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AN UPDATE ON CARONA VIRUS

Mohammed Adnan Ali¹, Dr. V. Asha Jyothi*

Department of Pharmacy Practice¹, Department of Pharmacology*,
ST. Pauls College of Pharmacy, Turkyamjal, Telangana.

Email: ashajyothivadlapudi@gmail.com

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Abstract:

Corona virus or SARS CoV-2 becomes a deadly infectious disease leading to severe respiratory distress and in more severity causes mortality/death. According to a study it has a fatality rate of 3.4%, Pathophysiology varies in both healthy and Co-morbid population. Mutations & Deletions in the viral genome leading more transmission between healthy and non healthy people irrespective of Ecological & geological distribution. The management in elderly patients is more complex which requires mechanical ventilation thereby increasing the hospital stay (Pharmacieconomics) only supportive care and symptomatic management is initiated as COVID-19 vaccines are in pre clinical stage.

Key Words: Zoonotic, SARS-CoV-2, Phylogenetic analysis, ACE-2, TMPRSS2, RT-PCR, Immunity.

Introduction:

“Corona virus disease (COVID-19) is an infectious disease caused by a newly discovered strain of coronavirus leads to moderate to severe respiratory illness”¹. WHO describes this new strain of corona virus "A threat to global public health". On 31st Jan 2020 WHO declares "A global health emergency" and this is the 3rd corona virus outbreak over past 2 decades leading to pandemic situation.² WHO on 11th Feb 2020 announced the official name of novel corona virus infectious disease as "COVID-19" & international virus classification commission named it as "SARS-CoV-2". WHO on 11th mar 2020 declared as " Pandemic situation"³. The ongoing virus outbreak from the Wuhan city of china and spreads to 72 countries in less than 3-month duration except Antarctica

⁴ Which is zoonotic in origin making this virus a highly virulent in transmission from host to host i.e.; (animal-

human & human-human) ⁴ Causing an increased hospitalization and multi organ failure (severe acute respiratory syndrome) ⁵.

History: First outbreak of corona virus in human was recorded in the year 1965 followed by SARS-CoV in 2003 and MERS in 2012 respectively⁶.

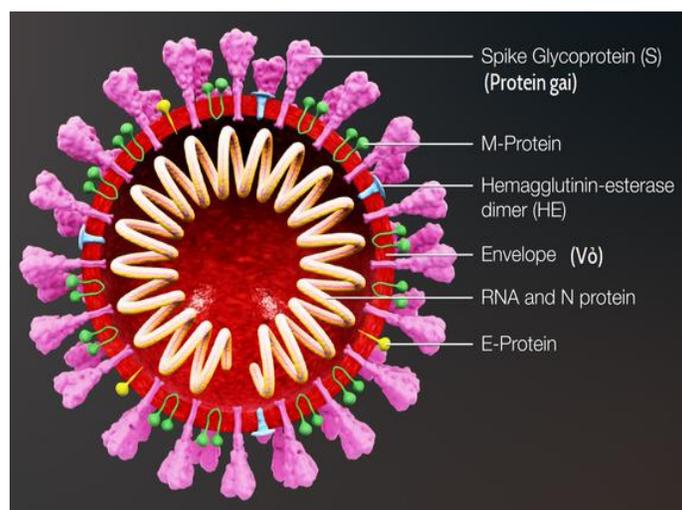
Origin:

It emerges with flu like symptoms from the Hunan south china sea food market in Wuhan city of china and then first case is identified in Wuhan city, Hubei province of china in 12- Dec- 2020². In 1965-HCoV-229E ⁶. Strain is identified to be the cause. S-Genes splits tree analysis shows gene based phylogenetic analysis and origin of virus over a decade.² SARS-CoV-2 is genetically 79% similar to SARS-CoV and 50% similar to MERS-CoV. Phylogenetic analysis of SARS-CoV-2 revealed that it is showing a similarity of 88% with two SARS like CoV strains from bat. i.e. Bat-sl-CoVZC45 and Bat-sl- CoVZXC21².

