlled Trials (RCTs) for early, PrEP, or PEP treatment report positive effects, the probability of this happening for an ineffective treatment is 0.0038.
- There is evidence of bias towards publishing negative results. 77% of prospective studies report positive effects, compared to 71% of retrospective studies. Studies from North America are 2.8 times more likely to report negative results than studies from the rest of the world combined, $p = 0.0000000160$. The probability that an ineffective treatment generated results as positive as the 302 studies is estimated to be 1 in 751 trillion.
- Negative meta analyses of HCQ generally choose a subset of trials, focusing on late treatment, especially trials with very late treatment and excessive dosages.
- While many treatments have some level of efficacy, they do not replace vaccines and other measures to avoid infection. Only 5% of HCQ studies show zero events in the treatment arm.
- Elimination of COVID-19 is a race against viral evolution. No treatment, vaccine, or intervention is 100% available and effective for all current and future variants. All practical, effective, and safe means should be used. Not doing so increases the risk of COVID-19 becoming endemic; and increases mortality, morbidity, and collateral damage.
- All data to reproduce this paper and the sources are in the appendix. See [Ladapo, Prodromos, Risch, Risch (B)] for other meta analyses showing efficacy when HCQ is used early.

Total	302 studies	4,799 authors	415,386 patients
Positive effects	219 studies	3,395 authors	292,860 patients
Early treatment	64% improvement	RR 0.36 [0.28-0.46]	
Late treatment	19% improvement	RR 0.81 [0.76-0.86]	



Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines

Bryant, Andrew MSc; Lawrie, Theresa A. MBBCh, PhD; Dowswell, Therese PhD; Fordham, Edmund J. PhD; Mitchell, Scott MBChB, MRCS; Hill, Sarah R. PhD; Tham, Tony C. MD, FRCP

Background:

Repurposed medicines may have a role against the SARS-CoV-2 virus. The antiparasitic ivermectin, with antiviral and anti-inflammatory properties, has now been tested in numerous clinical trials.

Areas of uncertainty:

We assessed the efficacy of ivermectin treatment in reducing mortality, in secondary outcomes, and in chemoprophylaxis, among people with, or at high risk of, COVID-19 infection.

Data sources:

We searched bibliographic databases up to April 25, 2021. Two review authors sifted for studies, extracted data, and assessed risk of bias. Meta-analyses were conducted and certainty of the evidence was assessed using the GRADE approach and additionally in trial sequential analyses for mortality. Twenty-four randomized controlled trials involving 3406 participants met review inclusion.

Therapeutic Advances:

Meta-analysis of 15 trials found that ivermectin reduced risk of death compared with no ivermectin (average risk ratio 0.38, 95% confidence interval 0.19–0.73; n = 2438; I^2 = 49%; moderate-certainty evidence). This result was confirmed in a trial sequential analysis using the same DerSimonian–Laird method that underpinned the unadjusted analysis. This was also robust against a trial sequential analysis using the Biggerstaff–Tweedie method. Low-certainty evidence found that ivermectin prophylaxis reduced COVID-19 infection by an average 86% (95% confidence interval 79%–91%). Secondary outcomes provided less certain evidence. Low-certainty evidence suggested that there may be no benefit with ivermectin for "need for mechanical ventilation," whereas effect estimates for "improvement" and "deterioration" clearly favored ivermectin use. Severe adverse events were rare among treatment trials and evidence of no difference was assessed as low certainty. Evidence on other secondary outcomes was very low certainty.

Conclusions:

Moderate-certainty evidence finds that large reductions in COVID-19 deaths are possible using ivermectin. Using ivermectin early in the clinical course may reduce numbers progressing to severe disease. The apparent safety and low cost suggest that ivermectin is likely to have a significant impact on the SARS-CoV-2 pandemic globally.

Source: American Journal of Therapeutics: July/August 2021
https://journals.lww.com/americantherapeutics/fulltext/2021/08000/ivermectin_for_prevention_and_treatment_of.7.aspx

I-MASK+

PREVENTION & EARLY OUTPATIENT TREATMENT PROTOCOL FOR COVID-19

PREVENTION PROTOCOL (for Delta variant)

ANTI-VIRALS & ANTISEPTICS

Ivermectin[2]

Chronic Prevention

0.2 mg/kg per dose (take with or after a meal) — twice a week for as long as disease risk is elevated in your community.

Post COVID-19 Exposure Prevention[3]

0.4 mg/kg per dose (take with or after a meal) — one dose today, repeat after 48 hours.

Gargle mouthwash

2 x daily – gargle (do not swallow) antiseptic mouthwash with cetylpyridinium chloride (e.g. Scope™, Act™, Crest™), 1% povidone/iodine solution or Listerine™ with essential oils.

IMMUNE FORTIFYING / SUPPORTIVE THERAPY

Vitamin D3	1,000–3,000 IU/day
Vitamin C	500–1,000 mg 2 x daily
Quercetin	250 mg/day
Zinc	30–40 mg/day (elemental zinc)
Melatonin	6 mg before bedtime (causes drowsiness)

IVERMECTIN ALTERNATIVE

Nigella Sativa 40 mg/kg daily [4]
(black cumin seed)

To be used if ivermectin not available or added to ivermectin for optimal prevention.

EARLY TREATMENT PROTOCOL → see page 2

Supporting information

Questions regarding the multiple additions to the I-MASK+ protocol for the Delta variant can be found in our Frequently Asked Questions page flccc.net/new-i-mask-faqs. Here you will find answers to the the critical role of anti-androgen therapy, the safety and need for higher dosing of ivermectin, and guidance on the number of components of the protocol that should be used in the treatment of an individual patient.

Efficacy of Ivermectin

Ivermectin is a medication uniquely suited to treat COVID-19 given its now well-described, potent anti-viral and anti-inflammatory properties.

The efficacy of ivermectin is supported by results from 64 controlled trials, 32 of them randomized, and 16 of those were double-blinded, the gold standard of research design. A summary (meta-analysis) of these trials find statistically significant reductions in transmission, time to recovery, hospitalization, and death.

The most up-to-date summary of the totality of the supportive evidence for ivermectin in COVID-19 can be found here: flccc.net/flccc-summary-of-the-evidence-of-ivermectin-in-covid-19

Finally, in a historic achievement of public health, as of September 16, 2021, the North Indian state of Uttar Pradesh has effectively eradicated COVID from its population of 241 million people after widely distributing ivermectin in their treatment and prevention protocols for COVID-19. Please see also The Latest Results of Ivermectin's Success in Treating Outbreaks of COVID-19.

For an overview of the developments in prevention and treatment of COVID-19, please visit flccc.net/covid-19-protocols.

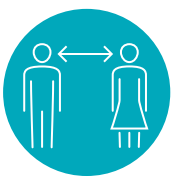
Please check our homepage regularly for updates of our COVID-19 Protocols! — New medications may be added and/or dose changes to existing medications may be made as further scientific studies emerge.

CONSULT HEALTH CARE PROVIDER

Discuss all protocol elements as well as the role of vaccination.[1]

WEAR MASKS

Wear a cloth, surgical, or N95 mask when in confined, poorly ventilated, crowded indoor spaces with non-household members.



KEEP DISTANCE

Until the end of the COVID-19 crisis, we recommend keeping a minimum distance of approx. 2 m / 6 feet in public from people who are not from your own household.

WASH HANDS

We recommend, after a stay during and after outings from home (shopping, subway etc.), a thorough hand cleaning (20–30 sec. with soap), or also to use a hand disinfectant in between.

I-MASK+

PREVENTION & EARLY OUTPATIENT TREATMENT PROTOCOL FOR COVID-19

EARLY TREATMENT PROTOCOL[5] (for Delta variant)

1. First line agents (use any or all medicines; listed in order of priority/importance)

ANTI-VIRALS

Ivermectin[2]
0.4–0.6 mg/kg per dose (take with or after a meal) — one dose daily, take for 5 days or until recovered. Use upper dose if: **1)** in regions with aggressive variants (e.g. Delta); **2)** treatment started on or after day 5 of symptoms or in pulmonary phase; or **3)** multiple comorbidities/risk factors.

and/or **Nitazoxanide**
500 mg 2 x daily for 5 days after meals. Combine with ivermectin (preferred) or substitute if ivermectin is not available. (Nitazoxanide is often unavailable or high-priced in the USA.)

ANTI-SEPTIC ANTI-VIRALS

Antiviral mouthwash: Gargle 3 x daily (do not swallow; must contain chlorhexidine, povidone-iodine, or cetylpyridinium chloride). **Iodine nasal spray/drops**: Use 1% povidone-iodine commercial product as per instructions 2–3 x daily. If 1%-product not available, must first dilute the more widely available 10%-solution[6] and apply 4–5 drops to each nostril every 4 hours. (No more than 5 days in pregnancy.)

