

Review Article**Pharmacotherapy for COVID-19****Princy Louis Palatty¹, Sathyajith G. Nair², Rosme David¹, Mamatha J.¹, Vanditha S.¹, Deepthi Mary George¹, Savithri P.¹, P. G. Nayar^{1*}**¹Department of Pharmacology, Amrita Vishwa Vidyapeetham, Health Sciences Campus, Amrita Institute of Medical Sciences, Elamakkara P.O., Kochi - 682 041 Kerala, India²Department of Pediatrics, Amrita Vishwa Vidyapeetham, Health Sciences Campus, Amrita Institute of Medical Sciences, Elamakkara P.O., Kochi - 682 041 Kerala, India

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Abstract

The past few months has witnessed mankind facing one of its toughest battles for survival till date. Severe acute respiratory syndrome caused by SARS CoV 2 has demonstrated its ability to bring humans to their knees at an unprecedented speed with no drugs or vaccine available till date. The objective of our review is to explore and compile various drugs tried for the Corona virus disease 19 across the world. We had vast literature search and shortlisted 164 articles. The drugs tried for the COVID -19 are given under category A, B and C. Category A need symptomatic treatment. Category B is given hydroxy chloroquine, azithromycin, and oseltamivir, Category C with hydroxy chloroquine and favipiravir. If favipiravir is contraindicated/not available, then hydroxychloroquine with either azithromycin or lopinavir/ritonavir for 14 days or 7 days after becoming asymptomatic is tried. In the Category C-moderate severity, Injection Remdesivir plus Injection Methyl prednisolone/Injection Dexamethasone is given. Patients with severe signs and symptoms (Respiratory Rate ≥ 30 , SpO₂ < 90 on room air) are suggested being initiated with Injection Remdesivir plus Injection Methyl prednisolone/Injection Dexamethasone. Convalescent plasma therapy to be initiated as per the respective state wise protocol in India. What we conclude is that, we advocates and describe the regimens used in everchanging guidelines for covid therapy in different part of the world. Special attention to symptomatic approach to treat the covid 19 disease in children has also been covered in this review article.

Keywords: COVID-19, regional guidelines, convalescent plasma, heparin, corticosteroids, remdesivir**Introduction**

The cataclysmic effect of a tiny virus has turned over the norms of the world and the people are social distancing, isolating and even shielding from others. Because we are battling with an unknown enemy, we started with some drugs that have a suspicion of potential against corona virus infection. The government is on toes in handling the lives of people, which leads to the frequent revised guidelines in the therapy, prevention, body disposal and drug/ vaccine development. The entirety of management of this disease is left to the acumens of astute finish. The outbreak was first identified in Wuhan, China,

in December 2019. WHO declared it as a pandemic on 11th March ("WHO, Novel Coronavirus – Thailand (ex-China)," 2020). As of September 9th, 2020, more than 2 crore 75 Lakh cases of COVID-19 have been reported globally resulting in more than 9 Lakh deaths, creating consequent fear and panic among ourselves. 229E, OC43, NL63, HKU1, MERS - CoV, SARS and SARS CoV2 are the seven corona viruses identified and causes mild common cold-like symptoms to lower respiratory tract infections in humans.

In SARS-CoV1 virus (van Doremalen et al., 2020) and SARS-CoV2-Virus, unlike Human Coronavirus infections, upper respiratory symptoms are notably infrequent. Intestinal presentations observed with SARS also appear to be uncommon, although two of six cases reported by Chan and colleagues had diarrhea (Chan et al., 2020). Small droplets are produced by coughing, sneezing, and talking, usually fall to the ground or onto the surfaces (Coronavirus disease (COVID-19): How is it transmitted?, 2020). Transmission also occurs through smaller droplets that can

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stay suspended in the air for longer periods of time.

Pathophysiology

A hyperactive immune response characterized by the release of interferons, interleukins, TNF, chemokines, and several other mediators (Coperchini et al., 2020). These mediators are part of a well-conserved innate immune response necessary for efficient clearance of infective agents. Cytokine storm implies that the levels of released cytokines are injurious to host (Neil Pearce et al., 2020). The disease is far more complex than a simple pneumonia. Formation of life-threatening blood clots can cause heart attacks, strokes, kidney failure, and additional lung damage. Such clots often cause death in younger patients too (Yuki et al., 2020). The impact of blood thinners on patient's survival and the duration of hospitalization are significant. Anticoagulants play a significant role at this stage (Figure 1).

