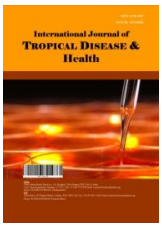

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A Novel Corona Virus (COVID-19) Pandemic, Pathogenesis, Clinical Features and Management Options, Public Health Measures

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Introduction: SARS-CoV-2 is an unknown corona virus causing COVID-19 disease responsible for the ongoing pandemic affecting over 190 countries, with a mortality rate of about 5%. The high mortality rate resulted from its ability to elicit cytokine storm via non-specific immune response with delay in specific immune response, notably worst in the elderly, HIV, immunocompromised and cancer diseased patients. The article therefore provides frontline health care workers, the opportunity to understand and equip themselves with management options, public health measures used in coping with COVID-19 infections and enables personnel to make quick preparation for Symptomatic COVID-19 infection in-order to reduce mortalities in health facilities. It also provides a summarised teaching material for medical and allied health students around the world.
Methodology: Credible data and information were obtained from the World health organization situation report, Johns Hopkins University Corona Virus resource centre and other notable journal publications. Most information was on public domain.
Results: Clinical features reported include pneumonia, renal dysfunction, hepatobiliary dysfunction and residual tissue damage, especially in the lungs in those that survive. The literature highlights the blood work-up picture (Leucopenia, increased cytokines IL-6, ferritin, Serum creatinine, urea, AST, GGT, ALT and Viremia) and radiological features of the disease. ELISA and RT-qPCR test

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are required for diagnosis using sputum, or pharyngeal swab, blood, serum, urine and faecal samples which lead to faeco-oral transmission. ELISA/RT-PCR is also required for disease exclusions in co-existing epidemics such as MERS-CoV, SARS-COV and other viral diseases. Treatment modalities employed thus far are trials that have produce results including targeted therapy, anti-retroviral, Favipiravir, Remdesivir, antibody-serum and antimalaria drugs such as chloroquine and quinine which are found among some protocols in African setting and other developing countries. Currently, ongoing preventive measures (face mask, social distancing and hand hygiene, community testing, isolation of confirmed cases and tracking of the exposed, remain the key corner-stone in the management of COVID-19 pandemic.

Conclusion: COVID -19 disease still remain unclear to many scientists and its pandemic still ongoing. There are many research and clinical trials ongoing while some drugs are used off-label in-order to mitigate the damage caused by the virus in Human body. Cytokine storm needs immunomodulators and viral targeted therapy as discussed in-order to reduce tissue damage, and eventually morbidity and mortalities from COVID-19 infections.

Keywords: COVID-19; SARS-CoV-2; corona virus; patho-physiology; prevention.

1. INTRODUCTION

COVID-19 (coronavirus 2019) infection by 21st July 2020 had a total of 3,858,686 confirmed cases with 141,426 deaths in USA only, 80102 death in Brazil and 45507 in UK (JHU 2020). The world had a total of 14,774,887 confirmed cases including five cruise [1] and a total of 611,599 confirmed deaths from complications of COVID-19. WHO mortality rate had been approximately 6.2% [2], while influenza had less than 1%. By this time transmission continues to rise Nigeria, while USA is having spikes from false-unorganized reopening of economy, Black Lives Matters Protest and Election campaign with large crowd attending not respecting social distancing or any public health measures. South-Korea and Italy had more mortalities due affectation of elderly and those with underlying disease condition or medical morbidities associated with old age such as diabetics, hypertension or advance cancer diseases. By the end of March 2020 Italy, France, Spain had 110574; 51487; 104118 confirmed cases and mortalities of 11.8%, 6.8%, 9% respectively [3]. However recently Italy had a reduction in fatalities, including Spain, due to control through strictly practiced general strategies for public health safety measures. Brazil seems to be epicentre of the Disease in South America because of the attitude of politicians and policies toward the diseases as alluded to the fact they have 1,368,195 confirmed cases, second to the USA, who is number one, as well as 58,314 numbers of death, which is low compared to USA [1]. There is little knowledge or none concerning the biology and clinical features and treatment options for the COVID-19 disease, prior to the beginning of the pandemic. So, therefore the World was caught unaware and ill-prepared. This manuscript intends to summarize experience from frontline health workers and facts from ongoing publication in-order to understand this new disease facing mankind.

