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Current Consensus on Drugs and Biologics against nCOVID-19 – A Systematic Review

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ABSTRACT

The deadly pandemic caused by the novel coronavirus continues to jeopardize humanity. The current situation report published by the World Health Organization (on 1st May, 2020) confirms 32,49,022 nCOVID-19 cases with 2,30,804 toll of human lives. This global statistical data reflects the contagiosity of SARS-CoV-2 across the world. This newly emerged strain has presented an unequalled challenge for identifying effective drugs & biologics. Till date, no proven effective therapy exists for SARS-CoV-2 infection. The past experience of managing viral aetiological outbreaks renders background for extrapolation to nCOVID-19, yet effectivity remains uncertain. This dire scenario has been addressed with an escalation in the number of clinical trials in order to come up with specific treatment. Repurposed drugs, Antibodies and Vaccines are under various stages of clinical trials currently. In the interim, supportive care, infection prevention measures and extended psychological assistance concords the core strategy to battle against this virus.

Key Words: Pandemic, World Health Organization, nCOVID-19, SARS-CoV-2

Level of Evidence: Level I

INTRODUCTION

Humanity is being jeopardized under the grip of the newly emerged strain of coronavirus (SARS-CoV-2). It was declared as a pandemic by the World Health Organization on 11th March, 2020. Since its inception, nCOVID-19 is spreading like a global wildfire. The ongoing pandemic has challenged the solidarity of rapidly progressing medical science and technology. The genomic studies render natural selection process as the plausible explanation of the emergence of SARS-CoV-2 and rules out the view of it as a product of laboratory manipulation[1]. The epidemiological studies have described bats as the reservoir host and Malayan pangolins as intermediate host[2]. The transmission occurs either by direct contact or indirect contact. Understanding of the pathogenesis has rendered insight into the potential target sites for therapeutics; however those identified are in trial and not specifically approved. The global statistical data confirms 32,49,022 nCOVID-19 cases with 2,30,804 toll of human lives (on 1st May, 2020)[3]. The incidence and mortality reported are subject to geographic variation[3].

The past experience of managing outbreaks of viral aetiology (SARS-CoV-1, Influenza, MERS-CoV and EBOV) paves the ground for extrapolation to SARS-CoV-2 pandemic. Yet no proven therapies to vanquish the virus are rationally validated. The data as on 15th April 2020 at ClinicalTrials.gov with the searched terms- nCOVID-19, SARS-CoV-2,

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2019-nCoV, 2019 novel coronavirus, severe acute respiratory distress syndrome, coronavirus-2 shows 833 enrolled studies and of all 541 are interventional studies[4]. This shows a glimpse of the global pace in the quest to find specific therapy with proven efficacy and rationality. Numerous authorities have collaborated for active clinical trials and these are underway. One such multinational megatrial launched by the WHO is 'Solidarity' which is directed to find the effectiveness of four subsets of drugs- Remdesivir; Lopinavir/Ritonavir; Lopinavir/Ritonavir with Interferon β-1a and Chloroquine or Hydroxychloroquine (selection based on evidence from laboratory, animal and clinical studies)[5]. In addition, few therapies which emerged as a result of divergent thought process include vitamin-D supplementation, the role of mesenchymal stem cells; monoclonal antibodies and convalescent plasma are also under clinical evaluation.

As of now, supportive care, strict implementation of infection control measures and extended psychological assistance are the concordant principles to deterrence. This review article adduces current consensus regarding proposed treatment, repurposed or experimental drugs and biologics for nCOVID-19 with a brief outline of preventive strategies advocated currently.

Viral pathogenesis of SARS-CoV-2 and Potential Drug Targets

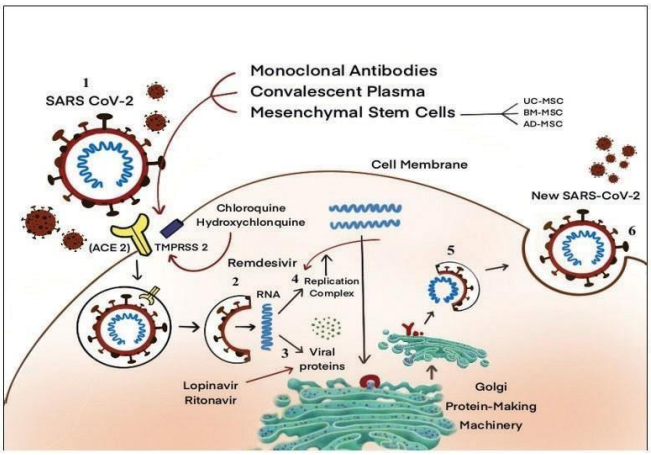

Figure 1: Simplified Representation of Molecular Pathogenesis of SARS-CoV-2 with Potential Target Site of Selected Repurposed and Investigational Drugs & Biologics.