ANTI-COAGULANTS / IMMUNE FORTIFYING

Aspirin	325 mg daily (unless contraindicated)
Vitamin D	Vitamin D3 5,000 IU daily. Preferred form if available: Calcitriol 0.5 mcg on day 1, then 0.25 mcg daily for 7 days
Melatonin	10 mg before bedtime (causes drowsiness)

SYNERGISTIC THERAPIES

Quercetin	250 mg 2 x daily
Zinc	100 mg/day (elemental zinc)
Vitamin C	500–1,000 mg 2 x daily

NUTRITIONAL THERAPEUTICS (for 14 days)[4]

Curcumin	(turmeric)	500 mg 2 x daily
Nigella Sativa	(black cumin seed)	80 mg/kg daily
Honey		1 gram/kg daily

PULSE OXIMETER

Monitoring of oxygen saturation is recommended (for instructions see page 3)

2. Second line agents (listed in order of priority/importance)

Add to first line therapies above if: 1) ≥5 days of symptoms; 2) Poor response to therapies above; 3) Significant comorbidities.

DUAL ANTI-ANDROGEN THERAPY

1. **Spironolactone** 100 mg 2 x daily for ten days.
2. **Dutasteride** 2 mg on day 1, followed by 1 mg daily for 10 days. If dutasteride not available, use **Finasteride** 10 mg daily for 10 days.

FLUVOXAMINE

50 mg 2 x daily for 10 days[7]
Consider **Fluoxetine** 30 mg daily for 10 days as an alternative (it is often better tolerated). Avoid if patient is already on an SSRI.

MONOCLONAL ANTIBODY THERAPY

Casirivimab/Imdevimab[8]
600 mg each in a single subcutaneous injection. Antibody therapy is for patients within 7 days of first symptoms and one or more risk factors as: Age > 65y; BMI > 25; pregnancy; chronic lung, heart, or kidney disease; diabetes; immunosuppressed; developmental disability; chronic tracheostomy; or feeding tube.

3. Third line agent

If below criteria are met, consider

CORTICOSTEROIDS

Prednisone or **Methylprednisolone**
1 mg/kg daily for 5 days followed by slow taper or escalation according to patient response.

Criteria:

After day 7–10 from first symptoms and patient has either: abnormal chest x-ray, shortness of breath, or oxygen saturations of 88–94%.

If oxygen saturation is lower than 88%, emergency room evaluation should be sought.

Notes

1 The I-MASK+ protocol is a bridge to vaccines and a safety net for those who cannot or have not been vaccinated; or are vaccinated and have concerns regarding declining protection against emerging variants. Vaccines have shown efficacy in preventing the most severe outcomes of COVID-19 and are an important part of a multi-modal strategy that must also include early treatment. The decision to get a vaccine should be made in consultation with your health care provider.

2 The dosing may be updated as further scientific studies emerge. The safety of ivermectin in pregnancy has not been definitively established. Use in the 1st trimester should be discussed with your doctor.

3 To use if a household member is COVID-19 positive, or you have prolonged exposure to a COVID-19 positive patient without wearing a mask.

4 For more information on nutritional therapeutics and how they can help with COVID-19 please see: flccc.net/covid-19-protocols/nutritional-therapeutics

5 For late phase – *hospitalized patients* – see the FLCCC's "MATH+ Hospital Treatment Protocol for COVID-19" on www.flccc.net

6 To make 1% povidone/iodine concentrated solution from 10% povidone/iodine solution, *it must be diluted first*.

One dilution method is as follows:
- First pour 1½ tablespoons (25 ml) of 10% povidone/iodine solution into a nasal irrigation bottle of 250 ml.
- Then fill to top with distilled, sterile or previously boiled water.
- Tilt head back, apply 4–5 drops to each nostril. Keep tilted for a few minutes, let drain.

7 Some individuals who are prescribed fluvoxamine experience acute anxiety which needs to be carefully monitored for and treated by the prescribing clinician to prevent rare escalation to suicidal or violent behavior.

8 This medication requires an infusion center. To find the nearest location in the U.S., visit www.infusioncenter.org or call for eligibility and location 1-877-332-6585 for English and 1-877-366-0310 for Spanish.

I-MASK+
PREVENTION & EARLY OUTPATIENT TREATMENT PROTOCOL FOR COVID-19

Additional information

Pulse Oximeter (usage instructions)

In symptomatic patients, monitoring with home pulse oximetry is recommended (due to asymptomatic hypoxia). The limitations of home pulse oximeters should be recognized, and validated devices are preferred. Multiple readings should be taken over the course of the day, and a downward trend should be regarded as ominous. Baseline or ambulatory desaturation < 94% should prompt hospital admission. The following guidance is suggested:

- Use the index or middle finger; avoid the toes or ear lobe.
- Only accept values associated with a strong pulse signal.
- Observe readings for 30–60 seconds to identify the most common value.
- Remove nail polish from the finger on which measurements are made.
- Warm cold extremities prior to measurement.

Calculation for ivermectin dose (0.2 mg per kg)

Body weight Conversion: 1 kg ≈ 2.2 lbs (doses calculated per upper end of weight range)		**Dose** 0.2 mg/kg ≈ 0.09 mg/lb (Each tablet = 3 mg; doses rounded to nearest half tablet above)	
70–90 lb	32–40 kg	8 mg	(3 tablets = 9 mg)
91–110 lb	41–50 kg	10 mg	(3.5 tablets)
111–130 lb	51–59 kg	12 mg	(4 tablets)
131–150 lb	60–68 kg	13.5 mg	(4.5 tablets)
151–170 lb	69–77 kg	15 mg	(5 tablets)
171–190 lb	78–86 kg	16 mg	(5.5 tablets)
191–210 lb	87–95 kg	18 mg	(6 tablets)
211–230 lb	96–104 kg	20 mg	(7 tablets = 21 mg)
231–250 lb	105–113 kg	22 mg	(7.5 tablets=22.5 mg)
251–270 lb	114–122 kg	24 mg	(8 tablets)
271–290 lb	123–131 kg	26 mg	(9 tablets = 27 mg)
291–310 lb	132–140 kg	28 mg	(9.5 tablets=28.5 mg)

For higher doses used in our I-MASK+ Protocol please multiply the value found in the table for 0.2 mg/kg, e.g.:

- **0.4 mg/kg:** double the 0.2 mg/kg dose
- **0.6 mg/kg:** triple the 0.2 mg/kg dose

Tablets can be halved for more accurate dosing. Then round to nearest half tablet above.

Note that Ivermectin is available in different tablet strengths (e.g. with 3, 5 or 6 mg) and administration forms (tablets, drops) depending on the country (please refer to the package information).

In our table we calculate doses using 3 mg tablets (the most common dose per tablet in the U.S.).

If your tablets contain a different amount of ivermectin than 3 mg, you must calculate the number of tablets to equal the dose of ivermectin required.

Disclaimer

The "I-MASK+ Prevention & Early Outpatient Treatment Protocol for COVID-19" is solely for educational purposes regarding potentially beneficial therapies for COVID-19. Never disregard professional medical advice because of something you have read on our website and releases. This protocol is not intended to be a substitute for professional medical advice, diagnosis, or treatment in regards to any patient. Treatment for an individual patient should rely on the judgement of your physician or other qualified health provider. Always seek their advice with any questions you may have regarding your health or medical condition. Please note our full disclaimer at: www.flccc.net/disclaimer

Please check our homepage regularly for updates of our COVID-19 Protocols!
New medications may be added and/or dose changes to existing medications may be made as further scientific studies emerge.

C19Protocols Reducing Risk of COVID-19 Infection and Severity

Early Treatment Protocols August 22, 2021

1. **Early Ambulatory Multidrug Therapy**, McCullough et al: https://rcm.imrpress.com/article/2020/2153-8174/RCM2020264.shtml (related interview and webinar)

2. **The I-MASK+** Early Outpatient Treatment Protocol for COVID-19: https://covid19criticalcare.com/i-mask-prophylaxis-treatment-protocol/i-mask-protocol-translations/

3. **Zelenko** Early Treatment Protocol: https://vladimirzelenkomd.com/treatment-protocol/

4. The following is the protocol **Drs. Fareed and Tyson** have jointly developed as most effective for their COVID-19 patients: https://www.thedesertreview.com/health/drs-george-fareed-and-brian-tyson-update-treatment-for-delta-variant/article_33835a28-472d-11ec-b838-07d39a4e8d01.html

5. **IppocrateOrg** "At Home Therapy" Protocol: https://ippocrateorg.org/en/2020/12/15/how-to-treat-covid-19/

6. **I-MASS** Prevention & At Home Treatment Mass Distribution Protocol for COVID-19 – https://covid19criticalcare.com/wp-content/uploads/2021/06/FLCCC-I-MASS-Protocol.pdf

7. **The Fleming Directed CoVid-19** Treatment Protocol (FMTVDM): http://c19protocols.com/wp-content/uploads/2021/01/fleming-protocol.pdf

8. **MATH+ Hospital Treatment** Protocol https://covid19criticalcare.com/wp-content/uploads/2020/07/FLCCC_Alliance-MATHplus_Protocol_v6-2020-11-12-ENGLISH.pdf

9. **Budesonide (Pulmicort) dosing for outpatient COVID** per the Oxford RCT: http://c19protocols.com/wp-content/uploads/2021/03/COVID_Budesonide_Oxford-Based_Dosing_Guidance.pdf

10. **Budesonide-focused** Treatment Protocol: https://secureservercdn.net/45.40.145.151/umz.e26.myftpupload.com/wp-content/uploads/2020/11/Full-Protocol_withOTC.pdf from https://budesonideworks.com/

