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MEDICAL INSIGHTS

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CLINICAL EVIDENCE FOR VARIOUS ANTI-COVID THERAPIES

The Complete Healthcare Experience for Women and Children

Message From The Editor

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Dear friends,

These days, there are several drugs available to treat COVID infection. This can be confusing not only to the patients but also to the prescribing doctors. Moreover, the scientific evidence for various drugs keeps changing every day. Medicines which were thought to be wonder drugs few months ago may not be so today. The aim of the current article is to help physicians and patients understand the benefits and limitations of various available therapies. The important clinical trials for the various drugs are mentioned for the benefit of doctors interested in doing further research. For the benefit of busy practitioners, the summary of current clinical evidence is highlighted. It must be remembered that supportive therapy like IV fluids, oxygen, ventilatory support etc. are as important as specific drugs in the management of COVID patients.

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CLINICAL EVIDENCE FOR VARIOUS ANTI-COVID THERAPIES

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Classification of drugs

The various therapies used in COVID-19 can be broadly classified into those with antiviral properties, immuno-modulatory effects, and others. The symptoms in the initial stages of the disease are due to the effects of the virus and in the later stages due to the host immune response. Hence, antivirals are more effective in the initial stages where as immunomodulators are more effective in the later stages.

Antiviral drugs

Drugs with postulated antiviral properties include Remdesivir, Monoclonal antibodies, Convalescent plasma, Favipiravir, Chloroquine/ Hydroxychloroquine, Interferon, Ivermectin, etc.

Immunomodulators

These include steroids (Dexamethasone, Methyl Prednisolone, Hydrocortisone), Inhaled Budesonide, Tocilizumab, Anakinra, Baricitinib, Colchicine, Azithromycin, Doxycycline etc.
These drugs may have a role in the later stages of the disease when the inflammatory reaction sets in. However, these drugs can cause potential side effects if used early, in exceedingly high doses, for prolonged period and without supervision of a doctor.

Others

These include drugs like Anticoagulants, Aspirin, Vitamin C and D, Zinc etc.

Effectiveness of drugs

The effectiveness of a drug is usually measured in terms of the impact on the following aspects of patient care:

- Mortality (death rate)
- Need for mechanical ventilation (invasive and non-invasive)
- Duration of hospital stay

Apart from the effectiveness, the drugs should also be free from serious side effects.

Based on the current evidence (May 2021), drugs can be grouped as follows:

Drugs with definitely proven evidence

Steroids (oral or IV)

Drugs with some/mixed evidence

Remdesivir, Tocilizumab, Inhaled steroids, Baricitinib, Low molecular weight Heparin, Plasma therapy

Drugs with no proven evidence

Antibiotics, Azithromycin, Doxycycline, Favipiravir, Hydroxychloroquine/Chloroquine, Ivermectin, Vitamins and Minerals

The clinical evidence for the various drugs in adult patients with summary of important clinical trials is mentioned in the table below:

Drug	Summary of evidence
Anticoagulants	Early initiation of prophylactic anticoagulation among patients admitted to hospital with COVID-19 was associated with a decreased risk of 30-day mortality and no increased risk of serious bleeding events (Rentsch et al. 11 February 2021). *Summary: Several experts including WHO and CDC agree that hospitalized adults with COVID-19 should receive prophylactic dose of anticoagulation to reduce the risk of thromboembolism, unless there are contraindications.*
Azithromycin	Published findings from the PRINCIPLE trial do not justify the routine use of Azithromycin for reducing recovery time or risk of hospitalization for COVID patients in the community (PRINCIPLE Trial Collaborative Group, 4 March 2021). *Summary: There is no evidence for the use of Azithromycin in treatment of COVID infection in the hospital or community.*
Baricitinib	Results of a randomized control trial (ACTT-2) shows that Baricitinib plus Remdesivir was superior to Remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with COVID-19, notably among those receiving high-flow oxygen or non-invasive ventilation (ACTT-2 trial, 11 December 2020). *Summary: Baricitinib may be considered in combination with Remdesivir in patients where a combination of Remdesivir and corticosteroids cannot be used.*
Chloroquine/ Hydroxy chloroquine	Among patients hospitalized with COVID-19, there was no evidence for reduced mortality in patients using Hydroxychloroquine (The RECOVERY collaborative group, 8 October 2020). A randomized controlled trial among persons with recent exposure to COVID showed no benefit when Hydroxychloroquine was taken for postexposure prophylaxis to prevent COVID infection (Barnabas et al, 8 December 2020). *Summary: Chloroquine/Hydroxychloroquine has no benefit in prevention or treatment of COVID infection. WHO has issued a guideline against the use of Chloroquine/Hydroxychloroquine in management of COVID-19 infection.*

