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Severe Acute Respiratory Failure Associated with Viral Respiratory Infections: A Multidisciplinary Approach to Diagnosis, Pharmacotherapy, Respiratory Support, and Critical Care Management

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Abstract

Background: Severe acute respiratory failure caused by respiratory viruses is an important cause of intensive care unit admission and is associated with substantial morbidity and mortality. Advances in molecular diagnostics have increased the detection of respiratory viruses in lower respiratory tract infections, while also highlighting challenges in distinguishing true viral disease from asymptomatic carriage and bacterial-viral co-infection. Respiratory viruses can cause direct epithelial injury, dysregulated inflammation, alveolar damage, and systemic complications.

Aim: This narrative review aimed to summarize current evidence on the epidemiology, molecular diagnosis, pathophysiology, clinical consequences, outcomes, treatment, and prevention of severe respiratory viral infections causing acute respiratory failure in immunocompetent adults.

Methods: A narrative review of published clinical and experimental evidence was conducted. The review focused on respiratory viruses causing community-acquired severe respiratory infections in immunocompetent adults, excluding SARS-CoV-2 and herpesviruses. Evidence concerning molecular diagnostic techniques, respiratory support, antiviral therapy, immunomodulation, outcomes, and vaccination was synthesized.

Results: Multiplex PCR has improved detection of respiratory viruses and bacterial-viral co-infections, with reported viral detection rates varying according to the population and sampling method. Influenza, respiratory syncytial virus, and human metapneumovirus are important causes of severe disease. Viral epithelial injury, cell death, immune dysregulation, and diffuse alveolar damage contribute to respiratory failure. Bacterial co-infections and cardiovascular complications further increase mortality. Management remains primarily supportive, although oseltamivir remains central for severe influenza. Evidence for corticosteroids in viral pneumonia is limited and inconsistent. Vaccination provides an important strategy for reducing severe disease, particularly among older adults.

Conclusion: Respiratory viruses represent important causes of severe acute respiratory failure. Early molecular diagnosis, appropriate respiratory support, pathogen-directed treatment, prevention of co-infections, and vaccination are central to improving outcomes.

Keywords: Respiratory viruses; acute respiratory failure; viral pneumonia; intensive care unit; multiplex PCR; influenza; respiratory syncytial virus; antiviral therapy; vaccination.

Introduction

The widespread adoption of molecular diagnostic technologies has increased the

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identification of respiratory viruses among critically ill adults presenting with severe respiratory disease. Depending on the population studied, clinical setting, duration of illness, specimen type, and diagnostic platform used, respiratory viruses have been detected in approximately 17% to 53% of patients with severe respiratory illness. This expanding recognition has altered the understanding of severe acute respiratory infections by demonstrating that viral pathogens can contribute substantially to critical illness rather than representing incidental findings. The respiratory viruses most frequently identified include influenza A and B viruses, picornaviruses such as rhinovirus and enterovirus including enterovirus D68, human coronaviruses including 229E, NL63, OC43, and HKU1, respiratory syncytial virus, human metapneumovirus, parainfluenza viruses, and adenoviruses. In addition, zoonotic coronaviruses responsible for severe acute respiratory syndrome, Middle East respiratory syndrome, and coronavirus disease have demonstrated the capacity to produce severe lower respiratory tract disease and critical respiratory failure. Despite advances in molecular diagnostics, establishing a direct causal relationship between viral detection and clinical disease remains challenging. Detection of a viral genome does not necessarily establish that the identified pathogen is responsible for the patient's clinical syndrome. Some respiratory viruses, particularly picornaviruses, may persist in or be detected within the upper respiratory tract without producing clinically significant disease. Conversely, reliance on upper respiratory tract specimens can result in false-negative findings when infection is predominantly located in the lower respiratory tract. The diagnostic interpretation becomes more complex when bacterial or fungal pathogens are detected concurrently. Such co-infections may influence disease severity, clinical progression, antimicrobial requirements, and patient outcomes. These considerations are particularly relevant in intensive care practice, where respiratory deterioration may result from multiple interacting infectious and host-related mechanisms.

Respiratory viral infections are now recognized as important causes of severe disease among older adults and individuals with underlying medical conditions, particularly those with impaired immune function. Nevertheless, severe viral respiratory disease can also occur in individuals without recognized immunosuppression or major comorbidities. Viral infection may directly produce extensive pulmonary inflammation and impaired gas exchange while also precipitating exacerbations of chronic cardiopulmonary disease. Furthermore, viral-induced epithelial injury and disruption of pulmonary host defenses can increase susceptibility to secondary bacterial infections. These processes may contribute to progressive hypoxemia, respiratory failure, prolonged intensive care admission, and the requirement for invasive or non-invasive respiratory support. This narrative review aims to synthesize current evidence regarding the clinical management of immunocompetent adults admitted to intensive care units with community-acquired severe acute respiratory infections caused by respiratory viruses, excluding SARS-CoV-2. Particular attention is directed toward viruses acquired through the respiratory route and their relevance to severe lower respiratory tract disease in adult critical care. The review considers diagnostic assessment, clinical recognition, respiratory support, pharmacological management, monitoring, and multidisciplinary care. Herpesviruses are excluded because they do not represent typical community-acquired respiratory pathogens and are more commonly encountered in hospital settings through viral reactivation. Their detection in mechanically ventilated patients is frequently associated with viral reactivation and relative immune dysfunction rather than primary respiratory acquisition [1,2]. This distinction allows the review to focus on respiratory viruses that are directly relevant to community-acquired severe acute respiratory infections and their management in immunocompetent adults requiring intensive care.

Impact of Molecular Testing in Discovering Viruses in Lower Respiratory Tract Infections

The introduction of multiplex polymerase chain reaction assays after 2007 has substantially changed the diagnostic and epidemiological understanding of viral lower respiratory tract infections. Unlike conventional diagnostic approaches that depend on the identification of individual pathogens, multiplex PCR platforms allow simultaneous detection of multiple respiratory viruses from a single clinical specimen. This expansion in diagnostic capacity has increased recognition of viral pathogens among patients with severe respiratory disease and has provided a broader understanding of the contribution of viruses to lower respiratory tract infections. Available multiplex molecular platforms have demonstrated positive predictive agreement exceeding 95% when evaluated against established reference methods, supporting their analytical performance and reliability for pathogen detection [1,2]. However, the detection of viral nucleic acid should not automatically be interpreted as evidence of active viral disease. Molecular positivity may represent active infection, residual viral nucleic acid, transient respiratory carriage, prolonged viral shedding, or incidental detection. The clinical interpretation therefore requires consideration of the specific virus, host characteristics, immune status, timing of specimen collection, disease stage, and anatomical location of infection. Nasopharyngeal molecular testing remains the standard approach for respiratory virus detection in many clinical settings. Its widespread use reflects the accessibility of the upper respiratory tract, the relatively non-invasive nature of specimen collection, and the established performance of molecular assays in respiratory virus

diagnosis. Nevertheless, its ability to accurately characterize lower respiratory tract infection remains subject to important limitations. A negative nasopharyngeal result does not necessarily exclude viral infection of the lower respiratory tract, particularly when viral replication is predominantly localized within the lungs or when viral shedding from the upper airway has declined during the course of illness. Conversely, a positive upper respiratory tract result may not establish that the detected virus is responsible for pneumonia. This issue is particularly relevant for viruses that can persist within the respiratory tract after resolution of clinical symptoms. Consequently, the anatomical site from which a specimen is obtained has a direct influence on the interpretation of molecular findings [3].

Longitudinal investigations provide evidence supporting the potential discrepancy between viral detection and clinically significant respiratory disease. In a U.S. household study involving 108 individuals from 26 families who underwent weekly nasopharyngeal sampling, 783 viral detections were identified through PCR testing, but only 56% were associated with respiratory symptoms [4]. This finding illustrates that molecular detection may occur in the absence of clinically apparent illness. The persistence of viral detection also varies according to the pathogen. Prolonged detection extending beyond four weeks was frequently observed with bocavirus and rhinovirus. Such prolonged positivity may reflect extended viral excretion, persistence of viral nucleic acid, or repeated infections. These observations complicate the interpretation of positive PCR results in patients with severe respiratory illness because a detected virus may not necessarily represent the primary cause of the current pulmonary syndrome. Clinical findings, radiological abnormalities, inflammatory markers, disease progression, and specimen characteristics must therefore be considered alongside molecular results. The limitations of upper respiratory tract testing become particularly important in critically ill patients with suspected viral pneumonia. Patients admitted to intensive care units may present after several days of illness, by which time viral concentrations in the upper respiratory tract may have decreased despite continuing infection in the lower respiratory tract. Lower respiratory tract specimens, including sputum or other respiratory samples obtained from the affected anatomical compartment, may therefore increase pathogen detection in selected patients. However, obtaining lower respiratory tract specimens can be more invasive and may not be feasible in every patient. The optimal diagnostic strategy consequently requires a balance between diagnostic yield, patient safety, disease severity, and the clinical probability of viral infection.

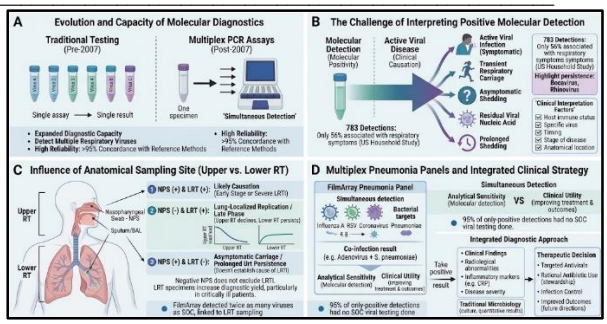

Figure 1: Impact of Molecular Testing in Discovering Viruses in Lower Respiratory Tract Infections.

The development of multiplex pneumonia panels that simultaneously detect bacterial and viral pathogens has further expanded the diagnostic potential of molecular testing. Among currently available commercial platforms, the FilmArray Pneumonia Panel represents a notable example because it incorporates eight viral targets alongside bacterial targets. This approach is particularly relevant because viral and bacterial infections may occur simultaneously and may contribute jointly to disease severity. Recognition of bacterial–viral co-infection can influence antimicrobial decisions, infection-control considerations, and interpretation of clinical deterioration. Nevertheless, the clinical value of detecting multiple pathogens remains incompletely defined, particularly when molecular assays identify organisms that may represent colonization rather than active infection [5-8]. Interpretation of epidemiological findings generated through the FilmArray Pneumonia Panel is complicated by considerable heterogeneity among published studies. Some investigations have specifically examined samples that were already positive for bacterial pathogens on the panel. Such study designs inherently increase the probability of identifying bacterial–viral co-infections and may overestimate the frequency of viral involvement in the broader population with lower respiratory tract infection [9-11]. Other investigations have combined community-acquired and hospital-acquired respiratory infections, despite important differences in pathogen distribution, host characteristics, antimicrobial exposure, and disease mechanisms. Studies restricted predominantly to patients with SARS-CoV-2 infection also provide limited information regarding the broader epidemiology of respiratory viruses [11,12]. These methodological differences make direct comparison of viral detection rates difficult and demonstrate the need for standardized study populations and diagnostic definitions.

