Review

Severe respiratory syncytial virus disease

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ABSTRACT

The burden of respiratory syncytial virus (RSV) disease is widely recognized. Main risk factors for severe disease, such as extreme ages, chronic cardiopulmonary conditions, and immunosuppression, typically coincide with poorer outcomes. While the majority of RSV hospitalizations involve healthy children, a higher proportion of hospitalized adults with underlying conditions need intensive care. Presently, treatment primarily consists of supportive measures. RSV-induced wheezing should be distinguished from respiratory tract thickening, without response to bronchodilators. Obstructive RSV disease frequently overlaps with viral pneumonia. Non-invasive mechanical ventilation and high-flow oxygen therapy represented significant advancements in the management of severe RSV disease in children and may also hold considerable importance in specific phenotypes of RSV disease in adults. Most severe infections manifest with refractory hypoxemia necessitating more advanced ventilatory support and/or extracorporeal membrane oxygenation therapy. Although bacterial co-infection rates are low, they have been associated with worse outcomes. Antibiotic prescription rates are high. Accurately diagnosing bacterial co-infections remains a challenge. Current evidence and antibiotic stewardship policies advise against indiscriminate antibiotic usage, even in severe cases. The role of currently developing antiviral therapies in severe RSV disease will be elucidated in the coming years, contingent upon the success of new vaccines and immune passive strategies involving nirsevimab.

Introduction

In the post-pandemic era, a shift in seasonal pattern and severity of respiratory syncytial virus (RSV) has been reported worldwide[1–3] in addition to the RSV disease burden in the adult population.[4–6] The immunity gap due to the pandemic measures, an increased RSV virulence, and a potential interaction between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and RSV along with the persistent immunological dysfunction following coronavirus disease 2019 (COVID-19) are the proposed reasons for this increase of RSV infection and severity,[7–9] apart from its raising awareness.[10] Höne-mann et al.[3] reported a mean age significantly younger in the post-pandemic adult RSV cohort (47.1 years vs. 64.7 years) compared to pre-pandemic seasons. Furthermore, concerns regard-

ing the burden of severe RSV disease among immunocompromised adults and children have persisted since pre-pandemic years.[11,12]

While existing definitions largely agree on cases of lower respiratory tract infections (RSV-LRTI), there remains a necessity to establish a standardized definition for severe RSV disease.[13] Severity assessment typically relies on criteria such as oxygen requirement, hospitalization, escalation of respiratory support, or intensive care unit (ICU) admission (Table 1). Clinical scores in children[14] and adults[15] are designed to predict the need for respiratory support mainly, but lack sufficient validation.[14] The aim of this narrative review is to depict risk factors and phenotypes of severe RSV disease that are critical for its current management. For the purposes of this review, severe RSV disease will be defined as extended severe acute respiratory

infection proposed by the World Health Organization global surveillance system for RSV.[16] Comprehensive updates on recently approved vaccines, monoclonal antibody use for prevention,[17] and ongoing advances in investigational therapeutic drugs[18] have been extensively covered in recent publications and are beyond the scope of the present review.

Epidemiology

Previously, healthy children <5 years represent the majority of RSV hospitalizations in childhood with low rates of intensive care admissions (2.3%) but higher and longer ICU stay compared with other viruses, including SARS-CoV-2.[10,19–21] Hospitalized RSV-infected adults and seniors (≥ 60-year-old) account for only 1% and 4% of the overall hospitalizations,[10] respectively, yet present higher proportions of underlying comorbidities (78%–90%) and have 5–10 fold increased risk for ICU admission (12%–26.9%) compared to children.[10,22–24] Among adults, the risk for ICU admission was higher for RSV compared to influenza (odds ratio [OR]=1.6) but lower than for SARS-CoV-2 (OR=0.37),[25] prior to the emergence of the Omicron variant and the introduction of COVID-19 vaccines. Recent data indicated that among hospitalized seniors, RSV was still less common, but associated with more severe disease than SARS-CoV-2 (adjusted odds ratio [aOR]=1.49) or influenza (aOR=1.55).[26] According to the RSV-Associated Hospitalization Surveillance Network and the overall RSV-ICU admission rates reported[10] among 605.2 hospitalizations per 100,000 <5 year-children and 90.9 per 100,000 adults during the 2022–2023 season, the overall estimated ICU admission rates were 13.2 per 100,000 children <5 years and 19.2 per 100,000 per adults. Among RSV-immunocompromised hospitalized patients, 28% for children[27] and 36% for adults.[28]

Risks Factors for Severe RSV Disease

Frequently, risk factors for RSV hospital admission overlap with risk factors for worse outcomes (Table 2). Age (younger than 3 months or >60 years) and chronic cardiopulmonary conditions have been defined as the main risk factors for severe RSV disease.[10,22–24,29–34] Hospitalization rates among senior adults were up 9-fold higher compared to other adults.[35] In comparison to influenza infection, adults with chronic obstructive pulmonary disease (COPD) were more susceptible to RSV infection and mechanical respiratory support.[36] Adult patients in the ICU with RSV infection also differ from adult patients with influenza, being more likely to have an underlying chronic respiratory condition and to be more immunocompromised.[37] Apart from immunocompromised status,[10,23,24] other RSV-high risk comorbidities described in adults include chronic renal disease and diabetes,[23,38] even in middle-aged RSV patients.[39] Surprisingly, Chatzis et al.[40] reported that adults with solid tumors (OR=5.2) or those requiring chronic immunosuppressive treatments, mainly for rheumatologic conditions (OR=4.1), were significantly more likely to be admitted to the hospital compared to hematopoietic stem cell (HSCT) recipients. This may be explained by a higher adherence to preventive measures among HSCT patients.

