LUMEN ET VIRTUS
ISSN: 2177-2789

HIGH-FLOW NASAL CANNULA VERSUS NONINVASIVE VENTILATION IN IMMUNOCOMPROMISED PATIENTS WITH ACUTE HYPOXEMIC RESPIRATORY FAILURE: A SYSTEMATIC REVIEW BETWEEN PULMONOLOGY AND INTENSIVE CARE

CÂNULA NASAL DE ALTO FLUXO VERSUS VENTILAÇÃO NÃO INVASIVA EM PACIENTES IMUNOCOMPROMETIDOS COM INSUFICIÊNCIA RESPIRATÓRIA HIPOXÊMICA AGUDA: UMA REVISÃO SISTEMÁTICA ENTRE PNEUMOLOGIA E TERAPIA INTENSIVA

CÁNULA NASAL DE ALTO FLUJO VERSUS VENTILACIÓN NO INVASIVA EN PACIENTES INMUNOCOMPROMETIDOS CON INSUFICIENCIA RESPIRATORIA HIPOXÉMICA AGUDA: UNA REVISIÓN SISTEMÁTICA ENTRE NEUMOLOGÍA Y CUIDADOS INTENSIVOS

https://doi.org/10.56238/levv17n61-032

André Marciano Neto[1], Isabela Arone de Lima[2], Elisabeth Dotti Consolo[3], Thiago Cunha Araujo[4], Amanda Guiotti Bruzadelli Macedo[5]

ABSTRACT

Introduction: Acute hypoxemic respiratory failure is a frequent and high-risk complication in immunocompromised patients, particularly among individuals with hematologic malignancy, solid organ transplantation, neutropenia, chemotherapy exposure, prolonged corticosteroid therapy, or other forms of clinically relevant immunosuppression. High-flow nasal cannula and noninvasive ventilation are commonly used to avoid endotracheal intubation, but their comparative effectiveness remains uncertain in this population. Objective: This systematic review aimed to compare high-flow nasal cannula with noninvasive ventilation in immunocompromised patients with acute hypoxem ic respiratory failure. Secondary objectives included evaluation of intubation, mortality, treatment failure, adverse events, comfort, tolerance, and factors influencing clinical selection between both strategies. Methods: A structured search was conducted in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform. Eligible studies included adult or mixed adult clinical populations with immunocompromise and acute hypoxemic respiratory failure treated with high-flow nasal cannula, noninvasive ventilation, or both. Randomized trials, post hoc analyses, prospective cohorts, and retrospective comparative studies were considered. Risk of bias was assessed using RoB 2 or ROBINS-I according to study design, and certainty of evidence was judged using GRADE. Results and Discussion: Seven studies were included in the final qualitative synthesis. Earlier post hoc and observational studies suggested lower intubation or mortality signals with high-flow nasal cannula compared with noninvasive ventilation, whereas later randomized evidence did not demonstrate mortality benefit from routinely adding noninvasive ventilation to high-flow nasal oxygen. The RENOVATE trial broadened the evidence base but did not

[1] Faceres. Netomarciano28@gmail.com
[2] Universidade Federal do Triângulo Mineiro (UFTM). Isadora.lima.arone@gmail.com
[3] Uniluz Fundação Luziada. vividel68@hotmail.com
[4] Centro Universitário de Brasília (CEUB). thiagoca@icloud.com
[5] Centro Universitário Unieuro. amandagbm2021@gmail.com

definitively resolve the immunocompromised hypoxemic subgroup. Overall, high-flow nasal cannula appears to be a reasonable first-line strategy for many immunocompromised patients with de novo hypoxemia, while noninvasive ventilation should be reserved for selected phenotypes with a plausible physiological benefit from positive pressure. Conclusion: High-flow nasal cannula should be considered a preferred initial strategy in many immunocompromised patients with acute hypoxemic respiratory failure when close monitoring and early escalation are available. Noninvasive ventilation remains useful in selected patients but should not be applied routinely without clear physiological indication and predefined failure criteria.

Keywords: Respiratory Insufficiency. Immunocompromised Host. High-Flow Nasal Cannula. Noninvasive Ventilation.

RESUMO

Introdução: A insuficiência respiratória hipoxêmica aguda é uma complicação frequente e de alto risco em pacientes imunocomprometidos, particularmente entre indivíduos com neoplasia hematológica, transplante de órgão sólido, neutropenia, exposição à quimioterapia, terapia prolongada com corticosteroides ou outras formas de imunossupressão clinicamente relevante. A cânula nasal de alto fluxo e a ventilação não invasiva são comumente usadas para evitar a intubação endotraqueal, mas sua eficácia comparativa permanece incerta nessa população. Objetivo: Esta revisão sistemática teve como objetivo comparar a cânula nasal de alto fluxo com a ventilação não invasiva em pacientes imunocomprometidos com insuficiência respiratória hipoxêmica aguda. Os objetivos secundários incluíram a avaliação de intubação, mortalidade, falha do tratamento, eventos adversos, conforto, tolerância e fatores que influenciam a seleção clínica entre ambas as estratégias. Métodos: Foi conduzida uma busca estruturada no PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e na International Clinical Trials Registry Platform. Estudos elegíveis incluíram populações clínicas adultas ou mistas com imunocomprometimento e insuficiência respiratória hipoxêmica aguda tratadas com cânula nasal de alto fluxo, ventilação não invasiva ou ambas. Ensaios randomizados, análises post hoc, coortes prospectivas e estudos comparativos retrospectivos foram considerados. O risco de viés foi avaliado usando RoB 2 ou ROBINS-I de acordo com o desenho do estudo, e a certeza da evidência foi julgada usando GRADE. Resultados e Discussão: Sete estudos foram incluídos na síntese qualitativa final. Estudos post hoc e observacionais anteriores sugeriram sinais mais baixos de intubação ou mortalidade com a cânula nasal de alto fluxo em comparação com a ventilação não invasiva, enquanto evidências randomizadas posteriores não demonstraram benefício de mortalidade ao adicionar rotineiramente ventilação não invasiva ao oxigênio nasal de alto fluxo. O ensaio RENOVATE ampliou a base de evidências, mas não resolveu definitivamente o subgrupo hipoxêmico imunocomprometido. No geral, a cânula nasal de alto fluxo parece ser uma estratégia razoável de primeira linha para muitos pacientes imunocomprometidos com hipoxemia de novo, enquanto a ventilação não invasiva deve ser reservada para fenótipos selecionados com um benefício fisiológico plausível da pressão positiva. Conclusão: A cânula nasal de alto fluxo deve ser considerada uma estratégia inicial preferencial em muitos pacientes imunocomprometidos com insuficiência respiratória hipoxêmica aguda quando monitoramento próximo e escalonamento precoce estão disponíveis. A ventilação não invasiva permanece útil em pacientes selecionados, mas não deve ser aplicada rotineiramente sem indicação fisiológica clara e critérios de falha predefinidos.

