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Review Article

Unheralded Entrance by COVID-19: A Concise Review

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Abstract

Novel corona virus(COVID-19) was first described in December 2019, identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. Since then world wide spread is reported affecting millions of people. India reported its first case of COVID-19 on January 30th in Kerala. On March 11, 2020 after spread to Spain, Italy, USA and other parts of the world, WHO declared it as a pandemic and it indicated widespread community transmission on at least two continents.

It belongs to the order Nidovirales , family Coronaviridae , and the subfamily Orthocoronavirinae.Corona virus is spherical, enveloped, and the largest of positive-strand RNA viruses. It uses, the angiotensin -converting enzyme 2 (ACE2) receptor, for cell entry. The incubation period for COVID-19 is thought to be within 14 days following exposure. In person to person transmission, respiratory droplets were considered the main mode as it can happen through coughing, sneezing, and even while speaking. Person to person transmission also occurs after touching the surface infected with respiratory droplets of an infected person, and touching the face (coming in contact with a mucous membrane of eyes, nose and oral cavity).

The spectrum of symptomatic infection ranges from mild to critical; most infections are not severe. It can range from a simple URTI to a complicated pneumonia. Fever(99%), Fatigue(70%), Dry cough (59 %), Anorexia (40%), Myalgias(35 %), Dyspnea (31 %), Sputum production (27 %) were the most common clinical features.

No treatment is approved or shown effective and safe. Remdesivir, Lopinavir/ritonavir and many other antiviral drugs are in trial. Acute respiratory distress syndrome , Cardiovascular complications, Acute liver injury, Cytokine release syndrome, Septic shock , Neurological complications are reported in some studies.

Key words: Covid-19,Corona Virus, Infectious disease.

Introduction

From the era of Antonine plague in 165 AD, times have changed from plague to legionnaires, AIDS, Ebola, the Severe acute respiratory syndrome , and now the ongoing pandemic has affected more than 1.7 million which is described as “one of the worst in the modern era”, across the world and the death toll peaking sky high as each day passes. Novel corona virus(COVID-19) was first described in December 2019, identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. Since then world wide spread is reported affecting millions of people.

With Indian population being one of the biggest threats, having substantial immigrant population, and estimating the likelihood of a probable vast increase in the positivity of cases and deaths due to it, The Ministry of Health and Family Welfare, Government of India, in collaboration with other agencies has appraised the situation and guidelines are being laid down and altered every other day.

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Taxonomy

Belongs to the order Nidovirales , family Coronaviridae , and the subfamily Orthocoronavirinae. Coronaviruses are spherical, enveloped, and the largest of positive-strand RNA viruses. Uses, the angiotensin-converting enzyme 2 (ACE2) receptor, for cell entry.[1] Whether COVID-19 virus is transmitted directly from bats or through some other mechanism (e g, through an intermediate host) is unknown[2].Though the SARS-CoV-2 virus has originated from bats, intermediate host through which humans are affected is uncertain. Current suspects are pangolins and snakes.

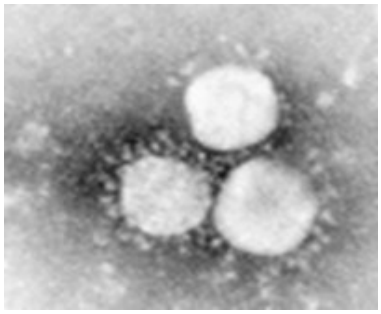

Figure 1: Electron micrograph showing human coronavirus 229E. Bar, 100 mn (Courtesy S.Sikotra, Leicester Royal Infirmary, Leicester, England.)

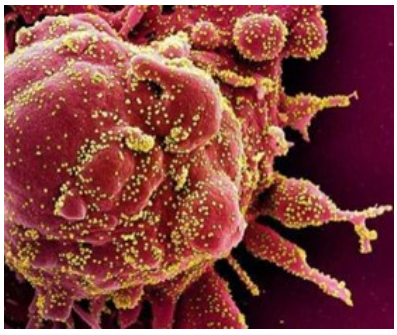

Figure 2: Colourised scan electron micrograph of apoptotic cell (red) which is heavily infected with SARS-CoV2 virus particles (yellow). Image captured at the NAID- Integrated Research Facility (IRF) in Fort Detrick, Maryland. NIAID

Epidemiology

In the beginning of December 2019, initially a cluster of people with pneumonia of unknown cause was identified in Wuhan, persons located in the central region of the People's Republic of China. Initial cases were reported at end of 2019 from Wuhan, since then more than 80,000 COVID-19 cases have been reported in China, with majority from Hubei and surrounding provinces. A joint World Health Organization (WHO)-China fact-finding mission estimated that the then considered epidemic, peaked between late January and early February 2020. On 7th January 2020,previously unknown corona virus, responsible for epidemic was identified as the etiological agent by investigators in China and was designated 2019-nCoV (for 2019 novel coronavirus)[3]. On March 11, 2020 after spread to Spain, Italy, USA and other parts of the world, WHO declared it as a pandemic and it indicated widespread community transmission on at least two continents. [4,5]

India reported its first case of COVID-19 on January 30th in Kerala. So far confirmed cases have been 27,000 increasing day by day with deceased being 780(*). Maximum cases being reported in Maharashtra followed by Gujarat and increasing trends seen in rest of India. First death reported was a 76 year old man who had returned from Saudi Arabia, deceased in Kalburgi (Karnataka).