[(1) Binding of spike protein to ACE-2 and TMPRSS-2 facilitates virion entry; (2) Release of RNA by virion; (3) Translation of RNA into proteins by protein making machinery; (4)Formation of Replication Complex to produce more RNA; (5) Assembling of protein & RNA in golgi apparatus; (6)Virion Released]

SARS-CoV-2 is a single-stranded positive sensed, RNA enveloped virus belonging to the beta subfamily of Coronaviridae family[1]. The virus glycoprotein- (S) spike protein targets angiotensin-converting enzyme 2 (ACE-2) receptors, which are widely distributed over the alveolar type II (AT2) cells and endothelium and binds to it[6]. Another host type 2 transmembrane serine protease (TMPRSS-2) facilitates the entry mechanism via S protein[7]. The complex procedure of the replication of SARS-CoV-2 following a series of steps has been depicted in figure 1. The understanding of viral lifecycle renders selection of a potential site for optimizing drug targets. Remdesivir is the most promising drug currently. However, the FDA has categorized it as an Investigational New Drug (IND)[8].

The Pipeline of Drugs & Biologics for nCOVID-19

Antiviral Drugs

A. REMDESIVIR (formally GS-5734)

Remdesivir is an investigational nucleoside analogue of Remdesivir triphosphate (RDV-TP) discovered amidst a screening procedure against RNA viruses such as Flaviviridae and Coronaviridae. During the outbreak of EBOV, this was found to be a 'promising agent' due to its low EC_{50} with host polymerase selectivity against EBOV[9]. It acts as an inhibitor of RNA-dependent RNA polymerase (RdRps). Remdesivir was found to prevent haemorrhage in the lungs with a reduction in viral lung titres more than the comparator agents in a murine lung infection model with MERS-CoV[10]. It is currently a promising potential drug due to its broad- spectrum effect with potent in-vitro activity against several corona-viruses including SARS-CoV-2 with EC_{50} and EC_{90} values found to be 0.77µM and 1.76µM respectively[11,12]. Single and multiple-dose phase-1 clinical trials evaluated the safety and pharmacokinetics of this drug where intravenous infusions ranging 3-225 mg were demonstrated to be well-tolerated without any substantiation of hepatic and renal toxicity. However, multiple dosing showed a rise in reversible aspartate aminotransferase and alanine transaminase levels[13]. Notably, it is not approved by the FDA at present and can be obtained via expanded access, enrolling in a clinical trial or for compassionate use only for children who are <18 years and pregnant women. Currently, clinical trials are going on for evaluating the safety and antiviral efficacy in patients of nCOVID-19 (NCT04292899, NCT04292730, NCT04321616, NCT04280705, NCT04315948, NCT04335123)[14]. The results of the randomized controlled trials are anticipatory for incorporating Remdesivir as a considerable drug against SARS-CoV-2.

B. LOPINAVIR/RITONAVIR

This oral combination approved by the US-FDA for treating HIV infection has been repurposed for nCOVID-19 treatment. In-vitro and animal model studies have outlined its potential activity against SARS-CoV-1 and MERS-CoV

respectively[15,16]. Recently, the in-vitro activity of lopinavir against SARS-CoV-2 has been adduced[17]. These are HIV protease inhibitors which act by binding to M^{Pro} enzyme which is regarded as the key enzyme of replication; thereby suppressing coronavirus activity[18]. Clinical outcomes from SARS-CoV-1 and MERS-CoV-1 confer no effect with delayed lopinavir/ritonavir therapy and put forth to have considerable importance when administered during the early phase of viral replication (early 7-10 days)[16,19].

