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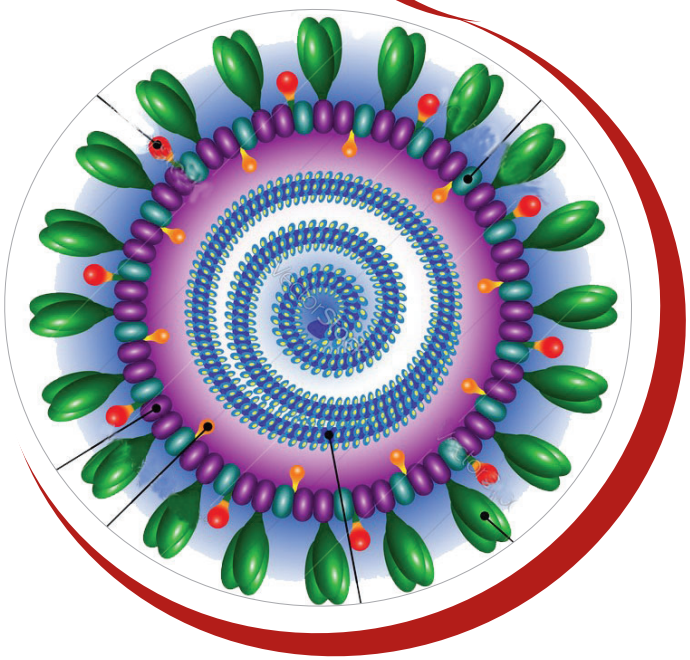

HIGHLIGHTS

COVID-19 and Elderly

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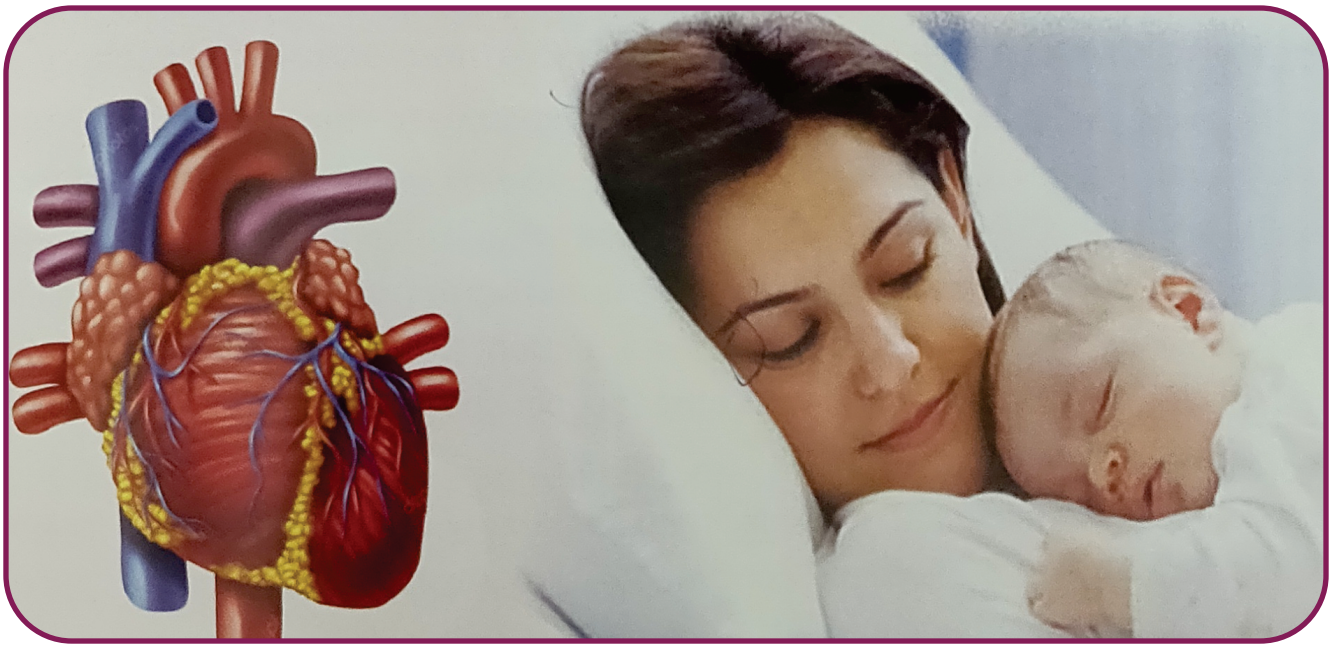

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COVID-19 and Elderly

A novel corona virus infection which made its appearance in Wuhan, Hubei Province, China at the end of December 2019, has spread to 179 countries in the course of 3 months, as Covid 19 and it has caused infection in 8,58,792 persons and death in 42,156 among them by 31 March 2020.

The disease which was mostly confined to China during January 2020, spread to far off Iran, Italy, Spain, France, Germany and UK, and later crossed Atlantic to reach USA. WHO has declared it a pandemic.

Our Government has drawn a plan to contain the disease. In that direction, it has locked down the country to restrict the movement and crowding of people. The trains have been stopped; buses are not running on the roads, and the planes are not flying. Mass quarantine, social distancing, hand cleaning, use of masks and taking precautions while coughing and sneezing are the measures applied. Screening of suspects, home quarantine and isolation and treatment in the hospitals are being carried out on war-footing.

The COVID 19 infection has caused collapse of economy of the World. It takes a long time to recover. It has put great hardships to the people and World has become standstill. All have to join hands to fight this. The elderly people are easily susceptible for this infection and their protection is of great concern. Since there is no specific treatment or vaccine to prevent the infection, we have to adapt the preventive measures.

Members of Geriatric Society of India felt the Society should bring out bring out a booklet on this condition as the elderly persons are highly susceptible to COVID 19. Further the co-morbid conditions worsen the condition. A request was made to our colleagues in the country and outside the country to write on various aspects of this disease and its influence on aged, and the measures they have to take to prevent its occurrence. They have written on these aspects at a very short notice of time. I express my gratitude to them. This booklet, I am sure will provide the guidelines that are to be adapted by the aged population.

The Need of Hour - to fight COVID-19 jointly

Like any other viruses CVID 19 also comes first time. This has originated from China and soon it had global spread. World medicos, leaders and public at large were caught unaware. No knowledge, no testing facilities, no experience of management, no treatment and no vaccine against it. The medical infrastructure, even in developed countries fell short in comparison to everyday growing demand. Panic spread as its virulence caused fatalities. Social and financial effects were seen. A gloom of pandemic engulfed the world.

The Governments geared up. Scientists faced the challenge. At this juncture, the data showed increased fatalities in elderly segment of population. Elderly are the part of population in whom the lowering down of immunity continues with advancing age. They have higher incidence of comorbidities. They have more of Diabetes type-II, heart failure, Chronic obstructive pulmonary disease, Chronic kidney disease, Chronic liver disease, Cancers etc. Besides above they stay indoors more, have sleep disorders, higher incidence of nocturnal aspirations, increased uses of steroids & smoking.

Geriatric Society of India in its endeavour of updating medicos, about the special aspects of medical issues of elderly, at this time has brough out this document "COVID19 & Elderly ". This will be an asset to medicos engaged in geriatric care, to treat elderly better.

Dr. O.P. Sharma
General Secretary.
Geriatric Society of India

Introduction

P.S. SHANKAR

Coronoviruses (CoV) are a large group of diverse groups of RNA viruses belonging to the family of Coronaviridae. Most human coronavirus infections that have been recognised in the last two decades have caused illness ranging from common cold to more severe pneumonia such as severe acute respiratory syndrome (SARS-CoV), Middle-East respiratory syndrome (MERS-CoV) and a novel coronavirus disease (COVID-19) from a new strain of virus that has not been previously identified in humans.

World Health Organization (WHO) has declared COVID-19 as a pandemic, following reports of a number of cases of pneumonia from Wuhan, China and subsequently other countries in the World. During a period of 3 months (first case was reported on 31st December 2019), the disease has spread to over 179 countries. The number of infected are 8, 58, 797 with a mortality of 42,156 (4.7%). The number of infected persons worldwide with mortality rate as on March 31, 2020 is shown in Table 1.

Table 1: The number of infected persons worldwide with mortality rate as on March 31, 2020

Country	No. of infected cases	No. of persons died	Mortality (%)
China	82, 278	3, 309	4.02
Italy	1,05, 792	12, 418	11.75
Spain	94, 412	8. 260	8.76
France	52, 128	3, 523	6.76
Iran	44, 605	2, 898	6.50
U K	25, 474	1, 789	7.02
U.S.A	1,88, 678	3, 890	2.06
Germany	71, 808	775	1,07
South Korea	9, 887	165	1.66
Japan	2, 229	66	2.96
India	1, 397	35	2.50

Older persons and persons with pre-existing medical conditions appear to be more vulnerable to becoming severely ill with the virus infection. In China, about 80% of those who died were over the age of 60 years and 75% of them had pre-existing health conditions. There was high mortality among elderly in Italy, Spain, US and UK. India has 10 per cent of population above the age of 60 years. As there are more easily susceptible for COVID, utmost attention has to be given to their welfare. South Korea, Japan, and Germany contained the disease at a very early stage of the epidemic and it should be a lesson to us.