*** Geographical map can be accessed** here

These numbers are possibly an underestimate of the infected patients and dead due to limitations of surveillance and testing facilities, especially in a developing country like India.

Transmission

Virus spread initially was thought to be from the sea food market in Wuhan where live animals were sold. COVID RNA virus has high homology to bat corona virus. That place was quarantined and disinfected at a later date, as the virus spread, person to person transmission was considered as the main route of transmission. [6]

In person to person transmission, respiratory droplets were considered the main mode as it can happen through coughing, sneezing, and even while speaking. As the respiratory droplets were considered heavy, the distance of spread was considered only around 2- 3 feet and aerosol spread was unlikely. Later, in few studies experimentally generated aerosols were found to stay in the air for around 3 hours but it is still inconclusive. [7]

Person to person transmission also occurs after touching the surface infected with respiratory droplets of an infected person, and touching the face (coming in contact with a mucous membrane of eyes, nose and oral cavity). Urine and stools of the infected was also found to have virus, infectivity of which is to be studied yet.[8-9]

SARS-CoV-2 was detectable in aerosols for up to 3 hours, up to two to three days on plastic and stainless steel , up to 24 hours on cardboard and upto 4 hours on copper as per study conducted by National Institutes of Health, CDC, UCLA and Princeton University scientists which provides key information about the stability of SARS-CoV-2 causing COVID-19

disease, and also suggesting that people can acquire the virus through the air and after touching contaminated objects. [10]

The risk of pregnant woman acquiring SARS CoV-2 and risk of placental seeding is unlikely. But in a study, done on 38 COVID positive pregnant women, 37 were shown to have vertical transmission, mechanism being unknown. [11]

Pathogenesis

Patients can be infectious for as long as the symptoms last and even after clinical recovery. Infected droplets can spread 1–2 m and get deposited over surfaces. With favorable atmospheric conditions virus can remain viable on surfaces for days. It can be easily destroyed in less than a minute by common disinfectants like sodium hypochlorite, hydrogen peroxide etc. [12]

It has been seen that SARS-CoV-2 can be transmitted during incubation period[15] and through out the course of illness. All highly pathogenic human CoV are found among the β-CoV, with SARS-1 and SARS-2 belonging to the lineage B (or βb, now called Sarbecovirus) and MERS belonging to the lineage C (βc), now renamed Merbecovirus. [13]

High susceptibility and increased risk of morbidity and mortality due to Covid-19 is seen in older adults. [14]Infections in the older adults are often, and they present atypically, masking the identification and its management. Contributing factors for poor health outcomes include the physiologic changes of aging, comorbidities like cardio-respiratory illness, diabetes; and associated confusion due to multiple medication in take especially in developing countries.

Various pathogenesis proposed showed that the ACEI hypothesis is more widely accepted hypothesis which created panic amongst the individuals, hence the American & European societies of Cardiology, expressed that ACEIs and ARBs are safe and should be continued and prescribed according to established guidelines. [15,16]

Among infected, 20% of them are prone to develop Severe Acute Respiratory Illness (SARI) resulting in pulmonary infiltrates. Some of these will develop very severe disease(2%).The virus reaches the gas exchange units of the lung and infects Alveolar type II cells. Infected Alveolar units tend to be peripheral and sub pleural. Ultimately there is diffuse alveolar damage with fibrin rich hyaline membranes. Elderly individuals are particularly at risk because of their diminished immune response and reduced ability to repair the damaged epithelium. In addition virus spread to the alveoli is aided by reduced mucociliary clearance.

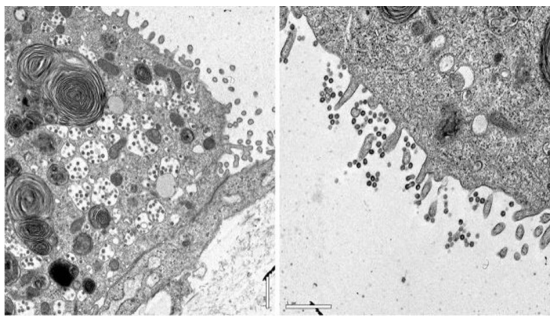

Figure 3: Human alveolar type II cells infected with SARS-CoV. Human type II cells were isolated, cultured *in vitro*, and then infected with SARS-CoV. Viral particles are seen in double membrane vesicles in the type II cells (left panel) and along the apical microvilli (right panel).[17]

Patients are said to have respiratory failure from acute respiratory distress syndrome (ARDS) which is recognisedas the leading cause of mortality. Secondary haemophagocyticlymphohistiocytosis (sHLH) is an under-recognised, hyper inflammatory syndrome characterisedby a fulminant and fatal hypercytokinaemia with multiorgan failure. [18]

Alternative theory for lung involvement in Covid-19

Some of the post-mortem revealed pulmonary thrombosis not typical Acute respiratory distress syndrome (ARDS) , also patient hypoxemia not responding to positive end expiratory pressure (PEEP). Likemethemoglobin , viral structural protein, sticks to heme displaces oxygen-displaces iron-free iron toxicity causes inflammation of alveolar macrophages. The virus attacks beta chain, dissociates heme, removing iron and converting into porphyrin.

