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Review article

Update on viral community-acquired pneumonia☆

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A B S T R A C T

Viral pneumonia is a prevalent cause of respiratory infection in immunocompetent adults. It has varied presentation, from mild to severe respiratory failure, requiring mechanical ventilation. However, in Brazil, there have been few studies on the clinical presentation and diagnosis of this infection. Thus, the authors of the present article intend to review the main viral agents that cause community-acquired pneumonia and to discuss the currently available diagnostic and therapeutic methods.

Atualização em pneumonia comunitária viral

Palavras-chave:
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R E S U M O

A pneumonia de origem viral é uma causa prevalente de infecção respiratória em adultos imunocompetentes. Tem apresentação variada, ocasionando desde formas leves a quadros graves de insuficiência respiratória com necessidade de ventilação mecânica. Contudo, em nosso país, há poucos estudos a respeito da apresentação clínica e diagnóstico dessa infecção. Dessa forma, os autores do presente artigo têm por objetivo revisar os principais agentes virais causadores de pneumonia na comunidade e discutir as modalidades diagnósticas e terapêuticas disponíveis atualmente.

Introduction

Pneumonia remains as one of the leading causes of worldwide morbidity and mortality[1] and, in spite of recent advances in the field of diagnosis, it has been estimated that the causative infectious agent is accurately identified in less than 50% of cases.[2]

In Brazil, the majority of studies on community-acquired pneumonia address mostly treatment options and clinical outcomes, and little is known about the local microbiological standards.[2]

Bacteria remain as the main group of identified pathogens, but the actual role of other agents such as fungi, protozoa, and viruses is yet to be elucidated.

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Although viruses have been identified as an important cause of community-acquired pneumonia, only recently, mainly due to the 2009 pandemic, there has been a greater interest in the role of these agents.[3] Among the main viruses that cause pneumonia in immunocompetent adults are the influenza virus, the respiratory syncytial virus (RSV), the adenovirus, and the human parainfluenza virus (HPIV). The use of new molecular techniques has allowed the identification of viruses that were seldom identified before, such as rhinovirus, metapneumovirus, and coronavirus.[1,4]

This review aims to demonstrate the modalities of complementary assessment and the currently available treatment options, and to discuss the main viruses implicated in the pathogenesis of community-acquired pneumonia in immunocompetent adults.

Complementary diagnostic investigation

The incidence of viral pneumonia has increased significantly in recent years, and, depending on the agent virulence and patient comorbidities, its presentation may range from mild and self-limiting to extremely severe cases, with respiratory failure. The results of laboratory tests, clinical outcomes, and specific patterns identified on imaging studies, considered in the past as reliable identifiers of the infection etiology, are nonspecific, and their importance in diagnosis remains uncertain.[5] Thus, the use of new complementary laboratory tests with higher sensitivity and specificity contributes to the definitive diagnosis, optimizing the treatment of this disease.[3]

However, it should be noted that the isolation of these agents does not necessarily mean an active infection. In this context, it is essential to know the diagnostic options for identification of viruses, as well as the limitations of each method for adequate clinical interpretation.

The currently validated methods to define the etiology of viral infection, summarized in Table 1, are serology, culture, cytological evaluation, rapid detection of antigens, and gene amplification techniques, even though they are not widely available and are often costly.

Serological analysis

Virtually all viruses can be diagnosed through serology. However, it is necessary to collect paired blood samples (acute/convalescent phases), as a four-fold titer increase in relation to the first sampling is necessary to confirm the diagnosis. Therefore, serology is not routinely used, as it has been shown to be of little use in the acute phase of the disease, because titers rarely increase at this stage.[4]

In the study's setting, serology is available for many of the community respiratory viruses such as adenovirus, RSV, and seasonal influenza.

