Respiratory Syncytial Virus (RSV).

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1. Introduction:

1.1 Introduction of the virus:

Human respiratory syncytial virus (RSV) is the leading viral agent of serious respiratory disease in infants and young children worldwide, infecting nearly all children one or more times by age, RSV can infect very early in life, and the peak of hospitalization for RSV disease occurs at 2–4 months of age, it can also infect adults , and causes infections of the lungs and respiratory tract ,This virus can be divided into two groups, A and B, which can be distinguished antigenically with polyclonal animal sera and monoclonal antibodies, Infants who are premature or have chronic pulmonary disease or congenital heart disease are at increased risk for serious RSV disease, but 60% of serious RSV disease occurs in infants who are without known risk factor[1]

1.2 Historical Information of RSV:

Respiratory syncytial virus (RSV) was first isolated in 1955, but its biochemical and molecular in cell culture, pleomorphic and characterization remained rudimentary for many years due to its relatively inefficient growth cell-associated nature, and physical instability. [2]A respiratory illness spread throughout the group of chimps and was given the name "chimpanzee coryza agent". It was discovered at a later time, that the respiratory virus was spread through lab personnel who cared for the chimpanzees , Robert Chanock and his colleagues were able to isolate and characterize the virus in 1963.The virus was named in observance of changes in airway epithelium infected with the pathogen.[3]

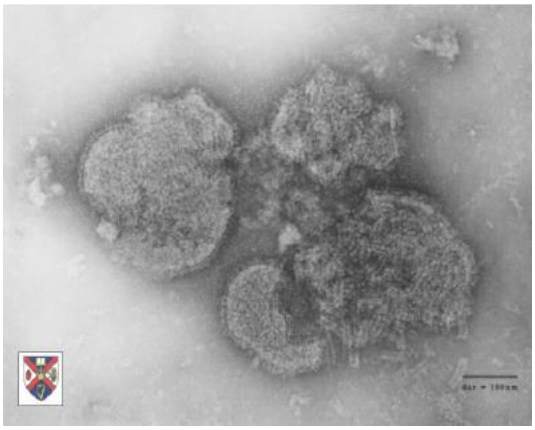
Detailed characterization began in 1981 with the molecular cloning and sequencing of RSV RNA[4] ,Different panels of monoclonal antibodies were later used to subdivide HRSV isolates into two antigenic groups, A and B , Further variability among viruses of the same antigenic group has been found, particularly in the attachment (G) glycoprotein.[5]

1.3 The Distribution and Epidemic of RSV:

In the United States alone, RSV was estimated to be responsible for 70,000–126,000 pediatric hospitalizations yearly due to bronchiolitis or pneumonia, with an estimated 90–1900 deaths . there is a considerable body of evidence showing that RSV epidemics are made up of multiple strains and that usually the predominant strain is replaced each year,In general, throughout the world, group A isolates are more often detected than group B isolates [5,]In the United States and other areas with similar climates, Respiratory syncytial virus (RSV infections generally occur during fall, winter, and spring. The timing and severity of RSV circulation in a given community can vary from year to year [6] , In Saudi Arabia the occurrence of respiratory syncytial virus (RSV) infection among young children hospitalized with lower respiratory tract illness, at King Khalid University Hospital in Riyadh, was examined during the autumn-winter season between September 1991 and February 1992. Sixty-nine cases were diagnosed by immunofluorescent antibody staining of viral antigen in nasopharyngeal aspirates from 127 children, constituting 54 per cent of these patients. Most children were < 1 year of age[7], Maletzky (1971) in Seattle USA found that the respiratory Syncytial Virus in children under six years of age reported(14%), Floyd (1986) in Carolina found that 22% of the lower respiratory tract infection (LRI) in non-hospitalized children caused by RSV, John (1991) In India examined 809 children under six years old found that RSV was the majority of these children(81%) had RSV infection and in Jamjoom (1993) in Riyadh found out the occurrence of RSV infection among young children, also in McIntosh (1991)in Boston, Forgie (1992) in Gambia, Yun (1995) in Korea, Hijazi (1995) in Kuwait.[8]