Intubation and survival rate

The survival rate of intubated patients treated with anticoagulants was 70.9% as compared to 37.3% for who did not. The time in the hospital for those who received anticoagulant therapy was shorter as compared to those who did not. New York hospital reported that 88% of intubated COVID-19 patients died who did not receive anticoagulants (Haseltine, 2020).

Methodology

We shortlisted 164 articles from the literature search and compiled here. The articles, e-journals, newspaper, and medical blogs are accessed via internet and we took 2 months to complete this review article. We searched the PubMed Central Data Base using the keywords 'Covid Treatment' and landed upon a humongous collection of 39260 articles, of which we have gone through around 800 articles, divided among the authors.

NCBI MeSH heading, 'Covid – 19' showed 18 articles, 'Corona virus' showed 73, 'Novel CoV' showed 15, 'Remdesivir' showed 3 articles, 'SARS COV 2' showed 35 articles. To extend our literature search, we also tried Google scholar and brought together the related articles from the above-mentioned headings. The journals with no treatment mentioned for SARS COV 2 are excluded during our primary selection. No statistical analysis is done. The various drugs, treatment guidelines and regional protocols for the different categories of disease severity in both adults and pediatric populations have been drawn together and incorporated into this review article.

Regional Protocol

To begin a protocol, it is important to define the clinical conditions one is dealing with. The current article elaborates the way, the Ministry of Health and Family Welfare, Government of Kerala, adopted a protocol for its State Health Program.

Suspect case

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath) and a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset;

OR

B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset.

OR

C. A patient with severe acute respiratory illness fever and

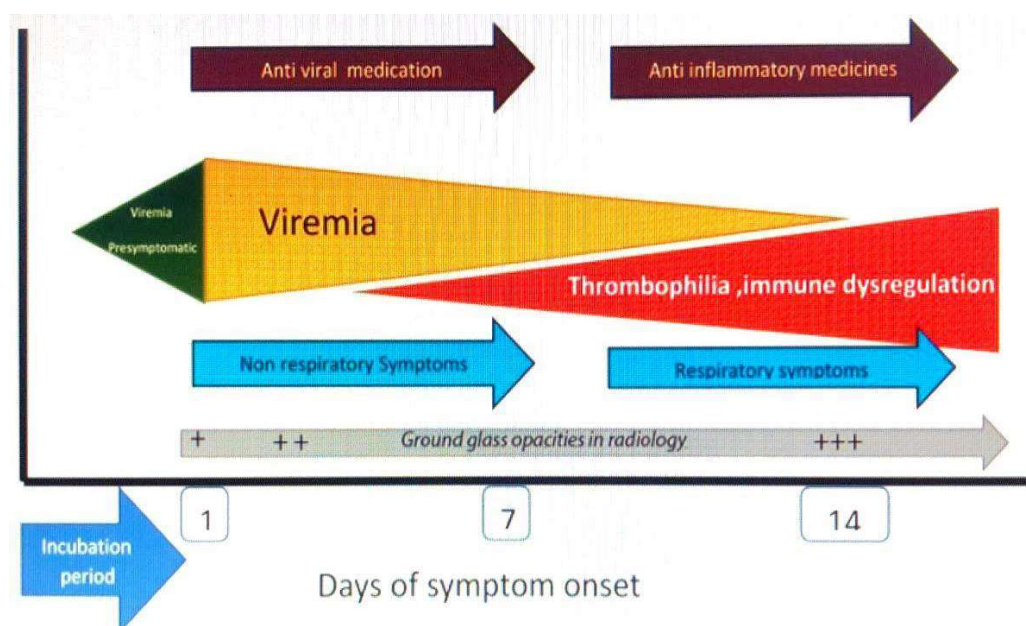


Figure 1. Pathophysiology of Covid 19

at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; requiring hospitalization in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case:

A. A suspect case for whom testing for the COVID-19 virus is inconclusive.

OR

B. A suspect case for whom testing could not be performed for any reason.

Confirmed case:

A person with laboratory confirmation of COVID-19 infection is irrespective of clinical signs and symptoms.

Categories based on symptomatology

Based on the symptomatology, the following categories were assigned (Table: 1).

Category A: Mild sore throat / cough / rhinitis /diarrhea

Category B: Fever and/or severe sore throat / cough /diarrhea OR Category-A with any one of the comorbidities concerning Lung/ heart / liver/ kidney / neurological disease/ Hypertension / hematological disorders/ uncontrolled diabetes/ cancer/ HIV-AIDS/ cardiovascular disease, on long term steroids/

immunosuppressive drugs, pregnant lady and age more than 60 years.