Among infants, a history of prematurity, low birth weight, or transient tachypnea of the newborn[41–43] was associated with severe RSV disease. Other higher-risk comorbidities in young children and infants, apart from cardiopulmonary conditions, include Down syndrome, neuromuscular, and metabolic disorders.[44,45] Nevertheless, most infants who require intensive care for RSV low respiratory tract infections are healthy and born at term.[46]

Viral factors may actively contribute to the clinical severity of RSV infection.[47–49] Serotype A is more prevalent and causes more severe cases in born–preterm infants.[47] Among adults, no clustering has been found according to severity.[50] A faster decline of viral loads is indicative of less severe RSV disease.[51] The role of viral co-detections remains unclear, and only RSV-human metapneumovirus co-infection was associated with a higher risk of ICU admission (OR=7.2) in children.[52] Interestingly, RSV and human metapneumovirus are very closely related viruses.[53] In adults, co-infection of RSV and influenza virus has been associated with higher rates of ICU admission, mechanical ventilation (MV), and mortality.[54]

Clinical Phenotypes of Severe RSV Infection: Wide Clinical Overlapping Phenotypes and Lack of Uniform Criteria

Bronchiolitis, bronchitis, viral pneumonia

Severe RSV disease manifests as acute-LRTI that can lead to respiratory failure and ICU admission across all age groups.[10] The typical diagnoses that belong to LRTI include bronchitis, bronchiolitis, and pneumonia. In newborns and infants up to 2 years old, its most specific manifestation is acute bronchiolitis, with subsequent episodes of RSV-induced wheezing/bronchitis occurring after the first RSV-infectious episode.[10,13,55] Children or adults with chronic cardiopulmonary conditions may also experience episodes of acute pulmonary decompensation, manifested by tachypnea, worsening gas exchange (e.g., increased oxygen requirement), and/or respiratory distress.

During a 10-year period, Niekler et al.[10] reported 49.5% of RSV-pneumonias in children, 62.9% in adults aged 18–59 years, and 60.2% in senior RSV-hospitalized patients. RSV-pneumonia, which often co-exists with obstructive phenotypes, can also progress to hyperinflammatory responses and pulmonary tissue damage, leading to acute respiratory distress syndrome (ARDS) at any age.[10] Notably, Estofolete et al.[56] found no significant differences in the manifestation of RSV between adult and senior patients, with wheezing and atelectasis being more common in RSV- compared to influenza-infected adults.[57] While certain groups of immunocompromised patients such as lung transplant and HSCT recipients are at higher risk for refractory hypoxemia and ventilator support, most severe RSV infections in the ICU often correspond to complicated viral pneumonias with bacterial co-infection and/or ARDS, even among immunocompetent non-senior adults[37] and previously healthy infants initially diagnosed with "simple" bronchiolitis.[13,58] This is consistent with data from two multicenter prospective studies showing no association between the day of illness admission and hospital outcomes among infants diagnosed with RSV-bronchiolitis, refuting a predictable disease trajectory and supporting the concept of overlapping phenotypes, particularly in severely hypoxemic cases.[46,59,60]

Additionally, there is a growing need for a more precise distinction between obstructive disease resulting solely from

Table 1
RSV Severity definition and risk factors.