Across published studies, viral detection using the FilmArray Pneumonia Panel has ranged from approximately 15% to 51%, while bacterial–viral co-infections have been reported in approximately 10% to 38% of cases [13-22]. The wide variation in these estimates likely reflects

differences in patient selection, disease severity, geographic setting, timing of sampling, specimen type, seasonal circulation of viruses, and definitions of pneumonia. The findings nevertheless indicate that respiratory viruses represent a substantial component of the pathogen spectrum in lower respiratory tract infections. Importantly, the detection of viral pathogens may be greater when lower respiratory tract specimens are examined rather than relying exclusively on nasopharyngeal samples. In one study, the FilmArray Pneumonia Panel detected almost twice as many viral pathogens as standard-of-care testing, an observation attributed in part to the broader application of sputum-based testing compared with nasopharyngeal sampling [18]. This finding supports the potential value of lower respiratory tract molecular diagnostics in selected patients with suspected viral pneumonia. However, the interpretation of this apparent increase in diagnostic yield requires caution. In approximately 95% of cases in which the FilmArray Pneumonia Panel represented the only method identifying a virus, standard-of-care viral testing had not been performed [[18]]. Therefore, the available evidence cannot establish with certainty whether the pneumonia panel identified additional true infections that would have been missed by conventional testing or whether differences in sampling and diagnostic strategy accounted for the observed discrepancy. This limitation highlights an important distinction between analytical sensitivity and clinical utility. A molecular assay may detect more viral nucleic acid without necessarily improving patient outcomes. The ultimate value of a diagnostic test depends on whether its results modify clinical decisions in a manner that improves treatment, reduces unnecessary antimicrobial exposure, supports appropriate infection-control measures, or improves patient outcomes.

The identification of a respiratory virus may have several potential consequences for clinical management. A confirmed viral etiology can support targeted antiviral treatment when an effective antiviral agent exists, assist decisions regarding the continuation or discontinuation of empirical antibacterial therapy, and provide information relevant to infection-control measures. It may also contribute to prognostic assessment in critically ill patients. However, these benefits depend on accurate interpretation of molecular findings. A positive result should be integrated with the patient's clinical presentation rather than considered independently. The presence of bacterial co-infection is particularly important because detection of a virus does not exclude simultaneous bacterial disease. Conversely, detection of bacterial nucleic acid does not always establish active bacterial pneumonia. Quantitative results, clinical findings, radiological evidence, inflammatory markers, and microbiological culture may therefore remain important components of diagnostic assessment. Overall, multiplex molecular testing has expanded the ability to identify respiratory viruses in patients with lower respiratory tract infections and has demonstrated that viral pathogens may contribute substantially to severe pneumonia. Its principal strength lies in rapid and simultaneous detection of multiple pathogens, including viruses that may not be routinely investigated using standard diagnostic strategies. Nevertheless, molecular positivity must be interpreted within the clinical and anatomical context because detection does not always establish causation. Differences between upper and lower respiratory tract sampling, prolonged viral shedding, asymptomatic carriage, bacterial–viral co-infection, and study population heterogeneity remain important limitations. Current evidence supports the use of multiplex molecular diagnostics as a valuable component of the evaluation of severe respiratory infections, particularly in critically ill patients, but the extent to which these technologies improve therapeutic decisions and clinical outcomes remains uncertain. Future prospective studies should evaluate whether molecular-guided management reduces inappropriate antimicrobial treatment, improves antiviral utilization, shortens intensive care or hospital stay, and ultimately reduces morbidity and mortality among patients with severe lower respiratory tract infections.

Physiopathology of Respiratory Viral Infections

Epithelial Tropism and Viral-Induced Cell Death

Respiratory viral infections produce pulmonary disease through a combination of direct viral replication, epithelial injury, disruption of airway defenses, and subsequent host-mediated inflammation. Influenza viruses, respiratory syncytial virus, and human metapneumovirus have a particular tropism for respiratory epithelial cells and can infect different anatomical regions extending from the upper airway to the distal bronchioles and alveolar compartments. Influenza demonstrates a broad cellular tropism that includes ciliated epithelial cells within the upper respiratory tract as well as secretory epithelial cells and type I and type II alveolar epithelial cells in the lower respiratory tract [23,24]. The ability of influenza virus to involve distal pulmonary structures is important in severe disease because injury to alveolar epithelial cells can compromise gas exchange and contribute to hypoxemia and acute respiratory failure. Evidence regarding the distribution of α2-6-linked sialic acid receptors has further contributed to understanding how influenza infection can extend beyond the upper airway. Although these receptors are predominantly expressed within the upper respiratory tract, their presence within respiratory bronchioles provides a potential route for viral infection and dissemination into the lower airways [25,26]. Once the distal respiratory epithelium becomes infected, viral replication and associated cellular injury can contribute to alveolar instability, impaired surfactant

function, epithelial barrier disruption, and alveolar collapse. Respiratory syncytial virus and human metapneumovirus similarly produce substantial epithelial injury, although their mechanisms and patterns of tissue involvement may differ from those associated with influenza. Both viruses can interfere with epithelial tight junctions and impair coordinated ciliary activity, thereby weakening the physical and functional barriers that normally restrict pathogen dissemination throughout the respiratory tract [27,28]. Disruption of tight junction integrity increases epithelial permeability and facilitates access of inflammatory mediators and pathogens to deeper tissue compartments. At the same time, impaired ciliary function compromises mucociliary clearance, allowing infected cellular debris, mucus, and microorganisms to remain within the airways for longer periods. These processes can contribute to airway obstruction, impaired ventilation, and progression from localized infection toward more extensive lower respiratory tract disease. Adenoviruses, although detected less frequently than influenza, RSV, or hMPV in severe respiratory infections, can also produce substantial pulmonary injury and may cause extensive alveolar involvement even among immunocompetent individuals [29,30].

Direct virus-induced cellular death represents another central component of respiratory tissue injury. Viral replication can activate intracellular pathways leading to apoptosis, necrosis, and other forms of regulated or uncontrolled cellular injury [31,32]. Influenza and RSV, for example, can induce mitochondrial dysfunction and activate caspase-dependent pathways, resulting in loss of infected epithelial cells and impairment of normal tissue repair [33,34]. The consequences extend beyond the death of individual infected cells because extensive epithelial loss can compromise the continuity of the respiratory barrier. Damage to type I alveolar epithelial cells interferes with gas exchange, while injury to type II alveolar epithelial cells can affect epithelial regeneration and pulmonary surfactant homeostasis. These effects become clinically important when viral injury is extensive enough to produce diffuse alveolar damage and severe impairment of pulmonary oxygenation. Experimental studies using advanced models, including respiratory organoids and transcriptomic approaches, have provided additional evidence that respiratory viruses can directly infect and damage alveolar epithelial populations [27,35]. Such findings support the concept that severe respiratory viral disease cannot be explained solely by upper airway infection. Instead, certain viruses can establish infection throughout multiple regions of the respiratory tree and directly affect cells that maintain alveolar structure and gas exchange. The combination of viral cytotoxicity, epithelial barrier failure, impaired mucociliary clearance, and loss of alveolar integrity provides a biological basis for progression from viral respiratory infection to severe lower respiratory tract infection and acute respiratory failure.

Immune Dysregulation and Inflammation-Mediated Injury

Although direct viral cytotoxicity contributes substantially to pulmonary injury, the host immune response represents another major determinant of disease severity. Activation of innate and adaptive immunity is necessary to control viral replication and eliminate infected cells. However, excessive or poorly regulated inflammation can transform an appropriate antiviral response into a major source of tissue injury [36]. The severity of respiratory viral disease therefore reflects the interaction between viral replication and the intensity, timing, and regulation of the host immune response. In severe infections, inflammatory pathways can become amplified beyond the level required for effective pathogen control, resulting in damage to the alveolar epithelium, pulmonary endothelium, and surrounding interstitial tissues. Influenza provides a well-characterized example of inflammation-mediated lung injury. Viral infection activates alveolar macrophages, dendritic cells, and other components of innate immunity, resulting in the production of inflammatory mediators including tumor necrosis factor-alpha, interleukin-6, and type I interferons [37]. These mediators contribute to recruitment and activation of immune cells and initiate adaptive antiviral responses. However, excessive production can produce a state of uncontrolled systemic and pulmonary inflammation frequently described as a cytokine storm. Excessive cytokine signaling increases vascular permeability, promotes inflammatory cell infiltration, and contributes to diffuse alveolar damage. In severe cases, these mechanisms can progress to acute respiratory distress syndrome, characterized by impaired alveolar gas exchange and profound hypoxemia [37].

RSV also activates innate immune pathways within respiratory epithelial cells. Engagement of toll-like receptors stimulates the production of inflammatory chemokines, including interleukin-8, which promotes recruitment of neutrophils and monocytes into infected respiratory tissues [27,38]. These cells play an important role in pathogen elimination but can simultaneously intensify pulmonary injury. Activated neutrophils generate reactive oxygen species and release proteolytic enzymes that can damage epithelial and endothelial structures. When recruitment becomes excessive or persists after effective viral control, the inflammatory response may therefore contribute more substantially to tissue injury than the direct cytopathic effects of the virus. Alveolar macrophages represent another important component of this process. These cells

contribute to pathogen recognition, inflammatory signaling, viral clearance, and restoration of tissue homeostasis. During severe respiratory viral infection, however, macrophages may acquire a strongly pro-inflammatory phenotype and release mediators such as TNF-α and interferon-gamma. Excessive activation can increase epithelial injury and disturb normal alveolar function [37]. CD8+ T lymphocytes provide another essential antiviral mechanism by recognizing and eliminating infected epithelial cells. Although this response limits viral replication, excessive cytotoxic activity can result in destruction of uninfected or structurally important tissue and may contribute to persistent inflammation and subsequent fibrotic remodeling [37]. The interaction between viral infection and bacterial superinfection further complicates the inflammatory response. Viral injury to the epithelial barrier and impairment of mucociliary clearance reduce the respiratory tract's ability to eliminate bacterial pathogens. Consequently, patients with viral respiratory infections may become susceptible to secondary bacterial pneumonia, particularly infections caused by *Streptococcus pneumoniae* and *Staphylococcus aureus* [39-41]. This susceptibility results from several interacting mechanisms, including epithelial disruption, altered airway clearance, changes in innate immune function, and impairment of alveolar macrophage activity. Interferon-gamma may further suppress macrophage-mediated bacterial clearance, creating an environment in which bacterial pathogens can establish secondary infection [39-41]. The resulting bacterial–viral interaction can intensify pulmonary inflammation, increase tissue destruction, and contribute to clinical deterioration.

Histopathological Evidence from Human Studies

Human histopathological studies provide direct evidence that respiratory viruses can produce extensive structural injury within the lower respiratory tract. Autopsy and biopsy findings from patients with severe influenza, RSV, hMPV, and adenovirus infection demonstrate that viral pneumonia involves both the conducting airways and distal pulmonary structures. In severe influenza infection, characteristic pathological findings include necrotizing bronchitis and bronchiolitis, diffuse alveolar damage, formation of hyaline membranes, pulmonary edema, and extensive inflammatory cell infiltration [42]. These findings indicate that severe influenza is not limited to superficial epithelial infection but can involve the alveolar compartment and produce the structural changes associated with severe impairment of pulmonary gas exchange. The histopathological changes observed in RSV infection demonstrate a similar capacity for extensive airway and alveolar injury. Sloughing of bronchiolar epithelial cells, accumulation of mucus within the airways, and neutrophilic alveolitis are frequently described pathological features [43]. Loss of epithelial cells and accumulation of mucus can narrow or obstruct small airways, impair ventilation, and produce regional abnormalities in ventilation-perfusion matching. At the alveolar level, inflammatory infiltration can interfere with gas exchange and contribute to hypoxemia. These mechanisms are particularly important in severe disease because simultaneous airway obstruction and alveolar inflammation can substantially increase the work of breathing and contribute to respiratory failure. Adenovirus can also produce severe structural pulmonary injury. Histological examination has demonstrated necrotizing bronchopneumonia and interstitial inflammatory changes, with severe pulmonary disease reported even among immunocompetent patients [44]. This observation is clinically important because severe viral pneumonia is not restricted to patients with major immunosuppression. Adenoviral infection can produce substantial tissue destruction in otherwise immunocompetent individuals, emphasizing the role of viral characteristics and host inflammatory responses in determining disease severity.

Available histopathological evidence concerning hMPV is more limited than that available for influenza or RSV. Nevertheless, reported findings support the capacity of hMPV to produce interstitial and alveolar inflammation [45]. The available pathological evidence complements molecular and experimental findings by demonstrating that respiratory viruses can produce structural changes consistent with severe lower respiratory tract disease. Across these viral infections, several common pathological processes emerge, including epithelial necrosis, airway inflammation, alveolar injury, interstitial inflammation, edema, and impaired pulmonary architecture. Taken together, the physiological and pathological evidence demonstrates that severe respiratory viral infection develops through interconnected mechanisms rather than a single pathogenic pathway. Viral tropism permits infection of epithelial cells throughout the respiratory tract, while direct cytotoxic effects produce epithelial loss and barrier disruption. The host immune response subsequently contributes to viral clearance but can also intensify tissue injury when inflammatory activation becomes excessive. Histopathological changes such as necrotizing bronchitis, bronchiolitis, diffuse alveolar damage, hyaline membrane formation, edema, and inflammatory infiltration provide structural evidence of these processes [23-45]. The resulting disruption of airway integrity, mucociliary clearance, alveolar structure, and gas exchange explains how respiratory viral infections can progress from localized respiratory symptoms to severe lower respiratory tract infection, acute hypoxemic respiratory failure, and acute respiratory distress syndrome. This multifactorial pathophysiology also explains why management of severe viral respiratory disease

requires attention not only to viral replication but also to respiratory support, inflammatory injury, secondary bacterial infection, and preservation of pulmonary function.

Clinical Consequences of Respiratory Virus in Severe Acute Respiratory Failure in ICU

Severe respiratory viral infections represent an important cause of intensive care unit admission and may produce a broad spectrum of clinical manifestations, ranging from acute respiratory failure without radiographic evidence of pneumonia to severe viral pneumonia associated with hypoxemia, diffuse pulmonary injury, and the need for mechanical ventilation. The clinical course is influenced by the specific viral pathogen, the extent of lower respiratory tract involvement, host age, baseline functional status, and the presence of chronic comorbidities. Non-pneumonic acute respiratory failure may occur when viral infection precipitates deterioration of pre-existing cardiopulmonary disease rather than producing direct extensive pulmonary parenchymal injury. This pattern is particularly relevant among patients with chronic obstructive pulmonary disease, in whom viral infections can trigger airway inflammation, bronchospasm, increased mucus production, and worsening ventilation-perfusion mismatch. Cardiovascular disease may also be destabilized during acute respiratory viral infections, resulting in decompensated heart failure, myocardial ischemia, arrhythmias, or other acute cardiovascular events [46]. The systemic effects of respiratory viral infections are increasingly recognized as an important component of severe disease. RSV infection, for example, has been associated with clinically significant cardiovascular complications among older adults requiring hospitalization. In a large cohort of 6248 adults aged 50 years or older with laboratory-confirmed RSV infection, 22.4% developed an acute cardiac event. Acute heart failure occurred in 15.8% of patients, acute ischemic heart disease in 7.5%, and hypertensive crises in 1.3% [47]. These observations indicate that the clinical consequences of respiratory viruses extend beyond the respiratory system. Influenza has also been associated with a substantial short-term increase in vascular events. During the first three days following laboratory-confirmed influenza infection, the incidence of myocardial infarction increased nearly tenfold, with an incidence rate ratio of 9.80, while the incidence of stroke increased approximately twelvefold, with an incidence rate ratio of 12.3 [48]. Such associations may reflect the combined effects of systemic inflammation, endothelial dysfunction, increased metabolic demand, thrombogenic activity, and destabilization of pre-existing cardiovascular disease. Consequently, assessment of critically ill patients with respiratory viral infections should extend beyond respiratory parameters and include evaluation for concurrent cardiovascular deterioration.

Respiratory viruses also constitute an important cause of community-acquired pneumonia, particularly among adults presenting with severe respiratory disease. Viral pathogens have been identified in approximately 30% to 40% of community-acquired pneumonia cases, although the reported proportion varies according to patient characteristics, season, diagnostic methods, sampling techniques, and the range of pathogens included in testing [5],[49],[50],[51]. Common clinical manifestations include fever, cough, myalgia, anorexia, headache, dyspnea, and constitutional symptoms. The incubation period for many respiratory viruses is generally seven days or less [52]. However, these clinical manifestations lack sufficient specificity to establish a viral etiology. Fever, cough, hypoxemia, inflammatory marker elevation, and radiological abnormalities can occur in both viral and bacterial pneumonia. Therefore, clinical presentation alone cannot reliably distinguish viral pneumonia from bacterial pneumonia, particularly in patients with severe disease [5,53]. The development of severe viral pneumonia can result from the interaction between direct viral epithelial injury and an excessive host inflammatory response. Damage to airway and alveolar epithelial cells compromises the pulmonary barrier and impairs mucociliary clearance. This process can increase airway secretions, promote alveolar inflammation, and interfere with gas exchange. In critically ill patients, progressive alveolar injury may lead to worsening hypoxemia and acute respiratory distress, ultimately requiring invasive or non-invasive respiratory support. The severity of respiratory compromise is therefore determined not only by viral replication but also by the host inflammatory response and the ability of the respiratory system to maintain adequate oxygenation and ventilation.

Bacterial co-infection represents another major clinical consequence of severe respiratory viral infection. Viral-induced epithelial disruption, impaired mucociliary clearance, and alterations in innate immune function can facilitate bacterial invasion of the lower respiratory tract. Bacterial pathogens may therefore emerge during or shortly after the initial viral infection. Co-infections have been reported in up to 25% of patients with viral pneumonia and are associated with a more severe clinical course, including increased rates of sepsis and mechanical ventilation [5,54]. The presence of bacterial co-infection can complicate diagnostic assessment because respiratory symptoms and inflammatory findings may be attributed initially to the viral infection. Conversely, detection of a respiratory virus does not exclude a simultaneous bacterial infection. This distinction is particularly important in ICU patients, in whom delayed

recognition of bacterial infection may contribute to clinical deterioration. Severe respiratory viral infection may therefore produce a continuum of clinical consequences rather than a single disease phenotype. Patients may present with isolated viral airway disease, exacerbation of chronic respiratory or cardiovascular disease, viral pneumonia, secondary bacterial pneumonia, sepsis, or progressive acute respiratory failure. The transition between these clinical states can occur rapidly in critically ill patients. Respiratory therapists play an important role in monitoring oxygenation, ventilation, respiratory mechanics, and response to respiratory support. Pharmacists contribute to antiviral therapy, antimicrobial stewardship, drug interaction assessment, and optimization of treatment in patients with complex comorbidities. Laboratory professionals support pathogen identification through molecular diagnostics and interpretation of microbiological results, while radiologists contribute to the assessment of pulmonary involvement and alternative causes of respiratory deterioration. Nurses provide continuous clinical assessment and monitoring of respiratory and systemic deterioration, while physicians integrate these findings into diagnostic and therapeutic decisions.

The recognition of these consequences supports a multidisciplinary approach to severe respiratory viral infections in the ICU. Molecular identification of viral pathogens can provide important diagnostic information, but results should be interpreted alongside clinical findings, radiological evidence, microbiological investigations, and the patient's underlying risk profile. Early recognition of respiratory deterioration, cardiovascular complications, and bacterial co-infection is essential because these factors may substantially influence the requirement for mechanical ventilation, ICU length of stay, and overall clinical outcome. Respiratory viral infections should therefore be regarded as potentially systemic illnesses capable of producing direct pulmonary injury, exacerbating chronic disease, and precipitating complications across multiple organ systems.

Outcomes

Severe respiratory viral infections can produce substantial morbidity and mortality among hospitalized and critically ill adults. However, population-based studies directly comparing outcomes between respiratory viruses remain limited. Available evidence indicates that prognosis varies according to the causative virus, patient age, underlying comorbidities, presence of bacterial co-infection, and development of extrapulmonary complications. Bajema et al. evaluated 219,577 non-hospitalized U.S. veterans with a median age of 66 years who underwent same-day testing for SARS-CoV-2, influenza, and RSV during the autumn–winter seasons of 2023 and 2024. Among patients with a single positive result, SARS-CoV-2 accounted for 63%, influenza for 26%, and RSV for 11% [64]. The 30-day hospitalization risk was comparable between SARS-CoV-2 and influenza infections, at 16.2% and 16.3%, respectively, while RSV was associated with a slightly lower risk of 14.3%. ICU admission occurred in 3.0% of SARS-CoV-2 cases, compared with 1.8% of RSV cases and 1.5% of influenza cases. Importantly, 90-day mortality was relatively similar across the three infections, at 1.8% for SARS-CoV-2, 1.4% for RSV, and 1.3% for influenza [64]. Among ICU patients, viral community-acquired pneumonia can produce a clinical severity comparable to bacterial pneumonia. Mechanical ventilation may be required for prolonged periods, with median durations commonly ranging from 7 to 10 days, while reported mortality rates range from approximately 10% to 30% [5],[50],[65],[66]. Influenza and RSV are among the respiratory viruses most consistently associated with severe disease in hospitalized and critically ill populations. Grangier et al. reported similar ICU lengths of stay for RSV and influenza, ranging from six to seven days, with mortality rates of 29% and 25%, respectively [[65]]. Similarly, Coussement et al. identified no significant difference in ICU mortality between patients with RSV and influenza, reporting mortality rates of 23.9% and 25.6%, respectively [[67]]. These findings suggest that both pathogens can produce substantial critical illness in adults and should not be regarded as infections with limited clinical consequences.