In a recent rapid review on the efficacy of lopinavir/ritonavir in nCOVID-19, Jienchi Dorward and Kome Gbinigie concluded that there is insufficient evidence to recommend the use of this combination of drugs for nCOVID-19 outside the research studies. The identified clinical trials are subject to methodological flaws. These conclusions are based on the final review of 2 clinical trials [Cao et al[20] and ELACOI[21]] and 4 cohort studies selected as per full-text screening by the authors (article yet to be peer-reviewed)[22]. This emphasizes its consideration on the basis of several ongoing clinical trials. The drug combination with and without interferon beta is included as subsets in the large megatrial launched by the World Health Organization[5]. Yet its role in nCOVID-19 treatment is limited.

The most studied lopinavir/ritonavir dose regime for nCOVID-19 treatment is 400mg/100mg BD (twice daily) for 14days[20,23]. A randomized controlled trial by Cao et al. revealed that 50% of the enrolled patients experienced an adverse effect and 14% discontinued this combination therapy because of gastrointestinal adverse effect. In nCOVID-19 patients, drug-induced transaminitis may exacerbate and may result in fatal liver injury. Several investigational clinical trials regarded an increase in alanine transaminase levels as the exclusion criteria.

Another protease inhibitor, Darunavir demonstrated activity against SARS-CoV-2 as per in-vitro cell study models. Currently, a randomized controlled trial is underway from China assessing the efficacy and safety of Darunavir and Cobicistat for nCOVID-19 (NCT04252274)[14].

C. FAVIPIRAVIR (formerly T-705)

It's a prodrug of a purine nucleotide. Its active form inhibits the RNA polymerase which in turn halts the viral replication. It is an IND (Investigational New Drug) mainly studied with respect to Influenza and Ebola virus infection. But in a study by Furuta Y et al., it demonstrated broad-spectrum activity against other RNA viruses as well[24]. The in-vitro study reported EC_{50} against SARS-CoV-2 to be 61.88µM/L in Vero-E6cells[25]. The drug dose regime recommended for this includes a loading dose of (2400 mg to 3000 mg every 12 hours × 2 doses) and thereafter maintenance dose of (1200 mg to 1800 mg every 12 hours) respectively[26]. Overall this drug is well-tolerated with mild adverse effect profile. Still, there is a limited adverse event profile for higher dose regime[27].

Chang Chen et al. conducted a prospective, randomized, controlled, open-label multicentre trial wherein 240 patients were randomized for assessment of Favipiravir v/s Umifenovir. These patients were randomly assigned in a ratio of 1:1 and were administered Favipiravir in a dose of (1600 mg x 2/first day followed by 600 mg x 2/day) and Umifenovir (200 mg x 3/day) for the duration of 10 days. The clinical recovery rate on day-7 did not significantly differ between both the group (P=0.1396, difference of recovery rate; 95% CI: 0.0305 to 0.2213)[28]. Another interventional study (randomized; open label) is underway from China with an enrolment of 150 patients belonging to age group 18-65 years. The primary purpose of this intervention is to study the combined effects of Favipiravir and Tocilizumab in the treatment for nCOVID-19 (NCT04310228)[14]. RCTs are the need of the hour in order to rationalize the use for nCOVID-19.

D. RIBAVIRIN

It is a guanine analogue inhibiting the viral RNA-dependent RNA polymerase. Based on the in-vitro evidence and the potency enhancing strategies developed during the SARS-CoV-1 and MERS-CoV outbreaks, this drug can be extrapolated for treating nCOVID-19. In-vitro studies on SARS-CoV-1 demonstrated the inhibition of viral replication at higher doses (1.2 g – 2.4 g orally every 8 hours) singly and in combination therapy[29]. Moreover, the clinical studies in connotation to these mentioned prior outbreaks outline its associated dose-dependent hematological toxicity and elevations of transaminases due to injury[29,30]. Ribavirin is contraindicated in pregnancy due to its known teratogenicity[31]. The wide availability, low cost, easy accessibility and substantial evidence from the past rendered it as an option to be used during the inception of the outbreak in China[32].

A randomized controlled, phase 2 study from Hong Kong evaluated the combination therapy with Lopinavir/Ritonavir, Ribavirin and Interferon-beta enrolling 127 patients. The study has been completed, yet results are awaited (NCT04276688)[14]. As of now, the data on the efficacy of ribavirin therapy is inconclusive and if used then combination therapy holds scope for a beneficial role in nCOVID-19 treatment.

