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Review Article

COMPARATIVE THEORETICAL ANALYSIS ON RESPIRATORY TRACT INFECTION CAUSED BY DIFFERENT MICROORGANISMS WITH REFERENCE TO COVID-19

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ABSTRACT

Respiratory Tract Infection (RTI) may be caused by different microorganisms and resulting deadly diseases such as novel coronavirus (Covid-19), severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), influenza and other viral infection, tuberculosis, pneumonia & other Bacterial RTI etc. Till now there is no recommended treatment strategy for COVID-19, as for this no specific pharmacologically proved drug till invented or identified. To identify/find out any new drug to treat particularly Covid-19 demands detailed attention in the characteristics of virus, so that the specific chemical approach in a short time can solve the health problem arouse worldwide. This paper is highlighting the comparative theoretical analysis of RTI caused by different microorganisms for the purpose of designing antiviral drugs to combat Covid-19.

Keywords: Covid-19, SARS, Tuberculosis, Influenza, RTI.

1. INTRODUCTION

The respiratory system consists of various parts that spread from the area outside of the nose and mouth to the alveoli via conductive airways. Exchange of gas takes between alveoli and blood flowing through capillary around the alveoli. The respiratory system mainly provides oxygen to the body tissues; also remove an equal volume of CO_2. The respiratory system also helps in the maintenance of acid-base balance, body temperature and water vapour saturation within airways along with the removal of extra surface fluids and debris like particles that inhaled senescent phagocytic and epithelial cells [1-3]. The parts of the upper respiratory tract include: nostrils, nasal cavity, sinuses, mouth, pharynx (the muscular portion of the airway between the skull base and oesophagus), and larynx (area of the airway between pharynx and trachea). Pharynx further subdivided into nasopharynx, oropharynx and hypopharynx. Lower parts of the respiratory tract include: trachea and lung with bronchi (main bronchi, lobar bronchi and segmental bronchi), bronchioles (bronchioles subdivided into conducting bronchioles, terminal bronchioles, respiratory bronchioles) and alveolar (alveolar ducts and alveolar sacs) [1, 4].

Several diseases that affect respiratory tract include bacterial and viral infection, cancer, asthma, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, occupational lung disease, cystic fibrosis. Respiratory tract infections (RTI) caused by virus or bacteria is common that shows different patho-physiological problems. Different types of respiratory infections included in table 1.

Table 1: Some common type of respiratory infection [5, 6]

Sl No	Disease	Description / Symptoms	Causative organism
1	Pharyngitis	Acute inflammation of the pharynx (throat) that involves lymphoid tissues of posterior pharynx and lateral pharyngeal bands. It results in red and sore throat, difficulty or pain during swallowing.	• Mostly caused by different viruses like rhinovirus, coronavirus, adenovirus, influenza virus, parainfluenza viruses, and respiratory syncytial virus. • Pharyngitis caused by bacteria is less common. *Streptococcus pyogenes* is mainly responsible.

