Ivermectin Use for COVID-19 Literature Review - COVID-19 Clinical Advisory Group Update
February 2021

Ivermectin is an antiparasitic drug that is approved by the Food and Drug Administration (FDA) for the treatment of onchocerciasis and strongyloidiasis. Ivermectin is not FDA-approved for the treatment of any viral infection. In general, the drug is well tolerated. It is currently being evaluated as a potential treatment for COVID-19.

Clinical Data
The results of several randomized trials and retrospective cohort studies of ivermectin use in patients with COVID-19 have been published in peer-reviewed journals or made available as preliminary, non-peer-reviewed reports. There are no well-designed controlled trials that have been published to date. However, pilot studies, or retrospective chart review of patients treated with ivermectin show a trend to benefit viral load reduction or overall decrease in mortality. The evidence table summarizes studies that have reported shorter time to resolution of disease manifestations attributed to COVID-19, greater reduction in inflammatory markers, shorter time to viral clearance, or lower mortality rates in patients who received ivermectin than in patients who received usual care or placebo.

Ivermectin was widely distributed among 8 states in Peru. Peru has reported a dramatic decrease in case fatality rates, especially among patients over 60 years old. These data, despite studied as part of controlled trial, resulted in the Peruvian government approving ivermectin use by decree on in May 2020. As a result of this, in vitro data and small reports, ivermectin use has created much interest and controversy in the scientific community.

Key points:
- No individual trial published to date is large enough to draw conclusions to incorporate into standard practice.
- Combined data from the controlled trials shows consistent benefit, however possible study bias and variances in standard of care therapies should be considered.
## NATIONAL GUIDANCE RECOMMENDATIONS SUMMARY:

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<th>GROUP (Last Updated)</th>
<th>RECOMMENDATION</th>
<th>RATIONALE/KEY POINTS</th>
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<td>ASHP (12/17/2020)</td>
<td>• If ivermectin therapy is considered, the patient/prescriber are encouraged to seek one of various clinical trials evaluating ivermectin for the treatment or prevention of COVID-19 are registered at clinicaltrials.gov</td>
<td>• No published data to date from randomized, controlled trials support the use in the treatment or prevention of COVID-19.</td>
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<td>IDSA (4/5/2021)</td>
<td>• The panel suggests against ivermectin in both inpatients and outpatients, unless in the context of enrollment in clinical trials.</td>
<td>• The panel determined the certainty of evidence to be low and a risk for bias ad imprecision within published studies.</td>
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<td>NIH (1/14/2021)</td>
<td>• The COVID-19 Treatment Guidelines Panel (the Panel) has determined that currently there are insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin for the treatment of COVID-19.</td>
<td>• The sample size of most of the trials was small. • Various doses and schedules of ivermectin were used. • Some of the randomized controlled trials were open-label studies in which neither the participants nor the investigators were blinded to the treatment arms. • In addition to ivermectin or the comparator drug, patients also received various concomitant medications (e.g., doxycycline, hydroxychloroquine, azithromycin, zinc, corticosteroids), confounding assessment of the true efficacy or safety of ivermectin. • The severity of COVID-19 in the study participants was not always well described. • The study outcome measures were not always clearly defined.</td>
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EVIDENCE

There are additional studies that have been conducted that are not included below – either because of design, or not published in full. The following studies are either most recent, most quoted or designed well enough to include.

