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SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

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ABSTRACT

SARS is a zoonotic acquired virus pandemic out broke in 2002-2003.Which is a contagious and sometimes causes fatal respiratory illness. Also its thought that a strain of the corona virus usually only found in small mammals mutated, enable it to infect humans. Which this SARS is a common form of virus that typically causes upper-respiratory tract illness. Six different kinds of corona virus are known to infect humans. Four of these are common, and most people will experience at least one of them at some time in their life. Before SARS appeared, corona virus had not been particularly dangerous to humans, but they had been known to cause severe disease in animals. As a result, Scientists first thought that animals transmitted SARS to humans. They now believe that an animal virus changed into a new, more deadly strain, it is also important to know the routes and understand their mode of transmission, pathogenesis, their complete background.

KEYWORDS: Zoonotic, SARS, Corona virus, Pandemic.

INTRODUCTION

Definition

Severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) is a novel virus that caused the first major pandemic of the new millennium. SARS-CoV is one of 36 coronaviruses in the family coronaviridaewithin the order Nidovirales. Members of the coronaviridae are known to cause respiratory or intestinal infections in humans and other animals.[1] that is highly contagious with significant morbidity and mortality.[2]

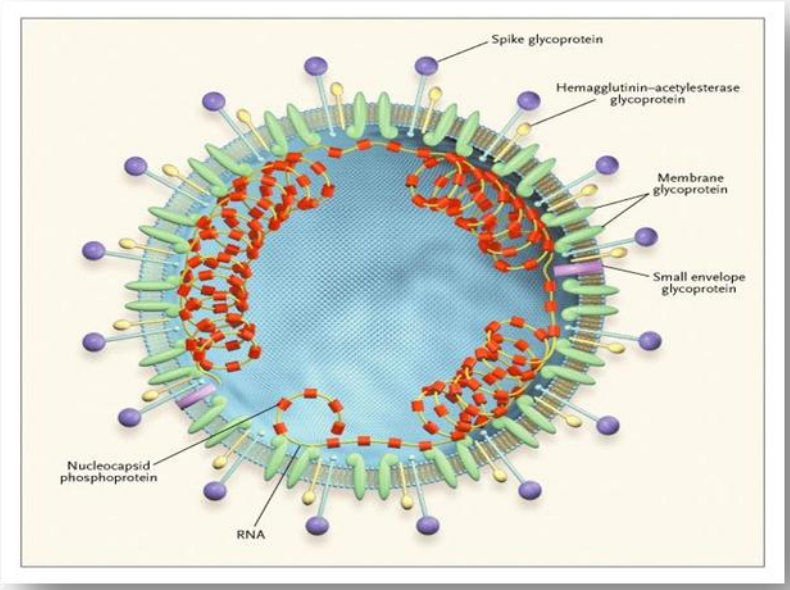


Fig. 1*: Illustrates the structure of virion*.[3]

In contrast, coronaviruses cause highly destructive epizootics of respiratory or enteric disease in live stock and poultry.[3]

Morphology and surveillance coronavirus

The message-sense RNA genome and the viral nucleocapsid phosphoprotein form a helical Nucleocapsid.

A Corona of large, distinctive spikes in the envelope makes possible for the identification of coronaviruses by electron microscopy.

The spikes, oligomers of the spike(s) glycoprotein, binds to sugar moieties on cell membranes

Coronaviruses in the group 2 also have a hemagglutinin-acetylesterase [HE] glycoprotein that binds to sugar moieties on cell membranes.

The unique RNA- dependant RNA polymerase of Coronaviruses often switches template strands during replication, causing RNA recombination when a cell is infected with several corona viruses.

The error- prone polymerase also generates point mutations and large deletions or insertions of foreign RNA into the viral genome.[3]

Virus is stable in faeces and urine at room temperature for atleast 1-2 days

Reduction in viral load occurs at 4℃ or -80℃. Heat at 56 degree kills the SARS Coronavirus around 10000 units per 15min

The incubation period of SARS is usually 2-7 days but may be as long as 10 days.[4,5]

Signs And Symptoms

The clinical course of SARS generally follows a typical pattern. Stage 1 is a flulike prodrome that begins 2-7 days after incubation, lasts 3-7 days, and is characterized by the following:

Fever

Fatigue

Headaches

Chills

Myalgias

Malaise

Anorexia

Less common features include the following:

Sputum production

Sore throat

Coryza

Nausea and vomiting

Dizziness

Diarrhea

Stage-2 is the lower respiratory tract phase and is characterized by following:

Dry cough

Dyspnea

Progressive hypoxemia in many cases

Respiratory failure that requires mechanical ventilation in some cases.