Palavras-chave: Insuficiência Respiratória. Hospedeiro Imunocomprometido. Cânula Nasal de Alto Fluxo. Ventilação não Invasiva.

RESUMEN
Introducción: La insuficiencia respiratoria hipoxémica aguda es una complicación frecuente y de alto riesgo en pacientes inmunocomprometidos, particularmente entre individuos con neoplasia hematológica, trasplante de órgano sólido, neutropenia, exposición a quimioterapia, terapia prolongada con corticosteroides u otras formas de inmunosupresión clínicamente relevante. La cánula nasal de alto flujo y la ventilación no invasiva se utilizan comúnmente para evitar la intubación endotraqueal, pero su eficacia comparativa sigue siendo incierta en esta población. Objetivo: Esta revisión sistemática tuvo como objetivo comparar la cánula nasal de alto flujo con la ventilación no invasiva en pacientes inmunocomprometidos con insuficiencia respiratoria hipoxémica aguda. Los objetivos secundarios incluyeron la evaluación de intubación, mortalidad, fracaso del tratamiento, eventos adversos, confort, tolerancia y factores que influyen en la selección clínica entre ambas estrategias. Métodos: Se realizó una búsqueda estructurada en PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov y la International Clinical Trials Registry Platform. Los estudios elegibles incluyeron poblaciones clínicas adultas o mixtas con inmunocompromiso e insuficiencia respiratoria hipoxémica aguda tratadas con cánula nasal de alto flujo, ventilación no invasiva o ambas. Se consideraron ensayos aleatorizados, análisis post hoc, cohortes prospectivas y estudios comparativos retrospectivos. El riesgo de sesgo se evaluó utilizando RoB 2 o ROBINS-I según el diseño del estudio, y la certeza de la evidencia se juzgó utilizando GRADE. Resultados y Discusión: Siete estudios fueron incluidos en la síntesis cualitativa final. Estudios post hoc y observacionales anteriores sugirieron señales más bajas de intubación o mortalidad con la cánula nasal de alto flujo en comparación con la ventilación no invasiva, mientras que la evidencia aleatorizada posterior no demostró beneficio de mortalidad al añadir rutinariamente ventilación no invasiva al oxígeno nasal de alto flujo. El ensayo RENOVATE amplió la base de evidencia pero no resolvió definitivamente el subgrupo hipoxémico inmunocomprometido. En general, la cánula nasal de alto flujo parece ser una estrategia razonable de primera línea para muchos pacientes inmunocomprometidos con hipoxemia de novo, mientras que la ventilación no invasiva debe reservarse para fenotipos seleccionados con un beneficio fisiológico plausible de la presión positiva. Conclusión: La cánula nasal de alto flujo debe considerarse una estrategia inicial preferida en muchos pacientes inmunocomprometidos con insuficiencia respiratoria hipoxémica aguda cuando hay monitoreo cercano y escalada temprana disponibles. La ventilación no invasiva sigue siendo útil en pacientes seleccionados pero no debe aplicarse rutinariamente sin indicación fisiológica clara y criterios de fracaso predefinidos.

Palabras clave: Insuficiencia Respiratoria. Huésped Inmunocomprometido. Cánula Nasal de Alto Flujo. Ventilación no Invasiva.

1 INTRODUCTION

Acute hypoxemic respiratory failure (AHRF) remains one of the most consequential complications in immunocompromised patients admitted to emergency departments, respiratory wards, and intensive care units, because deterioration may occur rapidly and the margin for delayed escalation is narrow.[1] In this population, hypoxemia frequently reflects pneumonia, opportunistic infection, drug-induced lung injury, diffuse alveolar hemorrhage, pulmonary edema, acute respiratory distress syndrome (ARDS), or overlapping mechanisms that are difficult to distinguish during the first hours of care.[1] The clinical challenge is not limited to restoring arterial oxygenation, but also includes avoiding injurious respiratory effort, preventing unnecessary intubation, and maintaining enough diagnostic clarity to treat reversible causes early.[1] High-flow nasal cannula (HFNC) and noninvasive ventilation (NIV) have therefore become central strategies in the initial management of AHRF, but their relative value remains controversial in immunocompromised hosts.[2] HFNC provides heated, humidified oxygen at high flow rates, improves matching between inspiratory demand and delivered flow, reduces anatomical dead space, and may generate low levels of positive airway pressure.[2] NIV provides higher and more controllable positive pressure support, may recruit alveolar units more effectively, and can unload respiratory muscles, but it also depends on interface tolerance, synchrony, secretion burden, and close monitoring.[2]

The historical appeal of NIV in immunocompromised patients was based on the possibility of avoiding endotracheal intubation, which may expose fragile patients to ventilator-associated pneumonia, sedation-related complications, hemodynamic instability, and difficult weaning.[3] This rationale is particularly relevant in hematological malignancy, solid organ transplantation, prolonged corticosteroid exposure, chemotherapy-induced neutropenia, and other states in which invasive mechanical ventilation has traditionally been associated with high mortality.[3] However, the physiological advantages of NIV may be offset when the disease is predominantly de novo hypoxemic respiratory failure rather than chronic obstructive pulmonary disease exacerbation or cardiogenic pulmonary edema.[3] In de novo AHRF, excessive tidal volumes during NIV, high respiratory drive, and delayed intubation may worsen lung injury, especially when patients remain tachypneic despite apparent improvements in peripheral oxygen saturation.[4] This concern has led to renewed interest in HFNC as a less intrusive modality that may improve oxygenation while preserving communication, nutrition, airway clearance, and tolerance during prolonged treatment.[4] The central uncertainty is whether these comfort and feasibility advantages translate into lower intubation rates, lower mortality, or safer trajectories among immunocompromised patients, whose deterioration may be abrupt and multifactorial.[4]

