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VIRUSES AND THE RESPIRATORY TRACT - A BRIEF REVIEW

Microbiology

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ABSTRACT

It is a well-established fact that majority of the acute respiratory infections have a viral etiology. Unlike other infectious agents, viruses gain easier access into the respiratory tract due to their small size (smaller than that of the smallest fungal spores). This helps them establish themselves and spread in a rampant manner. Most airborne viruses spread rapidly due to short incubation period and poor hygiene in community as well as poor infection control practices in hospitals. Due to their obligate intracellular nature, laboratory diagnosis is tedious and therefore diagnosis becomes subjective based on evidence based clinical findings documented in literature. There is limited role for viral diagnosis on routine basis, but play a pivotal role during epidemics and pandemics. Syndrome based approaches are much useful in immunocompromised and young children which makes this an interesting topic for discussion.

KEYWORDS

Viruses, viral pneumonia, pneumonitis, croup, viral URI, RNA viruses, DNA viruses.

INTRODUCTION

The spectrum of respiratory infections caused by viruses can broadly be divided into upper respiratory tract infections and lower respiratory tract infections. Specifically, viruses cause the following respiratory infections : rhinitis, sinusitis, pharyngitis, tonsillitis, laryngitis, laryngotracheobronchitis (croup), pneumonia (community and hospital acquired), bronchitis, bronchiolitis [Fig 1].[1] Both RNA and DNA group of viruses, predominantly RNA viruses are associated with respiratory tract infections in humans. The usual suspects causing viral upper and lower respiratory tract infections are listed in table 1. Unlike other infectious agents causing similar clinical syndromes, viruses leave a deleterious effect on the population. Apart from that, these viruses also pave way for super added bacterial infections during or post infection period. This results in longer time to recovery therefore impacting the country`s economy due to school and work absences.[2] Thanks to the discovery and use of real time PCR based techniques in the recent years which have resulted in characterization of these viruses causing respiratory infections. However, use of these techniques are limited to two situations : 1. When diagnosis of viruses may affect clinical management, 2. Surveillance of outbreaks/epidemics.

Fig 1. Classification of viral respiratory tract infections

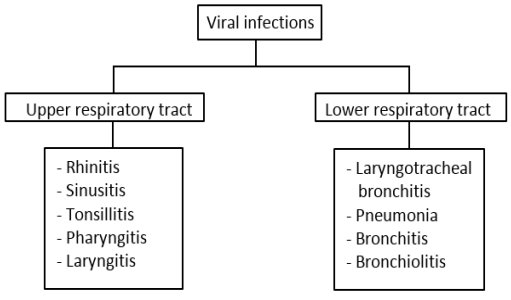


Table 1. Viral etiologies of respiratory tract infections[1,2,3]

Upper respiratory infections		Lower respiratory infections	
RNA viruses	**DNA viruses**	**RNA viruses**	**DNA viruses**
Rhinitis		**Laryngotracheobronchitis / Croup**	
• Coronavirus • Rhinovirus • Respiratory syncytial Virus (RSV) • Influenza virus • Parainfluenza virus • Metapneumovirus	• Adenovirus	• Parainfluenza virus (most common) • Respiratory syncytial virus • Influenza virus	• Adenovirus • Bocavirus
Sinusitis		**Pneumonia**	
• Rhinovirus • Influenza virus • Parainfluenza virus		• Respiratory syncytial virus • Influenza virus • Parainfluenza virus	• Adenovirus • Bocavirus
Pharyngitis and tonsillitis		**Bronchitis**	
• Influenza virus • Parainfluenza virus • Coronavirus • Rhinovirus • Coxsackievirus A	• Adenovirus • Epstein-Barr virus	• Coronavirus • Rhinovirus • Influenza virus	• Adenovirus
Laryngitis		**Bronchiolitis**	
• Influenza virus • Parainfluenza virus • Coronavirus • Rhinovirus • Metapneumovirus	• Adenovirus	• Respiratory syncytial virus • Influenza virus • Parainfluenza virus • Metapneumovirus • Enterovirus • Rhinovirus	• Adenovirus • Bocavirus

*Note :
- Bocavirus has also been reported as less common causative agent of URTI/common cold.
- Human Herpes Virus 8 (HHV 8) causes pleural effusion in HIV patients.
- Cytomegalovirus (CMV) causes pneumonia in post-transplant patients and HIV infected individuals.