Colchicine	The RECOVERY trial found no convincing evidence of the effect of Colchicine on clinical outcomes in patients admitted to hospital with COVID-19 (RECOVERY trial, March 2021). In a randomized trial (COLCORONA), Colchicine did not result in a statistically significant reduction in the death or hospitalization. *Summary: There is insufficient evidence for Colchicine in treatment of COVID-19 infection.*
Doxycycline	Interim analyses of data from the PRINCIPLE trial concluded that there was no beneficial effect in patients treated with Doxycycline at home in the early stages of COVID-19. The researchers also found that the treatment did not reduce the time taken for improvement of symptoms (PRICIPLE trial, January 25, 2021). *Summary: There is no clinical evidence for use of Doxycycline on its own or combined with other drugs in treating COVID infection.*
Favipiravir	In a meta-analysis of 13 studies (Prakash et al; PMID 33283773) assessing the efficacy and safety of Favipiravir in the treatment of COVID-19, there was no benefit with regards to viral clearance, requirement for oxygen or non-invasive ventilation. *Summary: Efficacy and safety of Favipiravir for treatment of COVID-19 not established. It can cause liver toxicity, hyperuricemia, and risk of teratogenicity.*
Interferon	Interim results from the Solidarity trial suggest that IFN beta-1a has little or no effect on mortality in patients who are hospitalized with COVID-19 (Solidarity trial, 5 October 2020). *Summary: Efficacy and safety of Interferon for treatment or prevention of COVID-19 are not established.*
Ivermectin	Findings from a randomized controlled trial of 476 patients do not support the use of Ivermectin for treatment of mild COVID-19 (López-Medina et al. 4 March 2021). The manufacturer (Merck) states that, to date, there is no scientific basis for a potential therapeutic effect of Ivermectin against COVID-19.

	The plasma concentrations attained with antiparasitic dosages of Ivermectin are substantially lower than concentrations associated with in vitro inhibition of SARS-CoV-2. *Summary: Ivermectin has no clinical benefit for prevention or treatment of COVID infection. WHO warns against the use of Ivermectin for COVID-19 infection.*
Monoclonal Antibodies (Casirivimab/ Imdevimab)	Results from a phase-III trial of recently infected asymptomatic COVID-19 patients found that REGEN-COV (a combination of two antibodies Casirivimab with Imdevimab) decreased the overall risk of patients progressing to symptomatic COVID-19, decreased the duration of symptoms and significantly reduced viral levels (Regeneron/NIAID trial, 12 April 2021). *Summary: Monoclonal antibodies to COVID like Bamlanivimab/Etesevimab and Casirivimab/Imdevimab may have some role in the outpatient management patients who are at high risk of severe disease. They have to be given early (within 7 days of symptoms) and in mild infection. They are not indicated in hypoxic or hospitalized patients.*
Plasma (convalescent)	The RECOVERY trial, the largest clinical trial of convalescent plasma did not find evidence that high-titre convalescent plasma improved survival or other clinical outcomes in patients hospitalized with COVID-19 (15th January 2021). Convalescent plasma has no benefit for patients with COVID-19 who are severely ill and in intensive care, according to early findings from the REMAP-CAP trial (12 January 2021). No difference in 28-day mortality or progression to severe disease among patients with moderate COVID-19 treated with convalescent plasma (ICMR-PLACID study 22 October 2020). *Summary: The evidence for plasma is controversial in COVID. Many studies suggest no benefit. Few initial studies suggest some benefit when given early. No benefit seen when given late or in severe disease.* *The ICMR has recently removed the use of convalescent plasma therapy from its treatment protocol for adult Covid-19 patients.*