Etiology

Droplets from coughing and sneezing and close human contact likely transmit the SARS virus. The respiratory droplets are probably absorbed into the body through the mucous membranes of the mouth, nose, and eyes.

This could be through:

- Hugging & Kissing,
- Sharing utensils for eating & drinking,
- Speaking to someone within a distance of 3 feet,
- Touching someone directly.

A person with the virus can spread the infection by leaving respiratory droplets on objects, such as door handles, doorbells, telephones etc. These are then picked up by someone else.

The virus is likely to remain active in the environment for several days.

Epidemiology

SARS is thought to be a zoonotic acquired virus pandemic out broke in 2002-2003. The disease first emerged in November 2002 in Guangdong Province, China. Early in the outbreak the infection had been transmitted primarily via household contacts and healthcare settings. In late February 2003 the infection was transmitted to Hong Kong.

According to WHO Investigation

Totally 2781 cases with 111 deaths, officialy notified by ministries of health. The global case-fatality rate for probable SARS is 4%

To date, 1290 cases and 55 deaths have been reported from mainland china.

Hong kong experienced second largest outbreak with 998 cases and 30 deaths

Canada has experienced an outbreak of 97 probable cases and 10 deaths

Viet Nam have effectively controlled the outbreak, with 4 deaths have been reported

A cumulative total of 126 cases with 9 deaths was reported in Singapore

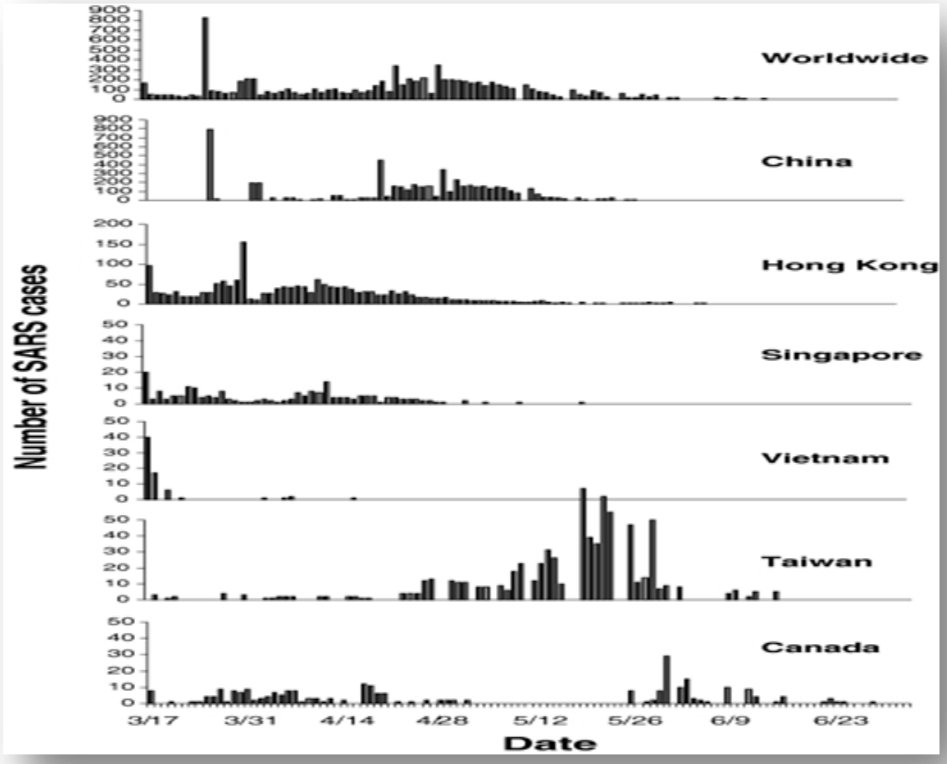
In US 154 persons was suspected with no deaths.

According to other research studies-

Table 1: Summary of probable SARS cases with onset of illness from 1 Nov 2002 to 31 July 2003 was shown in.

