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Pneumonia of Viral Etiologies

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Abstract

Pneumonia is a common illness that continues to cause significant morbidity and mortality in both adults and children. Bacteria such as *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* are generally considered as the main pathogens in community-acquired pneumonia and *Legionella* species, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* in atypical pneumonias. In contrast the proportion of pneumonias due to viruses has been both difficult to detect and quantify with any precision. However, with the advent of powerful molecular techniques and rapidly developing technologies a greater number of viruses are being implicated as pathogens and co-pathogens in pneumonia. In the case of adults, the most commonly detected viruses are influenza virus, RSV and parainfluenza. Other viruses that have recently received considerable attention, are H5N1 influenza virus and coronaviruses. Infectious causes of pneumonia in immunocompromised patients include measles, HSV, CMV, HHV-6 and Influenza viruses. Pneumonias caused by other viruses are more rarely reported and include outbreaks of rhinovirus, adenovirus (particularly serotype 14 in military institutions), coronavirus, and metapneumovirus. A range of promising therapeutic targets have been identified and numerous innovative therapeutic treatments demonstrated to improve lung injury due to viral infections.

Keywords: pneumonia, etiology, viruses, diagnosis, treatment

1. Introduction

Pneumonia was once known as Winter Fever and is an acute infection and inflammation of the lung parenchyma. It was first described by Hippocrates around 460 BC [1]. However, it wasn't until the 19th century that pneumonia was established as a true infection, and not just a symptom of other diseases. Edwin Klebs a German pathologist in 1875 observed bacteria under a microscope in cases of pneumonia [2]. Then, Carl Friedlander and Albert Frankel in

1884 and 1884 respectively identified two of the most common bacterial causes of pneumonia, *Streptococcus pneumoniae* and *Klebsiella pneumonia* [3]. By the 1930s, treatment for pneumonia had been developed with the introduction of penicillin playing a key role.

Pneumonia remains the leading cause of childhood mortality under the age of 5 and the most common reason for adult hospitalisation in low and middle income countries, despite advances in preventative and management strategies [4]. Pneumonia usually causes symptoms for 3–4 weeks, and daily activities may be impaired for a further 3 weeks on average. Community-acquired pneumonia (CAP) refers to pneumonia acquired outside of hospitals or extended-care facilities. Nosocomial pneumonia and hospital-acquired pneumonia describe infections acquired in the hospital setting. These are usually defined as pneumonia that occurs 48 h or more after hospital admission, and which was not incubating at the time of admission. Community-acquired pneumonia continues to be a significant health issue [5]. Annually in the United States there are around 4 million cases of which 20% of cases may require hospitalization. As a result there are more than 65 million days of reduced activity overall. Mortality rates can range from 1 to 30% making it the sixth leading cause of death [6]. In developing countries pneumonia is either the first or second leading cause of death. In Europe, around 14.4 per 10,000 children aged over 5 years and 33.8 per 10,000 under 5 years are diagnosed with CAP. CAP is more common in the developing world, estimated at 0.28 episodes per child per year and accounting for 95% of all cases [7].

2. Pathophysiology

Pneumonia is an inflammatory process in lung parenchyma most commonly caused by bacteria and viruses. Less common etiologies include mycoplasma, fungi and parasites. Organisms spread to the lungs through aerosolization, aspiration, or hematogenous spread due to inhalation of droplet or by aspiration of fluids in the oropharynx [8]. Pneumonia results if host defense mechanisms are unable to keep the respiratory network infection free. The pathophysiology varies depending on etiology. In the case of bacterial pneumonia there is an intra-alveolar suppurative exudate with consolidation [9].

In the case of viral pneumonia there is an inflammatory interstitial inflammation with infiltrate in the alveolar, causing damage to ciliated epithelium surfaces. The lungs become congested, hemorrhagic and Intracellular viral inclusions may form. Local host defenses, such as mucociliary clearance, or secretion of specific secretory IgA antibodies can remove some of the virus particles. However, if mucociliary clearance is impaired or secretory anti-influenza IgA antibodies are absent, infection continues to spread. Respiratory epithelial cells are invaded, and viral replication occurs. Newer viruses then infect larger numbers of epithelial cells, shut off the synthesis of critical proteins, and ultimately lead to host cell death [10].

There can be numerous types of immune response depending on how cytokine is produced. For example, cell-mediated immunity is initiated in type 1, while type 2 cytokines are responsible for allergic responses. Children infected with respiratory syncytial virus (RSV) with more serious acute bronchiolitis often have impaired type 1 immunity or augmented type 2 immunity [11].

Respiratory viruses such as RSV or rhinovirus that damage the respiratory tract cause release of multiple humoral factors, including leukotriene C₄, and histamine. In the case of RSV virus-specific immunoglobulin E is released. Rhinovirus infections can cause release of bradykinin, interleukin 1, interleukin 6, and interleukin 8. A further complication of RSV infections is that they can increase bacterial adherence to respiratory epithelium, impair mucociliary clearance, and cause changes in bacterial phagocytosis by host cells [12].