Human metapneumovirus also has clinically important implications despite being detected less frequently. Studies have reported ICU admission rates ranging from 10% to 30%, with early mortality estimates between 3% and 10% [61],[68],[69]. In contrast, the clinical significance of several other respiratory viruses in immunocompetent adults remains less certain. Adenovirus can produce severe pneumonia, particularly in immunocompromised populations, but severe disease appears less frequent among healthy adults. In a study of military trainees, only 4.7% of adenovirus infections required ICU admission, while severe manifestations such as acute respiratory distress syndrome were uncommon [50],[70],[71]. Parainfluenza viruses are also frequently detected but generally produce less severe disease in immunocompetent adults, with reported ICU mortality of approximately 3% and limited requirements for mechanical ventilation [72],[73]. The prognostic significance of rhinovirus remains difficult to determine. Retrospective ICU studies have reported mortality rates approaching 30%, but interpretation is complicated by the frequent presence of bacterial or viral co-infections and underlying chronic diseases [74],[75]. Similarly, seasonal human coronaviruses, including OC43, NL63, and 229E, are infrequently identified as primary causes of severe pneumonia in immunocompetent adults. Their detection may not necessarily establish a causal

relationship with severe lower respiratory tract disease [50],[76],[77]. Human bocavirus presents a similar diagnostic challenge, as adult cases involving acute respiratory distress syndrome or ICU admission have been reported only sporadically [78,79]. These observations emphasize that detection of a respiratory virus should be interpreted within the clinical context rather than considered an independent indicator of disease severity.

Bacterial co-infection is a major determinant of outcome among critically ill patients with viral respiratory infections. Mixed bacterial–viral infections have been reported in up to 25% of cases, although estimates vary according to patient characteristics, diagnostic methods, and the extent of microbiological sampling [5],[46],[50],[51],[80],[81],[82],[83]. Voiriot et al. reported substantially worse outcomes among patients with mixed infections. Mechanical ventilation and mortality were more frequent in patients with bacterial–viral co-infection, with mortality reaching 28.9% compared with 13% among patients with isolated bacterial infection and 11.3% among those with isolated viral infection [5]. A meta-analysis further demonstrated that mixed infections were associated with approximately twice the risk of mortality, with an odds ratio of 2.1 [51]. In a database study involving 15,906 patients with viral respiratory infections, mixed infections were associated with almost threefold higher odds of ICU admission and substantially increased 30-day mortality [82]. These findings indicate that identification of a respiratory virus does not exclude bacterial disease and that recognition of co-infection may have important prognostic implications. Cardiovascular complications further contribute to adverse outcomes. In patients hospitalized with RSV infection, acute cardiac events were associated with substantially higher ICU admission and in-hospital mortality. ICU admission occurred in 25.8% of patients with acute cardiac events compared with 16.5% without such events, while in-hospital mortality was 8.1% compared with 4.0%, respectively [47]. These findings demonstrate the importance of assessing cardiovascular status in patients with severe respiratory viral infections, particularly older adults and those with pre-existing cardiovascular disease.

The risk of severe outcomes is strongly influenced by patient characteristics. Advanced age and underlying cardiopulmonary disease are among the most consistent predictors of poor prognosis in immunocompetent adults [92,93]. RSV hospitalization rates increase markedly among individuals aged 65 years or older, reaching 136.9–255.6 per 100,000 population, with substantially greater risks among patients with COPD, coronary artery disease, or heart failure [[94]]. Severe respiratory viral infections may also produce consequences extending beyond the acute hospitalization. Approximately 33% of patients hospitalized with RSV have been reported to experience persistent functional impairment six months after discharge [95]. Influenza similarly produces disproportionate morbidity among individuals with pre-existing medical conditions, increasing the risks of hospitalization, ICU admission, and death [93]. Overall, outcomes following severe respiratory viral infection depend on a combination of viral characteristics and host-related factors. Influenza, RSV, and hMPV can produce severe lower respiratory tract disease requiring prolonged respiratory support, while other respiratory viruses generally demonstrate less consistent associations with critical illness in immunocompetent adults. Bacterial co-infection, cardiovascular complications, advanced age, and cardiopulmonary comorbidities further increase the likelihood of adverse outcomes. These findings support early identification of high-risk patients and close monitoring for respiratory and systemic complications. Preventive strategies remain particularly important for vulnerable populations, with vaccination against influenza and RSV representing key measures for reducing severe disease and its associated complications [96].

Treatment of Severe Respiratory Viral Infections

Management of severe respiratory viral infections in the intensive care unit is based on respiratory support, pathogen-directed antiviral therapy when available, careful use of immunomodulatory treatment, and prevention of secondary complications. Evidence remains stronger for influenza and SARS-CoV-2 than for other respiratory viruses. Therefore, treatment decisions for non-COVID-19 viral pneumonia often depend on the severity of respiratory failure, the identified pathogen, comorbidities, and the presence of bacterial co-infection.