Cultures

Viral culture can also be employed for most of the respiratory viruses, with the long time necessary to obtain the results being a disadvantage, as well as the need for specific culture mediums.[4]

To perform the cultures, tissue samples from the upper and/or lower airways, sputum, and nasopharyngeal and bronchoalveolar lavage can be used.[4] The cytopathic effects of the viruses are observed in cell cultures, such as the formation of syncytial collections of multinucleated giant cells, or evidence of viral growth. The subsequent identification of specific viruses in cell cultures may be accomplished by immunofluorescence techniques (direct or indirect), or nucleic acid probes.[4] Other disadvantages of this method are high cost, low availability in clinical practice, and also the low yield for some specific agents such as RSV, human metapneumovirus, and coronavirus.[4]

Cytological assessment

This model can use samples from respiratory tissues and also secretions such as nasal and bronchoalveolar lavage. The technique aims at identifying nuclear (virus DNA) or cytoplasmic (virus RNA) inclusions, which are normally present in infected cells. The identification of the presence of such inclusions confirms the diagnosis.[4]

Table 1 – Options available for diagnostic investigation of the major pneumonia-causing viruses in the community.

Virus	Serology	Culture	Cytological assessment	Rapid detection of antigens	Gene amplification
Influenza	+	HA/SV	–	IF/ELISA	RT-PCR
RSV	+	CE/SV	eosinophilic cytoplasmic inclusions	IF/ELISA	RT-PCR
Adenovirus	+	CE/SV	intranuclear inclusions	IF/ELISA	RT-PCR
Parainfluenza	-	HA/SV	eosinophilic cytoplasmic inclusions	IF/ELISA	RT-PCR

RSV, respiratory syncytial virus; IF, immunofluorescence; HA, hemagglutination; SV, shell viral culture; CE, cytopathogenic effects; ELISA, enzyme-linked immunosorbent assay; RT-PCR, reverse transcriptase polymerase chain reaction.

The disadvantage of this method is its low sensitivity, so that the absence of these findings cannot rule out active disease. [4]

Rapid antigen detection

These are rapid tests performed in easily obtainable specimens, such as nasal swab or wash. The enzyme-linked immunosorbent assay (ELISA) test is available for most pathogenic respiratory viruses; it is capable of detecting viral antigens, whereas the immunofluorescence requires intact infected cells. Both methods have varied sensitivity and specificity, depending on the agent analyzed. Specificity for seasonal influenza, for instance, is approximately 90% and sensitivity is 60%. However, when the suspected agent is the H5N1 influenza virus, the yield is extremely low, and therefore not recommended for confirmation of infection by this agent.[4]

The antigens remain positive for weeks, but are less sensitive than viral culture and can be used in a complementary way to increase the diagnostic yield of the sampled material.[6]

Gene amplification

The polymerase chain reaction (PCR) or reverse transcriptase-polymerase chain reaction (RT-PCR) techniques are extremely sensitive and specific to detect virus presence. It is the examination of choice for most respiratory viruses and, if available, should be employed together with the aforementioned diagnostic methods. The current development of this technique has allowed the knowledge of new causative agents of bronchiolitis and pneumonia in both pediatric and adult populations.[7]

This method can be applied to samples of nasopharyngeal or bronchial secretion swabs, and has the advantage that it can be performed in other body fluids such as blood of immunocompromised patients suspected of having cytomegalovirus infection.[4]

A new molecular technique called multiplex reverse transcriptase polymerase chain reaction (MRT-PCR) allows for the rapid detection of several respiratory viruses such as influenza A and B; RSV A and B; HPIV 1, 2, and 3; metapneumovirus; and adenovirus. Its disadvantage is the low sensitivity for H1N1 influenza, described by the method as nontypeable.[8]

Etiological agents, manifestations and treatment

Influenza

Influenza is an RNA virus of the *Orthomyxoviridae* family and three serotypes, A, B, and C, have been described. These viruses are responsible for approximately 4% to 8% of pneumonia cases in healthy adults, and higher rates were found during outbreaks and epidemics.[9,10]

Influenza A can be disseminated by aerosols and affect the entire respiratory tract. Commonly, it is the most virulent serotype, comprising a number of other subtypes. Influenza B usually causes disease in populations confined to closed spaces, such as daycare centers and boarding schools. Influenza C is the least common serotype, and is found as pathogenic agent in sporadic reports.[10]