E. UMIFENOVIR (ARBIDOL)

This drug is unique in its mechanism of action; targeting the S protein/ACE2 and inhibits the membrane fusion of the envelope of virus[33]. Currently, this drug is available in Russia and China as prophylaxis and therapeutics for Influenza. Here also it is seemingly of great interest due to its in-vitro activity against SARS-CoV-2[34]. The dosing regimen used in Influenza (200 mg orally every 8 hours) will be evaluated for

nCOVID-19 therapy (NCT04260594)[14]. In addition to this, two large phase-4 combination studies involving intervention with Arbidol or Lopinavir/ritonavir or Oseltamivir (NCT04255017) and Arbidol or Lopinavir/Ritonavir (NCT04252885) from China are underway[14].

F. OSELTAMIVIR

Oseltamivir, a neuraminidase inhibitor, is a specific drug for treating Influenza. No corroborative findings are available in context to its in-vitro activity against SARS-CoV-2. Notably, the influenza season in China masked the plausibility of the emergence of a new aetiological agent; thereby oseltamivir was administered as an empirical therapy during initial the phase of the outbreak[35]. The role in nCOVID-19 is ill-defined once influenza has been ruled out. On-going clinical trials have placed it as comparator rather than a therapeutic agent.

Antimalarial Drugs

A. CHLOROQUINE & HYDROXYCHLOROQUINE

The long-standing record of therapeutic efficacy can be traced back to approval for treating vector-borne disease like malaria and systemic inflammatory diseases[36]. The mechanism of action is by blocking the entry of the virus via inhibition of glycosylation of host receptors, proteolytic processing and acidification of endosomes. In addition to this, they impart an immuno-modulatory effect by attenuating the production of cytokines and inhibiting autophagy and lysosomal activity into host cells. The antiviral activity against SARS-CoV-2 has been noted in-vitro wherein hydroxychloroquine reported lower EC_{50} than chloroquine (hydroxychloroquine: EC_{50} = 6.14µM < chloroquine: EC_{50} = 23.90µM) respectively[37,38]. The dosing regimen for SARS-CoV-2 has been variable among the clinical trials and further delineation should be done on the basis of randomized controlled trials. This is presently tagged as a repurposed drug and being used as off-label across countries; briefly discussed in Table-1. Studies have reported hydroxychloroquine to be more potent than chloroquine. These agents are known to cause rare and serious adverse effects like the prolongation of QTc interval, hypoglycaemia, neuropsychiatric effects and retinopathy[39]. Chloroquine and hydroxychloroquine usage is considered safe in pregnancy. Further Osadchy A et al. in his literature review of 12 studies which enrolled 588 patients receiving hydroxychloroquine or chloroquine found no overt ocular toxicity in infants[40].

An open-label non-randomized clinical trial from France enrolling a small sample size (36 patients) noted that the treatment with hydroxychloroquine was significantly associated with a reduction in the viral load on day-6 in nCOVID-19 patients and further the effect was reinforced by Azithromycin[41]. Interestingly, a recent study by Mahevas M. et al concluded that the use of hydroxychloroquine in patients hospitalised for documented nCOVID-19 positive hypoxic pneumonia was not found to be effective[42]. This study was based on the data collected from 4 hospitals based in France.

This repurposed drug is one of the subsets to be studied under the WHO launched megatrial[5].

Several clinical trials are underway either assessing the efficacy of hydroxychloroquine as post-exposure prophylaxis or as a therapeutic agent for nCOVID-19 (NCT04322396, NCT04341727, NCT04341727, NCT04342221, NCT04321278, NCT04344951, NCT04316377, NCT04325893, NCT04304053, NCT04350684, NCT04351724)[14]. Among these clinical trials, NCT04304053 is a phase-3, open-label, randomized clinical trial for the treatment of nCOVID-19 cases and chemoprophylaxis of contacts as prevention which will be primarily completed by 15th June 2020. Small studies have reported it with positive effect however results are awaited for further substantiation of its efficacy and safety concerns.