11. Prophylaxis and Treatment for **COVID-19 in Nursing Homes** https://covexit.com/prophylaxis-and-treatment-for-covid-19-in-nursing-homes-video-highlights/

12. Government of India Ministry of Health & Family Welfare Revised guidelines for Home Isolation of mild / asymptomatic COVID-19 cases: https://www.mohfw.gov.in/pdf/RevisedguidelinesforHomeIsolationofmildasymptomaticCOVID19cases.pdf

13. COVID-19:THERAPEUTIC PLAN AND POTENTIAL THERAPIES. Aguirre-Chang, Gustavo; Trujillo F,Aurora; Córdova M, José Aníbal. February 2021 – https://www.researchgate.net/publication/348268812_TABLE_2021_COVID-19_THERAPEUTIC_PLAN_AND_POTENTIAL_THERAPIES_January_2021

14. Early ambulatory outpatient sequenced antiviral multidrug COVID-19 treatment (including for Delta or similar variants) for high-risk children and adolescents – https://earlycovidcare.org/wp-content/uploads/2021/09/Early-Child-Treatment.pdf

C19Protocols Reducing Risk of COVID-19 Infection and Severity

Prevention Protocols August 20, 2021

1. **The I-MASK**+ Prophylaxis Protocol for COVID-19: https://covid19criticalcare.com/i-mask-prophylaxis-treatment-protocol/i-mask-protocol-translations/
2. **Zelenko** Prophylaxis Protocol: https://vladimirzelenkomd.com/prophylaxis-protocol/
3. **Indian Council of Medical Research** (ICMR) – https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf
4. Prophylaxis and Treatment for **COVID-19 in Nursing Homes** https://covexit.com/prophylaxis-and-treatment-for-covid-19-in-nursing-homes-video-highlights/
5. **I-MASS** Prevention & At Home Treatment Mass Distribution Protocol for COVID-19 – https://covid19criticalcare.com/wp-content/uploads/2021/06/FLCCC-I-MASS-Protocol.pdf
6. **Vaccine Side-effects** Protocol: https://earlycovidcare.org/otc-medicines-nutraceuticals-to-prevent-reduce-covid-post-vaccination-side-effects/

More at: C19Protocols

Physicians/Facilities Offering Early Treatment

Patient Guides

Long COVID Protocols

Studies

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Review

Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19)

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The SARS-CoV-2 virus spreading across the world has led to surges of COVID-19 illness, hospitalizations, and death. The complex and multifaceted pathophysiology of life-threatening COVID-19 illness including viral mediated organ damage, cytokine storm, and thrombosis warrants early interventions to address all components of the devastating illness. In countries where therapeutic nihilism is prevalent, patients endure escalating symptoms and without early treatment can succumb to delayed in-hospital care and death. Prompt early initiation of sequenced multidrug therapy (SMDT) is a widely and currently available solution to stem the tide of hospitalizations and death. A multipronged therapeutic approach includes 1) adjuvant nutraceuticals, 2) combination intracellular anti-infective therapy, 3) inhaled/oral corticosteroids, 4) antiplatelet agents/anticoagulants, 5) supportive care including supplemental oxygen, monitoring, and telemedicine. Randomized trials of individual, novel oral therapies have not delivered tools for physicians to combat the pandemic in practice. No single therapeutic option thus far has been entirely effective and therefore a combination is required at this time. An urgent immediate pivot from single drug to SMDT regimens should be employed as a critical strategy to deal with the large numbers of acute COVID-19 patients with the aim of reducing the intensity and duration of symptoms and avoiding hospitalization and death.

Keywords

SARS-CoV-2; COVID-19; hospitalization; mortality; ambulatory treatment; anti-infective; anti-inflammatory; antiviral; corticosteroid; antiplatelet agent; anticoagulant; sequenced multidrug therapy

The pandemic of SARS-CoV-2 (COVID-19) is advancing unabated across the world with each country and region developing distinct epidemiologic patterns in terms of frequency, hospitalization, and death. There are four pillars to an effective pandemic response: 1) contagion control, 2) early treatment, 3) hospitalization, and 4) vaccination to assist with herd immunity (Fig. 1). Additionally, when feasible, prophylaxis could be viewed as an additional pillar since it works to reduce the spread as well as incidence of acute illness. Many countries have operationalized all four pillars including the second pillar of early home-based treatment with distributed medication kits of generic medications and supplements as shown in Table 1. In the US, Canada, United Kingdom, Western European Union, Australia, and some South American Countries there has been three major areas of focus for pandemic response: 1) containment of the spread of infection (masking, social distancing, etc., 2) late hospitalization and delayed treatments (remdesivir, convalescent plasma, antiviral antibodies), and 3) vaccine development (Bhimraj et al., 2020; COVID-19 Treatment Guidelines, 2020). Thus the missing pillar of pandemic response is early home-based treatment (as seen in Fig. 1).

The current three-pronged approach has missed the predominant opportunity to reduce hospitalization and death given the practice of directing patients to self-isolation at home. Early sequential multidrug therapy (SMDT) is the only currently available method by which hospitalizations and possibly death could be reduced in the short term (McCullough et al., 2020a). Most COVID-19 patients with progressive symptoms who arrive to hospital by emergency medical services do not require intubation or pressors initially in the field (Yang et al., 2020). Once hospitalized, if oxygen is required the mortality rate rises to ~12% (Palazzuoli et al., 2020). Approximately one quarter require mechanical ventil ation, advanced circulatory support, or renal replacement therapy and in that group the mortality exceeds 25% (S. Gupta et al., 2020a,b). Our observations suggest a majority of hospitalizations could be avoided with a first treat-at-home strategy with appropriate telemedicine monitoring and access to oxygen and therapeutics. Patients will have the best chance of therapeutic gain when trea ted before there is significant progression of disease (Argenziano et al., 2020; McCullough et al., 2020b; Rhodes et al., 2017).

The majority serious viral infections require early treatment with multiple agents and this approach has not been applied in trials of COVID-19 sponsored by governments or industry. Since COVID-19 syndrome is characterized by early exponential viral proliferation, cytokine-mediated organ damage and dysfunction, and endothelial injury with proximal platelet aggregation with thrombosis, (Fig. 2) it is not realistic to assume a single drug or antibody could comprehensively handle all of these manifestations. At this time there are no reports of conclusive randomized trials of oral ambulatory therapy for COVID-19 and none are expected in the short term. Most oral therapy trials reported to date have been small, underpowered, unblinded, relied on biased physician assigned endpoints, or in some cases, have been administratively stopped early without scientific justification or safety concerns.

Because COVID-19 is highly communicable, many U.S. ambulatory clinics do not care for patients with COVID-19 and studies suggest there has been little or no attempt to provide outpatient therapy to patients in the period before hospitalization (Price-Haywood et al., 2020). As the most notable early closure of a critically needed trial was U.S. National Institutes of Health study of hydroxychloroquine (HCQ) and azithromycin in ambulatory COVID-19 patients after 30 days with only 20 of 2000 budgeted patients enrolled (National Institutes of Health, 2020a,b). There has been no substantive federal effort since then on ambulatory trials and thus any future results are not expected in a time frame to influence public health policy (World Health Organisation, 2020). At the time of this writing, there are no planned trials of SMDT regimens designed to manage early viral replication, cytokine storm, and thrombosis in ambulatory patients with COVID-19 (Fig. 3). Hence, there is an urgent need for innovative early SMDT in COVID-19 to achieve the goal of reducing the intensity and severity of symptoms and lessening the risk of hospitalization or death. This outpatient ambulatory push could have a dramatic impact on reducing the strain on healthcare systems.

In the absence of evidence from or a commitment to clinical trials of early therapy, other scientific information on the pathophysiology, treated natural history, and clinical judgement together must guide contemporary ambulatory management of COVID-19 (McCullough et al., 2020b). Observational studies reporting outcomes in patient populations managed consistently with empirically derived early intervention regimens currently provide an acceptable level of evidence for safety and efficacy of these widely available, inexpensive and safe alternatives to the current standard of non-intervention (Khan et al., 2020). Based on pathophysiology and observational data, each physician and patient using shared decision making set the course for COVID-19 management: watch-

Table 1. Listing of early home-based treatment kits provided for acute COVID-19 illness by various countries.

