



Characteristics of viral pneumonia in the COVID-19 era: an update

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Abstract

Influenza virus, rhinovirus, and adenovirus frequently cause viral pneumonia, an important cause of morbidity and mortality especially in the extreme ages of life. During the last two decades, three outbreaks of coronavirus-associated pneumonia, namely Severe Acute Respiratory Syndrome, Middle-East Respiratory Syndrome, and the ongoing Coronavirus Infectious Disease—2019 (COVID-19) were reported. The rate of diagnosis of viral pneumonia is increasingly approaching 60% among children identified as having community-acquired pneumonia (CAP). Clinical presentation ranges from mild to severe pneumonitis complicated by respiratory failure in severe cases. The most vulnerable patients, the elderly and those living with cancer, report a relevant mortality rate. No clinical characteristics can be useful to conclusively distinguish the different etiology of viral pneumonia. However, accessory symptoms, such as anosmia or ageusia together with respiratory symptoms suggest COVID-19. An etiologic-based treatment of viral pneumonia is possible in a small percentage of cases only. Neuraminidase inhibitors have been proven to reduce the need for ventilatory support and mortality rate while only a few data support the large-scale use of other antivirals. A low-middle dose of dexamethasone and heparin seems to be effective in COVID-19 patients, but data regarding their possible efficacy in viral pneumonia caused by other viruses are conflicting. In conclusion, viral pneumonia is a relevant cause of CAP, whose interest is increasing due to the current COVID-19 outbreak. To set up a therapeutic approach is difficult because of the low number of active molecules and the conflicting data bearing supportive treatments such as steroids.

Keywords Viral pneumonia · SARS-CoV-2 · Remdesivir · Neuraminidase inhibitor · Steroids · Heparin

Background

Viral pneumonia is a complex disease because the diagnosis can be difficult and frequently based on the exclusion of bacterial etiology, and its treatment can be ineffective due to the low number of molecules active against viruses commonly involved [1].

In recent times, the availability of PCR-based Multiplex tests, which enable the simultaneous identification of

a wide number of viruses, is contributing to the increase of the number of viral pneumonia diagnosis, improving the awareness of viruses as causative agents for respiratory mild and severe infections [2, 3]. As a general concept, viruses belonging to adenovirus, meta-pneumovirus, para-influenza virus, respiratory syncytial virus (RSV), and influenza A and B viruses families cause the majority of cases of viral pneumonia, which generally report mild symptoms and low mortality. Instead, Herpes Virus (HSV), Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) are responsible for severe and life-threatening cases among immunocompromised patients [4].

Coronaviruses have been commonly identified as the etiologic agents of the ‘Common cold’ (HCoV 229E and OC43), but during the last decades they have been associated with 3 novel severe diseases, all caused by a zoonotic spillover namely Severe Acute Respiratory Syndrome (SARS), Middle-East Respiratory Syndrome (MERS), and the ongoing coronavirus infectious disease—19 (COVID-19) outbreak [5, 6].

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Treatment of severe viral pneumonia is mostly supportive. Antiviral medications, such as acyclovir, ribavirin, palivizumab, oseltamivir, zanamivir, amantadine and rimantadine, are available and effective in selected cases only [7]. Polyclonal intravenous immunoglobulin-based immunotherapy has been used, but current data do not allow their large-scale employment [8]. Management of patients requiring intensive care unit (ICU) admission for severe viral pneumonia is based on mechanical ventilation using lower tidal volumes and correction of septic shock, besides appropriate antiviral treatment, when feasible.

Here, we aim to summarize the current knowledge on epidemiology, etiology and treatment of viral pneumonia by means of a narrative review, highlighting similarities and differences between those caused by SARS-CoV-2 and those caused by previously known viral agents.

Epidemiology

Viral pneumonia is predominant among very young children (< 5 years) and adults aging > 50 years. The most common isolates in adults are adenoviruses, coronaviruses, human metapneumovirus, human rhinoviruses, influenza viruses, parainfluenza viruses and respiratory syncytial virus, but an exact picture of epidemiologic findings is difficult to establish due to not optimal surveillance systems in all countries, a high rate of coinfections, and the lack of a precise definition of viral pneumonia [9].