Category C: (1) Breathlessness, chest pain, drowsiness, fall in blood pressure, hemoptysis, cyanosis [red flag signs]. (2) Children with ILI (influenza like illness) with *red flag signs* (Somnolence, high/persistent fever, inability to feed well, convulsions, dyspnea /respiratory distress, etc.) along with worsening of the underlying chronic conditions.

The categorization should be reassessed every 24-48 hours for Category A & B. The severity of the illness was staged based on clinical condition (Table 2).

Management

The first line investigation at admission is to include: CBC, Renal function tests, Liver function tests, C-reactive protein, Blood glucose levels, S. electrolytes, Electrocardiogram and Pulse oximetry. As and when the clinical scenario demands, the following tests need to be done: a Portable Chest X-ray, HIV and HBsAg screening, HCV, D-Dimer, Ferritin, LDH, CPK, procalcitonin, Blood culture, Trop-T/I, HRCT Thorax. In the case of an immune compromised host, tests to rule out opportunistic infections like Mycobacterium tuberculosis, pneumocystis jiroveci etc. should be done.

Table 1. Clinical Severity Stages

Clinical Severity	Clinical Parameters
Mild	No breathlessness or Hypoxia
Moderate	Adult: dyspnea and/ or hypoxia, fever, cough, SpO ₂ ≤94% (range 90-94%) on room air, Respiratory Rate ≥24 per minute. Child – dyspnea and or hypoxia, fever, cough, including SpO ₂ ≤94% (range 90-94%) on room air, Respiratory Rate ≥ 24 per minute. Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40
Severe	Adult: Pneumonia plus one of <ul style="list-style-type: none"> • respiratory rate ≥30 breaths/min • severe respiratory distress • SpO₂ ≤90% on room air. Child: cough/dyspnea, plus one of <ul style="list-style-type: none"> • central cyanosis or SpO₂ ≤90%. • severe respiratory distress (e.g. grunting, chest indrawing). • signs of pneumonia with danger signs: (inability to breastfeed or drink, lethargy, unconsciousness, or convulsions). • Other signs of pneumonia like chest in drawing, fast breathing (in breaths/min): <2 months ≥60; 2–11 months ≥50; 1–5 years ≥40.

Table 2. Severity categorized into the following

Mild	Respiratory Rate < 24/min, SpO ₂ > 94% on room air
Moderate	Respiratory rate between 24-29, SpO ₂ between 91-94% on room air
Severe	Respiratory Rate ≥ 30, SpO ₂ < 90% Respiratory Rate ≥ 30, SpO ₂ < 90

High risk individuals are those with Uncontrolled diabetes [HbA1C >7.6%, Hypertension, Cardiovascular disease, Pre-existing pulmonary disease, Chronic kidney disease, Chronic lung disease, on immunosuppressive/ biological, HIV CD4 <200cells/mm³, congenital immunodeficiency disorders, Age > 65 yrs and BMI >30.

In symptomatic patients with suspected COVID-19, HRCT thorax may be considered for diagnosis of COVID-19 when initial RT-PCR testing is negative. CT guided approach should be used in RTPCR negative cases with high clinical index of suspicion of COVID-19. A typical appearance of a COVID-19 infected lung would have peripheral bilateral Ground glass opacity (GGO) appearance with or without consolidation or visible intra lobular lines ('crazy paving') Multifocal GGO of rounded morphology with or without consolidation or visible intra lobular lines ('crazy paving'), reverse halo sign or other signs of organizing pneumonia.

Treatment

Patients categorized to A, B, C must be further risk stratified into mild, moderate, and severe. The major things to be considered seriously are:

- ✓ AVOID using NSAIDs other than paracetamol unless necessary.
- ✓ AVOID using nebulized drugs to avoid aerosolization of virus, use a metered dose inhaler instead.
- ✓ Oseltamivir should be initiated in all symptomatic patients with influenza like illness till RTPCR/Antigen test result is obtained.
- ✓ In patients with COVID-19 pneumonia, secondary bacterial or viral infection is uncommon. Initiation/continuation of antibiotics solely due to COVID-19 is not indicated (Table 3). Extended duration of fever is typical in COVID-19 patients. Based on literature to date, no unique association between specific pathogens, such as MRSA or Pseudomonas, had been found with COVID-19. Antibiotic selection in case of secondary bacterial pneumonia should be as per institutional antibiogram.
- ✓ The prevalent guidelines against Asthma have recommended in continuation of inhaled steroids even in patients with

COVID-19. Currently there are no data to support either starting or stopping ACEi /ARBs in any patients with COVID-19. ACEi /ARB may be continued in patients who are already on them. However, if acute kidney injury, hypotension or other contraindication develops, consider stopping them at that time. If secondary pneumonia is not improving on broad spectrum antibiotics, consider the possibility of CAPA (Covid Associated Pulmonary Aspergillosis) also.