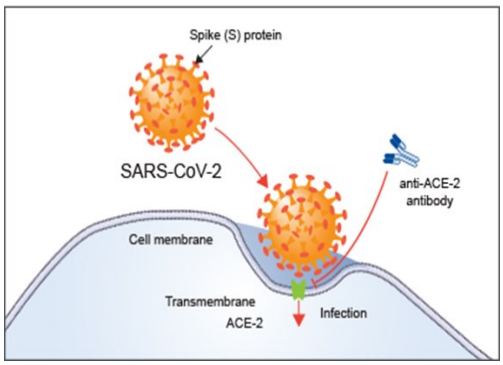

Figure 4: Pictorial representation of Covid-19 virus entering into the mucosal cells via ACE-2.[1]

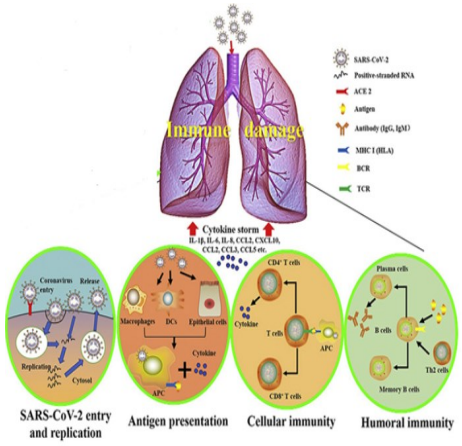

Figure 5: Pathogenesis of Covid-19.[12]

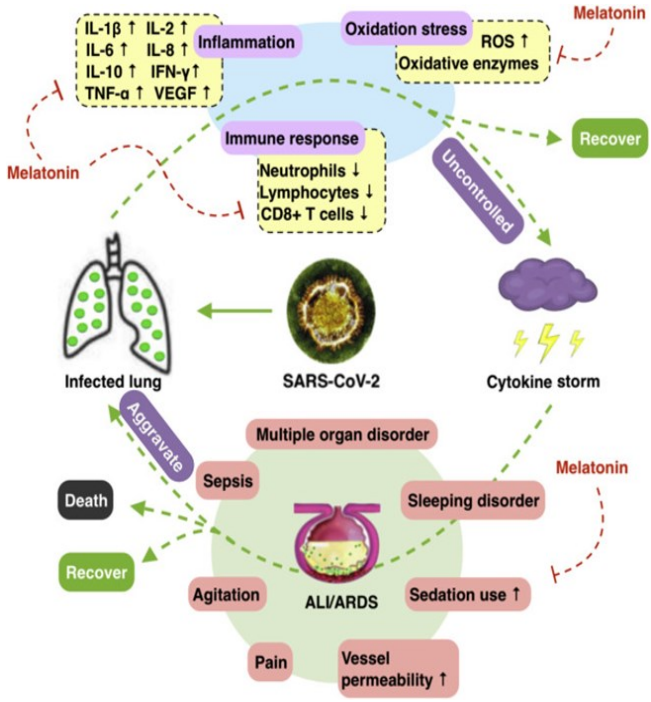

Figure 6: Diagram representing the pathogenesis of MODS due to SARS CoV-2.[10]

Clinical Features

The incubation period for COVID-19 is thought to be within 14 days following exposure, with most cases occurring approximately four to five days after exposure. In a study on 1099 patients with confirmed symptomatic COVID-19, the median incubation period was four days (interquartile range two to seven days). [19]

- Age affected –mostly middle aged(>30years) and elderly
- Symptomatic infections in children appears to be uncommon and usually mild

The spectrum of symptomatic infection ranges from mild to critical; most infections are not severe. It can range from a simple URTI to a complicated pneumonia.

- Mild illness -80%
- Severe Illness(Hypoxemia>50% lung involvement on imaging within 24-48hrs)-15%
- Critical Illness-(Respiratory failure,Shock,MODS)-5%
- Overall Case fatality Rate-2.5-5%
- Fever-88%
- Fatigue-38%
- Dry cough-67%
- Myalgia-15%
- Dyspnea-20%

Less common reported symptoms include headache, diarrhea, hemoptysis, rhinorrhea.

Patients with mild symptoms were reported to recover after 1 week while severe cases were reported to experience progressive respiratory failure due to alveolar damage from the virus, which may lead to death.

