



Editorial

Impact of Respiratory Syncytial Virus in Patients With Chronic Respiratory Disease[☆]

Impacto del virus respiratorio sincitial en el paciente con enfermedad respiratoria crónica

If, within a wide variety of viruses causing respiratory infections, there is a virus that we must pay special attention to, then it is the respiratory syncytial virus (RSV). For many years, RSV has been identified as one of the main causes of lower respiratory tract (LRT) infection in newborns and young children. However, recent researches show that there is a significant burden of RSV in respiratory infections in adults, which is even greater than that of influenza.¹ Moreover, the mortality rate of RSV infection in people over 70 years of age is higher than in other age groups.² A recent meta-analysis in adults over 60 years of age has estimated an acute respiratory infection rate at 1.62%, hospitalization attack rate at 0.15%, and in-hospital case fatality rate at 7.13%.³

Respiratory infection caused by RSV in adults has different presentations, ranging from asymptomatic cases to exacerbations of underlying chronic pathologies or serious complications such as pneumonia. Furthermore, we know that immunosuppressed elderly people with chronic diseases, especially respiratory ones, have an increased risk of a serious illness related to RSV.⁴

One of the main challenges facing this infection is to reduce underdiagnosis in adult population. To achieve this an early recognition of this virus through efficient diagnostic tests is necessary. An appropriate supportive treatment is also necessary, particularly due to the lack of effective antiviral drugs. The arrival of new tools, such as artificial intelligence, could facilitate the creation of predictive models of RSV infection, allowing us to reduce the burden of disease and its morbidity and mortality, as well as to provide better immunization strategies.

Until relatively recently, the bacterial infection was thought to be the main cause of infectious exacerbation in chronic obstructive pulmonary disease (COPD). Nevertheless, the development of PCR tests and their implementation in clinical practice have revealed the true prevalence of the viruses as the cause of infectious exacerbations in COPD,⁵ being responsible for at least 50%,⁶ with a 60-day mortality of 12.6%.⁷ A recent review that used the detection of respiratory viruses with the help of PCR in the exacerbations has detected that rhinovirus (16.39%), RSV (9.9%) and influenza (7.83%) were the most frequent infections.⁸ However, after the SARS-Cov2 pandemic, the prevalence of coronavirus is probably higher. The

patient with COPD has an increased risk of admission (2–4 times higher than general population) when the infection is due to RSV,⁹ presenting a similar impact on non-pandemic influenza A in the 60-year-old group with high-risk pathologies.¹⁰

Epidemiological studies carried out with PCR in asthmatic patients have shown that viral respiratory infection is the most frequent trigger of exacerbations, both in adults (80%) and in children (85–95%).¹¹ Rhinovirus is the most frequent cause of asthma exacerbation (42.1%), followed by RSV (13.6%) and, to a lesser extent, herpes simplex virus (12.3%), enterovirus (10.1%), or influenza (10.0%).¹²

There are few references on the role of respiratory viruses in exacerbations of bronchiectasis (BE) not due to cystic fibrosis (CF). In a recent systematic review, respiratory viruses were detected in 48% of exacerbations, identifying 16 types, with coinfection existing in 8% of cases. The most frequent viruses were rhinoviruses, followed, in descending order of frequency, by enterovirus, bocavirus, adenovirus, metapneumovirus, influenza A, RSV, parainfluenza 3 or 4, coronavirus and parainfluenza 1 or 2.¹³ Therefore, despite the scarcity of data, the role of viruses in BE exacerbations is far from being minor, so new prospective studies are needed to clarify the clinical consequences of the presence of viruses in LRT beyond exacerbations, during recovery and stability.

In patients with interstitial lung disease (ILD), although it is a progressive disease, exacerbations may occur which causes acute respiratory deterioration with an impact on morbidity and mortality. Despite common underdiagnosis, viral respiratory infections are a known cause of these exacerbations. RSV favors the production of different proinflammatory cytokines and the local recruitment of neutrophils in the bronchiolar epithelium, promoting an exacerbation of ILD.¹⁴ Furthermore, the accelerating role of RSV infection in the pathogenesis of pulmonary fibrosis has been demonstrated in animal models.¹⁵ It is worth highlighting the greater vulnerability to RSV infection in patients with ILD associated with systemic autoimmune diseases or undergoing immunosuppressive treatment.

Although there is hardly any data on the incidence and severity of RSV infection in patients with pulmonary hypertension (PH), infections are one of the main causes of its decompensation.¹⁶ In addition, pneumonia causes up to 7% of deaths in patients with PH,

[☆] The Spanish version is available in the [supplementary material](#).

which underlines the pernicious effect that respiratory infections have on this population.¹⁷

RSV is one of the main causes of LRT infection in lung transplant patients, within whom it is associated with high morbidity and mortality.¹⁸ This special vulnerability is explained by the high degree of pharmacological immunosuppression, local factors of the transplanted lung, as well as by the presence of chronic graft dysfunction (IGD). It should be noted that RSV, in comparison with other respiratory viruses, is more associated with the development of this IGD, one of the main determinants in post-transplant survival.¹⁹ For all these reasons, different therapeutic options aimed at treating severe RSV infection in the lung transplant patient, including ribavirin, intravenous immunoglobulins and pavilizumab, have been proposed. However, the results were contradictory, which makes it even more necessary to optimize currently available prevention measures.

Patients with lung cancer should also be considered within risk groups due to their susceptibility to develop severe forms of presentation of RSV infection, especially in situations of neutropenia, an active oncological treatment and a greater degree of tumor extension.²⁰

Given the lack of available effective specific treatments, it is urgent to implement preventive measures such as immunization against RSV in patients with chronic respiratory diseases, as has already been done previously with other microorganisms that cause serious respiratory infections such as influenza, SARS-CoV2 and pneumococcus.²¹ Regulatory agencies have recently approved different RSV vaccines that have demonstrated their effectiveness and safety in the adult population, which offers new and promising opportunities to protect better our respiratory patients, particularly vulnerable to infection.^{22,23} Therefore, responsible health authorities must prioritize patients with chronic respiratory diseases in immunization programs.

One of the aims of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) is to collaborate in the prevention of respiratory diseases and to contribute to improving the health care of these patients. SEPAR promotes the acquisition of more knowledge derived from research in this field and, therefore, must lead the strategies for the prevention and treatment of RSV infection.

We can conclude by saying that, despite underdiagnosis, RSV is one of the respiratory viruses that most frequently causes symptomatic infections of LRT, being an important cause of morbidity and mortality in patients with chronic respiratory diseases. For that reason, these patients should be considered a high-risk population vulnerable to the most severe forms of RSV infection. All the above justifies the need to optimize the diagnostic, therapeutic, and, of course, preventive management of this respiratory infection in our patients with underlying respiratory diseases. Consequently, SEPAR urges the responsible health authorities to prioritize patients with chronic respiratory diseases in RSV immunization programs in order to mitigate its current impact on this particularly vulnerable population.

Funding

The authors received no financial support for the authorship of this article.

Authors' contributions

All authors made substantial contribution to the design and drafting of the manuscript, and critical review of the content.

Conflicts of interest

FV-Á declares having attended or participated in activities organized or funded by the pharmaceutical companies Almirall, Bial, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Esteve, Ferrer, Menarini, Novartis, Mundipharma, Orion, Oximesa, Pfizer, Teva y Zambon.

AG-O declares having attended or participated in activities organized or funded by the pharmaceutical companies GlaxoSmithKline, Janssen, MSD, AstraZeneca, Menarini, Bial, Ferrer.

ME-C declares having attended or participated in activities organized or funded by the pharmaceutical companies AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, FAES, Gebro, GlaxoSmithKline, Menarini, Sanofi, Teva y Zambon.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.opresp.2024.100345](https://doi.org/10.1016/j.opresp.2024.100345).