Country	Drugs and supplements	References
Algeria	Chloroquine/Hydroxychloroquine	(Belayneh, 2020)
Argentina	Ivermectin	(Mega, 2020)
Brazil	Hydroxychloroquine, Ivermectin, Azithromycin (Vitamin D and zinc only for those who can afford)	(Coronavirus a Tarde, 2020; Ministério da Saúde, 2020)
Bangladesh	Ivermectin, Doxycycline	(Trial Site News, 2020)
Cameroon	Chloroquine/Hydroxychloroquine	(Belayneh, 2020; Bösmüller et al., 2020)
China	Chloroquine/Hydroxychloroquine plus other traditional medicine up to 23 different Chinese herbal medicines	(Fan et al., 2020)
Colombia	Ivermectin	(Mega, 2020)
Egypt	Chloroquine/Hydroxychloroquine	(Mohhamad, 2020)
France	Hydroxychloroquine, Azithromycin, and Lopinavir-Ritonavir	(Gérard et al., 2020)
Ghana	Chloroquine/Hydroxychloroquine	(Isaac, 2020)
India	Hydroxychlorquine, Ivermectin, alone or in combination with other drugs	(Vora et al., 2020)
Korea	Hydroxychloroquine	(Hong et al., 2020)
Mexico	Ivermectin, hydroxychloroquine	(Pacheco, 2020)
Morocco	Chloroquine/Hydroxychloroquine	(Brian, 2020; McFadyen et al., 2020; Mussa, 2020)
Mozanbique	Chloroquine/Hydroxychloroquine	(Belayneh, 2020; McFadyen et al., 2020)
Nigeria	Chloroquine/Hydroxychloroquine	(Felix, 2020; McFadyen et al., 2020)
Peru	Ivermectin, Azithromycin	(Diario oficial del bicentenario, 2020; Trial Site News, 2020)
Senegal	Chloroquine/Hydroxychloroquine	(Huaxia, 2020; McFadyen et al., 2020)
South Africa	Chloroquine/Hydroxychloroquine	(Katharine , 2020; McFadyen et al., 2020)
Spain	Patients who are already taking hydroxychloroquine within or outside of clinical trials for COVID-19 as well as patients undergoing chronic treatment with these drugs should continue taking them and, in any case, maintain their usual follow-ups with their doctors	(Agencia Española de Medicamentos y Productos Sanitarios, 2020)
Taiwan	Hydroxychloroquine	(Sheng, 2020)
Uganda	Chloroquine/Hydroxychloroquine, Azithromycin	(McFadyen et al., 2020; The Independent, 2020)
USA	No kits provided from public health agencies, Association of American Physicians and Surgeons Home COVID-19 Treatment Guide recommendends adjuvant neutraceuticals, and sequenced multidrug therapy by prescription	(AAPS, 2020)

ful waiting in self-quarantine or empiric treatment with the aim of lessening the intensity and duration of symptoms and reducing the risk of hospitalization and death (Gopalakrishnan et al., 2020). Fortunately, most healthy individuals with COVID-19 under age 50 years have a self-limited illness and no specific treatment is advised in the absence of severe symptoms. However, they should be advised that development of lower respiratory symptoms warrant evaluation of oxygenation status and consideration chest imaging which may prompt interventions with documentation of hypoxemia or pulmonary infiltrates.

However, those over age 50 and or those with one or more comorbidity have increased risks for hospitalization and death over 1% which increase substantially up to 40% with advancing age and more medical illnesses (obesity, diabetes mellitus, heart disease, pulmonary disorders, renal disease, and malignancies) and thus, warrant early ambulatory treatment according to best medical judgement weighing the benefits and risks of oral therapy. SARS-CoV-2 as with many viral infections, may be amenable to multiple drugs early in its course but is less responsive to the same treatments when administration is delayed and given in the hospital (Vaduganathan et al., 2020). Innovative SMDT regimens for COVID-19 utilize principles learned from hospitalized patients as well as data from treated ambulatory patients.

For the ambulatory patient with recognized signs and symptoms of COVID-19 on the first day (Fig. 2), often with nasal real-time reverse transcription or oral antigen testing not yet performed, the following three therapeutic principles apply (Centers for Disease Control and Prevention, 2020) : 1) combination anti-infective therapy to attenuate viral replication, 2) corticosteroids to modulate cytokine storm, and 4) antiplatelet agent/antithrombotic therapy to prevent and manage micro- or overt vascular thrombosis. For patients with cardinal features of the syndrome (fever, viral malaise, nasal congestion, loss of taste and smell, dry cough, etc) with pending or suspected false negative testing, therapy is the same as those with confirmed COVID-19.

1. Reducing viral spread and contamination

A major goal of self-quarantine is control of contagion (Nussbaumer-Streit et al., 2020). While there has been a great emphasis on masking and social distancing in congregate settings, many sources of information suggest the main place of viral transmission occurs in the home (respiratory, contact, oral-fecal) (Jef-

Fig. 1. The four pillars of pandemic response to COVID-19. The four pillars of pandemic response to COVID-19 are: 1) contagion control or efforts to reduce spread of SARS-CoV-2, 2) early ambulatory or home treatment of COVID-19 syndrome to reduce hospitalization and death, 3) hospitalization as a safety net to prevent death in cases that require respiratory support or other invasive therapies, 4) natural and vaccination mediated immunity that converge to provide herd immunity and ultimate cessation of the viral pandemic.

ferson et al., 2020; Xu et al., 2020). Masks for all unaffected contacts within the home as well as frequent use of hand sanitizer and hand washing is mandatory in the setting when one or more family members falls ill. Sterilizing surfaces such as countertops, door handles, phones, and other devices is advised. When possible, other close contacts can move out of the house and seek shelter free of SARS-CoV-2. Findings from multiple studies indicate that policies concerning control of the spread SARS-CoV-2 are only partially effective and extension into the home as the most frequent site of viral transfer is reasonable (Hsiang et al., 2020; Xiao et al., 2020). One of the great advantages of home treatment of COVID-19 is the ability of an individual or family unit to maintain isolation and complete contact tracing. If therapy is offered in the home with delivery of medications, then trips to urgent care centers, clinics, and hospitals can be reduced or eliminated. This limits spread to drivers, other patients, staff, and healthcare workers. On the contrary, therapeutic nihilism on the part of primary care physicians and health systems drives anxiety and panic among patients with acute COVID-19 who feel abandoned, making them more likely to break quarantine and seek aid at urgent care centers, emergency rooms and hospitals.

SARS-CoV-2 exists outside the human body in a bioaerosol of airborne particles and droplets. Since exhaled air in an infected person is considered to be "loaded" with particulate inoculum, each exhalation and inhalation in theory reinoculates the nasopharynx and tracheobronchial tree (Chen, 2020). We propose that fresh circulating air could reduce reinoculation and potentially lessen the severity of illness and possibly limit household spread during quarantine (Melikov et al., 2020). This calls for open windows, fans for aeration, or spending long periods of time outdoors away from others with no face covering in order to disperse and not reinhale the viral bioaerosol. These are principles used in the hospital with negative pressure ventilation deployed in isolation rooms to reduce bioaerosol contagion.

2. Adjunctive nutraceuticals

There has been considerable interest and study of the use of micronutrients and supplements for COVID-19 prophylaxis and treatment in combination with anti-infectives as first proposed by Zelenko and colleagues (Derwand et al., 2020). In general these agents are not curative but assist in treatment regimens to augment the therapeutic response. The aim of supplementation is to replenish in those with deficiencies associated with COVID-19 mortality, and to aid in reducing viral replication and tissue damage. Zinc deficiency is common among adults (Sharma et al., 2020). Zinc alone is a potent inhibitor of viral replication. Zinc in combination with hydroxychloroquine (HCQ) is potentially synergistic in reducing viral replication since HCQ is a zinc ionophore facilitating intracellular entry and inhibition of intracellular viral replication (Derwand and Scholz, 2020). This readily available nontoxic therapy could be deployed at the first signs of COVID-19 (Rahman