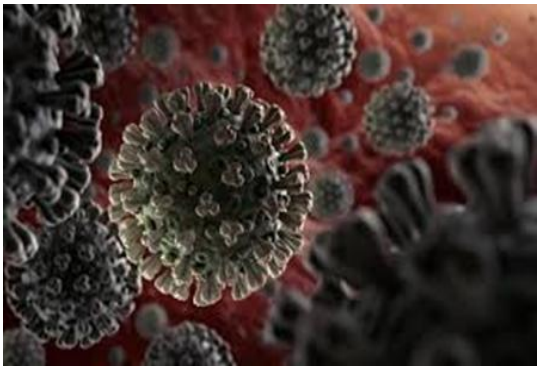

Fig. 1a. Schematic diagram of Covid-19
Source: Adapted from WHO

2. METHODOLOGY

Credible data and information were obtained from the World health organization situation report, Johns Hopkins University Corona Virus resource centre and other notable journal publications. Most on public domain. Clinical information about the pandemic were sourced online publications such as lancet, some experience was sourced from the China (Mainland) frontline health workers who had some of their pre-print, online published in Lancet as well as Centre for Diseases Control (CDC) situation report sites.

3. RESULTS AND DISCUSSION

World Health Organization (WHO) recognized SARS-CoV-2 as a new viral infectious disease posing a serious public health issue and risk. Several viral epidemics such as the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 to 2003, and H1N1 influenza in 2009, have been recorded. The most recent of them was the Middle East respiratory syndrome coronavirus (MERS-CoV), first reported in Saudi Arabia in 2012 [4].

On 31st December 2019, the Wuhan Municipal Committee of Health and Healthcare (Hubei Province, China) reported 27 cases of pneumonia of unknown origin. Seven cases were deemed serious from common exposure in a local market where shellfish, fish, and live animals were sold in the city of Wuhan. On 7 January 2020, the agent causing the outbreak was temporarily called new coronavirus (2019-nCoV) belonging to the Coronaviridae Family. By the end of January WHO declared the outbreak as an International Emergency and assigned it, SARS-CoV2 and COVID-19 disease by February [5]. By this time of publishing this paper the origin of the virus is still debatable.

It was suggested that COVID-19 may be of the zoonotic origin [6], because of the large number of people exposed to the wet animal market in Wuhan City, China. It is transmitted airborne from man to man via droplets during coughing, sneezing: surviving 8 hrs in the Air, On copper and steel for 2 hours, paper and plastic for 3-4 hrs. Recent report also stated that it could be air borne with any carrier. Its survival in air depends on several conditions such as heat and humidity, though the effect of high temperature of the tropics has yet to be proven as reason for its slow transmission rate in Africa. Its incubation period ranging from 1-14 day before symptoms appear, average 5-7 day after exposure. Reports also revealed that amount of virions available on surfaces by 48 hour of exposure would be insignificant [7].

3.1 Biology of Corona Virus

COVID-19 is a +single stranded RNA virus which belongs to the Coronaviridae Family, see Fig. 1a. Its size was about 30 kbp. SARS-CoV-2 shares 82% genome sequence similarity to SARS-CoV and 50% genome sequence homology to MERS-CoV — all three causing severe respiratory symptoms [8]. COVID-19 (SARS-CoV-2) is coated by a capsid which has glycoproteins/spike (Fig. 1b) proteins that bind to receptors on the epithelium of mucous membrane of the respiratory system, gastrointestinal and other mucosa. By uncoating itself, its RNA binds to the human genome which lead to viral protein and new virus production, triggering tissue cell death process. The spike Protein binds to type11 Pneumonocytes (Surfactant producing alveolar cells) which have ACE-2 (Angiotensin Converting enzyme-2), leading to docking of the virus on the membrane, therefore initiating a cascade of process that leads to destruction of the cells and production of new viruses. Immune cells are activated by Damage associated molecular Pattern (DAMP) and viremia, which leads to pathological changes, cellular migration and cytokines release in astronomical proportions (Cytokine storm). The pathogenesis leads to increase capillary permeability and extravasation of plasma and inflammatory cells into the lung tissue leading to inflammation as well as pneumonia, caused by superimposed bacterial infection or super-colonization. Viremia ensues as the inflammatory process begins with blood vessels, kidney and liver leading to organ dysfunction and failure. Corona and Rhino viruses have been known to be the principal causes of common cold among many viruses [9].