2. RSV classification

Human RSV exists as two antigenic subgroups, A and B, that exhibit genome-wide sequence divergence ,The other members of this genus are bovine RSV (BRSV), ovine RSV(ORSV), and pneumonia virus of mice. Table (1)[10] These types account for differences in the G (attachmen glycoprotein) composition and the conservation of the F (glycoprotein that mediates fusion of the viral and cell membranes)protein [11] Both G and F form the characteristic spikes of HRSV virions seen by Electron Microscope Figure(1) .[12]



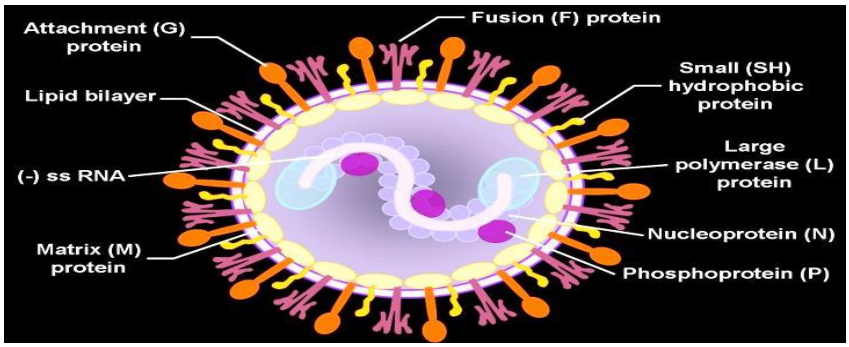
Figure(1): showing the virus under the microscope

Order	Mononegavirales
Family	Pneumoviridae
Subfamily	Unassigned
species of Genus	Orthopneumovirus 9

Table (1): showing RSV Classification

3. RSV Structure

The RSV virion has a pleomorphic spherical or filamentous. It has Medium-size , membrane-bound. [13] The nucleic acid in the virus are single-stranded RNA . [14] RSV is an enveloped nucleocapsid that encodes 11 separate proteins, and thus is more complex than most members of Paramyxovirinae .[15]



figure(2): structure of RSV.

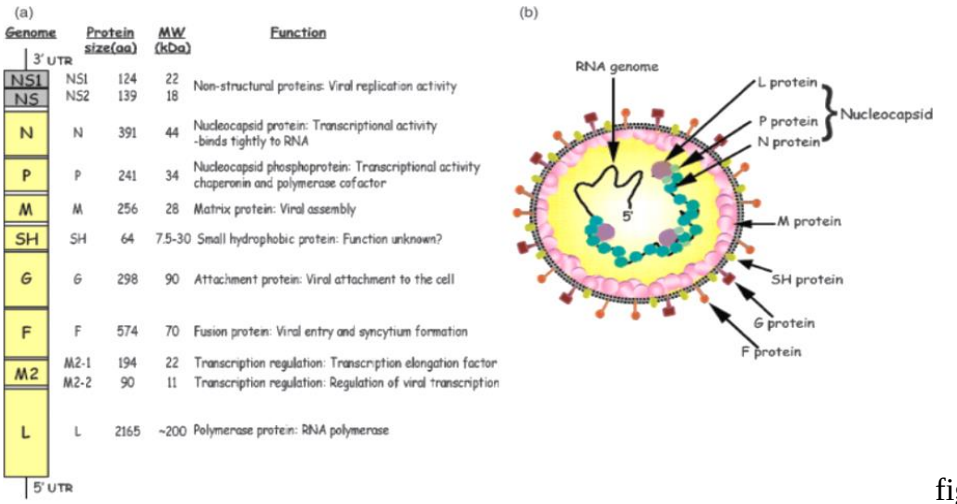
4. Proteins

4.1 Structural Proteins

The G and F proteins are the only RSV neutralization antigens and are major protective antigens . The virion of the RSV is enveloped with a lipid bilayer, which is obtained from the host's plasma membrane. It contains three surface glycoproteins, the attachment protein G, fusion protein F, and the small hydrophobic SH protein, which are separated from each other and can be seen as "spikes" that project out of the virion, The major function of the F protein is to direct viral penetration by the fusion between the virion and the host plasma membrane. The F protein is also able to mediate fusion with other neighboring cells forming syncytia, when it is expressed on the cell surface. The glycoprotein, G, is a type II transmembrane glycoprotein and is the major RSV attachment protein.[16]

