CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
http://doi.org/10.5281/zenodo.4412666

Avalable online at: http://www.iajps.com *Research Article*

SEVERE RESPIRATORY VIRAL INFECTIONS: NEW EVIDENCE AND CHANGING PARADIGMS

[1]Dr Abubakar Obaid , [2]Dr Muhammad Huzaifa Javaid, [3]Dr Sana Eman.

[1]MBBS,Nawaz Sharif Medical College,Gujrat.
[2]MBBS,Faisalabad Medical University,Faisalabad.
[3]MBBS,Rawalpindi Medical University,Rawalpindi.

Article Received November 2020 **Accepted:** December 2020 **Published:** January 2021

Abstract:

Respiratory infections have a variety of forms and dimensions. The viral nature of various infections and the phenomenon of mutation has brought about changes in the whole pretext of respiratory infections. Infections in the Lower Respiratory Tract are a major contributor to the casualties in the United States Of America in particular and North America in general[1]. Although advancements in testing methods have improved our ability to detect pathogens the journey is not yet over. With modern statistical methods, we have come to know that viral Pathogens are the major causal pathogens for immunocompetent patients. With an increasing number of Elderly Adults or patients with a chronic medical condition, the burden of viral respiratory infections increases as well[2]. With the advent of the coronavirus, its probable mutations, conventional approaches in the treatment of community-acquired pneumonia by targeting bacterial pathogens, and the aging of the population in various developed countries the whole landscape has changed upside down.

It becomes imperative for all practitioners and clinicians to have a thorough knowledge of the characteristics of Coronavirus, Rhinovirus, Human Adenoviruses, Respiratory Syncytial Virus, and human Metapneumovirus[3]. Major challenges in this regard include clear cut segregation of True Infection and Asymptotic Carriage. It is equally important to characterize patients with severe lower tract infection who do not have a causative pathogen. Our focus will remain on the Respiratory Viral Pathogens and Community-Acquired infections. Widespread and common knowledge of the role of Influenza in severe Respiratory Infections being quite common, our focus will remain on the infections other than conventional forms of influenza including, CoronaVirus, Rhinovirus, Human Adenovirus(hADv), Respiratory Syncytial Virus(RSV), and Human Metapneumovirus(hMPV)[4].

Corresponding author:
Dr. Abubakar Obaid,
MBBS,Nawaz Sharif Medical College,Gujrat.

QR code

Please cite this article in press Abubakar Obaid et al, ***Severe Respiratory Viral Infections: New Evidence And Changing Paradigms.,*** *Indo Am. J. P. Sci, 2021; 08[01].*

INTRODUCTION :

severe respiratory infections:

With successful childhood vaccination programs and proactive health initiatives, it is evident that the population of Elderly adults has been increasing the developed societies[2]. The number of patients brought to the hospitals with pneumonia is also increasing. After the advent of Coronavirus, and its impact on the aging population, things have got complicated in the developed societies in particular and throughout the world in general. In several studies, we can find that people on or above 65 years of age are particularly prone to severe viral infections[2]. In a study conducted on the US society, hospitalization of people with severe respiratory infections having 65 or more years of age increased up to 15% over fifteen years[5]. Even the incidents of Rhinovirus and Respiratory Syncytial Virus infections were found ten times higher than the other age groups of society[6].

Another aspect is that as the number of adults susceptible to severe viral infections has increased, the incidence of invasive bacterial pneumonia has decreased owing to enhanced pneumococcal vaccination, increased awareness about the importance of early antimicrobial therapy, and considerable awareness regarding smoking. As one study shows, a 30% decrease in Pneumococcal disease in adults greater than 50 years of age over five(5) years[7]. This shift in Community-Acquired Pneumonia pathogenesis may in part explain why the percentage of pneumonia hospitalizations with no reported pathogen increased by almost 20% from 1993 to 2011 despite improvements in diagnostic testing[8]. In parallel with this, our ability to diagnose viral infections has improved a lot. This has been possible with the evolution of testing methods and techniques. Conventional diagnostic tests for respiratory viral pathogens include viral culture, acute, and convalescent-phase viral serologies, and direct fluorescence antibody staining[9]. These methods are limited by slow turnaround time and limited sensitivity. But nucleic acid amplification testing with Polymerase Chain Reaction (PCR) platforms has greatly improved the diagnosis of respiratory viral infections. The sensitivity of PCR testing is up to 5 times higher than conventional diagnostic methods, which may be particularly important in elderly patients who shed lower titers of virus[10]. Polymerase Chain Reaction can also aid with viral subtyping and quantification of viral burden. Multiplex assays are now available, which allow for the testing of up to 19 viruses simultaneously[9].

