Review

Review of Non-bacterial Infections in Respiratory Medicine: Viral Pneumonia

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ABSTRACT

Although bacteria are the main pathogens involved in community-acquired pneumonia, a significant number of community-acquired pneumonia are caused by viruses, either directly or as part of a co-infection. The clinical picture of these different pneumonias can be very similar, but viral infection is more common in the pediatric and geriatric populations, leukocytes are not generally elevated, fever is variable, and upper respiratory tract symptoms often occur; procalcitonin levels are not generally affected. For years, the diagnosis of viral pneumonia was based on cell culture and antigen detection, but since the introduction of polymerase chain reaction techniques in the clinical setting, identification of these pathogens has increased and new microorganisms such as human bocavirus have been discovered. In general, influenza virus type A and syncytial respiratory virus are still the main pathogens involved in this entity. However, in recent years, outbreaks of deadly coronavirus and zoonotic influenza virus have demonstrated the need for constant alert in the face of new emerging pathogens. Neuraminidase inhibitors for viral pneumonia have been shown to reduce transmission in cases of exposure and to improve the clinical progress of patients in intensive care; their use in common infections is not recommended. Ribavirin has been used in children with syncytial respiratory virus, and in immunosuppressed subjects. Apart from these drugs, no antiviral has been shown to be effective. Prevention with anti-influenza virus vaccination and with monoclonal antibodies, in the case of syncytial respiratory virus, may reduce the incidence of pneumonia.

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Revisión sobre las infecciones no bacterianas del aparato respiratorio: neumonías víricas

RESUMEN

Aunque las bacterias son los principales patógenos involucrados en la neumonía adquirida en la comunidad, algunos virus son responsables directos o en coinfección de un importante número de neumonías adquiridas en la comunidad. La clínica de estas neumonías puede ser muy similar, en el caso de los virus afectan más frecuentemente a la población infantil y geriátrica, con frecuencia no elevan la cifra de leucocitos, la fiebre es inconstante y frecuentemente acompañan de síntomas de vías respiratorias altas. Característicamente no elevan la procalcitonina. Duras años el diagnóstico ha recaydo en cultivos celulares y en detección de antígenos; desde la incorporación en la clínica de la PCR, la identificación de estos patógenos ha aumentado, descubriéndose nuevos microororganismos como el bocavirus. En general, el virus influenza A y el virus respiratorio sincitial siguen siendo los principales virus implicados. Sin

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Introduction

According to WHO estimates for 2012, around 450 million cases of pneumonia occur worldwide every year, causing 3 million deaths, and accounting for 5.5% of overall mortality worldwide.\(^1\)\(^,\)\(^2\) It is the fourth cause of death worldwide, and is a particularly a serious threat to children and the elderly.\(^1\)\(^,\)\(^3\)

Bacterial infections, being more common, have been more extensively studied. In contrast, research into viral community-acquired pneumonia (CAP), despite its growing epidemiological significance in developing countries and in the pediatric population, has been limited.\(^4\) Assuming the rate of diagnosis to still be lower than real incidence, around 200 million cases of viral pneumonia occur annually throughout the world, half of which are in children.\(^5\) Viral pneumonia is of great interest due to its impact on infant mortality, its role as a facilitator of bacterial infections (co-infections), and its ease of transmission, a factor which has transformed it into a worldwide threat.

In this review, we will focus on CAP caused by respiratory viruses in immunocompetent patients.

Differentiating Between Viral and Bacterial Pneumonia

It is important to distinguish between CAP of viral and bacterial origin. Clinical, radiological and laboratory variables that are commonly used to distinguish between these entities are listed in Table 1.