Epidemiology of viral respiratory infections
1) Seasonality[4,5] :
Summer – Increased propensity of respiratory tract infections due to Picornaviruses (Enterovirus, Rhinovirus), Parainfluenza virus and Influenza virus.

Winter – Increased propensity of infection with Influenza virus, Respiratory Syncytial virus, Metapneumovirus, Bocavirus.
Throughout the year – Irrespective of seasonal variation, viruses such as Picornaviruses and Parainfluenza virus cause infection throughout the year.

Adenoviruses are an exception to the above seasonal distribution as they have caused infections either throughout the year or during winter in the previous decade.[4] The reason for Picornaviruses causing upper respiratory tract infections in summer is due to their property of replicating effectively at a temperature of 33°C.[6]

2) Geographic importance :
Respiratory viral infections are common in the southern hemisphere of the globe signifying the likelihood of active viral replication at temperate zones. Most statistics and data are available on childhood pneumonia of viral etiology as pneumonia remains the second leading cause of infant mortality.[7] As expected, developing countries witness more than 95% of cases and most of them require hospitalization. Fifteen countries top the table in reporting pneumonia cases every year. Among these countries, India reports maximum number of cases but manages to keep the mortality rates low. Mortality rates are higher in countries like Afghanistan and African countries probably due to poor access to health care and under development of health care facilities.

Respiratory syncytial virus, the commonest in causing most respiratory viral infections is prevalent in Russia, Canada, South America, African countries, India, Australia, Thailand (WHO 2017 surveillance report). An active surveillance report has been established by the WHO for RSV due to its commonality.

Coronaviruses cause infections in a subtle manner, though full-blown outbreaks have been reported twice, termed as SARS (Severe Acute Respiratory Syndrome Coronavirus) in 2002 and MERS-CoV (Middle East Respiratory Syndrome – Coronavirus) in 2012.[8] SARS was reported from Hong Kong, China, Singapore and other South East Asian countries. MERS-CoV as the name suggests was reported from Middle East nations like Saudi Arabia, Qatar, Jordan, Oman, UAE and spread thereon to European countries and USA.[9,10]

Metapneumovirus was first discovered in 2001 in Netherlands. It has then subsequently been identified in United Kingdom, Australia and North America.[11] Analysis suggests that this virus was circulating about 25 years before its discovery, although masked due to unavailability of effective diagnostic tools to identify the virus.

Influenza viruses are well known in causing pandemics apart from yearly epidemics caused by them. Human and Avian pandemics are distinct being caused at various time zones. The human pandemics so far have been named “Spanish influenza”, “Asian influenza” and “Hong Kong influenza” based on where the pandemic originated.[12] The most recent surveillance report on Influenza released by WHO shows distribution of all subtypes from all continents across the globe.[13]

3) Viral characteristics :
Viral respiratory infections are caused by RNA and DNA viruses. They belong to the families Coronaviridae (Coronavirus), Orthomyxoviridae (Influenza viruses), Paramyxoviridae (Parainfluenza virus, RSV, Metapneumovirus), Picornaviridae (Enterovirus, Rhinovirus), Adenoviridae (Adenovirus), Parvoviridae (Bocavirus), Herpesviridae (HHV 8, CMV). The characteristics of individual viruses causing respiratory tract infections in humans is detailed in table 3.