Aetiology

SACHIN V DESAI

Agent: Corona viruses belong to a large family of enveloped, single stranded positive- strand helical structured RNA viruses. They are ecologically diverse and circulate in humans and animals. They are divided into 4 genera: alpha, beta, delta, and gamma, Alpha and Beta CoVs infect humans. There are four subtypes of Human Corona Viruses (HCoVs) which are endemic globally.

Corona-virus' envelope is studded with projecting glycoproteins, and surrounds a core consisting of matrix protein enclosed within which is a single strand of positive-sense RNA (Mr 6 × 106) associated with nucleoprotein.[1] The envelope glycoproteins are responsible for attachment to the host cell and also carry the main antigenic epitopes, particularly the epitopes recognized by neutralizing antibodies (Figure 1).

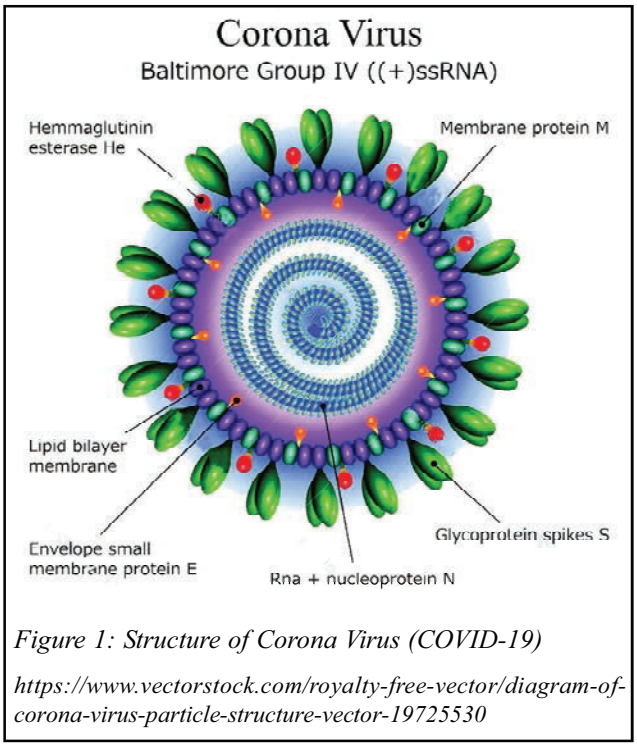

Figure 1: Structure of Corona Virus (COVID-19)

https://www.vectorstock.com/royalty-free-vector/diagram-of-corona-virus-particle-structure-vector-19725530

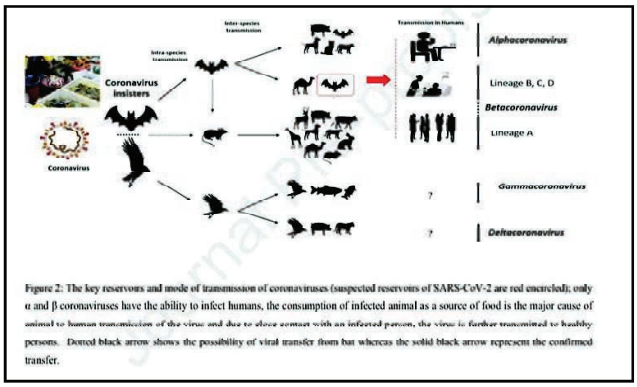

Figure 2: The key reservoirs and mode of transmission of coronaviruses (suspected reservoirs of SARS-CoV-2 are red encircled); only α and β coronaviruses have the ability to infect humans, the consumption of infected animal as a source of food is the major cause of animal to human transmission of the virus and due to close contact with an infected person, the virus is further transmitted to healthy persons. Dotted black arrow shows the possibility of viral transfer from bat whereas the solid black arrow represent the confirmed transfer.

Incubation period: Ranges from 1-14 days (around five days).

Risk Factors: Case fatality is highest in those with multiple comorbidities and, recent travel history to the countries with Corona epidemic, and those coming in contact with a suspect case, and those having low immunity.

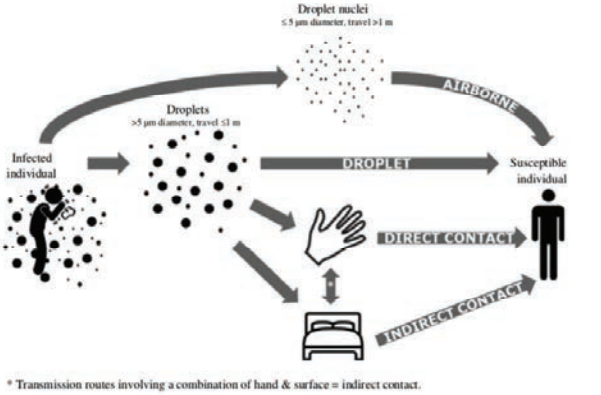

Figure 3: Transmission of COVID-19 through droplet infection.

Host factors: ***Age and Gender*****:** Age above 70 years with a Median age of 51 years, and an Interquartile range of 39-63 years and 51% of the individuals affected are males.

Mode of transmission and reservoir of transmission: (Figure 2)[2] About one in five colds, are due to coronaviruses. The main way the disease spreads is through respiratory droplets expelled by someone who is coughing or sneezing and through fomites. In animate objects harbouring the infected droplets are fomites (Figure 3). The virus survives for twelve hours on steel surfaces and nine hours on fabrics.

Droplets can be of different sizes: when the droplet particles are >5-10 μm in diameter they are referred to as respiratory droplets, and when then are <5 μm in diameter, they are referred to as droplet nuclei.[1] According to current evidence, COVID-19 virus is primarily transmitted between people through respiratory droplets and contact routes (Fig, 3).[3]

Environmental factors: The disease peaks in winters and a temperature of more than 27^0 C would disrupt the structure of the virus. Coronaviruses are fairly fragile and survive outside the body for only about 24 hours.

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Immunology of Ageing

SAJESH ASOKAN

The human immune system undergoes significant changes especially after the sixth decade of life. The ageing immune system loses the ability to protect the susceptible individual against infections, cancer, with an inability to maintain homeostasis and immune response as well as surveillance. Immune ageing or immunosenescence is closely related to organismal ageing. Immunosenescence affects both the innate and adaptive immunity. Amongst these it is primarily the adaptive immunity and the T-cell subset which is most susceptible to the deleterious change especially with the involution of the Thymus gland by midlife. Hormonal influences from endocrine disorders with increased incidence in the elderly such as diabetes, hypothyroidism and adrenal dysfunction are associated with increased susceptibility to infection.

The combined effects of changes in the cellular and humoral immunity leading to organ-specific changes determine the susceptibility of the individuals to infections. Normal ageing is determined genetically. The actual state of the immune system in the elderly is the result of a continuous remodelling process. Oxidative stress is believed to be a major factor of accelerated ageing, possibly due to an increased pace of telomere shortening resulting from DNA damage. Telomeres are DNA+protein complexes at the end of chromosomes and are supposed to be the molecular clock of ageing, including that of the immune system, especially lymphocytes. Age-related deficits in innate immune functions might therefore alter both cell-mediated and humoral adaptive immune reactions.

Innate immunity is a key element of the immune response including several cellular components such as macrophages, NK cells,and neutrophils, which provide rapid first-line defence against pathogens. The functions of these cells decline with age. In the elderly macrophages have a reduced ability to secrete tumour necrosis factor(TNF),a key inflammatory cytokine .Macrophage-derived TNF and interleukin(IL)-1 are essential for the secretion of other cytokines critical for bone marrow stromal integrity, such as IL-6,IL-11,monocyte colony stimulating factor (M-CSF),granulocyte-monocyte (GM)-CSF and receptor activators of NF-kB ligand. Ageing also dampens the secretion of IL-7 by bone marrow stromal cells.IL-7 is an essential survival cytokine for developing lymphocytes. Both the chemotactic and phagocytic activities of neutrophils show reduced efficacy with ageing. NK cells account for about 10-20% of peripheral blood lymphocytes. Most mature NK cells (approximately 90%) express high levels of CD16 and CD56.The NK cell function and dynamics may be affected by ageing. The decline of NK cells may offer an explanation for the increased incidence of bacterial and viral pneumonia, as well as gastrointestinal and skin infections in old age.

Haematopoietic system cells (HSCs) give rise to all cellular components of the immune system (lymphoid and myeloid).The reservoir of naïve B cells might be one of the factors that make centenarian off-springs able to keep fighting off new infections, hence prolonging their life. The loss of naïve B cells represents a hallmark of immunosenescence. The quality of the humoral immune response declines with age. There is a decrease in the diversity and functional integrity of both the $CD4^+$ and $CD8^+$ T-cell subsets, which contributes to a decreased ability to respond adequately to reinfection.

Aged individuals (>65 years) have an increase in peripheral blood T_{reg} cells, but the lack of IL-7 receptor(CD127) expression on the surface of these cells results in their functional damage. T_{reg} lymphocytes downregulate the immune response after elimination of an antigen, control the host immune response to prevent damages to host tissues, and protect the host from self-reactive lymphocytes by deleting autoreactive immunocompetent cells.