Treatment strategies according to clinical categorization and risk stratification

Patients in the Category A need just symptomatic treatment. Categorization should be reassessed every 28-48 hours for Category A. Those in the category B are recommended to start on Tab HCQs along with Tab Azithromycin and Tab Oseltamivir in all symptomatic patients with influenza like illness until PCR report. The patient in the Category C is to be started on Tab HCQs with Tab Favipiravir. If Favipiravir is not available or contraindicated, consider HCQs PLUS Azithromycin or HCQs along with Tab Lopinavir / Ritonavir for 14 days or for 7 days after becoming asymptomatic. Lopinavir/ritonavir should be used only on a compassionate grounds after informed consent. It must be started within 10 days of symptom onset.

In the C category with moderate severity i.e. respiratory rate between 24-29, SpO₂ between 91-94 in room air, Injection Remdesivir (If not available treat as Cat C) PLUS Injection Methyl prednisolone Or Injection Dexamethasone is to be considered ("Clinical management of COVID-19," 2020). Convalescent plasma therapy and anti-coagulation may be initiated as per state protocol. Anti coagulation as per state protocol. Patients who satisfy the category C with severe signs and symptoms i.e. Respiratory rate \geq 30, SpO₂ < 90 on room air, are suggest to be initiated with Injection Remdesivir (If not available treat as Cat C) with Inj Methyl prednisolone for 5-7 days Or Inj Dexamethasone for 5-7 days. Convalescent plasma therapy to be initiated as per the respective state protocol. Inj Tocilizumab may be tried for cytokine release syndrome grade 3 and 4, along with the anti-coagulation as per state protocol (Table 4).

Table 3. Antibiotics used in SARS CoV 2

Drugs	Dosage
Azithromycin	500mg 1-0-0 x 1 day and 250mg 1-0-0 x 4 days Children: 10 mg/kg (max 500mg) day 1, Followed by 5mg/kg/day on days 2 to 5.
Doxycycline	200 mg stat doxycycline day-1 followed by 100mg doxycycline 12hrly for 4 day (i.e. day2-day5)
Cotrimoxazole	160mg of trimethoprim and 800mg sulphamethoxazole 12hrly for 5 days