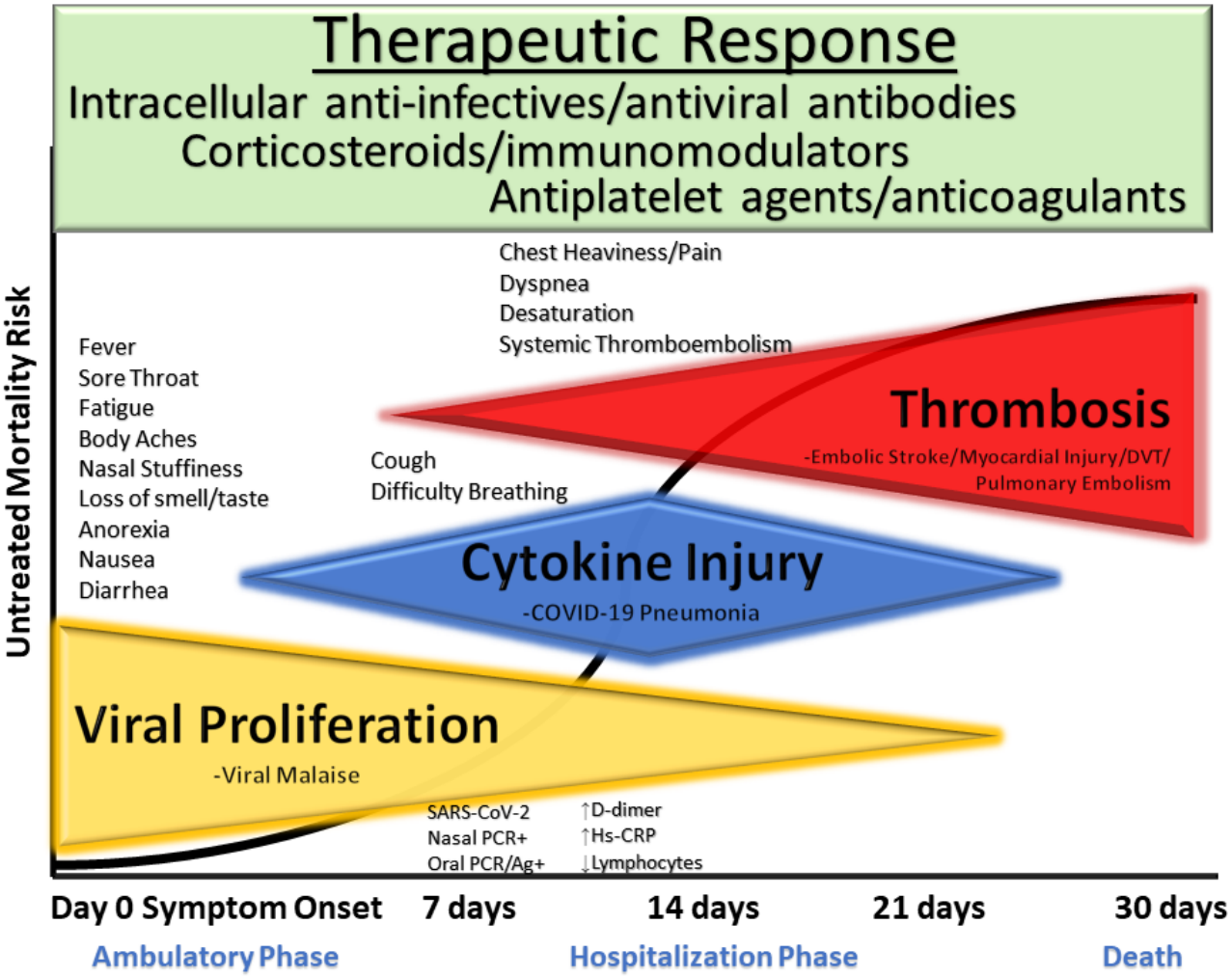

Fig. 2. Major dimensions of COVID-19 infection that call for a multi-drug strategy in the early ambulatory period with available medications including anti-infectives (hydroxychloroquine, ivermectin, azithromycin, doxycycline), corticosteroids, and anti-platelet drugs and anticoagulants. The three dimensions of the infection and their time-course allow for the sequenced multi-drug approach to be utilized with the goal of reducing hospitalization and death.

and Idid, 2020). Zinc sulfate 220 mg (50 mg elemental zinc) can be taken orally per day (Pormohammad et al., 2020).

Vitamin D deficiency has been associated with increased COVID-19 mortality and is commonly confounded by increasing age, obesity, diabetes, darker skin tones, and lack of fitness (Meltzer et al., 2020; Pereira et al., 2020) With good rationale, one small, randomized trial of vitamin D_3 supplementation found reduced mortality in patients with COVID-19 (Entrenas et al., 2020; Zhang et al., 2020a). The suggested dose is 5000 IU of vitamin D_3 per day.

Vitamin C has been used in a variety of viral infections and could be useful in combination with other supplements in COVID-19 (Carr and Rowe, 2020). Multiple randomized trials of vitamin C given intravenously or orally are planned or in progress at the time of this writing (Beigmohammadi et al., 2020; Liu et al., 2020) A reasonable dose would be vitamin C 3000 mg po qd.

Quercetin is a polyphenol that has a theoretical mechanism of action that could reduce the activity of a SARS-CoV-2 entry through the ACE2 receptor, inhibit viral proteases via conveyance of zinc, and attenuate inflammatory responses mediated through interleukin-6 (Bastaminejad and Bakhtiyari, 2020; Cione et al., 2019; Dabbagh-Bazarbachi et al., 2014; Derosa et al., 2020). The mechanisms of action favorably affect viral replication and immune response, so it is conceivable that this agent taken in combination with others discussed could play an assistive role in reducing early viral amplification and tissue damage (Colunga Biancatelli et al., 2020). The suggested dose of quercetin is 500 mg po bid.

3. Anti-infective therapy with intracellular activity

Quickly reducing the rate, quantity, and duration of viral replication, is a goal of antiviral therapy aimed at starting on the first day of symptomatic illness. The compelling rationale for prompt therapy is to minimize the degree of direct viral injury to the respiratory epithelium, vascular endothelium, and organs (Izzedine et al., 2020). Maladaptive host responses dependant on replication of SARS-CoV-2 could be attenuated by early initiation of combination anti-infectives including activation of inflammatory cells, cytokines, endothelial injury, and thrombosis (Singhania et al., 2020). Because SARS-CoV-2 infection is associated with severe disease and increased mortality in patients over age 50 years and those with one or more comorbidities, clinicians should use of at least two commercially available, anti-infective agents where it is

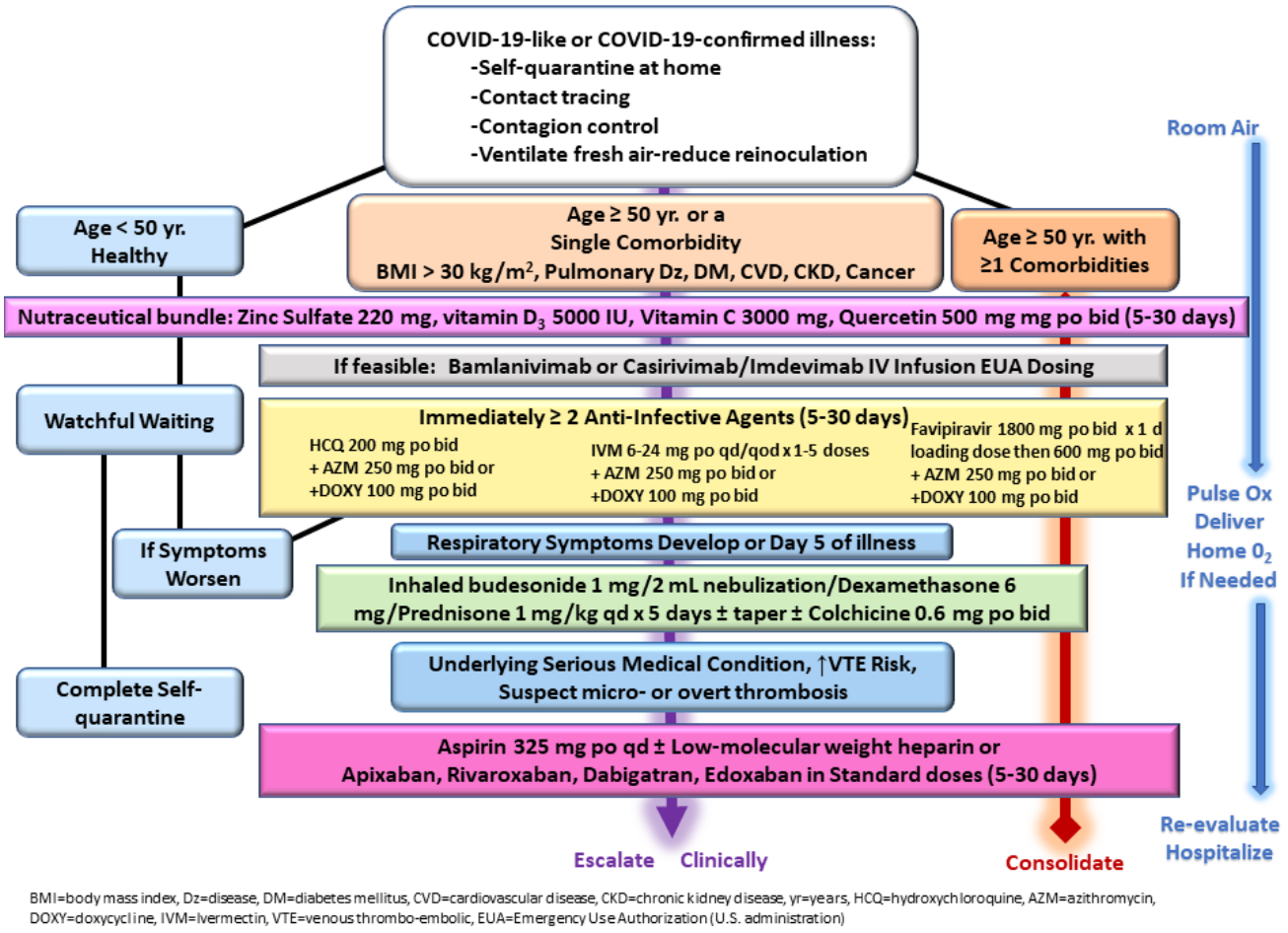

Fig. 3. Sequential multidrug treatment algorithm for ambulatory acute COVID-19 like and confirmed COVID-19 illness in patients in self-quarantine. Yr = year, BMI = body mass index, Dz = disease, DM = diabetes mellitus, CVD = cardiovascular disease, chronic kidney disease, HCQ = hydroxychloroquine, IVM = ivermectin, Mgt = management, Ox = oximetry, reproduced with permission from reference.

appropriately considered clinically indicated, medically necessary "off-label" prescription (Shojaei and Salari, 2020). Conversely, the decision to withhold oral therapy early in a potentially fatal illness should be made in a shared-decision making process with the patient given the full understanding that the natural untreated history of COVID-19 in high risk adults includes the risk of hospitalization, hospital-acquired complications, and death. The physician and patient should understand that the only method by which a hospitalization could be avoided would be the empiric use of SMDT that have a reasonable chance of success with acceptable safety. Recent expanded use authorization of IV administration of bamlanivimab is another option available to a limited number of patients, but supplies will be insufficient to treat everyone who meets the broad criteria for the therapy, so availability of oral alternatives remains essential.