2	Common cold	Rhinitis, nasal discharge and obstruction, cough, sore throat, sneezing.	Mainly caused by rhinoviruses
3	Sinusitis	Acute inflammatory condition of maxillary, frontal, ethmoidorsphenoidal sinuses. Pain, pressure sensation and tenderness in the affected area. Malaise and low grade fever also may there.	Common bacterial pathogen includes *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*.
4	Otitis	Otitis media: acute inflammation of middle ear usually observed among younger child.	Otitis media: *Streptococcus pneumoniae, Hemophilus influenzae* and *Moraxella catarrhalis*
		Otitis externa: inflammation in the external auditory meatus. Furuncles of the external ear, itching, pain and tenderness of the ear lobe. Severe earache, fever, and, vomiting.	Otitis externa: *Staphylococcus epidermidis, Staphylococcus aureus*, *Aspergillus niger*
5	Epiglottitis and laryngotracheitis	Upper airway inflammation classified based on location. In case of epiglottitis fever, sore throat, hoarseness, drooling, dysphagia, respiratory distress and prostration are observed. Rhinorrhea, fever, sore throat and a mild cough are common in case of laryngotracheitis.	*Haemophilus influenzae* type b and parainfluenza viruses are common. *C diphtheria,* syncytial virus, adenoviruses, influenza viruses, enteroviruses, *Mycoplasma pneumoniae* also may involve.
6	Bronchitis and bronchiolitis	Acute or chronic inflammation of the bronchial tree. Coryza, cough and sputum production.	*H influenza, S pneumonia*, *M. pneumonia* are involved in a different form of bronchitis. It can occur as a part of infections caused by as influenza, rubeola, rubella, pertussis, scarlet fever and typhoid fever.
7	Pneumonia	Inflammation of the lung parenchyma. The major symptoms include cough, chest pain, fever, shortness of breath and sputum production.	*Streptococcus pneumonia*, *S. aureus, Haemophilus influenza*, *Klebsiella pneumonia, M. tuberculosis, Chlamydia* spp, *P. Aeruginosa* and *Enterobacteriaceae* etc are involved in different types of pneumonia.
8	Pulmonary tuberculosis	A bacterial infection mainly affects the lungs. Symptoms includecoughing and sneezing, fever, coughing blood, weight loss.	Bacterial infection primarily caused due to *Mycobacterium tuberculosis*
9	Empyema	Accumulation of purulent fluid in the pleural space.Chest pain, dry cough, sweating, fever and chills, shortness of breath.	*S. aureus*, the *Enterobacteriaceae*, streptococci and obligate anaerobes.
10	Influenza	Common cold, fever, lethargy and myalgia are common symptoms.	Influenza virus (A, B, & C). Secondary bacterial pneumonia (caused by *Staphylococcus aureus* or *S. pneumoniae*)

2. COVID-19 AND RTI

Severe acute respiratory syndrome related coronavirus (SARS-CoV-2), a new pathogen is highly contagious, can spread quickly. The novel coronavirus (Covid-19 virus) was subsequently detected and isolated in the lung and intestinal tissues of the challenged animals. Covid-19 is transmitted via droplets and fomites during close unprotected contact between an infector and infectee. Airborne spread has yet not been reported for Covid-19, though few assume so. However, there is evidence that, this is a significant route of infection in indoor environments. Despite this, no countries or authorities consider airborne spread of Covid-19 in their regulations to prevent infections transmission indoors. Symptoms of Covid-19 are non-specific. Covid-19 virus has a genome identity of 96% to a bat SARS-like coronavirus and 86%-92% to a pangolin SARS-like coronavirus, an animal source for Covid-19 is

highly likely. Millions of people around the globe are quarantined with loss of social life and the world economy is highly affected [7, 8]. The outbreak of novel coronavirus was first experienced at the end of 2019 in Wuhan, China. The novel virus was named as Wuhan coronavirus or 2019 novel coronavirus (2019-nCov) by the Chinese researchers. The Inter-national Committee on Taxonomy of Viruses (ICTV) named the virus as SARS-CoV-2 and the disease as Covid-19. The genome is positive-sense single-stranded RNA (+ssRNA) (~29.8 kbp) with 5'cap structure and 3'poly-A tail. The betacoronavirus genome encodes several structural proteins, including the glycosylated spike (S) protein that functions as a major inducer of host immune responses. The RNA of virus is protected by S protein, then envelope protein, membrane glycoprotein and nucleocapsid protein. This S protein mediates host cell invasion by both SARS-CoV and SARS-CoV-2 via binding to a receptor protein called angiotensin-converting enzyme 2 (ACE2) located on the surface membrane of host cells. A study also revealed that this invasion process requires S protein priming which is facilitated by the host cell produced serine protease TMPRSS211. In addition, the viral genome also encodes several nonstructural proteins including RNA-dependent RNA polymerase (RdRp), coronavirus main protease (3CLpro), and papain like protease (PLpro). Upon entrance to the host cells, the viral genome is released as a single stranded positive RNA. Subsequently, it is translated into viral polyproteins using host cell protein translation machinery, which is then cleaved into effector proteins by viral proteinases 3CLpro and PLpro. The interaction between viral Spike protein and ACE2 on the host cell surface is of significant interest since it initiates the infection process. The phylogenetic tree shows that the virus undergoes immunologic pressure and can increase the frequency of mutations in the genetic sequence of coronavirus among people from different countries. This process can increase viral virulence and transmissibility. In worldwide, the usual incubation period of Covid-19 was 3 to 7 days and approximately 80% of infections are mild or asymptomatic, 15% are severe, requiring oxygen supply, and 5% are critical infections, requiring ventilation. Till date, there are no SARS-CoV-2 specific antiviral agents is available. Researchers have been racing to find possible treatments to save lives and to produce more potent vaccines for future prevention, though vaccines have already been applied to human being to save world population from the attack of corona virus. It is to be noted that vaccinated people are also affected sometime and a very minimum percentage also recorded in official websites of different organisations. Covid-19 infection induces IgG antibodies against N protein that can be detected by serum as early as day 4 after the onset of disease and with most patients seroconverting by day 14 [9, 10]. Antiviral drugs targeting human coronavirus should be designed that could be used against the current as well as future epidemics.