4.2 Non- Structural Proteins

Nonstructural (NS) proteins have multiple functions during the virus life cycle, including antagonizing the antiviral effects of interferon and directly augmenting virus replication. This review will outline the progress in understanding the functions of the NS proteins and how altering these functions by reverse genetic manipulation can be a useful path toward rationally designing a safe and effective live-attenuated.[17]



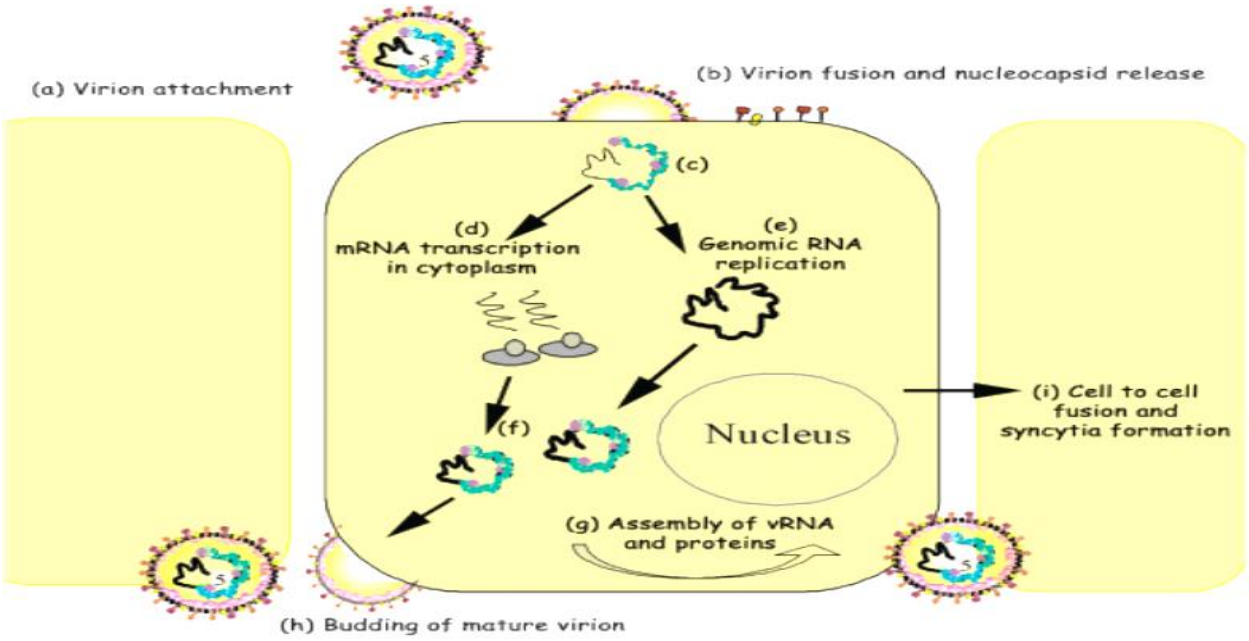
figure(3):protein structural

5. Transmission

RSV is highly contagious, and spreads through droplets containing the virus when someone coughs or sneezes. It also can survive on hard surfaces (tables) for many hours and lives on soft surfaces (hands) for shorter amounts of time[18], so it can easily spread when a person touches something contaminated. Children are often exposed to and infected with RSV through schools and childcare centers. Infants often get it when older kids carry the virus home from school and pass it to them. Almost all kids are infected with RSV at least once by the time they're 2 years old[19] ,Also through direct contact with respiratory droplets such as sneezing or coughing or through close indirect contact with contaminated fomites such as used tissues[20] .

6. Penetration and the Target Organ

Respiratory Syncytial Virus (RSV) is a highly pathogenic paramyxovirus. We developed assays for RSV endocytosis, intracellular trafficking, membrane fusion, and infection. The results showed that RSV was rapidly and efficiently internalized, and that acid-independent membrane fusion occurred intracellularly after endocytosis. Cell biological studies demonstrated that endocytosis was macropinocytic, and that it was required for infection. RSV induced transient actin rearrangements accompanied by plasma membrane blebbing, elevated fluid uptake, and internalization of intact RSV particles into large macropinosomes. The reason why RSV, unlike most paramyxoviruses, depended on endocytic entry was found to be the need for activation of the F protein by a second proteolytic cleavage. It occurred after endocytosis, and involved most likely a furin-like, vacuolar enzyme.[21]



Figure(4): Penetration and Replication of virus

7. Replication Cycle (the main site).

Replication occurs in the cytoplasm and the virus can grow in enucleated cells and in the presence of actinomycin D, indicating a lack of essential nuclear involvement.[22] The first step in RSV replication is attachment of the virus particle to a host cell, generally a ciliated epithelial cell in the nasal epithelium, mediated by G (Fig1). The general features of RSV transcription and replication resemble those of other paramyxoviruses, Viral replication and transcription are carried out by a single polymerase complex requiring N, P and L proteins. Transcription is guided by short conserved signals that flank each mRNA coding unit, comprising transcription gene start (GS) and termination gene end (GE) signals and involving the M2–1 anti-termination protein RNA replication occurs when the polymerase switches to a read-through mode in which the transcription signals are not recognized. This results in the synthesis of a positive-sense replicative intermediate, or anti-genome, which serves as the template for new negative-sense genomes. RNA synthesis is regulated by the M2-2, and possibly NS1, proteins, allowing the transition from transcription to replication and production of genomic RNA[23].

8. Assembly and release

RSV completes its replication and assembly in the cytoplasm of infected cells, with no involvement of the host cell nucleus postulated. Virus assembly is via budding (Fig. 4), through mechanisms that are probably similar to those in otherparamyxoviruses. Assembly is co-ordinated by M, where the envelope glycoproteins are translocated to the cell membrane, forming patches that exclude cellular membrane proteins. The cytoplasmic tails of the viral proteins interact with M, which forms a layer under the plasma membrane. The preformed nucleocapsids are recruited to these sites through interaction with M, facilitating final assembly and budding. In RSV, M has been shown to be present under theplasma membrane, to interact with nucleocapsids in the cytoplasm associate with the plasma membrane and to interact with envelope glycoproteins, suggesting that it plays a major role in virus assembly. Cell-to-cell spread of the virus, via fusion of neighbouring plasma membranes by F proteins, forms large syncytia leading to lesions in the epithelium (see Fig. 4). The rapid destruction of ciliated epithelial cells lining the airways ultimately causes the symptoms characteristic of the infection.

9. RSV Symptoms

Infants and children infected with RSV usually show symptoms within 4 to 6 days of infection , Most will recover in 1 to 2 weeks. However, even after recovery, very young infants and children with weakened immune systems can continue to spread the virus for 1 to 3 weeks[24] When (RSV) infection affects the nose and throat (upper respiratory system camera.gif), symptoms are usually mild and resemble those of the common cold,They include: Cough , Stuffy or runny nose , Mild sore throat Earache ,Fever, usually at the beginning of the illness, A high fever does not mean the illness is more severe , Babies may have additional symptoms, including: A decreased interest in their surroundings , Listlessness and sleepiness, Fretfulness (irritability) and not sleeping well ,Poor feeding , Apnea, where breathing stops for about 15 to 20 seconds, This usually occurs only in babies who were born prematurely and who also have a history of apnea, It is hard to distinguish between a common cold and RSV infection. But unless you or your child has an increased risk of complications from RSV, it usually is not important to know which virus causes symptoms , RSV infection sometimes leads to bronchiolitis or pneumonia or both Symptoms of these complications include: Difficulty breathing, which may include breathing more rapidly than normal , Wheezing , Coughing that is getting worse ,

A child may choke or vomit from intense coughing , Lethargy, increased tiredness, decreased interest in surroundings, or loss of interest in food.[25]

figure (5): RSV Symptoms

10. Diagnosis Of RSV Infection and Cytopathic effect.

The specific diagnosis of RSV infection is based on the detection of virus or viral antigens or virus specific nucleic acid sequences in respiratory secretions ,Antigen based tests are widely available, easy to perform and the results are available in a short time but their reduced sensitivity and specificity represent a considerable shortcoming, Among the methods available isolation in cell culture was considered the gold standard for the sensitive identification of RSV but is gradually replaced by highly sensitive and specific nucleic acid amplification assays that provide more rapid results. Of these reverse transcription polymerase chain reaction (PCR) was the first and is still the most frequently used nucleic acid-based assay.[26]detection by isolation or antigen detection, is usually identifies only a single suspected agent ,To permit identification of more than one respiratory virus in clinical specimens, a rapid detection method involving a single-step, multiplex reverse transcription-PCR (RT-PCR) assay was developed ,The assay included five primer sets that amplified the RNA of respiratory syncytial virus subtypes A and B. [27] ,The disadvantages of the nucleic acid based assays are their high costs and their limited standardization.[28]

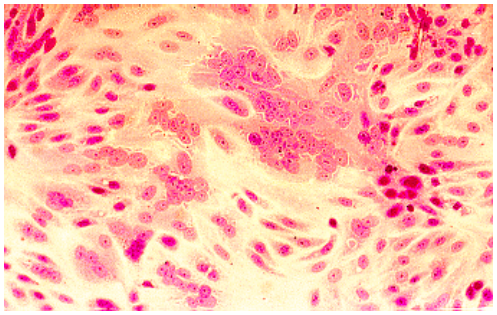


Figure (6): Cytopathic effect of the virus under the microscope.

Figure (7): PCR device.

11. Treatment

No RSV vaccine is licensed anywhere in the world. While prophylactic treatment with RSV-specific neutralizing antibody is effective in reducing RSV morbidity in infants, its use is currently limited to select populations in high-resource settings because of its expense and because of challenges with its delivery , Since it is unlikely that RSV infection can be prevented altogether, the goal of immunization is to provide sufficient protection to prevent serious lower respiratory tract disease leading to hospitalization and to decrease the frequency of complications such as otitis media High-risk infants can be substantially protected by monthly intramuscular injections of a commercially available RSV-neutralizing antibody (palivizumab, Synagiss) administered during the RSV epidemic season However,this treatment is too expensive and inconvenient for broader use at the present time. There is also no clinically effective antiviral therapy against RSV. Control of RSV by an antiviral agent is challenging because it is a rapid acute infection and by the time the infection is recognized it may be too late to control the disease by antiviral therapy alone An alternative therapy involving topical administration of RSV-neutralizing antibodies has not been effective therapeutically, probably for the same reason [29]

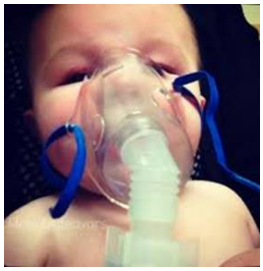


Figure (8): Treatment of virus.

Figure (9): Treatment of virus.

12. Control the virus and Prevention:

Unfortunately, options for prevention and control are limited. No RSV vaccine is licensed anywhere in the world. While prophylactic treatment with RSV-specific neutralizing antibody is effective in reducing RSV morbidity in infants, its use is currently limited to select populations in high-resource settings because of its expense and because of challenges with its delivery ,Prevention of severe RSV disease through active immunization of infants would be optimal but has been extremely challenging

to implement, given the young age by which immunity is necessary and the legacy of vaccine-enhanced illness leading to deaths in a number of young children after receipt of a formalin-inactivated RSV vaccine in the 1960s.[30]

Severe disease caused by RSV can be reduced by monthly injections of the monoclonal antibody palivizumab (Synagis) but the high cost of treatment restricts its use. Thus, the creation of a safe and effective RSV vaccine is still urgently needed.[31]

Fiuger(10): protect from RSV.

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