In co infections, secondary bacterial superinfection makes for a poor prognosis of the original viral infection [13]. Interleukin-10, is purported to attract large numbers of macrophages and neutrophils to the lung. The presence of these cytokines increases the immune response, causing inflammatory damage and preventing the proper removal of bacteria.

3. Epidemiology

Numerous studies by the WHO have estimated there are over 450 million cases of pneumonia globally with approximately 3 million deaths particularly prone are the elderly and children [14]. The annual rate of CAP increases from 6/1000 in the 18–39 age group to 34/1000 in 75 years and over age group. Incident rates tend to be higher in colder climates of the North and hospitalization is required in 20–40% cases. In severe cases mortality can vary from 5 to 10% of cases [15].

Viral pneumonias are common in the Mideast. In an Iranian study viruses causing pneumonia were Influenza A (7.4%), influenza B (3.5%), RSV (12.9%), and adenovirus (5.9%). Parainfluenza-1,2 and 3 were 6.4, 6.4 and 15.8% respectively [16]. More recently, avian influenza has become endemic in some parts of the Middle East, especially Egypt and Turkey [17].

WHO data published in May 2014 Influenza and Pneumonia Deaths in Saudi Arabia reached 5689 or 7.08% of total deaths. The age adjusted death rate is 44.89 per 100,000 of population [18]. Middle East respiratory syndrome is caused by a novel coronavirus (MERS-CoV) first isolated in the Kingdom of Saudi Arabia in 2012 from the respiratory tract secretions of a Saudi businessman who died from viral pneumonia [19]. Subsequently, cases were identified in patients living outside the Arabian Peninsula and the Middle East, who were infected either during a stay in the Middle East or by close contact with an individual from an endemic country. Most affected patients were previously healthy men with a median age of 50 years [20]. In 2016, the World Health Organization (WHO) published a report on 1698 laboratory-confirmed cases of MERS-CoV infection. The mortality rate was 36%. All cases were directly or indirectly linked through residence or travel to Saudi Arabia, the UAE, Jordan, Qatar, Oman, Lebanon, Kuwait, Yemen, Egypt, and Iran. There were also reports of sporadic reports in other countries including the United Kingdom, France, Malaysia, Tunisia, Italy, Austria, Greece, Turkey, the United States of America, Germany, Philippines, and Thailand [21]. The largest outbreak of the virus outside its endemic region was recorded in 2015, in South Korea. One-hundred and eighty-six additional cases were confirmed, including the first in China, with a total of 36 deaths. MERS-CoV is a zoonotic virus that can lead to secondary human

infections. Dromedary camels are considered as the intermediate host, with closely related virus sequences in bats. Human-to-human transmission has been noted in households and health care setting. But community-wide transmission has not been observed [22].

3.1. Pneumonia in children

The World Health Organization (WHO) established the Child Health Epidemiology Reference Group (CHERG) to monitor the incidence of childhood [23]. In 2000, CHERG compiled pneumonia statistics in children under age 5. It was found that there were 150 million new cases of pneumonia in children under 5. Of these, approximately 4 million occurred in developed countries, while the majority occurred in developing nations [24]. Hospitalization rates for pneumonia were approximately 9%. More than half of all worldwide cases of childhood pneumonia occurred in just five countries: India, China, Pakistan, Indonesia, Nigeria and Bangladesh. Europe had the lowest rate (0.06 episodes per child-year), while Southeast Asia and Africa had the highest overall incidence rates (0.36 and 0.33 episodes per child-year, respectively). Factors that increased the risk of developing childhood pneumonia included low birth weight, malnutrition, crowded living quarters, indoor air pollution, insufficient breast feeding, and lack of vaccinations. Other possible contributing factors included pre-existing medical conditions such as asthma, and annual rainfall levels. Also, parents who smoked and lack of parent education [25].

3.2. Pneumonia in adults

Pneumonia is a serious concern in adults and viruses cause 15–30% of cases in immunocompetent adults hospitalized with pneumonia [26]. Increased rates of pneumonia-associated hospitalizations have been reported in the United States, Denmark, United Kingdom, and the Netherlands. In 2010, approximately 1.1 million patients in the USA were hospitalized for pneumonia with an average length of hospital stay 5.2 days [27]. In the UK, the number of hospitalizations due to pneumonia increased by 34% during the period from 1997 to 2005. This was particularly notable in older adults. Approximately 26,000 people died from pneumonia and influenza in England and Wales in 2013 according to national statistics. Contributing factors may be due to other chronic diseases such as heart disease, diabetes, and immunocompromised patients [28].