The immunocompromised population cannot be treated as a homogeneous subgroup, because prognosis and response to ventilatory support differ substantially according to the underlying disease, the reversibility of immune suppression, and the etiology of AHRF.[5] Patients with hematologic malignancies may present with neutropenic sepsis, invasive fungal infection, leukemic pulmonary infiltration, transfusion-related lung injury, or chemotherapy-associated pneumonitis, each with distinct implications for oxygenation and respiratory mechanics.[5] Patients receiving solid organ transplantation or biological immunosuppression may instead have viral pneumonia, Pneumocystis jirovecii pneumonia, bacterial coinfection, pulmonary edema, or rejection-related inflammatory injury, making the respiratory support decision inseparable from etiologic investigation.[5] This heterogeneity matters because HFNC may be sufficient when oxygenation failure is moderate and respiratory effort is controlled, whereas NIV may be more attractive when recruitment, positive end-expiratory pressure, or ventilatory unloading is urgently needed.[6] Conversely, NIV may be poorly tolerated in patients with altered mental status, abundant secretions, vomiting risk, facial lesions, severe agitation, or rapidly progressive shock.[6] The comparison between HFNC and NIV therefore cannot be reduced to a binary device question, because it also depends on timing, monitoring intensity, interface expertise, oxygenation reserve, and readiness for intubation.[6]

Recent evidence has reshaped the broader field of noninvasive respiratory support in AHRF, but immunocompromised patients remain underrepresented or inconsistently analyzed across trials.[7] Randomized and meta-analytic data in unselected AHRF populations suggest that HFNC may reduce intubation compared with conventional oxygen therapy in some settings, while NIV or continuous positive airway pressure may offer advantages in selected phenotypes, particularly when positive pressure addresses the dominant pathophysiology.[7] The coronavirus disease 2019 (COVID-19) pandemic accelerated research on HFNC, helmet NIV, continuous positive airway pressure, awake proning, and escalation pathways, but these data cannot be automatically extrapolated to non-COVID immunocompromised respiratory failure.[7] In patients with COVID-19-related AHRF, trials comparing HFNC, continuous positive airway pressure, and helmet NIV have shown that different noninvasive strategies may influence intubation, comfort, adverse events, and resource use in divergent ways.[8] Yet COVID-19 trials often included disease-specific inflammatory patterns, infection-control constraints, and pandemic-era thresholds for intubation that may not apply to neutropenic pneumonia, transplant-related infection, or chemotherapy-associated lung toxicity.[8] For this reason, the literature must be interpreted through the lens of both general AHRF physiology and the specific vulnerabilities of immunocompromised patients.[8]

The choice between HFNC and NIV has important implications beyond oxygenation because respiratory support may influence diagnostic timing, bronchoscopy feasibility, secretion management, patient communication, and multidisciplinary decision-making.[9] HFNC is often considered easier to implement, permits oral intake and speech more readily, and may facilitate repeated clinical assessment without interrupting oxygen delivery.[9] These characteristics are clinically meaningful in immunocompromised patients because early microbiological diagnosis, antimicrobial adjustment, and hematology or oncology input frequently occur during the same interval in which respiratory support is being escalated.[9] NIV, by contrast, may achieve more immediate improvement in work of breathing and oxygenation when applied by experienced teams, particularly when pressure support and positive end-expiratory pressure are titrated carefully.[10] Nevertheless, mask intolerance, air leaks, gastric distention, skin injury, patient-ventilator asynchrony, and interruptions for procedures may undermine its effectiveness in the very patients who require continuous and stable support.[10] The balance between physiological efficacy and practical tolerability is therefore central to any systematic comparison of HFNC and NIV in this population.[10]

Another key issue is the risk of delayed intubation, which may occur with either modality when clinicians overinterpret transient oxygenation improvement as true reversal of respiratory failure.[11] In HFNC-treated patients, persistent tachypnea, rising fraction of inspired oxygen (FiO2) requirement, poor respiratory rate-oxygenation index, accessory muscle use, hyperlactatemia, or worsening mental status should prompt early reconsideration of the strategy.[11] In NIV-treated patients, failure to reduce respiratory effort, persistent large tidal volumes, hemodynamic instability, poor synchrony, or inability to maintain the interface should similarly trigger escalation.[11] These warning signs are particularly important in immunocompromised patients because progression from moderate hypoxemia to severe respiratory failure may occur while clinicians are still pursuing etiologic confirmation.[12] The need for early intubation should not be interpreted as failure of multidisciplinary care, but rather as part of a protective strategy when noninvasive support is insufficient or unsafe.[12] A systematic review focused on HFNC versus NIV should therefore evaluate not only intubation and mortality, but also treatment failure definitions, crossover policies, rescue strategies, and escalation thresholds.[12]

Guidelines and expert statements increasingly emphasize individualized selection of noninvasive respiratory support, close monitoring, and avoidance of delayed intubation, yet their recommendations remain limited by indirectness for immunocompromised adults.[13] This indirectness arises because many trials include mixed AHRF populations, combine immunocompromised and nonimmunocompromised participants, compare one modality

against conventional oxygen rather than directly against another modality, or use subgroup analyses with limited statistical power.[13] As a result, clinicians often extrapolate from general AHRF, COVID-19, ARDS, chronic obstructive pulmonary disease exacerbation, or cardiogenic pulmonary edema evidence, even though these syndromes differ in mechanics, recruitability, reversibility, and tolerance of noninvasive support.[13] The most recent randomized comparisons between HFNC and NIV across acute respiratory failure phenotypes have strengthened the evidence base, but the immunocompromised hypoxemic subgroup remains a major area of uncertainty.[14] In particular, trial designs that use adaptive methods, dynamic borrowing, or early stopping may provide important overall conclusions while leaving clinically relevant subgroup questions unresolved.[14] These methodological features make a dedicated synthesis necessary to clarify what can be concluded specifically for immunocompromised patients with AHRF.[14]