Antiparasitic Drugs

A. IVERMECTIN

Ivermectin is an FDA approved drug for the treatment of parasitic infections. It has been recently reported to have broad-spectrum anti-viral activity in-vitro against SARS-CoV-2 wherein it has shown about 5000 fold reduction in viral RNA at 48 hours following the addition of single dose to vero-h SLAM cells 2 hours post infection[43]. It acts via inhibition of nuclear transport. However, there is lack of evidence on safety measures, especially during pregnancy.

B. NITAZOXANIDE

This anti-helminthic drug has a broad spectrum of antiviral activity with favorable relative safety perspective. Antiviral activity in-vitro against MERS and SARS-CoV-2 has been demonstrated[44]. But the lack of evidence warrants further detailed study.

Adjunctive Drugs

A. CORTICOSTEROIDS

The rational use of corticosteroids is for downregulating the inflammatory process in the lungs and thereby preventing the onset of acute respiratory distress syndrome (ARDS). On the contrary, these benefits can be outweighed by its adverse effects associated with delayed viral load clearance and additionally paving the ground for secondary infections. It can be substantiated from a randomized controlled trial by Wong et al. in SARS-CoV patients wherein they noted higher concentrations of viral RNA in 2nd - 3rd week of infection upon measuring at regular intervals in non- intubated patients treated with corticosteroids when compared to placebo[45]. On the other hand, another Chinese Study on SARS-CoV separated patients into 4 treatment groups and it was identified that early high dose steroids administered in

combination with a quinolone yielded the most favorable outcome[46]. Arecent retrospective study from China, reported decreased risk of death in patients with ARDS when treated with methylprednisolone in comparison to interventions without steroids (23/50 [46%] with steroids vs 21/34 [62%] without; HR, 0.38 [95%CI, 0.20-0.72])[47]. Due to the lack of proven data, the cautious use of corticosteroids is justifiable rather than a routine use in nCOVID-19 patients.

B. AZITHROMYCIN

This macrolide antibiotic is reported to curb pulmonary inflammation due to its immunomodulatory effect. In addition, it prevents bacterial superinfection. In a clinical study from France; notable was its enforced effect on the decrease in viral load when administered as an adjunct to HCQ[41]. It is to be used cautiously as it is associated with QT-interval prolongation. The documentation of its role as an adjunct in severe cases is limited. It may be effective singly or as an adjunct, but its widespread adoption calls for more number of randomized controlled trials for the same.

C. MONOCLONAL ANTIBODIES

These represent another potential class of adjunctive drugs which target the specific inflammatory cytokine or innate immune response resulting in an immunomodulatory effect. Cytokine storm phenomenon accounts for mortality seen in nCOVID-19 patients as it triggers the uncontrolled release of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-8, IL-33, TNF-α, TGF-β) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL-10 etc)[6,48].

Early case series from China identified IL-6 as the driving factor behind such dysregulation[49]. So, theoretically, monoclonal antibodies against IL-6 lessen the cytokine storm and improvise clinical outcome. Tocilizumab, Sarilumab and Siltuximab are IL-6 receptor antagonists approved by FDA for the treatment of Chronic Inflammatory disorders. Among all, Tocilizumab has been studied in clinical trials and viewed to have a favorable clinical outcome. China reported a beneficial outcome of Tocilizumab as a single dose in a study, but it lacked comparator group warranting further studies for its efficacy. In a recent retrospective study on 15 patients, Pan Luo et al. noted that Tocilizumab is beneficial in relieving inflammation in nCOVID-19 patients; however, repeated dosing is recommended for critically ill-patients and stated the need to study more number of cases in order to verify the same[50]. Currently, several randomized controlled trials are underway in China assessing it as single or combination therapy (NCT04310228, ChiCTR200002976)[14]. Sarilumab is also included in clinical trials and one such study including it in an adaptive phase 2/3, randomized, double-blind, placebo controlled study with 300 participants to assess its efficacy and safety for hospitalized nCOVID-19 patients (NCT04327388)[14].

Currently, other monoclonal antibodies like Eculizumab (inhibition of terminal complement; NCT04288713); fingolimod (immunomodulator approved for treating multiple sclerosis; NCT04280588) and bevacizumab (anti–VEGF medication; NCT04275414) are being studied as a part of clinical trials in China or as expanded access in the U.S.