4. Atypical pneumonia

Atypical pneumonia refers to pneumonia caused by atypical bacteria, including *Legionella* species, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* [29]. It is called “atypical” because the symptoms and signs differ from those of pneumonia due to other common organisms. It is generally regarded that *M. pneumoniae*, *Legionella* spp., *C. pneumoniae*, *Chlamydophila psittaci* and *Coxiella burnetii* are the key CAP pathogens not readily identified by standard culture methods [30]. Other atypical pathogens include viruses, atypical mycobacteria, *Francisella tularensis* and an extensive list of agents of bioterrorism.

4.1. Organisms that cause atypical pneumonias include

Mycoplasma pneumoniae, the most common atypical pneumonia organism spreads when someone carrying the infection comes in close contact with others. The condition, also known as “walking pneumonia,” is generally mild and seen in the outpatient setting. It appears to occur mostly in school-aged children and young adults. Less common is *Chlamydia pneumoniae* which causes 10% of all CAP cases and is usually mild but usually more severe in the elderly [31]. *Legionella pneumophila* causes Legionnaires’ disease commonly found in hotels, cruise ships, hospitals and commercial buildings, where people come into contact with contaminated droplets from cooling towers and evaporative condensers. Other reports of infection have been noted near whirlpools and saunas [32]. It is believed the organism causes up to 4% of all pneumonia cases. Known viral causes of atypical pneumonia include respiratory syncytial virus (RSV), influenza A and B, parainfluenza, adenovirus, severe acute respiratory syndrome (SARS) and measles [33].

5. Viral pneumonia

The advent of molecular diagnostics has greatly improved the identification of viruses in patients with CAP. Over the last decade, several studies have used PCR to establish the importance of viruses in the etiology of CAP. Globally, it is estimated that 200 million cases of viral pneumonia occur annually. Most commonly are influenza viruses (A and B), parainfluenza viruses 1, 2 and 3, rhinoviruses, and coronaviruses [34].

Viral pneumonia prevails mostly in young children and older adults. Etiologies include influenza, adenovirus, parainfluenza, H1N1 and respiratory syncytial virus (RSV). Influenza A and B occurs in the winter and spring. Symptoms include, headache, fever, and muscle aches. Respiratory syncytial virus (RSV) is most common in the spring and infects young children. Adenovirus and parainfluenza viral pneumonias exhibit cold symptoms (runny nose and conjunctivitis). Post-influenza pneumonia is often accompanied by secondary bacterial infection due to *Staphylococcus pneumoniae* and *Staphylococcus aureus*. Pneumonia in immunocompromised patients is attributed to measles, HSV, CMV, HHV-6 and Influenza viruses. There is also an increased risk of secondary bacterial lower respiratory tract infection (LRTI). The known complication following influenza infection is *Staphylococcus aureus* pneumonia [35].

Respiratory syncytial virus (RSV) has been identified as an important cause of pneumonia in adults, especially in the elderly. The rate of RSV, overall is between 2 and 5% throughout the year and between 5 and 14% during winter. Adults with severe immunodeficiency are at particular risk of severe RSV infection [36].

Viral pneumonia infections include both DNA and RNA viruses. Some are well-known lung pathogens that produce common clinical and radiologic manifestations. Others are rarely involved as lung pathogens. Many viruses can cause pneumonia, either directly or indirectly. They include:

5.1. Adenoviruses

Adenoviruses are enveloped DNA viruses and a diverse group that cause a wide spectrum of clinical illnesses. At least 52 serotypes exist, classified into 7 subgroups or species (A-G). Adenovirus pneumonia typically is limited to newborns, immunocompromised hosts, and school or military camp populations. Severe adenovirus pneumonia has been more commonly described in immunocompromised patients. Respiratory infection in immunocompetent patients is usually self-limited and mild [37]. However, with advances in molecular techniques, adenovirus has been increasingly discovered to be involved in sporadic cases and in severe CAP in healthy adults. Pulmonary disease is predominantly caused by serotypes 1, 2, 3, 4, 5, 7, 14, and 21. Adenovirus infection accounts for up to 20% of childhood pneumonias, primarily in those children younger than 5 years of age, but such pneumonias occur infrequently in the non-military adult population. Types 4 and 7 viruses can cause outbreaks of respiratory disease in military recruits, whereas Type 7 viruses can cause bronchiolitis and pneumonia in infants. A virulent strain of Adenovirus, serotype 14 (subgroup B) has been reported to cause greater symptoms of respiratory illness and pneumonia. It was first observed in 2005 among civilian and military populations. Outbreaks occurred subsequently at military academies throughout the United States and in the Pacific Northwest [38].

5.2. Coronavirus

Coronaviruses are from the family Coronaviridae and are single-stranded RNA viruses. As the name indicates the surface is covered by crown like projections. This virus is spread via droplet and fomite exposure. Coronaviruses were not thought to significantly cause pneumonia until recently. However, the severe acute respiratory syndrome (SARS) pandemic in 2003 brought the ability of this virus to cause life-threatening pneumonia to worldwide attention.