References

1. Kwon YS, Park SH, Kim MA, Kim HJ, Park JS, Lee MY, et al. Risk of mortality associated with respiratory syncytial virus and influenza infection in adults. *BMC Infect Dis.* 2017;17:785.
2. Du Y, Yan R, Wu X, Zhang X, Chen C, Jiang D, et al. Global burden and trends of respiratory syncytial virus infection across different age groups from 1990 to 2019: a systematic analysis of the Global Burden of Disease 2019 Study. *Int J Infect Dis.* 2023;135:70–6.
3. Savic M, Penders Y, Shi T, Branche A, Pircon JY. Respiratory syncytial virus disease burden in adults aged 60 years and older in high-income countries: a systematic literature review and metaanalysis. *Influenza Other Respir Viruses.* 2023;17:e13031.
4. Bruyndonckx R, Coenen S, Butler C, Verheij T, Little P, Hens N, et al. Respiratory syncytial virus and influenza virus infection in adult primary care patients: association of age with prevalence, diagnostic features and illness course. *Int J Infect Dis.* 2020;95:384–90.
5. Linden D, Guo-Parke H, Coyle PV, Fairley D, McAuley DF, Taggart CC, et al. Respiratory viral infection: a potential “missing link” in the pathogenesis of COPD. *Eur Respir Rev.* 2019;28:180063.
6. Seemungal T, Harper-Owen R, Bhowmik A, Moric I, Sanderson G, Message S, et al. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2001;164:1618–23.
7. Anderson NW, Binnicker MJ, Harris DM, Chirila RM, Brumble L, Mandrekar J, et al. Morbidity and mortality among patients with respiratory syncytial virus infection: a 2-year retrospective review. *Diagn Microbiol Infect Dis.* 2016;85:367–71.
8. Zwaans WA, Mallia P, van Winden ME, Rohde GG. The relevance of respiratory viral infections in the exacerbations of chronic obstructive pulmonary disease – a systematic review. *J Clin Virol.* 2014;61:181–8.
9. Osei-Yeboah R, Johannesen CK, Egeskov-Cavling AM, Chen J, Lehtonen T, Fornes AU, et al. Respiratory syncytial virus-associated hospitalization in adults with comorbidities in 2 European countries: a modeling study. *J Infect Dis.* 2024;229 Supplement.1:S70–7.
10. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med.* 2005;352:1749–59.
11. Urbani F, Cometa M, Martelli C, Santoli F, Rana R, Ursitti A, et al. Update on virus-induced asthma exacerbations. *Expert Rev Clin Immunol.* 2023;19:1259–72.
12. Zheng XY, Xu YJ, Guan WJ, Lin LF. Regional, age and respiratory-secretion-specific prevalence of respiratory viruses associated with asthma exacerbation: a literature review. *Arch Virol.* 2018;163:845–53.
13. Kartsouni E, Chatzipanagiotou S, Tamvakaras P, Douros K. The role of viral infections in pulmonary exacerbations of patients with non-cystic fibrosis bronchiectasis: a systematic review. *Respir Investig.* 2022;60:625–32.
14. Ushiki A, Yamazaki Y, Hama M, Yasuo M, Hanaoka M, Kubo K. Viral infections in patients with an acute exacerbation of idiopathic interstitial pneumonia. *Respir Investig.* 2014;52:65–70.
15. Wang L, Cheng W, Zhang Z. Respiratory syncytial virus infection accelerates lung fibrosis through the unfolded protein response in a bleomycin-induced pulmonary fibrosis animal model. *Mol Med Rep.* 2017;16:310–6.
16. Hooper MM, Benza RL, Corris P, de Perrot M, Fadel E, Keogh AM, et al. Intensive care, right ventricular support and lung transplantation in patients with pulmonary hypertension. *Eur Respir J.* 2019;53:1801906.
17. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med.* 1987;107:216–23.
18. de Zwart A, Riezebos-Brilman A, Lunter G, Vonk J, Glanville AR, Gottlieb J, et al. Respiratory syncytial virus, human metapneumovirus, and parainfluenza virus

- infections in lung transplant recipients: a systematic review of outcomes and treatment strategies. *Clin Infect Dis.* 2022;74:2252–60.
19. Allyn PR, Duffy EL, Humphries RM, Injean P, Weigt SS, Saggar R, et al. Graft loss and CLAD-onset is hastened by viral pneumonia after lung transplantation. *Transplantation.* 2016;100:2424–31.
 20. Belluomini L, Caldart A, Avancini A, Dodi A, Trestini I, Kadrija D, et al. Infections and immunotherapy in lung cancer: a bad relationship? *Int J Mol Sci.* 2020;22:42.
 21. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2013;187:347–65.
 22. Walsh EE, Pérez Marc G, Zareba AM, Falsey AR, Jiang Q, Patton M, et al. Efficacy and safety of a bivalent RSV prefusion F vaccine in older adults. *N Engl J Med.* 2023;388:1465–77.
 23. Papi A, Ison MG, Langley JM, Lee DG, Leroux-Roels I, Martinon-Torres F, et al. Respiratory syncytial virus prefusion F protein vaccine in older adults. *N Engl J Med.* 2023;388:595–608.

Felipe Villar-Álvarez^a, Alberto García-Ortega^b,
Marta Entrenas-Castillo^{c,*}

^a *Pneumology Department, IIS Fundación Jiménez Díaz, CIBERES, Universidad Autónoma of Madrid, Madrid, Spain*

^b *Pneumology Department, Hospital Doctor Peset, Valencia, Spain*

^c *Pneumology Department, Hospital Quirónsalud Córdoba, Córdoba, Spain*

* Corresponding author.

E-mail address: marta.entrenas@quironsalud.es
(M. Entrenas-Castillo).