In studies of hospitalized patients with Community-Acquired Pneumonia, between 15% and 35% have evidence of a viral infection[11]. This was best illustrated in the recent Centers for Disease Control and Prevention (CDC) EPIC (Etiology of Pneumonia in the Community) study, a multicenter population-based surveillance study conducted in the United States, which used rigorous microbiologic testing in 2259 hospitalized adults with Community-Acquired Pneumonia[6]. This study is illustrated graphically in Fig 1:

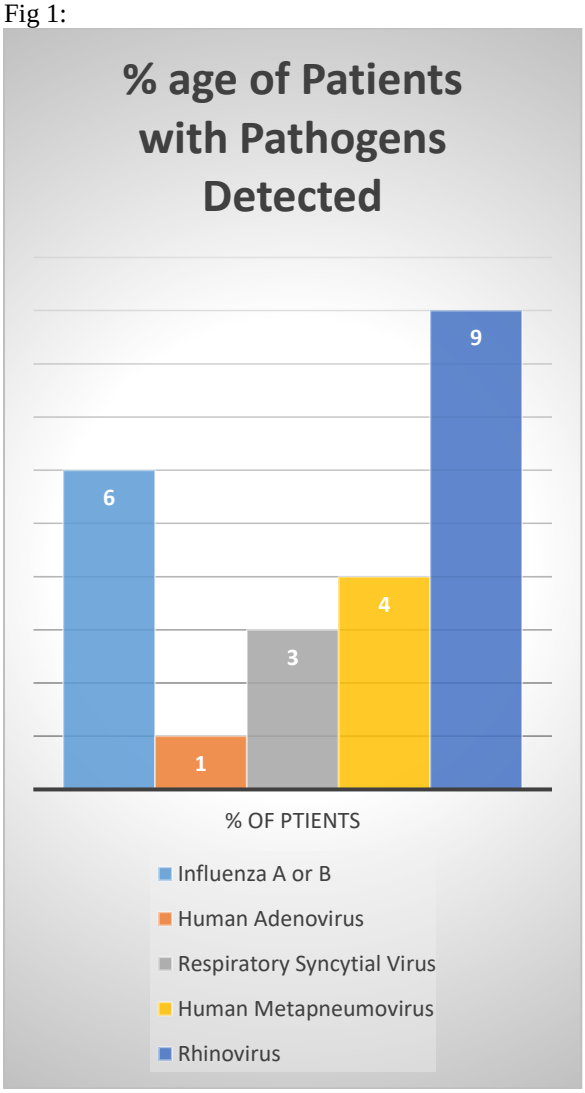

Figure :1

Percentage of all adults in the Centers for Disease Control and Prevention EPIC (Etiology of Pneumonia in the Community) study in whom specific respiratory viral pathogens were detected[6].In a single-site study from Korea, viral pathogens were isolated by reverse transcription PCR (RT-PCR) from nasopharyngeal swabs or lavage fluid in 72 of 198 (36%) patients with severe Community-Acquired Pneumonia or healthcare-

associated pneumonia[4]. Viral detection rates in similar studies of ICU patients have ranged from 16% to 41%[4].Studies have also found respiratory viral pathogens present in over 20% of patients with hospital-acquired pneumonia (HAP) and between 14% and 29% of patients undergoing bronchoalveolar lavage for suspected infection[4, 12] .