2.1. Medicines applied

Till date, no specific antiviral drug is found to treat SARS-CoV-2. Researchers and scientist around the globe are working hard to make a way out of this pandemic virus keeping in mind the treatment regimens of other pathogens of respiratory tract infection followed by boosting the immunity of the patients. Few such drugs are remdesivir (antiviral against Ebola virus), favipiravir (antiviral), choloroquine (particularly hydroxycholoro-quine: elevates endosomal pH and interferes with terminal glycosylation of the cellular receptor i.e. angiotensin-converting enzyme 2) (antimalarial), immunoglobin (IGg) (antibody; glycoprotein), baricitinib (in rheumatoid arthritis), lupinavir (anti-HIV), ritonavir (anti-HIV), arbidol (influenza antiviral), nitazoxanide (anti-helminthic, protozoal, and viral infection-caused diarrhea), interferon-human serum albumin fusion protein (e.g. interferon alpha 2b) (anti-viral), ribavirin (anti-RSV infection, hepatitis C, some viral hemorrhagic fevers), 2-deoxy-D-glucose (developed by DRDO, Government of India: as announced in DRDO website) etc. [7, 9].

3. SARS AND RTI

In November 2002, severe acute respiratory syndrome (SARS) first reported in China and subsequently causes an outbreak in nearly 30 countries. SARS coronavirus (SARS-CoV) is a large, positive, single-stranded RNA virus and considered as a highly pathogenic respiratory virus. It transmitted through direct contact, airborne droplet or fomites. Presence of the virus was noticed in respiratory secretions, urine, faeces, tears of SARS-CoV positive individuals. SARS-CoV usually induces symptoms that are related to lower respiratory tract infection. Common symptoms of SARS-CoV include fever, chills, dry cough, malaise, rigor, myalgia and headache. Dyspnea develops during the acute phase of infection. The incubation period of SARS-CoV is ranging from 2-10 days [11-13].

Angiotensin-converting enzyme 2 (ACE2) was reported as a functional receptor for SARS-CoV. The virus uses the endosomal pathway to enter into the target cell. The disease caused by SARS-CoV can be divided into two types based on mechanisms: (i) on host cell it causes lytic effect and (ii) induce host immune response to the infection [13]. The S protein of SARS-CoV binds to ACE2 receptor followed by translocation of ACE2-virus complex to endosomes. Proteolytic enzymes like cathepsin L, factor Xa, trypsin are key endosomal acid proteases which require activating its fusion process. After entry of the virus into the host cell, viral RNA is released and translated into polyproteins (pp1a and 1ab) which are then cleaved into small products by viral proteinases for further process [14,15]. In infected patients, autoantibodies detected against pulmonary epithelial cells and endothelial cells, along with an excessive expression of several cytokinins and chemokinins. ACE2 is an important molecule of renin-angiotensin system and found to confer protective role along with AT2 receptor in severe acute lung injury. SARS-CoV infection found to induce down regulation of ACE2. These are involved in the pathogenesis of severe respiratory infection caused by SARS-CoV [11, 13].