The covid-19 pandemic typifies the immune response in an elderly person. The rapid rate of spread of infection and

delayed immune response to such new infections in the elderly who make them vulnerable as they are in the 'twilight of immunity'! That it is not the chronological age alone but having multiple chronic diseases and frailty also matters and contributes to the higher mortality rate seen. The silver lining is the reports of many elderly especially centenarians-the overcomers the ongoing studies on use of BCG vaccine, and development of new vaccines.

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Pathophysiology

SANDEEP TAMANE

Immunosenescence (decline in the functioning of immune system) is a concern in Elderly, making them vulnerable to various infections.

There is reduction in synthesis of T and B lymphocytes and there is reduced capacity of these cells to mount a specific immune response. The risk of infection increases in persons with impaired IgG synthesis, impaired phagocytosis and defective clearance of secretions.

The data available so far indicates that the Covid 19 viral infection is capable of producing an excessive immune reaction in the host. In some cases, A reaction takes place which as a whole is labelled as " Cytokine Storm ". The effect is extensive tissue damage. The protagonist of this Storm is Interleukin 6 (IL - 6).

IL -6 is produced by activated leukocytes and acts on large number of cells and tissues. It is able to promote the differentiation of B lymphocytes, promotes the growth of some categories of cells and inhibits the growth of others. It also stimulates the production of Acute Phase Proteins.

Although the main role played by IL-6 is pro- inflammatory, it can also have anti- inflammatory effects. IL- 6 is also implicated in the pathogenesis of the Cytokine Release Syndrome, that is an Acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction.

Structural analysis suggests that the virus may be able to bind to the angiotensin- converting enzyme 2 (ACE 2) receptor in humans, which suggests that it may have a similar pathogenesis to SARS.[1]

However, a unique structural feature of the spike glycoprotein receptor binding domain of SARS-CoV - 2 (which is responsible for the entry of the virus into host cells) confers potentially higher binding affinity for ACE 2 on host cells compared to SARS-CoV.[2]

A furin- like cleavage site has been identified in the spike protein of the virus, This does not exist in other SARS-like Corona viruses.[3]

Evidence also points to virus attacking enough alveoli in the lungs to cause fluid build-up and collapse of sections of the lungs. SARS - CoV 2 also appears to reduce the O2 carrying capacity of red blood cells, that is why people with Cardiovascular disease and Diabetes Mellitus have higher risk of complications.

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Pathogenesis

AGAM VORA

A **corona** is an aura of plasma that surrounds the Sun and other stars. It is an optical phenomenon produced by the diffraction of sunlight or moonlight (or, occasionally, bright starlight or planet light) by individual small water droplets and sometimes tiny ice crystals of a cloud or on a foggy glass surface.

Virus Corona belongs to the family *Coronaviridae* and the sub family Orthocoronavirinae. They are enveloped viruses with a positive-sense single-stranded RNA genome and a nucleocapsid of helical symmetry. The genome size of corona viruses ranges from approximately 27 to 34 kilobases, the largest among known RNA viruses.

The name "corona virus" is derived from Latin *corona*, meaning "crown" or "wreath", itself a borrowing from Greek κορώνη korónē, "garland, wreath". The name refers to the characteristic appearance of virions (the infective form of the virus) by electron microscopy, which have a fringe of large, bulbous surface projections creating an image reminiscent of a crown or of a solar corona. This morphology is created by the viral spike peplomers, which are proteins on the surface of the virus

Human corona viruses were discovered in the 1960s. The earliest ones studied were from human patients with the common cold, which were later named human corona virus 229E and human corona virus OC43. Other human corona viruses have since been identified, including SARS-CoV in 2003, HCoV NL63 in 2004, HKU1 in 2005, MERS-CoV in 2012, and the most recent SARS-CoV-2 in 2019. Most of these have involved lower respiratory tract with mild disease, except for MERS, SARS & COVID 2019 most the other members of the family.

The current strain is called a novel corona virus (nCoV) as it is a new strain that has not been previously identified in humans and it has been given the nomenclature as **COVID-19 (COrona Virus Disease)** – disease caused by a new strain of corona virus (SARS CoV-2). It is believed to be a zonotic disease. Genetic sequence of COVID 2019 has more than 80% identity to SARS-CoV and 50% to the MERS-CoV.

In humans, corona viruses cause respiratory tract infections that can be mild, such as some cases of the common cold (among other possible causes, predominantly rhinoviruses), and others that can be lethal, such as SARS, MERS, and COVID-19.

Symptoms in other species vary: in chickens, they cause an upper respiratory tract disease, while in cows and pigs they cause diarrhoea. The most common symptoms of COVID 2019 are cough, throat irritation, Fever – high grade and Shortness of breath. A small proportion of patients also had loose motion and vomiting. Majority of patients in India had only mild respiratory illness. Only small proportion of patients especially with underlying co morbidities like cardiac diseases, COPD or other immune compromised disease state had complication like cytokine storm that would lead to ARDS & multi system organ involvement.

Infection begins when the viral spike glycoprotein attaches to its complementary host cell receptor. After attachment, a protease of the host cell cleaves and activates the receptor-attached spike protein. Depending on the host cell protease available, cleavage and activation allows the virus to enter the host cell by endocytosis or direct fusion of the viral envelop with the host membrane. Several groups of scientists in China have all discovered that SARS-CoV-2 (COVID 2019), just like SARS-CoV, requires the angiotensin-converting enzyme 2 (ACE2) as a receptor to enter cells. The binding of the virus with host cell receptors is a significant determinant for the pathogenesis of infection. SARS-CoV most likely originated in bats and adapted to non-bat ACE2 variants as it crossed species to infect humans.

On entry into the host cell, the virus particle is uncoated, and its genome enters the cell cytoplasm. The corona virus RNA genome attaches to the host cell's ribosome for translation. The host ribosome translates the initial

overlapping open reading frame of the virus genome and forms a long polyprotein. The polyprotein has its own proteases which cleave the polyprotein into multiple nonstructural proteins.

A number of the nonstructural proteins like RNA-dependent RNA polymerase (RdRp) & exoribonuclease lead to replication and transcription of RNA. RNA translation occurs inside the endoplasmic reticulum & Progeny viruses are then released from the host cell by exocytosis through secretory vesicles.

Clinical Features

ANAND P AMBALI

Covid 19 presents with clinical manifestations affecting the respiratory system.

The incubation period is 2 to 14 days. Exact mode of transmission is not known. Bats are the rich source of Coronaviruses. Human-to-Human transmission is by droplets, fomites and small particle aerosols. Most transmission occurs in households, Hospitals and little in communities from the infected person. Serious illness has been reported in outbreaks among elderly patients in nursing homes.

Risk factors: Older patients with Diabetes Mellitus, Chronic Lung disease, Cardiac Diseases and compromised immune systems are more prone.

Clinical features: Common Features during epidemic

a) Fever and equivalent features of fever in older people like Increased thirst, altered behavior, confusion
b) Small, frequent bouts of cough,
c) Breathlessness manifesting as decreased activities & short sentences
d) Pressure in the chest
e) Fatigue, anorexia
f) Sore throat, sneezing
g) Diarrhea
h) Laryngitis
i) Loss of smell and taste
j) Cervical Lymphadenopathy

History of traveling: Traveler's diarrhea common in people who travel to Latin America and Asia.

Atypical Presentation: Expected signs and symptoms may be obscured. Atypical feature are common in older people or manifest with complications like ARDS.

Blunted febrile response leads to delay in the diagnosis and Treatment.

The clinical signs may be in the form of tachycardia, tachypnoea, cyanosis, crepitations in basal lung fields. Hypotension in shock.

Clinical syndromes associated with COVID-19 are:

1. Mild illness
2. Pneumonia
3. Severe pneumonia
4. Acute respiratory distress syndrome
5. Sepsis
6. Septic shock

Clinical Classification:

1) Mild disease - Uncomplicated respiratory symptoms
2) Severe disease - Dyspnea, hypoxia or >50% lung involvement on imaging within 24 to 48 hours
3) Critical disease - Respiratory failure, shock or multi-organ dysfunction

Table. Detection Results of Clinical Specimens by Real-Time Reverse Transcriptase–Polymerase Chain Reaction

Specimens and values	Bronchoalveolar lavage fluid (n = 15)	Fibrobronchoscope brush biopsy (n = 13)	Sputum (n = 104)	Nasal swabs (n = 8)	Pharyngeal swabs (n = 398)	Feces (n = 153)	Blood (n = 307)	Urine (n = 72)
Positive test result, No. (%)	14 (93)	6 (46)	75 (72)	5 (63)	126 (32)	44 (29)	3 (1)	0
Cycle threshold, mean (SD)	31.1 (3.0)	33.8 (3.9)	31.1 (5.2)	24.3 (8.6)	32.1 (4.2)	31.4 (5.1)	34.6 (0.7)	ND
Range	26.4-36.2	26.9-36.8	18.4-38.8	16.9-38.4	20.8-38.6	22.3-38.4	34.1-35.4	
95% CI	28.9-33.2	29.8-37.9	29.3-33.0	13.7-35.0	31.2-33.1	29.4-33.5	0.0-36.4	

(Adapted from Wang W, Xu Y, Gao E, et al. Mar 11, JAMA 2020)

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Evaluation of a patient of COVID-19

PUNEET KHANNA

Affected countries across the world have used both clinical and epidemiologic information to determine who should have testing performed. In India, criteria have been described by the ICMR as per case definitions for investigations of COVID-19 affected persons. The WHO[1] recommends collecting specimens from both the upper respiratory tract (naso-and oropharyngeal samples) and lower respiratory tract such as expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage.[1] Table-1[2] describes the sensitivity of various techniques in detection of COVID -19. Bronchoalveolar lavage should be avoided due to high risk of infection to HCW and only be performed in mechanically ventilated patients with full precautions if initial tests are negative.