Types of Viral Infections and Their Treatment :
As our understanding of the importance of respiratory viral pathogens in the pathogenesis of severe respiratory infection continues to evolve, clinicians need to be familiar with the unique characteristics of the most commonly identified pathogens, especially when the phenomena associated with COVID-19 are still evolving.

Corona-Virus:
Extreme intense respiratory condition Covid 2 (SARS-CoV-2) is a novel serious intense respiratory disorder Covid. It was first segregated from three individuals with pneumonia associated with the group of intense respiratory disease cases in Wuhan China. All highlights of the novel SARS-CoV-2 infection happen in related Covids in nature. Outside the human body, the infection is obliterated by a family unit cleanser, which blasts its defensive air Symptoms are illustrated in Fig:2.

pocket. SARS-CoV-2 is firmly identified with the first SARS-CoV. It is thought to have a creature zoonotic inception. The hereditary examination has uncovered that the Covid hereditarily bunches with the class Betacoronavirus, in subgenus Sarbecovirus along with two bat-inferred strains. It is 96% indistinguishable at the entire genome level to other bat Covid tests. The primary proteins of SARS-CoV-2 incorporate film glycoprotein (M), an envelope protein (E), nucleocapsid protein (N), and the spike protein (S). The M protein of SARS-CoV-2 is 98.6% like the M protein of bat SARS-CoV, keeps up 98.2% homology with pangolin SARS-CoV, and has 90% homology with the M protein of SARS-CoV; though, the similitude is just 38% with the M protein of MERS-CoV[12]. The human in vulnerable framework produces antibodies that focus on a few locales of the spike protein.

Signs Cause and Symptoms:
Caused by Severe Acute Respiratory Syndrome Coronavirus-2 virus strain, symptoms range from mild to severe. Main symptoms include cough, fever, fatigue, difficulties in breathing, and loss of smell and taste. Symptoms may change or get swear depending upon the conditions.