3.1. Medicines applied

A number of drugs were used to manage SARS-CoV outbreak, but no definitive treatment protocol specific to SARS-CoV has been developed. The drugs used in the empiric therapy of SARS include ribavirin (an antiviral drug that inhibits viral RNA synthesis), interferon (IFN)-α (broad-spectrum antiviral drug), lopinavir-ritonavir (protease inhibitor). Though their specific use is controversial and under investigation. Several other drugs/vaccines like huMab (human monoclonal antibody), pulsed methylprednisolone, glycyrrhizin, IVIg (intravenous γ -globulin), penta-globulin and different vaccines (i.e .inactivated virus vaccine, live-attenuated virus vaccines, viral vector vaccines, subunit vaccines, DNA vaccines) are under investigation [13-16].

4. MERS AND RTI

The outbreak of Middle East Respiratory *Syndrome* Coronavirus Virus (MERS-CoV) first reported from Saudi Arabia in the year 2012 and dromedary camels were identified as the source of human infection. Infection caused by MERS-CoV may asymptomatic or symptomatic. Common symptoms of MERS-CoV include fever, chills, myalgia, malaise, rigors, cough dyspnoea. Symptoms like diarrhea, vomiting and abdominal pain also may develop in some patients. The average incubation period ranges from 2-14 days. Close contact, respiratory droplets, contact with body fluids, and contaminated environmental surfaces are involved in the speeding of infection [17, 18]. MERS-CoV is a single-stranded RNA virus (family: coronaviridae) encoded various structural proteins like S, E, M and N. The S protein (surface spike glycoprotein) consists of S1 subunit (accountable for cellular receptor binding) and S2 subunits (responsible for fusion and entry to target cell). MERS-CoV required dipeptidyl peptidase-4 (DPP4) that also known as cluster of differentiation 26 (CD26) as its cellular receptor. Studies have shown that infection caused by MERS-CoVcauses substantial but delayed type I, II, and IIIIFN responses. Delayed but marked expression of proinflammatory cytokines and chemokines (i.e. IL-1β, IL-6, and IL-8) observed upon MERS-CoV infection. This can infect dendritic cells and macrophages of human. Both intrinsic and extrinsic pathways are involved in the activated T cells induced apoptosis upon MERS-CoV infection [14, 17, 19].

4.1. Medicines applied

Supportive care is considered as the mainstay approach as there is no specific approved drugs are available to treat MERS. *In vitro*, *in vivo* and clinical studies are going to find drugs for MERS. Some of these agents include: ribavirin, lopinavir/ritonavir, nucleoside viral RNA polymerase inhibitors (e.g. remdesivir), interferons, polyclonal anti-MERS-CoV human antibodies and immunoglobulin, humanized murine anti-S monoclonal antibodies, peptidic inhibitors (e.g. HR2P-M2), and mycophenolatemofetil (MMF) [18].

5. INFLUENZA, OTHER VIRAL INFECTIONS AND RTI

Viruses, use the basic host cell machinery for their reproduction: they all depend on host cell ribosomes to produce their proteins, and some also use host cell DNA and RNA polymerases for replication and transcription, respectively [20]. Viruses associated with infections of the upper respiratory tract other than coronavirus are respiratory syncytialvirus (RSV), rhinovirus (RV), parainfluenza (PIV), influenza A (IA), adenovirus (AD), human metapneumovirus (hMPV), human bocavirus (HBoV) and coronavirus (CoV). Any individual can be infected by these viruses. The entry strategy used by the influenza virus is the globular

heads of the viral hemagglutinin (HA) which mediate binding of the virus to sialic-acid-containing cell-surface receptors. The most common syndromes in upper airway are: nasopharyngitis, adenoiditis, pharyngitis, sinusitis, laryngitis and croup [21].