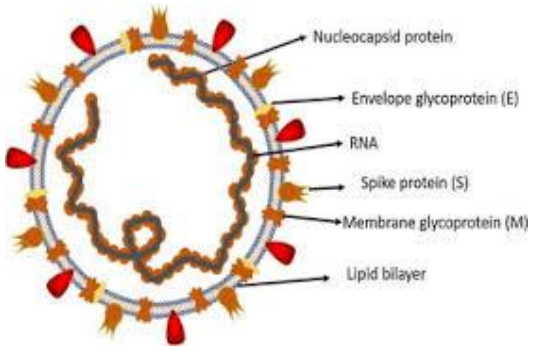

Fig. 1b. Schematic diagram of COVID-19

3.2 Serological and Molecular Pathogenesis

High levels of interferon-induced proteins, monocyte chemotactic protein 1, macrophage inflammatory protein 1A and TNF-α have been reported and noted to correlate with severity of the disease [10].

On the cellular level there is significant reduction of immune cells CD-4, CD-8 T lymphocyte cells as well as natural killer cells in severe disease

than in mild disease. Cytokine storm syndrome has been responsible for the cellular immune changes, characterized by an overwhelming imbalance between proinflammatory cytokine and anti-inflammatory cytokines, causing dysregulation of immune response and acute positive feedback on the immune pathway causing CD-4+ AND CD-8+ T cells to be acutely low in severe COVID-19 disease. The cytokine storm is a responsible for the high fever and headache [11,12,13].

The Specific Immune response involves Major Histocompatibility Pathway to form MHC-11 antigen peptide complex by antigen-presenting cells which release cytokine that causes CD-4+cells to differentiate into Th1 cells and secrete IL-6, IF-γ, GM-CSF which activate monocytes that releases more IL-6 and other cytokines that mobilize more macrophages to digest the virus and produce delay immune response. Th1 also activate the humoral system therefore producing antibodies [10].

In addition, endogenous protein secreted by COVID-19 infected cells activate CD-8+ cells Via MHC-1 pathway, promoting differentiation and proliferation to cause cell cytotoxicity to infected body cells.

The Non-specific immune response involves macrophages, natural killer cells respond to Pathogen associated molecular pattern (PAMP) via their receptors and recruit neutrophil and monocytes via cytokines. These cells aggregate tries to clear out virus, virus infected body cells and destroying normal tissues. Non-specific response also activates coagulation system and activate fibroblast [11,12,13].

The cytokine storm is also responsible for imbalance between body specific and non-specific immune response.

Reports have stated that the elderly and those with impaired immune system. have dysfunctional specific immune response which leads to delayed immune response while their non-specific response may continuously working leading to cytokine storm which was responsible for high mortality recorded among them [14] as noticed in Italy.

Furthermore, the spike protein on the virus also binds to Angiotensin converting enzyme-2(ACE-2) cholangiocytes leading to inflammation of biliary tree, stasis of bile and hepatobiliary dysfunction.

3.3 Clinical Presentation

Most patients may present as simple flu-like symptoms, fever 85%, cough 55-80%, dyspnoea 20-40%, myalgia or fatigue followed with sudden and rapid respiratory distress, tachypnoea, fever, tachycardia, feeling of drowning, choking and with distress while on ventilator as fluid accumulated inside their lungs. Rales and

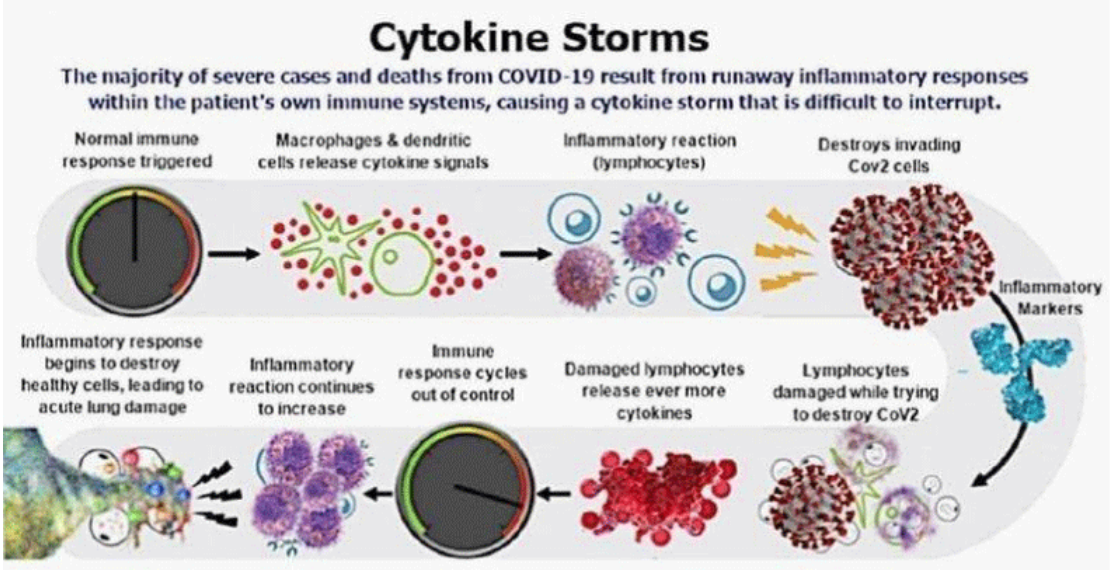

Fig. 1c. Schematic representation of Cytokine storm effect
Source: Iyer AP, et al. 2020