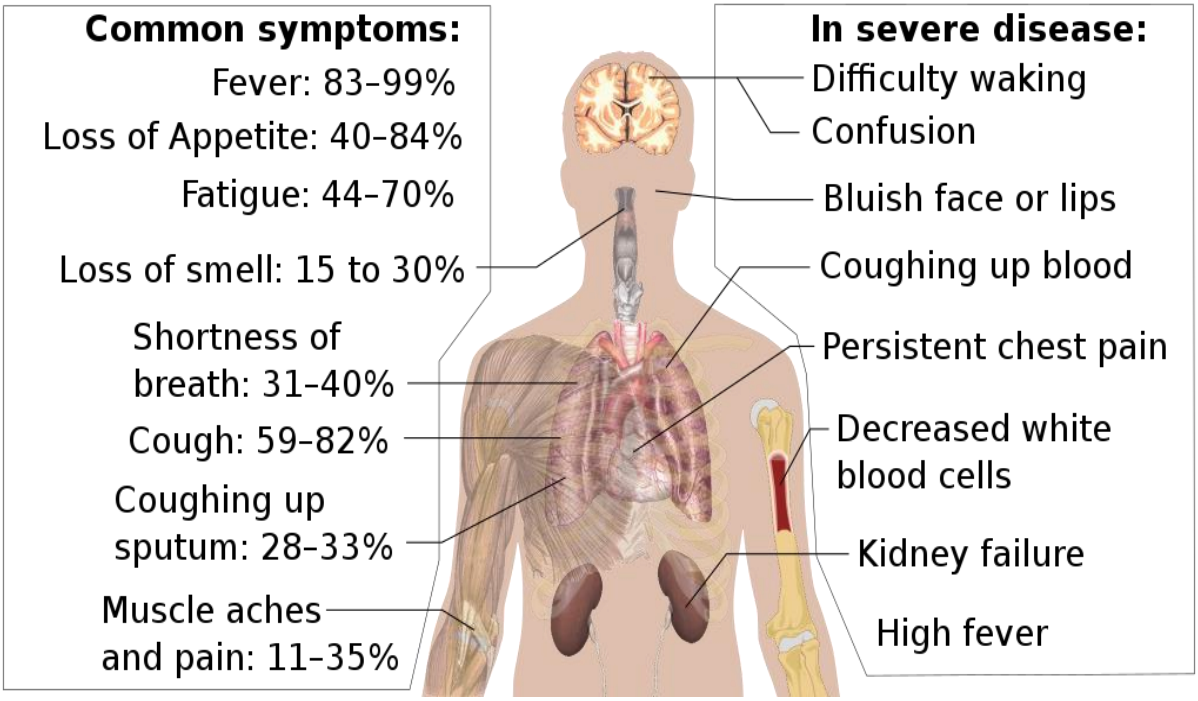

Figure 2: Covid-19 Symptoms

Transmission and Diagnosis:
COVID-19 spreads from person to person through the respiratory route if a person talks cough, laughs, sneezes, or breathes. During interpersonal interactions, around 1000 viruses are thought to start a new infection.Diagnosis can provisionally be done based on symptoms and confirmed through Reverse Transcript Polymerase Chain Reaction(RT-PCR) testing of infected secretions' addition to this, CT scans of the chest can also help in the diagnosis of COVID-19[12].

Prevention And Cure:
The spread of COVID-19 can be minimized by staying at home, avoiding public gatherings and meetings, wearing a face mask in public places, and ensuring a proper social distance of six(6) feet during interactions with fellow human beings.National Health Agencies have approved the "Tozanimeran" vaccine developed by Pfizer biotech. In addition to this 17 other vaccines are in phase-ii and phase-iii trials[12].

Rhinovirus:
Rhinoviruses are single-stranded negative-sense RNA viruses that are divided into 3 species (rhinovirus-A, -B, -C) and more than 160 distinct serotypes[12]. Rhinovirus infections occur throughout the year with increased prevalence noted in the late spring and early fall.

Transmission of Rhinovirus:
Transmission occurs most commonly through autoinoculation after contact with contaminated objects, although aerosolization also contributes to viral spread. The clinical importance of rhinovirus is well described in children where it may be responsible for more than 70% of asthma exacerbations in children greater than 2 years of age[13]. Rhinovirus has been recognized as a major cause of Pediatric Community-Acquired Pneumonia.
In immunocompetent adults, rhinovirus most commonly causes a self-limited upper respiratory tract infection (URI) and may be responsible for more than 80% of common colds during the fall and spring[14]. The frequent association with benign URIs has led many clinicians to question its relevance to pneumonia. However, rather than simply a precursor to more serious infections, rhinovirus can itself be an important pathogen. In the clearest example, immunocompromised patients are particularly prone to severe rhinovirus infection. Infection after lung transplantation is common and may contribute to graft dysfunction[4].

Diagnosis and Cure:
Sore throat and rhinorrhea are typical early symptoms of rhinovirus infection. Common presenting symptoms in patients with Community-Acquired Pneumonia secondary to rhinovirus are not well-described.Reverse Transcript Polymerase Chain Reaction (RT-PCR) is the preferred diagnostic test for severely ill patients with rhinovirus owing to improved sensitivity and more rapid turnaround time than conventional culture-based diagnostic methods.Treatment of even severe rhinoviral infection is supportive. Case reports have described the use of pegylated interferon-α2A and ribavirin in immunosuppressed patients with evidence of persistent infection, but this strategy has not been tested in randomized trials[4].

Human AdnoViruses:
Human Adenoviruses are nonenveloped double-stranded DNA viruses that have long been recognized as an important cause of respiratory tract infections in children. Human Adenoviruses(HAdVs) are divided into seven species (HAdV-A through HAdV-G) with species B, C, and E most commonly associated with respiratory infections[4]. Based on serotypes and genomic analysis, 67 subtypes of adenovirus have been identified[15].

Transmission and Symptoms of Human Adenoviruses:
Transmission can occur via inhalation of aerosolized droplets, direct conjunctival inoculation, fecal-oral spread, and contact with infected environmental surfaces. Patients with human immunodeficiency virus and those who have undergone solid organ transplantation or allogeneic stem cell transplantation are, particularly at risk.Common disease manifestations in the immunocompromised patient include pneumonia, colitis, hemorrhagic cystitis, hepatitis, and graft dysfunction. Patients with pneumonia owing to Human Adenoviruses(HAdV) present with symptoms indistinguishable from other types of pneumonia, including fever, cough, and shortness of breath.Crowded living environments are a risk factor for outbreaks of severe Human Adenoviruses (HAdV) in otherwise healthy individuals[4].

Diagnosis And Cure of Human Adenoviruses:
Numerous methods are available to diagnose Human Adenoviruses(HAdV) infection, although Polymerase Chain Reaction(PCR) is the most practical choice for acutely ill patients. The viral culture was previously considered the "gold standard" although the time needed to observe the characteristic cytopathic effect in human epithelial cells makes it impractical for use in critically ill patients.The mainstay of therapy for

immunocompetent patients with Human Adenoviruses(HAdV)infection is supportive care. No high-quality randomized trials inform the decision to use pharmacologic therapy in any patient population. Of available antiviral agents, cidofovir, the nucleoside analog of cytidine monophosphate, has the most supporting data and several case reports have described the safe and successful use of cidofovir in the treatment of severe Human Adenovirus(HAdV) infection in immunocompromised patients[4].

Respiratory Syncytial Virus(RSV)

Respiratory Syncytial Virus (RSV) is an enveloped, negative-sense, single-stranded RNA virus first identified more than 50 years ago[16]. The 2 serotypes, RSV-A and RSV-B, are discriminated by reactivity to monoclonal antibodies. RSV has a worldwide circulation and peak infectivity in temperate climates between December and February[17].

Transmission And Symptoms:

RSV is highly infectious and can spread via aerosolized droplets or contact with infected secretions. Flare-ups of RSV diseases in hospitalized patients are all around depicted and exacting contamination control conventions are basic when thinking about tainted patients. The clinical and economic burden of RSV infection in children is substantial. Globally, RSV is the most common cause of Lower Respiratory Tract Infections(LRTIs) in children, with more than 3 million hospitalizations and up to 200,000 deaths in children less than 5 years of age per year[18].As with other respiratory viruses, immunocompromised patients are at particular risk of severe RSV infection. Severe Lower Respiratory Tract Infections(LRTIs) have been described in multiple patient populations, including after hematopoietic stem cell transplantation, patients with hematologic malignancies, and after solid organ transplantation, where infection may predispose to graft dysfunction. Episodes of serious RSV diseases in bone marrow transplantation wards feature the vulnerability of this patient populace to contamination[4].

Among adults presenting to the hospital with confirmed RSV infection, wheezing is encountered more frequently than with other viral infections, including influenza. Cough, shortness of breath, and fever are other common presenting symptoms. Chest radiography is frequently normal, although radiographic evidence of pneumonia may be found more frequently than in patients with influenza. On chest computed tomography scans, tree-in-bud opacities and abnormalities in a broncho centric distribution are more common in RSV infection than with other respiratory viruses[4].

Diagnosis And Cure:

As with other respiratory viruses, nucleic acid amplification, specifically with RT-PCR, has become the test of choice for suspected RSV infection in adults. Culture techniques including shell vial culture are challenging given the unstable nature of the RSV virus and lack of sensitivity. Rapid antigen detection tests, which are used commonly in children, perform less well in adults likely owing to lower viral titers present in the secretions of elderly patients[19].

The mainstay of therapy for immunocompetent adults with severe RSV infection is supportive care. In immunocompromised patients and other select high-risk adult groups, additional therapy may be considered. The guanosine analog ribavirin has been used with some success in patients with RSV infection after hematopoietic stem cell transplantation. In a recent single-center study of 280 patients after allogeneic stem cell transplantation, the early use of aerosolized ribavirin was associated with a reduction in progression to Lower Respiratory Tract Infection(LRTI) and improved mortality. In children, passive monoprophylaxis with palivizumab, a monoclonal antibody directed against the RSV F glycoprotein, has been used with success and is recommended by the American Academy of Pediatrics for use in infants with hemodynamically significant heart disease or chronic lung disease of prematurity[4].

s are not well-described, but outbreaks of Human Metapneumovirus(hMPV) at long-term care facilities and hospital wards highlight the importance of infection control protocols when caring for infected patients. Human Metapneumovirus(hMPV) is recognized as an important respiratory pathogen in immunocompromised adults. Studies utilizing RT-PCR have recognized hMPV as the reason for extreme pneumonia in hematopoietic undifferentiated cell relocate beneficiaries, patients with hematologic malignancies, and strong organ relocate beneficiaries where contamination may expand the danger of uniting brokenness[20].

Patients hospitalized with hMPV present with nonspecific symptoms. In 1 study of 91 hospitalized adults with hMPV, the most common symptoms were dyspnea (98%), cough (94%), wheezing (79%), and sputum production (74%)[21]. High rates of wheezing have been noted in other studies and are similar to the incidence of bronchospasm found with RSV infection. Chest imaging is similarly nonspecific and

may be normal in more than one-third of hospitalized patients. Reports of chest computed tomography findings in hPMV infection are limited. In 1 study of high-resolution computed tomography findings in 4 patients with hMPV, ground-glass opacities, consolidation, and parenchymal bands were present in all patients[4].

Diagnosis and Cure:

RT-PCR is most commonly used for the diagnosis of Human Metapneumovirus. Treatment of severe hMPV infection is supportive and no pharmacologic therapies are currently approved for use. Ribavirin has shown promising activity in murine models of infection, and several case reports describe the drug's potential efficacy in humans when used in conjunction with intravenous immunoglobulins[4].

Next Course of Action:

With the improved sensitivity of PCR-based testing, a major challenge in the diagnosis and treatment of viral pneumonia is distinguishing true infection from the asymptomatic carriage. This is especially true for samples obtained from the upper respiratory tract in patients with suspected LRTI[22]. The specificity of PCR testing likely depends on both the age of the patient and the pathogen identified and further studies are needed to refine test interpretation. The results of the CDC EPIC study, where only 2% of 238 asymptomatic control subjects had a pathogen identified, suggest that the majority of identified respiratory viral pathogens play a causal role in disease pathogenesis[6]. Measuring convalescent-phase serum antibodies may help to improve the diagnostic yield and specificity of PCR-based testing although further studies are needed to validate this approach.

Perhaps the greatest challenge facing both clinicians and researchers is a large number of patients with a clinical diagnosis of pneumonia in whom a causative pathogen is never identified. Of the more than 2000 patients in the CDC EPIC study, 62% had no identifiable pathogen despite a degree of microbiologic testing that exceeded usual clinical practice[6]. Over the past 2 decades, the percentage of patients hospitalized with pneumonia who had no reported pathogen increased by almost 20% in the United States[2]. Research that better characterizes this large group of patients has the potential to profoundly impact health care costs and antimicrobial stewardship. Our evolving understanding of the link between the respiratory microbiome and pneumonia pathogenesis may prove an important engine of innovation in the coming years[23].

CONCLUSION:

The world has covered a lot of space in this evolutionary journey, unearthing various diseases and causes of those diseases. Proactive testing methods combined with statistical analysis have helped the medical scientists and researchers formulate medicines for various Respiratory infections either caused by common influenza, Rhinovirus, Human Adenovirus, or Human Metapneumovirus. But with the advent of COVID-19 and its aftermath, a new horizon is open for scientific research, exploration, and brainstorming to ensure that every form and mutation for respiratory infections is unearthed for the well being of humanity.

REFERENCES:

1. Vincent, J.-L., et al., *International study of the prevalence and outcomes of infection in intensive care units.* Jama, 2009. **302**(21): p. 2323-2329.
2. Fry, A.M., et al., *Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988-2002.* Jama, 2005. **294**(21): p. 2712-2719.
3. Merckx, J., et al., *Diagnostic accuracy of novel and traditional rapid tests for influenza infection compared with reverse transcriptase polymerase chain reaction: a systematic review and meta-analysis.* Annals of internal medicine, 2017. **167**(6): p. 394-409.
4. Walter, J.M. and R.G. Wunderink, *Severe respiratory viral infections: new evidence and changing paradigms.* Infectious Disease Clinics, 2017. **31**(3): p. 455-474.
5. Falsey, A.R. and E.E. Walsh, *Viral pneumonia in older adults.* Clinical infectious diseases, 2006. **42**(4): p. 518-524.
6. Jain, S., et al., *Community-acquired pneumonia requiring hospitalization among US adults.* New England Journal of Medicine, 2015. **373**(5): p. 415-427.
7. Lexau, C.A., et al., *Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine.* Jama, 2005. **294**(16): p. 2043-2051.
8. Smith, S.B., et al., *Trends in pathogens among patients hospitalized for pneumonia from 1993 to 2011.* JAMA internal medicine, 2014. **174**(11): p. 1837-1839.
9. Folgueira, L., et al., *Comparison of the Panther Fusion and Allplex assays for the detection of respiratory viruses in clinical samples.* Plos one, 2019. **14**(12): p. e0226403.
10. Diederen, B.M., et al., *Detection of respiratory viruses and Legionella spp. by real-time polymerase chain reaction in patients with*

community acquired pneumonia. Scandinavian journal of infectious diseases, 2009. **41**(1): p. 45-50.
11. Ferguson, G.D., et al., *Clinical outcomes and macrolide resistance in Mycoplasma pneumoniae infection in Scotland, UK.* Journal of medical microbiology, 2013. **62**(12): p. 1876-1882.
12. Greenberg, S.B. *Respiratory Viral Infections: Update on Human Rhinovirus and Coronavirus Infections*. in *Seminars in respiratory and critical care medicine*. 2016. Thieme Medical Publishers.
13. Rakes, G.P., et al., *Rhinovirus and respiratory syncytial virus in wheezing children requiring emergency care: IgE and eosinophil analyses.* American journal of respiratory and critical care medicine, 1999. **159**(3): p. 785-790.
14. Arruda, E., et al., *Frequency and natural history of rhinovirus infections in adults during autumn.* Journal of clinical microbiology, 1997. **35**(11): p. 2864-2868.
15. Ison, M. and R. Hayden, *Adenovirus. Microbiol Spectr. 2016; 4 (4)*.
16. Griffiths, C., S.J. Drews, and D.J. Marchant, *Respiratory syncytial virus: infection, detection, and new options for prevention and treatment.* Clinical microbiology reviews, 2017. **30**(1): p. 277-319.
17. Bont, L., et al., *Defining the epidemiology and burden of severe respiratory syncytial virus infection among infants and children in western countries.* Infectious diseases and therapy, 2016. **5**(3): p. 271-298.
18. Nair, H., et al., *Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis.* The Lancet, 2010. **375**(9725): p. 1545-1555.
19. Kelly, S.G., et al., *Respiratory syncytial virus outbreak on an adult stem cell transplant unit.* American journal of infection control, 2016. **44**(9): p. 1022-1026.
20. Englund, J.A., et al., *Brief communication: fatal human metapneumovirus infection in stem-cell transplant recipients.* Annals of Internal Medicine, 2006. **144**(5): p. 344-349.
21. Walsh, E.E., D.R. Peterson, and A.R. Falsey, *Human metapneumovirus infections in adults: another piece of the puzzle.* Archives of internal medicine, 2008. **168**(22): p. 2489-2496.
22. Ruuskanen, O., et al., *Viral pneumonia.* The Lancet, 2011. **377**(9773): p. 1264-1275.
23. Yan, Q., et al., *Metagenomic analysis of sputum microbiome as a tool toward culture-independent pathogen detection of patients with ventilator-associated pneumonia.* American journal of respiratory and critical care medicine, 2016. **194**(5): p. 636-639.