Noninvasive Respiratory Support

Noninvasive respiratory support has become an important component of acute hypoxemic respiratory failure management. High-flow nasal cannula (HFNC) can provide heated and humidified oxygen at high flow rates and may reduce the need for invasive mechanical ventilation in selected patients. In the COVID-19-ICU cohort of 4754 patients, HFNC was associated with lower oxygenation failure than standard oxygen therapy (adjusted OR 0.60, 95% CI 0.36–0.99). However, noninvasive ventilation was associated with increased 90-day mortality (adjusted OR 2.75, 95% CI 1.79–4.21) [97]. These observational findings were not confirmed by the COVIDICUS randomized trial, which found no significant difference in 28-day intubation between HFNC, CPAP, and standard oxygen [98]. Evidence specific to non-COVID-19 viral pneumonia remains limited. A 2024 meta-analysis involving 10,230 patients found that HFNC

reduced escalation to invasive ventilation compared with conventional oxygen therapy (RR 0.85, 95% CI 0.76–0.95), but did not reduce hospital mortality (RR 1.08, 95% CI 0.93–1.26). Thus, HFNC may be appropriate for selected patients with hypoxemic respiratory failure, but no specific noninvasive strategy has established superiority in non-COVID-19 viral pneumonia.

Antiviral Therapy

Antiviral treatment is most established for severe influenza. Neuraminidase inhibitors, particularly oseltamivir, remain the principal treatment. A meta-analysis of eight randomized trials found no significant mortality or ICU admission benefit compared with placebo, although oseltamivir and peramivir reduced hospital stay by approximately 1.6 and 1.7 days, respectively [99]. Observational evidence suggests that prolonged oseltamivir therapy may benefit critically ill patients, but randomized confirmation is required [100]. Combination therapy and newer agents such as baloxavir have not demonstrated clear superiority over standard neuraminidase inhibitor treatment [101,102]. Treatment options for RSV remain limited. Ribavirin has inconsistent efficacy and potential toxicity, restricting its use in immunocompetent adults [81,103]. New antiviral agents are under investigation. For most other respiratory viruses, management remains supportive and includes oxygen therapy, ventilatory support, fluid management, and surveillance for bacterial superinfection.

Immunomodulation

The use of corticosteroids in viral pneumonia remains uncertain. Evidence from influenza-associated pneumonia has linked corticosteroid treatment with increased mortality and hospital-acquired infections [115]. However, these findings may reflect treatment of patients who were already more severely ill. An individual participant data meta-analysis of severe community-acquired pneumonia found no significant treatment-effect difference according to microbiological cause, although mortality estimates generally did not favor corticosteroids in viral and influenza-associated pneumonia [116]. Therefore, corticosteroids should not be used routinely for viral pneumonia unless another established indication exists. Their use should consider the risk of delayed viral clearance and secondary infection.

Vaccination as a Key Strategy Against Severe Respiratory Viral Infections

Vaccination remains the main strategy for preventing severe respiratory viral disease, particularly among older adults and individuals with cardiopulmonary comorbidities. Influenza vaccination reduces laboratory-confirmed influenza among adults aged ≥65 years and contributes to lower influenza-associated mortality [118,119]. Its effectiveness varies according to the match between vaccine strains and circulating viruses. RSV vaccination has also demonstrated substantial protection in older adults. Real-world data from 2023–2024 showed 77% effectiveness against RSV-associated emergency department visits, 80% against hospitalization, and 81% against ICU admission or death among adults aged ≥60 years [121]. Maintaining vaccination coverage is also important for viruses that have become uncommon but can re-emerge when immunization declines. Measles illustrates this risk. The recommended two-dose vaccination strategy provides approximately 90–99% protection [124]. Although pneumonitis is usually mild in immunocompetent individuals, approximately 3% of infected patients may develop acute respiratory failure requiring ICU admission [125]. Severe ICU disease has been associated with incomplete vaccination and can progress to ARDS and death [126]. Overall, treatment of severe respiratory viral infections requires early recognition of respiratory deterioration, appropriate oxygen and ventilatory support, targeted antiviral therapy when evidence supports its use, and cautious selection of immunomodulatory treatment. Vaccination remains central to reducing ICU admissions, severe complications, and mortality.

Conclusion:

Severe respiratory viral infections represent an important cause of acute respiratory failure and ICU admission in immunocompetent adults. Molecular diagnostic techniques have improved pathogen detection and demonstrated that respiratory viruses contribute substantially to lower respiratory tract infections. However, interpretation requires consideration of sampling site, viral persistence, bacterial co-infection, and clinical context. The pathophysiology involves direct epithelial injury, disruption of mucociliary function, immune-mediated inflammation, diffuse alveolar damage, and impaired pulmonary defense mechanisms. Influenza, RSV, and hMPV have the strongest association with severe outcomes. Older age, cardiopulmonary comorbidities, bacterial co-infection, and cardiovascular complications increase the risk of ICU admission and death. Treatment remains centered on appropriate respiratory support and intensive monitoring. Oseltamivir remains important for severe influenza, while therapeutic options for most other respiratory viruses remain limited. Corticosteroids should be used selectively because evidence for benefit in viral pneumonia remains uncertain. Vaccination against influenza and RSV provides an important means of reducing severe disease. Further randomized studies are needed to define optimal diagnostic and therapeutic strategies for non-COVID-19 viral pneumonia.

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