Remdesivir	Interim results from the Solidarity trial suggest that Remdesivir has little or no effect on mortality in patients who are hospitalized with COVID-19 (2 December 2020). One RCT showed that Remdesivir was superior to placebo in shortening the time to recovery by 30% in adults hospitalised with COVID-19 pneumonia (ACTT-1 trial, October 2020). "No statistically significant differences" for mortality and serious adverse events in COVID-19 patients treated with Remdesivir (National Institute for health and Care Excellence [NICE]. *Summary: WHO recommends against the use of Remdesivir in COVID infection. ICMR recommends use in early stages (< 10 days of symptom onset) of the disease in hospitalized patients who are hypoxic. In patients requiring oxygen or ventilation, Remdesivir should be used in combination with corticosteroids. Where steroids cannot be given, Remdesivir can be used in combination with Baricitinib. Remdesivir is not indicated in patients managed at home and not requiring oxygen/ventilatory support. It may not be helpful when given late in the illness.*
Steroids (parenteral)	The Recovery trial showed that in patients hospitalized with COVID-19, the use of Dexamethasone resulted in lower 28-day mortality among those who received invasive mechanical ventilation or oxygen. There was no benefit among those who did not receive any respiratory support (RECOVERY Collaborative Group, 25 February 2021). As per the REMAP-CAP trial, patients with severe COVID-19 who are treated intravenously with the steroid, Hydrocortisone, are more likely to have a better outcome compared to patients who are not given the drug. However, the trial was stopped early (Angus et al, 2 September 2020). The WHO Guideline Development Group strongly recommends the use of systemic corticosteroids (e.g., Dexamethasone 6 mg oral/IV daily or Hydrocortisone 50 mg IV every 8 hours for 7-10 days) for the treatment of patients with severe and/or critical COVID-19. *Summary: There is definite clinical evidence for parenteral steroids in reducing mortality and duration of ventilation in patients receiving oxygen or mechanical ventilation. Corticosteroids should not be used early in the disease as the drugs can inhibit the immune response to the infection. They are not indicated in asymptomatic/mild cases. When given in high doses or prolonged periods, they can cause hyperglycemia and risk of infections including mucomycosis.*

Steroids (inhaled)	Interim findings from the PRINCIPLE trial suggest that Budesonide shortens recovery time in non-hospitalized patients with COVID-19 by a median of three days (PRINCIPLE trial, 12 April 2021). A Phase-II randomised controlled trial suggests that early administration of inhaled Budesonide reduces the likelihood of needing urgent medical care and reduces recovery time (STOIC trial, April 2021). *Summary: There is some evidence that inhaled Budesonide when given early (within 7 days of symptoms) in non-hospitalized patients with mild COVID can shorten the recovery time and need for hospitalization.*
Tocilizumab	In a randomized trial involving hospitalized patients with severe COVID-19 pneumonia, the use of Tocilizumab did not result in significantly better clinical status or lower mortality at 28 days (COVACTA trial, April 22, 2021). Roche announces that the global phase-III randomized, double-blind, multicentre REMDACTA study of Tocilizumab plus Remdesivir versus Placebo plus Remdesivir did not meet its primary endpoint (endpoint i.e., improved times to hospital discharge) (REMDACTA trial, 11 March 2021). Preliminary results from RECOVERY trial suggest that Tocilizumab reduces the risk of death when given to hospitalized patients with severe COVID-19. The study also showed that Tocilizumab shortens the time of hospital stay and reduces the need for a mechanical ventilator. *Summary: There is mixed evidence for Tocilizumab. It may be indicated in combination with steroids in severe COVID patients requiring high flow oxygen/ventilation and not responding to steroids and having raised inflammatory markers.*

Vitamins and Minerals	Among hospitalized patients with COVID-19, a single high dose of vitamin D3 did not significantly reduce hospital stay. (Murai et al. 17 February 2021). Evidence from a randomized clinical trial of 214 patients suggests that treatment with zinc, ascorbic acid or both does not affect COVID symptoms (Thomas et al. 12 February 2021). *Summary: There is no direct benefit of taking Vitamins C and D, and Zinc in treatment of COVID. However, there is no harm in taking normal daily doses of the above as nutritional supplements.*

Pediatric use

The above clinical evidence of various drugs should be interpreted with caution in children.

Mild disease:

Treatment is mainly symptomatic and supportive. There is no role for several drugs including Azithromycin, Doxycycline, Ivermectin, Chloroquine, Favipiravir etc.

Moderate to severe disease:

Drugs like Remdesivir and Steroids should be considered only in pediatric patients admitted to hospital and requiring oxygen or ventilation.

References:

1. Summary of various studies
   https://pharmaceutical-journal.com/article/feature/everything-you-need-to-know-about-the-covid-19-therapy-trials

   https://www.ashp.org/-/media/8CA43C674C6D4335B6A19852843C4052.ashx

2. IAP guidelines
   https://iapindia.org/get-latest-guidance-on-COVID-19

3. ICMR guidelines
   https://www.icmr.gov.in/pdf/covid/techdoc/COVID19_Management_Algorithm_22042021_v1.pdf

4. Recovery trial
   https://www.recoverytrial.net/results

5. REMAP-CAP study
   https://www.remapcap.org/covid19publications

6. PRINCIPLE trial
   https://www.principletrial.org/results

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