In the 21st century, three coronaviruses (CoVs) caused three major epidemic of respiratory distress syndrome, which include severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 with epicenter in Guangdong, China; Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 in Saudi Arabia; and the third epidemic of respiratory coronavirus the 2019-novel coronavirus (2019-nCoV) or coronavirus disease (COVID-19) mainly centered in Wuhan province, China. The case fatalities vary from 2.5% (2019-nCoV), 10% (SARS), to 35% (MERS-CoV). Till now, there is no approved antiviral or vaccine for the management of infection by CoV. However, from earlier experience of the management of SARS-CoV and MERS-CoV, many agents are being used in the treatment of 2019-nCoV.

### Antivirals

#### Nucleoside analog

Ribavirin, a nucleoside analog, shows antiviral activity against some animal CoVs, and in the SARS-CoV epidemic, many patients were treated with ribavirin along with corticosteroids and became a standard regimen for the treatment of SARS-CoV. However, lack of control group hindered the estimation of true effect size. Again, in vitro testing did not show efficacy of ribavirin against SARS-CoV. Ribavirin is known for its side effects (hemolytic anemia, hypocalcemia, and hypomagnesemia). Many subsequent studies questioned the efficacy of ribavirin. Many patients on ribavirin and corticosteroid combination even showed an increase in viral load following the treatment. Thus, its use declined over a period. Other important nucleoside analogs are favipiravir and galidesivir, but these are not evaluated till now in 2019-nCoV.

#### Neuraminidase inhibitors

Neuraminidase inhibitors are indicated in the management of influenza. In a study on possible MERS-CoV cases in Paris from 2013 to 2016, a total of 35 patients received oseltamivir (37.6%). In patients positive for influenza virus (n = 25), 52% (n = 13) received oseltamivir and it was concluded that empirical oseltamivir can be started in suspected MERS-CoV cases. Many other studies also evaluated oseltamivir in MERS-CoV. Oseltamivir was also used in the management of 2019-nCoV; however, definite evidence of efficacy is inconclusive because of lack of suitable control group in the studies.

#### Protease inhibitor

There are two types of protease present in SARS-CoV, the CL-like protease and the papain-like protease, which is important for cleaving the polyproteins and releasing the nonstructural proteins (NSP1–16), which carry out important functions in the CoV life cycle. Among protease inhibitors, lopinavir was the most inhibitor and saquinavir was the least powerful inhibitor of CoV protease. In molecular dynamic studies, flap closing was observed when these inhibitors bound to the SARS-CoV 3CL (pro). Hong Kong University researchers demonstrated anti-SARS-CoV action of lopinavir at concentration of 4 µg/ml in vitro against the HKU-39849 isolate. Ritonavir boosting along with lopinavir is used in the management of HIV. A clinical study at the same Hong Kong University suggests that even after adjustment for LDH level (possible confounder), a significant association was seen between lopinavir/ritonavir use and better outcome. As per the current guidelines, lopinavir/ritonavir is the recommended protease inhibitor for the treatment of 2019-nCoV (weak recommendation).

#### Immunomodulators

#### Corticosteroids

Corticosteroids were widely used for the treatment of SARS-CoV and MERS-CoV and are also used in the management of the current epidemic of 2019-nCoV. However, the interim guidelines by the WHO prohibit the use of routine corticosteroids unless indicated for other clinical ground. Use of corticosteroid is reported to be associated with delayed clearance of viral RNA (both in case of SERS-CoV and MERS-CoV) and other steroid-related complications such as psychosis.

#### Interferon

Interferons (IFNs) are broad-spectrum antivirals, primarily used in the treatment of hepatitis B. In SARS-CoV patients, compared to ribavirin or interferon (IFN) alone, the benefit was seen on IFN-α + high-dose corticosteroid group. Other observational studies
also support these findings and the combined use of IFN-α and corticosteroid (corticosteroid arm n = 13; corticosteroid + IFN-α arm n = 9) showed less disease-associated oxygen saturation impairment.\[^{21}\] For the treatment of 2019-nCoV (7), IFN-α (5 million U bid inh) is recommended along with lopinavir + ritonavir combination.\[^{17}\]

**Immunoglobulins**

In case of critically ill SARS, who show signs of deterioration, further escalation of immunomodulation is indicated and intravenous (i.v.) immunoglobulin may be considered.\[^{22}\] Patients who show poor response to initial empirical therapy may get benefit from i.v. immunoglobulin.\[^{23}\]

**Host-Directed Therapies**

Host-directed therapies basically target improvement of the status of the host, improvement of host immune response, or handling of host-related factors associated with viral replication.\[^{6}\] Apart from immunomodulators, metformin, atorvastatin, fibrates, as well as nutritional supplements may help in treating acute respiratory distress syndrome (ARDS) by boosting immunity. However, evidence of efficacy in SARS-CoV or MERS-CoV is poorly reported.\[^{24}\]