Epidemiological studies have been published by many authors. Ruiz-González et al.\(^6\) included patients with viral and intracellular bacterial pneumonia in the same group. They concluded that pneumonia caused by intracellular pathogens affected older patients, had a more insidious disease course, and often did not produce leukocytosis. Johnstone et al.\(^7\) found that patients with viral pneumonia had more cardiac comorbidities and were older; Ma et al.\(^8\) found that institutionalization led to a greater risk of viral CAP. Liu et al.\(^9\) reported that viral pneumonia caused more cough and less pleuritic pain, while Jennings et al.\(^10\) found myalgia to be the symptom most commonly associated with the viral disease. Despite the many publications, predicting the viral etiology from clinical parameters is difficult and often inaccurate, as affirmed recently by Virasus et al.\(^11\)

With regard to radiological changes, focal alveolar infiltrates have been traditionally associated with the bacterial entity, and bilateral, interstitial infiltrates with the viral form.\(^2\) However, recent studies using chest computed tomography (CT) have shown that a viral etiology cannot be ruled out by the appearance of localized alveolar infiltrates, and these may even signal the onset of many viral pneumonias.\(^12\)

Viral infections do not usually affect the number of leukocytes, so the use of acute phase reactants, such as procalcitonin, as biomarkers may be of great help in reaching a diagnosis.\(^13\) Procalcitonin production depends on the presence of circulating tumor necrosis factor (TNF-α); in viral infections, macrophages produce interferon-α that can inhibit TNF-α, suppressing the elevation of procalcitonin, thus suggesting a viral origin.\(^14\)

Despite these assertions, there is no gold standard for differentiating the etiology of pneumonia.\(^15\) Moreover, we must not forget that CAP, whether viral or bacterial, is a dynamic entity: differences in biomarker values or the appearance of infiltrates on radiology are only snapshots of an active process that can vary widely from day to day.

Types of Viruses

The list of viruses that can cause respiratory infection is long (Table 2). In this review, we will focus particularly on seasonal respiratory viruses. Other viruses that have recently received considerable media attention, such as H5N1 influenza virus or coronaviruses (responsible for severe acute respiratory syndrome or the Middle East respiratory syndrome, MERS-CoV) will be examined in less depth.

The relative incidence and clinical and epidemiological characteristics of the different respiratory viruses are listed in Table 3.

Overall, syncytial respiratory virus (SRV) remains the primary causative agent of CAP in children, and the main cause of severe pneumonia in this population.\(^16\)\(^,\)\(^17\)\(^,\)\(^18\) Since the widespread introduction of PCR techniques, rhinoviruses are more often detected as the causative agent of viral pneumonia in children.\(^19\)\(^,\)\(^20\) However, because it is so frequently detected in asymptomatic individuals

Table 1 Differential Factors Between Viral Pneumonia and Bacterial Pneumonia.

<table>
<thead>
<tr>
<th>Age</th>
<th>Suggestive of viral origin</th>
<th>Suggestive of bacterial origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger than 5 and older than 65 years</td>
<td>Seasonal or epidemic outbreaks</td>
<td>Adults</td>
</tr>
<tr>
<td>Slow onset</td>
<td>Most frequently rhinitis and wheezing</td>
<td>Throughout the year</td>
</tr>
<tr>
<td>&lt;10×10⁶ c/L</td>
<td>&gt;15×10⁶ c/L and &lt;4×10⁹ c/L</td>
<td>Rapid onset</td>
</tr>
<tr>
<td>&lt;20 mg/L</td>
<td>&gt;60 mg/L</td>
<td>Most frequently high fever and tachypnea</td>
</tr>
<tr>
<td>&lt;0.1 µg/L</td>
<td>&gt;0.5 µg/L (&gt;1 µg/L with greater specificity)</td>
<td>Lobar alveolar infiltrates</td>
</tr>
<tr>
<td>Bilateral, interstitial infiltrates</td>
<td>Slow response or no response</td>
<td>Rapid</td>
</tr>
</tbody>
</table>

Adapted from Ruuskanen et al.\(^1\)
(15%), the etiologic role of rhinovirus continues to be questioned, although it could be an indication of real, subclinical infections.23 Recently identified pathogens, such as metapneumovirus and human bocavirus,24–27 are less commonly encountered. Although the prevalence of viral pneumonia caused by adenovirus is low (2%–12%), it must be identified, as it can lead to necrotizing pneumonia.28 In this case, PCR techniques are much more sensitive than antigen detection techniques.29