coarse crepitations can be heard in patients with Lung affectation. The late stages are known as acute respiratory distress syndrome and Multi-organ dysfunction or failure [15]. Severity of the disease depends on age of the affected persons, existing co-morbidities and immune status of the affected person [10].

3.4 Respiratory System

Some specific findings on radiological investigations as given by frontline doctors include ground-glass opacities, involving multiple lobes with sub-pleural and peripheral involvement in virtually all symptomatic cases. Other features include consolidations 77%, septa thickening 55%, bronchial dilatation and wall thickening 55%.

3.5 Gastrointestinal Tract

COVID-19 develop intestinal symptoms in 10% like diarrhoea, although low percentage as well as MERS-CoV patients [6,16]. the use of Pantoprazole, to inhibit gastric acid reduce stress ulcer and reduce fluid loss. The classical respiratory symptom may also latter finding in these patients, rather they may present with only abdominal and gastrointestinal symptoms at first. Therefore, proper rehydration with adequate electrolyte replacement is important for survival.

3.6 Hepatobiliary System

About 14–53% [8] cases have abnormal levels of alanine aminotransferase and aspartate aminotransferase (AST) during COVID-19 disease progression. Gamma-glutamyl transferase (GGT) and alkaline phosphatase have also been reported in some cases. ACE 2-positive cholangiocytes provide receptor for binding of COVID-19 which lead to hepatobiliary dysfunction [17], though autopsy report has not shown inclusion of viral bodies within hepatocyte [18]. Bilirubin level has also been documented in cases by Seattle doctors battling the pandemic. These conditions are notably worst, with people having underlying liver disease.

3.7 Cardiovascular System

A report revealed that 12% of COVID-19 disease patients had fulminant myocarditis [15] reported case review [16] showed hypotension and dyspnoea. COVID-19 therefore may worsen patient conditions in heart failure and may need cardiac support therapy both medical and where necessary surgical.

3.8 Nervous System

COVID-19 has been reported to affect central nervous system by causing loss of consciousness, altered mental status and abnormal bilateral extensor plantar reflexes. Loss of smell and taste are common symptoms seen in people admitted in our centre (ABUTH). Reported Brain CT scan showed massive Intra Cerebral Haemorrhage (ICH) in right hemisphere accompanied with Intra ventricular and subarachnoid haemorrhage [19]. Another report [20] showed symmetric hypoattenuation within the bilateral medial thalami on Non-contrast CT though angio-venograms were normal while brain MRI demonstrated haemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes and sub-insular regions. In one of the report other suspected viral infections (herpes simplex virus 1 and 2, varicella zoster virus, and West Nile virus) were excluded [20]. Furthermore, Brain tissue may react to the indirect effect of other system failures/dysfunction such as cardiac failure, hypoxia, hyperuricemia and immune suppression, also HIV neuropathy may worsen in COVID-19 patients.

3.9 Diagnosis of SARS-CoV-2

Real-time quantitative fluorescence polymerase chain reaction (RT-qPCR) testing have been used for confirmation of case definition using sputum/bronchial samples as standard, others are oropharyngeal swab [19], urine [21], blood/serum [22] including feaces [23] which have been reported positive even after patient's recovery and may lead to faeco-oral transmission. [24]. Blood work up to explore severity of the disease as revealed by frontline physicians in Seattle (USA) and China include lymphopenia in 80% cases, increase in BUN/serum creatinine, aspartate transaminase, Alanine transaminase and serum bilirubin, IL-6, ferritin with decrease in pro-calcitonin. Serum ferritin can be used for routine screening to determine the severity of the disease due to its availability and cheap cost. Serology test (ELISA)/Electrophoresis are positive for IgM few days after infection followed by IgG, titre levels may vary.

Investigations for exclusion include nucleic acid tests for influenza A virus, adenovirus, bocavirus,

rhinovirus, influenza A (H1N1) 2009, parainfluenza, chlamydia, partial pulmonary virus, influenza B virus, mycoplasma pneumoniae, influenza A virus H3N2 and respiratory syncytial virus. These exclusions are necessary where these endemic, epidemic and COVID-19 pandemic co-exist.