LABORATORY FINDINGS

In the early stages, total white blood cell count may be normal or decreased with relative lymphopenia and thrombocytopenia. Lymphopenia, elevated levels of ferritin (above 500 mcg/dl), raised liver enzymes, LDH, muscle enzymes, C-reactive protein with increased D-dimer levels

Table : Treatment Protocol for Older adults with COVID-19

Category	Treatment	Preacautions
A (mild symptoms)	Elderly will not fall in this category at all. However fit elderly without comorbidity may be included here. (Azithromycin 500mg once a day for day 1 followed by 250 mg once a days for 4 days if tolerated Anti-inflammatory agents, antitussives, anti-histaminics to be avoided in elderly	Older adults may have severe GI side effects such as abdominal cramps and diarrhea for azithromycin. Also Azithromycin can prolong Q-TcSmaller doses of 250 mg per day is safer
B (category with comorbidity or severe cough, sore throat, diarrhea)	1.Tab Hydroxychloroquine 400mg BD X1 day followed by 200mg BDX4 days Plus 2. Azithromycin 500 mg x1 day followed by 250mgX4 days 3.Tab Oseltamavir 75 mg BD for 5 days or until Covid report comes or influenza symptoms are predominant	Contraindications to HCQ 1. Q-Tc>500ms 2. Retinal pathology 3. Epilepsy 4. Myasthenia Gravis 5. Previous cardiac arrhythmia Hydroxychloroquine dose may be prescribed by modifying it as 200m BD for 7 days as it is safer and it is often used for rapid virological clearance and rapid symptomatic improvement and no mortality benefit. Frequent ECG monitoring for QTc is necessary Avoid- Azithromycin if diarrhea is the symptom
C (severe)	Category B treatment plus Lopinavir/ ritonavir(400mg+100mg) for 14 days in patients where hydroxychloroquine is contraindicated It has to be used on compassionate ground and after informed consent in people who present within 10 days of symptoms Recent guidelines do not recommend it Oseltamavir unitl report	For protease inhibitors drug interactions are many Hence to be avoided in elderly with polypharmacy GI intolerance may be seen. Monitor LFT while on therapy Oseltamavir dose for critically ill elderly will be 75 mg once a day since they often have low GFR

appear to be negative prognostic factors. Procalcitonin levels are usually normal but may increase in the critically ill with onset of multiorgan failure or secondary sepsis.

MOLECULAR TESTING

COVID-19 antigen is detected by polymerase chain reaction (RT-PCR) and the results are generally available within 2 days. A single positive test is confirmed by a second RT-PCR assay targeting a different SARS-CoV-2 gene. If initial testing is negative but the suspicion for COVID-19 remains, the WHO recommends re-sampling and testing from multiple respiratory tract sites along with sampling for other viral/ bacterial pathogens. COVID-19 Rapid Test qualitatively detects IgG and IgM antibodies to SARS-CoV-2 in human whole blood, serum and plasma samples by lateral flow immuno-chromatography. The IgM-IgG combined assay, though not approved yet, has better sensitivity for rapid screening of carriers in the community.

RADIOLOGY

Chest radiography or computed tomography are not routinely recommended to diagnose the COVID-19 infection. The findings on chest imaging are non-specific, and could overlap with influenza and other infections. The most common features include lobar/ multi-lobar / bilateral lung consolidation with ground glass opacities (GGO) involving predominantly the lower lobes with sub-pleural distribution. USG findings though non-specific include irregular pleural lines, sub-pleural areas of consolidation, areas of White lung and thick B lines

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Treatment Protocol for Older adults with COVID-19

PRABHA ADHIKARI,M.R.

1. All elderly with COVID-19 positive must be treated as high risk category and admitted and observed for complications
2. Treatment may be based on the category as follows

Management of ARDS

1. Use supplemental oxygen
2. Elective intubation and mechanical ventilation using low tidal volume and prone ventilation
3. Avoid noninvasive ventllation due to fear of aerosol generation
4. Avoid nebulization
5. Use low dose methyl prednisolone if no contraindication if ARDS is a part of cytokine storm syndrome

Management of Cytokine Release syndrome in older adults with MODS

- Cytokine release syndrome Grade 3 to be monitored by IL-6 or CRP,Ferritin
- Consider tocilizumab 8mg/Kg IV maximum of 400mg over 60 minutes
- If no response repeat two more doses 8hours apart
- Consider low dose steroids especially septic shock
- Use antibiotics for possible septic shock .
- Fluid resuscitation should be less aggressive –saline bolus to be given to see the response,if dyspnea is worsening ,start low dose inotropes Noradrenaline 0.5mcg/kg/minute
- High IL-6, Rising CRP,hyperferritenemia,elevated LDH,low procalcitonin ,confirms cytokine storm syndrome and low dose methyl prednisolone is life saving. Methyl prednislone 0.5-1mg /kg per day in two divided doses intravenously for a maximum of 6 days
- Steroids: Chinese experts recommend cautious use in selected patients of Indications (the following 4 conditions need to be met at the same time): (1) Adults (age ≥ 18 years); (2) Patients with new coronavirus infection confirmed by polymerase chain reaction (PCR) or serum antibodies; (3) Symptoms (including fever, cough, or other related infection symptoms) Within 10 days, imaging confirmed pneumonia and progressed rapidly; (4) The patient's blood oxygen saturation (SPO 2) ≤ 93% or shortness of breath (breathing frequency ≥ 30 beats / min) or oxygen in the state of no oxygen at rest

Use with caution in older patients and rule out refractory hyperglycemia, refractory hypertension, delirium, glaucoma, hypokalemia, bacterial or fungal infections, severe lymphopenia

Hemophagocytic syndrome: Macrophage activation syndrome is also known to occur in Covid-19 patients and judicious use of low dose methylprednisolone as mentioned above is warranted.

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Prevention of COVID -19

PRABHA ADHIKARI M.R.

In a country like India prevention is the most important option. preventing exposure in the community.

The following general measures are recommended to reduce transmission of infection. In particular, older adults and individuals with chronic medical conditions should be encouraged to follow these measures.

DO'S

1. All elders should be encouraged to practice social distancing by staying home as much as possible
2. Diligent hand washing, particularly after touching surfaces in public. Use of hand sanitizer that contains at least 60 percent alcohol is a reasonable alternative if the hands are not visibly dirty. Wash hands when you get a opportunity with soap and water.
3. Respiratory hygiene (e.g., covering the cough or sneeze). Cough into your elbows
4. Avoiding touching the face (in particular eyes, nose, and mouth).
5. Individuals who are caring for patients with suspected or documented COVID- 19 at home, however, should wear a tightly fitting medical mask when in the same room as that patient.

DON'TS

1. Chemoprophylaxis with hydroxychloroquine is not safe for the elderly since side effects such as insomnia, convulsions,cardial arrhythmias and hypoglycaemia can occur upto one month after loading dose of chloroquine
2. For people without respiratory symptoms, wearing a medical mask in the community **is not recommended**, even if COVID-19 is prevalent in the area[1] wearing a mask does not decrease the importance of other general measures to prevent infection, and it may result in unnecessary cost and supply problems.[2]

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COVID-19 and Elderly Diabetics

JUGAL KISHOR SHARMA

COVID-19 is a new medical issue, and there is not enough data about the connection between this viral infection and diabetes and absolutely no data on elderly diabetics. The IDF website says, "Older people and people with pre-existing medical conditions such as diabetes, heart disease, and asthma appear to be more vulnerable to becoming severely ill with the COVID-19 virus. When people with diabetes develop a viral infection, it can be harder to treat due to fluctuations in blood glucose levels and, possibly, the presence of diabetes complications. There appear to be two reasons for this. Firstly, the immune system is compromised, making it harder to fight the virus and likely leading to a longer recovery period. Secondly, the virus may thrive in an environment of elevated blood glucose."

It is always necessaary to avoid infections and maintain good control of diabetes. Diabetes patients should aim to keep the fasting blood sugar below 110 mg/dl and below 160 mg/dl after meals, . Elderly people should have blood sugar 10% - 20% above these levels and should avoid hypoglycemia. The best way to monitor sugar levels is to have a reliable blood glucose monitor at home and monitor the fasting and after meals blood sugar twice a week.

People on insulin should check more often. If there is a wide fluctuation in the blood sugar level, it is now possible to have a sensor attached to the skin and do a bloodless ambulatory glucose monitoring, which gives more than 1000 readings over 14 days. Maintaining good control of diabetes also helps to build one's immunity to fight infections. Several adult vaccinations have been advised for people with diabetes. The flu vaccine and the pneumonia vaccine are the two common vaccins advised for people with diabetes, especially elderly diabetics.