Author (year)	Case number	Population	Clinical setting	Severity definition	Risks factors and other findings
Grimaldi et al. (2002)[31]	484	<1 year	General ward	Pediatric ICU admission	Term newborn (OR=0.86, 95 % CI: 0.75 to 0.98), neonatal distress syndrome (OR=4.23, 95 % CI:1.31 to 13.03), congenital heart disease (OR=5.26, 95 % CI:1.02–21.01)
Flamant et al. (2005)[58]	151	<1 year Mechanically ventilated	Pediatric ICU	Prolonged MV (>6 days) ECMO support	<32 GA (aOR=4.2, 95% CI:1.3 to 13.7), 33–36 GA (aOR=2.5, 95% CI:1.1 to 6.2), oxygen supplementation (aOR=3.4, 95% CI:1.2 to 10.4], BPD (aOR=11.9, 95% CI:1.4 to 10.0), bacterial colonization* (OR= 3.4, 95% CI:1.5 to 7.7) Only independent risk factor for ECMO support BPD (aOR=11.8, 95% CI: 2.2 to 63.1)
Ciarlitto et al. (2019)[47]	422	<1 year	General ward	Oxygen supplementation Pediatric ICU admission	RSV-A caused most of severe cases in the premature group Increased bronchiolitis severity over the years
Heinonen et al. (2019)[41]	1,042,045	<1 year	Population-based cohort	Hospital admission	Transient tachypnea of the newborn (OR=1.31, 95% CI:1.16 to 1.48)
Shmueli et al. (2019)[30]	1124	<2 years	General ward	Hospitalization LOS PICU admission PICU readmission rate	Chronic diseases Down's syndrome Respiratory tract malformation
Meenaghan et al. (2020)[42]	557	≤2 years	General ward	PICU admission	Younger age, being underweight at the point of admission (aOR=3.15, 95% CI:1.46 to 6.70), the use of HFNC
Zhang Y et al. (2020)[54]	574	≥18 years	General ward	ICU admission Invasive MV	Influenza-RSV virus co-infection (47.4%) vs. only RSV (20.1%) (P=0.004) Influenza-RSV virus co-infection (47.4%) vs. only RSV (13.2%) (P <0.001)
Nygaard et al. (2023)[32]	310,423	<18 years	Population-based cohort	Hospital admission MV	Increased severe RSV disease between the epidemic period (2020–2021) compared with the pre-COVID-19 seasons, mostly among children aged 24–59 months
Celante et al. (2023)[22]	1168	>18 years	General ward	Invasive MV	Chronic heart failure (aOR=1.98, 95% CI:1.20 to 3.26), respiratory failure (aOR=2.83, 95% CI:1.67 to 4.80), co-infection (aOR=2.62, 95% CI:1.60 to 4.30)
Hill-Ricciuti et al. (2023)[33]	244	>18 years	General ward	Respiratory support escalation Need for MV ICU admission	Hospital-acquired-RSV patients at higher risk for escalation resp support and chronic disease, less pulmonary conditions. Obesity. Community-acquired RSV, more pulmonary conditions
Saiman et al. (2023)[34]	122	≤18 years	General ward	Increased respiratory support Pediatric ICU admission	Respiratory comorbidities (aOR=3.36) for increased respiratory support
Kobialka et al. (2023)[100]	594	≤2 years	General ward	Oxygen therapy Respiratory failure PICU admission Prolonged hospital LOS	Bacterial pneumonia: Fever duration (OR=1.70, 95% CI:1.31 to 2.26), aspiration (OR=40.75, 95% CI:5.94 to 444.64), CRP (OR=1.06, 95% CI:1.02 to 1.10), PCT (OR=0.61, 95% CI:0.38 to 0.95), hypercapnia (OR=4.36, 95% CI:1.56 to 11.97) Respiratory failure: Apnea (OR=29.37, 95% CI: 3.12 to 231.43) Oxygen therapy: Apgar (OR=1.60, 95% CI:1.06 to 2.58), breastfeeding (OR=0.49, 95% CI: 0.26 to 0.92), dyspnea (OR=5.22, 95% CI: 2.43 to 12.51)
Descamps et al. (2022)[62]	539	>18 years	General ward	Respiratory failure, ARDS, ICU admission, invasive MV	Compared to influenza-positive hospitalized patients, RSV-positive hospitalized patients had higher adjusted risk for developing respiratory failure (aPR=1.6, 95% CI:1.1 to 2.3), ARDS (aPR=2, 95% CI:1.3 to 3.1), ICU admission (aPR=2, 95% CI:1.4 to 2.9), invasive MV (aPR=1.7, 95% CI:1.1 to 2.4).
Coussement et al. (2022)[37]	618	>18 years	ICU	ICU admission	Patients with RSV infection were significantly more likely to have an underlying chronic respiratory condition (60.2% vs. 40.1%; P <0.001) and to be immunocompromised (35% vs. 26.2%; P=0.02) than patients with influenza infection. Several differences in clinical signs and biological data at diagnosis were found between the groups. In-hospital mortality was not significantly different between the two groups (23.9% in the RSV group vs. 25.6% in the influenza group; P=0.63), even after adjustment for prognostic factors in a multivariate model
Sivgin et al. (2023)[39]	46	>18 years	General ward	Parenquimal infiltrates + oxygen supplementation (starting if oxygen saturation <90%)	Age (OR=1.17, 95% CI:1.06 to1.28 per unit change of age); hypertension (OR=13.9, 95% CI:2.5 to 75.9), diabetes (OR=17.4, 95% CI:3.4 to 87.5), heart failure (OR=10.3, 95% CI:2 to 53.2), bacterial co/superinfection (OR=15, 95% CI:3.1–73.6)
Tongyoo et al. (2023)[57]	335	>18 years	ICU	MV	RSV group had significantly higher proportions of bronchospasm (98.5% vs. 60.8%; P <0.001), ventilator-associated pneumonia (52.2% vs. 33.8%; P=0.005), and lung atelectasis (10.4% vs. 3.0%; P=0.009) than the non-RSV group.
Kim et al. (2023)[12]	257	>18 years	ICU	ICU admission	Structural lung disease, diabetes mellitus, and malignancy were common underlying diseases in RSV group and influenza group, with no statistically significant differences Immunocompromised state (57.6% vs. 34.4%; P <0.001) and hospital acquisition (47.8% vs. 23.9%; P <0.001) were significantly more common in the RSV group. Co-infection with Streptococcus pneumoniae (3.3% vs. 9.8%; P=0.08) and methicillin-susceptible Staphylococcus aureus (1.1% vs. 6.8%; P=0.06) tended to be less frequent in the RSV group compared to influenza group. The 90-day mortality was high in both groups (39.1% vs. 40.5%; P=0.89).

* Identification of positive tracheal aspiration culture.

aHR: Adjusted hazard ratio; aOR: Adjusted odds ratio; aPR: Adjusted prevalence ratio; ARDS: Acute respiratory distress syndrome; BPD: Bronchopulmonary dysplasia; CI: Confidence interval; COVID-19: Coronavirus disease 2019; CRP: C reactive protein; ECMO: Extracorporeal membrane oxygenation; GA: Gestational age; HFNC: High-flow nasal cannula; ICU: Intensive care unit; LOS: Length of stay; MV: (invasive) Mechanical ventilation; OR: Odds ratio; PCT: Procalcitonin; PICU: Pediatric intensive care unit; RSV: Respiratory syncytial virus.

Table 2

RSV disease severity: Changes in microbiome, potential pathogenic bacteria detection, and viral factors.