4. Hydroxychloroquine

Hydroxychloroquine (HCQ) is an antimalarial/anti-inflammatory drug that impairs endosomal transfer of virions within human cells. HCQ is also a zinc ionophore that conveys zinc intracellularly to block the SARS-CoV-2 RNA-dependent RNA polymerase which is the core enzyme of the virus replication (te Velthuis et al., 2010). A continuously updated synthesis of HCQ studies supports the following (COVID-19 Treatment, 2020): 1) 63% of studies of HCQ administered late in the hospital course have demonstrated benefit, 2) 100% of the early treatment studies have demonstrated benefit with a composite 64% relative risk reduction in the progression of disease, hospitalization, and death (Arshad et al., 2020; Mikami et al., 2020; Prodromos and Rumschlag, 2020; Rosenberg et al., 2020). The small randomized trials to date are inconclusive for the following reasons: 1) no placebo control, 2) unblinded, 3) altered primary endpoints, 4) biased unblinded physician assigned endpoints (such as need for oxygen), 5) markedly truncated sample sizes and administrative termination of trials, 6) pretreatment with other antivirals.

Hydroxychloroquine was approved by the U.S. Food and Drug Administration in 1955, has been used by hundreds of millions of people worldwide since then, is sold over the counter in many countries and has a well characterized safety profile (Fram et al., 2020; Schrezenmeier and Dörner, 2020). Asymptomatic QT prolongation is well-recognized though an infrequent (< 1%) occurrence with HCQ (Prodromos et al., 2020). In those with glucose-6-phosphate dehydrogenase deficiency HCQ should not be used (Aguilar, 2020). In the setting of acute severe COVID-19 illness, symptomatic arrhythmias can develop in the absence of HCQ and are attributed to cytokine storm and critical illness (Elsaid et al., 2020). Data safety and monitoring boards have not declared safety concerns in HCQ clinical trial published to date. Rare pa-

tients with a personal or family history of prolonged QT syndrome, those on additional QT prolonging, contraindicated drugs (e.g. dofetilide, sotalol), should be treated with caution and a plan to monitor the QTc in the ambulatory setting. A typical HCQ regimen is 200 mg bid for 5 to 30 days depending on continued symptoms.

5. Ivermectin

Ivermectin (IVM) is a broad spectrum anti-parasitic agent that has been shown to have anti-viral activity against a range of viruses including recently, SARS-CoV-2 (Heidary and Gharebaghi, 2020). This drug is well tolerated, has a high therapeutic index and proven safety profile with over 3.7 billion treatments, and has been used alone or combined with either doxycycline or azithromycin in early clinical studies of patients with COVID-19 (Rahman et al., 2020). There are a number of randomized and prospective studies and all have shown efficacy in clinical outcomes at the time of this report (Alam et al., 2020; Chowdhury et al., 2020; Gorial et al., 2020; Khan et al., 2020; Nunez et al., 2020). Hence, it is reasonable in patients where HCQ cannot be used and favipiravir is not available, that IVM (200-600 mcg/kg [6-36 mg] single oral dose given daily or every other day for 2-3 administrations) could be the base of SMDT intended to reduce viral replication early in the course of COVID-19. However, uncertainty remains at this time concerning optimal dosing and schedule (Schmith et al., 2020). In the ICON study, IVM use in the hospital was associated with a 48% relative risk reduction in COVID-19 mortality (Rajter et al., 2020). Currently, there are 36 randomized clinical trials of ivermectin alone or in combination for ambulatory and hospitalized patients listed on clinicaltrials.gov.

6. Favipiravir

Favipiravir is an oral selective inhibitor of RNA-dependent RNA polymerase, and is approved for ambulatory use in COVID-19 in multiple countries (Coomes and Haghbayan, 2020). Favipiravir is safe and it shortens viral nasal shedding to less than 7 days in most studies (Ivashchenko et al., 2020; Pilkington et al., 2020). A dose administration could be 1600-1800 mg po bid on day 1, following by 600-800 mg po bid for 14 days depending on the dose sizes available in 30 different countries (Li et al., 2020). At the time of this writing, there are large ambulatory clinical trials in progress but are not expected to report in time to aid in the crisis at hand in the U.S.

7. Antibiotics with intracellular anti-infective activity

Azithromycin (AZM) is a commonly used macrolide antibiotic that has antiviral properties mainly attributed to reduced endosomal transfer of virions as well as established anti-inflammatory effects (Pani et al., 2020). French reports indicated that AZM in combination with HCQ was associated with reduced durations of viral shedding, fewer hospitalizations, and reduced mortality as compared to those untreated (Lagier et al., 2020; Million et al., 2020). In a large observational inpatient study (n = 2451), those who received AZM alone had an adjusted hazard ratio for mortality of 1.05, 95% CI 0.68-1.62, $P = 0.83$ (Colunga Biancatelli et al., 2020). The combination of HCQ and AZM has been considered a standard of care outside the US for COVID-19 in more than 300,000 older adults with multiple comorbidities (Risch, 2020). AZM like HCQ can prolong the QTc in $< 1\%$ of patients, yet has demonstrated safety in co-administration with HCQ (Huang et al., 2020). A reasonable regimen is 250 mg po bid for 5 to 30 days for persistent symptoms or evidence of bacterial superinfection.

Doxycycline is another common antibiotic with multiple intracellular effects that may reduce viral replication, cellular damage, and expression of inflammatory factors (Malek et al., 2020; Sodhi and Etminan, 2020). It has been shown to have in vitro activity against COVID-19 at clinically used concentrations, acting in post-entry stages of the infection with SARS-CoV-2 in Vero E_6 cells (Gendrot et al., 2020). It has also been shown to concentrate in the lungs at levels twice that of plasma. When combined with ivermectin early in the infection it appears to enhance efficacy to near complete eradication of COVID-19 in less than 10 days. This drug has no effect on cardiac conduction and has the main caveat of gastrointestinal upset and esophagitis. Both AZM and doxycycline has the advantage of offering antibacterial coverage for superimposed bacterial and atypical infection in the upper respiratory tract (Ailani et al., 1999). Doxycycline can be dosed 200 mg po followed by 100 mg po bid for 5 to 30 days for persistent symptoms or evidence of bacterial superinfection.

8. Antibody therapy

Recently, bamlanivimab a monoclonal antibody directed against the SARS-CoV-2 spike protein has been approved for the early ambulatory treatment of COVID-19. In the BLAZE-1 randomized trial, the pooled secondary endpoint of COVID-19 hospitalizations occurred 4/136 and 7/69 of the Bamlanivimab and placebo groups respectively (Chen, 2020). While these results are not considered conclusive nor robust, given the emergency context, bamlanivimab is authorized for COVID-19 patients who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 or hospitalization. The authorized dosage for bamlanivimab is a single IV infusion of 700 mg administered as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. The infusion should occur over an hour with another hour of monitoring for systemic reactions (expected $< 5\%$).

A humanized antibody blend of casirivimab and imdevimab has also received emergency approval in the United States and for a similar population as bamlanivimab. This pair of antibodies binds at different regions of the SARS-CoV-2 spike protein. This antibody combination is dosed 1,200 mg of casirivimab and 1,200 mg of imdevimab together as a single IV infusion over at least 60 minutes with another hour of monitoring for reactions (Regeneron Pharmaceuticals, Inc., 2020). In the phase II program, the secondary endpoint of hospitalization occurred in 8/434 and 10/231 of casirivimab/imdevimab and placebo groups, respectively. These results should be interpreted with caution and cannot be characterized as being conclusive or robust, yet as with all therapies discussed in this paper, casirivimab/imdevimab can be integrated into an innovative sequenced multi-drug regimen for SARS-CoV-2 infection.

If SARS-CoV-2 is diagnosed by rapid testing in a facility that performs antibody infusion such as an emergency room, urgent care center, or clinic, it is reasonable to start COVID-19 with the antibody infusion. Conversely, if it can be safely arranged by home infusion while maintaining quarantine, physicians may prescribe this therapy to augment the effects of longer courses of oral treat-

ment. At this time, it is unattractive to ask a patient to break quarantine and risk spread of infection to drivers and healthcare personnel in order to receive an outpatient infusion.

9. Corticosteroids

The manifestations of COVID-19 that prompt hospitalization and that may well lead to multi-organ system failure are attributed to a cytokine storm. The characteristic profile of an acutely ill COVID-19 patient includes leukocytosis with a relative neutropenia. Among COVID-19 patients, serum IL-6 and IL-10 levels are elevated in the critically ill (Han et al., 2020). In COVID-19, some of the first respiratory findings are cough and difficulty breathing. These features are attributable to inflammation and cytokine activation. Early use of oral corticosteroids is a rational intervention for COVID-19 patients with these features as they would be in other inflammatory lung disorders (Kolilekas et al., 2020; Singh et al., 2020). Inhaled budesonide 1 mg/2 mL via nebulizer or 200 mcg/inhaler up to every four hours can be utilized however, there are no published reports of efficacy in COVID-19. The RECOVERY trial randomized 6425 hospitalized patients with COVID-19 in a 2 : 1 ratio to open label dexamethasone 6 mg po/IV qd for up to 10 days and found dexamethasone reduced mortality, HR = 0.65, 95% CI 0.51-0.82, $P < 0.001$ (Horby et al., 2020) . Concordantly, a meta-analysis involving 1703 critically ill COVID-19 patients found a 36% relative risk reduction in death (Sterne et al., 2020). Safety concerns regarding prolonged viral replication with steroids have not been substantiated (Masiá et al., 2020). A clinical extension of these findings is administration of steroids in COVID-19 patients at home on day five or beyond with moderate or greater pulmonary symptoms (Szente Fonseca et al., 2020). Dexamethasone 6 mg po qd or prednisone 1 mg/kg can be given orally per day for five days with or without a subsequent taper.