A rigorous systematic review is justified because the clinical question sits at the intersection of pulmonology, intensive care, infectious diseases, hematology, oncology, transplantation medicine, and emergency medicine.[15] The decision to initiate HFNC or NIV frequently occurs before the final diagnosis is known, which means that clinicians must rely on severity markers, immune status, bedside physiology, and local expertise rather than definitive etiologic classification.[15] Evidence synthesis must therefore distinguish direct randomized evidence from observational data, separate immunocompromised subgroup findings from general AHRF results, and evaluate whether outcomes are affected by treatment setting, interface type, disease etiology, and escalation protocols.[15] This review was designed to compare HFNC and NIV in immunocompromised patients with AHRF, prioritizing clinically meaningful outcomes such as intubation, mortality, treatment failure, intensive care unit length of stay, hospital length of stay, adverse events, comfort, and rescue therapy.[16] It also aims to identify whether current evidence supports preferential first-line use of either modality or whether individualized selection remains the most defensible approach.[16] By integrating recent clinical trials, comparative studies, and systematic evidence under a structured risk-of-bias and certainty framework, this review seeks to provide a practice-oriented synthesis for specialists managing high-risk hypoxemic respiratory failure.[16]

2 OBJECTIVES

The main objective of this systematic review was to compare high-flow nasal cannula with noninvasive ventilation in immunocompromised patients with acute hypoxemic respiratory failure, focusing on clinically relevant outcomes that guide respiratory support decisions in pulmonology and intensive care. The secondary objectives were: to evaluate

differences between both strategies in endotracheal intubation rates; to compare short-term mortality, including intensive care unit mortality, hospital mortality, and 28-day or 30-day mortality when reported; to assess treatment failure, escalation to invasive mechanical ventilation, and need for rescue respiratory strategies; to analyze adverse events, interface-related complications, tolerance, comfort, and interruptions of therapy; and to examine how heterogeneity in immune status, etiology of respiratory failure, severity of hypoxemia, treatment setting, and study design influenced the certainty and applicability of the available evidence.

3 METHODOLOGY

This systematic review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. A structured search was conducted in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform. The search strategy combined controlled vocabulary and free-text terms related to high-flow nasal cannula, high-flow oxygen therapy, noninvasive ventilation, noninvasive positive pressure ventilation, acute hypoxemic respiratory failure, immunocompromised host, hematologic malignancy, solid tumor, transplantation, neutropenia, immunosuppression, intensive care, and mechanical ventilation. No language restriction was applied, and studies in languages other than English were considered eligible if the title, abstract, or full text contained extractable data relevant to the review question.

The primary time window included studies published within the last five years. Because fewer than ten directly eligible comparative studies were available in the most restrictive search, the window was expanded to ten years for the identification of directly relevant clinical studies, while prioritizing the most recent evidence in the final interpretation. Human studies were prioritized, including randomized controlled trials, pragmatic trials, prospective cohorts, retrospective cohorts, post hoc analyses, and comparative observational studies. Animal and in vitro studies were eligible only for separate mechanistic consideration and were not incorporated into the main clinical synthesis. Small samples were accepted when they addressed the target population or intervention comparison, but their limitations were explicitly considered during risk-of-bias assessment and certainty grading.

Studies were included when they evaluated adult or mixed adult populations with acute hypoxemic respiratory failure and reported data on immunocompromised patients treated with high-flow nasal cannula, noninvasive ventilation, or both. Eligible immune-compromising conditions included hematologic malignancy, solid tumor receiving active treatment, solid

organ transplantation, hematopoietic stem cell transplantation, acquired or drug-induced immunosuppression, prolonged corticosteroid use, neutropenia, and immunosuppressive therapy for inflammatory or autoimmune disease. Studies were excluded when they focused exclusively on chronic obstructive pulmonary disease exacerbation, cardiogenic pulmonary edema, postoperative respiratory support without acute hypoxemic respiratory failure, chronic home ventilation, pediatric-only populations, purely perioperative prophylaxis, or conventional oxygen therapy without extractable high-flow nasal cannula or noninvasive ventilation data. Case reports, narrative reviews, editorials, letters without original data, and non-systematic expert opinions were excluded from the evidence table, although systematic reviews and guidelines were used to contextualize the discussion when appropriate.

Two reviewers independently screened titles and abstracts, assessed full texts, and selected eligible studies. Disagreements were resolved by consensus, and a third reviewer was planned for arbitration when consensus could not be reached. Extracted data included author, year, country, study design, population, immune-compromising condition, etiology of acute hypoxemic respiratory failure, intervention, comparator, respiratory support settings, treatment location, intubation criteria, mortality outcomes, treatment failure, crossover, adverse events, length of stay, and main conclusions. Duplicate records were removed before screening, and multiple reports from the same study population were assessed to avoid double counting. The flow of records from identification to final inclusion was summarized according to the PRISMA framework.

Risk of bias was assessed according to study design. Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 tool. Nonrandomized comparative studies were assessed using the Risk Of Bias In Non-randomized Studies of Interventions tool. Diagnostic accuracy studies, if identified, were planned for assessment with the Quality Assessment of Diagnostic Accuracy Studies 2 tool, although such studies were not expected to form the core comparative evidence for this review. The certainty of evidence for each major outcome was judged using the Grading of Recommendations Assessment, Development and Evaluation approach, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. A quantitative meta-analysis was planned only if studies were sufficiently homogeneous in population, intervention, comparator, and outcome definition; otherwise, a structured narrative synthesis was performed, with particular attention to directness of evidence for immunocompromised patients.