Influenza viruses A and B are responsible for approximately 50% of community-acquired viral pneumonia in adults. Their impact is greater in the elderly and other at-risk populations such as pregnant women, immunocompromised patients, and patients with chronic diseases, especially heart and lung diseases.[10]

Recently, a subtype of influenza A, H1N1, known as the swine-flu agent, has emerged as an important and threatening pandemic, severely affecting immunosuppressed patients such as transplant recipients and other high-risk populations such as pregnant women, obese patients, and those with heart and lung disease. The affected individuals were generally younger than those affected by seasonal influenza.[11,12] It has been estimated that there were approximately 16,226 deaths from April 2009 to January 2010 according to estimates by the World Health Organization. In Brazil, 10% to 30% of the admitted patients required admission to an intensive care unit, and of the total, 60% to 88% required mechanical ventilation. The mortality rate for H1N1 in the country was 70 deaths per 100,000 inhabitants.[12,13]

Infection by the influenza virus leads to cell death, especially in the upper airways. When the virus infects the lower airways directly, there may be bleeding without proportional accumulation of inflammatory cells. There is also mucociliary clearance impairment, which may determine bacterial adherence to the respiratory epithelium. Impaired function of T-cells, macrophages, and neutrophils also occurs, which leads to decreased host defenses. All these events together facilitate the frequently observed concomitant bacterial infection.[14]

The incubation period is one to two days and symptoms typically last three to five days. There are three clinical presentations: primary influenza pneumonia, influenza infection with secondary bacterial pneumonia, and simultaneous coinfection (viral and bacterial).[14]

Primary pneumonia manifests as persistent cough, pain in the throat, headache and myalgia for over five days, associated with the onset of progressive dyspnea and cyanosis. This is the less common, albeit more severe, presentation. Influenza pneumonia with secondary bacterial infection is characterized by intensification of high fever, cough, and purulent sputum after initial improvement, associated with the appearance of new opacities on chest radiography. The main agents involved are *Streptococcus pneumoniae* (48%), *Staphylococcus aureus*, and *Haemophilus influenzae*. Pneumonia caused by viral and bacterial coinfection manifests similarly to pneumonia with secondary bacterial infection, but there is no initial improvement. In this context, both the virus and the bacterial agent are isolated together in the microbiological analysis.[14]

Inflammatory markers such as C-reactive protein and procalcitonin are also of little use when differentiating between bacterial and viral pneumonia, as the most severe cases, as observed in the H1N1 pandemic, showed high levels of these two substances in patients with viral pneumonia.[15]

The pulmonary and radiological alterations are nonspecific and can be seen as perihilar and peribronchial opacities, consolidations, and diffuse bilateral interstitial opacities, especially in more severe forms of the disease or in neutropenic patients (Fig. 1).[16]

The influenza virus can be isolated in sputum, nasal lavage, or nasal and pharyngeal swabs, with lower yield for the latter in culture medium. 90% of the positive cultures are detected within three days of inoculation and the remainder up to the seventh day. Rapid tests have high specificity for influenza viruses A and B (85% to 100%), but low sensitivity (40% to 80%).

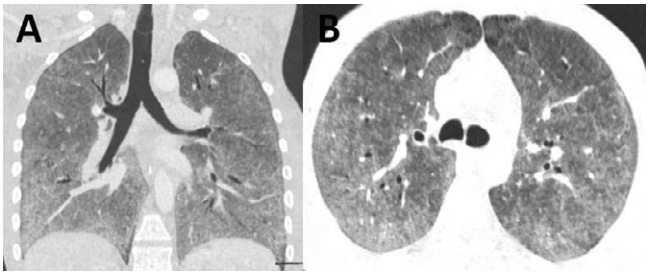

Fig. 1 - Coronal (A) and axial (B) views of chest CT scan in a patient with pneumonia caused by seasonal influenza A virus, showing diffusely distributed ground-glass opacities.