10. Colchicine

Colchicine is a non-steroidal anti-mitotic drug used in gout and pericarditis which blocks metaphase of inflammatory cells by binding to the ends of microtubules preventing their intracellular assembly. The GRECCO-19 randomized open-label trial in 105 hospitalized patients with COVID-19 (treated with HCQ and AZM in 98 and 93% respectively) found that colchicine was associated with a reduction in D-dimer levels and improved clinical outcomes (Deftereos et al., 2020). The clinical primary end point (2-point change in World Health Organization ordinal scale) occurred in 14.0% in the control group (7 of 50 patients) and 1.8% in the colchicine group (1 of 55 patients) (odds ratio, 0.11; 95% CI, 0.01-0.96; $P = 0.02$) (World Health Organisation, 2020). Because the short-term safety profile is well understood, it is reasonable to consider this agent along with corticosteroids in an attempt to reduce the effects of cytokine storm and myopericarditis. A dosing scheme of 0.6 mg po bid x 3 days then 0.6 mg po qd for 30 days can be considered.

11. Antiplatelet agents and antithrombotics

Multiple studies have described increased rates of pathological macro and micro-thrombosis (Bösmüller et al., 2020; McFadyen et al., 2020). COVID-19 patients have described chest heaviness associated with desaturation that suggests the possibility of pulmonary thrombosis (Bhandari et al., 2020). Multiple reports have described elevated D-dimer levels in acutely ill COVID-19 patients which has been consistently associated with increased risk of deep venous thrombosis and pulmonary embolism (Artifoni et al., 2020; Chan et al., 2020; Mestre-Gómez et al., 2020). Autopsy studies have described pulmonary micro thrombosis and overt embolism with deep venous thrombus found in over half of fatal COVID-19 cases (Ackermann et al., 2020; Burlacu et al., 2020). These observations support the hypothesis that a unique endothelial injury and thrombosis are playing a role in oxygen desaturation, a cardinal reason for hospitalization and supportive care (Zhang et al., 2020b). Because thromboxane A_2 is markedly upregulated with SARS-CoV-2 infection, early administration of aspirin 325 mg per day is advised for initial antiplatelet and anti-inflammatory effects (Chow et al., 2020; Glatthaar-Saalmüller et al., 2017; A. Gupta et al., 2020a; Turshudzhyan, 2020). Ambulatory patients can also be treated with subcutaneous low-molecular weight heparin or with oral novel anticoagulant drugs (apixaban, rivaroxaban, edoxaban, dabigatran) in dosing schemes similar to those used in outpatient thromboprophylaxis. In a retrospective study of 2773 COVID-19 inpatients, 28% received anticoagulant therapy within 2 days of admission, and despite being used in more severe cases, anticoagulant administration was associated with a reduction in mortality, HR = 0.86 per day of therapy, 95% CI: 0.82-0.89; $P < 0.001$. Contemporary use of in hospital anticoagulants has remained in ~30% of cases (Vahidy et al., 2020) . Pre-emptive use of low molecular weight heparin or novel anticoagulants have been associated with $>$ 50% reduction in COVID-19 mortality (Billett et al., 2020). Anticoagulants also reduce death in COVID-19 hospitalized patients with thrombotic complications, elevated D-dimer levels, and higher comorbidity scores (Tang et al., 2020) . Finally, many acutely ill outpatients also have general indications or risk for cardioembolic/venous thromboembolic prophylaxis applicable to COVID-19 (Moores et al., 2020; Ruocco et al., 2020). There are ambulatory randomized trials of aspirin and novel oral anticoagulants underway. However, given reports of catastrophic stroke and systemic thromboembolism and the large reductions in mortality for both prophylactic and therapeutic use, administration of aspirin 325 mg po qd for all COVID-19 high-risk patients and systemic anticoagulation is prudent in patients with a history of heart, lung, kidney, or malignant disease (Yamakawa et al., 2020).

12. Delivery of oxygen and monitoring

Telemedicine is a tractable means for the initial evaluation and management of COVID-19 allowing the patient to remain in self-quarantine at home. Clinical impressions of the patient can be gained with audio and video feeds. Key supplemental information includes self/family measurement of vital signs and temperature. A significant component of safe outpatient management is maintenance of arterial oxygen saturation on room air or prescribed home oxygen (oxygen concentrators) under direct supervision by daily telemedicine with escalation to hospitalization for assisted ventilation if needed. Self-proning could be entertained for medically sophisticated patients with good at-home monitoring (Westafer et al., 2020) .

The interventions discussed in this review could be extended to seniors in COVID-19 treatment units within nursing homes and other non-hospital settings. In addition to oral medications, these centers could deliver intravenous fluid and parenteral medications (i.e. bamlanivimab, casirivimab/imdevimab), oxygen, and assisted pressure ventilation with the goal of reducing the risk of

hospital transfer.

13. Summary

The SARS-CoV-2 outbreak is a once in a hundred-year pandemic that has not been addressed by rapid establishment of infrastructure amenable to support the conduct of large, randomized trials in outpatients in the community setting. The early flu-like stage of viral replication provides a therapeutic window of tremendous opportunity to potentially reduce the risk of more severe sequelae in high risk patients. Precious time is squandered with a "wait and see" approach in which there is no anti-viral treatment as the condition worsens, possibly resulting in unnecessary hospitalization, morbidity, and death. Once infected, the only means of preventing a hospitalization in a high-risk patient is to apply treatment before arrival of symptoms that prompt paramedic calls or emergency room visits. Given the current failure of government support for randomized clinical trials evaluating widely available, generic, inexpensive therapeutics, and the lack of instructive outpatient treatment guidelines (U.S., Canada, U.K., Western EU, Australia, some South American Countries), clinicians must act according to clinical judgement and in shared decision making with fully informed patients. Early SMDT developed empirically based upon pathophysiology and evidence from randomized data and the treated natural history of COVID-19 has demonstrated safety and efficacy. In newly diagnosed, high-risk, symptomatic patients with COVID-19, SMDT has a reasonable chance of therapeutic gain with an acceptable benefit-to-risk profile. Until the pandemic closes with population-level herd immunity potentially augmented with vaccination, early ambulatory SMDT should be a standard practice in high risk and severely symptomatic acute COVID-19 patients beginning at the onset of illness.

Footnote: To understand which drugs are being used in the early treatment of COVID-19 in these countries' websites of government agencies such as Brazil, Peru, Spain, Taiwan, and USA were searched. We also looked for researchers published in PUBMED by China, France, India, Korea, and African countries. Additional Information was also obtained from reliable sources of internet such as Argentina, Bangladesh, Colombia, Mexico and African Countries.

Author contributions

PAM wrote the first draft and created the figures, all authors provided critical edits and comments, PEA did the final proofreading and key finalization of the text. SR created the first draft of the table.

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Conflict of Interest

There is nothing to disclose. Author had access to the data and wrote the manuscript.

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One Page Summary of the Clinical Trials Evidence for Ivermectin in COVID-19

Ivermectin, an anti-parasitic medicine whose discovery won the Nobel Prize in 2015, has proven, highly potent, anti-viral and anti-inflammatory properties in laboratory studies. In the past 4 months, numerous, controlled clinical trials from multiple centers and countries worldwide are reporting consistent, large improvements in COVID-19 patient outcomes when treated with ivermectin. Our comprehensive scientific review of these referenced trials can be found on the Open Science Foundation pre-print server here: https://osf.io/wx3zn/.

Properties of Ivermectin

1) Ivermectin inhibits the replication of many viruses, including SARS-CoV-2, influenza, and others;
2) Ivermectin has potent anti-inflammatory properties with multiple mechanisms of inhibition;
3) Ivermectin diminishes viral load and protects against organ damage in animal models;
4) Ivermectin prevents transmission of COVID-19 when taken either pre- or post-exposure;
5) Ivermectin hastens recovery and decreases hospitalization and mortality in patients with COVID-19;
6) Ivermectin leads to far lower case-fatality rates in regions with widespread use.

Evidence Base Supporting the Efficacy of Ivermectin in COVID-19

as of January 11, 2021

(RCT's = randomized controlled trials, OCT's = observational controlled trials). Every clinical trial shows a benefit, with RCT's and OCT's reporting the same direction and magnitude; nearly all are statistically significant.