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<tr>
<th>AUTHORS/Country</th>
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<td>Ahmed S, et al. ¹ 2020 in Dhaka, Bangladesh</td>
<td>RCT, DB, Goal: to evaluate the rapidity of viral clearance and safety of a 5-day course of • ivermectin 12 mg PO daily x 5 days (n=24), vs. • single dose of ivermectin 12 mg + 5-day course of doxycycline 200mg day 1, 100 mg days 2-5. (n=24). • Placebo (n=24) 72 hospitalized patients were evaluated.</td>
<td>Virological clearance occurred earliest in the ivermectin x 5 days group (9.7 days) compared to Placebo (12.7 days) ( p=0.02 ). The ivermectin + doxy arm virological clearance was not statistically improved over placebo group ( p=0.27 ). In all 3 groups Blood biomarkers dropped by day 7, but was statistically significant in the 5-day ivermectin group for CRP and LDH: CRP ( (p=0.02) ), LDH ( (p = 0.01) ) Procalcitonin ferritin No severe adverse events noted</td>
<td>The results provide potential benefit of early intervention with ivermectin in adult patients with early COVID-19. Presumably, the faster viral clearance at disease onset may prevent significant immune system involvement and hasten recovery. Additionally, clearance of viral load may block further transmission. One single dose of ivermectin (plus doxycycline) did not have a statistically significant benefit over the placebo treated group. Authors recommend larger randomized trial. It should be noted that all patients received 12 mg. Weight variability among the subjects was not provided.</td>
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<td>Kory P, et al. 2021</td>
<td>Protocol of individual drugs/dose criteria based on severity of disease, O2 requirements, ICU, etc. MATH: methylprednisolone + ascorbic acid + thiamine + heparin+ • vit D3 5000 IU/day • atorvastatin • melatonin • zinc • famotidine • therapeutic plasma exchange GOAL: to study the efficacy of the MATH+ protocol with “supportive care only”, AND against other novel proposed treatment approaches Formation of patient registry</td>
<td>Authors summarize their protocol of MATH+ and the evidence supporting the efficacy of ivermectin in the prophylaxis and treatment. Most of data are from pilot or case series. Reports show patients who received early (usually single doses) of 0.4 mg/kg</td>
<td>MATH+ protocol not studied. So many variables, it is unclear how ivermectin adds to the other unproven but theoretical therapies.</td>
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<td>Chaccour C, et al 2021 Spain</td>
<td>RCT, DB, single center, parallel arm Goal: to evaluate the efficacy of a single ivermectin dose in reducing transmission of SARS-CoV-2 when administered early. A reduction of at least 50% in proportion of positives desired. Inclusion: • Patients were not high risk • Non-severe COVID • Onset of symptoms ≤ 72 hours Exclusion: • High risk co-morbidities • COVID pneumonia • Antibody positive 1:1 randomization: • Ivermectin 400 mcg/kg x1 (n=12)</td>
<td>• Initially, there was no difference in proportion of PCR positives between the groups for genes E and N in the same order of magnitude. • The median viral load for both genes was lower at days 4 and 7 post in the ivermectin group 3-fold lower at day 4 to around 18-fold lower at day 7, p &gt; 0.05. • There was a marked reduction in anosmia/hyposmia, reduction in cough • A trend to lower viral loads, lower IgG</td>
<td>A larger trial is warranted to evaluate the positive trend in symptom improvement in the treatment group compared to placebo. There is a need to evaluation ivermectin treatment with disease severity, inflammation and antibody titers. The results raise questions about the possible mechanism of ivermectin in COVID-19. Ivermectin may downregulate the expression of pro-inflammatory genes; it may have an effect on the nicotinic receptor; the mechanism may be immunomodulatory. Dose given was 2x general recommended dose but only administered as one-time single dose.</td>
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<td>Rajter J C., et al. 2021 FL, USA</td>
<td>Retrospective chart review of consecutive patients hospitalized at 4 health system hospitals. Hospital treatment guidelines were available but prescribing was at the discretion of the prescribing physician. Total charts = 280 173 tx’d ivermectin Received at least one dose of 200 mcg/kg, orally. A second dose could be prescribed at day 7, at the physician’s discretion. 107 did not receive ivermectin (usual care) <strong>Primary Endpoint</strong> All cause in-hospital mortality <strong>Secondary Endpoints</strong> - Mortality with pulmonary involvement - Extubation rates - LOS Inclusion Laboratory confirmed SARS-CoV-2 Enrollment March 15-May 11, 2020 Adult patients only Usual treatment care may have included: hydroxychloroquine treatment</td>
<td>Mortality rates: Overall the ivermectin gp had significantly lower mortality the usual care gp (15% vs 25.2%, p=0.03). Ivermectin-tx’d with severe pulmonary involvement Mortality 38.8% vs 80.7%, respectively. P = 0.001). In a matched cohort, the absolute risk reduction from ivermectin was 11.2% (95% CI, 0.38%-22.1%). The number need to treat was 8.9 to prevent one death. No difference found in extubation rates.</td>
<td>Ivermectin was associated with lower mortality as part of treatment of COVID-19 patients, especially in patients who required higher inspired O2 or ventilator support. Study not powered to detect difference in mortality from hydroxychloroquine treatment. Authors note that there may have been preferential treatment of more severe patients with ivermectin There may have been a treatment timing bias. Appropriate dosing of ivermectin for this indication is not known</td>
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| Hashim et al. 2020 Iraq | Corticosteroids Azithromycin Severity of pulmonary involvement assessed (severe vs non-severe). Severe pulmonary involvement defined as $\text{FiO}_2 \geq 50\%$, high flow nasal $\text{O}_2$, noninvasive ventilation, or mechanical ventilation. | Progression: 
4.28\% of all and 9\% (severe) progressed to more severe disease in the ivermectin group vs 10\% (all) and 31.8\% (severe) in the control group ($p>0.05$). In subanalysis, progression was lowered if ivermectin given within the first two days of severe stage. 
Mortality: Was 0\% in mild-moderate and 18\% in severe Covid for the ivermectin group vs 0\% and 27.3\%, respectively ($p=0.052$) 
Mean time to recovery: 
For the ivermectin group it was 6.34, 20.27 and 24.13 for the mild-moderate, severe, and critical patients respectively versus 13.7 and 24.25 in the mild-moderate and severe patients treated with stand care, respectively ($p < 0.01$). | Ivermectin with doxycycline significantly reduced the time to recovery. The combination also decreased progression to more severe disease. Mortality was also reduced but bordering significance. |