Table 4. Drugs used to treat corona virus disease 19

Drugs	Mechanism of action	Route	Dose	Precautions
Hydroxy-Chloroquine	Inhibits viral entry and endocytosis glycosylation of ACE-2 receptors. Acts in micro molar concentrations	Oral	10mg/kg. stat. After 12 hours 5mg/kg then 5mg BD for 4days	QT prolongation. porphyria, myasthenia gravis. Retinal pathology
Azithromycin (Rodvold et al., 1997)	Binds to the 50S subunit of the bacterial ribosome, inhibiting translation of mRNA.	Oral	500mg 1-0-0 x 1 day and 250mg 1-0-0 x 4 days Children: 10 mg/kg (max 500mg) day 1, Followed by 5mg/kg/day on days 2 to 5.	Epilepsy, Pregnancy is NOT a contraindication
Oseltamivir	Inhibits the neuraminidase enzyme, which is expressed on viral surface. Prevents the release of virus from infected cells in the respiratory tract.	Oral	75mg 1-0-1 Children: 3mg/kg/dose BD	Dose adjustment for those with renal Insufficiency. If Baseline QT is prolonged – frequent ECG monitoring is required
Favipiravir	Ability to inhibit RNA polymerase. Selectively inhibits the influenza viral RNA-dependent RNA polymerase.	Oral	1800mg PO BID for two doses then 800mg BID for total 7 to 10 days	Assess for drug-drug interactions (including with calcineurin inhibitors) before starting. Gastrointestinal intolerance should be used only on a compassionate ground after informed consent. It must be started within 10 days of symptom onset. Monitor liver function tests while on therapy.
Lopinavir / Ritonavir	Protease inhibitor and inhibits. Proteolysis.	Oral	(400/100) 1-0-1 for 14 days or for 7days after becoming asymptomatic. Children • 14 days to 6 months: 16mg/ kg (based on lopinavir component) PO BD • < 15kg: 12 mg/kg PO (based on lopinavir component BD) • 15-25 kg: 200 mg-50 mg PO BD • 26-35 kg: 300 mg-75 mg PO BD • >35 kg: 400 mg-100 mg PO BD	should be used only on a compassionate ground after informed consent. It must be started within 10 days of symptom onset. Monitor liver function tests while on therapy.
Remdesivir	Inhibits RNA dependent RNA polymerase.	I.V.	200 mg IV on day 1 followed by 100 mg IV daily for 5 days	contraindicated in: • AST/ALT > 5 times Upper limit of normal (ULN) [AST /ALT must be monitored daily] • Severe renal impairment (i.e., eGFR < 30ml/ min/m2 or need for hemodialysis) • Pregnancy or lactating females DM, HTN, Gastritis, Glaucoma
Methyl prednisolone Dexamethasone	The benefit of corticosteroids in septic shock results from tempering the host immune response to bacterial toxin release. In viral disease it is not known.	I.V. I.V.	0.5-1mg/kg/day for 5-7 days 0.2-0.4 mg/kg/day for 5-7 days	
Tocilizumab (Jordan et al., 2020)	Interleukin-6 receptor antagonist. Prevents its activation.	I.V.	>30kg- 8mg/kg Stat. If no improvement repeats the same dose after 8 hours for 3 more doses. If weight is <30kg- 12mg/Kg. If no improvement repeats the same dose after 8 hours for 3 more doses	Serious bacterial, viral & other opportunistic infections, Neutropenia.
Heparin (Yuriditsky et al., 2020)	Binding to COVID spike protein and to the IL-6 causing down regulation	Injection	Heparin 18 units/kg/hr IV (TBW) with standard boluses and titrations per protocol (max initial rate 2,000 units/hr)	Thrombosis, thrombophlebitis, myocardial infarction, bleeding in women over 60 years of age.
Apixaban (Anticoagulation Strategy - ClinicalTrials)	Inhibits Factor.10A & the conversion of prothrombin to thrombin	Oral	(5 mg Q12h; 2.5 mg Q12h for patients with at least two of three of age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL)	
Enoxaparin		Injection	Enoxaparin 1 mg/kg SC BID (TBW)	

Convalescent plasma

This mode of therapy has been advocated only on grounds of compassion (Agarwal et al., 2020; Epstein and Burnouf, 2020; India, 2020; “Recommendations for Investigational COVID-19 Convalescent Plasma | FDA,” n.d.) treatment of patients with moderate to severe COVID 19 infection as of date.

Compassionate use of convalescent plasma may be considered in:

- Laboratory confirmed diagnosis of infection with SARS CoV 2
- COVID – 19 with moderate/severe disease
- Informed consent provided by the patient or relative
- Emergency approval from state medical board

Moderate COVID 19:

- (a). Respiratory rate 24-29/min
- (b). SpO₂ ≤94% on room air

Severe COVID infection:

- (a). Respiratory rate ≥30/min
- (b). SpO₂ ≤90% on room air
- © Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- (d). Lung infiltrates > 50% within 24-48 hours

Exclusion criteria:

- ✓ Lack of consent
- ✓ Known hypersensitivity to blood products
- ✓ Known IgA deficiency or immunoglobulin allergy.

Eligibility of Donor

- ✓ 18 years of age and above
- ✓ Males or female donors of weight with weight more than 55kg
- ✓ Prior diagnosis of COVID – 19 documented by a laboratory test (RT-PCR) with symptomatic disease with at least fever and cough OR preferably plasma IgG titre [against S-protein] should be above 1:640.

A Complete resolution of symptoms at least 28 days prior to donation

- ✓ Further technicalities regarding donor eligibility will be decided by transfusion medicine departments of designated COVID-19 treatment facilities.
- ✓ In addition donor eligibility criteria for whole blood donation will be followed in accordance to the drugs and cosmetics Act 1940 and rules 1945 therein (as amended till March 2020).

Interim guidelines on clinical management of COVID 19 infection in children:

Coronavirus disease 2019 (COVID-19) is rarer in children compared to adults. Incidence of disease in children has been reported to be around 2% in most studies. Exact cause of lower incidence is not known. It may be due to lower susceptibility or higher incidence of asymptomatic disease in children. Nevertheless, severe manifestations and deaths are being increasingly reported in children and they can act as an important source of infection for adults and health care workers as they cannot follow cough etiquettes as efficiently as adults.