There are six human coronaviruses (HCoV) that are established human pathogens with worldwide distribution, causing upper and lower respiratory tract infections: HCoV-229E, OC43, HKU1, NL63, MERS-COV (Middle East respiratory syndrome) and SARS-COV (severe acute respiratory syndrome) [39].

MERS-COV was first identified in Saudi Arabia in September 2012, approximately 2000 MERS-CoV cases have been detected in over 20 countries. The newly reported cases lift Saudi Arabia's MERS-CoV total since the virus was first detected in humans in 2012 to 1598 cases, 661 of them fatal and the majority of MERS-CoV cases continue to be reported from the Middle East. The source of the virus has remained a mystery but transmission and virological studies point toward dromedary camels in the Middle East by which humans may become infected through zoonotic transmission. Human-to-human transmission is then exacerbated through close household contacts and in healthcare settings [40].

5.3. Cytomegalovirus

Cytomegalovirus (CMV) is a herpesvirus that is a common cause of infections. In hosts who are immunocompetent, acute CMV infection causes a mononucleosis-like syndrome. CMV

pneumonia may occur and is often fatal in immunocompromised individuals, primarily hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients. The severity of pneumonia is related to the extent of immunosuppression [41]. CMV pneumonia has a prevalence of 15% and a mortality rate of approximately 85% in cancer patients receiving allogeneic bone marrow transplants. The major risk factor for CMV pneumonia in these patients is acute graft-versus-host disease.

Pneumonia is the most common presentation of CMV disease following lung transplantation. CMV infection in lung transplant recipients is approximately 50%. Lung is a CMV latency site and viral reactivation has been associated with direct systemic infection and indirect effects such as acute rejection. The risk of CMV infections in these cases is dependent on the immunosuppressive therapy and serologic status of the donor and recipient.

Moreover CMV pneumonia is identified to be a predictive factor for the later development of chronic rejection in lung transplant. Several studies have been carried to find the optimal preventive strategy to avoid CMV infection after lung transplantation. An effective treatment strategy has been valganciclovir prophylaxis for at least 180 days following combined prophylaxis together with ganciclovir and CMV-immune globulin (CMV-IG) [42].

5.4. Epstein-Barr virus

Epstein-Barr virus (EBV) is well-known to be transmitted through infected saliva. The virus can cause pneumonia without mononucleosis. Lung involvement secondary to EBV infections usually only occurs in immunocompromised people. However, in 25% of pediatric patients with HIV infection, the virus can cause lesions due to lymphocytic interstitial pneumonia or pulmonary lymphoid hyperplasia.

Infectious mononucleosis occurs in young adults aged 15–30 years and usually resolves without *sequelae*. This disorder may cause chronic tiredness and fevers but can also be complicated by life-threatening problems. Pulmonary involvement associated with Epstein-Barr virus infection is uncommon but can occur as a complication of infectious mononucleosis. Pathologically, mononuclear inflammatory cells are evident along interlobular septa in interstitial pulmonary infiltrates [43].

5.5. Herpes simplex virus

Herpes simplex virus (HSV) is primarily implicated in severely immunocompromised patients primarily, e.g., solid organ transplant recipients, patients who are undergoing chemotherapy or are neutropenic, or those who have congenital immunodeficiency. Herpes simplex virus is spread by viral shedding from asymptomatic excretors or from active lesions. It is a rare cause of lower respiratory tract infections. HSV pneumonia can occur as a secondary infection to upper airway infection or following viremia due to genital or oral lesions [44]. Herpes simplex virus can also cause pneumonia in compromised hosts, with a mortality rate of 80%.

Herpes simplex virus type 1 pneumonia is relatively uncommon that generally affects patients who are immunocompromised. It often occurs as a polymicrobial infection and is frequently

associated with coexisting bacterial pneumonia. Pneumonia is usually characterized by a proteinaceous exudate and alveolar necrosis. There is a variable polymorphonuclear inflammatory response [45].

5.6. Human metapneumovirus

Human metapneumovirus (hMPV) is in the Paramyxoviridae family and was initially described in the Netherlands in 2001 [46]. It is a pleomorphic-shaped virus with protein projections from the surface. hMPV is a ubiquitous organism and almost all children have been exposed to it by age 5 years. Morbidity in lower respiratory tract infections in children and infants was reported to bronchiolitis (59%), croup (18%), asthma (14%), and pneumonia (8%) [47]. Reinfection continues to occur throughout life. The virus is spread via droplet and fomite exposure.

The severity of infection increases with older age and with complications such as immunosuppressive conditions or cardiopulmonary disease. Adult hospitalizations with hMPV infection are associated with chronic obstructive pulmonary disease (COPD) exacerbations, pneumonia and bronchitis. Severe pneumonitis requiring intensive care is required in immunocompromised hosts (e.g., hematologic malignancies).