3.10 Management

The management of confirm cases begin with prevention with self-isolation or programmed isolation protocol as reported by the affected countries with multi-disciplinary management involving the pulmonologist, radiologist, cardiologist, infectious disease expert, virologist, intensivist and physician as well as infection control team. All must be fully dressed with personal protective equipment (Fig. 2).

3.11 Radiological Presentation

The X-ray film showed in Fig. 2, revealed a wide heterogenous opacity in both lung zones otherwise known as ground glass appearance.

Chest computerized tomography (CT) scan may show cardiomegaly and pleural effusion. On ECG tracings, changes include: ST-segment elevation myocardial infarction (III, AVF ST-segment elevation). Myocardial markers such as Troponin T, Creatine kinase isoenzyme (CK-MB). B-type natriuretic peptide (BNP) has been reported to increase.

Echocardiography revealed an enlarged heart and a marked decrease in ventricular systolic function with reduce LV ejection fraction and trace 2 mm pericardial effusion.

Fig. 2. An intensivist in Italy ICU monitory a COVID-19 victim with PPE

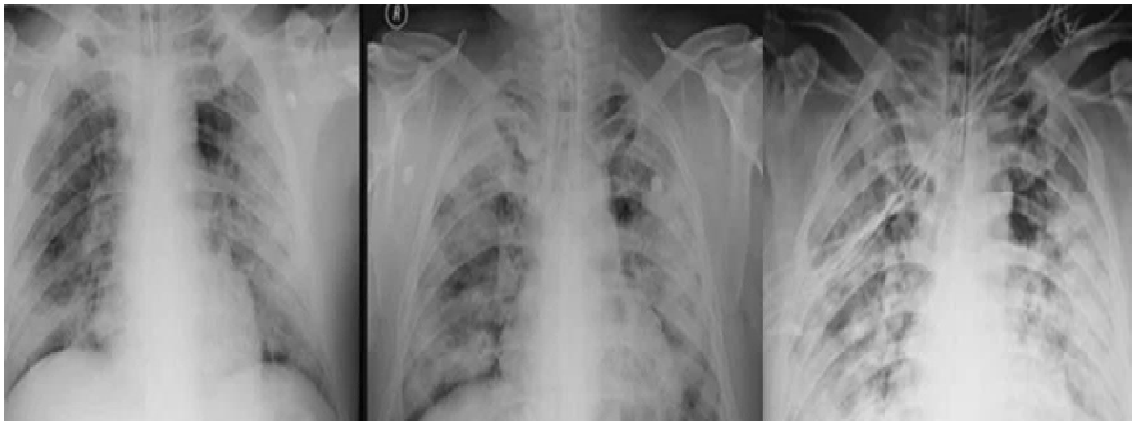

Fig. 3. Chest X-ray PA view: Images of an early casualty of COVID-19
Source: Lijuan Qian, Jie Yu and Heshui Shi in Propublica (2020)

Ventilators: The ventilator setting were reported to have been set-up at high positive end-expiratory pressure (PEEP), which keeps the lung inflated in-order to achieve oxygen saturation of at least 90%.

Continuous cardiac monitoring: The use of ECG continuous monitoring machine is indicated in those with fulminant myocarditis or with severe COVID-19 disease.

Treatment and pharmacological interventions available treatment options for consideration are placed at different stage of clinical trial, they include:

Reinfusion of recovered patient serum: This method was reported to achieve excellent results in the treatment of SARS and Influenza viruses [25-27].

Tocilizumab: This is IL-6 receptor blocker which is partly responsible for cytokine storm and has been employed in acute lymphocytic leukaemia [28,29]. Presently, a multi-centre clinical trial is ongoing after an initial clinical trial [13].

Glycyrrhetic acid can also block IL-6 signalling and signa transduction of transcription activator protein -3 (STAT-3) [30]. Other drugs that were tried during this pandemic included IL-1 and IF-γ blockers.

Oxygen: The strategy for oxygen therapy is known as HAPPY OXYGEN , where oxygen supply is ensured by using supply system such as AMBU bag, Ventilators or nasal prong depending on situation and indication and monitoring is carried our using simple Pulse Oximeter. Patients with COVID from frontline doctors have been found to be critical when SPO2 becomes 70%.

Some ill patient before transport to a place where medical help is available, may lie down prone on their belly so as to improve hypoxia.