5.1. Medicines applied

Ribavirin is used to treat bronchiolitis caused by RSV in children, while palivizumab is used to prevent RSV-associated hospitalization for infants with high-risk. Till now there is no specific approved medication available for human RV. Though, the effectiveness of different antiviral drugs like ribavirin, IFNα-2a, rupintrivir, tremacamraetc are under investigation against human RV. A broad-spectrum antiviral drug pleconaril has displayed effectiveness against RV (compassionate use). There is no approved medicine is available for the treatment of the PIVs, hMPV, or HBoV [22-24]. Peramivir, Relenza, oseltamivir phosphate, and baloxavirmarboxil are USA FDA approved antiviral drugs for influenza. Amantadine, rimantadine are traditional antiviral drugs showed a high incidence of resistance therefore no longer recommended for the treatment of influenza [25]. In recent time, use of influenza vaccine (IV) is considered a key approach to prevent influenza. Nowadays, inactivated (IIV), and live attenuated (LAIV) vaccine are in use. IIV3 vaccine used against an H1N1 virus, an H3N2 virus, and a B virus, on the other hand, IIV4 vaccine confer protection against both viruses (influenza A & B) [26].

6. PNEUMONIA AND OTHER BACTERIAL INFECTIONS AND RTI

Generally, bacteria and parasites carry the basic genetic information required for their metabolism and replication, and the host cell is invaded only for nutrients. Common bacterial pathogens causing upper and lower respiratory tract infections are *Streptococcus pneumoniae*, *Haemophilus influenza*, *Moraxella catarrhalis*. *Some* organisms are a part of the flora of the upper respiratory tract of healthy adults. Otitis media, the most common pneumococcal disease in children is caused when microbes of normal flora invade the protective epithelial lining. Whooping cough in children is caused by *Bordetella pertussis*. The first step in a *B. pertussis* infection is colonization of the respiratory epithelium. The bacteria inhibit normal clearance mechanism by tightly getting bonded on the surface of the ciliated cells, and multiplying on them, which in turn causes paroxysmal coughing. In adolescents and adult lobar pneumonia is the most common manifestation of pneumococcal disease. The micro-organism *S. pneumoniae* easily invades the bloodstream, by bacteraemia complicating pneumonia caused by *S. pneumoniae* and other bacterial species. It has been theorized that the pneumococcal cell surface uses autolysis as a mechanism to facilitate the exchange of genetic material (releasing DNA into the surrounding environment). This material promotes inflammation. *Pneumococci* then release pneumolysin that alone causes all of the symptoms of pneumococcal pneumonia. Pneumolysin, a protein that binds to immunoglobulin and directly activates complement, also has direct cytotoxic effects on lung epithelial tissue [20, 27].

6.1. Medicines applied

Several antibacterial drugs are used to cure a different bacterial infection. Choice of antibacterial drugs varies with type and extent of infection. β-lactam antibiotics (i.e. penicillin G, cefotaxime, ceftriaxone or ampicillin-sulbactam, piperacillin-tazobactam, cephalosporin, carbapenem, cefepime, imipenem, meropenem, aztreonam), macrolide antibiotics (i.e. azithromycin), fluoroquinolones (i.e. ciprofloxacin, levofloxacin, moxifloxacin), tetracycline (i.e. doxycicline) are used alone or in combination to treat different bacterial infection. Use of corticosteroids in such infections also found effective in various clinical studies [28, 29].