4 RESULTS

The database and registry search identified 20 potentially relevant records after removal of duplicates. After title and abstract screening, 12 records were excluded because they evaluated conventional oxygen only, chronic respiratory failure, pediatric populations, postoperative prophylaxis, noncomparative respiratory support, or nonclinical designs. Eight full-text records were assessed for eligibility. Two full-text records were excluded because they did not provide extractable comparative data between high-flow nasal cannula and noninvasive ventilation in immunocompromised patients with acute hypoxemic respiratory failure. Six clinical studies met the inclusion criteria and were included in the final qualitative synthesis.

Tabela 1

Characteristics and main findings of the included studies

Reference	**Population / Intervention / Comparison**	**Outcomes**	**Main conclusions**
Frat *et al.*, 2016	This post hoc analysis of a randomized trial evaluated immunocompromised adults with severe acute hypoxemic respiratory failure treated with high-flow nasal cannula, standard oxygen, or noninvasive ventilation as first-line oxygenation strategies.	The study assessed endotracheal intubation, mortality, and associations between initial oxygenation strategy and clinical outcomes.	Noninvasive ventilation was associated with higher risks of intubation and mortality than high-flow nasal cannula, suggesting that noninvasive ventilation should be used cautiously in immunocompromised patients with de novo hypoxemic respiratory failure.
Coudroy *et al.*, 2016	This observational cohort study compared immunocompromised adults with acute respiratory failure treated with high-flow nasal cannula alone versus noninvasive ventilation as first-line therapy.	The study assessed endotracheal intubation, intensive care unit mortality, hospital mortality, and clinical predictors of treatment failure.	High-flow nasal cannula was associated with lower intubation and mortality signals than noninvasive ventilation, although the observational design limited causal interpretation.
Tu *et al.*, 2017	This comparative study evaluated renal transplant recipients with acute hypoxemic respiratory failure secondary to severe pneumonia treated	The study assessed avoidance of invasive mechanical ventilation, oxygenation response, mortality,	High-flow nasal cannula achieved outcomes similar to noninvasive ventilation in renal transplant recipients, supporting its

	with high-flow nasal cannula versus noninvasive ventilation.	and treatment tolerance.	feasibility as an alternative initial strategy in a selected immunocompromised subgroup.
Dumas *et al.*, 2018	This analysis of a large multinational cohort evaluated immunocompromised patients with hypoxemic acute respiratory failure managed with different oxygenation and noninvasive ventilation strategies.	The study assessed the association between oxygenation strategy, risk of intubation, and subsequent clinical outcomes.	Initial oxygenation or noninvasive ventilation strategy did not independently determine next-day intubation risk, but failure of any noninvasive strategy was associated with adverse outcomes, emphasizing the importance of early recognition of treatment failure.
Wang *et al.*, 2020	This observational cohort study evaluated immunocompromised patients with acute respiratory failure treated with high-flow nasal cannula, conventional oxygen therapy, or noninvasive ventilation.	The study assessed short-term mortality, intubation rate, intensive care unit length of stay, and comparative effectiveness among noninvasive oxygenation strategies.	High-flow nasal cannula was not associated with a significant short-term mortality difference compared with noninvasive ventilation, but it was associated with shorter intensive care unit length of stay than noninvasive ventilation in the analyzed cohort.
Coudroy *et al.*, 2022	This multicenter randomized clinical trial evaluated critically ill immunocompromised adults with acute respiratory failure treated with high-flow nasal oxygen alone versus high-flow nasal oxygen alternating with noninvasive ventilation.	The study assessed 28-day mortality, endotracheal intubation, intensive care outcomes, and adverse events.	Alternating noninvasive ventilation with high-flow nasal oxygen did not reduce mortality compared with high-flow nasal oxygen alone, indicating that routine addition of noninvasive ventilation may not improve outcomes in this population.
RENOVATE Investigators *et al.*, 2025	This multicenter adaptive randomized clinical trial compared high-flow nasal oxygen with noninvasive ventilation across acute respiratory failure phenotypes, including an	The study assessed the composite outcome of endotracheal intubation or death within 7 days, as well as subgroup-specific noninferiority conclusions.	High-flow nasal oxygen met noninferiority criteria in several acute respiratory failure groups, but the immunocompromised hypoxemic subgroup was stopped for futility, leaving

	immunocompromised hypoxemic subgroup.		uncertainty about whether high-flow nasal oxygen can be considered noninferior to noninvasive ventilation in this specific subgroup.

5 RESULTS AND DISCUSSION

The post hoc analysis by Frat *et al.* provided one of the earliest direct signals that the type of first-line noninvasive respiratory support may influence prognosis in immunocompromised patients with severe acute hypoxemic respiratory failure.[17] Its main contribution was the separation of immunocompromised patients within a randomized framework originally designed to compare high-flow nasal cannula, standard oxygen, and noninvasive ventilation in de novo hypoxemic respiratory failure.[17] The analysis suggested that noninvasive ventilation was associated with higher intubation and mortality than high-flow nasal cannula in this subgroup, raising concern that positive-pressure support may be harmful when it masks persistent respiratory distress or delays intubation.[17] However, the interpretation must remain cautious because the analysis was post hoc, the subgroup was not the primary population of the original trial, and treatment effects may have been influenced by baseline severity, interface tolerance, and clinician decisions regarding escalation.[18] The study nevertheless remains clinically important because it redirected attention from oxygenation alone to the broader question of whether noninvasive ventilation may expose selected immunocompromised patients with de novo hypoxemia to excessive tidal volumes, poor tolerance, and delayed invasive mechanical ventilation.[18]

The observational study by Coudroy *et al.* reinforced this concern by comparing immunocompromised adults treated with high-flow nasal cannula alone versus noninvasive ventilation as the first-line strategy for acute respiratory failure.[18] In this cohort, high-flow nasal cannula was associated with more favorable signals for intubation and mortality than noninvasive ventilation, although residual confounding could not be eliminated.[19] The relevance of this study lies in its pragmatic design, because it reflected real intensive care unit practice in patients whose respiratory failure was often driven by pneumonia, immunosuppression-related complications, or multifactorial lung injury.[19] At the same time, treatment allocation was not randomized, and clinicians may have preferentially selected noninvasive ventilation for patients perceived to have more severe respiratory distress or greater need for ventilatory unloading.[19] This limitation reduces certainty, but the consistency between the physiological concerns about noninvasive ventilation and the observed clinical

outcomes supports the need for close monitoring when this modality is used in immunocompromised hypoxemic patients.[20]

The study by Tu *et al.* added a narrower but clinically meaningful perspective by focusing on renal transplant recipients with acute hypoxemic respiratory failure secondary to severe pneumonia.[20] This population differs from patients with hematologic malignancy or neutropenia because transplant-related immunosuppression, renal dysfunction, infection pattern, and fluid balance may alter both the cause of hypoxemia and the response to positive-pressure support.[20] The study suggested that high-flow nasal cannula achieved outcomes broadly comparable to noninvasive ventilation, supporting its feasibility as an initial strategy in selected transplant recipients without immediate indications for intubation.[21] Nevertheless, the sample size was limited, and the findings should not be generalized to all solid organ transplant recipients or to patients with shock, severe encephalopathy, abundant secretions, or rapidly worsening gas exchange.[21] The main clinical value of this study is that it showed high-flow nasal cannula may be a practical alternative in a defined immunocompromised subgroup, particularly when patient comfort, airway access, and secretion clearance are relevant to ongoing management.[21]

The multinational cohort analysis by Dumas *et al.* shifted the discussion from device superiority to the consequences of noninvasive strategy failure.[22] In this large immunocompromised population with hypoxemic acute respiratory failure, initial oxygenation strategy did not independently determine next-day intubation risk after adjustment, suggesting that patient trajectory may depend more on early response than on the initial device alone.[22] This finding is important because it challenges simplistic interpretations in which high-flow nasal cannula is universally protective or noninvasive ventilation is universally harmful.[22] Instead, the study emphasizes that early recognition of treatment failure is probably more important than prolonged persistence with either modality when respiratory effort, oxygenation, hemodynamics, or neurologic status fail to improve.[23] From a practical standpoint, the findings support structured reassessment within the first hours of therapy, using respiratory rate, oxygen requirement, work of breathing, gas exchange, hemodynamic stability, and clinician judgment rather than peripheral oxygen saturation alone.[23]

The observational cohort by Wang *et al.* provided more recent comparative data on high-flow nasal cannula, conventional oxygen therapy, and noninvasive ventilation in immunocompromised patients with acute respiratory failure.[23] The study did not demonstrate a clear short-term mortality advantage of high-flow nasal cannula over noninvasive ventilation, which tempers earlier interpretations suggesting strong superiority of high-flow nasal cannula in all immunocompromised hypoxemic patients.[24] However, the association

between high-flow nasal cannula and shorter intensive care unit length of stay suggests that tolerance, ease of application, and fewer interruptions may translate into operational advantages even when mortality differences are not statistically evident.[24] This distinction is clinically relevant because mortality in immunocompromised respiratory failure is strongly influenced by malignancy status, infection control, organ dysfunction, treatment limitations, and reversibility of the underlying disease.[24] Therefore, absence of a mortality difference does not necessarily imply equivalence in bedside usability, patient experience, nursing workload, or feasibility outside highly specialized intensive care units.[25]

The randomized trial by Coudroy *et al.* in critically ill immunocompromised patients provided the most direct evidence comparing high-flow nasal oxygen alone with a strategy of high-flow nasal oxygen alternating with noninvasive ventilation.[25] The trial found no mortality reduction with the routine addition of noninvasive ventilation, suggesting that systematic alternation may not improve outcomes when high-flow nasal oxygen is already used as the foundational therapy.[25] This finding is especially relevant because the intervention tested a clinically common compromise, in which clinicians attempt to combine the comfort and continuity of high-flow nasal oxygen with the theoretical recruitment and unloading effects of noninvasive ventilation.[26] The negative result indicates that adding noninvasive ventilation should not be considered automatically beneficial in immunocompromised acute respiratory failure, especially when applied without a clear physiological target or predefined failure criteria.[26] In practice, noninvasive ventilation may still have a role for selected patients with recruitable lung disease, cardiogenic edema overlap, obesity-related mechanics, or marked ventilatory load, but this role should be individualized rather than routine.[26]

The RENOVATE trial broadened the evidence base by comparing high-flow nasal oxygen with noninvasive ventilation across multiple acute respiratory failure phenotypes, including an immunocompromised hypoxemic subgroup.[27] In the overall trial, high-flow nasal oxygen met noninferiority criteria in several acute respiratory failure groups, strengthening the argument that it can be safely used in many hospitalized patients requiring noninvasive respiratory support.[27] However, the immunocompromised hypoxemic subgroup was stopped for futility, and the subgroup-specific data did not establish noninferiority of high-flow nasal oxygen compared with noninvasive ventilation.[27] This result does not prove that noninvasive ventilation is superior in immunocompromised hypoxemic patients, because the subgroup was small and the trial was not able to provide a definitive estimate for that specific population.[28] It does, however, prevent overextension of the overall RENOVATE conclusions and reinforces the need for trials specifically powered for immunocompromised acute hypoxemic respiratory failure.[28]

Across the included studies, the evidence does not support a universal rule that one modality should always replace the other in immunocompromised patients with acute hypoxemic respiratory failure.[28] Earlier post hoc and observational data favored high-flow nasal cannula, mainly because of lower apparent intubation or mortality and better tolerance.[29] Later randomized evidence showed that routine addition of noninvasive ventilation to high-flow nasal oxygen does not reduce mortality, while broader acute respiratory failure evidence left uncertainty in the immunocompromised hypoxemic subgroup.[29] These findings suggest that high-flow nasal cannula is a highly reasonable default strategy for many immunocompromised patients with de novo hypoxemia, particularly when respiratory effort is moderate, oxygenation improves promptly, and no immediate need for positive-pressure support is present.[29] Noninvasive ventilation should be reserved for patients in whom its physiological benefits are plausible and measurable, rather than applied reflexively because of immune suppression or fear of intubation.[30]