COVID suspect

- ✓ All symptomatic children (cough / sore throat / URI / Diarrhea / shortness of breath with or without fever) who have:

- ✓ History of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset.
- ✓ History of contact with suspected or confirmed case of Covid 19 in last 14 days prior to symptom onset.
- ✓ Severe acute respiratory illness in the absence of an alternative diagnosis that fully explains the clinical presentation.

Testing

The preferred sample is nasopharyngeal. Nasal, throat swabs, ET aspirates and bronchoalveolar lavage may also be tested. The various methods of testing for Covid19 include RT PCR which is considered the gold standard. Other ways to test are using the Pooled RT PCR, CBNAAT, True Nat and Rapid antigen test.

Clinical syndromes associated with COVID infection include mild uncomplicated illness with fever, sore throat, malaise, cough, diarrhea or vomiting, mild pneumonia, severe pneumonia, ARDS, sepsis and septic shock with multi organ involvement. There is limited timeline data for infections in children. They may also complain of myalgia, headache, and fatigue. Fever and cough are seen less frequently in children comparatively.

MISC (Multisystem inflammatory syndrome in children) should be considered in any individual less than 21 years of age presenting with fever with high inflammatory markers (high CRP, ESR, Ferritin, Fibrinogen, D Dimer, LDH, IL-6, elevated Neutrophils, low lymphocytes, Low albumin etc.) with multi system (>2) organ involvement causing severe disease requiring admission, with no plausible alternative diagnosis and evidence of recent or past Covid-19 infection as evidenced by positive RT PCR, antibody or antigen study or exposure to a suspected or confirmed Covid 19 case within the 4 weeks prior to admission.

All children with suspected COVID infection should be categorized into 3.

Category A

Presenting with mild sore throat, cough, rhinorrhea, diarrhea, vomiting. They need to be managed with symptomatic treatment. Avoid NSAIDs other than paracetamol. Use oral bronchodilators or MDI (Metered Dose Inhaler) for those with wheeze. Maintain adequate hydration. ORS and zinc for those with diarrhea and vomiting.

Mildly symptomatic patients

Symptomatic treatment to include paracetamol for fever and avoidance of NSAIDs:

- ✓ Oral bronchodilators or MDI with spacer and mask should be provided for children with wheeze. Use of nebulizers should be avoided due to the risk of aerosolization even though it is unclear if visible aerosols come from patient's airway during nebulization.
- ✓ Ensuring euvoemia is essential. Advice adequate fluid and feed intake to be ensured. Advice regarding use of ORS and other home available fluids in case of diarrhea and vomiting should be provided to the caregivers.
- ✓ Categorization should be reassessed every 24-48 hours.

Category B

Those who present with Fever, severe sore throat, increasing cough. Category A symptoms in children with chronic heart, kidney, lung, neurological or liver disease and children on long term steroids, congenital or acquired immunosuppression are included in this category as well. These children can be managed with Oseltamivir 3mg/kg/dose BD till Nasopharyngeal swab results are available if criteria for treatment of ILI fulfilled. Hydroxychloroquine at a dose of 6.5mg/kg/dose twice a day, on day 1 followed by 3.25mg/kg/dose BD for 4 more days. Azithromycin may be added on with a dose of 10mg/kg, Once a day, on day 1 followed by 5mg/kg OD on days 2 to 5. ECG should be taken prior to starting treatment to look for QT prolongation. Zinc may be added with a dose 2mg/kg/day.

Children with ILI (Influenza like illness) who fulfill the criteria for treatment can be started on Oseltamivir 3mg/kg/dose BD till nasopharyngeal swab results are available. Antibiotics may be started as per treating physician's discretion if deemed necessary according to the local antibiogram. Once the swab report is available and diagnosis confirmed Oseltamivir may be stopped and patient started on Hydroxychloroquine 6.5mg/kg/dose BD on day 1 followed by 3.25mg/kg/dose BD for 4 more days along with zinc 2mg/kg/day (role of these chemotherapeutic drugs are still not proven and future guidelines may have a change in recommendation). Azithromycin 10mg/kg OD on day 1 followed by 5mg/kg OD on days 2 to 5. ECG should be taken prior to starting treatment to look for QT prolongation.