5.7. Influenza virus

The influenza viruses are RNA viruses in the family Orthomyxoviridae, they are enveloped, single-stranded, and are the most common viral cause of pneumonia. Influenza has three serotypes A, B, and C. Influenza type A can infect livestock allowing a reservoir for infection and opportunity for epidemics in humans. For this reason it is usually the most virulent pathogen. The structure of influenza virus includes two envelope glycoproteins, known as hemagglutinin (H) and neuraminidase (N). The hemagglutinin enables infectivity of the virus by attaching to cellular sialic acid residues, whereas the N protein allows spread of the virus to other cells through cleavage of the new virus. Severe pneumonia complications can occur in high-risk individuals [48]. Two influenza types have emerged of particular importance: H5N1 avian influenza strain and the novel H1N1 swine influenza strain. In the influenza A (H1N1) pandemic of 2009–2010, the World Health Organization estimated approximately 16,000 deaths. The majority of these deaths corresponded to patients with underlying risk factors contributing to worse outcomes. Influenza type B causes illness seems to occur more in closed populations, e.g., boarding schools. Influenza type C is less common and occurs as sporadic cases [49].

5.8. Measles virus

Measles is a respiratory tract virus that causes a febrile illness with rash in children and a mild pneumonia in healthy adults. It is a single-stranded RNA virus in the Paramyxoviridae family and the genus *Morbillivirus*. It comprises a nucleocapsid surrounded by an envelope. Measles is a highly contagious disease that results from infection with measles virus and is still responsible for more than 100,000 deaths every year [50]. Measles virus is transmitted by

the respiratory route and illness begins with fever, cough, coryza. Complications of measles affect most organ systems, with pneumonia accounting for most measles-associated morbidity and mortality.

Pulmonary disease from measles virus infection can occur as a primary measles virus pneumonia with secondary bacterial pneumonia or as an atypical measles virus pneumonia. Measles virus can cause pneumonia in 3–4% of infected patients mostly with secondary bacterial infection such as *Haemophilus influenzae* and *Neisseria meningitidis*. The prevalence of measles virus pneumonia is higher in immunocompromised patients and pregnant women. Measles virus pneumonia without a secondary bacterial infection appears with diffuse alveolar damage and epithelial hyperplasia. Epithelial hyperplasia is seen in bronchioles and peribronchial alveoli as well as in the tracheobronchial epithelium with cystic dilatation of mucous glands. Histologically, measles virus pneumonia displays multinucleated giant cells containing up to 50 nuclei within the bronchiolar and tracheobronchial epithelium [51].

5.9. Parainfluenza virus

Parainfluenza virus (PIV) consists of nucleocapsids, which propagate in the cytoplasm of infected cells, with hemagglutinin present in the virion envelope. PIV is a common virus infection of childhood. PIV is second in importance to only RSV in causing children pneumonia and bronchiolitis in infants younger than 6 months and lower respiratory tract disease. Transmission is through direct contact or large-droplet spread.

Although there are four subtypes of PIV, PIV types 1 and 2 tend to peak during the fall season where as type 3 is endemic year-round. Recurrent upper or lower respiratory tract infections occur throughout life because Immunity is short term. The infections vary from a self-limiting illness to life-threatening pneumonia especially in immunocompromised hosts leading to lung injury and respiratory failure [52]. In one study, hematopoietic stem cell transplant (HSCT) patients with PIV progressed to develop pneumonia. Of 44% of these patients with pneumonia there was a mortality rate of 37% [53].

5.10. Respiratory syncytial virus

Respiratory syncytial virus (RSV) consists of only one serotype and is in the Paramyxoviridae family. Structurally, it consists of 10 viral polypeptides, 4 of which are associated with virus envelope, and 2 of these (F and G) are important for infectivity and pathogenicity. RSV is highly contagious, spreading via droplet and fomite exposure. RSV is the most frequent cause of lower respiratory tract infections among infants and children and the second most common viral cause of pneumonia in adults [54]. The majority of children are infected by the age of 5 years in settings such as daycare centers but the resulting immunity is incomplete. Reinfection when it occurs in older children and young adults is mild. But, with advancing age there is a greater likelihood severe disease and pneumonia. Diagnosed adult RSV hospitalizations have increased significantly in the United States. Respiratory syncytial virus hospitalizations appear to be greater in severity than influenza hospitalizations, especially immunocompromised and in older adults [55].

5.11. Rhinovirus

Many reports from the literature report that rhinovirus accounts for approximately 30% of cases of all virus-related pneumonia. Rhinovirus is considered the second most frequently recognized agent associated with pneumonia and bronchiolitis in the young. The virus is associated with asthma hospitalizations in both old and young patients [56].