D. ACE INHIBITORS & ARBs

ACE2 is an enzyme which is physiologically involved in the activation of RAAS mechanism. Recognition of the fact that the SARS-CoV-2 viral infectivity is mediated by ACE2 receptors led to preclinical trials which suggested that RAAS inhibitors may further increase the expression. However, the insufficient data impels to ponder upon whether this translates to humans or not. The abrupt withdrawal in high-risk individuals may result in clinical instability with adverse outcome. Muthiah et al. recommend the continuation of RAAS inhibitors in otherwise stable patients with underlying co-morbidities until further substantiation is done from clinical trials[51]. Currently, two randomized controlled studies from Ireland (NCT04330300), France (NCT0439195) and one cross-sectional study from Italy (NCT04331574) are advancing for understanding the role of ACE inhibitors and ARBs in nCOVID-19 respectively[14].

E. INTERFERON-α and β

These have been studied in the prior outbreaks and interferon β notably demonstrated antiviral activity against MERS-CoV[29]. Current guidelines by Chinese authorities have enlisted it as an alternative treatment[23]. These have been studied as a combination therapy with lopinavir/ritonavir or ribavirin so far. Sallard E et.al. concluded that interferon-β may be regarded as safe and easy for upscaling treatment against nCOVID-19 in early stages of the infection[52]. Currently included in WHO launched megatrial in combination with lopinavir/ritonavir for evaluation of efficacy and safety[5]. Clinical trials which have been registered to evaluate this potential therapy include (ChiCTR2000029387) and (NCT04276688).

F. VITAMIN- D

Its imperative role has been demonstrated previously for preventing respiratory infections which renders it for consideration as an adjunct in boosting up immunity. Three mechanisms have been reported wherein it strengthens physical barrier, channelizes cellular innate immunity for antimicrobial activity and modulates adaptive immunity leading to further inhibition and suppression of the inflammatory response and attenuation of cytokine storm respectively[53,54]. An observational study (case-control; prospective) enrolling 80 participants is afoot for assessing prophylaxis for healthcare professionals with hydroxychloroquine adjunct with vitamin C&D and zinc during nCOVID-19 pandemic (NCT04326725)[14].

Cell & Plasma based Biologics

A. MESENCHYMAL STEM CELLS

Novel therapeutics stemmed out from the core principles of regenerative medicine to be optimized for nCOVID-19. Mesenchymal Stem Cells are specialized cells which lack key entry points (ACE-2 & TMPRSS-2) for nCOVID-19 and hence they are immune to it, whereby imparting the immunomodulatory effect by attenuating the cytokine storm and repairing the damaged tissue[55]. Zikaun Leng et al. reported that mesenchymal stem cells transplantation in 7 enrolled nCOVID-19 patients at Beijing Youan Hospital had improved clinical outcomes[6]. The evidence cited was put forth for considering it as a treating modality in severely- ill patients after proven efficacy and safety in large cohorts. Currently, 9 studies are afoot to optimize mesenchymal stem cells for nCOVID-19[14].

B. CONVALESCENT PLASMA

The beneficial experience in managing prior viral aetiological outbreaks of SARS-CoV-1, MERS-CoV and EBOV renders it as a potential therapy to be optimised for SARS-CoV-2. The management of SARS-CoV-1 with convalescent plasma therapy is the best way to reduce viral load in a short span of time. The principle strategy is passive immune therapy involving retrieval of plasma (rich in virus neutralising antibodies) from the recovered patients and transfusing the same to exposed individuals or positive cases. Currently, the US FDA has approved the emergent use of convalescent plasma as an investigational drug for critically-ill patients and has also instructed the doctors to follow the usual system for an investigational new drug (IND) application in case if they want to study[56,63]. However, the randomized control trials may be undertaken to rationalize the titres for utility and establish safety measures.