Areas No.	Cumulative deaths	No. of ratio	Case fatality (%)	Age (median range) years	No.(%) of health care workers
Australia	6	0	0	15(1-45)	1(16)
Taiwan	346	37	11	42(0-93)	68(20)
Malaysia	5	2	40	30(26-84)	0
Philippines	14	2	14	41(29-73)	4(29)
China	5327	349	7	-	1002(19)
Canada	251	43	17	49(1-98)	109(43)
Singapore	238	33	14	35(1-90)	97(41)
Thailand	9	2	22	42(2-79)	1(11)
UK	4	0	0	59(28-74)	0
USA	29	0	0	33(0-83)	0
Vietnam	63	5	8	43(20-76)	36(57)
Hong Kong	1755	299	17	40(0-100)	386(22)
Global	**8098**	**774**	**9.6**	**N/A**	**1007(21)**

-Probable cases of SARS by date of Onset or reporting worldwide- China, Hong Kong, Vietnam, Singapore, Canada, Taiwan. From WHO investigation as shown in graph.1



Clinical Presentations

Table 2: ***Clinical presentations of SARS.***

Symptom	% Prevalence
Persistent fever (>38C)	99-100
Non productive cough	57-75
Myalgia	45-61
Chills/ rigor	15-73
Headache	20-56
Dyspnoea	40-42
Malaise	31-45
Nausea & vomiting	20-35
Diarrhoea	20-25
Sore throat	13-25
Dizziness	4.2-43
Sputum production	4.9-29
Coryza	2.1-23
Arthralgia	10.4

Risk Factors For Sars Transmission

Close contact with the airway of severely ill patients and failure of infection control practices to prevent exposure to respiratory secretions were associated with transmission of SARS-CoV. Rates of transmission of SARS-CoV varied widely among patients.

Pathogenesis

The pathogenesis of SARS appears to be multifactorial and complex. The most plausible and possible mechanism appears to consists of a direct injury to the target cells by the virus and an indirect injury mediated by subsequent immune system dysfunction.

By means of droplet inhalation, the virus reaches the respiratory tract and invades the epithelial cells of the trachea, bronchi, bronchioles and alveoli, as supported by the presence of viral genomic sequences in such cells. Virus infection and replication in target cells cause direct damages to the respiratory tract. Local inflammatory changes destroy the integrity of the blood-gas barrier and increase the permeability of the capillary blood vessels. Exudation of fibrin results in the formation of hyaline membranes. The infection and associated inflammation bring about acute injury of type alveolar cells, decreasing the secretion of alveolar surfactant resulting in alveolar collapse. At the same time, SARS virus infects resident and circulating immune cells. The infected immune cells include mainly macrophages and T cells. Circulating immune cells disseminate the virus to other organs, including the spleen and the lymph nodes. The destruction of immune cells together with

extensive damage to the splenic white pulp results in immunodeficiency. A weakened immune defense exacerbates the infection and replication of the virus in the lungs and viral damage to the respiratory alveoli, resulting in respiratory distress. The degree of such immune deficiency as determined by the peripheral lymphocyte count may predict both severity and outcome of the disease. It has been found to infect the immune system, involving circulating immune cells, lymph nodes and spleen, in addition to injuring pneumocytes. T lymphocytes and macrophages/monocytes are the key immune cells that are infected. Severe damage to the splenic white pulp, has been demonstrated, which is accompanied by the marked decrease in splenic immune cells. In addition, epithelial cells both of intestine and distal renal tubules, together with neurons in the central nervous system are infected by virus.[6]

Autoimmunity

Autoimmunity may also be involved in the pathogenesis of SARS. Autoantibodies against pulmonary epithelial cells and endothelial cells have been detected. These autoantibodies may cause cytotoxic injury to the pulmonary epithelial cells and may induce systemic vasculitis. IgG antibodies against the domain 2 of spike protein have indeed been found to cross react with pulmonary epithelial cells. Another mechanism that possibly explains autoimmunity is the exposure of auto antigens caused by cytokine-induced organ injury.

Host Factors

Certain host factors have been found to affect the course of disease and outcome of SARS, including age, sex and pre-existing co- morbid conditions.[7]

Diagnosis

According to the WHO guidelines there are certain Diagnostic tests which are used to interpret the patient issue. Such as

PCR testing (Polymerase Chain Reaction)
ELISA (Enzyme Linked Immuno Sorbent Assay)
IFA (Immuno Fluorescence Assay)
Virus isolation
Chest X-ray etc.

Despite when SARS first surfaced, no specific tests were available. But now several tests can help detect the virus. BUT no known transmission of SARS has occurred anywhere in the world since 2004.

1. PCR testing

Collection of blood plasma for RT-PCR:- Collect 5-10ml of blood in an EDTA(purple tube) tube. Centrifuge briefly and collect all resulting plasma in vials with external caps and internal o-ring seals/ parafilm. Sample should be stored at 4℃. Do not freeze.

Procedure:-The sample is now assembled with the cofactors for the further steps :-
The basic steps are:

- Denaturation (96℃)
- Annealing (55-65)
- Extension (72℃)

These cycles are repeated for 25-35 times in a typical PCR reaction, which generally takes 2-4 hours, depending on the length of the region being copied. If the reaction is efficient, the target region can go from just one or a few copies to billions.

Using of gel electrophoresis to visualize the results of PCR

The results of a PCR reaction are usually visualized using gel electrophoresis, which it is a technique in which fragments of a DNA are pulled through a gel matrix by an electric current, and it separates DNA fragments according to size. A standard, or DNA ladder, is typically included so that the size of the fragments in the PCR sample can be determined.

DNA fragments of the sample of the same length form a “band” on the gel, which can be seen by eye.

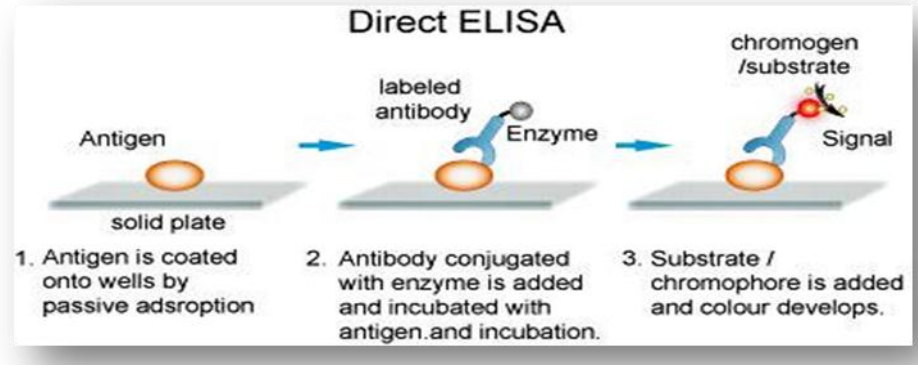
A DNA band contains many, many copies of the target DNA region, not just one or a few copies. Because DNA is microscopic, lots of copies of it must be present before we can see it by eye. This is a big part of y PCR is a DNA sequence that we can see or manipulate that region of DNA.

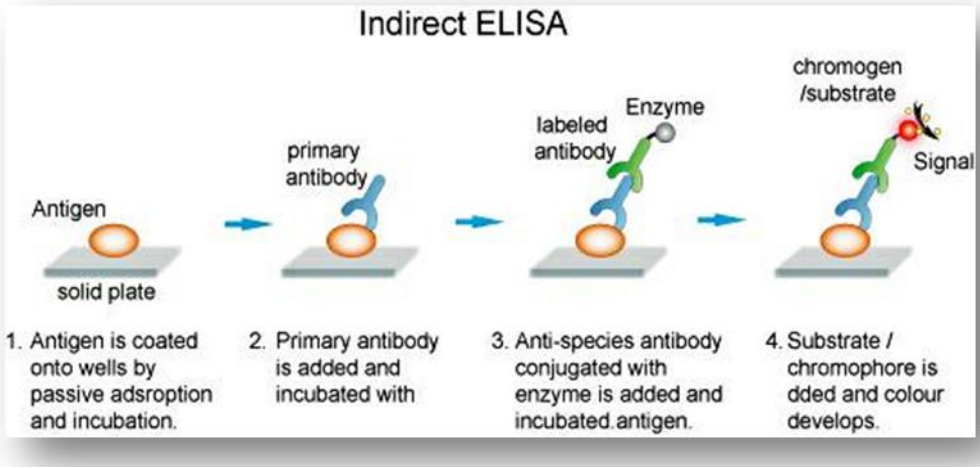
ELISA:-The enzyme linked immunosorbant assay(ELISA) is one of the most commonly used labeled immunoassay techniques. It is based on an enzyme-labeled antibody capable of

detecting an antigen immobilized to a solid surface, 96-well or 384-well polystyrene plates. A substrate is added to produce either a color change or light signal correlating to the amount of the antigen which presents in the original sample. It is a sample and rapid technique to detect antibodies or antigens attached to a solid surface. Being one of the most sensitive immunoassay, ELISA offers commercial value in laboratory research, diagnostic of disease biomarkers and quality control in various industries.

ELISA format:-According to the difference of the antigen immobilizing strategy, and the type of antibody-antigen reaction (direct recognition or competition), ELISA can be presented in a variety of formats. Each has its own advantages and disadvantages. One can choose an optimal ELISA format flexibly according to the requirements.

Which these are barely used to detect the mixture of IgM and IgG antibodies in the serum of SARS patients and reliably yields positive results at around day 21 after onset of illness. Whereas it involves an enzyme (a protein that catalyzes a biochemical reaction). It also involves an antibody or antigen (immunologic molecules) that may form an antigen-antibody reaction provide a positive result or, if they do not react, a negative result.





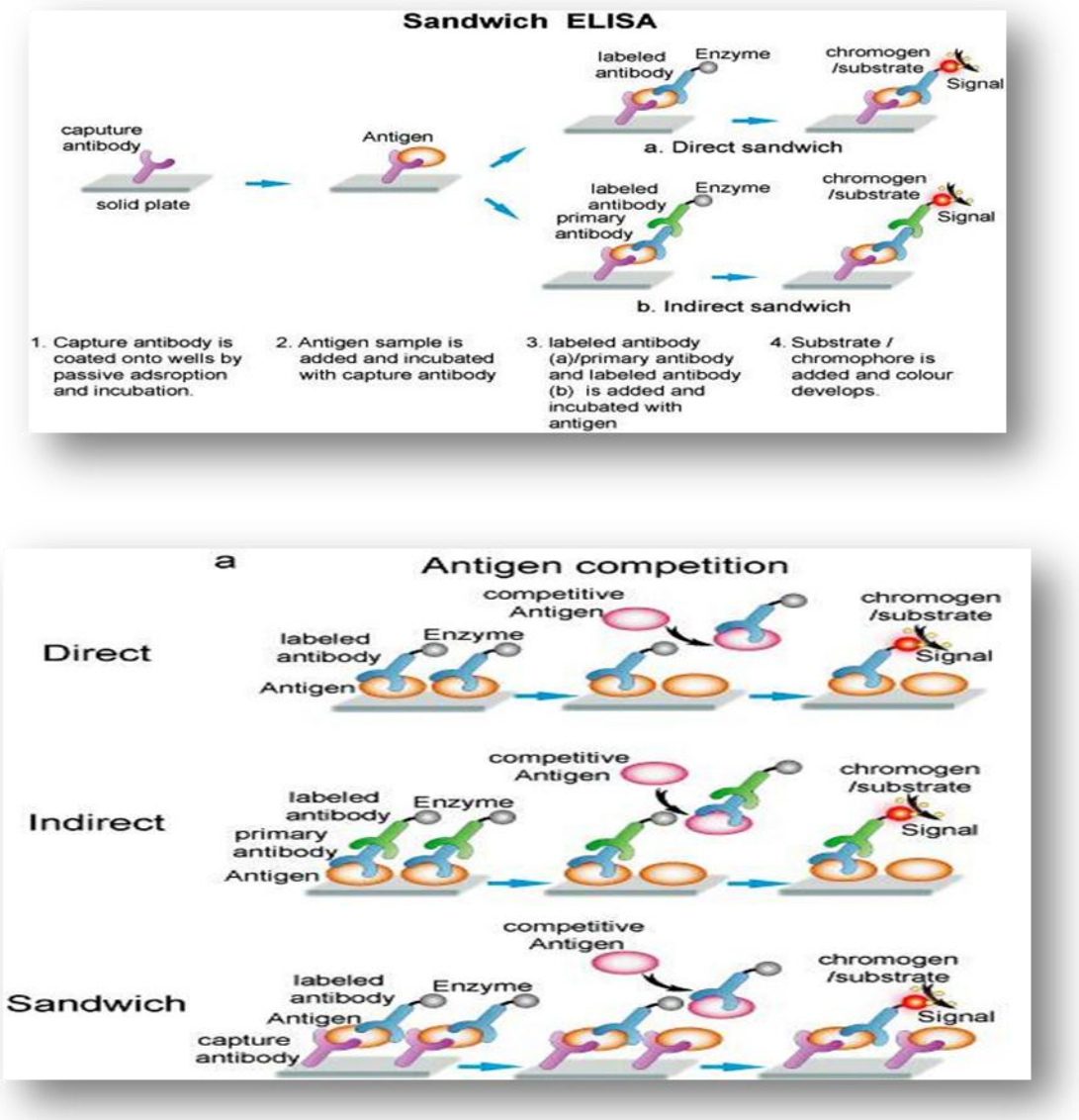


Fig. 2: Types of Elisa.

Virus isolation

The presence of the infectious virus can be detected by inoculating suitable cell cultures (e.g., Vero cells) with patient specimens (such as respiratory secretions, blood or stools) and propagating virus in vitro. Once isolated, virus must be identified as SARS-CoV using further tests. Cell culture is a very demanding test, but currently (with the exception of animal trials) the only means to show the existence of a live virus. It has to be performed under at least biosafety safety level (BSL).

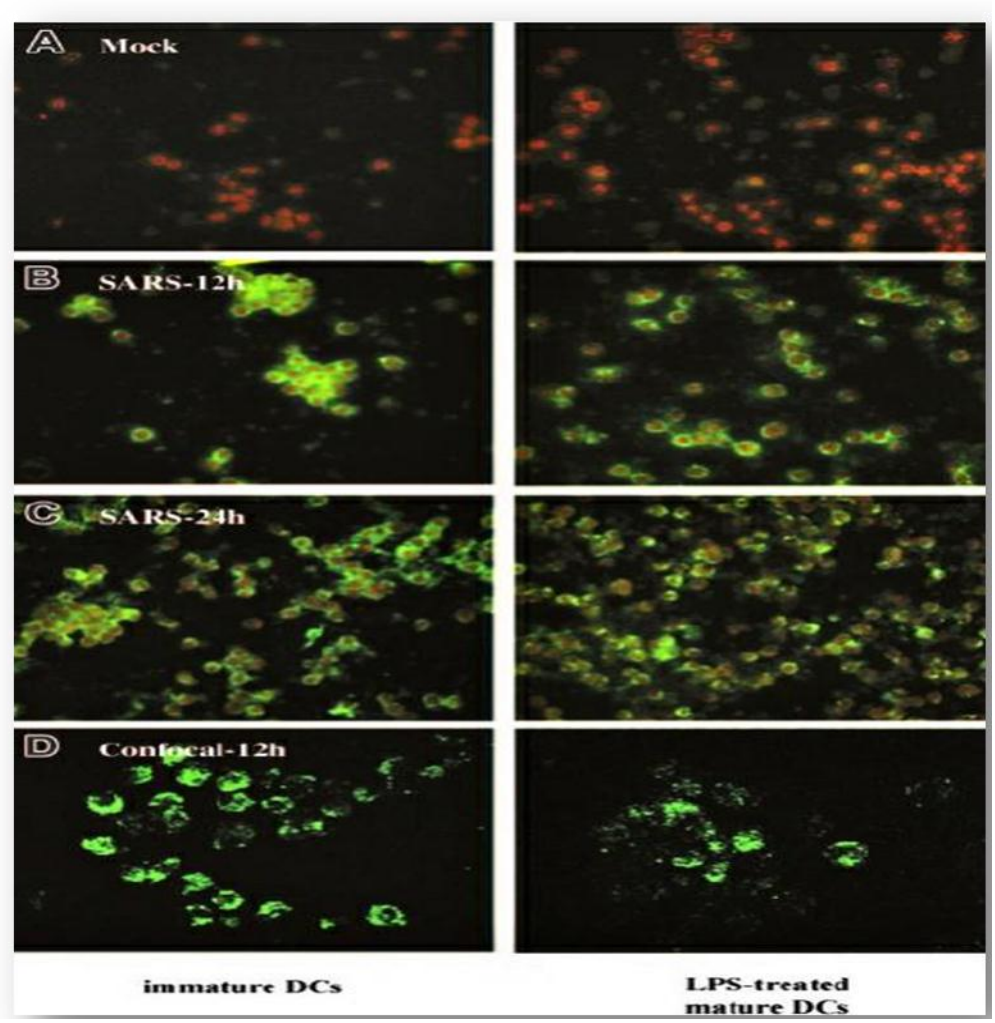
Positive cell culture results indicate the presence of live SARS-CoV in the sample tested.