In the case of adults, the most commonly detected viruses are influenza virus (IV), SRV and parainfluenza,3,10,30,31 although incidence varies depending on the diagnostic techniques used. These viruses are also the most important in Spain.32 Pneumonia caused by other viruses are more rarely reported and include outbreaks of rhinovirus,33,34 adenovirus35 (particularly serotype 14 in military institutions36), coronavirus,37 metapneumovirus,38 and even bocavirus (in immunocompromised patients).39

**Co-infection**

Infections involving both respiratory bacteria and viruses or 2 different viruses are common. The most widely accepted hypothesis is that the viral infection occurs first, followed by the bacterial form. Viral-mediated activation of proinflammatory molecules, such as interleukin-10, is thought to attract large numbers of neutrophils and macrophages to the lung. The arrival of these cytokines amplifies the immune response, causing inflammatory damage and preventing the proper clearance of bacteria.40 Bacterial superinfection worsens the prognosis of the original viral infection. Indeed, research into the influenza pandemics of 1918, 1957, and 1968 shows that most deaths were caused by a secondary bacterial infection.41 During the 2009 H1N1 pandemic, 4%–24% of cases presented secondary bacterial infection.42–44 In infections caused by other viruses, however, especially H5N1 avian influenza, the associated pneumonia appears to be caused (more frequently) by direct viral action.45

In clinical practice, this type of co-infection is particularly common in children (up to 45% of cases with CAP), and mainly involves pneumococcus,46–49 thus increasing clinical severity.50 *Mycoplasma pneumoniae* and several species of *Chlamydophila*51 are also common,51 while simultaneous co-infection with 2–3 viruses is not unusual.52

CAP of mixed etiology has been characterized less in adults than in children, and prevalence is estimated at less than 5%.7,13 The most common combinations reported are rhinovirus+pneumococcus and influenza A virus+pneumococcus. More serious infections have been identified with the combination of viruses with *Legionella pneumophila.*53

Data on morbidity and mortality in bacterial/viral co-infection are contradictory. Hong et al.54 consider that these co-infections are no more severe than purely bacterial infections, and affect older patients and those with chronic lung diseases. In contrast, Johansson et al.55 and Seki et al.56 found that mixed etiologic pneumonia was associated with higher severity scale scores and poorer progress.

**Respiratory Virus Outbreaks: Experience with H1N1 Influenza Virus in 2009, Avian Influenza (H5N1 and H7N9), SARS and Middle East Coronavirus (MERS-CoV)**

Some very well-known families of respiratory viruses have produced new species and some very virulent serotypes, which in recent years have caused epidemics with significant associated morbidity and mortality.57

The great H1N1 IV-A epidemic of 2009 was unusual: transmission was enhanced by the lack of prior immunity, causing a serious medical situation worldwide.52 Studies performed subsequently showed that the younger population and certain risk groups were more affected, resulting in the loss of many more life-years.58 However, from an inter-generational perspective, the burden of death and major complications was no higher than that caused by normal seasonal influenza.59,60

In 2003, an outbreak of coronavirus in the Far East caused a severe acute respiratory syndrome. In the Middle East in 2012, another outbreak of a new coronavirus occurred, called Middle East respiratory syndrome coronavirus (MERS-CoV).61 In both epidemics, the incidence was reduced to a few hundred cases, partly due to the protective measures implemented62 but mortality was high due to high virulence.63 Clinical symptoms were not only limited to rapidly developing bilateral pneumonia, but also included acute renal failure and severe hematological disturbances.55,64

Recombinations in animals of different IV subtypes are a global concern, as they are potentially capable of passing the species barrier, and occasionally propagating among humans.65 The serious cases of H5N1 avian influenza recorded in 2005 in Southeast Asia,66 or more recently the H3N2-porcine variant in the United States (2012),67 and H7N9 avian influenza in China (2013),68 are examples of this new threat. Fortunately, surveillance systems for monitoring animal reserves and activating a rapid medical response are improving.69