Mesenchymal Stem Cell (MSC) therapy: May be considered for COVID-19 Inhibit abnormal activation of T-lymphocyte and Macrophages. It also Induces differentiation of T-cell to Treg and anti-inflammatory macrophages, inhibits IL-1α, TNF, IL-6, IL-12, IF-γ reducing storm, secret IL-10, hepatocyte growth factors and keratinocyte growth factor, VEGF to ease respiratory distress initiating repair of damage lungs and resisting fibrosis [31].

Cortisol and Steroid: Large doses of steroid have been employed in so many degenerative diseases and even in Nephropathy. This effect is because of its anti-inflammatory response therefore may be considered in cytokine storm in ARDs [32,33] but has limitation due to effects such as vascular necrosis and increase risk of diabetes [11]. Recent report from the United Kingdom also attest to the usefulness of dexamethasone. These drugs can reduce cytokine storm which lead to mortality.

Lopinavir and Ritonavir: These anti-retroviral drugs were developed against HIV infection but had shown to have positive results in China and India, especially in this pandemic when administered in combination with Interferon beta (IF-β) [34].

Remdesivir (GS-5734): Currently a promising nucleotide analogue in clinical trials for treating Ebola virus infections. Remdesivir inhibited the replication of SARS-CoV and MERS-CoV in tissue cultures [34], displaying efficiency in animal models has shown promising result in COVID-19 pandemic. Also, FAVIPIRAVIR has been considered. These drugs can prevent patients from becoming very sick.

Other anti-virals been evaluated include Nafamostat, Nitazoxanide, Ribavirin, Penciclovir, Favipiravir, Ritonavir, AAK1, Baricitinib, [35] as well as Arbidol ,which exhibited moderate results when tested against infection in patients and in vitro clinical isolates as revealed by Sheahan, et al. and his colleaques.

Antimalarial: Chloroquine and hydroxychloroquine. Chloroquine has some efficacy in HIV-AIDS and blocks infection by 2019-nCoV *in vitro*, perhaps by inhibiting glycosylation of viral ACE-2 or inhibition of quinone reductase 2, reducing synthesis of viral sialic acid; A trial combined it with lopinavir/ritonavir [30]. However, caution must be taken in-regards to adverse effects and limited to minimum. It still plays a role in treatment protocol in Africa, which las the lowest death rate from COVID-19 infection.

Colchicine; It has been used for many decades to treat Gout and considered having reduction effect on alpha defensin, produced by patient with COVID-19 inducing micro-cloth formation in Blood vessels of the lungs leading to progressive hypoxia.

Antibiotics: The use of azithromycin, Doxycycline and Amoxicillin has been found useful by frontline physician against pneumonia due to superimposed bacterial infection. They must be used according to their standard dosage for weight and age.

Other immune targeted therapy: These drugs may be considered, although not confirmed. Etoposide to deplete CD-8+ Tcell [36], rituximab to deplete B-lymphocyte, Alendizumab which target CD-52 expressing cells.

These may be considered as last measures due their immune suppression effect but helps in alleviating effect of cytokine storm.

Currently, WHO co-sponsors the solidarity trial1, which includes some off-label medicine. There are a total of 382 [30] Clinical trial registered with the WHO by the middle of march since the onset of the pandemic, though only 108 are Pharmacological interventions, 98 Traditional Chinese Medicine (TCM including 48 named TCMs; 27 unspecified methods; 18 combinations with unspecified Western therapies; and 5 others, e.g. acupuncture) and 38 Advanced therapy medicinal products which include mesenchymal stem cells and infusion of plasma from patients who have recovered. Other interventions that have been used in COVID-19 pandemic include vitamin, Zinc supplements and physical exercise, enteral feeding, psychotherapy and renal therapy.

COVID-19 associated cardiomyopathy therapy include: They include the use of Methylprednisolone to suppress inflammation and serum immunoglobulin to regulate immune status, Norepinephrine improves low Blood pressure, Diuretic therapy (torsemide and furosemide) to reduce cardiac load while Milrinone to increase myocardial contractility, Piperacillin sulbactam for infection [37]. High dose of vitamin C was also been use off-label African protocol.

3.12 Discharge and Follow-up

This stage of care depends on the clinical entity or system mostly affected. Covid-19 Testing affirming recovery of patient includes RT-PCR testing, which must be negative at least twice. Samples must be from two sources, Nasopharyngeal and any other. A Chest X-ray is usually done to investigate resolving pneumonia and the return of the heart size to normal size. Decision to discharge a patient is made if they show no relevant symptoms and at least two sequential negative confirmed results by real-time RT-PCR of sputum or respiratory tract samples collected over 24 hrs apart [24]. The titres of serological marker must have return to normal or reduced significantly including serum troponin, creatine MB-kinase and others. Social distancing, hand hygiene, use of face mask and other public health preventive measures remain main stay to prevent re-infection.