Specific COVID-19 precautions for people with diabetes

During the lockdown period, keep enough stock of your oral antidiabetic medications, insulin, blood glucose strips, special pouch for keeping the insulin, and tablets to treat a low sugar reaction, special diabetic footwear, medications for other comorbid conditions. Don't miss out on your exercise even if you are forced to be inside your house. Elderly diabetics should find time and space to do some simple exercises like stretching, walking, and yoga for at least 30 minutes a day. It is also better to avoid high-calorie snacks that have more calories and salt. Several people with diabetes are worried that they are more prone to this virus. The first thing is to get this thought out of the mind as it may cause anxiety disturbing the blood sugar levels.

What can the elderly diabetics and their loved ones do?

For people living with diabetes, it is important to take precautions to avoid the virus. The recommendations that are being widely issued for the general public are doubly important for diabetics and people in their close contact. Any infection is going to raise your glucose levels and increase your need for fluids, so make sure you have access to a sufficient supply of water. Think of what you would need if you had to quarantine yourself for a few weeks. Make sure you have access to enough food and that you will be able to correct the situation if your blood glucose drops suddenly. If you live alone, ensure that you have assistance in case of emergencies.

Keep a regular schedule, avoiding overwork and having a good night's sleep. Healthy nutrition is an essential component of diabetes management, it is therefore important for people with diabetes to eat a varied and balanced diet to keep their blood glucose levels stable and enhance their immune system. It is recommended to give priority to foods with a low glycaemic index (e.g. vegetables, whole wheat pasta/noodles, etc.).

Covid 19 and Elderly with Hypertension

M E YEOLEKAR

In relation to Covid 19 situation, a frequently asked question is how to manage Hypertension (HTN) in elderly patient. It is important to remember that being above sixty and Hypertension makes for four points on the 12- point adversity scale in Covid 19 score. Three factors probably matter: a) the duration of HTN; b) the degree of control, obviously related to compliance, and. c) the target organ damage — Left ventricular enlargement, symptoms of cardiac failure, and renal involvement. The patient is better of with Hypertension alone and under control, and without target organ damage (TOD). It is particularly important to follow the lifestyle measures— moderation in calorie intake, salt under 2000 mg and indoor physical activity that 'stay at home ' permits. In relation to drugs — one needs to continue if on CCBs, or ACE inhibitors such as Ramipril, Enalapril, Perindopril and others

ARBs such as Telmisartan, Losartan, Olmesartan and others a controversy had arisen based on Chinese observation.[1] But subsequently, experts have stressed there is not enough evidence to suggest these medications can worsen COVID 19 morbidity and mortality.[2] Certain professional societies around the world have issued statements urging patients taking ACE inhibitors and ARBs to continue taking their treatment even if they develop COVID 19, unless told to do otherwise by their doctors.

In COVID 19 treated in ICU, the intensivist monitoring the patient is the best judge for the fluctuating cardiac dynamics. For the anxiety neurosis that may develop during COVID 1, there is no recommendation as yet on usage of beta blockers.

Lifestyle, dietary measures and compliance to antihypertensive treatment are most crucial for elderly with hypertension. Needless to add that extreme caution is necessary if associated co-morbidities such as DM, IHD, CKD, COPD also exist.

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COVID-19: Socio-economic Issues of Elderly

KAUSHIK RANJAN DAS

In India, we have been passing days mostly staying at home in a total lockdown state , with the intend to break the chain of COVID-19 transmission –outbreak of which has started in Wuhan, China in December 2019 and travelled to many other countries notably USA, UK, France, Italy, Spain and also reached India on 30.01.2020.[1] Due to age-related changes and presence of multiple co-morbidities, COVID-19 affected senior citizens who are prone to produce severe symptoms, and increased mortality has been found among them.[2]

Central and State Governments with all their machinery, have been working relentlessly to mitigate the pandemic by all possible ways. But number of new cases have been rising day-by-day. It is not known when the incidence and spread of this highly infectious disease will come down. There have been predictions that by the end of August 2020, onslaught will come lower.[3]

As days are passing problems (other than COVID-19) related to life of elderly has been emerging and increasing. These are attributable to lock down, other steps and propagandas nationally and internationally. Only socio-economic issues and their consequences are discussed.

Internationally

There has been news of keeping elderly left out of treatment in Italy.[4] In Spain, the Defence Minister states, there is death and abandonment of elderly.[5] Also, there is news of decision of treatment is vested upon doctors. This news is very much shocking and disgraceful and will affect health of the elderly in many ways and also contravenes human rights and UN Principles for older persons.[6]

Nationally

(a) ***Mobility:*** Due to lock down elderly can't go out for a walk, for want of vehicles they cannot go for attending health facilities, financial institutions etc., All those will affect their health significantly.

(b) ***Procurement of essential commodities:*** Although there has been effort for smooth supply and availability of essential commodities, it is observed that there has been non-availability of essential commodities and also price hike –making it difficult for elderly to cope with and increasing chances of adverse health consequences.

(c) ***Preparation and supply of food***: Cooks and maids have been barred to attend houses of their employers, as a result there is inability/disability to prepare meals and disturbance in maintaining hygiene. Home delivery is also being disrupted. All these have been throwing senior citizens in a state of malnutrition, even starvation and chances of accidents – those may turn to grave consequences.

(d) ***Availability of Medicines***: Availability of medicines in retail shops have already emerged as a matter of great concern for elderly who have to take medicines for multiple co-morbidities. It is evident from medias that elderly have been expressing their difficulty in taking medicines from different facilities *viz*. CGHS, Railway hospitals, Army base hospitals etc. and urging for an alternative means so that they can get the medicine at their place. This situation has created a great anxiety in them.

(e) ***Financial Issue***: Livelihood of huge number of elders depends on fixed income from pension or interest from small deposits. Prices of essential commodities are on hike on one hand and on the other banks are decreasing the rates of interest – this situation has made elderly in a pecuniary disadvantageous status.

There are chances of emergence of other issues like non availability of hospital beds, end of life care etc.

Proposed measures to mitigate the issues:

1. United Nations - open ended working group on ageing for the purpose of strengthening protection of the human

rights of older persons" should remain extreme vigilant and act on human right issues in different countries during this COVID-19 outbreak.

2. Central and State Governments need to make aware of the emerging situation with an appeal to inform all machinery to remain vigilant on the issues. Central Govt. should take care so that bank interest is not decreased further. Incremental amount of financial assistance must be provided to our senior citizens by both Centre and States.
3. Neighbors, members of local bodies, social workers, NGO's, volunteers are required to take care on the issues of elderly, specially those who have no family help due to any cause. At least local Block development officer, Officer in Charge of local Police station or SDO or other administrative officer be informed of the situation of an elderly as they(volunteers) come to know.

CONCLUSION

It is hoped that by joining hands together India will win the battle against COVID-19 & life of our elderly will remain secured at this unprecedented crisis. We shall overcome!!

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Covid 19 and Elderly with Sleep Problems

S. RAMNATHAN IYER

Sleep, which is essential for physical, mental and emotional well-being is affected both subjectively and polysomnographically in the elderly. Sleep is also essential for building immunity. Sleep deprived subjects are prone to infections. In elderly the main alteration in sleep is reduced and sleep duration is to about 6 hours.

In the present scenario of Corona Virus infection, the elderly persons have become anxious for various reasons. Anxiety is known to affect the sleep adversely. This can affect Sleep onset and Sleep maintenance and Insomnia. The causes for anxiety are:

1. Unable to go out for morning walks. Not able to have gossip with friends.
2. Unable to go for regular health check-ups.
3. Children who are abroad are unable to come home.
4. They are more prone to get infected with Corona virus.
5. Majority of the news are related to Covid 19. (Elderly usually like watching news but the fear of Corona makes them worried)

Geriatricians and attending physicians must note that the common sleep disorders in elderly are sleep deprivation, insomnia and sleep disordered breathing (SDB)-obstructive sleep apnoea (OSA). During this lockdown period sleep habits and behaviours can be observed by the adults in the house *viz* sleep postures, snoring, choking, number of nocturia episodes, parasomnias and others. Nocturia is common and is a prominent symptom of obstructive sleep apnoea in elderly. Poor quality sleep also reduces immunity. There is increased risk for respiratory infections in subjects with SDB –(OSA). Gastroesophageal reflux disease, and nocturnal aspirations increase the chances of respiratory infections. Presence of co-morbid conditions such as diabetes and hypertension also contribute to reduced immunity.

MANAGEMENT

The elderly needs to practice the following at home:

1. Programmed walking at home.
2. Spend time with their children and grand children- tell stories etc.
3. Nutritious diet.
4. Yoga and Meditation
5. Practice sleep hygiene which consists of
   (a) Regular time to bed and awakening.
   (b) No Coffee/tea near sleep times.
   (c) Go to bed at least two hours after dinner.
   (d) Listen to light music
   (e) Limit blue light exposure near bedtime. It is applicable to all members at home.
6. Management of all co-morbid conditions.
7. Insomnia may require hypnotic medication.
8. Detect and treat SDB-OSA.