| | RCT COVID-19 pts (n=70) ARM 1 Ivermectin 200 mcg/kg/d x 2-3 days plus doxycycline 100 mg BID x 5-10 days Mild/moderate (n=48) Severe disease (n=11) Critical patients (n=11) ARM 2: Usual Care (MATH + regimen above) Mild/moderate (n=48) Severe disease (n=22) Critical patients (n=0) Endpoints: 
• Time to recover 
• Progression of disease 
• Mortality | | |

Abbreviations: DB=double blind; H/A=headache; LOS=length of stay; RCT=randomized controlled trial; tx’d=treated;
KEY POINTS TO CONSIDER

Ivermectin (Stromectol®)
- Available as a 3-mg oral tablet.
- Tablets should be taken on an empty stomach with water.

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<th>PARASITIC INFECTIONS</th>
<th>COVID-19</th>
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<td><strong>USUAL ADULT DOSE</strong></td>
<td>150-200 mcg/kg</td>
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**COMMON ADVERSE EVENTS**
*From Package Insert of listed side effects occurring ≥ 3%
- Skin rash or itching
- Lymph node enlargement/tenderness
- Dizziness
- Diarrhea
- Joint or muscle pain
- Lightheadedness
- Peripheral edema
- Tachycardia

**PRECAUTION**
- May make bronchial asthma worse
- Elevation of liver enzymes and bilirubin

**COST**
- 12 mg x 1 = $13.40 (GPO)
- 12 mg x 1 dose = $13.40 (GPO); Repeat in 7 days = $27
- 12 mg x 5 days = $66.65 (GPO)

**EFFICACY**
- Intestinal strongyloidiasis
- Onchocerciasis
- Pilot study in mild Covid-19 may decrease viral load; may hasten improvement of anosmia/hyposmia and cough
  For more severe patients, may decrease overall mortality
Select References: