



UPDATE IN INTENSIVE CARE MEDICINE: CRITICAL PATIENT WITH SERIOUS INFECTION

Acute viral infections in immunocompetent patients

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Abstract Viruses play a significant role in serious infections in adults and sometimes lead to the need for hospitalization and admission to intensive care units, especially in cases of severe respiratory distress or encephalopathy. Influenza and parainfluenza viruses, syncytial respiratory virus, herpes viruses and adenoviruses are the most frequent causes of these severe infections. A review of the literature has been performed in order to update the epidemiology, pathogenesis and therapeutic approach of viral infections affecting immunocompetent patients. Furthermore, ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection in intensive care units and has a high morbidity and mortality rate. It is mainly a bacterial disease, although the potential role of viruses as pathogens or copathogens in VAP is under discussion. Therefore, a brief review of the potential pathogenic role of viruses in VAP has also been performed.

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PALABRAS CLAVE

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Infecciones virales graves en pacientes inmunocompetentes

Resumen Los virus tienen un papel importante dentro de las infecciones graves en los pacientes adultos, que en algunas ocasiones llegan a necesitar hospitalización e ingreso en unidades de cuidados intensivos, especialmente en casos de síndrome de distrés respiratorio del adulto y encefalitis. Las infecciones por virus influenza y parainfluenza, virus sincitial respiratorio, herpes virus y adenovirus son las que más frecuentemente causan estos cuadros. Se ha realizado una revisión de la literatura pormenorizada y actualizada de epidemiología, patogénesis, manifestaciones clínicas y aproximación terapéutica de las infecciones virales en pacientes inmunocompetentes. Por otro lado, si bien la neumonía asociada a ventilación mecánica tiene como

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etiología más frecuente las infecciones bacterianas, recientemente el papel de los virus como patógenos en estas infecciones está en debate, por lo que se hace una breve revisión de su papel etiopatogénico en la neumonía asociada a ventilación mecánica.

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Serious community-acquired viral infections

Introduction

Septic processes remain one of the main causes of morbidity-mortality in ICUs throughout the world. In this context, viral infections cause many community-acquired infections in the general population and are also of great relevance in critical patients -particularly serious respiratory viral infections.¹

Among the causes of serious community-acquired pneumonia requiring hospital admission, viruses account for 15-40% of all cases in which the underlying etiology is known.²

Types of virus

Viruses that invade through the airway can be grouped as follows:

1. Upper airway infections. Clinical conditions found in immune deficient and in some cases also immunocompetent critical patients:
 - Viruses that limit their action to the epithelial surface: common cold viruses (human rhinoviruses, Coxsackie A and echoviruses) and mild cases of influenza and parainfluenza. Mild clinical picture with a generally favorable course.
 - Viruses that invade the epithelium and spread to other parts of the body: viruses producing measles, mumps, rubella, herpes viruses (herpes simplex virus [HSV], varicella zoster virus [VZV], Epstein-Barr virus [EBV] and some cases of cytomegalovirus [CMV]).
2. Lower airway infections and pneumonias. A description is provided below of the main acute viral entities causing the most common serious respiratory disorders in immunocompetent adults, and which can be encompassed under the term "febrile respiratory illnesses (FRIs).³ The causal viruses (Table 1) are grouped into two main categories: myxoviruses (including the different types associated with influenza A, B and C) and adenoviruses (involving 23 different types, of which 18 have been isolated in humans). Another parallel category corresponds to the parainfluenza viruses, of which a number of types are known. No description will be given here of the pneumonic conditions caused by HSV, VZV, EBV and CMV, as these have been described in the review corresponding to immune deficient patients.

Influenza

The seasonal flu virus, the influenza virus,⁴ is an RNA virus with three known subtypes (A, B and C), belonging to the

family Orthomyxoviridae, and which shows great genetic variability and capacity to cause epidemics and pandemics. It clinically manifests as self-limiting upper airway disease with a sudden onset, fever, chills, malaise, headache, muscle pain and non-productive cough that lasts for 3 or 4 days. There may be complications of different types, including particularly pneumonias and secondary bacterial infections, fundamentally in individuals with chronic respiratory disease and in patients over 65 years of age. The respiratory secretions of patients with influenza represent the main source of contagion, being eliminated by coughing or sneezing. The virus is transmitted via the aerial route during the symptomatic period of the disease. The virulence and antigenicity of the virus, the immune condition of the host, and the environment all interact, conditioning person-to-person transmission of the disease. Type A influenza virus exhibits greater virulence as a result of its frequent antigenic variations. The diagnosis is generally based on the clinical manifestations, though complementary techniques can be of help, such as antigen determination tests, nucleic acid tests, polymerase chain reaction (PCR) amplification or viral cultures. The drug treatment options include neuraminidase inhibitors (oseltamivir and zanamivir), which are preferred to amantadine and rimantadine, due to the important existence of resistances to the latter. The role of the latest H1N1 virus pandemic will not be examined in this review, since we feel that its complexity and characteristics require an exhaustive description such as that being carried out by the study group created to the effect by our Society (SEMICYUC).

Respiratory syncytial virus (RSV) and parainfluenza virus

Parainfluenza virus and RSV⁵ share structural similarities (RNA viruses), belong to the same family (Paramyxoviridae), and also share features relating to their epidemiology, pathogenesis and clinical manifestations. Both cause serious disease, particularly in elderly patients or individuals belonging to risk groups for serious respiratory infection (e.g., chronic obstructive pulmonary disease [COPD], cystic fibrosis, lung transplants), where cases of bronchiolitis and pneumonia have been described, with infrequent progression to adult respiratory distress syndrome (ARDS). Clinical manifestations similar to those associated with the influenza virus are seen, with the frequent appearance of bronchospasm and bronchiolitis. The diagnosis is based on the clinical manifestations, antigenic detection tests, viral isolation and the use of PCR. Treatment in turn consists of supportive measures, the administration of bronchodilators and corticosteroids, and the use of nebulized ribavirin in high risk patients. The mortality rate is close to 10% in elderly individuals. Transmission takes place via fomites or infected secretions.

Table 1 Principal characteristics of febrile respiratory illnesses

| | Influenza | RSV | SARS-CoV | Adenovirus | Hantavirus |
|----------------------------------|---|--|---|---|---|
| Epidemiology | Any age interval. More serious manifestations in risk groups | Old age, seasonal (winter) | Old age and risk groups | Healthy population, more prevalent in institutions | Contact with infected or dead mice |
| Clinical picture | Self-limiting influenza-like manifestations. Complications: pneumonia, myocarditis, encephalitis, COPD exacerbation | Bronchiolitis with bronchospasm and pneumonia | Biphasic: initial prodrome, with severe hypoxemia, respiratory failure and ARDS in 7-8 days | Pneumonia with ARDS and extrapulmonary manifestations | Hemorrhagic fever with renal failure syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS) |
| Diagnosis | Clinical, antigen detection, PCR and viral isolation | Clinical, antigen detection, PCR and viral isolation | PCR, IF, cultures, ELISA | PCR, antigen detection and viral cultures | Serology (early IgM, late IgG) |
| Treatment | Supportive, neuraminidase inhibitors | Supportive, corticosteroids and bronchodilators. Nebulized ribavirin | Supportive, corticosteroids | Supportive | Supportive and ribavirin in HFRS |
| Transmission | Via droplets and contact (scant role of aerial route) | Fomites or infected secretions | Droplets, aerial route and contact | Droplets and contact | Urine or excrements of infected mice |
| Isolation | Not required | From contact | Aerial | From contact | Not required |
| Mortality | < 1% | Close to 10% | About 11% | | About 20% |
| Reporting to preventive medicine | No | No | Yes | No | Yes |

Coronavirus-SARS (SARS-CoV)

Severe acute respiratory syndrome (SARS) is caused by a recently manifesting RNA virus, coronavirus⁶ (Coronaviridae), first described after an epidemic outbreak in 2003. The disease exhibits a biphasic clinical course with prodromic manifestations (fever, chills, muscle pain, nausea, headache) that progress within about 7-8 days to respiratory alterations with severe hypoxemia (in 45% of the cases), respiratory failure and ARDS (in 20%). The diagnosis is established by PCR and immunofluorescence, though viral cultures and ELISA can also be used. Treatment is fundamentally supportive, and in some cases corticosteroids can prove useful (following the development of ARDS). The reported mortality rate is about 11%, and is greater in patients over 65 years of age. Transmission is via droplets, the aerial route and contact.

Other respiratory viruses

Adenoviruses⁷ have been seen to cause lower airway disease in healthy military recruits. In rare cases pneumonia with progression towards ARDS can be observed, along with extrapulmonary symptoms (gastritis, hepatitis, meningitis, hemorrhagic cystitis). The diagnosis is established by PCR and viral cultures. Treatment comprises supportive measures; cidofovir and ganciclovir appear to have activity *in vitro*. Transmission of the disease is via droplets and contact.

Hantavirus³ in turn produces two different clinical

conditions: hemorrhagic fever with renal failure syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS). The clinical picture is characterized by prodromic manifestations (fever, chills, muscle pain, abdominal pain) and rapid progression towards respiratory failure, ARDS, coagulopathy and shock. The diagnosis is based on serological tests. Treatment comprises supportive measures and the administration of ribavirin in HFRS (not effective in HCPS). Transmission is through contact with the urine or excrements of infected mice.

Other serious viral clinical conditions

1. Hemorrhagic fever conditions: Most of the diseases associated with hemorrhagic exanthema are caused by arboviruses (belonging to the families Alphaviridae and Flaviviridae). Of special mention in this group are the viruses that cause yellow fever (a biphasic condition characterized by an onset with fever, remission and reappearance with systemic bleeding, liver failure, gastrointestinal disorders and exanthemas - being endemic to equatorial Africa, equatorial America, and areas of the Caribbean and Asia) and dengue (the most important insect transmitted disease in humans, with acute manifestations involving fever, headache, nausea and vomiting, maculopapular exanthema, muscle pain and joint pain), and the Ebola and Marburg viruses (both

of which are equally dangerous, though while Marburg⁸ has only infected a few people, the Ebola virus causes sporadic human epidemics in sub-Saharan Africa, spreading through contact with body fluids and infecting the endothelial cells - no treatment or vaccine being available to date).

2. Infections of the central nervous system: Viruses that penetrate the central nervous system can cause meningitis (known as "aseptic meningitis"), as in mumps, and in infections caused by echoviruses and Coxsackie; or encephalitis, as in infections caused by herpes simplex virus (responsible for 10% of all cases of viral encephalitis as a result of reactivation or secondary infection - early diagnosis being crucial, with intravenous acyclovir therapy, since the mortality rate is high if the disease is not adequately treated); rabies (a disease usually spread by bites from an infected animal, with an incubation period of between 5 days and 2 years, and difficult diagnosis in the early stages - rapid treatment being very important, with cleaning of the wound, vaccination and antibodies against the virus); and St. Louis encephalitis virus (the main cause of viral encephalitis in the United States; birds are the principal reservoir, and the vectors are insects - the clinical picture being characterized by initial fever with nausea and headache that evolve towards neck stiffness, vertigo, ataxia, mental confusion and disorientation). West Nile virus in turn produces a condition very similar to this latter disease.
3. Gastrointestinal infections: A number of groups of viruses infect the digestive tract. Some in turn spread to other parts of the body, such as the enteroviruses (poliovirus, Coxsackie and echoviruses), while others are confined to the digestive tube and cause diarrhea (particularly rotaviruses and Norwalk virus, in adult individuals).

Diagnosis, treatment and non-pharmacological management

Recent advances in virological diagnosis have resulted in substantial improvements in viral culture yield and rapidity (shell-vial assays), increased sensitivity and specificity of viral antigen detection techniques, an expansion of the available serological techniques, and particularly advances in the methods based on nucleic acid amplification procedures such as polymerase chain reaction (PCR). The most widely used diagnostic techniques⁹ in the main clinical conditions are reported in Table 2.

The currently available antiviral agents (Table 3) belong to two groups, according to their mechanism of action. On one hand, amantadine and rimantadine act upon protein M2 of the influenza A virus, inhibiting its capacity to lower the endosomal pH - this being essential in order to destroy the viral envelope and release the nucleocapsid. Amantadine is effective against influenza A virus, but not against influenza B virus (the latter lacks protein M2, and instead has a substituting protein called NB that is not affected by amantadine). On the other hand, oseltamivir (Tamiflu[®]) and zanamivir (Relenza[®]) block the active site of neuraminidase, thus preventing the spread of the virus. These drugs have demonstrated activity against the influenza A and B viruses.

Among the supportive measures common to the treatment

of many of these diseases (Table 1), mention must be made of appropriate oxygen therapy, corticosteroids and aerosol therapy (bronchodilators, corticosteroids or ribavirin). The non-pharmacological management³ of critical patients with serious febrile respiratory illness varies according to the implicated infectious agent (suspected or confirmed) and the severity of the respiratory condition - though most cases present clinical similarities allowing us to establish a certain management pattern. Thus, in all cases intensive supportive measures are necessary (fluids, amines, renal replacement therapy), such as those used in septic shock of other origins. These patients usually suffer serious lung injuries, thus leading to the need for mechanical ventilation. In cases where ARDS has developed, protective strategies must be applied to mechanical ventilation (low tidal volume [6 ml/kg], high PEEP values to reduce atelectatic areas). The more milder cases sometimes respond favorably to early noninvasive ventilation (NIV), though there is controversy over the use of this technique in such patients.

Serious nosocomial infections produced by viruses; ventilator-associated pneumonia (VAP)

Introduction

Although the etiology of ventilator-associated pneumonia (VAP) has always been classified as bacterial, that fact is that at present episodes are recorded in which the etiology has not been defined. Particularly following the introduction of highly sensitive techniques for the detection of viruses in the respiratory tract, studies have been published in the last decade pointing to a possible role of viruses in the pathogenesis of these important infections that are especially prevalent in ICUs. Although to date no regular diagnostic standard has been established, none of these publications have established a causal relationship between isolation and the infectious episode; moreover, there is no evidence from studies or clinical trials on the role of antiviral agents in these purportedly viral processes.

Epidemiology

A French prospective study¹⁰ conducted in a university hospital included all patients ventilated for more than 48 hours during a period of 9 months (n = 139). Tracheal aspirates were studied to detect the presence of viruses using different techniques, including PCR. The isolated viruses were rhinovirus, herpes simplex, influenza, respiratory syncytial, enterovirus, parainfluenza, adenovirus, coronavirus and CMV, detected in 25% of the patients. No cases of attributable viral pneumonia were identified in the VAP episodes, though it must be mentioned that herpes simplex virus type I (HSV1) was isolated in 31% of the VAP episodes. Therefore, HSV1 appears as the most likely implicated viral agent, as also suggested by a recent national series¹¹ and by several international studies published in the last decade.¹²⁻¹⁶ The reported frequency varies between 5-64%, with a median of 15-20%.

Although reactivation and CMV disease classically have

Table 2 Viral diagnostic methods

| | Time to results | Advantages | Disadvantages |
|------------------------------------|-----------------|---|--|
| <i>Detection of viral antigens</i> | | | |
| Rapid antigenic tests | < 30 min | Rapid, easy, minimum experience required | Does not distinguish subtypes of influenza |
| Immunofluorescence | 1-4 hours | Rapid and versatile. High sensitivity | Requires experience |
| <i>Detection of nucleic acids</i> | | | |
| Nucleic acid testing (NAT) | 4-24 hours | Very sensitive, detects other pathogens | Requires experience. Limited standardization |
| <i>Viral isolation</i> | | | |
| Viral cultures | 3-14 days | Very sensitive, detects other respiratory viruses and resistances | Requires experience. Slow results |
| Shell-vial | 18-48 hours | Faster than conventional culture. Detects other respiratory viruses | Use limited to safety level 3 laboratories |
| <i>Determination of antibodies</i> | | | |
| Viral neutralization tests | Several weeks | Very sensitive and specific | Slow results, laborious. Requires standardization controls |
| Hemagglutination inhibition tests | Several weeks | Simpler than neutralization. Similar sensitivity | Slow results, laborious |
| Complement fixation test | Several weeks | Measures seroconversion | Requires long time period |
| Enzyme immunoanalysis (EIA) | Several weeks | Greater efficacy in relation to time employed | Requires paired negative controls |

been linked to patients with cellular immune alterations,¹⁷ in the last decade reactivation also has been reported in immunocompetent critical patients.¹⁸⁻²¹ The incidence is variable, depending on the diagnostic method used (culture or PCR), and ranges from 12-33%.¹⁸

In a recent study,²² 19% of the ventilated patients with suspected VAP yielded positive serological tests for *Acanthamoeba polyphaga* (though 64% of the episodes showed positivity in the BAL bacterial culture) - a mimivirus that had been previously associated to episodes of community-acquired and nosocomial pneumonia.²³

Pathogenesis and risk factors

The reactivation of a latent virus appears to be the initial mechanism in all patients with HSVI-caused pneumonia in the ICU. The existence of prior positive serological tests

with the preceding presence of mucocutaneous lesions and/or a positive pharyngeal smear in most episodes, confirms this point.^{12,16} Reactivation caused by instrumentation or trauma of the airway can occur in the oropharyngeal mucosa and upper respiratory tract, with posterior microaspiration towards more distal zones, or directly in the bronchial mucosa itself.²⁴ Reactivation starts between the third and fifth day of mechanical ventilation, reaching a peak in viral load after exponential expansion by day 12 (up to 10⁸ copies/ml),²⁴ followed by a slow decline. Viral load has been correlated to the diagnosis of viral bronchopneumonitis.

The most frequent risk factors^{12-16,25} for HSVI infections of the lower respiratory tract have been the presence of mucocutaneous herpetic lesions, a positive pharyngeal smear, tracheal mucosal lesions, thrombocytopenia, high SOFA and/or APACHE II scores, mechanical ventilation for over 7 days, old age, the use of corticosteroids during

Table 3 Antiviral agents

| | Administration route | Adult dosage | Adjustment in RF | Adjustment in LF |
|-------------|----------------------|---------------------|----------------------|----------------------|
| Amantadine | Oral | 100 mg/12 h, 5 days | 100 mg/48 h | No adjustment needed |
| Rimantadine | Oral | 100 mg/12 h, 5 days | 100 mg/24 h | No adjustment needed |
| Oseltamivir | Oral | 75 mg/12 h, 5 days | 75 mg/24 h | No adjustment needed |
| Zanamivir | Inhaled | 10 mg/12 h, 5 days | No adjustment needed | 100 mg/day |
| Ribavirin | Inhaled | 1 g/24 h | 600-800 mg/12 h | No adjustment needed |

LF: liver failure; RF: renal failure (creatinine clearance < 30 ml/min).