**Microbiological Diagnosis**

The detection of virus or viral antigens in upper (nasopharyngeal aspirates) and lower (bronchoalveolar lavage and induced sputum) respiratory tract samples is usually based on culture and immunofluorescence microscopy. The detection of antibodies generated during the process of viral infection has also been used for years: seroconversion in 2 samples obtained over a period of time is suggestive of a new exposure to the pathogen. The introduction of polymerase chain reaction (PCR) techniques has improved the detection of respiratory viruses, particularly with the use of real-time techniques.7

The preferred specimen for upper respiratory samples, particularly in children, is nasopharyngeal aspirate, which combines a mixture of nasal and retropharyngeal secretions.70 The use of sterile cotton wool swabs yields a similar sensitivity for most viruses, with the exception of SRV.71,72 Devices that combine a nylon fiber swab and a container of universal transport medium provide a high diagnostic yield at all ages, comparable to nasopharyngeal lavage.70,73

Samples from the lower respiratory tract, being obtained at the site of the infection, have obvious advantages when determining the cause of pneumonia. However, contamination may occur during

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccines Related to Community-Acquired viral Pneumonia in Children and Adults.</strong></td>
</tr>
<tr>
<td>Syncytial respiratory virus</td>
</tr>
<tr>
<td>Rhinovirus</td>
</tr>
<tr>
<td>Influenza A, B and C virus</td>
</tr>
<tr>
<td>Human metapneumovirus</td>
</tr>
<tr>
<td>Parainfluenza virus type 1, 2, 3 and 4</td>
</tr>
<tr>
<td>Human bocavirus</td>
</tr>
<tr>
<td>Coronavirus type 229E, OC43, NL63, HKU1, SARS and MERS-CoV</td>
</tr>
<tr>
<td>Adenovirus</td>
</tr>
<tr>
<td>Enterovirus</td>
</tr>
<tr>
<td>Varicella zoster virus, Epstein–Barr virus, human herpesvirus 6 and 7, cytomegalovirus</td>
</tr>
<tr>
<td>Hantavirus</td>
</tr>
<tr>
<td>Parechovirus</td>
</tr>
<tr>
<td>Mimivirus</td>
</tr>
<tr>
<td>Measles virus</td>
</tr>
</tbody>
</table>