Table 1: Available Guidelines for Repurposed Drugs in treatment of nCOVID-19

Guidelines/Study	Country	Dose (Adults)
Expert Consensus- Department of Science and Technology and Health Commission of Guangdong Province (57)	*China*	*Chloroquine phosphate* – 500 mg BID x 10 days.
Central Clinical Task Force (58)	*Korea*	Moderate to Severe nCOVID-19 *Lopinavir* – 400 mg/*Ritonavir* – 100 mg BID or; *Chloroquine* –500 mg orally per day or; *Hydroxychloroquine* – 400 mg orally per day x 7 – 10 days.
Centre for Disease Control and Prevention (MICC Version 1) (59)	*Atlanta*	URTI + Positive PCR *Chloroquine phosphate* – 500 mg BID x 5 days *Oseltamivir* – 150 mg BID x 5 days nCOVID-19 PNEUMONIA *Chloroquine phosphate* – 500 mg BID x 5 days + *Darunavir* – 800 mg / *Cobicistat* – 150 mg OD x 2 weeks
Italian Society of Infectious and Tropical Diseases (Lombardy Section) (60)	*Italy*	Mild to Moderate nCOVID-19 *Lopinavir/ritonavir* + *Chloroquine* – 500mg x 2/day or *Hydroxychloroquine* – 200 mg orally per day x 10 days. Severe or Critical nCOVID-19 *Remdesivir* + *Chloroquine*– 500 mg x 2/day or *Hydroxychloroquine* – 200 mg orally per day x 10 – 20 days.
Mount Sinai Health SystEM(61)	*Canada*	Moderate to Severe nCOVID-19 *Hydroxychloroquine* – 400 mg BID x 2 doses then 12 hour later start 400 mg OD x 5 – 10 days.
Gauret etal (41)	*France*	Critical nCOVID-19 *Remdesivir* x 10 days + *Chloroquine* x 5 days *Hydroxychloroquine* – 200 mg TID x 10 days
Indian Council of Medical Research (ICMR) (62) (64)	*India*	Chemoprophylaxis *Hydroxychloroquine* Asymptomatic healthcare workers involved in care of suspected or confirmed cases of nCOVID-19400mg BID on day-1; followed by 400 mg once/week x 7 weeks (to be taken with meals) Asymptomatic household contacts of laboratory confirmed cases – 400 mg BID on day-1; followed by 400mg once/week x 3 Weeks (to be taken with meals) Severe or Critical nCOVID-19 *Hydroxychloroquine* – 400mg BD on day 1 followed by 200mg BD x 4 days + *Azithromycin* 500 mg OD x 5 days+/- Glucocorticoids for short period (3 – 5 days).

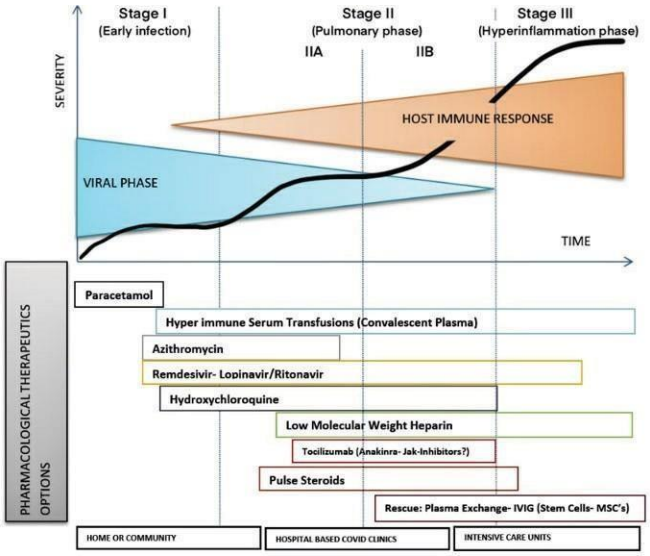

Figure 2: Schematic Representation of Rationalised Use of Drugs & Biologics (As per current clinical studies in relation to clinical spectrum) for nCOVID-19 (Modified from Siddiqu et.al [65])

Preventive strategies

In the interim, due to lack of definitive licensed drugs, biologics and vaccines, implementation of infection control measures is the key strategy to deterrence. Re-allocation of resources and global solidarity can gear-up the fight against nCOVID-19. The front liners are at the highest risk and should undertake all the indicated biosafety level measures. The need of the hour calls for the practice of quarantine, isolation, social distancing, hand hygiene and respiratory etiquettes wisely. Amidst all, it has fueled up anxiety, stress, panic, apprehension, phobia, depression, disturbed sleep etc. People are experiencing varied emotions such as anger out-burst, aggression, loneliness, irritation, fatigue, frustration, guilt, emotional dissatisfaction which in turn is responsible for triggering depression, self-harm and suicide. People have bottled up feelings of helplessness and hopelessness which in turn challenge their psychological resilience. At present, the practice of tele-medicine and the concerned protocols are made available. Counselling sessions in person or as tele-medicine practice focus on the relaxation techniques like breathing exercises and JPMR (Jacobson Progressive Muscle Relaxation) in order to deal with issues of anxiety, stress, psychosomatic symptoms etc. Various countries have devised helpline numbers to provide information to its residents regarding nCOVID-19.