Negative cell culture results do not exclude SARS.

Chest X-ray

Small or large patchy shadows with intensive density in both lungs, ground-glass like opacification, small patchy shadows in one lung lobe or one lung segment in, nodular shadows in one lung segment. Rapid changing consolidations revealed with SARS infections, and they were not affected by treatment with antibiotics.

IFA(Immunofluorescenceassay) :-This requires the use of SARS-CoV-infected cells fixed on microscope slide; patient antibodies bind to a viral antigens and are in return detected by immunofluorescent-labelled secondary antibodies against human IgM or IgG or both, using an immunofluoresence microscope. IFA typically yields a positive result after about day 10 after the onset of illness. Results may be quantified by using serial titrations of patient sera. Chest X-ray too provides sensitive and specific method for the diagnosis and treatment of SARS, and those present with symptoms and signs should undergo chest X-ray scanning every 1-3 days.



IFA of SARS-CoVdetection in human CDs.

Figure.3. *Immunofluorescence assay for SARS-CoV detection in human DCs. Mock-infected human DCs were included as a control(A). Positive immunofluorescence staining was detected in human immature and mature DCs at 12hours(B) and 24hrs(C) after infection with SARS-CoV. Confocal microscopy showed positive staining in the cytoplasm of DCs(D). Images are representative of immature and mature DCs from 11 independent adult or CB donors.*

Treatment

From initial clinical experience, SARS can develop in stages, including acute constitutional symptoms, acute viral pneumonitis, acute lung injury, and even acute respiratory distress syndrome, evolving over 1 to 2 week. Initial infection followed by a hyperactive immune response appears to underlie the severe manifestations. Therefore corticosteroids can be used to dampen excessive lung damage due to an anti-inflammatory response.[8]

Antiviral therapy

Antiviral agents used in the therapy of SARS include Ribavirin, IFN-α, Lopinavir-Ritonavir. Ribavirin is a nucleoside analogue with invitro activity against number of RNA and DNA viruses.[9]

Ribavirin regimen for 10-14 days

Ribavirin 400mg every 8hours (1200mg daily) intravenously for atleast 3 days (or) until become stable. Then Ribavirin 1200mg twice daily (2400mg daily) orally.[8]

Anti-inflammatory therapy

Anti-inflammatory (or) immune modulatory therapies include corticosteroids, intravenous immunoglobulin (IVIG) and convalescent phase serum and plasma exchange.[9]

Standard corticosteroid regimen for 21 days

Methylprednisolone 1mg/kg every 8hours (3mg/kg daily). Then Methylprednisolone 1mg/kg every 12 hours (2mg/kg daily intravenously for 5 days). Then Prednisolone 05mg/kg twice daily (1mg/kg daily orally for 5 days). Then Prednisolone 05g/kg daily orally for 3 days. Then Prednisolone 025mg/kg daily orally for 3 days. Then off.

Ribavirin and methylprednisolone

Combination treatment with ribavirin and methylprednisolone when

Extensive or bilateral chest radiographic involvement (or)Persistent chest radiographic involvement and persistent high fever for 2 days (or)Clinical, chest radiographic, or laboratory findings suggestive of worsening (or)Oxygen saturation <95% in room air.

Antibacterial treatment

Levofloxacin 500mg once daily intravenously or orally (or) Clarithromycin 500mg twice daily orally plus Coamoxiclav (amoxicillin and c acid) 375mg three times daily orally if patient is < 18 years old, pregnant (or) suspected to have tuberculosis.

Pulsed Methylprednisolone

Give pulsed methylprednisolone if clinical condition, chest radiograph or oxygen saturation worsens (atleast two of these) and lymphopenia persists.

Give methylprednisolone 500mg twice daily intravenously for 2 days, then back to Standard corticosteroid regimen.

Mechanical ventilation: Traditional approaches to mechanical ventilation use tidal volumes of 10 to 15ml per kilogram of bodyweight and may cause stretch-induced lung injury in patients with acute lung injury and the acute respiratory distress syndrome.[8]

Preventive Measures

Following are the preventive health behaviors to prevent the contracting and spreading of SARS:-

Maintaining good person hygiene.

Developing a healthy lifestyle.

Ensuring good ventilation.

Wearing face mask.[10]

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