Table 4 Principal characteristics of ventilator-associated pneumonias of viral origin

| Etiology | Incidence, % | Risk factors | Mortality, % | Clinical consequences |
|-----------|--------------|--|--------------|---|
| HSV | 5-64 | Herpetic skin and mucosal lesions, positive pharyngeal smear, tracheal mucosal lesions, thrombocytopenia, high SOFA and/or APACHE II scores, mechanical ventilation > 7 days, old age, use of corticosteroids and HSV type I IgG positivity upon admission | 26-57 | Longer time on mechanical ventilation and longer hospital stay, though no study has demonstrated an increase in mortality |
| CMV | 15-30 | Hemotransfusion, prior admission to hospitalization wards, age and previous corticosteroid use | 54 | Longer stay, more days on mechanical ventilation, and more nosocomial infections. Independent mortality factor |
| Mimivirus | 19,4 | Duration of mechanical ventilation prior to bronchoalveolar lavage (BAL), no detection of other viruses, and absence of enteral nutrition | 50 | Longer time on mechanical ventilation and longer hospital stay, though without an increase in mortality |

CMV: cytomegalovirus; HSV: herpes simplex virus; VAP: ventilator-associated pneumonia.

admission to the ICU, and HSVI IgG positivity upon admission.

As has been mentioned, the reactivation of CMV is frequent in the critical patient, and occurs between days 14 and 21 of stay in the ICU.¹⁸⁻²¹ Reactivation may begin in the lung parenchyma²⁵ activated by sepsis, as has been demonstrated in animal models involving latent CMV infection, and can cause a persistent increase in cytokine-mediated inflammatory response.²⁶

The risk factors described for active CMV infection in immunocompetent patients subjected to mechanical ventilation are blood transfusion, previous hospitalization, age and prior corticosteroid use.²⁰

In the only clinical study published on mimivirus and VAP, the risk factors associated to positive serology testing for this virus were the duration of mechanical ventilation prior to bronchoalveolar lavage, the detection of no other viruses, and the absence of enteral nutrition.²²

Clinical conditions according to etiology

The role of HSV as a cause of lower respiratory tract infection remains to be defined, and isolation of the virus may correspond to contamination from the upper respiratory tract, mucosal viral excretion or bronchopneumonitis, since over half of the cases of purported viral VAP show coexisting bacterial isolation^{12,24}; accordingly, isolation may simply be a severity marker or may reflect the existence of a pathogen in its own right.²⁷

A number of studies have attempted to document the true incidence of VAP caused by CMV.^{20,25,28} A total of 29.4% out of 85 patients diagnosed with ARDS with suspected VAP and with negative culture results had histopathological findings compatible with CMV pneumonia²⁵ in a study published in 1996. Eleven years later, these same authors, based on *in vivo* biopsies in a population of 100 patients, demonstrated a high incidence of CMV pneumonia (30%)

and a low diagnostic yield for both PCR and BAL sample culture (sensitivity 53% and specificity 92%).²⁸ In a recent study, the incidence of active CMV disease was found to be high in a series of 242 immunocompetent patients subjected to ventilation for over 48 hours (16.1%).²⁰ In view of the above, CMV should be suspected as the cause of VAP in the presence of persistent infiltrates, a lack of clinical improvement and negative bacterial cultures - using PCR to evaluate the possibility of CMV reactivation. Antiviral therapy should be started, and where necessary, confirmation of the diagnosis may be established by lung biopsy.

Prognostic implications and treatment

Patients infected with HSV require longer mechanical ventilation and hospital stay, though no studies have been able to demonstrate an increase in mortality.^{12,13,16,24} No data from adequate studies are available to allow the recommendation of antiviral treatment in cases of HSV infection, though clinical trials are clearly needed given the growing incidence of these infections and their association to longer stays and mechanical ventilation, since patient benefits could be derived as a result.

In a previously cited study evaluating the incidence, risk factors and prognosis of patients with active CMV disease,²⁰ the latter was seen to be associated to longer stays, more days on mechanical ventilation, and an increase in the number of nosocomial infections compared with patients without active CMV disease. Mortality both in the ICU (54% versus 37%; $p = 0.082$) and in hospital (59% versus 41%; $p = 0.058$) was higher in the CMV disease group, with an important tendency towards statistical significance. In the multivariate analysis, active disease was found to be independently associated to mortality in the ICU, along with the APACHE II score.

Table 4 summarizes the main characteristics of VAP of

possible viral origin.

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