Subgroup with severe Covid-19 can have cytokine storm syndrome as per accumulating evidence. Presenting with persistent fevers, elevated inflammatory markers (e g, D-dimer, ferritin), and elevated pro-inflammatory cytokines; these abnormalities in laboratory parameters are usually associated with critical and fatal illnesses.

Fever(99%), Fatigue(70%), Dry cough (59 %), Anorexia (40%), Myalgias(35 %), Dyspnea (31 %), Sputum production (27 %) were the most common clinical features in a study done at Wuhan with 138 Covid-19 patients. Eye involvement can manifest as conjunctivitis (i.e., hyperaemic conjunctiva, chemosis, epiphora) seen in 32% of patients. Gastrointestinal manifestations(1%-11%)- Nausea, vomiting, pain abdomen and diarrhoea is reported.18% of patients had gastrointestinal symptoms in a study conducted by Hong Kong. [20]

Other uncommon symptoms may be Haematochezia ,confusion , dizziness, headache haemopty-

sis ,rhinorrhoea, chest pain, cutaneous manifestations (e.g., erythematous rash, petechiae, urticaria, vesicles) ,cyanosis.In the initial cohort studies from China, smell and taste disorders (eg, anosmia and dysgeusia) are also reported as common symptoms. [20]

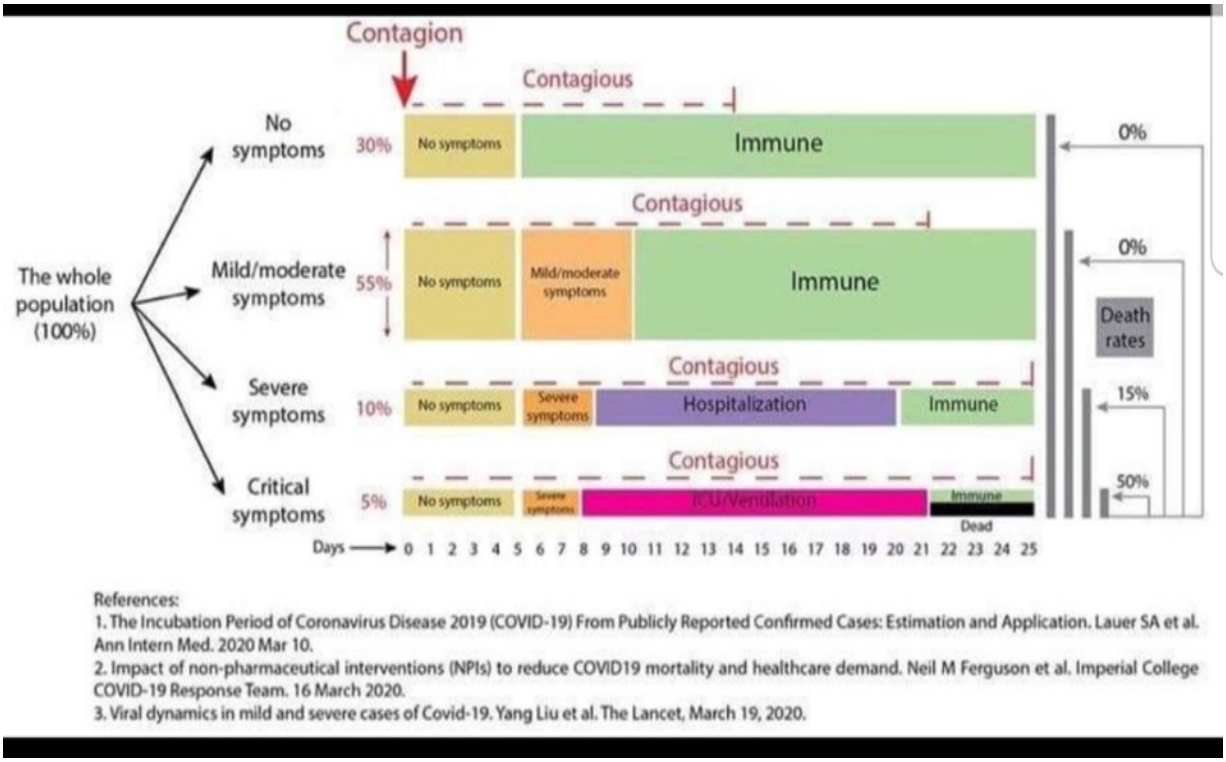

Figure 7: Viral dynamics of Covid-19.[3]

Differential Diagnosis

Middle East respiratory syndrome (MERS), Severe acute respiratory syndrome (SARS), Community-acquired pneumonia, Influenza infection, Common cold, Avian influenza A (H7N9)virus infection, Avian influenza A (H5N1) virus infection, Other viral or bacterial respiratory infections, Pulmonary tuberculosis, Febrile neutropenia.[20]

Diagnostic Criteria

World Health Organization: case definitions[21]

Suspect case

A. Patients with acute respiratory illness (i.e., fever and at least one sign/symptom of respiratory disease such as cough or shortness of breath) AND a history of travel to or residence in a location reporting community transmission of COVID-19 during the 14 days prior to symptom onset; OR
B. Patients with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset; OR
C. Patients with severe acute respiratory illness (i.e., fever and at least one sign/symptom of respiratory disease such as cough or shortness of breath) AND requiring hospitalization AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case

A. Suspect case for whom testing for the COVID-19 virus is inconclusive (inconclusive being the result of the test reported by the laboratory); OR
B. Suspect case for whom testing could not be performed for any reason.