Category C

Moderate symptoms

Admit these patients preferably in dedicated Covid-19 care hospitals, District hospitals, Medical colleges or other tertiary care hospitals catering to Covid patients. Send nasopharyngeal swab for confirmation of Covid 19 infection as per the prevalent protocol.

Apart from oxygen through appropriate devices necessary for each patient, these children need to be started on Hydroxychloroquine 6.5mg/kg/dose BD on day 1 followed by 3.25mg/kg/dose BD for 4 more days along with azithromycin

10mg/kg OD on day 1 followed by 5mg/kg OD on days 2 to 5. ECG should be taken prior to starting treatment to look for QT prolongation. Zinc 2mg/kg/day helps as an adjuvant therapy.

If a patient is on oxygen support they should be started on Remdesivir 5mg/kg IV (max. 200mg) loading dose over 30-120 minutes on day 1 followed by 2.5mg/kg (max. 100mg) IV OD on days 2-4 and start methyl prednisolone IV 1-2mg/kg/day. Prophylactic low molecular weight heparin may be started if no contraindication at a dose of 1mg/kg subcutaneously once daily. In case of unavailability of remdesivir, Lopinavir/ritonavir combination may be given along with HCQ.

Lopinavir ritonavir combination has not shown much promise as an effective treatment for Covid19 infection. Favipiravir used in adults, is not yet licensed by DGCI (Director General Controller of India) for use in children. It is a teratogenic drug, hence contraindicated in pregnancy. Favipiravir may be given in a case to case basis if deemed necessary after state medical board concurrence.

Severe and critical disease

According to the severity of disease these children may require intensive care. All children with moderate to severe ARDS, shock, multi organ involvement and those with SpO₂ < 94% with increased frequency of breathing should be preferably admitted in the PICU. Treatment involves considering the use of Tocilizumab at a dosing as follows:

(<18yrs): < 30kg – 12mg/kg IV in 50-100ml normal saline over 60 minutes and > 30kg - 8mg/kg IV over 60minutes (max. 800mg per infusion).

Steroids may be considered in patients requiring oxygen support Dose: Methyl Prednisolone 1- 2mg/kg/day for 5- 7 days.

Management of MISC (Multisystem inflammatory syndrome in children)

These children need to be resuscitated judiciously with normal saline 5- 10ml/kg over 20mts if patient has features of shock, looking for features of fluid overload like hepatomegaly, respiratory distress, basal crepitations. These children usually do not tolerate large volume fluids more than 20ml/kg. After taking sample for blood culture start antibiotics as ceftriaxone and clindamycin to cover sepsis or TSS. Inotropic support i.e. Methyl prednisolone or epinephrine as per physiological status to be incorporated as need be. IVIG 2gm/kg slow IV infusion may be started if MISC is diagnosed by clinical and laboratory markers. Sample for serology should be taken before starting IVIG.

No specific antiviral therapy is proven to be effective as per

current available literature. Drugs being used in clinical trial settings include:

- Hydroxychloroquine / Chloroquine
- Remdesivir
- Nitazoxanide
- Ivermectin
- Favipiravir

If there is access to remdesivir (an antiviral agent with activity against SARS-CoV-2 that is currently available for compassionate use in young children and with limited clinical trials), this should be considered, particularly for those known to be PCR positive and/or with a presentation consistent with typical COVID-19. The current proposed dose for children is 5 mg/kg load IV once (max dose 200 mg) on day 1, then 2.5 mg/kg (100 mg max dose) IV daily for nine days.

Many centers have treated children who present most like Kawasaki Disease (KD) with traditional therapy used for KD. We recommend giving IVIG 2 g/kg and aspirin 20–25 mg/kg/dose every 6 h (80–100 mg/kg/day) for all patients with KD-like illness, evidence of excessive inflammation (ferritin > 700 ng/mL, CRP > 30 g/dL, or multisystem organ failure), or cardiac involvement.

Other Therapies

Convalescent plasma

It may be considered as per state protocol for patients with moderate and severe disease. It is an off-label use. It should be avoided in patients with IgA deficiency or immunoglobulin allergy.

According to ICMR guidelines ABO compatible cross matched plasma with neutralizing titer above the threshold level or plasma IgG titer against S - protein RBD above 1: 640 should be used. It may be administered at a Dose of 10ml/kg. As of today, there is no specific drug or vaccine to shield us from this potentially devastating virus. In an uneven socio-economic profiled country like ours, the mortality and morbidity are varied. With such uncertain conditions always, prevention is better than cure. Social distancing, usage of mask, frequent hand washing and sanitation, avoidance of crowded locations need be followed strictly to 'flatten the curve'. A new lifestyle has been adopted by the citizens of the world. Life will never be the same. It could take years to regain the pre-covid19 state.