Spread:

As corona strain is zoonotic in nature it has believed to be spread from animals like bats, sea foods, camel, dogs, pigs, snakes and pangolin & Human to Human via above animals get infected and later the local people of Wuhan city get affected by eating them and thereby infected person via nasal or oral salivary droplets or close contact [2,4,7].

About Covid-19 Virus: ¹²



CLASSIFICATION

Order:- *Coronaviridae*.

Subfamily:- *Orthocoronavirinae*.

Genera1:-*Alphacoronaviru*.

Genera2:-*Betacoronavirus*.

Genera3:-*Gammacoronavirus*.

Genera4:-*Deltacoronavirus*.

Covid-19 belongs to *Betacoronavirus* genera, Subgenus *sarbecovirus*. It has a single stranded positive sense RNA genetic material with genome 29,891bp long.

Nucleocapsid help in viral binding in helical symmetry fashion, the diameter is about 60-140 nm & 9-12 nm glycoprotein spikes with crown like appearance. ⁸

Accessory genes like 3a/b, 4a/b and Hemagglutinin - Esterase gene & sub genomes 6ORF's they as follows ORF 1a/b: produces 16nsps,

Two Polyproteins: PP 1a & PP 1b, MPro (main protease), 3CLpro (Chymotrypsin -like protease), PLP's (papain like protease). Major proteins are structural proteins like spike S which has Crown like appearance has Large protein 1160-1400 amino acids and Vital immunodominant protein & Divided in two sub domains S1- NTD (N terminal) which helps in binding & S2- CTD (C terminal) which helps in fusion. M-protein is the most abundant viral protein which gives shape to viral envelop with 3 transmembrane domains with short amino terminal outside and long carboxyl terminal inside the virion and promotes M-M interaction. E protein is Most enigmatic and smallest protein which has Multifunctional role in pathogenesis, assembly and release of virus.

Membrane polypeptide acts as viroporin which has 3 domains

- 1) Short hydrophilic amino terminal domain,
- 2) Large hydrophilic transmembrane domain
- 3) Efficient C- terminal domain.

N protein has Multipurpose like Complex formation with viral genome, facilitates interaction of M protein during virions assembly, Increases Transcription efficiency of virus, has highly conserved domain, NTD (electrostatic interaction), RNA binding domain or LKR (Ser- Arg), CTD, till date six CoV's strains were known to infect human beings. (Human CoV229E, HCoV-NL 63, HCoV-OC 43, HCoV HKU1, SARS-CoV, MERS-CoV)²

Epidemiology: ^{2,3,6,8,9}

Table 1: Summary of epidemiology: ^{2,3,6,8,9}

S.NO.	COUNTRY	YEAR	CONFIRMED CASES	DEATH CASES
1.	Globally	6-feb-2020	28276	565
2.	Globally	28-feb-2020	83704	2859
3.	Globally	8-apr-2020	896450	45526
	China	8-apr-2020	81620	-
	Dubei	8-apr-2020	3322	3203
	US	8-apr-2020	187302	-
	Italy	8-apr-2020	110574	-
	Spain	8-apr-2020	102136	-

	UK	8-apr-2020	29478	-
4.	Globally	13-may-2020	4170424	287399
	China	13-may-2020	84458	4644
	US	13-may-2020	1322054	79634
	Italy	13-may-2020	221216	30911
	UK	13-may-2020	226467	32692

Region Wise: Region of Americas > European region > Eastern Mediterranean region > Western pacific region > South east Asia region > African region > ship cases.