Confirmed case

- Patients with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Definition of contact

- A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:
- Face-to-face contact with a probable or confirmed case within 1 meter (3 feet) and for more than15 minutes

- Direct physical contact with a probable or confirmed case
- Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment
- Other situations as indicated by local risk assessments.
- Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken that led to confirmation.

Investigations

Blood examination revealed Leukopenia, lymphopenia, leucocytosis , elevated liver transaminases, elevated lactate dehydrogenase, and elevated C-reactive protein in most patients admitted with Covid-19. Other abnormalities include neutrophilia, thrombocytopenia, decreased hemoglobin, decreased albumin, decreased ferritin, increased d-Dimer, and renal impairment.[20]

Cultures from blood and sputum before start of empirical antibiotics to be collected for ruling out other causes of pneumonia and sepsis.

Nucleic acid amplification tests (NAAT) for COVID-19 virus.

COVID-19 cases are routinely confirmed by detection of unique sequences of virus RNA by NAAT such as real-time reverse-transcription polymerase chain reaction (rRT-PCR) with confirmation by nucleic acid sequencing when necessary. Targeted viral genes include the N, E, S and RdRP genes.

Serological testing

In patients with strong epidemiological link to COVID-19 infection and negative NAAT, paired serum samples (in the acute and convalescent phase) could support diagnosis once validated serology tests are available. Serum samples can be stored for these purposes. Cross reactivity to other corona viruses can be challenging,[22] but commercial and non-commercial serological tests are currently under development. [23,24]Significance and interpretation of the serological tests is described in table No.2 and 3

Viral sequencing

In addition to providing confirmation of the presence of the virus, regular sequencing of a percentage of specimens from clinical cases can be useful to monitor for viral genome mutations that might affect the performance of medical countermeasures, including diagnostic tests. Virus whole genome sequencing can also inform molecular epidemiology studies. Viral culture Virus isolation is not recommended as a routine diagnostic procedure.

Laboratory confirmation of cases by NAAT in areas with no known COVID-19 virus circulation To consider a case as laboratory-confirmed by NAAT in an area with no COVID-19 virus circulation, one of the following conditions need to be met:

- A positive NAAT result for at least two different targets on the COVID-19 virus genome, of which at least one target is preferably specific for COVID-19 virus using a validated assay (as at present no other SARS-like corona viruses are circulating in the human population it can be debated whether it has to be COVID-19 or SARS-like corona virus specific);

OR

-One positive NAAT result for the presence of beta coronavirus, and COVID-19 virus further identified by sequencing partial or whole genome of the virus as long as the sequence target is larger or different from the amplicon probed in the NAAT assay used.

Resampling to be done when there is discordant results and if appropriate virus sequencing from NAAT assay, different from the one used initially should be obtained for providing reliable result. One or more negative results does not rule out the possibility of infection. Factors which affect the results are quality of specimen, time of collection of specimen, transportation and handling, technical issues, etc. If a negative result is obtained from a patient with a high index of suspicion for COVID-19 virus infection, particularly when only upper respiratory tract specimens were collected, additional specimens, including from the lower respiratory tract if possible, should be collected and tested.

Table 1: Specimens to be collected from symptomatic patients and contacts.[21]

	Test	Type of sample	Timing
Patient	NAAT	**Lower respiratory tract** - sputum - aspirate - lavage **Upper respiratory tract** - nasopharyngeal and - oropharyngeal swabs - nasopharyngeal wash/nasopharyngeal aspirate **Consider stools, whole blood, urine, and if diseased, material from autopsy**	Collect on presentation. Possibly repeated sampling to monitor clearance. Further research needed to determine effectiveness and reliability of repeated sampling.
Patient	Serology	Serum for serological testing once validated and available	Paired samples are necessary for confirmation with the initial sample collected in the first week of illness and the second ideally collected 2-4 weeks later (optimal timing for convalescent sample needs to be established).
Contact (in health-care centre associated outbreaks or other settings where contacts have symptoms, or where asymptomatic contacts have had high-intensity contact with a COVID-19 case.	NAAT	Nasopharyngeal and oropharyngeal swabs	Within incubation period of last documented contact.
	Serology	Serum for serological testing once validated and available	Baseline serum taken as early as possible within incubation period of contact and convalescent serum taken 2-4 weeks after last contact (optimal timing for convalescent sample needs to be established).