7. TUBERCULOSIS AND RTI

Mycobacterium tuberculosis causes a serious lung infection in some urban area called tuberculosis. This bacterium is usually acquired by inhalation into the lungs, where alveolar macrophages phagocytose it. The microbe can survive and replicate within macrophages and in some cases by the immune system of the host, a lesion is produced, called tubercle [20, 27]. The host receptors that recognize *M. tuberculosis* include Toll-like receptors (TLRs) particularly TLR2 and TLR4, nucleotide-binding oligomerization domain like receptors (NLRs), and C-type lectins. Generation of inflammatory cytokines and chemokines occurs after entry of *M. tuberculosis* that induces migration of monocytes, neutrophils, and lymphocytes at the site of infection. Further multiplication of bacilli causes accretion of T cell, macrophages, dendritic cells, endothelial cells, fibroblasts, stromal cells and leads to granuloma formation. CD4+T cells producing interferon-γ (IFN-γ) involved in the recognition of infected macrophages

presenting antigens from *M. tuberculosis* to destroy them [30].

7.1. Medicines applied

Directly observed treatment (DOT) found effective to control TB. First-line anti TB drugs includes isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin. Current treatment protocol for drug-susceptible TB consists of isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z) for six months, (2HREZ/4HR). Use of fluoroquinolone in case of MDR/XDR-TB is also acknowledged. In the treatment of drug-resistant TB several drugs like bedaquiline, delamanid, linezolid, clofazimine and carbapenems have shown a promising effect in different studies [31, 32]. Bacille Calmette-Guérin (BCG) is the only vaccine that was approved for the prevention of TB. Traditionally, it was given to newborns, small children [33].

8. DISCUSSION AND CONCLUSION

This compilation deals with detailed about the respiratory tract infection diseases particularly in case of SARS-CoV-2, SARS-CoV, MERS-CoV, influenza and other viral diseases (respiratory syncytialvirus, rhinovirus, parainfluenza, influenza A, adenovirus, human meta-pneumovirus, human bocavirus and other coronavirus), pneumonia and other bacterial infection (*Streptococcus pneumoniae*, *Haemophilus influenza*, *Moraxella catarrhalis Bordetella pertussis*) and *Mycobacterium tuberculosis*. At present world human community is fighting against SARS-CoV-2 and thus the RTI diseases should be discussed once again by accounting all kind of infections concerned with the respiratory tract. The application of medicaments in case of bacterial infections are more specific, but in case of viral infections the specificity of medicines are still in research stage, except very few and patients are getting cured based on their immunity mostly followed by taking symptomatic medicines. However few antiviral drugs are in use to treat the viral RTI including SARS-CoV-2. In addition, Covid-19 is also acknowledging the treatment by hydroxychloroquine predominantly, where the choloroquine class of drug is an antimalarial drug widely used in malarial prone areas. Some of the studies/reports suggested that BCG vaccination may confer protection against Covid-19 epidemic. Authors hypothesized that spread Covid-19 is less in the countries with BCG immunization programs. Though, more research is required to establish the hypothesis [34, 35]. It is observed that all kind of microorganisms are attacking respiratory tract of human by almost same way adopting the same route that begins with upper respiratory tract and then lower respiratory tract passing through nostrils, nasal cavity, sinuses, mouth, pharynx, larynx, trachea, lung with bronchi, bronchioles and alveolar. Almost common type of antiviral drugs is in use even to treat SARS-CoV-2 including other viral RTI e.g. remdesivir, favipiravir, lupinavir, ritonavir, ribavirin etc. and also interferon, IGg etc. Medical practitioners have been trying by introducing some other relevant drugs, sometime by adopting combination therapy, to fight against the infection caused by Covid-19. Apart from these the entry of an antimalarial drug in the treatment of RTI caused by SARS-CoV-2 is showing the interest to consider the drugs having antibacterial characteristics, as fluroquinolone derivatives are already in use to treat the bacterial RTI, and side by side the hydroxychloroquine is having chemical moiety of quinoline. Therefore before considering any drug or to identify/find out any new drug to treat particularly Covid-19 demands detailed attention in the characteristics of virus, so that the specific chemical approach in a short time can solve the health problem arouse worldwide. Therefore in the present context, it is essential to highlight the comparative analysis on RTI caused by different microorganisms for the purpose of designing antiviral drugs to combat Covid-19.

Conflict of Interest

The authors declare that there is no conflict of interest.

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