Americas > Europe > Mediterranean > Africa > South east Asia > Pacific > others.^{2,9} The fatality rate of COVID-19 is 3.4% which is less than SARS and MERS⁵. It is observed that initially china mortality rate is more as the situation becomes more worsen then Spain and Italy then in USA making it health emergency^{2,3,6}. As age increases the prevalence of getting COVID-19 increases and presence of any Co- morbid condition like diabetes, hypertension, asthma worsening the health. Usually, 80+ age group are hospitalized more followed by 40+ age group without hospitalization.⁹

Etiology:

Causative agent of COVID-19 or SARS CoV-2 is beta corona virus belonging to *coronaviridae* family and later human to human transmission is figured out from wet seafood market of Wuhan and bats are considered to be the host reservoir and pangolin as intermediate host.^{2,5,8,9}

Pathophysiology:^{5,9,10}

Before understanding the pathophysiology lets have a brief information about virus. The incubation period is 1-14 days for second exposure up to 24 days the incubation period varies with travel history, presence of respiratory illness and underlying autoimmune disorders⁶. Flowing are the sequence of the steps involved in the pathophysiology of COVID-19:

Nasal and bronchial exudates like saliva, watery nose etc via coughing and sneezing.

The viral structural proteins (spikes) get attached to nasal and bronchial epithelial cells and pneumocytes.

Structural protein plays important role in binding pathogenesis, assembly and release of virions.

The S protein of virus has higher affinity to binds ACE-2 receptor of host i.e., type 2 transmembrane serine protease (TMPRSS 2).

ACTIVATION **CLEAVAGE**

Thereby fusion occurs.

Promotes Viral uptake thereby leading to viral component entry into host.

Above protein binding facilitates fusion with the help of S, M, EN proteins.

ENDOCYTOSIS

Uncoated RNA is then translated to synthesis viral protein in the presence of RNA dependent RNA polymerase.

VIRION ASSEMBLY

New virions are produced.

The cell undergoes lysis (increases virion load).

Virions infects and kills T lymphocytes cells and also releases pro inflammatory cytokines causing cytokine storm by disturbing both innate and adaptive immune response.

Leading to lymphocyte apoptosis.

Presence of Comorbidities like diabetes, hypertension, asthma, obesity, cardiovascular diseases.

S-Spike protein binding

Binds to ACE-2 receptor leading to Vascular and endothelial dysfunction pulmonary embolism and VTE. +

ADAMT S13 + **VWF & P-Selectin**

Disrupt vascular integrity and capillary basement membrane.

Activation

Coagulation cascade and ARDS^{5,9,10}

Clinical Manifestations:

There are two types of population existing Symptomatic Asymptomatic and Symptoms may vary from person to person, Usually the duration of symptoms is 14 days (5days – hospital & 7days - ADRS), Presence of history of disease increases the onset of symptoms and severity of the disease.

Table-2: Summary of Clinical Manifestation

	SYMPTOMATIC	ASYMPTOMATIC
MILD	Flu like symptoms like rhinorrhoea, pharyngitis, sneezing, cough and throat pain.	Isolated gastrointestinal symptoms and Anosmia
COMMON	Fever, dry cough, dyspnoea/SOB, diarrhoea, vomiting and myalgia.	Olfactory/ gustatory dysfunction.
MODERATE	Abdominal pain, headache, SOB, vomiting, anorexia, pharyngeal pain and conjunctival infection.	Mild upper respiratory tract illness and Multi-focal pneumonia
SEVERE	Pneumonia, ARDS, arrhythmias, shock, acute renal failure, acute cardiac injury, multi-organ damage and death.	Respiratory failure & death

Risk Factors: Older age with Co morbidities (HTN, DM, ALD, cancer, CAD, organ transport, immune suppression & asthma, Chronic kidney patients (dialysis)) are at higher risk to develop symptoms. Male gender and social habits like smoking cigarettes, Chronic kidney patients (dialysis) ^[10].

Complications: Impaired function of brain, heart, lungs, liver, kidney and coagulation system and Acute cerebrovascular disease (shock), Cardiomyopathy; ventricular arrhythmia is common. VTE occurs mostly due pulmonary embolism in ICU patients. Elevated levels of liver and renal (AST, bilirubin, troponin, creatinine, D-dimer) are also reported ⁹.

Diagnosis: Various diagnostic test helps us to Real time PCR, IgM antibody rapid detection test and D-dimer test and Bronchoalveolar lavage fluid, sputum, nasal swabs, Biochemistry serum test [ELISA] – Inflammatory factors – IL-1 β ; IL-2R; IL-6, TNF α ; IL-8 & IL-10 CT imaging and X- ray.

Laboratory Findings:

In ICU patients: Elevated levels of IL 2; IL 7 and IL-10, GSCF & IP10: MCP1, M1P1A & TNF α ; IL-8 &IL-10 are found.

CT findings: Bilateral pneumonia Ground glass opacity. Multiple peripheral Ground glass opacity, Pulmonary patchy GGO with pulmonary consolidation, Ground glass opacity, Multiple peripheral Ground glass opacity,

Pulmonary patchy GGO with pulmonary consolidation Diffuse- GGO with bronchial inflation. Large lung consolidation.

IgM kit: Presence of IgM antibodies in blood,

RT PCR: To detect the presence of 3 genes Gene- E, *RdRp*, N.

Biomedical Screening: Biomedical screening parameters like Lymph count, Platelet count, CPR, ESR, ALT/AST, D-dimer, CPK, LDH; PT; creatinine levels help in diagnosing COVID-19.

CHEST X-RAY: shows Bilateral infiltrates.

Differential Diagnosis: Differential diagnosis help to identify the underlying disease pattern such as Influenza, Para influenza, RSV, Adenovirus, Metapneumovirus etc^{3, 5, 6, 8,9, 11}.

Management: Covid-19 infection can be managed by both pharmacological and non - pharmacological methods.

Non pharmacological:

Dietary Modifications:

Like Advice to avoid meat, sweets and fruits with highly water content & completely avoid fish. Advice to consume citrus fruits and sour fruits like grapes apples, lemon etc. Avoid street foods like noodles fried rice, raw cooked chicken /meat etc.⁴

Pharmacological: Initial days of outbreak there is no vaccine and hence supportive care and symptomatic management is only sole treatment option to treat/ manage COVID-19.

Antiviral drugs:

Remdesivir, Galidesivir, favipiravir are currently use to inhibit viral synthesis. Antibiotic drugs like Convalescent plasma therapy, Hyper immune immunoglobulins are used. To manage inflammatory process Anti-inflammatory agent like Dexamethasone is used, another therapy called Targeted Immuno-modulatory therapy such as IL- 1; IL- 6 inhibitors and monoclonal antibodies & (Tocilizumab, Sarlumab, Anakinra, Ruxolitinab). Based on Prospective study and cohort study Chloroquine / Hydroxychloroquine + Azithromycin shows good result in management of COVID-19. In severe conditions Anti-fibrotic agent like Tyrosine kinase inhibitors used to reduce the fibrosis in lungs. Antipyretic and Corticosteroids are also used for symptomatic treatment and Alternative agents like Complement factor 5a and Convalescent plasma therapy is used, as patients who recovered from COVID-19

donates their plasma which helps in producing antibodies against COVID survivals. Prophylaxis Subcutaneous

Heparin is given to avoid coagulation.

Various other combination of antiviral are:

A) Combination of lopinavir/ritonavir: Used in hospitalized patients,

B) Remdesivir,

C) Interferon beta / riboviran.

Symptoms are categorized based such as Symptoms are mild and no signs to have pneumonia and Patient experience fever and respiratory distress + pneumonia in moderate condition while in severe condition like RR ≥ 30 times /min. and O₂ saturation is 93% & Pulmonary imaging shows 50%, Prognosis of lesions with 24-48 hours.

Critical: Respiratory failure which requires mechanical ventilation & ICU monitoring.

Supportive Care: Antipyretic & Hydration maintenance, Mechanical ventilation usually in elderly people Oxygenation for asthma patients, Extra corporal membrane oxygenation (ECMO).

Covid -19 Vaccinations: Later vaccines are existed in middle of 2020:

1. S- protein target vaccine,
2. Multi epitope vaccine.INO-4800,
3. Covaxin,
4. ChAdOX1 n CoV -19 (COVISHIELD)^{2,5,6,7,9,11}

Table-3: List of the Vaccines in World^{12, 16}

S.No	Vaccine Company	Vaccine name	Type	Age in years	Dose& Doses	Duration	Storage	Price	Efficacy
1	Pfizer-BioNTech New York.	Pfizer-BioNTech vaccine	mRNA	12 & above	0.3 ml & 2	21 Days apart	-94°F	\$19.50 /dose	95%
2	ModernaTX, Inc	Moderna COVID-19 Vaccine	mRNA	18 & above	0.5 ml & 2	28 Days apart	36 to 46°F	\$25-37 / dose	94.5 %
3	Astrazenca	COVID-19 Vaccine AstraZeneca	(ChAdOx1-S (recombinant))	Not yet approved		28 Days apart	2-8° C	\$2.15 / dose	70%
4	Janssen Biotech Inc., a Janssen	Janssen COVID-19	Adenovirus base	18 & above	0.5 ml &	----	36 to 46°F	\$10 / dose	66%

	Pharmaceutical Company of Johnson & Johnson.	Vaccine			1	-			
5	Panacea Biotec	Sputnik -V	Non-Replicating Viral Vector	18 & above	-- & 2	21 Days apart	2-8° C	\$10 / dose	91.4 %
7	Sinovac Biotech/Sinovac/China National Pharmaceutical Group	Sinovac-CoronaVac	Inactivated SARS CoV2 virus	18- 48	0.5 ml & 2	2-4 weeks	Below 38.5°C	\$60 / dose	50.38 - 91.25 %
8	Novavax	Covovax	Protein subunit based vaccine	18 & above	0.5 ml & 2	21 Days apart	36 to 46°F	\$16 / dose	65.7 - 90.98 %
9	Serum Institute of India (SII).	Covishield	(ChAdOx1-S (recombinant)	18 & above	0.5 ml & 2	12-16 weeks	2-8° C	Rs 400/ dose	70-90%
10.	Bharat Biotech International Ltd	Covaxin	Whole virion inactivated verocell	18 & above	0.5 ml & 2	4-6 weeks	2-8° C	Rs 150 / dose	78-95%

Table-4: Summary of the variants.¹²⁻¹⁶

COUNTRY	VARIANT
1.UK	B.1.1.7
2.South Africa	B.1.351
3.Brazil	P.1
4.Newyork	B.1526
5.California	B.1427/B.1429
6.India	B.1617

Prevention:

Use Sanitization while touching and shaking hands and use of Chemical based purifier in home to have pure air. Decoction is an excellent in relieving bronchospasm. Disinfectants to wash flooring in home reduces infection. N 95 face mask or surgical mask helps in keeping you away from diseases. Usage of ginger improves immunity & Vitamin C tablet usage. Home quarantine for mild respiratory people. Completely home quarantine for elderly.

PPE suit for health care workers. Travelling bans or 14 days quarantine in isolated room with well ventilated room.

Avoid long journeys and unnecessary outings Washing the clothes with detergents. Safely disposed the mask properly in dustbin. Avoid domestic animals Disinfectants the doorknobs and tabletops etc helps in prevention of diseases. ^{4,5,8,9}

Conclusion: At present world need a vaccine in order to have a stable health all over the world. Many countries get affected due to COVID-19 both from Economic perspective as well as Health sector usually in developing countries like India has a great impact of COVID -19 and lockdown strategies. India needs to improve the health sector to conduct this pandemic and following proper guidelines of WHO and prevention guidelines.

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Corresponding Author:

Dr. V. Asha Jyothi*,

Email: ashajyothivadlapudi@gmail.com