Table 2: Diagnostic Tests Sensitivity.[25]

	Days after symptom onset		
SARS-CoV TEST	**1-7**	**8-14**	**15-39**
RNA by RT-PCR	67%	54%	45%
Total Antibody	38%	90%	100%
IgM	29%	73%	94%
IgG	19%	54%	80%

Table 3: Clinical significance of PCR and antibody tests at various stages of disease.[26]

PCR	IgM	IgG	CLINICAL SIGNIFICANCE
+	-	-	Window period
+	+	-	Early stage of infection
+	+	+	Active phase of infection
+	-	+	Late or recurrent stage of infection
-	+	-	Early stage of infection, PCR may be false negative
-	-	+	Past infection and has recovered
-	+	+	Recovery stage, PCR may be false negative

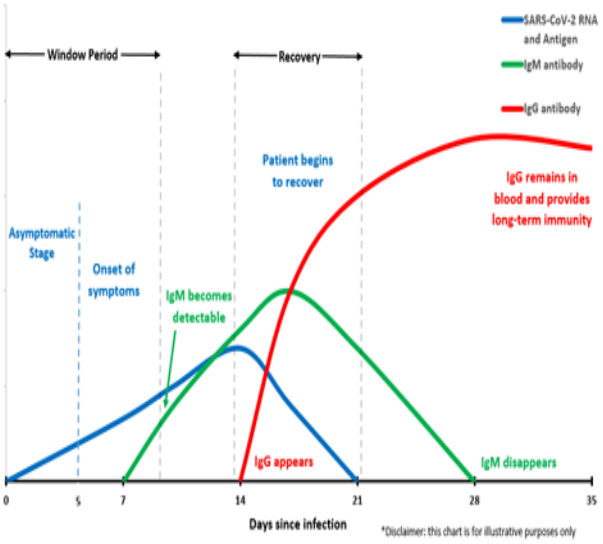

Figure 8:Scheme of typical laboratory features of Covid-19 Infection.[16]

Table 4: Corona testing positivity rates

Corona testing positivity rates- Journal of American Medical Association (JAMA)		
Sl No	Type of specimen	Positive %
1	Bronchoalveolar lavage fluid	93 %
2	Fibrobronchoscope brush biopsy	46 %
3	Sputum	72 %
4	Nasal swabs	63 %
5	Pharyngeal swabs	32 %
6	Feces	29 %
7	Blood	1 %
8	Urine	0 %

Note: Nasal swab will detect only 2/3rd of cases and pharyngeal swabs will detect only 1/3rd of cases and Nasal swab testing is better of two for unadmitted patients

Ref: Detection of SARS-CoV-2 in Different Types of Clinical Specimens
Wenling Wang, Yanli Xu, Ruqin Gao, Roujian Lu, Kai Han, Guizhen Wu, Wenjie Tan
JAMA. 2020 Mar 11 : e203786. Published online 2020 Mar 11.

CT thorax

Its reserved for patients admitted in hospital and symptomatic patients as per recommendations by American College of Radiology which emphasises that normal CT doesn't rule out Covid-19 and that abnormal findings is not specific for the infection.[13]

In a meta analysis on 50,466 patients hospitalised Covid-19 patients ,97% had abnormal CT findings like.

Typical features

- Most patients had multiple bilateral lobular and sub segmental areas of consolidation or ground-glass opacity , usually with a peripheral or posterior distribution, mainly in the lower lobes and less frequently in the right lower lobe. Other classic findings include crazy-paving pattern, air Broncho grams, and a reverse halo/perilobular pattern (i.e., organising pneumonia patterns). small comparative study showed bilateral involvement with multiple mottling and ground-glass opacity. Extensive lung involvement ,interstitial changes and thickened pleura was more common in older patients compared to younger ones.[16] In children small nodular ground-glass opacities was more common. Adjacent pleural thickening, septal/ interlobular thickening were atypical findings which was seen in later stages of the disease. Bronchiectasis, pleural effusion, cavitation, pneumothorax, cystic changes were rare presentations in some patients.

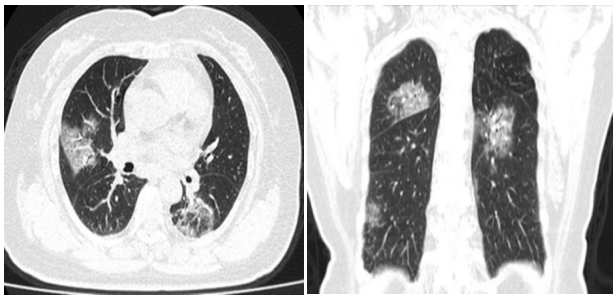

Figure 10 and 11: CT Thorax showing multiple patchy ,peripheral ,bilateral ground glass opacity.[13]

Ultrasound thorax

Sensitivity is higher for subpleuralconsolidation, pleural thickening and ground glass opacities with ultrasound thorax. Some of the advantages are bedside evaluation, portability and repeatability. B-lines, white lung, pleural line thickening, and consolidations with air Broncho grams are some of the characteristic findings seen in Covid-19 patients.[20]

Treatment

No treatment is approved or shown effective and safe. Chloroquine and hydroxychloroquine are told to have in vitro activity against SARS-CoV-2, with hydroxyl chloroquine having higher potency relatively and are being trialed in patients with mild to severe illness and for prophylaxis among healthcare workers.