Table 2. Viruses associated with respiratory infections

Viruses	Year of origin and outbreaks	Places of outbreaks
Avian Influenza (H5N1)	1997, 2003, 2004 - 2013	China, Hong Kong
Avian Influenza (H7N9)	2013	China
Avian Influenza (H5N9)	2016	France
Avian Influenza (H9N2)	1994-2013	China
Swine flu - Influenza A (H1N1)	1918 (Spanish flu), 2009	USA, Hungary, China
Swine flu - Influenza A (H1N2)	2018	Asia, Europe
Swine flu - Influenza A (H2N2)	1957 (Asian flu)	Asia
Swine flu - Influenza A (H3N2)	1968 (Hong Kong flu)	Asia
SARS-CoV (Severe Acute Respiratory Syndrome – Coronavirus)	2002, 2003	Guangdong province of southern China
MERS-CoV (Middle East Respiratory Syndrome – Coronavirus)	2012, 2013	Saudi Arabia, Qatar
Human Coronavirus NL63, HKU1	2004	Europe, Japan, China, Australia, and North America
Hanta virus	1993	United States of America
Nipah virus	1999, 2001, 2007, 2018	Nipah village - Malaysia, Bangladesh, India
Human Bocavirus	2005, 2010	Sweden
Human Metapneumovirus	2001	Netherlands

Table 3. Characteristics of respiratory viruses

Virus	Properties
RNA viruses	
Coronavirus	Single stranded, positive sense; helical, enveloped, size : 120 - 160 nm
Influenza virus	Single stranded, negative sense; helical, enveloped, size : 80 - 120 nm
Parainfluenza virus	Single stranded, negative sense; helical, enveloped, size : 150 - 300 nm
Respiratory syncytial virus	Single stranded, negative sense; helical, enveloped, size : 150 - 300 nm
Metapneumovirus	Single stranded, negative sense; helical, enveloped, size : 150 - 300 nm
Enterovirus	Single stranded, positive sense; icosahedral, non-enveloped, size : 28 - 30 nm
Rhinovirus	Single stranded, positive sense; icosahedral, non-enveloped, size : 28 - 30 nm
DNA viruses	
Adenovirus	Double stranded, linear; icosahedral, non-enveloped, size : 70 - 90 nm
Bocavirus	Single stranded, linear; icosahedral, non-enveloped, size : 18 - 26 nm
Human Herpes Virus 8	Double stranded, linear; icosahedral, enveloped, size : 150 - 200 nm
Cytomegalovirus	Double stranded, linear; icosahedral, enveloped, size : 150 - 200 nm

Host – virus interaction / Pathogenesis
Viral entry / receptors :
Viral entry into the host is the first step in any viral infection without which further steps in pathogenesis cannot take place. This dynamic process might involve co-receptors thereby resulting in a multistep process in itself.[14] Receptors for all respiratory viruses are present on the respiratory epithelium.

Table 4. Viral receptors for attachment of respiratory viruses[15,16]

Virus	Name of receptor
Coronavirus	Aminopeptidase-N (APN) SARS : Angiotensin converting enzyme 2 (ACE 2) or Liver - specific intercellular adhesion molecule-3–grabbing nonintegrin (L-SIGN)
Adenovirus	Coxsackie virus-Adenovirus receptor (CAR)
Rhinovirus	Intracellular adhesion molecule (ICAM-1), LDLR (low-density lipoprotein receptor)
Enterovirus	Scavenger Receptor-B2 (SR-B2) or P-selectin glycoprotein ligand-1 (PSGL-1)
Influenza virus A	Sialic acid receptor
Metapneumovirus	Heparan sulfate
RSV	Heparan sulfate

Replication :

Viruses have a complex replication cycle. Unlike bacteria which divide by binary fission, the steps involved in their replication include attachment, penetration, uncoating, biosynthesis, assembly, maturation, release. The common rule in viral replication is that all respiratory DNA viruses replicate in the nucleus. All respiratory RNA viruses replicate in the cytoplasm except Influenza virus which synthesizes its RNA in the nucleus.[17]

Pathogenesis :

1. Route of entry – All respiratory viruses gain entry through inhalation into the respiratory tract. Infective aerosols generated during sneezing, coughing when inhaled result in viral entry into the host.

2. Attachment – Viruses use their glycoprotein surface receptors to attach to various receptors on human epithelial cells.

3. Penetration – Viruses are taken into the cell by one of these mechanisms : receptor mediated endocytosis (viropexis), membrane fusion (for enveloped viruses).

4. Replication – After entry into cells, viruses locally replicate and multiple daughter virions are generated by cell lysis or exocytosis. Cell destruction during release of viruses result in symptoms of viral URI and also make the host susceptible to secondary bacterial infections.