Controlled trials studying the prevention of COVID-19 (8 trials completed)

- 3 RCT's with large statistically significant reductions in transmission rates, a total of 774 patients
- 5 OCT's with large statistically significant reductions in transmission rates, a total of 2,052 patients

Controlled trials in the treatment of both early and hospitalized COVID-19 patients (19 trials completed)

- 5 RCT's with large, significant reductions in time to recovery or hospital length of stay, a total of 774 patients
- 1 RCT with a large, statistically significant reduction in rate of deterioration/hospitalization, total of 363 patients
- 2 RCT's with significant decreases in viral load, days of anosmia, cough, or time to recovery, a total of 85 patients
- 3 RCT's with large, significant reductions in mortality, a total of 695 patients
- 3 OCT's with large, statistically significant reductions in mortality, a total of 1,688 patients

Number of Studies and Patients Among the Existing Clinical Trials of Ivermectin in COVID-19

- 27 controlled trials, including a total of 6,612 patients have been completed using well-matched control groups
- 16 trials, including over 2,500 patients, are prospective, randomized, controlled studies
- 11 of the 27 trials have been published in peer-reviewed journals, 3,900 patients, remainder are in pre-print

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Even restricting analysis to just the 16 randomized controlled trials (totaling over 2,500 patients), the majority report a statistically significant reduction in transmission or disease progression or mortality. Further, a meta-analysis recently performed by an independent research consortium calculated the chances that ivermectin is ineffective in COVID-19 to be 1 in 67 million.[1]

The FLCCC Alliance, based on the totality of the existing evidence, supports an A-I recommendation (NIH rating scheme; strong level, high quality evidence) for the use of ivermectin in both the prophylaxis and treatment of all phases of COVID-19.

Furthermore, we encourage all regulatory agencies to review our manuscript detailing these studies above as well as the multiple population-wide "natural experiments" that occurred in numerous cities and regions after the initiation of ivermectin distribution programs.[2] The widespread use of ivermectin resulted in a significant reduction in cases and mortality rates that approached pre-pandemic levels in these areas. As evidenced by what occurred in these regions, ivermectin is clearly an essential and vital treatment component in achieving control of the pandemic.

[1] **ivmmeta.com**

[2] Kory P, Meduri GU, Iglesias J, Varon J et al. Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. *Open Science Foundation.* https://osf.io/wx3zn/

Table 2e. Characteristics of Antiviral Agents That Are Approved or Under Evaluation for the Treatment of COVID-19

Last Updated: July 8, 2021

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**Monitoring Parameters**	**Drug-Drug Interaction Potential**	**Comments and Links to Clinical Trials**
Remdesivir				
The doses and indications listed below come from the FDA product information. Please see Therapeutic Management of Hospitalized Adults With COVID-19 for the Panel's recommendations on when to use RDV. **For Hospitalized Adults and Children (Aged ≥12 Years and Weighing ≥40 kg)** *For Patients Who Are Not Mechanically Ventilated and/or on ECMO:* • RDV 200 mg IV[a] on Day 1, then RDV 100 mg IV on Days 2–5 • For patients who do not show clinical improvement after 5 days of therapy, treatment may be extended to up to 10 days. *For Mechanically Ventilated Patients and/or Patients on ECMO:* • RDV 200 mg IV[a] on Day 1, then RDV 100 mg IV on Days 2–10 **Suggested Dose in EUA[b] for Hospitalized Children** *For Patients Weighing 3.5 kg to <40 kg:* • RDV 5 mg/kg IV[a] on Day 1, then RDV 2.5 mg/kg IV once daily starting on Day 2 • For patients who are not mechanically ventilated and/or on ECMO, the duration is 5 days. If patients have not shown clinical improvement after 5 days, treatment may be extended to up to 10 days. • For mechanically ventilated patients and/or patients on ECMO, the recommended treatment duration is 10 days. *For Patients Aged <12 Years and Weighing ≥40 kg:* • Same dose as for adults	• Nausea • ALT and AST elevations • Hypersensitivity • Increases in prothrombin time • Drug vehicle is SBECD, which has been associated with renal and liver toxicity. SBECD accumulation may occur in patients with moderate or severe renal impairment. • Each 100 mg vial of RDV lyophilized powder contains 3 g of SBECD, and each 100 mg/20 mL vial of RDV solution contains 6 g of SBECD. • Clinicians may consider preferentially using the lyophilized powder formulation (which contains less SBECD) in patients with renal impairment.	• Infusion reactions • Renal function and hepatic function should be monitored before and during treatment as clinically indicated. • In the FDA product information, RDV **is not recommended** when eGFR is <30 mL/min. See the Remdesivir section for a discussion on using RDV in people with renal insufficiency. • RDV may need to be discontinued if ALT level increases to >10 times ULN and should be discontinued if there is an increase in ALT level and signs or symptoms of liver inflammation are observed.[1]	• Clinical drug-drug interaction studies of RDV have not been conducted. • In vitro, RDV is a substrate of CYP3A4, OATP1B1, and P-gp and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.[1] • Minimal to no reduction in RDV exposure is expected when RDV is coadministered with dexamethasone (Gilead Sciences, written communication, July 2020). • CQ or HCQ may decrease the antiviral activity of RDV; coadministration of these drugs **is not recommended**.[1] • No significant interaction is expected between RDV and oseltamivir or baloxavir (Gilead Sciences, personal and written communications, August and September 2020).	• RDV should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital. • RDV is approved by the FDA for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). • An EUA[b] is available for hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg. • A list of clinical trials is available here: Remdesivir
Ivermectin				

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Adults: • The dose most commonly used in clinical trials is IVM 0.2–0.6 mg/kg PO given as a single dose or as a once-daily dose for up to 5 days.	• Generally well tolerated • Dizziness • Pruritis • GI effects (e.g., nausea, diarrhea) • Neurological AEs have been reported when IVM has been used to treat parasitic diseases, but it is not clear whether these AEs were caused by IVM or the underlying conditions.	• Monitor for potential AEs.	• Minor CYP3A4 substrate • P-gp substrate	• Generally given on an empty stomach with water; however, administering IVM with food increases its bioavailability.[2] • A list of clinical trials is available here: Ivermectin
Nitazoxanide				
Adults: • Doses reported in COVID-19 studies range from NTZ 500 mg PO 3 times daily to 4 times daily.[3,4] Higher doses are being studied (*ClinicalTrials.gov* Identifier NCT04746183). • Doses used for antiprotozoal indications range from NTZ 500 mg to 1 g PO twice daily.	• Generally well tolerated • Abdominal pain • Diarrhea • Headache • Nausea • Vomiting • Urine discoloration • Ocular discoloration (rare)	• Monitor for potential AEs.	• Drug-drug interactions may occur if NTZ is administered concurrently with other highly plasma protein-bound drugs due to competition for binding sites.[5] • If NTZ is coadministered with other highly protein-bound drugs with narrow therapeutic indices, monitor the patient for AEs.	• NTZ should be taken with food. • The oral suspension is not bioequivalent to the tablet formulation. • A list of clinical trials is available here: Nitazoxanide

[a] Infuse over 30–120 minutes.

[b] The FDA EUA permits the emergency use of RDV for the treatment of suspected COVID-19 or laboratory-confirmed SARS-CoV-2 infection in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg.[6]

Key: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; CQ = chloroquine; CYP = cytochrome P450; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; GI = gastrointestinal; HCQ = hydroxychloroquine; IV = intravenous; IVM = ivermectin; LPV/RTV = lopinavir/ritonavir; MATE = multidrug and toxin extrusion protein; NTZ = nitazoxanide; OATP = organic anion transporter polypeptide; the Panel = the COVID-19 Treatment Guidelines Panel; P-gp = P-glycoprotein; PO = orally; RDV = remdesivir; SBECD = sulfobutylether-beta-cyclodextrin; ULN = upper limit of normal

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Epidemiology of Acute Myocarditis/Pericarditis in Hong Kong Adolescents Following Comirnaty Vaccination

https://pubmed.ncbi.nlm.nih.gov/34849657/

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Abstract

Background: Age-specific incidence of acute myocarditis/pericarditis in adolescents following Comirnaty vaccination in Asia is lacking. This study aimed to study the clinical characteristics and incidence of acute myocarditis/pericarditis among Hong Kong adolescents following Comirnaty vaccination.

Methods: This is a population cohort study in Hong Kong that monitored adverse events following immunization through a pharmacovigilance system for COVID-19 vaccines. All adolescents aged between 12 and 17 years following Comirnaty vaccination were monitored under the COVID-19 vaccine Adverse Event Response and Evaluation Programme. The clinical characteristics and overall incidence of acute myocarditis/pericarditis in adolescents following Comirnaty vaccination were analysed.

Results: Between 14 June 2021 and 4 September 2021, 33 Chinese adolescents who developed acute myocarditis/pericarditis following Comirnaty vaccination were identified. 29 (87.88%) were males and 4 (12.12%) were females, with a median age of 15.25 years. 27 (81.82%) and 6 (18.18%) cases developed acute myocarditis/pericarditis after receiving the second and first dose, respectively. All cases are mild and required only conservative management.The overall incidence of acute myocarditis/pericarditis was 18.52 (95% Confidence Interval [CI], 11.67-29.01) per 100,000 persons vaccinated. The incidence after the first and second doses were 3.37 (95%CI 1.12-9.51) and 21.22 (95%CI 13.78-32.28 per 100,000 persons vaccinated, respectively. Among male adolescents, the incidence after the first and second doses were 5.57 (95% CI 2.38-12.53) and 37.32 (95% CI 26.98-51.25) per 100,000 persons vaccinated.

Conclusions: There is a significant increase in the risk of acute myocarditis/pericarditis following Comirnaty vaccination among Chinese male adolescents, especially after the second dose.

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