Aspirin: The survival rate has notably improved, because of more researched findings been published about the virus, therefore aspirin and heparin has been added to protocol in management of the treatment regimen of COVID 19. In some centres.

Prevention measures: WHO and Country's CDC authorities are the leaders attempting to curb the COVID-19 pandemic. Designed and researched measures include Social distancing (1.6-3 meters or more), hand hygiene (Washing and sanitizers), calling health emergency phone lines and visiting nearest infection disease control centres to mention a few. In-order to increase the numbers of Hospital support workers during this pandemic, models such as the reports adapted in training people in low capacity settings may be adopted using WHO tools for training [38,39].

Isolation: Those with clinical disease carry out self-isolation or hospital isolation with restriction in visitors. They may report themselves via phone or report to the nearest infection control centers. People were advised to cough into disposable handkerchief and paper tissue. Apply social distancing until admitted for treatments and all surfaces surrounding the patient should be clean with antiviral/decontaminants solutions including sterilizing the instruments used for managing them.

4. CONCLUSION

COVID-19, a new novel virus pandemic is spreading rapidly due to little knowledge about its cure. A summarized literature may help those in frontline to understand its management in-order to avert more mortalities or reduce fatality rate.

5. LIMITATION

The pandemic is still ongoing; So much about the biology and infectivity of the virus seem to change with time. Secondly many of the

suggested therapeutic are used off label or still on trial. Therefore, the article may need review for update as time and the virus evolve.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. John Hopkins University. Corona Virus Resource Centre, COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU); 2020.
Available:https://coronavirus.jhu.edu/map.html
(Accessed 21/7/2020)
2. WHO; Coronavirus Disease 2019 (COVID-19) Situation Report – 72; 2020.
3. Wilkepedia 2019–20, Coronavirus pandemic by country and territory. Encyclopedia; 2020.
Available:https://en.wikipedia.org/wiki/2019%E2%80%9320
(Retrieved 1st April 2020)
4. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation and treatment coronavirus (COVID-19). StatPearls Publishing; 2020.
5. Calvo C, García López-Hortelano M, de Carlos Vicente JC, Vázquez Martínez JL, Ramos JT, Baquero-Artigao F, Navarro ML, Rodrigo C, Neth O, Fumadó V, Menendez Suso JJ, Slocker Barrio M, Bustinza Arriortua A, Jordán García I, Pilar Orive J. Recommendations on the clinical management of the COVID-19 infection by the new coronavirus, SARS-CoV2. Spanish Paediatric Association Working Group; An Pediatr (Barc). 2020;S1695-4033(20)30076-X.
DOI: 10.1016/j.anpedi.2020.02.001
6. Hussin A. Rothana, Siddappa N. Byrareddy. Review article the epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity; 2020.
[PMID: 32113704]
DOI: 10.1016/j.jaut.2020.102433
7. WHO; Europe Regional Office. Preparedness, prevention and control of COVID-19 in prisons and other places of detention Interim guidance; 2020.
8. Chao Zhang, Lei Shi, Fu-Sheng Wang. Liver injury in COVID-19: Management and challenges; Gastroenterology and hepatology. The Lancet; 2020.
9. Mark Gladwin, Bill Trattler. Clinical microbiology made ridiculously simple 3rd Edition. Publisher MedMaster Inc; 2020.
10. Chen C, Zhang XR, Ju ZY, He WF. Advances in the research of cytokine storm mechanism induced by Corona Virus Disease 2019 and the corresponding immunotherapies. Chinese Journal of Burns. 2020;36.
11. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020;395:473-475.
12. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: Reanalysis of a prior phase III trial. Crit Care Med. 2016;44:275-281.
13. Chinese Clinical Trial Registry: A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19).
Available:http://www.chictr.org.cn/showproj en.aspx?proj=49409
14. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020;395(10223): 470-473.
DOI: 10.1016/S0140-6736(20)30185-9
15. Huang CL, Wang YM, Li XW, et al. Clinical features of patient infected with 2019 novel corona virus in Wuhan, China [J]. Lancet. 2020;395(10223):497-506.
DOI: 10.1016/s0140-6736(20) 30183-5
16. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with

glucocorticoid and human immunoglobulin. Eur Heart J; 2020.
17. Chai X, Hu L, Zhang Y, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. bioRxiv; 2020.
18. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med; 2020.
19. Sharifi-Razavi A, Karimi N, Rouhani N. COVID 19 and intra cerebral hemorrhage: Causative or coincidental. New Microbes and New Infections.
Available:https://doi.org/10.1016/j.nmni.2020.100669
20. Neo Poyiadji, Gassan Shahin, Daniel Noujaim, Michael Stone, Suresh Patel, Brent Griffith. COVID-19–associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features; Reviews and Commentary, Images in Radiology; 2020.
Available:https://doi.org/10.1148/radiol.2020201187
21. Wang L, Li X, Chen H, et al. SARS-CoV-2 infection does not significantly cause acute renal injury: An analysis of 116 hospitalized patients with COVID-19 in a single hospital, Wuhan, China. medRxiv; 2020.
Accessed:www.medrxiv.org/content/10.1101/2020.02.19.20025288v1
22. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
[PMID: 31986264]
DOI: 10.1016/S0140-6736(20)30183-5
23. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA; 2020.
[PMID: 32159775]
DOI: 10.1001/jama.2020.3786
24. Yongjian Wu, Cheng Guo, Lantian Tang, Zhongsi Hong, Jianhui Zhou, Xin Dong, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. Lancet Gastroenterol Hepatol; 2020.
Available:https://doi.org/10.1016/S2468-1253(20)30083-2
25. Cheng Y, Wong R, Soo YOY, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong [J]. Eur J Clin Microbiol Infect Dis. 2005;24(1):44-46.
DOI: 10.1007/s10096-004-1271-9
26. Zhou B, Zhong N, Guan Y. Treatment with convalescent plasma for influenza A (H5N1) infection [J]. N Engl J Med. 2007;357(14):1450-1451.
DOI: 10.1056/NEJMc070359
27. Hung IF, To KK, Lee CK, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection [J]. Clin Infect Dis. 2011;52(4):447-456.
DOI: 10.1093/cid/ciq106
28. Barrett DM, Teachey DT, Grupp SA. Toxicity management for patients receiving novel T-cell engaging therapies [J]. Curr Opin Pediatr. 2014;26(1):43-49.
DOI: 10.1097/MOP.0000000000000043
29. Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia [J]. N Engl J Med. 2013;368(16):1509-1518.
DOI: 10.1056/NEJMoa1215134
30. Jeffrey K. Aronson, Robin E. Ferner, Nicholas DeVito, Carl Heneghan. COVID-19 trials registered up to 8 March 2020 — An analysis of 382 studies. CEBM Research, Oxford COVID-19 Evidence Service; 2020.
31. Lee JW, Fang XH, Krasnodembskaya A, et al. Concise review: Mesenchymal stem cells for acute lung injury: Role of paracrine soluble factors [J]. Stem Cells. 2011;29(6):913-919.
DOI: 10.1002/stem.643
32. Zhou W, Liu YS, Tian DD, et al. Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia [J]. Signal Transduction and Targeted Therapy. 2020;5:18.
DOI: 10.1038/s41392-020-0127-9
33. Liu Youning. Thinking about new drugs for coronavirus infection. Chinese Journal of Tuberculosis and Respiratory Diseases. 2020;43.
34. Martinez MA. Compounds with therapeutic potential against novel respiratory 2019 coronavirus. Antimicrob Agents Chemother; 2020.
DOI: 10.1128/AAC.00399-20
35. Iyer AP, Al-Ghamdi MA. Inhaled statins to combat COVID-19 – prophylactic and treatment approach. Int J Clin Virol. 2020;4:079-080.
36. Johnson TS, Terrell CE, Millen SH, et al. Etoposide activated ablates activated T cells to control the immunoregulatory disorder hemophagocytic lymph histiocytosis. J Immunol. 2014;192(1):84-91.
DOI: 10.4049/jimmunol.1302282

37. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. Eur Heart J; 2020.
38. Mukoro Duke George. Improving wound dressing techniques and infection control through support from International Non-governmental organizations in Sub-Sahara Africa. Asian Journal of Research in Medical and Pharmaceutical Sciences. 2017;2(1):1-8. Available:https://doi.org/10.9734/AJRIMPS/2017/37161
39. Mukoro Duke George. Revamping infection control through International Non-governmental support in autoclaving training for low capacity hospitals in the Sub-Sahara. Journal of Advances in Medicine and Medical Research. 2018;26(3):1-10. Available:https://doi.org/10.9734/JAMMR/2018/39980

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