It is noteworthy that in suspected H5N1 cases, this test is not recommended, as the RT-PCR analysis has greater diagnostic usefulness. Histological assessment is another possible diagnostic option, achieved by ultrastructural analysis through lung biopsy.[17]

The treatment must be performed with supportive measures such as supplemental oxygen, analgesics, antipyretics, and antiviral therapy in selected cases. The drugs approved for the treatment of influenza infection are amantadine, rimantadine, oseltamivir, and zanamivir (Table 2).[17]

Amantadine and rimantadine have been approved for prevention and treatment, and are not effective against influenza B. They work by blocking the ion channels of the viral M2 protein and inhibit its decapsulation. Its use should be indicated within 48 hours of symptom onset in uncomplicated cases, but its effectiveness has not been tested in severe pneumonia. Furthermore, many strains are now resistant to these drugs, thus they should not be recommended as an empirical single-drug therapy.[3]

Oseltamivir and zanamivir are drugs that block the surface protein neuraminidase and trap the virus within the infected respiratory epithelium, preventing its dissemination. They too should be preferably administered within 48 hours of symptom onset. They are active against influenza A and B, and have low potential to induce resistance, although some cases have been described in the United States during the H1N1 pandemic. In cases of severe pneumonia, medication can be provided even after 48 hours of symptom onset.[18]

When there is potentially fatal respiratory failure, as in many cases of the H1N1 pandemic, rescue maneuvers for refractory hypoxemia, such as recruitment and ventilation in the prone position, may be instituted in combination with antiviral therapy.[19]

Respiratory syncytial virus

RSV is part of the *Paramyviridae* family, and is the most common cause of lower respiratory infection in children.[20] It has currently been identified as an important cause of pneumonia in adults, especially in the elderly, and has become the second most frequent cause among the viruses found in this population. RSV is highly contagious, spreading through droplets and fomites. The population at risk consists mainly of children younger than six months; patients with chronic diseases, such as cystic fibrosis; patients with congenital heart disease; institutionalized elderly individuals; and immunosuppressed patients.[21] The overall mortality in adults varies according to the immune status, from 1% to 5% in healthy adults to 41% in bone marrow transplant recipients.[22]

Table 2 – Main drugs used to treat the principal viruses that cause community-acquired pneumonia

Action mechanism	Drugs	Posology	Virus
Neuraminidase Inhibitors	Oseltamivir	75-150 mg twice a day for five days (oral route)	Influenza A and B
	Zanamivir	10 mg twice a day for five days (aerosol)	
M2 protein inhibitors	Amantadine	100 mg twice a day for five days (oral route)	Influenza A
	Rimantadine	200 mg once a day for five days (oral route)	
Unknown	Ribavirin (20 mg/mL)	18 hrs/day (aerosol) for three to six days with a nebulizer	RSV Adenovirus[a] Parainfluenza

RSV, respiratory syncytial virus.
[a]For adenovirus, consider the association with cidofovir (5 mg/Kg – once a week, IV route).

RSV is rarely diagnosed in adults. The infection is characterized by persistent symptoms in the upper airways, such as runny nose, earache, and sore throat, associated with prolonged cough (whether dry or productive), dyspnea, and wheezing; it may cause bronchitis, bronchiolitis, and severe pneumonia requiring mechanical ventilation. Compared to the influenza virus infection, a higher frequency of rhinorrhea and purulent sputum is observed, as well as a lower frequency of fever and gastrointestinal symptoms.[23]

Some inflammatory markers obtained from airways and blood, such as soluble intercellular adhesion molecule type I (sICAM-1), interleukin 10 (IL-10), and IL-6 were tested in children and appear to show a positive correlation, at higher concentrations, with the severity and duration of hospitalization.[24]

The pulmonary radiological findings associated with RSV infection are nonspecific; bilateral alveolar opacities and interstitial alterations are described in most cases, similar to those observed in influenza virus infection.[21,22]