Heparin: LMW Heparin remains the best choice till date (Atallah et al., 2020; Kreuziger et al., 2020).

Apixaban: Is a highly selective, orally bioavailable, and reversible direct inhibitor of free and clot-bound factor Xa. Factor Xa catalyzes the conversion of prothrombin to thrombin. Apixaban inhibits this stage. Elimination half-life: 9–14 hrs. On multiple doses it becomes 68hrs. Dose: - 5mg BD for 2wks on

discharge of the patients. Remdesivir shortens hospitalization by about four days on an average. "The role of remdesivir needs to be tested in combination with dexamethasone & HCQ. There are many studies going on that topic. Gilead Sciences, the company that makes IV. Remdesivir is testing an inhaled version in less ill COVID patients. trying to avoid hospitalization as the hospitals are overwhelmed with patients. The company is also testing in a small group of children with same idea.

Favipiravir: Nucleoside analog with an ability to inhibit RNA polymerase which is required for viral replication. It is converted to the ribofuranosyl triphosphate derivative by host enzymes and selectively inhibits the influenza viral RNA-dependent RNA polymerase which is required for the multiplication of the virus.

Oseltamivir: M.O.A.: Inhibits the neuraminidase enzyme, which is expressed on viral surface. The enzyme promotes release of virus from infected cells & facilitates viral movement within the respiratory tract.

Corticosteroids: In a clinical trial in UK it has benefited critically ill patients. For patients on ventilators, the treatment was shown to reduce mortality by about one third, and for patients requiring only oxygen, Mortality was reduced by about one fifth. The evidence in asthma is less clear cut, but at least one observational study has shown an increased risk of pneumonia or lower respiratory infection (McKeever et al., 2013). In vitro studies have suggested that corticosteroids may impair antiviral innate immune responses (Davies et al., 2011; Simpson et al., 2016) and that ICS use leads to delayed virus clearance (Singanayagam et al., 2018). Other studies, however, have shown normal responses in patients on ICS (Southworth et al., 2020). It is important to note that most studies have been carried out with rhinovirus and there may be differences in the response to other viruses.

Ranitidine bismuth citrate a new approach: In vitro studies in golden Syrian hamster model showed that ranitidine bismuth citrate (Tritec) and its related compounds exhibited inhibition towards both the ATPase (IC₅₀= 0.69 μM) and DNA-unwinding (IC₅₀= 0.70 μM) activities of the SARS-CoV-2 helicase via an irreversible displacement of zinc(II) ions from the enzyme by bismuth (III) ions (Southworth et al., 2020). So, this knowledge, metallo-compounds exhibit potent activity against the virus in vitro, will be used in humans after research. Ranitidine bismuth citrate suppressed SARS-CoV-2 replication, leading to decreased viral loads in both upper and lower respiratory tracts, and relieved pneumonia with a high selectivity index of 975 (Yuan et al., 2020).

Glucose: 2 drops of 25% glucose 2 times a day, in each nostril will prevent virus entry through upper airways because the oxygen ions in the glucose could break the lipid membrane of the coronaviruses. Further studies need to be conducted and when there is no other alternative, this simple harmless well-known drug is worth a try (Organiser, 2020).

Conclusion

The varied regimens used in different geographical areas have proved useful to same extent as reflected by the statistical data available for positivity rates, conversion rates and mortality rates. The drugs used have been tried with prior knowledge of their use in similar situations and repurposed for the use in covid-19. And these drugs belong to the wide array of chemical classes. Although the present-day regimens for the covid-19 has described, they are subject to change. The therapy of covid-19 has been successful in most, even the small percentage of mortality rate can be reduced by better use of these drugs, as we learn by trial and error, with time.

Future Perspectives

As of today, there is no specific drug or vaccine to shield us from this potentially devastating virus. In an uneven socio-economic profiled country like ours, the mortality and morbidity are varied. With such uncertain conditions always, prevention is better than cure. Social distancing, usage of mask, frequent hand washing and sanitation, avoidance of crowded locations need be followed strictly to 'flatten the curve'. A new lifestyle has been adopted by the citizens of the world. Life will never be the same. It could take years to regain the pre-covid19 state until vaccine or specific antiviral is found.

Conflicts of interest

None

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