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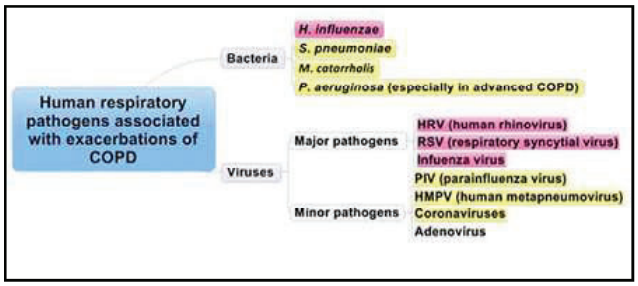
Covid 19 and Elderly COPD / Asthma

ARVIND GHONGANE

- HCoV infection has been viewed as a contributor to exacerbations of underlying COPD, asthma, CCF, and severe illnesses requiring emergency care and hospitalization of patients
- Although HCoV-229E and HCoV-OC43 were the most frequent HCoV strains identified, HCoV-NL63 and HCoV-HKU1 co-circulated during the 1998-1999 season. [1]
- COVID-19 is a new disease that is caused by a novel strain of coronavirus that is different from the common cold, influenza, or pneumonia. People with COPD and other lung conditions are at an increased risk for severe outcomes if they become infected, which is also true for seasonal influenza and pneumonia.[2]



- Who is regarded as extremely vulnerable? [4]
  - All types of cystic fibrosis
  - Severe asthma
  - Severe chronic obstructive pulmonary disease (COPD)
  - Lung cancer and mesothelioma, who are having active chemotherapy or radical radiotherapy
  - Severe bronchiectasis
  - Interstitial lung disease, Pulmonary fibrosis and Sarcoidosis
    - * The COPD Foundation released practical recommendations for patients living with COPD who may have concerns about the COVID-19 infection. [5]
    - * Additional precautions for COPD / Asthma patients to avoid getting sick. [5]
  - Maintain at least a 30-day supply of your prescribed medications.
  - Check with your oxygen supplier to see how it will deal with COVID-19.
  - Establish a COVID-19 hygiene routine for people entering home
  - Stay inside unless absolutely necessary

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COVID-19 & Elderly: Family Physician's Perspective

ANIL MANCHANDA

Covid-19 can spread from person-to-person and through fomites. Due to lot of asymptomatic transmission during incubation period which is 2-14 days (Median 5.1-5.2 days)[1,2] Short -serial interval (The time between successive cases in a chain of transmission) of 4-4.6 days (15) and large reproductive number (RO) from 1.5 to 3.5 makes it more transmissible than many other organisms.[3,4]

Besides Virulence of the Virus the progression of disease depends a lot of Host factors. Elder patients (> 65years) due to Immunosenescence have high fatality rate. Other Comorbid conditions like Hypertension, CAD, Diabetes mellitus, COPD, CKD etc (which are more prevalent in elderly patients) may further worsen the outcome. Early diagnosis, appropriate treatment and early quarantine of the contacts give elderly patients chance of better outcome. Therefore, it is responsibility of family physician to identify these cases early, treat early, differentiate between COVID-19 *v/s* non COVID-19 patients and refer COVID patients to nearby Centre.

Few protocols should be followed to avoid exposure to self, HCW, Elderly patients and their attendants.

1) Use of telecommunication and digital prescription (Meddo,Healthplix, Practo etc) as per rules laid down should be emphasized to minimize community exposure.
2) Distinguish between Covid v/s non Covid patients based upon symptoms, History of Travel or contact with Covid-19 patients,
3) If direct examination of patients to be done Implement Protective Precautions, Adhere to Standard, Contact, and Airborne Precautions and wear appropriate personal protective equipment (PPE) including respiratory protection. At the facility entrance, provide face masks and other respiratory hygiene supplies (tissues, hands free trash receptacles) and alcohol-based hand sanitizers. Allow patients to wait in a personal vehicle or outside the healthcare. Perform hand hygiene both before and after all patient contact, and after contact with potentially infectious material. Clean the stethoscope and instruments after every examination.
4) During Pandemic only those patients who are in emergency should be admitted

Vaccination

Judicious use of vaccination for elderly as per recommendation will help to bring down secondary infections like Pneumococcal Pneumonia and H1N1 Influenza which may reduce mortality.

HCQS Prophylaxis

ICMR recommended use of HCQS for COVID-19 infection in high risk groups (approved by (DCGI).[5] Trial of Use of Hydroxychloroquine as post exposure prophylaxis is underway.(Please enroll for HAPPY trial (HCQ as Post exposure Prophylaxis to prevent COVID-19 at dskinfdis@gmail.com. This is to emphasize that PPE is better than Post exposure prophylaxis.

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Corona and Respiratory Vaccines

MANGESH TIWASKAR

COVID-19, which was first unmasked in December in Wuhan, China, has sickened and unhinged more than 179 countries worldwide and killed many victims. There are no Food and Drug Administration-approved vaccines or therapies for the disease. Many researchers and pharma companies are working vehemently for the development of a vaccine against COVID 19. But while we wait to find solutions during this calamity, we can protect ourselves from common community acquired respiratory infections by advocating respiratory vaccines. And this may be more relevant in elders, people with respiratory decrepitude and immuno-compromised population who are more vulnerable to COVID 19 related respiratory catastrophe.

Below table tries to bestow bird's eye on the available respiratory vaccines which may offer benefits during this CIVD outbreak.

Table 1: Vaccination for Adults with Lung Disease in COVID 19 Epidemic

Name	Beneficial	Dose	Even though vaccinated before
Influenza	Definitely	Yearly	Yes
Pneumococcal	Definitely	Once in Life	No
Zoster	Definitely	2 doses	Yes
Hepatitis A	May be*	2 doses: 6 to 12 months apart	May be*
Hepatitis B	May be*	2 or 3 doses	May be*
Meningococcal B	May be*	1 dose	No
Varicella	May be*	1 dose	Yes

*Very high-risk patients especially Immunocompromised, Transplant, Splenectomy, Malignancies

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Corona Virus Experience in Japan

RENU WADHWA

Japan has adopted relatively restrained approach for the novel coronavirus testing and keeping the outbreak under control without the mandated lockdowns so far. People are calm and organized. Social distancing and wearing masks are way of life here. Hand-shaking is not a usual practice; people separate their indoor and outdoor shoes/cloths and take bath upon returning home from work. Some highlights are sketched here.

February 28: As a first effort to prevent the spread of new coronavirus, Japan's Prime Minister Shinzo Abe asked all elementary, middle and high schools nationwide to close until early April. This came as a sudden decision and left working parents perplexed. Extra support system at schools and day care centers, including serving food for kids took some stress off. Graduation day in Japan falls on March 23. Most schools held graduation ceremony either briefly or online. Business meetings that require more than 10 people are mostly cancelled. Even when held, measures like wearing mask, intra-seat distance of 1-meter and air circulation every hour were prime requisites.

2020-TOKYO Olympics has been postponed to next year. On March 28-29 (week-end) when the cherry blossoms are at peak and traditional cherry blossom parties (called Hanami in Japanese, means cherry blossom viewing) would have taken place, the governor of Tokyo asked people to stay home. Although trains and other transport services are running normally, there is an overall decrease in number of people seen outside and travelling. At the same time, largest daily increase in new infection cases so far has been recorded today (March 28).

As elsewhere worldwide, shortage of masks and sanitizer are in short supply in Japan too. Several companies, outside the field of medical and health care including the electronic company Sharp, have launched ventures to make masks and supply in big numbers soon. On the science front, Japanese researchers at Nagasaki University have developed a novel coronavirus test kit that provides results within 10 minutes - much faster than standard testing methods.

Japan-developed a flu drug 'Avigan' which was endorsed as a treatment for COVID-19 in China. Researchers at the University of Tokyo reported that the drug 'Nafamostat', an enzyme inhibitor typically used to prevent blood clots, holds potential to treat COVID-19. The drug could potentially suppress the protein that mediates virus entry to host cells. Like rest of the world, Japan is preparing to fight the war against new Coronavirus in its own ways.

Covid 19: UK Experience

SANGEETA KULKARNI

Older people are not at any higher risk than general population of contracting COVID-19. However they are much more likely to suffer worse outcomes should they contract the disease due to increasing frailty. A number of factors are important in caring for such older population. In addition to the advice provided by UK Government about social distancing and self-isolation, General Practitioners are playing a huge role in completing Advanced Care Plans and ReSPECT[1] (Recommended Summary Plan for Emergency Care and Treatment) forms in the community. ReSPECT form is a nationally adopted document that aims to respect both clinical judgement and patient's wishes and is accessible to out of hours GPs and paramedics.

Older people presenting to the Emergency Department should have their Clinical Frailty Score (CFS[2]) measured alongside their presenting symptoms according to National Institute for Clinical Excellence (NICE[3]). CFS, presence of co-morbidities and ReSPECT form help in focusing the decision regarding escalation of care. In addition, delirium is highly likely to be either the presenting or subsequent feature of COVID-19 in the older person. Management is going to be potentially challenging in hyperactive delirium with risk of harm caused to healthcare individuals likely to override harm caused by rapid tranquilisation to the patient[4]. Therefore, consideration needs to be given towards early identification and management of hyperactive delirium through a rigorous use of 4AT[5] (Test score) on admission.