The virus can be isolated in culture, where the highest yield is found in samples of nasopharyngeal lavage and tracheal secretions. In immunosuppressed patients, a positive culture is found in up to 15% of nasopharyngeal lavage samples, in up to 71% of tracheal secretions, and in up to 89% of bronchoalveolar lavage. Rapid tests for detection of viral antigens have a sensitivity of 50% to 90% and a high specificity (90%-95%). Gene amplification with RT-PCR is also available.[23]

Ribavirin works by preventing viral transcription and is the only currently available antiviral drug for the treatment of RSV pneumonia (Table 2). The current recommendation is that the medication should only considered for severe cases or in patients at high risk of complications. Intravenous immunoglobulin specific for RSV (palivizumab) can also be used in combination with ribavirin in critically-ill patients and those at high risk for complications, especially in bone marrow transplant recipients.[24]

Adenovirus

Adenovirus is a highly contagious DNA virus, and there are 52 different serotypes. Adenovirus infection can occur at any time of the year, accounting for approximately 10% of pneumonias in children. Historically, this virus is also identified as an important causative agent of respiratory infection outbreaks in military bases in the United States.[25]

Its serotypes are classified into seven subgroups or species (A to G), and pulmonary infections are caused predominantly by serotypes 1, 2, 3, 4, 5, 7, 14, and 21. Although it is a virus that determines low mortality, subtype 14 can cause severe respiratory failure in susceptible patients, such as solid-organ transplant recipients, individuals with HIV infection, and patients with other types of impaired cell immunity, although there are reports of fatal cases in the postoperative period after cardiac surgery in previously immunocompetent patients.[26] Adenovirus dissemination occurs by direct inoculation into the conjunctiva, aerosol, feces, and fomites; the virus is capable of surviving in contaminated areas of the environment for several weeks. Viral reactivation can also occur in immunosuppressed patients, resulting in several clinical syndromes, including keratoconjunctivitis, gastroenteritis, hepatitis, and hemorrhagic cystitis, associated or not with pneumonia. Pneumonia mortality rates range from 38% to 100%, especially in bone marrow transplant recipients.[27]

The clinical picture is characterized by fever, cough, runny nose, sore throat, tonsillitis, and otitis media, with a mean duration of three to five days. Leukocytosis and elevated inflammatory activity can be observed, and it is important to differentiate from bacterial infections. Pulmonary opacities are often reticulonodular in radiological images, but consolidations can also be observed.[27,28]

Respiratory secretion cultures can be performed to confirm the diagnosis, which can be demonstrated by cytopathic effects two to 20 days after onset. Serotype 14 can be diagnosed by rapid antigen detection and PCR techniques, especially in immunosuppressed patients.[27,28]

There are no controlled studies regarding the best treatment option, or which drug is more adequate for each specific clinical syndrome. Thus, the use of antivirals is based on recommendation from experts and case reports. The drugs that can be used are ribavirin, cidofovir, ganciclovir, and vidarabine, with a larger number of reports favoring the combined therapy with cidofovir/ribavirin, especially in patients with a history of unfavorable evolution and bone marrow transplantation (Table 2).[28]

Human parainfluenza virus

HPIV is a paramyxovirus classified into four subtypes (1, 2, 3, and 4). This virus is the second most common cause of viral infection in children, accounting for approximately 30% to 40% of respiratory infections; it is also identified as a causative agent of pneumonia in adults (mainly HPIV serotypes 1 and 3). Transmission can occur through direct contact with the infected host, by respiratory droplets, or by fomites.[29]

Once installed, the infection causes the secretion of high levels of inflammatory cytokines such as interferon alpha, IL-2, IL-6, and tumor necrosis factor alpha (TNF-alpha). These mediators are responsible for the abundant production of mucus in the respiratory epithelium, submucosal edema, and vocal cords, which can determine the partial obstruction of the upper airway and the characteristic stridor of this disease.[29]