5. Localized replication and infection – Most respiratory viruses cause localized infections leading to symptoms of upper respiratory tract inflammation. Viremia does not occur at this stage, however few viruses may spill into the lower respiratory tract.

In case of lower respiratory tract involvement due to RSV, lymphocytes get activated and migrate to viral replication site. Cytokines secreted by activated lymphocytes lead to peribronchial inflammation, necrosis of bronchiolar epithelium, formation of plugs of mucus, fibrin and cellular debris occluding smaller bronchioles. In Influenza, a phenomenon termed "cytokine storm" develops resulting in alveolar and submucosal edema.

Human Herpes Virus 8 and Cytomegalovirus are associated with respiratory infections only in immunocompromised (solid organ / bone marrow transplant) individuals and HIV positive patients.

Clinical features and radiological features

All upper respiratory tract infecting viruses produce similar clinical features. Diagnosis is subjective and there is no role for laboratory and radiological diagnosis in such cases. Viral lower respiratory tract infections are of concern due to morbidity and mortality. Apart from the usual viruses causing viral pneumonia, certain miscellaneous viruses such as Hantavirus, Parechovirus, Mimivirus, Measles virus can also cause pneumonia.[18]

Symptoms of viral upper respiratory tract infections are rhinorrhea, nasal congestion, sneezing, coryza, otitis media. Viral pneumonia on the other hand presents with cough, expectoration, fever, dyspnea and chest pain.[19]

Radiological diagnosis is not the gold standard for diagnosis of viral lower respiratory infections. It can be used as a supportive diagnostic modality. X ray are usually vague and show bilateral interstitial infiltrates. Viral LRTI usually presents as four patterns in Computed Tomography : i) airway-centric disease , ii) multifocal pneumonia, iii) focal consolidation, iv) ground glass opacity.[20] A varied and sometimes normal CT finding has been observed in few viral pneumonia cases especially caused by Influenza virus.[21]

- Distinct radiological lesions produced by certain viruses are as follows Respiratory syncytial virus pneumonia : produces airway centric pattern, tree-in-bud opacities, bronchial wall thickening, peribronchial consolidation.[22,23]
- Adenovirus pneumonia : No airway abnormalities, multifocal regions of consolidation or ground glass opacities are typical and strongly suggestive of Adenoviral infection.[24,25]
- Parainfluenza virus pneumonia : Bronchiolitis pattern characterized by bronchial wall thickening and tree-in-bud opacities, similar to RSV pneumonia.
- Metapneumovirus : Bilateral alveolar opacities, nodular opacities and pleural effusion.[26]
- Coronavirus pneumonia : Diffuse ground glass opacities.[26]

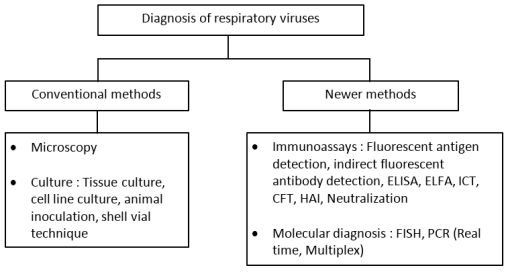
Atypical presentations are not uncommon especially in immunocompromised individuals.

Laboratory diagnosis of respiratory viruses

The main reason behind diagnosing a viral respiratory infection is to prevent indiscriminate use of antibiotics in patients presenting with these infections. Most of the antibiotic abuse occurs while treating respiratory tract infections due to misconception on etiology of RTIs. Identifying the etiological agent therefore plays a major role for epidemiological reasons rather than for treatment.

Viral diagnosis has evolved over the years with a paradoxical shift from time consuming culture based methods to rapid molecular methods. With many added advantages, molecular methods are currently dominating the era of viral diagnosis.

Fig 2. Flowchart on diagnostic methods for respiratory viral infections



*ELISA – Enzyme Linked Immunosorbent Assay, ELFA – Enzyme Linked Fluorescent Assay, ICT – Immunochromatography, CFT – Complement Fixation Test, HAI – Haemagglutination inhibition, FISH – Fluorescent In-situ Hybridization.