The dire need is to address the scenario holistically and collaboratively in order to combat SARS-CoV-2.

DISCUSSION

The recent guidelines unrolled by the World Health Organization explicably mentions that currently there is no evidence favouring recommendation of any drug as a specific nCOVID-19 treatment for patients with nCOVID-19 conformational status. These guidelines direct to provide supportive care in relation to the severity of the presenting nCOVID-19 illness and doesn't support the routine use of systemic corticosteroids for treating pneumonia of viral aetiology outside clinical trials. Further to add on; INDs for nCOVID-19 treatment are to be used in an approved randomized controlled clinical trial only[66]. Similarly the guidelines issued by the Centre for Disease Control and Prevention outlines the unavailability of a specific drug for nCOVID-19 treatment at present. These direct for prompt implementation of infection prevention and control measures along with supportive management of associated complications. Systemic corticosteroids should not be used unless indicated otherwise. In context to INDs; the CDC recommends their utilization either via compassionate use or through clinical trials[67].

Evidence is emerging on prevention and divergent plausible therapeutics for nCOVID-19. Recently, the BCG vaccine has been linked to reduced morbidity and mortality due to nCOVID-19. However, the WHO stated that due to lack of evidence at present it is inconclusive and doesn't substantiate enough for amending prevailing policies across various countries[68]. Apart from this; the role of herd immunity for nCOVID-19 has emerged as a debatable issue with one of the prime reasons being a lack of vaccination against SARS-CoV-2. Amidst, tele-medicine is popularizing as the key practice and due guidelines have been issued for the same.

Currently, lockdown measures have been adopted as a public health measure to curb down SARS-CoV-2 contagiosity by one-third of the countries across the globe. The linchpin for addressing prevailing scenario calls for strategic steps to break the chain of transmission. This in turn rests on escalating procedures for testing and tracing contacts respectively. In addition to these; there is an urgent need to scale up clinical trials for repurposed drugs, other plausible therapeutics (Stem Cells; Convalescent Plasma; Plasma Lysate therapy; NK cell therapy & SVF) and more importantly vaccines so as to come-up with specifically proven treatment for nCOVID-19. Notably, many prospective randomized controlled trials are underway for the same with a beacon of hope to find a specific agent for pulverizing SARS-CoV-2.

CONCLUSION

The world is battling nCOVID-19 pandemic wherein this generation is confronting the global health crisis. No proven therapy to vanquish SARS-CoV-2 exists currently. A holistic

approach should be considered whilst this period lasts. The global rush of clinical trials launched for investigating the potential drugs, biologics and vaccines outlines the need and potential to provide high-quality substantiation amidst the pandemic. It is critical for clinicians to continually monitor, rapidly adapt to the emerging evidence-based literature and report their experience in managing and treating nCOVID-19 to the medical fraternity for further optimization of the treatment recommendations and protocols.

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Abbreviations

ACE2 – Angiotensin-Converting Enzyme 2; ARDS – Acute Respiratory Distress Syndrome; AT2 – Alveolar Type 2; nCOVID-19 – Novel Corona Virus Disease-2019; EBOV – Ebola Virus Disease; FDA – Food and Drug Administration; HCQ – Hydroxychloroquine; ICMR – Indian Council of Medical Research; IND – Investigational New Drug; JPMR – Jacobson Progressive Muscle Relaxation; MERS – Middle East Respiratory Syndrome; RAAS – Renin-Angiotensin-Aldosterone-System; RDV-TP – Remdesivir Triphosphate; SARS – Severe Acute Respiratory Syndrome; TMPRSS2 – Transmembrane Protease Serine 2; WHO – World Health Organization.

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