The incubation period lasts one to three days and the characteristic symptoms of croup, such as hoarseness and stridor (steeple sign), common in children, are less prevalent in immunocompetent adults. HPIV-3 is the primary strain causing bronchiolitis and pneumonia, leading to the onset of nonspecific symptoms such as fever, runny nose, wheezing, dry cough, and dyspnea. The symptoms can mimic a number of other respiratory infections, especially in immunosuppressed individuals; the identification of marked upper airway involvement, such as sinusitis and stridor, is an important clue for diagnosis. Reports of bronchiolitis obliterans with organizing pneumonia and giant-cell pneumonia have also been described after infection by this agent.[29]

From the radiological point of view, the alterations often observed are the focal alveolar opacities, although a diffuse interstitial pattern has also been described. A previous study showed that infection may be associated with the presence of multiple noncavitated nodules < 5 mm with peribronchial distribution.[29,30]

Isolation by culture can be carried out preferably in nasal secretions. RT-PCR is the faster and most sensitive diagnostic method.[29,30]

Supportive care is usually enough, and specific therapy should be recommended only for patients at high risk or with severe symptoms. In these cases, the agent of choice, based on *in vitro* study and a case study, is oral or aerosolized ribavirin (Table 2).[31]

Other agents

With the advancement of diagnostic methods and greater access to PCR, other agents such as metapneumovirus, rhinovirus, and coronavirus have been currently recognized as causing community-acquired pneumonia.[32]

The human metapneumovirus is a relatively new virus as a respiratory pathogen, and was initially described in 2001 in the Netherlands. This virus belongs to the same family as RSV and HPIV, is usually acquired in early childhood, and causes bronchiolitis, croup, and pneumonia. Reinfection can occur in adulthood, with the most severe cases affecting the elderly, individuals with heart and lung disease, and immunocompromised patients. The incubation period is approximately five days; the clinical picture is similar to that of other viruses, with nasal congestion, coughing, wheezing, fever, and dyspnea. Hoarseness is the most common finding in RSV infection. Chest images show bilateral alveolar opacities in 43% of cases, and nodular opacities and pleural effusion can also occur. It is a difficult virus to isolate in cultures, with extremely slow replication rates. RT-PCR is the method of choice for the diagnosis.[33] The treatment is yet to be well established, but the use of ribavirin alone or in combination with immunoglobulin appears to be promising in more severe cases.[34]

Coronaviruses have been recognized as causing pneumonia after a serious epidemic in China during 2003. Four human subtypes have been recognized: HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1. The incubation period of coronavirus-associated infection is of two to five days; the most common symptoms are myalgia, chills, and dyspnea, with possible progression to respiratory failure, while fever is uncommon. Other findings that may be observed are thrombocytopenia, elevated levels of transaminases, and D-dimer. The radiological pattern is nonspecific, commonly demonstrating diffuse pulmonary ground-glass opacities on chest tomography. Cases of pneumomediastinum have also been reported.[35,36] In cases of severe outcome, protease inhibitors, such as lopinavir and ritonavir, and interferon-alpha and -beta can be administered. There is no evidence of efficacy for ribavirin use.[37]

The Rhinovirus, a member of the *Picornaviridae* family, is the major cause of colds in the general population, and it is the second most prevalent agent as the cause of bronchiolitis in the pediatric population - in some studies, it has been shown to be the agent more often related to exacerbations in asthmatic children.[38] Although controversial, some studies have shown a prevalence of this virus in up to 30% of cases of severe pneumonia hospitalized in intensive care.[39] The diagnosis is difficult; it is attained through PCR techniques, as other methods (such as serological tests and cultures) are not feasible, and the rapid detection of antigens is not standardized.[40]

Final considerations

As observed in the most recently published studies, viruses have been increasingly considered as the cause of serious respiratory infections or co-infections, even in immunocompetent patients. In this context, it is essential to consider the presence of these pathogens as potential causes of lung disease, and to increase the capacity to identify them. Together with the greater possibility of diagnosing viral infections, it will be feasible not only to increase the knowledge on epidemiological profile of viral community-acquired pneumonia, but also to plan better therapeutic and prevention strategies for society.

Conflict of interest

All authors declare to have no conflict of interest.

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