Rhinovirus is genetically diverse with more than 100 serotypes identified. In addition to common colds, reports have suggested that rhinovirus is associated with bronchiolitis, bronchitis, pneumonia and acute asthma exacerbation. Rhinovirus has been detected by molecular methods in 10–30% of hospitalized children with lower respiratory tract infections. Rhinovirus is also considered to be the second most common cause of bronchiolitis after respiratory syncytial virus (RSV) [57]. Rhinoviruses have long been known to cause common colds and exacerbations of Chronic obstructive pulmonary disease (COPD), but because rhinoviruses grow poorly at 37°C lower respiratory tract infections were thought to be rare. However, it has been demonstrated that rhinoviruses can replicate at body temperature and infect cells of the lower respiratory tract. Molecular studies have consistently identified rhinoviruses in nasopharyngeal or pharyngeal specimens from children and adults with lower respiratory tract infections. Rhinovirus has also been detected in 2–17% of adults and 4–45% of children with CAP [58].

5.12. Varicella-zoster virus

Varicella-zoster virus (VZV) is a highly contagious herpes virus and primary infection manifests as chickenpox. The reactivation in later life results in zoster (shingles). It is spread by the respiratory route or direct contact with skin lesions. This pneumonia is rare in otherwise healthy children but does occur in immunocompromised children causing life-threatening complications [59]. VZV-related community-acquired pneumonia (VZV-CAP) has become increasingly recognized as a very serious and life-threatening complication invasive mechanical ventilation in more than half of the cases. Complications include secondary bacterial infections, encephalitis, hepatitis, and, with concomitant aspirin use, Reye syndrome. VZV pneumonia also tends to be more severe in individuals who smoke. In fatal cases of pneumonia, laboratory findings include extensive alveolar hemorrhage, pulmonary edema and mononuclear cell infiltration with histological evidence of intranuclear inclusion bodies.

Varicella-zoster virus pneumonia is a serious complication of disseminated varicella-zoster virus infection with mortality rates of 9–50%. In adults prevalence of varicella-zoster virus pneumonia has varied from 5 to 50% of all varicella infections. Varicella-zoster virus is a self-limited benign disease in children known as chickenpox. But in adults it causes significant complications such as varicella-zoster virus pneumonia and over 90% of cases occur in patients with lymphoma and immunocompromised patients. Patients exhibit diffuse alveolar damage, spherical nodules are seen throughout the lung parenchyma. The nodules are composed of an outer fibrous capsule enclosing areas of necrotic tissue [60].

5.13. Zoonotic viral pneumonias

Zoonotic viral pneumonias include those caused by avian influenza, hantavirus, severe acute respiratory syndrome (SARS), and H1N1 (swine) influenza. In 1997, an influenza virus (H5N1 virus) which normally only infects only birds was found to infect humans in Hong Kong. Manifestations included pneumonia, which in some cases led to fatal acute respiratory distress syndrome (ARDS) or multisystem organ failure. The rising incidence and widespread reporting of disease from H5N1 influenza viruses can probably be attributed to the increasing spread of the virus from existing reservoirs in domestic waterfowl and live bird markets, leading to greater environmental contamination [61]. Recombinations of viruses in animals are a global concern. The H5N1 outbreak in Southeast Asia, H3N2 variant in the USA in 2012, and H7N9 avian cases in China 2013 are examples of such new threats. Effective surveillance is required to monitor such developments [62].

There is a growing danger that in the future avian influenza, a subtype of influenza A, may result in a worldwide pandemic. A/H5N1 exhibits several serious characteristics, such as increased virulence and human-to-human transmission in some cases, rather than bird-to-human transmission. The disease causes high morbidity and mortality due to pneumonia and respiratory failure [63].

H1N1 was first reported in Mexico and spread to the United States. The infection from a novel swine-origin influenza A (H1N1) virus rapidly spread to become a worldwide pandemic in 2009. Virus-associated hemophagocytic syndrome may play an important role in development of multiorgan failure and ensuing death in H1N1 infection [64].

SARS is a respiratory infection caused by a coronavirus, which appears to have jumped from animals to humans. The disease was first reported in China in 2003 and rapidly spread from to the rest of the world in a 1 year period. It resulted in more than 8000 patients in 29 countries causing 774 deaths [65].

5.14. Co-infections

Co-infection Infections involving both respiratory bacteria and viruses or are common. Viral infection usually occurs first, followed by a secondary bacterial infection, as observed in the influenza pandemics of 1918, 1957, and 1968 where most deaths occurred due to secondary bacterial infection. In some infections however, especially H5N1 avian influenza, the associated pneumonia appears to be caused by direct viral action.

Co-infections are particularly common in 45% of children with CAP, and mainly involve pneumococcus [66], *Mycoplasma pneumoniae* and several species of *Chlamydia*. CAP of mixed etiology has been characterized less in adults than in children, and prevalence is estimated at less than 5%. The most common combinations reported are pneumococcus with rhinovirus or influenza A virus [67].

6. Laboratory testing

Laboratory diagnosis of viral pneumonia has relied on detection of virus or viral antigen in upper-respiratory specimens (e.g., nasopharyngeal aspirates) and lower respiratory samples (e.g., induced sputum) by culture or immunofluorescence microscopy.

Traditional microbiological methods for detection of respiratory tract pathogens are relatively slow, often are not sensitive and are influenced by previous antibiotic therapy. Molecular diagnostics on the other hand hold much potential for detection of both common and atypical pathogens causing CAP. Analysis can be completed in hours, rather than days, for detection of typical pathogens and weeks for detection of atypical pathogens [68].

There are >200 known respiratory viruses, but accurate data on how many are etiological agents in CAP are lacking. The discovery of 6 new respiratory viruses since 2000—including metapneumovirus (hMPV), the severe acute respiratory syndrome coronavirus, influenza virus strain H5N1, coronavirus strains NL63 and Hku1, and human bocavirus—has presented new challenges for comprehensive viral diagnostics [69]. The significance of respiratory viral infections in patients with sepsis is underestimated. During the winter season, viral such as coronavirus, influenza A virus, human metapneumovirus, and respiratory syncytial virus are clinically underdiagnosed in 70% of patients detected by the multiplex PCR assay [70].

Quantitative multiplex PCR testing of respiratory secretions is recognized as a highly sensitive method for the diagnosis with the ability to detect viral pathogens and atypical bacterial pathogens. An acute viral infection can be confirmed with detection of influenza virus, parainfluenza virus, RSV, or hMPV. The presence of nucleic acid from adenoviruses, bocaviruses, coronaviruses or rhinoviruses is often found in asymptomatic persons. In the future the study of the virus concentration over time will contribute to distinguishing acute infections from protracted nucleic acid excretion [71].

7. Treatment

Antiviral drugs have been developed targeting viral proteins that can be inhibited by small molecular receptors or larger biotherapeutics. Consequently, most approved antiviral drugs are highly specific for a particular virus or family of viruses (e.g., neuraminidase inhibitors and adamantanes for influenza). The benefits of this approach are that there is greater selectivity and may lower the risk of adverse host effects. The disadvantages are that there is a limited antiviral spectrum, and greater risk of antiviral resistance [72].

Treatment of Influenza Virus Neuraminidase, is essential interrupting intercellular viral propagation. Selective inhibitors, e.g., oseltamivir, peramivir, and zanamivir have been used to prevent infection during the first 24–72 hours, improving clinical symptoms and reducing morbidity and mortality. Reductions in the incidence of pneumonia in patients has been observed in numerous studies who received treatment in the early stages of infection [73].

Virus family	Virus	Morphology	Treatment	Prevention	Seasonality
Adenoviridae	Adenoviruses	90–100 nm, non-envelope, icosahedral nucleocapsid, double-stranded DNA	Cidofovir and brincidofovir	Hand hygiene, oral vaccine for military recruits	All year
Coronaviridae	(Coronaviruses)—SARS, MERS	75–160 nm, envelope, helical, nucleocapsid, ssRNA (positive sense)	Supportive therapy	Preventive measures, e.g., hand hygiene	Winter
Bunyaviridae	(Arboviruses)—Hantavirus	90–100 nm, envelope spherical virions. RNA- single stranded	Supportive therapy	Preventive measures, e.g., limit vector breeding	Widespread, all year
Herpesviridae	Herpes simplex virus 1 (HSV-1) herpes simplex virus 2 (HSV-2), herpesvirus 6, herpesvirus 7, and herpesvirus 8 Varicella-zoster virus (VZV), Cytomegalovirus (CMV), Epstein-Barr virus (EBV)	130–300 nm, enveloped, double-stranded DNA	Acyclovir, ganciclovir, and foscarnet	V-Z immunoglobulin Intravenous immunoglobulin Vaccine	All year
Orthomyxoviridae	(Orthomyxoviruses)—Influenza A,B virus, H1N1	200–300 nm enveloped pleomorphic RNA single stranded	Oseltamivir, peramivir, zanamivir, amantadine, and rimantadine	Influenza vaccine chemoprophylaxis	End of autumn and winter
Papovaviridae	(Polyomavirus)—JC virus, BK virus	18–28 nm non-envelope Icosahedral DNA single strand	Limited treatments, surgical removal	Vaccines, e.g., Gardasil, Cervarix	All year
Paramyxoviridae	(Paramyxoviruses)—parainfluenza virus, respiratory syncytial virus (RSV), human metapneumovirus (hMPV), measles virus	150–200 nm, enveloped helical symmetry RNA-negative strand	Ribavirin protease inhibitors (e.g., lopinavir/ritonavir) Ribavirin	Preventive measures, measles vaccination for immune serum immunoglobulin	End of autumn, beginning of winter
Picornaviridae	(Picornaviruses)—enteroviruses, coxsackievirus, echovirus, enterovirus 71, rhinovirus	20–30 nm non-envelope cubic symmetry RNA-positive strand	Pleconaril	Alfa interferon (intranasal)	All year

Virus family	Virus	Morphology	Treatment	Prevention	Seasonality
Retroviridae	(Retroviruses)—human immunodeficiency virus (HIV), human lymphotropic virus type 1 (HTLV-1)	80–100 nm envelope helical RNA-single strand	Nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI)	Education, preventive measures	All year

Table 1. Characteristic features of viral pathogens causing pneumonia.

Laninamivir octanoate, a new neuraminidase inhibitor administered by inhalation, can be effective in the treatment of IV infection, including oseltamivir-resistant strains. They are exclusively specific to influenza virus type A. However, side effects and rapid development of resistances, has meant that they have fallen into disuse. Immunomodulators are also being studied for reducing viral-mediated inflammation and its effect on the host [74].

Ribavirin has shown effectiveness in the management of acute episodes of pneumonia or for improving respiratory parameters during recovery. Meta-analysis studies performed in children, indicated that inhaled ribavirin can reduce hospital stay and time on ventilator times during pneumonia, however, the overall mortality rates are not affected. Ribavirin has also been used in severely immunocompromised patients, e.g., lung transplant recipients with positive outcomes. General use of bronchodilators, antibiotics, or corticosteroids are not recommended in the American pediatric guidelines for SRV bronchiolitis [75].

Acyclovir (Zovirax), inhibits viral DNA synthesis by competitively binding to viral DNA polymerase. Due to poor absorption, intravenous acyclovir at a dosage of 250 mg/m² every 8 hours is currently the treatment of choice for HSV pneumonia. The dosage of acyclovir should be decreased in patients with underlying renal insufficiency. Adverse reactions are infrequent, but renal impairment secondary to precipitation of acyclovir in the tubules can occur in 5–10% of patients if not properly rehydrated. Having a proven HSV pneumonia appears to be associated with high morbidity in solid tumor patients. This group of patients have been shown to benefit from acyclovir therapy [76]. There is little doubt that intravenous acyclovir is beneficial in the rare cases of varicella-zoster pneumonia in immunocompromised patients.

Supportive treatment was only available for other respiratory viruses until recently, However, some antiviral drugs are currently under investigation. Cidofovir is an acyclic nucleoside phosphonate analog of cytidine monophosphate. Upon conversion to its diphosphate form it leads to viral DNA chain termination. Limitations of cidofovir include poor cellular uptake and nephrotoxicity. Brincidofovir, a derivative of cidofovir which is active against double-stranded DNA viruses, is a major improvement in anti-adenovirus therapy [77]. Lung transplant recipients with metapneumovirus infections have been treated with success using intravenous ribavirin. Rhinovirus and Enterovirus, have been successfully used in limited studies using Pleconaril, which is incorporated into the virus capsid (**Table 1**) [78].

8. Prevention

Measures in infectious infection control, particularly of the respiratory tract, involve using barrier methods preventing infection. Use of gloves, masks and hand-washing have been shown to be effective in reducing transmission rates in the health care centers. Isolation of patients during the clinical phase of the disease is also strongly recommended and reduces overall incidence. Immunization plays a very important role in prevention, but is only available for a few viruses. As the population ages and rates of pneumonia increase. Hospitalizations for pneumonia will continue to show an upward trend unless effective intervention strategies are devised and implemented. This includes recommending immunization with PPV and annual

influenza vaccinations. Although the effectiveness of these vaccines decreases with age and comorbid conditions [79].

9. Future strategies

Vaccines are still considered the great hope in disease prevention and control strategies. However, among respiratory viruses there has been little progress, only influenza has vaccines. A different approach is needed in developing new vaccines with longer term efficacy and broader response. Current vaccines are prone to changing antigenicity and need to be administered annually. Vaccine development has been in progress for decades but faces numerous technical challenges. Respiratory viruses such as RSV, PIV and hMPV initiate incomplete immune responses and so reinfections tend to occur. The pace of progress is slow both for Both live-attenuated and subunit vaccines. It may be years before such vaccines are available in the market place. However, once available then adult immunization may offer protection to young infants as is the case with influenza vaccines [80].

9.1. Stem cell

Stem cells are unique in that they possess the capacity to self-renew and capable of differentiation into many cell types hence leading to the regeneration of injured organs. In lung injury, stem cells have been shown to promote endothelial and epithelial repair by engrafting into tissue and interacting with neighboring cells. Furthermore, stem cells beneficially influence the host's immune response by reducing harmful inflammatory reactions. Paracrine mediators and mitochondria-containing micro-vesicles released by stem cells appear responsible for the beneficial effects on immune responses and cellular functions [81].

9.2. Gene expression

Gene expression profiles of peripheral blood leukocytes can differentiate viral from bacterial infections with 95% accuracy. They can also identify unique profiles in patients with bacterial and viral respiratory tract infections. Application of gene expression profile analysis in children with CAP can significantly enhance the ability to classify patients according to the class of pathogen causing the infection and disease severity. Molecular distance to health (MDTH) is a novel metric that in a single score can provide a global assessment of the perturbation of the patient immune profile compared to healthy controls. It has been shown to accurately classify the severity of the disease in for example cases of bacterial sepsis, staphylococcal infections, as well as in children with respiratory viral infections [82].

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