Adapted from Ruuskkanen et al.1
<table>
<thead>
<tr>
<th>Virus</th>
<th>Family</th>
<th>Subtype</th>
<th>Incidence of CAP</th>
<th>Risk factors</th>
<th>Seasonality</th>
<th>Differential clinical factors</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>Picornaviridae</td>
<td>–</td>
<td>≈18%</td>
<td>All ages, but more in children</td>
<td>All year (more in autumn)</td>
<td>Upper airway symptoms; rhinorrhea, cough and nasal congestion</td>
<td>Pleconaril (compassionate use)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≈6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncytial respiratory virus</td>
<td>Paramyxoviridae</td>
<td>1 and 2</td>
<td>≈11%</td>
<td>Newborn and premature babies. Immunosuppression</td>
<td>End of autumn, beginning of Winter</td>
<td>Marked bronchial reactivity</td>
<td>Inhaled ribavirin (children), IV ribavirin (immunosuppression)</td>
</tr>
<tr>
<td>(SRV)</td>
<td></td>
<td></td>
<td>≈3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza virus (IV)</td>
<td>Orthomyxovirida</td>
<td>A and B seasonal</td>
<td>≈10%</td>
<td>Children and geriatrics</td>
<td>End of autumn and winter</td>
<td>General asthenia, Influenza-like syndrome</td>
<td>NAI (OSE-resistant Amantadines (not in B) NAI (ZAN and PER in critical patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≈8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>H1N1 09 pandemic</td>
<td>–</td>
<td>&lt;65 years</td>
<td>Specific outbreaks in waves</td>
<td>More pneumonias, ICU and mortality</td>
<td>High does NAI Amantadines not beneficial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H5N1</td>
<td>–</td>
<td>Contact with birds</td>
<td>Thrombocytopenia and kidney failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parainfluenza virus (PIV)</td>
<td>Paramyxoviridae</td>
<td>1, 2, 3 and 4</td>
<td>≈8%</td>
<td>Geriatric care homes</td>
<td>Laryngeal croup (children with PIV-1)</td>
<td></td>
<td>Ribavirin iv (immunosuppression)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≈2%</td>
<td></td>
<td>Wheezing. Asthma exacerbations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metapneumovirus</td>
<td>Paramyxoviridae</td>
<td>–</td>
<td>≈8%</td>
<td>Children&lt;5 years</td>
<td>End of Winter and Spring</td>
<td></td>
<td>Ribavirin iv (immunosuppression)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≈1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronavirus</td>
<td>Coronaviridae</td>
<td>229E, NL63, OC43,</td>
<td>≈7%</td>
<td>Geriatric care homes</td>
<td>Winter</td>
<td>Diarrhea (OC43, and intermittant)</td>
<td>No proven treatment. Chloroquine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KU1</td>
<td>≈5%</td>
<td></td>
<td></td>
<td></td>
<td>No specific treatment. Corticosteroids used</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SARS</td>
<td>–</td>
<td>Bats and civets in Asia. Healthcare personnel</td>
<td>Outbreaks throughout the year</td>
<td>Prodrome with fever and myalgia followed by a respiratory distress</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Adenoviridae</td>
<td>7, 14, 16</td>
<td>≈3%</td>
<td>Prisons (outbreaks)</td>
<td>All year</td>
<td>Conjunctivitis, diarrhea, encephalitis</td>
<td>Cidofovir (proven in immunosuppression)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≈2%</td>
<td>Pneumococcus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bocavirus</td>
<td>Parvoviridae</td>
<td>–</td>
<td>≈5%</td>
<td>Children&lt;2 years</td>
<td>End of autumn, beginning of winter</td>
<td></td>
<td>No specific treatment. Cidofovir used</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;1%</td>
<td>Poorly defined</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI: body mass index; COPD: chronic obstructive pulmonary disease; IV: intravenous; NAI: neuraminidase inhibitors (OSE: oseltamivir; PER: peramivir; ZAN: zanamivir).
These agents include oseltamivir (Tamiflu) and zanamivir (Relenza), which are non-nucleoside neuraminidase inhibitors. Oseltamivir is typically administered orally, while zanamivir is given via inhalation.

Another option is ribavirin, a nucleoside analog that inhibits viral replication. It is commonly used in the treatment of respiratory syncytial virus (RSV) and influenza. Ribavirin can be administered intravenously or inhaled as a aerosol. However, its use is associated with a high rate of side effects, including fever, chills, and gastrointestinal disturbances.

Chemokine receptor 1 antagonists, such as maraviroc, have also been explored as potential antivirals. Maraviroc blocks the attachment of HIV to CD4+ T cells, thereby preventing viral entry.

In summary, the treatment of influenza involves a combination of antiviral drugs and supportive care. Early administration of antiviral medications is crucial for reducing the severity of disease and preventing complications. However, the use of these agents comes with potential risks and side effects, and their efficacy can vary depending on the strain of the virus and the stage of infection.
In addition to vaccines, chemoprophylaxis with neuroaminidase inhibitors has been successfully tested during seasonal influenza epidemics. As yet, no effective vaccine is available for SRV, but palivizumab has been used as chemoprophylaxis. This is a humanized monoclonal antibody that has shown a reduction of up to 50% in the incidence of pneumonia and associated hospital admissions in neonates with a high risk of infection.

**Conflict of Interests**

The authors declare that they have no conflict of interests.

**References**