Comparison with contemporary guideline logic supports this interpretation because modern acute respiratory failure management increasingly prioritizes phenotype, monitoring, and early escalation over rigid device hierarchy.[30] In de novo hypoxemic respiratory failure, high-flow nasal cannula is often favored because it improves oxygen delivery, preserves comfort, and may reduce escalation compared with conventional oxygen, while avoiding some hazards associated with poorly tolerated positive-pressure ventilation.[30] Noninvasive ventilation remains well established for chronic obstructive pulmonary disease exacerbation, cardiogenic pulmonary edema, and selected postoperative or hypercapnic states, but its benefit is less consistent in purely hypoxemic respiratory failure without ventilatory pump failure.[31] Immunocompromised patients frequently fall into this uncertain zone, because they may have severe pneumonia, acute respiratory distress syndrome, opportunistic infection, or mixed cardiopulmonary contributors.[31] Therefore, guideline-consistent practice should select the modality according to pathophysiology, severity, tolerance, and institutional expertise rather than immune status alone.[31]

The main source of heterogeneity was clinical rather than purely methodological.[32] Included studies differed in the definition of immunocompromise, underlying disease distribution, proportion of hematologic malignancy, transplant status, neutropenia, infection type, severity of hypoxemia, and thresholds for intubation.[32] They also differed in how noninvasive ventilation was delivered, including interface, session duration, pressure settings, alternation with high-flow nasal oxygen, and criteria for discontinuation.[32] High-flow nasal cannula protocols varied in flow rates, fraction of inspired oxygen titration, duration before failure assessment, and use as rescue after noninvasive ventilation intolerance.[33]

These differences limit the validity of pooled conclusions and explain why a narrative synthesis is more appropriate than a simplistic combined estimate of effect.[33]

The certainty of evidence was judged as low to moderate for intubation and mortality when restricted to immunocompromised patients with acute hypoxemic respiratory failure.[33] Randomized evidence improves confidence, but directness remains limited because some studies were post hoc analyses, some were observational cohorts, and the largest modern randomized trial was not definitive for the immunocompromised hypoxemic subgroup.[34] Risk of bias was mainly related to confounding by indication in observational studies, subgroup imprecision in post hoc analyses, and heterogeneity in escalation decisions across centers.[34] Inconsistency was also present, because some earlier studies favored high-flow nasal cannula while later evidence supported a more neutral interpretation regarding mortality.[34] Overall, the Grading of Recommendations Assessment, Development and Evaluation judgment supports cautious clinical preference for high-flow nasal cannula in many patients, but not a strong recommendation against noninvasive ventilation when positive-pressure support is physiologically justified.[35]

For clinical practice, the most defensible approach is to begin with high-flow nasal cannula in immunocompromised patients with de novo acute hypoxemic respiratory failure who are alert, hemodynamically stable, able to clear secretions, and not showing signs of immediate ventilatory collapse.[35] Noninvasive ventilation should be considered when there is a clear target such as high work of breathing with potential for unloading, cardiogenic pulmonary edema overlap, obesity-related mechanics, atelectatic recruitability, or transient reversible deterioration under close intensive care monitoring.[35] Regardless of the initial modality, clinicians should define failure criteria before therapy begins, including persistent tachypnea, escalating oxygen requirement, worsening mental status, hemodynamic instability, inability to tolerate the interface, or absence of early improvement in respiratory effort.[36] In immunocompromised patients, delayed intubation may be especially harmful because sepsis, opportunistic pneumonia, and diffuse lung injury can progress rapidly while antimicrobial and diagnostic decisions are still unfolding.[36] Thus, the safest strategy is not simply choosing high-flow nasal cannula or noninvasive ventilation, but integrating the selected modality into a protocolized, multidisciplinary pathway with early reassessment, prompt etiologic treatment, and readiness for invasive mechanical ventilation when noninvasive support fails.[36]

6 CONCLUSION

The available evidence suggests that high-flow nasal cannula is an appropriate first-line respiratory support strategy for many immunocompromised patients with acute hypoxemic respiratory failure, especially when hypoxemia is not accompanied by immediate ventilatory collapse, severe hemodynamic instability, or inability to protect the airway. Noninvasive ventilation did not show consistent superiority over high-flow nasal cannula in this population, and routine alternation between both strategies did not reduce mortality in the most directly relevant randomized evidence. The overall synthesis supports a cautious, phenotype-based approach rather than a universal preference for either modality.

From a clinical perspective, high-flow nasal cannula offers important advantages in comfort, continuity of oxygen delivery, airway access, communication, secretion clearance, and feasibility during diagnostic investigation. These characteristics are particularly relevant in immunocompromised patients, in whom early antimicrobial therapy, etiologic clarification, hematology or oncology input, and repeated bedside reassessment often occur simultaneously. Noninvasive ventilation remains clinically useful in selected patients when positive-pressure support has a clear physiological target, but it should be applied under close monitoring and with predefined criteria for escalation.

The main limitations of the literature include the small number of directly comparative studies, the presence of post hoc and observational designs, heterogeneity in the definition of immunocompromise, and variability in respiratory support protocols. The evidence base also includes studies conducted across different clinical contexts, including hematologic malignancy, transplantation, pneumonia, mixed acute respiratory failure, and broader acute respiratory failure phenotypes. These differences reduce the certainty of pooled conclusions and explain why strong modality-specific recommendations remain difficult to justify.

Future studies should be specifically powered for immunocompromised patients with acute hypoxemic respiratory failure and should stratify participants according to immune status, etiology of respiratory failure, severity of hypoxemia, respiratory effort, and risk of delayed intubation. Trials should also standardize failure criteria, escalation thresholds, noninvasive ventilation settings, high-flow nasal cannula flow targets, and clinically meaningful outcomes beyond mortality, including comfort, adverse events, time to intubation, and resource utilization. Prospective research should also evaluate whether early physiological response tools can identify which patients benefit from high-flow nasal cannula, noninvasive ventilation, or early invasive mechanical ventilation.

In conclusion, the most evidence-based strategy is not simply choosing high-flow nasal cannula or noninvasive ventilation, but integrating the selected modality into individualized,

multidisciplinary, and closely monitored care. Pulmonologists, intensivists, infectious disease specialists, hematologists, oncologists, transplant teams, nurses, and respiratory therapists should work together to identify reversible causes, monitor early response, and avoid harmful delays in intubation when noninvasive support fails. In immunocompromised acute hypoxemic respiratory failure, respiratory support should remain dynamic, protocolized, and centered on the patient's physiology rather than on device preference alone.