Remdesivir (GS-5734)-is a investigational,

intravenous nucleoside analogue with broader antiviral activity that shows in vitro activity against SARS-CoV-2. Patients with mild to severe illness are started on trials with this and currently approved by United States.

Lopinavir/ritonavir: antiretroviral protease inhibitor, currently approved for HIV treatment is being used in clinical trials for the treatment of COVID-19. Clinical benefit has been observed in one small case series. A randomised controlled Trial conducted in china with 200 severely ill hospitalised patients has found no benefit with this drug compared to standard care alone.

Previously during outbreaks with SARS, Influenza, Ebola viruses, plasma from recovered patients was being used for treating patients in active phase. To determine safety and efficacy of convalescent plasma containing antibodies to SARS-CoV-2 in patients with COVID-19 trials have been initiated.

Stem cell therapy-inhibition of cell mediated immune response and reduction of pathological changes by mesenchymal cells is the proposed mechanism for which investigation is going on.

Tocilizumab, sarilumab are the monoclonal antibodies, C-C chemokine receptor type 5(CCR5) antagonist leronlimaband Janus kinase inhibitor fedratinib drugs are used for cytokine storm in clinical trials.Other antiviral drugs like oseltamivir, darunavir, ganciclovir, favipiravir, baloxavirmarboxil, umifenovir, ribavirin, interferon alfa, nebulised interferon beta are in trial for treatment of COVID-19 patients.[20]

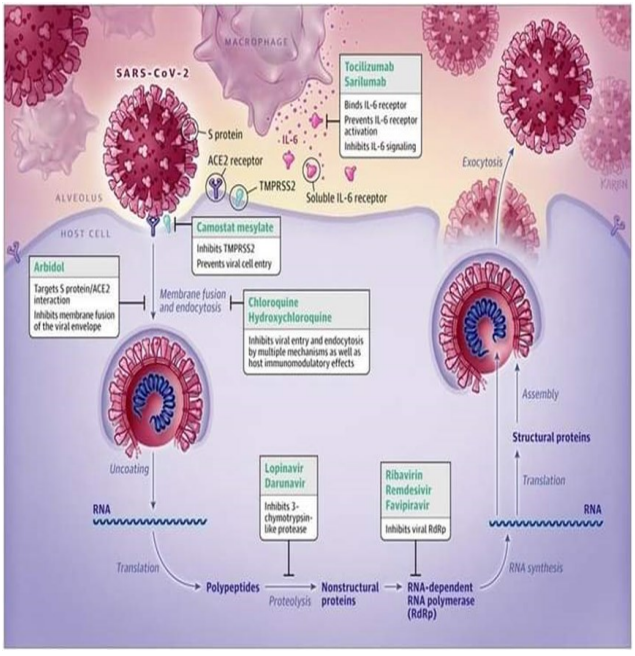

Figure 12: Drugs acting at various stages of viral replication.[20]

Mild to Moderate Disease

Such patients can be managed at home. i.e. Patients without pneumonia and hypoxia. Decision will depend on the clinical presentation, requirement for supportive care, potential risk factors for severe disease, and the ability of the patient to self-isolate at home. High risk patients for severe illness should be monitored closely given the possible risk of progression to severe illness in the second week after symptom onset.

Severe Disease

Corticosteroids are tried for patients with severe illness who are hospitalized in China, benefit not determined.

Inpatient management revolves around the supportive management of common complications of severe COVID-19 like : pneumonia, hypoxemic respiratory failure/ARDS, sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and complications from prolonged hospitalization including secondary bacterial infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy.[20]

Complications [20]

Acute respiratory distress syndrome (ARDS) reported in 15% to 33%. Risk factors are older age, neutrophilia, high lactate dehydrogenase and D-dimer levels. Acute respiratory failure(8%)which is the leading cause of mortality.

Cardiovascular complications-Increased prevalence in critically ill causing high mortality, High inflammatory burden can cause vascular inflammation, cardiac arrhythmias, Fulminant myocarditis, Cardiomyopathy. Acute cardiac injury reported in 7% to 20% which is indicated by increase in cardiac biomarkers. Patients with cardiac injury requiredventilatorysupport compared with patients without cardiac injury. Early corticosteroid therapy and immunoglobulin may be beneficial in these patients. Infection may have longer-term implications for overall cardiovascular health; however, further research is required.

Acute liver injury - abnormal amino transferase levels was noted in patients with severe illness.

Cytokine release syndrome: serum proinflammatorycytokines (e.g., tumour necrosis factor alpha, interleukin-2, interleukin-6, interleukin-8, interleukin-10, granulocyte-colony stimulating factor, monocyte chemoattractant protein and inflammatory markers (e.g., C-reactive protein, serum ferritin) are elevated in critically ill patients and most likely due to virus-induced secondary haemophagocyticlymphohistiocytosis.

Septic shock (4% to 8%),Disseminated intravascular coagulation(71%),secondary infection, Acute kidney injury(3% to 8%),pancreatic injury (17%),rhabdomyolysis.