Zinc is reported to have antiviral effect,\[^{25}\] and it inhibits CoV RNA polymerase activity and thus hampers replication in cell culture experiments.\[^{26}\] As cytokine storm is a pathognomonic feature of COVID-19, inhibition of these pro-inflammatory cytokines may theoretically prove useful (e.g., inhibition of IL-6 by tocilizumab).\[^{27}\]

**Other Therapies**

Other treatment options, which are either used rarely or in experimental state, are SiRNA, tumor necrosis factor-alpha inhibitors, neutralizing antibodies, pentoxifylline, etc. However, the level of evidence is quite poor and hence not recommended for routine care.\[^{28}\]

**Management of 2019-Novel Coronavirus (Coronavirus Disease-19)**

Clinical care of suspected patients with 2019-nCoV should focus on recognition of the disease condition at the earliest, isolation and adoption of proper infection control measures, and delivery of optimized supportive care toward the suspected/confirmed cases.\[^{29}\] For preventive measure, the WHO guideline “Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected” mainly focuses on avoiding close contact with persons suffering from acute respiratory infections, frequent hand wash, and avoidance of unwanted contact with wild animals. In case of patients with respiratory distress, the patient is to be evaluated for the presence of shock. Empirical antimicrobial coverage is to be given (to cover up the likely causative organisms, which may be responsible for severe acute respiratory infection). Special concern is to be given for other comorbid conditions. In case of hypoxemic respiratory failure, it needs to be managed aggressively with high-flow nasal oxygen or noninvasive ventilation or by endotracheal intubation and positive pressure ventilation as required. Special concern is to be taken for the identification and management of septic shock.\[^{27}\]

**Treatment of 2019-Novel Coronavirus: Evidence from China**

The details of treatment reported in case of 2019-nCoV are presented in Table 1. The antiviral agents which are used in the management of 2019-nCoV episodes are lopinavir, ritonavir, arbidol,\[^{29}\] oseltamivir,\[^{12}\] i.v. ganciclovir.\[^{29}\] Among immunomodulators, the commonly used agents are systemic corticosteroids,\[^{12,20}\] and i.v. immunoglobulin was used in more serious cases who were refractory to initial therapy.\[^{28}\] Among herbal medicines, Chinese herbal medicinal products Tanreqing i.v. gtt,\[^{31}\] shufeng jiedu capsule (a traditional Chinese medicine) was used.\[^{28}\] The WHO has specified that at this present time there is no high level evidence is available, which favours use of a single specific antiviral agent for the treatment of patients with suspected or confirmed 2019nCoV infection.\[^{27}\] Although many of the death cases were in higher age group\[^{32}\] and many were smokers and had bilateral disease,\[^{33}\] lack of appropriate control group is the main hindrance in interpreting these prognostic factors.

**Recent Advances in the Treatment of 2019-Novel Coronavirus**

**Remdesivir and chloroquine**\[^{33}\]

Using clinical isolates of 2019-nCoV, Wang et al., 2020 evaluated the efficacy of seven agents (ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine, remdesivir [GS5734], and favipiravir [T-705]) in in vitro conditions. Cytotoxicity was evaluated in vero E6 cells, which was followed by infection of the cells with 2019-nCoV clinical isolates, and the test drug was evaluated at different doses. Reverse transcription polymerase chain reaction-based quantification was done to get the viral yield, which was later confirmed by immunofluorescence microscopy (nucleocapsid protein visualization). Both chloroquine and remdesivir inhibited virus infection
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All patients were treated in isolation. Antibiotic therapy was administered in 100% cases (n=99 patients). 4 patients with secondary bacterial infection received antibiotic therapy. The duration of antibiotic therapy ranged from 3 to 17 days. In case of secondary bacterial infection, culture and sensitivity were used as a guide for antibiotic therapy. The duration of antibiotic therapy ranged from 3 to 17 days. 137 2019-nCoV-infected patients received oseltamivir. The most commonly used antibiotics were ceftriaxone (25%), moxifloxacin (64%), and azithromycin (18%). Around 45% of patients received additional glucocorticoid therapy. 9.4% of patients required additional vasopressor and 1.44% of patients required renal replacement therapy. Severity of disease was an important determinant of antiviral and corticosteroid therapy. However, no effective outcomes were observed in patients with higher age at presentation and concomitant disease were more likely to show features of respiratory failure and had poorer outcome.