Author (year)	Case number	Samples	Sample collection	Assays	Endpoint	Population	Findings
Flamant et al. (2005)[58]	151	Tracheal aspirates	Once at admission (first 24 h of MV)	Culture	RSV severity Prolonged MV (>6 days)	Children <1 year Mechanically ventilated RSV children	Positive ETA culture (OR=3.4, 95% CI:1.5 to 7.7) (bacterial colonization)
Munywoki et al. (2015)[49]	205	Deep nasopharyngeal swabs	Twice/week 6-month follow-up	qPCR Genomic sequencing	RSV-load dynamics Factors influencing the rates for recovery from RSV infection	Naïve infants and households	Age (<1 year ref.) 1–4 years (HR=1.98, 95% CI:1.30 to 3.02) 5–14 years (HR=1.82, 95% CI:1.16 to 2.87) ≥15 years (HR=1.97, 95% CI:1.11 to 3.51) Detection of other viruses[*,†] Before RSV episode (HR=1.56, 95% CI:1.02 to 2.39) During RSV episode (HR=0.48, 95% CI:0.32 to 0.73) Other household members infected (%) ≥33–66% (HR=0.59, 95% CI:0.40 to 0.87) >66% (HR=0.51, 95% CI:0.35 to 0.74)
Hasegawa et al. (2017)[94]	11,016	Nasopharyngeal aspirates	Once at hospital admission (first 24 h)	16 s sequencing	RSV severity (PICU admission admission)	<1 year-old (Inpatient)	Changes in microbiota associated with RSV severity in the group with IL-37 lower levels
Brealey (2018)[90]	58	Nasal swabs or nasal washes	Twice. At the emergency room and 8 weeks after	qPCR	RSV severity (Bronchiolitis score)	<2 years Emergency department Mild comorbidities included	Higher severity scores associated with RSV and *S. pneumoniae* co-detection. Not associated with admission to hospital and the use of supplemental oxygen
García-Mauriño et al. (2019)[51]	150	Nasal midturbinate swabs	Daily	qPCR	Viral load dynamics RSV severity (bronchiolitis score, supplemental oxygen, PICU admission, Hospital LOS)	Previously healthy <2 years (Inpatient/outpatient)	Outpatients higher viral loads than inpatients Faster and consistent viral clearance associated with lower oxygen needs
Harding et al (2020)[89]	95	Stool samples	Within 72 h of admission	16 s sequencing	RSV severity (PICU admission)	<1 year-old (Inpatient) Mild comorbidities included	Gut microbiome alpha diversity lower in severe RSV Gut microbiome beta diversity different among groups non-RSV/moderate RSV/severe RSV
Brealey (2020)[93]	54	Nasal swabs	Weekly	qPCR	Bacterial colonization dynamics associated with RSV during early childhood	<2 years A prospective longitudinal birth cohort	*S. pneumoniae* and *M. catarrhalis* co-detection was frequent during RSV episode (61.1% and 48.1% respectively) In most cases, *S. pneumoniae* and *M. catarrhalis* preceded the viral infection, with the nasal load of each increasing during RSV infection
Diaz-Diaz et al. (2022)[103]	681	Nasopharyngeal and midturbinate swabs	Once at hospital admission At 24 h (18–34) from hospital admission	qPCR	RSV severity (Hospital admission and LOS, oxygen need, bronchiolitis score)	Previously healthy <2 years (Inpatient/outpatient)	Codetection *S. pneumoniae* and *H. influenzae* increased the risk for severe RSV disease Hospitalization (OR=2.2, 95% CI:1.07 to 4.74) Bronchiolitis score (OR=1.93, 95% CI:1.14 to 3.26) Oxygen need (OR=2.23, 95% CI:1.01 to 4.91) Hospital LOS (OR=2.53, 95% CI:1.33 to 4.79)
Cuthbertson et al. (2022)[96]	37	Nasal wash samples Oropharyngeal swabs	Daily (first 10 days) at day 14 and 28 post-RSV inoculation	qPCR 16 s sequencing	RSV infection (non-infection, asymptomatic, clinical cold)	Previously healthy non-smoking subjects 18–50 year-old	Significant viral loads differences between uninfected and infected at days 5, 6, 7, 8 (P ≤0.001) Day 3 viral load increased in patients who went on to develop symptoms; Day 7 peak of infection and viral load fell thereafter. Bacterial load in the asymptomatic infected group fluctuated more than in the other groups in the first 4 days of infection. No significant differences in bacterial load, alpha diversity measures or species turnover among groups over the course of viral infection

[*] Detection of other respiratory viruses during the 14 days prior to the start of RSV episode only.

[†] Other viruses were adenoviruses, rhinoviruses, and coronaviruses no SARS-CoV-2.

CI: Confidence interval; ETA: Endotracheal aspirate; HR: Hazard ratio; IL: Interleukin; LOS: Length of stay; MV: Mechanical ventilation; OR: Odds ratio; PICU: Pediatric intensive care unit; qPCR: Quantitative polymerase chain reaction; RSV: Respiratory syncytial virus; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

the respiratory tract thickening and secretions – without response to bronchodilators – and those exhibiting RSV-induced wheezing.[61]

ARDS

Reported ARDS incidence rates among hospitalized RSV-adults range between 0.7% and 9%, increasing to 20.4% among those requiring ICU admission.[10,37,62] It is noteworthy that a significant proportion of adult studies may have underestimated RSV-infection and RSV-induced ARDS due to the lack of routine testing.[63–67] In immunocompromised adults, particularly those with hematologic malignancies, there is a description of rapidly progressive severe bilateral pneumonia leading to ARDS,[68] a condition not limited to this population. Few studies have accurately reported the frequency of RSV-induced pediatric ARDS in infants and its impact on prognosis. Among hospitalized RSV-children, Niekler et al.[10] reported an ARDS incidence of 0.1%. However, among RSV-children under 2 years admitted to the ICU, the incidence of ARDS has been reported to be around 20% (7% for severe pediatric-ARDS, up to 33% among children with RSV and acute -or acute-on-chronic- respiratory failure).[21,69] Despite ARDS being more common among children with RSV than those with other viruses,[21] the clinical course, risk factors, and outcomes of RSV-induced pediatric-ARDS do not seem to differ from other virus types.[69] In contrast to the lower mortality rates of overall RSV-infections in the pediatric ICU (5.4%–12.94%)[54] mortality rates from 40% to 70% have been reported in pediatric patients with ARDS,[70,71] similar to the adult population.[72,73] Overall mortality among RSV-hospitalized adult patients (4%–9%)[10,23,62] was close to mortality rates of critically ill RSV-pediatric patients.

Risk factors for MV and RSV-mortality

Shortness of breath on presentation and the need for supplemental oxygen are associated with severe disease in both populations.[14,24,74] Although immunosuppressed patients bear the greatest relative burden of RSV hospitalizations (1288–1562 per 100,000 immunocompromised patients),[35] no pre-existing condition was significantly overrepresented compared to others in adult and senior patients requiring ICU admission.[24,28] Among critically ill patients, bacterial co-infection/superinfection and ARDS were the main factors associated with the need of MV and mortality across all ages and underlying conditions.[24,40,57,58,75,76] Among adults admitted to the ICU due to respiratory failure, mortality in those infected with RSV did not differ from that in patients admitted without RSV infection despite their higher incidence of complications such as bronchospasm, ventilator-associated pneumonia, and lung atelectasis.[57] Although infants with a history of birth before 37 weeks had a 1.5-fold higher risk of requiring ventilation compared to those born at term,[43] mortality did not differ significantly between them in the era of palivizumab and ECMO support. No specific risk factors for the need of MV and mortality have been described for immunocompromised RSV-children or adults requiring ICU admission beyond their underlying condition or extreme ages of life.[22,40,77] Moreover, among 370 immunocompromised adults with virus-detected acute respiratory failure, the type of virus (14% RSV)

was not associated with mortality. Furthermore, after matching, patients with virus-detected acute respiratory failure had lower mortality (OR=0.77) than immunocompromised patients suffering from other causes of acute respiratory failure, with an in-hospital mortality of 26%.[77]

According to death certificate data from RSV-associated deaths in the United States,[78] among children under 5 years, the cause of death was nearly evenly divided between RSV-bronchiolitis (50.6%) and RSV-pneumonia (46.4%), whereas the code for RSV-pneumonia was assigned for almost all (90.8%) of the RSV-associated deaths among those children aged 5 years and older and in adults. RSV-bronchitis as a cause of death was rarely documented in any age group.

### Extrapulmonary manifestations of severe RSV infection

In infants up to 3 months, severe RSV disease can also present as a central apnea with few respiratory symptoms or sudden death (16%–21% admissions), especially in those who were preterm-born.[79] Other non-specific clinical signs in young infants include lethargy and hydroelectrolytic disturbances. Confusion and disorientation might be frequent in adults, particularly the elderly. Hyponatremia is a common extrapulmonary manifestation of RSV that has been related to an increased antidiuretic hormone secretion in both populations.[79,80]

Direct myocardial injury with the need of inotropic support or arrhythmias has also been described in both populations.[81,82] Interestingly, elevated aspartate aminotransferase levels on admission (but not elevated alanine aminotransferase levels) were associated with longer ventilation periods and ICU length of stay (LOS) in previously healthy infants with RSV-bronchiolitis on invasive MV.[83] N-terminal prohormone of brain natriuretic peptide (NT-proBNP) has been suggested as a biomarker for RSV-bronchiolitis severity and cases complicated by acute cardiac failure.[84] The higher cardiovascular morbidity and mortality among RSV-infected adults (up to 45% a history of underlying heart disease, 16.7% mortality related to an acute cardiovascular event) has also led to the hypothesis of a direct damage.[85,86] Hepatitis, defined as transient transaminase elevation, is frequently reported, with rates up to 46%–49% in ventilated infants.[79,87] While most of these findings may be explained by secondary damage, hepatic involvement should alert to screening for heart disease-causing ischemic hepatitis in the light of the above.[86]

Systemic dissemination of the virus during severe disease, sepsis-like with fatal development, has also been reported in young infants.[88] RSV was found in meningeal swabs, cerebrospinal fluid, myocardium, pericardium, abdominal fluids, liver, and brain autopsies.[79]

The Role of the Respiratory Microbiome and Bacterial Co-infections in Severe RSV Disease

There is increasing evidence of a complex interplay between the microbiome, innate immunity, and viral infections causing severe pulmonary disease (Figure 1).[89–92] Changes in the upper airway microbiota diversity may precede most clinically significant RSV infections in children.[93] Co-detection of potentially pathogenic bacteria in lower respiratory samples within the first 24 h after intubation also was associated with prolonged
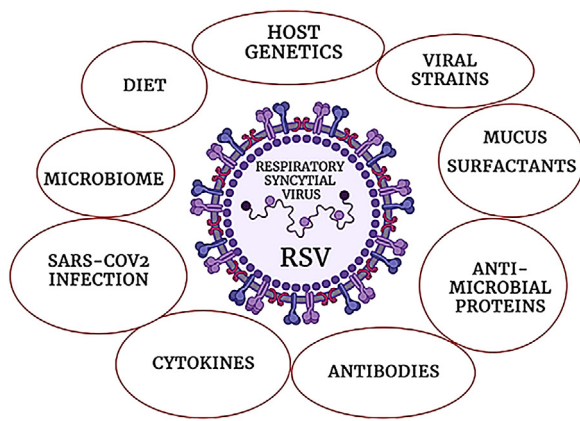
Figure 1. Microbiome-RSV interactions and other host & viral-related factors. RSV: respiratory syncytial virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

MV among them.[58] Nevertheless, distinguishing between colonization and true lower bacterial respiratory infection remains challenging. Hasegawa et al.[94] reported that associations between microbiota profile and severe RSV disease differed by the status of the interleukin (IL)-37, a cytokine transducing anti-inflammatory signals.[95] Among infants with lower IL-37 levels, *Haemophilus*-dominant profile was associated with a higher risk of ICU use (aOR=4.14). Conversely, with higher IL-37 levels, no significant associations between microbiota profiles and risk of ICU admission were found. It is plausible that microbiota regulate the immune response to RSV, among other factors. In adults, although some microbial signatures have been associated with SARS-CoV-2- and influenza-infection severity and poor clinical outcomes, Cuthbertson et al.[96] failed to find significant changes in the bacterial community over the course of RSV infection. It is worth noting that this study only involved a small number of adults with upper respiratory tract RSV-infection compared to studies among hospitalized children with LRT-RSV disease. As microbial composition within the human respiratory tract is impacted by SARS-CoV-2 and influenza, in both, children and adults, the relative stability of the immune system and microbial community reported in this study would be better explained by the milder disease experienced by these healthy adults rather than a true resilience of the adult respiratory microbiome against RSV. Interestingly, bacterial microbiome load in the asymptomatic infected group fluctuated more than in the other groups in the first days of infection. Relative abundances of potential protective bacteria were not provided.

On the other hand, silent micro-aspirations are more common than previously acknowledged among previously healthy children with RSV-bronchiolitis.[97] They have been associated with a decrease in oxygen saturation[98] and rapid deterioration,[99] leading to aspiration pneumonitis and bacterial pneumonia (OR=40.7),[100] which in turn can progress to ARDS. Takahashi et al.[101] reported that up to 20% of the RSV severe pneumonia patients were initially diagnosed as having aspiration pneumonia in an adult cohort, 63% of them corresponding to mixed co-detections with other common respiratory pathogens. It is possible that changes in the lower respiratory tract and lung microbiota may promote complicated interactions that dysregulate immune homeosta-

sis and affect the inflammatory response in the lung.[102] Notably, despite the overall low rates of bacterial co-infections among RSV-hospitalized children (1%–3.5%) and adults (12%), they have been associated with worse outcomes and ARDS development.[21,22,75,76,103]

Current Management of Severe RSV Disease

Despite extensive efforts to develop specific antivirals against RSV, the main therapeutic approach for acute RSV infection remains supportive care. Current evidence-based guidelines for bronchiolitis advice against pharmacological interventions such as corticosteroids, beta2-agonists, and epinephrine.[104] However, there are no specific guidelines for managing each specific phenotype needing intensive care. In RSV-infected adults, the standard of care for managing severe RSV infection mainly involves bronchodilators, supplemental oxygen, intravenous fluid, and antipyretics,[105] with systemic corticoids being associated with bacterial superinfection (aHR=3.1).[76] Thus, the use of bronchodilators and corticosteroids should be carefully considered in selected cases with high suspicion of airway hyperreactivity/RSV-induced wheezing such as positive bronchodilator tests defined by tidal breathing flow-volume loops changes.[106] Fluid restriction and/or isotonic fluids for parenteral therapy have been suggested to avoid hyponatremia.[80] In ventilated RSV-children, avoiding early fluid overload may shorten ventilator periods and ICU LOS.[107]

Respiratory support

In the recent decades, the development of non-invasive mechanical ventilation (NIV) along with high-flow heated and humidified oxygen therapy has decreased the rate of intubation in infants with RSV-bronchiolitis from 50%–60%[71] to 12%–24%.[46,108–110] High-flow nasal cannula (HFNC) support was initially positioned as a rescue therapy for those bronchiolitis not adequately supported by standard oxygen therapy, one step before NIV use. Although there is increasing data indicating the reasonable clinical benefit of early HFNC therapy,[111] the lack of standard practices seems to explain significant variations in respiratory support, ICUs admission rates, and outcomes in infants with moderate–severe bronchiolitis,[47,112,113] raising concerns about its overuse in the ward.[114] Conversely, standardized higher initial HFNC flows (2 mL/kg) and protocolized escalation/weaning practices have been associated with a lower HFNC failure rate and a decreased ICU and hospital LOS in RSV-bronchiolitis patients.[115–117] More studies are needed to determine the impact of HFNC on the number of interhospital transfers, ICU admissions, and its benefit in avoiding NIV in children.[118–121]

In adults, a significantly higher proportion of RSV-hospitalized patients presented respiratory failure compared to influenza-hospitalized patients (31% *vs.* 16%),[62] and they were also more likely to receive invasive MV or die compared with them (OR=2).[26] In the adult population, HFNC use increased due to COVID-19 patients,[77,82,122–124] reducing the need for intubation compared to standard oxygen therapy, although a reduction in mortality was not demonstrated. It would be logical to extend its use to other common viral lower respiratory tract infection (LTRI) from the community, as RSV or influenza-LTRI.

In the pre-COVID era, non-invasive ventilation was discouraged in adult patients with acute hypoxemic failure, only being recommended in mild early acute hypoxemic respiratory failure (partial pressure of oxygen [PaO$_2$] /fraction of inspired oxygen [FiO$_2$] ratio <300 and >200) under close supervision.[125] Otherwise, its main indications were COPD exacerbations with mild acidosis or cardiogenic pulmonary edema taking into account that, especially in elderly patients, RSV can very often be a factor in the decompensation of chronic heart and/or lung disease.[63] In recent years, evidence shows the benefits of its use also in SARS-CoV-2 acute hypoxemic respiratory failure,[126] one successful case being recently reported in a senior patient with RSV-hypoxemic failure.[127] Nowadays, HFNC and NIV may be considered a viable alternative in well-monitored patients when administered by expert groups, balancing the benefits against the potential harms of delaying intubation.

Hypoxemic respiratory failure and viral pneumonia have been associated with a higher likelihood of transition to invasive ventilation than other LTRI phenotypes.[128] Nevertheless, studies focusing on mechanically ventilated children showed that RSV-LRTI behaves as a heterogeneous disease with three distinctive patterns: restrictive, obstructive, or mixed pattern, even when clinically labeled only as bronchiolitis[129] Tongyoo et al.[57] reported higher proportions of bronchospasm and lung atelectasis in RSV-ventilated adults for respiratory failure compared to the non-RSV group (98.5% *vs.* 60.8%). Strategies for the use of invasive ventilation should be tailored accordingly.[130]

In the absence of specific guidelines for the management of RSV-pneumonia, the "protective ventilation" approach should be employed on the most hypoxemic RSV patients, using low tidal volume ventilation strategies (in the range of 4–8 mL/kg predicted body weight [PBW], depending on lung compliance) along with appropriate levels of positive end-expiratory pressure (PEEP) to limit lung distension and atelectrauma with the goal of maintaining plateau airway pressure. This is below 28–30 cmH$_2$O in adults and ≤28 in children according to the last consensus[131,132] Furthermore, PEEP values may be adjusted according to the dynamic patient's condition and its clinical response, as two ARDS phenotypes with divergent clinical outcomes and differential response to MV have been described.[133]

Hyperinflated RSV-infants benefit from slow rates and long expiratory times.[130] In adults, ventilatory support reducing minute ventilation, low tidal volumes, and prolonged expiratory time to limit hyperinflation has been suggested in obstructive airway disease, independently of its pathogenesis or underlying condition.[134] Interestingly, some authors reported that the elastic component of working pressure was predominant during some severe RSV infections in infants, similar to ARDS pathophysiology, despite not fulfilling ARDS criteria.[70] A personalized and dynamic characterization of the respiratory mechanics at the bedside in RSV patients with apparently the same RSV phenotype but ventilatory mixed patterns (obstructive and restrictive) has been suggested to tailor the ventilator settings according to which component is predominant.[129]

In cases of severe respiratory failure, the consideration of extracorporeal membrane oxygenation (ECMO) support is recommended. Infants suffering from bronchopulmonary dysplasia are at highest risk for it (aOR=11.8).[58] Before the pandemics, ECMO use in RSV-adults was reported in 2.4% of RSV-

adults needing intensive care.[10] As ECMO use in adults has increased notably in recent years, this rate is expected to increase if new preventive measures and treatments to address respiratory conditions caused by RSV are not successful. Its administration should be individualized in accordance with the protocols of each medical center.

Prone positioning and mucus clearance strategies

As in COVID and other viral pneumonias, prone positioning would be recommended even in non-intubated patients with a PaO$_2$/FiO$_2$ ratio <150 mmHg and PEEP ≥5 cmH$_2$O, as well as in patients on ECMO support.[135,136] Given that atelectasis and mucus plugging are more frequent in RSV disease than other viruses, ventilation/perfusion mismatch is a significant concern, particularly in young infants. The use of hypertonic saline is broadly reported in this population.[109,137,138] In a meta-analysis of randomized controlled trials,[139] nebulization of 3% saline solution was effective in decreasing the severity of symptoms and hospital LOS compared with 0.9% saline solution. The latest Cochrane update[140] states its safety, although more evidence is needed in the guidelines. Conversely, the use of mucolytics as N-acetylcysteine or dornase-alfa has been strongly discouraged due to the lack of evidence.[141,142] Pharmacological mucus clearance therapies are rarely used in older children and adults with RSV-infection. Current evidence discourages routine normal saline solution lavage for artificial airway suctioning.[143] Moreover, O'Neal et al.[144] documented a significant increase in the level of dyspnea after suctioning senior adults. Conventional and forced expiratory techniques have not demonstrated any impact on outcomes, being even harmful in severe bronchiolitis.[145] In adults, a recent meta-analysis concluded that patients with acute exacerbation of COPD disease may benefit from high-frequency chest wall oscillation therapy.[146] High-frequency chest wall oscillation plus fibrobronchoscope alveolar lavage may also reduce the duration of MV and ICU stay in pneumonia among the adult population.[147] Nevertheless, current evidence is very uncertain about the effects of chest physiotherapy on improving mortality in adults with pneumonia and no data referring specifically to RSV-patients has been reported.[148,149]

Pharmacotherapeutic treatments for selected cases

Ribavirin, a broad-spectrum, non-interferon virustatic chemotherapeutic agent, was the first antiviral treatment approved for severe RSV in children, but only in its aerosolized form. Its routine use was not recommended to prevent MV, ECMO, or death among RSV children due to its limited efficacy, side effects, and potential teratogenic risk for healthcare providers, though. Its use was relegated to immunocompromised patients or severe influenza co-infections.[148,149] Current evidence shows that oral ribavirin is a well-tolerated alternative for endovenous or aerosolized ribavirin, including critically ill adults or children.[150] It may be also a reasonable option to treat hematologic malignancies and HSCT recipients in the absence of other effective antiviral agents.[150,151] As for lung transplant recipients and other conditions requiring chemotherapy (solid tumors) or chronic immunosuppression, there is limited data supporting its use on them.[150] Interestingly,[152]

oral ribavirin was reported as the only factor associated with reduced mortality (HR=0.19) in a non-immunocompromised adult cohort of RSV-hospitalized patients.

Palivizumab, a specific RSV monoclonal antibody historically used for passive immunoprophylaxis among preterms and some other high-risk pediatric populations, has been described as off-label immunomodulator treatment alone or in combination with ribavirin for RSV-infected high-risk children.[153] Intravenous immunoglobulin (with or without palivizumab) also has been used as co-adjuvant therapy in some lung and heart-lung transplant recipients[154] but there is insufficient evidence of the use of these immunoglobulins for the treatment of severe RSV infection. The administration of hyperimmune immunoglobulin, non-specific immunoglobulins containing high antibody titers against a range of respiratory viral pathogens of concern, has also been reported in children on MV with high support.[132]

Multiple investigational drugs against specific RSV viral compounds are currently in development.[18] Fusion inhibitors (rilematovir, presatovir, and sisunatovir), seem to have good safety profiles and efficacy in reducing viral load, showing promise against RSV disease when administered in early stages. The role of all the above therapies and future antiviral therapies in severe RSV disease will be determined in the next few years, depending on the success of the new emerging forms of prevention for RSV disease: Arexvy (GSK, Middlesex, UK), Abrysvo (Pfizer, NY, USA) vaccines, and the recently approved long-acting monoclonal antibody against RSV – nirsevimab – for passive immunity, which offered around 80% protection against severe disease among infants who were 12 months of age or younger before entering their first RSV season.[155]

Antibiotic practices in severe RSV disease

In an era where antibiotic stewardship is emphasized to preserve antibiotic efficacy, reduce costs, and limit toxicity, antibiotic prescribing practices among patients with viral respiratory infections are concerning (33%–87%).[156,157] Among 1016 RSV-hospitalized children, an increased likelihood for antibiotic misuse was associated with variables indicative of severe patient status such as lower oxygen saturation.[157] Despite recent research linking the presence of some potential pathogen respiratory microbiota with severe RSV disease, current evidence does not support universal antibiotic therapy in LRTI-RVS with respiratory failure.[69,158] Among 11,029 children with bronchiolitis admitted to the ICU for NIV, Ortmann et al.[159] did not find better clinical outcomes with early antibiotic use. The interaction between the respiratory microbiota and RSV seems to be more complex, enhancing the potential damage caused by the virus when baseline microbiota profiles are lost and replaced by the abundance of potential pathogens, more than by the potential pathogens by themselves. Antibiotics could also add more harm in most cases. Nevertheless, co-bacterial infection is reported around 25% of RSV episodes among critically ill adults and children, being associated with worse outcomes in both populations.[22,85,152,156] A prudent approach to identify and optimally treat bacterial co-infection is needed.[158] Clinicians frequently are reluctant to discontinue antibiotics in critically ill-patients, especially in those severely hypoxemic, since the diagnosis of secondary bacterial pulmonary infection is often challenging. Interestingly, antibiotic overuse has been reported to be more frequent in adults than in children with RSV or other viral LRTI (37% *vs.* 87%).[160,161] The increased consumption of antibiotics during the COVID-19 pandemic posed a threat for antimicrobial resistance exacerbation.[162,163] Efforts to identify a real bacterial co-/superinfection using white cell counts and other blood biomarkers have been reported.[164,165] Among them, procalcitonin has been proved to be more sensitive and specific than C-reactive protein reactive in detecting bacterial infection in infants with severe bronchiolitis admitted to the ICU.[164] Implementation of procalcitonin cut-off values inside the framework of specific stewardship programs, and the proper categorization of each severe RSV disease may prevent unnecessary antibiotic use and other invasive diagnostic procedures. Limitations of the present studies include the under-characterization of the spectrum of the RSV disease, without discrimination from exacerbations of previous pulmonary conditions, and the difficulty for an accurate diagnosis of bacterial pneumonia, especially in patients on MV. Moreover, early ventilator-associated pneumonia (superinfection) frequently shares some of the causative microorganisms with the most frequent co-infections and microbiota profiles associated with severe RSV. Further research characterizing the changes in the microbiota and host response in lower tract respiratory samples is needed to elucidate its role in mixed infections and the most severe RSV disease development.

Conclusions

RSV affects individuals of all ages and manifests as a heterogeneous disease with a wide spectrum of severity, influenced by age and other factors. While most RSV hospitalizations involve bronchiolitis in healthy infants, the disease extends beyond this age group and phenotype. Compared to children, a significant portion of hospitalized adults, especially those with underlying cardiopulmonary conditions, immunosuppression, or other less recognized risk factors (diabetes, chronic renal disease) require intensive care. The main risk factors for severe disease usually correlate with worse outcomes. Currently, supportive care constitutes the primary treatment approach for RSV infection. Distinguishing RSV-induced wheezing from respiratory tract thickening, unresponsive to bronchodilators, is crucial. Additionally, obstructive RSV may coexist with viral pneumonia and progress to severe hypoxemic disease. The role of microbiome profiles in severe RSV disease development, amplifying viral damage capacity and increasing susceptibility to secondary bacterial infections, is becoming increasingly apparent. Respiratory support for RSV-infected patients requiring intensive care ranges from HFNC to ECMO support. NIV and HFNC are emerging as important modalities, particularly in specific phenotypes in the adult population, mirroring their efficacy in children. A comprehensive characterization of RSV disease phenotypes and pathophysiology holds promise for optimizing management strategies and comparing outcomes. Bacterial co-infections are associated with worse outcomes in both pediatric and adult populations, although their accurate diagnosis remains challenging. Current evidence and antibiotic stewardship policies discourage indiscriminate antibiotic practices, even in severe cases. The role of currently-in-development antiviral therapies for RSV disease hinges on the success of new vaccines and immune passive strategies with nirsevimab.

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Ethics Statement

This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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