Patients being discharged back to the community are generally supported in the UK by Rapid Response Teams and District Nurses especially those who are already residing within Nursing and Residential Homes. It is vital that throughout this entire process clear lines of communication are established with patients, families and carers. Lastly let's not forget that self- isolation and social distancing will not stop patients with falls and fractures from attending the emergency department and there should be enough resilience in the system to address these issues. Therefore, the older person needs even more attention from geriatricians whilst the world is focusing on this dreaded illness.

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Lessons from Wuhan, China

GONG ZUOJIONG

A key lesson from Wuhan's battle was breaking the chain of transmission through widespread testing and isolating all patients, even those with mild symptoms, away from their homes in central quarantine.

New Infection: COVID 19 has been brought under control through two months of prevention and management in Wuhan and Uiibei province. No new patient has been diagnosed right now. However strict monitoring is being continued.

At the beginning, there were too many patients that needed to be confirmed. The hospital did not have so many beds for the patients' hospitalisation. There was a shortage of personal rotective equipment (PPE). Our hospital dedicated a separate campus, our east campus as a designated hospital to receive severe and critical patients.

'Turning point' was achieved at the end of February, when the numbers of new confirmed and suspected cases dramatically decreased. Now, we are reporting zero cases.

For prevention and control of a high contagion, the important measures are to manage and control those infected, and break down the transmission. For those cases that were mild and moderate,we found that transferring them to the ark hospital (makeshift hospitals of which 16 were build) is a good method that we would recommend. It is necessary to avoid people gathering. Wearing masks and hand hygiene are also important. In addition, doctors should pay more attention for finding severe cases early in order to diagnose and treat critical cases to reduce the risk of mortality.

Quarantine and isolation: Quarantine and home isolation depends on different countries' conditons. In China and India, because we have such a large population, one family may have several members. Cross infection occurs commonly. For mild and moderate type confirmed cases, the ark hospital is a good quarantine and isolation place, and this helps avoid cross infection and breaks down the transmission.

Testing: By the middle of January, when PCR reagents (nucleic acid testing) became available, our hospital alone tested around 1,000 samples daily. Testing for COVID 19 plays an important, even central role, because we want to find new cases and suspected cases as quickly as possible. Only then we can isolate patients and break down the transmission.

Courtesy: The Hindu, 31 March 2020 Interview by Ananth Krishnan with the author

Corona in Nepal

SUMANTA BANJADE

The global COVID 19 pandemic entered Nepal when the first confirmed Corona positive case was reported on 24 Jan 2020. Till date Nepal has reported total of 5 cases out of which the first case is said to be completely recovered and remaining four are kept in isolation ward in Teku hospital, Kathmandu. All these cases share common history of travel from infected country.

Starting from cancelation of visits to Nepal 2020 to completely sealing of its borders, the authorities are trying to focus on preventive measure. Highlighting on elderly age group, Government have decided to provide Rs 10000 per month for the next 3 months to the senior people staying at various rehabilitation centers and elderly care home across the country as a relief package. This package includes almost 1500 elderly people in the first phase. Beside this, government has provided masks, and sanitizers in elderly house. Government is making extra efforts to elderly age group residing in social elderly house. Social distancing, and other hygiene related points are focused there.

Elderly age group in Nepal is relatively less and the effect of this disease in this group has been null till date.

Immunomodulators in Geriatrics

SHIKHAR GARG*, A.K. SINGH**

Our immune system is a network of special cells, tissues, proteins and organs which work in harmony to protect us from damaging foreign invaders and diseases. If our body comes in contact with foreign invaders like bacteria, viruses or parasites then it triggers an immune response against them. The first work of the immune response is to discriminate between self and non-self and if it is non-self then it destroy them. Immunity is of two types, innate or natural and adaptive or learned. Innate immunity is that with which we are born with and is the first line of our defense against infections. Adaptive immunity is that which we learn or acquire throughout our life after getting exposed to various diseases or after getting vaccination against them. Adaptive immunity takes 5-10 days for its proper action and before that innate immunity fights against invaders. Immunosenescence is the senescence of the immune system or decline in the immune system or dysregulation of the immune system with increasing age.[1,2] As actions of the immune system is invisible hence it is very difficult to quantify them. The clinical manifestations of declining immune system are progressive and take decades and may also be mingled with other manifestation of aging. Biomarkers of immunosenescence are unreliable which makes monitoring of immunosenescence and interventions against it very difficult. The overwhelming decrease in T-cell functions is the hallmark of immunosenescence.[3] Declining immunity in elderly make them more susceptible to diseases, more prone to infections and there is also a poor response to treatment with vaccination in them.[4]

CHANGES IN IMMUNE SYSTEM WITH AGEING

Aging is associated with the gradual decrease in lean body mass combined with gradual increase in fatty tissue at various parts of the body. Increased fat accumulation in bone marrow and thymus causes reduction in effective bone marrow and thymic tissue respectively which further results in decreased production of B-cells from bone marrow and naive T-cells from thymus.[5,6] Adipose tissue expansion with aging is also a major source of inflammation in elderly(inflammaging) which has a marked influence on systemic metabolism and may results in increased incidence of insulin resistance, type-2 DM and various cardiovascular disorders in them.[7] Innate immunity declines with aging. In elderly dendritic cells became less effective and functions of neutrophils also declines eg. slow response to chemotaxis, phagocytosis, superoxide generation and alteration in signal transduction and membrane lipid rafts.[8] Aging is also associated with decreased ability of the peripheral lymphoid cells to undergo clonal expansion or regeneration which leads to decreased cell mediated immune response, phagocytic activity and reduced effectiveness of functions of monocytes and macrophages. There is reduced thymopoiesis in elderly which results in reduced number and frequency of naïve T-cells and increased number and frequency of memory T-cells in them. In the presence of persistent infectious agents like CMV, expansion of the memory T-cell pool occurs. It is good for control of CMV but it fills the immunological space with clones specific for CMV and reduces the space for naïve T-cells and memory T-cells against other infectious agents and effectively reduces T-cell repertoire diversity. So knowing immunological history (number and frequency of antigens encounter during life) is very informative and is also a strong determinant of immunological aging. The immunological aging is the extent of senescence seeing at the immunological level. This mostly involve T-cells but B-cells can also be senescent. Reduced thymopoiesis may occur due to age related thymic involution or due to fat deposition in thymus or due to both. As naïve T-cells are the main cells which fight against new infections hence its reduction strongly correlates with reduced efficiency of the elderly to fight against infections. Thymic involution also occurs in stress and in pregnancy but unlike age related thymic involution, they are completely reversible[9]. Studies have shown that the involuted thymus of most elderly persons are still able to produce some naïve T-cells though it is very less as compared to their younger counterparts.[10] Both the production and functions of B-cells decline with aging which may be responsible for increased susceptibility to diseases, reduced response to vaccination and increased

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cancer incidence in them.[11] Number of naïve B-cells are much less in elderly as compared to their younger counterpart with increase in antigen experienced memory cells in cell pool of elderly, some of which may be exhausted B-cells. The overall antibody affinity in elderly is also reduced due to a general isotype switching from I_gG to I_gM antibodies.[11,12]

Here two questions arise, first if modulation of this immunosenescence is possible? And second If it is possible then what are the interventions against it?. The answer is yes, it is possible. For immunomodulation there are certain objectives which must be kept in mind. First- antigenic load reduction both acute and chronic types, second- thymic restoration and third- modulation of T-cell functions. Interventions may be preventive i.e. nutrition, exercise etc. or curative or supportive i.e. therapy for the damage already occurred.

NUTRITION

The efficiency of immune system declines with nutritional deficiency. A number of factors may be responsible for undernutrition in elderly eg. Loss of denture, atrophy of taste buds, poor absorption from gut, poor diet etc. The nutritional interventions may be beneficial for prevention or retardation of progression of immunosenescence and in some cases it can even reverse the established immunosenescence. The immune system needs adequate energy, macro and micro nutrients for its proper functioning. Normally naive T-cells remain in a quiescent state and after encountering an antigen they change their metabolism and become an activated T-cell. This successful activation is followed by an increased uptake of nutrients, increased mitochondrial oxidative phosphorylation and the cell metabolism become predominantly glycolytic and energy demand is increased[13]. Prolong fasting has been linked with stem cell regeneration of older and damaged immune cells. Calorie restriction has been seen to prolong the life span in experimental animals. So, calorie restriction without undernutrition is the very important nutritional intervention in elderly. Macronutrients like antioxidants, dietary fiber, omega-3 poly unsaturated fatty acids (PUFAs), micronutrients like vitamin-E (200mg/day), Zinc (20mg/day), Selenium (100mcg/day), Iron, copper, folic acid, vitamin B-12, vitamin-C, fish oil (DHA) etc. have proven immune boosting properties in elderly.[14,15,16] Soluble fiber switches immune system from pro-inflammatory to anti-inflammatory which helps in faster healing from infections. Vitamin-E restores depressed Th1 response, down regulates prostaglandin E2 synthesis, enhances response to influenza vaccination, reduces oxidative stress and also increases NK cell activity.[17,18] Zinc supplementation leads to normalization of thymic architecture and functions, enhances T cell and NK cell activity, increases T lymphocyte proliferation and also increases neutrophil functions.[16,19,20] Selenium also increases T lymphocyte proliferation in elderly.[20] Daily zinc and selenium supplementation decreased infection rates in elderly.[21] Vitamin C (200mg/day) was effective as an adjunctive therapy for respiratory tract infections in elderly patients[22]. Fish oil rich in DHA enhances B cell activity.