Microscopy has no major role to play in diagnosing respiratory viruses. Cowdry type A inclusion bodies are produced by Adenovirus, owl`s eye inclusion bodies are produced by CMV. Electron microscopic appearance of Coronavirus shows petal shaped peplomers and Adenovirus has a space vehicle shaped appearance.

Animal inoculation is not usually used for isolation of respiratory viruses. Egg inoculation is used for primary isolation of Influenza virus in amniotic fluid. Coronaviruses can be cultivated in tracheal rings and Adenoviruses in minced tissue (explant culture).

Viral cytopathic effects are detected on cell lines infected with viruses. Various cytopathic effects produced by respiratory viruses are as follows :

Respiratory Syncytial Virus – Syncytium or multinucleated giant cell formation.

Adenovirus – Large granular clumps resembling bunch of grapes.
Enterovirus – Rapid crenation and degeneration of the entire cell sheet.
CMV – Enlargement of infected host cells with multinucleated giant cells.

Parainfluenza virus – Little or no cytopathic effect.

All these methods have become obsolete due to the tedious nature of work process, longer turnaround time as well as requirement of expertise for performing these procedures. These drawbacks formed the basic need to develop newer diagnostic tools which combatted the disadvantages of conventional methods in viral diagnosis. Then broke the dawn of syndrome-based diagnostic modalities for diagnosing viral respiratory tract infections.

Syndrome-based diagnostics : Broad coverage of detecting etiological agents is the need of the hour. The same can be achieved by molecular detection methods as well as hybridization techniques. Polymerase Chain Reaction (PCR) and its modifications such as Real Time PCR, Reverse Transcriptase Real Time PCR, Multiplex PCR are used for viral diagnosis. Multiplex PCR platforms have high sensitivity and specificity, lesser turnaround time, more target pathogens from single sample.[27] Patient benefits incurred are short length of hospital stay, low exposure to antibiotics, better infection control practices due to early detection of viruses.[28] Bio fire film array is the recently available multiplex PCR for detecting multiple respiratory pathogens from nasopharyngeal swabs in viral transport media. All the above mentioned benefits are achieved in this assay with a sensitivity of 97.3% and specificity of 99.3%.[29]

Treatment of respiratory viral infections

Treatment does not play a major role in viral infections of the respiratory tract. Very few treatable viral infections are encountered as most viral infections are self-limiting and resolve on their own. However, in some cases such as Influenza neuraminidase inhibitors like Oseltamivir, Zanamivir and Peramivir are effective for treatment as well as prophylaxis.[30] These drugs act by inhibiting the enzyme responsible for intracellular viral replication. Adamantanes (Amantadine and Rimantadine) are used as intravenous infusions for treatment of Influenza A infections.[31]

In immunocompromised patients with LRTI due to Respiratory Syncytial Virus, Ribavirin can be used as it helps inhibition of viral replication. Intravenous Ribavirin is also given as treatment for immunosuppressed patients infected with Parainfluenza virus and Metapneumovirus.[32] A monoclonal antibody to RSV fusion protein named Palivizumab can prevent RSV infection in certain high-risk infants.

Other antivirals used for treatment are : Cidofovir, a cytidine analog for treatment of Cytomegalovirus and Adenovirus. However, this drug is not found to be very effective in immunocompromised patients.[33] Pleconaril, a drug which acts by incorporating itself into the capsid of Rhinovirus and Enterovirus is yet to be marketed.[34] Acyclovir administered intravenously may be beneficial in rare cases of immunocompromised individuals with Varicella Zoster pneumonia.[35]

Conclusion

Most of the respiratory tract infections are caused by viruses, be it that of the upper or lower respiratory tract. Although self-limiting in nature, few viruses establish themselves and cause severe illness and complications. This review has highlighted key features in epidemiology, presentation, diagnosis and management of respiratory viruses commonly encountered in clinical practice. A thorough knowledge will help in making appropriate decisions and treat patients wisely by avoiding antibiotics, the abuse of which is commonest in treating respiratory tract infections.

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