Neurological complicationscan manifest as acute cerebrovascular disease, impaired consciousness, ataxia, seizures, neuralgia, skeletal muscle injury, and encephalopathy with poor prognosis.

Pregnancy-related complications: miscarriage (2%), intrauterine growth retardation (10%), and preterm birth (39%) are reported, Effects on newborns includefoetal distress, premature labour, respiratory distress, thrombocytopenia, and abnormal liver function .No maternal mortality has been reported till now.

Prognosis: Case Fatality Rate

Overall case fatality rate is currently approximately 5.7% globally based on WHO data as of 7 April 2020,increases with increase in age andit varies between countries.Currently higher in countries such as Italy and Spain, and lower in countries such as Germany and Australia.[20]

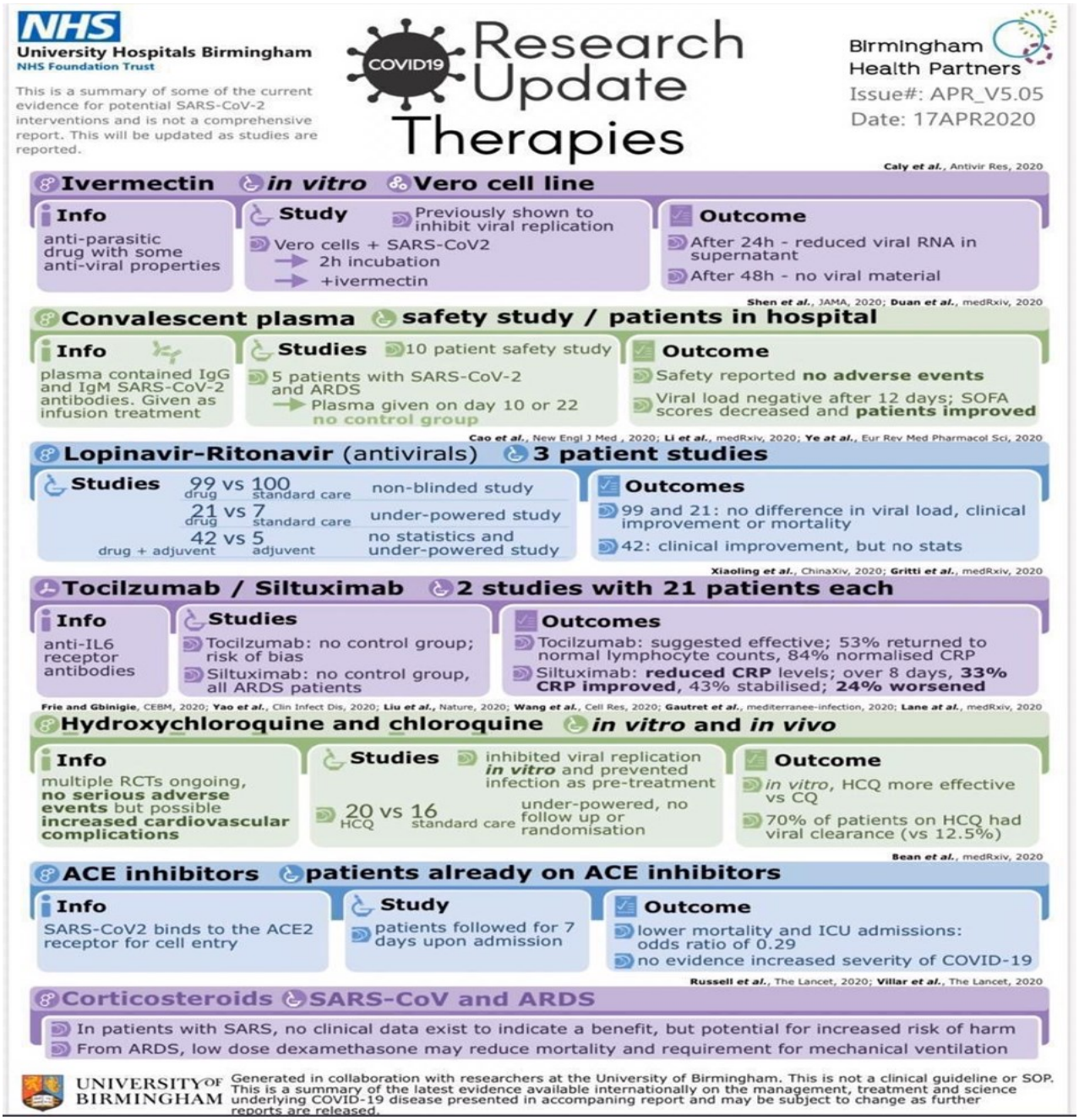

Figure 13: Research update therapies-Covid-19 by NHS.[15]

Conclusion

All the governments in the world working hard to counter the possible devastating effects. Round the world,scientists are working tirelessly and information about the transmission mechanism ,the clinical spectrum of disease,newer diagnostics and prevention and therapeutic strategies are developing.

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