Large studies suggest that the etiology of pneumonia is more frequently viral than bacterial. The “EPIC” (Etiology of Pneumonia in the Community) study, a prospective multicenter study based on the analysis of a large population in the United States, demonstrated that the prevalence and the incidence of pneumonia vary by age. Among 2222 children included in the study a pathogen was detected in 1802 (81%) children; 66% of them (1472 in total) reported a viral infection; otherwise, bacteria were found in 175 (8%) cases and viral and bacterial coinfection was found in 155 cases (7%). The most common viruses were RSV (28%), human rhinoviruses (27%), human metapneumovirus (13%), adenoviruses (11%), parainfluenza 1 to 3 viruses (7%), influenza A and B viruses (7%) and coronaviruses (5%); indeed, RSV, adenoviruses and human metapneumovirus were commonly detected in children younger than 5 years old. Among 2259 adults enrolled in the same study, a pathogen was detected in 853 (38%) patients only; 530 (23%) had viral pneumonia, while bacterial pneumonia was diagnosed in 247 (11%); coinfections were found in 59 cases (3%), and fungal as well as a mycobacterial pathogen in 17 (1%) cases. The most common viruses were human rhinoviruses (9%), influenza A and B viruses (6%), human metapneumovirus (4%), RSV (3%), parainfluenza 1 to 3 viruses (2%), coronaviruses (2%) and adenoviruses (1%) [10].

A large systematic review on the etiology of CAP in European adults identified 28 studies reporting quantitative data on viral pneumonia prevalence [11]. Based on a meta-analysis of studies investigating patients diagnosed as having CAP, the cumulative incidence of viral pneumonia was estimated as 22%. Studies included in the systematic review had a large variability in the percentage of viral isolates and those using polymerase chain reaction (PCR)-based methods for diagnosis had the highest number of viral isolates. Interestingly, studies reporting a low risk of bias highlighted a percentage of viral isolates approaching 30%. Pooled analysis revealed that influenza virus A and B were the most common viruses identified accounting for 9% of the cases, and that rhinovirus, coronavirus and parainfluenza virus were identified in a percentage of cases between 2 and 7% [11]. Based on a retrospective study including patients with respiratory tract infection diagnosed by a multiplex PCR test, RSV can be detected during the influenza season in parallel to influenza virus infection in an approximate 1:7 relation [12].

In approaching viral pneumonia diagnosis, PCR-based diagnostic tests are more sensitive than standard methods, but viral genomic material identified by these tests can derive from recent viral infections, which are not responsible for the ongoing pulmonary infection. A study investigating over 300 patients suffering from CAP, whose etiologic diagnosis was based on both standard culture and multiplex-based analysis of respiratory specimens, identified viral pathogens in 30% of respiratory specimens, but in many cases, viruses and bacteria were simultaneously detected and a precise diagnosis of viral pneumonia could be obtained in 5.6% of the cases only [13].

Viral pneumonia has an important impact on ageing populations and in those living with cancer. A Swiss study enrolling patients ageing > 65 years with suspected CAP screened for viral pathogens by PCR analysis of nasopharyngeal swabs demonstrated the presence of a viral genome in 31% of the cases. Rhinovirus and Influenza A/B viruses were those most identified and evidence of both bacterial and viral infection was detected in about 10% of the cases [14]. Instead, a study including a large population of patients with viral pneumonia highlighted that an active cancer was a strong independent predictor of 30-day mortality [15].

Currently, the ongoing outbreak of COVID-19 is reporting high mortality and morbidity with over 80 million cases diagnosed in every part of the world. COVID-19 has rapid diffusion and reports a high mortality rate in elderly and immunocompromised patients. As for other etiologies of viral pneumonia, bacterial super infections were reported especially in severe cases [16, 17]. COVID-19 spreads rapidly when CAP viruses are at their annual peak and preliminary studies suggest that SARS-CoV-2 could have a competitive effect on other respiratory viruses circulation [18].

Clinical presentation

Clinical presentation of viral pneumonia ranges from mild pneumonia with fever, cough, and shortness of breath to severe pneumonia with sepsis and respiratory distress. Symptoms severity is related to the individual local and systemic immune response. Non-productive cough along with dyspnea and pleuritic chest pain are the most common symptoms of viral pneumonia. Fever, chills, fatigue, malaise, pleuritic chest pain, and anorexia are frequently reported. In severe cases, signs of physical examination also include tachypnea, an increase in breathing rate, and abnormal loud breath sounds. Hypoxemia is commonly reported due to the impairment of alveolar gas exchange [19].

The initial presentation of sepsis secondary to viral pneumonia may be based on new-onset or worsening hypotension, altered mental status and other signs of organ dysfunction, such as renal dysfunction, liver dysfunction, or thrombocytopenia and should be differentiated by bacterial superinfection. Sometimes, ageing patients, immunocompromised patients, or those living with chronic obstructive pulmonary disease can have a less specific presentation with rapidly worsening clinical conditions [20]. In some cases, the activation of the inflammatory response caused by a viral infection can trigger a pro-coagulative status thereby increasing the risk of cerebrovascular events in apparently low-risk patients [21].

Influenza

Approximately one-third of patients recurring to hospital care because of Influenza virus-associated pneumonia, which can be directly related to Influenza virus or caused by bacterial superinfection [22]. A study investigating 579 hospitalized adult patients with influenza virus infection, highlighted that those presenting with acute respiratory failure (OR 4.525; 95% CI 2.964–6.907) and those presenting with productive cough (OR 8.173; 95% CI 3.674–18.182) had the higher risk to be affected by pneumonia [23]. In a small percentage of cases, pneumonia can lead to severe hypoxemic respiratory failure, evolving towards acute respiratory distress syndrome (ARDS), with shock and acute renal failure. Pneumonia caused by Influenza A (H1N1) can have a severe clinical impact, as demonstrated by a study comparing each other patients with a respiratory infection admitted in hospital during 4 years. In this study, patients affected by Influenza A (H1N1) were younger at admission and reported a higher percentage of pulmonary complications, ICU admission, and mortality rate. Despite these differences in terms of

outcome, no difference between Influenza A (H1N1) and Influenza A/H3N2 can be reported looking for symptoms at admission [24].

Parainfluenza virus

Patients suffering from Parainfluenza virus infection report mild and rapidly resolving upper respiratory symptoms and only a few cases evolve towards severe clinical conditions. Parainfluenza virus 3 reports the highest rate of complications. A Chinese study investigating 178 patients with an upper respiratory specimen positive for Parainfluenza viruses revealed that most cases were in pediatric age and one-third were co-infected with other respiratory pathogens. The main symptoms reported were cough (94%) and fever (55%) and the proportion of patients with pneumonia was 16%, but no difference in terms of disease presentation was reported [25]. A systematic review on patients affected by hematologic malignancy or receiving hemopoietic cell transplantation with parainfluenza virus infection highlighted a 37% incidence of pneumonia and an associated mortality rate equal to 27%, irrespective of the underlying condition [26].

Respiratory syncytial virus

Respiratory syncytial virus (RSV) is responsible for recurrent respiratory infections in infants (bronchiolitis during the first year of life) and mild pneumonia in immunocompetent adults. A study considering elderly and high-risk patients hospitalized after the onset of RSV-associated illness, demonstrated a 20% incidence of pneumonia [27]. Patients with RSV report a longer time from the beginning of symptoms to hospital admission when compared to other cases with an Influenza-like illness (ILI), and bacterial super infections in 12% of cases [28]. Another study investigating the clinical characteristics of patients affected with an ILI, demonstrated that those reporting RSV infection had a diagnosis of pneumonia in over 40% of cases and had a high rate of respiratory failure. Anti-cancer or immunosuppressive treatments were significant risks for RSV pneumonia [29].

Adenovirus

Adenovirus affects the upper respiratory tract, but it can even cause pneumonia whose clinical findings are like other viral pneumonia. In a multicenter surveillance study investigating 969 patients with pneumonia in China, 5% had pneumonia sustained by adenovirus. These cases had a median age remarkably lower than the ones reported for other patients with an ILI. Those infected by adenovirus serotype 55 were older and had a major probability to be affected by an underlying disease. More than 50% of patients with adenovirus

pneumonia required hospitalization, 29% needed oxygen therapy and two patients needed mechanical ventilation [30]. Similar findings were reported in a meta-analysis of 228 case-report of patients with adenovirus disease [31]. After an outbreak of adenovirus infection occurred at the Korean military training center in 2015, 191 patients with pneumonia were investigated: five patients had severe pneumonia and one died. High prolonged fever, nasal congestion and sore throat were common symptoms. Febrile leukopenia (62.7%) and thrombocytopenia (41%) were frequent, while only 12% presented with leukocytosis [32].