Lipids like conjugated linoleic acid (CLA) and omega-3 Poly-unsaturated fatty acids (PUFAs) have proven anti-inflammatory properties. CLA increases lymphocyte proliferation and decreases pro-inflammatory cytokine secretion and also increases the response to Hepatitis B vaccination in elderly and has been shown to have anticarcinogenic, antiatherogenic and antidiabetic properties.[23,24] PUFAs have potent anti-inflammatory effects when used against autoimmune diseases, osteoporosis and cognitive decline[25]. Their most important anti-inflammatory effect is to reduce the risk and severity of atherosclerosis induced cardiovascular diseases. As immunosenescence is also a lwo grade inflammatory state hence the anti-inflammatory effect of these lipids (CLA and PUFAs) can be used for prevention or retardation of established immunosenescence. Lipids also have immunomodulatory properties. With increasing age membrane lipid rafts of T cells become less functional. Human high density lipoprotein (HDL) can extract accumulated cholesterol from membrane lipid rafts of T cells and increases signal transduction via TCR.[26] Statins reduces LDL cholesterol and correspondingly increases HDL cholesterol. Futher studies are needed to establish if this increased HDL could also have similar results on T cell membrane lipid rafts. For proper nutrition optimal diet from very beginning and throughout the life is the fundamental rule.

EXERCISE

Exercise relaxes body and mind, improves heart health, promotes blood circulation and is a potential mean to modulate dysregulated immune system with aging. Long term, moderate intensity aerobic exercises are best suited for elderly. Exercise have some immunorestorative properties on the decreased immune response with aging and the main benefits are on T cell functions, anti-body production and macrophage responses with improvement in imbalance between Th1 and Th2 responses as well as in between naïve and memory T cell imbalance.[27,28,29]

Chronic sleep deprivation has negative impact on

immune system by reducing immune response and WBC circulation where as adequate and deep sleep has positive impact by strengthening immune system's memory to previously encountered pathogens. Sun light energizes infection fighting T cells. The blue light present in sun ray makes T cells more faster so that they can reach quickly to infection site for their action. Chronic stress suppresses the immune system and its ability to fight against infections.

Hormones: - Many hormones have immunomodulatory properties. Estrogen modulates innate immune system especially during stress.[30] Insulin directly influences innate immunity,[31] hence insulin resistance with aging can also be an important contributor of immunosenescence. Thus drugs like glitazones, which restore insulin sensitivity, may have immunorestorative effects in elderly.[32] Insulin like growth factor-1(IGF-1) promotes the survival and function of peripheral T cells and also increases the functions of B cells, NK cells and macrophages. Dehydroepiandrosterone (DHEA) increases IL-2 production and NK Cell activity and decreases IL-6 levels.[33, 34] Growth hormone and melatonin also have some immunoregulatory properties but there effect on elderly is not well established. Hormone like vitamin, vitamin D modulates T cell activation.[35]

ANTIGENIC LOAD DECREASING INTERVENTIONS

As previously stated bad immunological history or chronic antigenic load exhausts immunological cell repertoire and is also an important contributor of immunosenescence, hence, every effort should be made to either eliminate or reduce both acute and chronic types of antigenic load from the body. Tumors present in the body also behaves in the same way and need same type of treatment.

1. **Vaccination:** Vaccination is an important tool to reduce infections and antigenic load in elderly. It is effective not only against acute but also against chronic latent infections. Vaccination against pneumococcal pneumonia, influenza and tetanus are rewarding in elderly. Some level of antibody response after vaccination is seen even in immunocompromised elderly.[36] Re-vaccination, as in cases of tetanus, is also an important way to boost immunity.[36] If we would become able to develop effective vaccine against chronic infectious agents like CMV, HSV, EBV etc. then probably we can halt or reduce declining immunity in elderly.

2. **Viral load reduction:** Viral load reduction by appropriate anti viral drugs as in HIV is another way to reduce antigenic load.

3. **Antibiotics:** Appropriate antibiotics are effective in treating bacterial infections and subsequently reducing antigenic load. Subclinical bacterial infections like UTI must be treated to reduce antigenic load. Though these subclinical infections are not causing any problem to the patient but they are constantly increasing antigenic load which has an harmful effect on declining immunity in elderly.

THYMIC RESTORATION

Restoration of declining efficiency of thymus with increasing age is an important way to prevent development of immunosenescence. There are many possibilities for it. First is the physical graft of functionally intact thymus to the older person, but ethical and logistic issues are there with it. Second is stem cell therapy for thymus. Third is the use of IL-7. IL-7 is a cytokine having a crucial role in the development and maintenance of the peripheral T cell pool. IL-7 induces some degree of thymic rejuvenation in mice.[37] Zinc supplementation normalizes thymic architecture and functions in zinc deficient persons.

MODULATION OF T CEL FUNCTION

Antiinflammatory agents-As inflammaging is an important cause of declining immunity in elderly, hence, antiinflammatory drugs are useful in retarding declining immunity in them. Here anti TNF alfa, anti IL-1, anti IL-6 and anti IL-15 monoclonal antibodies are useful. They should be used with caution in persons having cardiac diseases and infections. Non steroidal anti inflammatory drugs (NSAIDs) and statins also have anti inflammatory properties and are safe even in very old persons and can also prevent atherosclerosis, dementia, sarcopenia etc. in elderly.[38]

MODULATING TELOMERE LOSS

Antioxidants are capable of modulating telomere loss by retarding or preventing erosion of telomeres even after several cell division cycles.[39] Decreasing chronic viral load by appropriate vaccination is another way to maintain telomere length.

INJECTION OF AUTOLOGUS T CELL

This is a promising therapy for immunological restoration in elderly but further researches are needed for its confirmation. Here from healthy young person, ideal T cells for in vitro expansion are obtained and stored in liquid nitrogen. These T cells can be expanded and transfused in his latter life when he needs immunocompetent T cells due to declining immunity.

CONCLUSION

Both innate and adaptive immunity decreases in elderly which causes increased susceptibility to diseases and infection and also poor response to treatment with vaccination. The preventive and promotive interventions for immunomodulation are well balanced diet, caloric restriction without under nutrition, antioxidents, soluble fibers, PUFA, vitamin E, zinc, selenium, vitamin D, vitamin A, vitamin B12, folic acid, copper, vitamin C etc. Long term moderate aerobic exercises are also among good preventive and promotive interventions. Certain hormones like estrogen, insulin, IGF1, DHEA, melatonin, vitamin D etc. also have immunosupportive properties. The main objectives and interventions for immunomodulation are to reduce antigenic load either by vaccination and cytokine (IL-2, IL-7) therapy or by antiviral antibiotics, restore thymic output and modulate T cell functions by antiinflammatory drugs like NSAIDs and statins and by anti inflammatory monoclonal antibodies. Telomere loss modulation can be done by antioxidents and vaccination against chronic diseases. Autologus T cell injection is a promising therapy.

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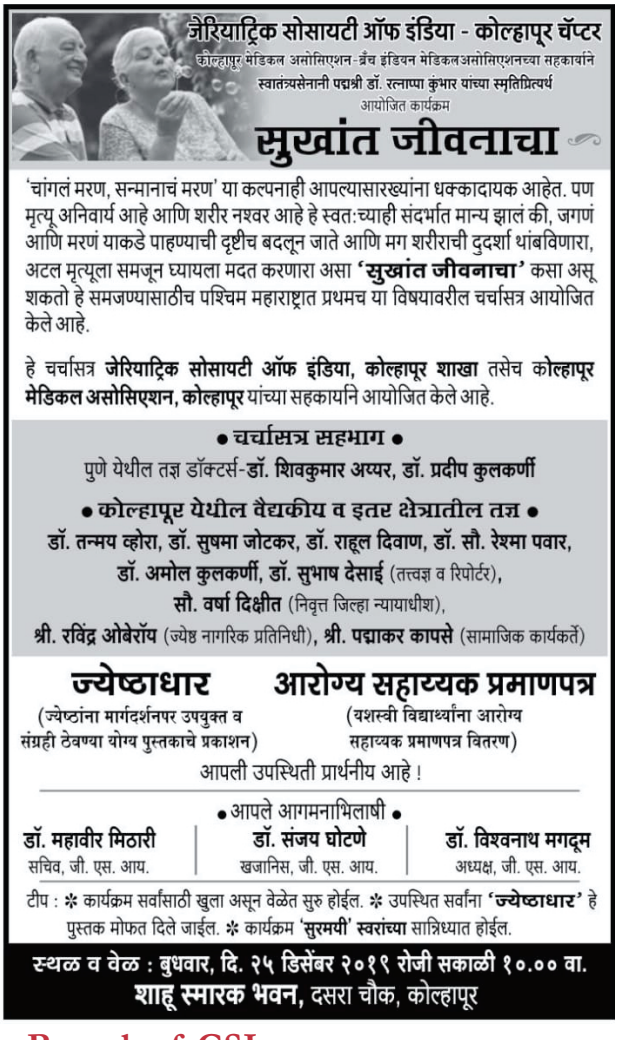

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