### Table 1: Details of reported therapeutic strategies to counter 2019-nCoV infection

| Study details | Sample size | Therapeutic agents | Outcome |
|---------------|-------------|--------------------|---------|
| [28]          | 4 patients  | All patients received oxygen therapy and mechanical ventilation. All patients were treated with antibiotic, lopinavir, ritonavir, arbidol, and SFJDC (a traditional Chinese medicine). However, only one seriously ill patient received i.v. immunoglobulin. All patients were treated with antivirials for 6-15 days. | 3 patients improved, last patient still on ventilator (but improved) |
| [12]          | 41 patients | Antibiotic therapy was administered in 100% cases (n=41). 93% (n=38) patients received oseltamivir. 22% (n=9) patients received systemic corticosteroids. Antiviral therapy: Overall 38 (93%), ICU setting 12 (92%), non-ICU care 26 (93%). Antibiotic therapy: Overall 41 (100%), ICU setting 13 (100%), non-ICU setting 28 (100%). Use of corticosteroid: Overall 9 (22%), ICU settings 6 (46%), non-ICU settings 3 (11%). | Discharged=68% (n=28) Death=6 patients Death: Overall 6/41, ICU 5/13, non-ICU 1/28 |
| [32]          | Clinical data from 137 2019-nCoV-infected patients | Patients were treated symptomatically and given respiratory support. Immunoglobulin was given to few patients depending upon clinical severity and response. No benefit was observed from systemic corticosteroid. Notably, early respiratory support facilitated disease recovery and improved prognosis. The risk of death was primarily associated with age, underlying chronic diseases, and median interval from the appearance of initial symptoms to dyspnea. | Patients with higher age at presentation and concomitant disease were more likely to show features of respiratory failure and had poorer outcome |
| [30]          | 138 patients | 90% of patients received oseltamivir. The most commonly used antibiotics were ceftriaxone (25%), moxifloxacin (64%), and azithromycin (18%). Around 45% of patients received additional glucocorticoid therapy. 9.4% of patients required additional vasopressor and 1.44% of patients required renal replacement therapy. Severity of disease was an important determinant of antiviral and corticosteroid therapy. However, no effective outcomes were observed in patients with higher age at presentation and concomitant disease were more likely to show features of respiratory failure and had poorer outcome. | 31% (n=31) Died=11 (11%) Details of death patients: 7/11 deaths age >60 years Long history of smoking=3 MultIBSTA score could predict outcome Lymphopenia=8 Bilateral pneumonia=7 Hypertension=3 |
| [29]          | 99 patients | All patients were treated in isolation. Antiviral therapy given to 76% patients (n=75). The antivirals used were oral oseltamivir, i.v. ganciclovir and lopinavir/ritonavir tablets. The duration of antiviral therapy ranged from 3 to 14 days. 70 patients received antibiotic treatment. In case of secondary bacterial infection, culture and sensitivity were used as a guide for antibiotic therapy. The duration of antibiotic therapy ranged from 3 to 17 days. 19 (19%) patients were also treated with additional corticosteroids for a duration of 3-15 days. | Discharged=36% (n=47) Death=4.3% (n=6) |
| [31]          | 2 patients  | Both the patients were treated with i.v. corticosteroid, human gamma globulin, antibiotics (moxifloxacin), antiviral (oseltamivir and abidol hydrochloride) and Chinese herbal medicine Tanreqing i.v. gtt. | Both patients recovered |

SFJDC=Shufeng Jiedu Capsule, ICU=Intensive care unit, i.v.=Intravenous, ECMO=Extracorporeal membrane oxygenation, RRT=Renal replacement therapy

at micromolar level (0.77–1.13 µM) and with high selectivity.\(^{[35]}\)

Being an adenosine analog, remdesivir gets incorporated into viral RNA and causes premature chain termination.\(^{[34]}\)

The importance of chloroquine as an antiviral agent is coming up. Chloroquine even showed efficacy as a potent antiviral against SARS-CoV infection and spread.\(^{[35]}\)

Pretreatment with chloroquine renders vero E6 cells refractory to SARS CoV infection. Moreover, in the postinfection period, treatment with chloroquine prevents the spread of SARS-CoV infection.\(^{[35]}\)

Chloroquine increases endosomal pH and thus makes the environment unfavorable for the virus/cell fusion. Chloroquine also affects the glycosylation process of angiotensin-converting enzyme 2 (ACE-2, receptor for binding of viral spike protein, which is essential for interaction with the host).\(^{[35]}\)

Being nonexpensive and easily available agent, chloroquine may prove as a promising candidate.

**Baricitinib**

The SARS-CoV and the 2019nCoV both enters host cells through ACE2 receptormediated entry, especially through AT2 cells present in lungs.\(^{[36]}\)

Downstream signaling of this receptor mediates the endocytosis process, and AP2-associated protein kinase 1 (AAK1) plays a major role in this process. Thus, AAK1 represents
an important target. Richardson et al., 2020 evaluated 378 ligands, of which 47 were already approved for use in other conditions. Among these ligands, six inhibited AAK1 with high affinity. Considering the side effect profile, they found janus kinase inhibitor baricitinib to be the most important agent. In addition to AAK1, baricitinib also binds to another endocytosis regulator protein (cyclin G-associated kinase). Thus, the authors suggest that baricitinib can be evaluated in the *in vitro* conditions as well as in the clinical trial settings for 2019-nCoV.[90]

**Limitations of current research**

Lack of high-quality evidence (especially randomized controlled trails [RCTs]) is the most important limitation of the current CoV research. As most of the CoV strains are genetically different and the outbreaks occur extremely randomly, conducting an RCT is extremely difficult, and we have to rely on observational studies (most of which do not have proper control group), which hamper the estimation of proper treatment effect.

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