Rhinovirus

Rhinovirus affects the upper respiratory tract in adults and children causing an infection characterized by sneezing and secretions, sore throat, and low-grade fever in many cases. Lower respiratory tract infection and acute respiratory distress syndrome (ARDS) are reported in a few cases among elderly and immunocompromised patients. A study comparing the characteristics of patients with severe rhinovirus -pneumonia to those with Influenza virus, reported an immunocompromised status or immunosuppressive drug administration. It is relevant to state that in this study patients admitted to ICU with viral pneumonia sustained by rhinovirus or influenza virus reported a mortality approaching 50% [33, 34].

Cytomegalovirus

CMV pneumonia has a very low frequency among immunocompetent patients. A recent literature review reports 17 cases only of viral pneumonia sustained by CMV in immunocompetent, most of these patients presented with fever, flu-like illness and shortness of breath and cough. Jaundice and abdominal pain were the main extrapulmonary symptoms reported. Interestingly, 2 women were in the peripartum period [35].

CMV interstitial pneumonitis reports the highest frequency in hematopoietic stem cell transplant (HSCT) recipients and in solid organ transplant recipients, where it is associated with an increase in terms of mortality [36]. A study investigating the complications of patients undergoing bone marrow transplantation identified 16 cases of CMV pneumonia. In these cases, fever and cough were the main symptoms, hypoxia was reported in about 60% and dyspnea in 53%. A 31% mortality rate was reported in these cases. Similar findings were reported in another study on patients receiving allogeneic BMT transplantation. Both studies found a relationship between CMV pneumonia and an increase of procedure-related mortality rate [37, 38].

Other viral etiologies of viral pneumonia

Besides CMV, other viruses belonging to the Herpesvirus family can cause pneumonia. A study evaluating 102 adult cases with severe VZV pneumonia demonstrated that over half of the cases were immunocompromised patients. Clinical findings included fever and dyspnea in virtually all cases, the cough was reported in 44%, hemoptysis in 10%. Immunocompromised patients had a more severe course of the disease, as demonstrated by the higher rate of cases requiring mechanical ventilation. Hospital mortality was 24% [39]. Herpes Simplex Virus (HSV) pneumonia is rather uncommon and diagnosed mainly in immunocompromised. Its diagnosis is difficult due to HSV shedding can be reported in 2–3% of individuals in the general population making its presence in low tract respiratory specimens difficult to interpret. A study on immunocompromised patients using strict parameters including cytopathologic examination demonstrated the presence of HSV-DNA in 42% of low respiratory tract specimens, but only 24% fulfilled the criteria for HSV pneumonia. Mortality approached to 25% in these cases. Another study evaluating patients with viral pneumonia highlight that HSV1-DNA was detected in 32% of the cases, but no difference in terms of mortality could be detected after treatment with acyclovir, making rather questionable the role of HSV in these cases [40, 41].

COVID-19

COVID-19 has clinical characteristics, which were reported rarely in the cases of pneumonia sustained by other viral agents. While general symptoms of pulmonary involvement are quite indistinguishable from other etiology of viral pneumonia, many aspects deserve particular attention. A large systematic review shows that, besides common accessory symptoms (fever, cough, and dyspnea), loss of gustatory and olfactory functions, gastrointestinal symptoms, and headache can be reported in some cases. These accessory symptoms should be considered in suspecting COVID-19 in patients presenting with worsening respiratory symptoms to provide supportive care and limit intra-hospital diffusion. Severe cases evolve towards an ARDS and require ventilatory support. In some cases, signs of neurologic involvement can be reported as late complications of COVID-19. About 50% of the patients have relevant comorbidities and bacterial coinfections can be reported in about 20% of the cases at the time of Intensive Care Unit admission. Clinical manifestations in children are usually mild, because of a less pronounced inflammatory response. Patients surviving to COVID-19 can report alteration in lung function that can benefit of a rehabilitative treatment [42–46].

Management of viral pneumonia

Viral pneumonia has few opportunities in terms of therapy and the standard of care is supportive treatment in most cases. Most common antiviral agents have limited availability in many areas and the use of drugs such as steroids or heparin is not supported by large controlled studies.

Antivirals

In the suspicion of pneumonia caused by the Influenza virus, drug therapy should begin before laboratory confirmation. Oseltamivir, zanamivir and peramivir reduce morbidity and mortality in Influenza virus A and B infection, acting as neuraminidase inhibitors and affecting viral propagation [47, 48]. Early antiviral treatment is preferred and zanamivir is recommended as first-line therapy because of the potential resistance of influenza A (H1N1) virus to oseltamivir [49, 50]. CDC guidelines recommend therapy with oseltamivir for influenza virus pneumonia and with peramivir when a deficit in oseltamivir oral absorption is suspected.

Neuraminidase inhibitors investigations regard mainly patients with uncomplicated Influenza A infection. PRIDE study analyzing a large sample of patients with Influenza pneumonia demonstrated that early treatment (≤ 2 days) with neuraminidase inhibitors did not reduce the risk of pneumonia onset compared with untreated subjects. Instead, in patients with Influenza pneumonia, early neuraminidase inhibitor treatment compared to later treatment was associated with significantly lower rates of ventilatory support and death [51]. Amantadine and rimantadine have been proposed for the treatment of Influenza because they act on viral membrane protein M2, which is implicated in the fusion of the viral envelope with the cytoplasmic membrane and can block viral RNA replication. The quality of studies on Amantadine and rimantadine activity is low and their use is limited by adverse drug reactions and rapid development of resistance. No data are currently available in their role on Influenza pneumonia treatment [52].

Ribavirin has been largely employed in the treatment of infants with bronchiolitis, but only a few data support its use in the treatment of RSV pneumonia. Ribavirin can be administered by mouth, intravenously, or aerosolized and can be difficult to administer to mechanically ventilated patients because aerosols can deposit in the ventilator delivery system. Concerns about the risk of hemolytic anemia and teratogenicity limit the use of ribavirin. Experience on ribavirin treatment of adults with pneumonia sustained by RSV is limited mainly to immunocompromised patients. In these cases, treatment efficacy is influenced

by the immune status of patients and the benefit derived by ribavirin treatment is poor, also when specific immunoglobulins are administered [53, 54].

Valganciclovir or ganciclovir are routinely administered to patients receiving organs from CMV seropositive donors or to patients with HIV at high risk of CMV disease [55, 56]. When valganciclovir and ganciclovir are administered to patients with CMV pneumonia, a considerable benefit can be observed, as reported in patients with CMV pneumonia complicating bone-marrow transplantation [57]. The efficacy of these drugs can be well demonstrated by a study enrolling 100 immunocompromised patients who developed ARDS after CMV pneumonia that had an improvement in terms of mortality rate after ganciclovir treatment [58].

In an observational study, one hundred-two patients suffering from VZV pneumonia admitted to an intensive care unit received acyclovir 10 mg/kg every 8 h during an average of 11 days. Hospital mortality was 24%, regardless of acyclovir administration, and patients receiving steroids experienced a longer duration of mechanical ventilation and prolonged hospitalization [39]. Treatment of rhinovirus pneumonia is primarily supportive. In this setting, several antiviral drugs such as pleconaril, rupintrivir, or repurposing drugs such as itraconazole have been evaluated, but none have achieved solid results in terms of efficacy [59].

Although several drugs with antiviral activity have been proposed for the treatment of COVID-19 patients, no study can support their routine use. Remdesivir, lopinavir, aminoquinolines and other drugs with proven antiviral activity against other viruses have been investigated, but no efficacy was demonstrated by large trials as either treatment or prophylaxis [60–62].

Pharmacological options for Influenza Virus Pneumonia, along with other viral pneumonia, are summarized in Table 1.

Steroids

The use of steroids in patients with viral pneumonia can be proposed to reduce the deleterious effects of immune response triggered by viruses, but their efficacy is long to be demonstrated. Current IDSA/ATS guidelines on community-acquired pneumonia do not support steroids use. A meta-analysis including ten studies evaluating patients with influenza pneumonia associated the use of steroids with a higher risk of death, a longer length of stay in the intensive care unit, and a higher rate of secondary infections, only risk of mechanical ventilation duration was not affected [63]. Furthermore, a cohort study on 241 patients affected by ARDS after influenza virus infection highlights that early treatment with steroids can be associated with an increase in hospital mortality rate (43.5% vs. 19.2%, $p < 0.001$) [64].

Table 1 Main antiviral treatments active in patients with viral pneumonia

Main indication for the treatment	Medication	Dosage	Notes
Uncomplicated Influenza Influenza pneumonia	Oseltamivir	Oral 75 mg twice daily for 5 days	Dose adjustment for CrCl < 50 ml'
	Peramivir	Intravenous 600 mg single dose (5 days for complicated Influenza)	Efficacy is not established for severe Influenza A and for Influenza B
	Zanamivir	Intravenous 300 mg daily for 5–10 days 10 mg inhaled q12hr for 5–10 days	Bronchospasm can occur in patients with asthma
RSV infection in immunocompromised	Ribavirin	Aerosolized 2 g over 2 h every 8 h Systemic oral or intravenous (dosage variable)	Inhalatory formulation can deposit in the delivery system if ventilated Hemolytic anemia Teratogenic
Severe adenovirus infection	Cidofovir	Intravenous 5 mg/kg/weekly, until symptoms resolve	Very limited data Nephrotoxicity
Varicella pneumonitis	Acyclovir	Intravenous 10 mg/kg/dose every 8 h for at least 7 days	Nephrotoxicity
CMV pneumonia	Ganciclovir	Intravenous 5 mg/kg/dose every 12 h for at least 2 weeks	Hematologic toxicity Nephrotoxicity (dose adjustment for CrCl < 70)
COVID-19	Remdesivir	Day 1 loading dose: 200 mg IV over 30–120 min Day 2–6: 100 mg IV q Day	Hepatotoxicity

CMV cytomegalovirus, CrCl creatinine clearance, HCW healthcare workers, HMPV human metapneumovirus, PIV parainfluenza viruses, RSV respiratory syncytial virus

Despite all these investigations arguing against steroid use in patients with viral pneumonia, there is a growing body of evidence on the effectiveness of low-dose steroids in selected cases. In a case-control study on 2141 influenza A (H1N1) patients with viral pneumonia, the subgroup of patients with PaO₂/FiO₂ < 300 mmHg receiving low/moderate doses of steroids had a significant reduction in both 30-day and 60-day mortality [65]. Further data favoring steroids administration are reported in patients with COVID-19. RECOVERY trial highlights a favorable outcome for

patients needing oxygen supplementation receiving 6 mg of dexamethasone over a 10-day period [66]. A meta-analysis of 7 studies on the effects of steroids administration to COVID-19 patients admitted in ICU, intubated, or receiving high-flow oxygen, reported an advantage in terms of mortality reduction for the studies considering dexamethasone administration, but not for those considering hydrocortisone or methyl-prednisolone administration. No change in terms of mortality was reported after the use of high doses of steroids or in those receiving vasoactive drugs at enrollment

Table 2 Studies assessing the effectiveness of steroids in patients with viral pneumonia

Article	Study type	Therapy	Etiology	Patients (n)	Effects
63	Meta-analysis	CS vs No CS treatment	Influenza virus	4916	Higher mortality (OR 1.98, 95% CI 1.62–2.43, <i>p</i> < 0.00001) in CS group
64	Retrospective cohort study	Early CS treatment vs Non early CS treatment	Influenza virus	241	Higher hospital mortality rate in CS group
65	Case control study	Low-to-moderate dose vs High-dose CS	Influenza A (H1N1)	2141	Reduced 30-day and 60-day mortality in patients receiving low-to-moderate-CS dose with PaO ₂ /FiO ₂ < 300 mm Hg
66	Randomized controlled trial	Dexamethasone vs Standard of care	COVID-19	6425	Reduced 28-day mortality rate in the dexamethasone group receiving ventilatory support
67	Meta-analysis	CS vs Standard of care	COVID-19	1703	Advantage after treatment with dexamethasone (6 mg daily)

CS: corticosteroid, ARDS: Acute Respiratory Distress Syndrome, aHR: adjusted Hazard Ratio, IMV: invasive mechanical ventilation

Table 3 Efficacy of NIV in patients with viral pneumonia

Reference	Study type	NIV	Etiology	Patients (n)	Effects
72	Retrospective analysis of a registry	Conventional invasive ventilation vs Non-invasive ventilation	Influenza A(H1N1)	685	No difference in respect to NIV use Lower APACHE II score, lower SOFA score, fewer than two chest X-ray quadrant opacities, hemodynamic stability and absence of renal failure or MODS were associated with NIV success
73	Retrospective single-centre study	Conventional invasive ventilation vs Non-invasive ventilation	Influenza A(H1N1)	32	SOFA score at ICU admission in patients receiving NIV was higher than in patients with successful NIV
74	Case control study	Conventional invasive ventilation vs Non-invasive ventilation	COVID-19	203	CPAP resulted in a lower risk of death for patients admitted within 7 days;

[67]. Main studies assessing steroids effects of patients with viral pneumonia are summarized in Table 2.

Heparins

Before the current COVID-19 pandemic, only a retrospective study on patients with ARDS after Influenza A (H1N1) supported the use of thromboprophylaxis with heparin in patients with viral pneumonia [68]. A retrospective study comparing patients with COVID-19 to those with Influenza A evaluated the effects of different thromboprophylaxis strategies on 152 patients admitted to 2 intensive care units. An association between high dose (200 UI x kg per day) dalteparin and reduction of mortality in respect to those receiving low or middle dose of heparin was reported (hazard ratio of death 0.33; 95% confidence intervals 0.13–0.87) [69, 70]. Although the majority of the studies report a favorable effect of anticoagulant therapy, no consensus exists about the timing and dosage of heparins in patients with COVID-19 [71].

Non-invasive ventilation

The ongoing COVID-19 pandemic has increased the need for the treatment of acute respiratory failures and the awareness of non-invasive ventilation (NIV), which gives the advantage of managing respiratory failure possibly avoiding endotracheal intubation.

An observational study evaluating patients with influenza A (H1N1) admitted in ICU established that an NIV was associated with a success rate of 40.6% and mortality comparable to that reported among patients intubated from the beginning of the respiratory failure. The success of NIV was predictable by fewer than 2 chest X-ray quadrant opacities and no vasopressor requirements by multivariate

analysis. Another retrospective study investigating the efficacy of early NIV treatment for respiratory failure in patients with severe CAP identified 32 patients with NIV failure. The main factors associated with failure were comorbidities, high chest X-ray score, high LDH and lack of PaO₂/FiO₂ improvement after one hour of ventilation. NIV complications were not severe and limited to skin lesions in many cases. A retrospective case–control retrospective study investigating the efficacy of different approaches to NIV in COVID-19 patients demonstrated an advantage after early (within 7 days from admission) continuous positive air pressure (CPAP) intervention. Instead, an increase in the risk of death was reported for patients receiving CPAP after 7 days from admission [72–75] (Tab. 3).

Conclusions

Viral pneumonia is an underestimated pathology with a relevant impact on elderly and immunocompromised patients. The most common etiologic agent of viral pneumonia in adults is rhinovirus. Influenza virus is frequently diagnosed, and several cases are reported among patients infected by Influenza A (H1N1) virus. Presenting signs of viral pneumonia are non-productive cough, dyspnea, fever, and pleuritic chest pain, but severe cases can report rapidly worsening respiratory failure. Drugs currently available have limited efficacy.

The current COVID-19 pandemic is increasing the awareness of viral pneumonia focusing the attention on previously under-investigated treatments and procedures such as steroids, immunosuppressive combination therapies, or NIV [60, 75]. Limited availability and efficacy of antivirals active against etiologic agents of viral pneumonia prompt

the investigators to reposition drugs currently used for other viral etiologies, as already performed for other pathologies [76, 77]. Present investigations have failed in demonstrating the efficacy of virtually all the antiviral drugs examined.

Declarations

Conflict of interest The authors declare no affiliations with or involvement in any organization or entity with any financial or nonfinancial interest related to this manuscript.

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