REFERENCES

Agarwal A, Basmaji J, Muttalib F, Granton D, Chaudhuri D, Chetan D, Hu M, Fernando SM, Honarmand K, Bakaa L, Burns KEA, Friedrich JO, Mehta S, Murthy S, Adhikari NKJ, Lamontagne F, Guyatt GH, Rochwerg B. High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. Can J Anaesth. 2020;67(9):1217-1248.

Aswanetmanee P, Akkermans A, Blot S, Depuydt P, Benoit DD. Noninvasive ventilation in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. Crit Care. 2023;27(1):156.

Azoulay E, Lemiale V, Mokart D, Nseir S, Argaud L, Pène F, Kontar L, Bruneel F, Klouche K, Barbier F, Reignier J, Berrahil-Meksen L, Louis G, Constantin JM, Mayaux J, Wallet F, Kouatchet A, Peigne V, Théodose I, Perez P, *et al.* Effect of high-flow nasal oxygen vs standard oxygen on 28-day mortality in immunocompromised patients with acute respiratory failure: the HIGH randomized clinical trial. JAMA. 2018;320(20):2099-2107.

Carteaux G, Millán-Guilarte T, De Prost N, Razazi K, Abid S, Thille AW, Schortgen F, Brochard L, Brun-Buisson C, Mekontso Dessap A. Failure of noninvasive ventilation for de novo acute hypoxemic respiratory failure: role of tidal volume. Crit Care Med. 2016;44(2):282-290.

Chaudhuri D, Granton D, Wang DX, Burns KEA, Friedrich JO, Heels-Ansdell D, Cook DJ, Murthy S, Meade MO, Rochwerg B. High-flow nasal cannula compared with noninvasive positive pressure ventilation in acute hypoxic respiratory failure: a systematic review and meta-analysis. Crit Care Med. 2023;51(9):1247-1257.

Coudroy R, Frat JP, Ehrmann S, Pène F, Terzi N, Decavèle M, Voiriot G, Prat G, Lascarrou JB, Boulain T, Frat JP, Thille AW, Azoulay E. High-flow nasal oxygen alone or alternating with non-invasive ventilation in critically ill immunocompromised patients with acute respiratory failure: a randomised controlled trial. Lancet Respir Med. 2022;10(7):641-649.

Coudroy R, Jamet A, Petua P, Robert R, Frat JP, Thille AW. High-flow nasal cannula oxygen therapy versus noninvasive ventilation in immunocompromised patients with acute respiratory failure: an observational cohort study. Ann Intensive Care. 2016;6(1):45.

David-João PG, Guedes MH, Réa-Neto Á, Chaiben VBO, Baena CP. Noninvasive ventilation in acute hypoxemic respiratory failure: a systematic review and meta-analysis. J Crit Care. 2019;49:84-91.

Dumas G, Chevret S, Lemiale V, Pène F, Demoule A, Mayaux J, Kouatchet A, Nyunga M, Perez P, Argaud L, Bruneel F, Seguin A, Reignier J, Papazian L, Rabbat A, Benoit D, Azoulay E. Oxygenation/non-invasive ventilation strategy and risk for intubation in

immunocompromised patients with hypoxemic acute respiratory failure. Oncotarget. 2018;9(71):33682-33693.

Ferreyro BL, Angriman F, Munshi L, Del Sorbo L, Ferguson ND, Rochwerg B, Ryu MJ, Saskin R, Wunsch H, da Costa BR, Scales DC. Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: a systematic review and meta-analysis. JAMA. 2020;324(1):57-67.

Frat JP, Coudroy R, Thille AW. Non-invasive oxygenation strategies in immunocompromised patients with acute hypoxaemic respiratory failure. Lancet Respir Med. 2016;4(8):591-593.

Frat JP, Quenot JP, Badie J, Coudroy R, Guitton C, Ehrmann S, Gacouin A, Constan A, Mercier E, Grelon F, Chudeau N, Robert R, Caille V, Frat JP, Thille AW. Effect of high-flow nasal cannula oxygen vs standard oxygen therapy on mortality in patients with respiratory failure due to COVID-19: the SOHO-COVID randomized clinical trial. JAMA. 2022;328(12):1212-1222.

Frat JP, Ragot S, Coudroy R, Constantin JM, Girault C, Prat G, Boulain T, Demoule A, Ricard JD, Razazi K, Lascarrou JB, Devaquet J, Mira JP, Argaud L, Chakarian JC, Thille AW. Predictors of intubation in patients with acute hypoxemic respiratory failure treated with a noninvasive oxygenation strategy. Crit Care Med. 2018;46(2):208-215.

Frat JP, Ricard JD, Quenot JP, Pichon N, Demoule A, Forel JM, Mira JP, Coudroy R, Lascarrou JB, Caille V, Girault C, Argaud L, Gacouin A, Devaquet J, Prat G, Mercat A, Thille AW. Non-invasive ventilation versus high-flow nasal cannula oxygen therapy with apnoeic oxygenation for preoxygenation before intubation of patients with acute hypoxaemic respiratory failure: a randomised controlled trial. Lancet Respir Med. 2019;7(4):303-312.

Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, Prat G, Boulain T, Morawiec E, Cottereau A, Devaquet J, Nseir S, Razazi K, Mira JP, Argaud L, Chakarian JC, Ricard JD, Wittebole X, Chevalier S, Herbland A, *et al.* High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372(23):2185-2196.

Grieco DL, Menga LS, Cesarano M, Rosà T, Spadaro S, Bitondo MM, Montomoli J, Falo G, Tonetti T, Cutuli SL, Pintaudi G, Tanzarella ES, Piervincenzi E, Bongiovanni F, Dell'Anna AM, Delle Cese L, Berardi C, Carelli S, Menato L, De Pascale G, *et al.* Effect of helmet noninvasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients with COVID-19 and moderate to severe hypoxemic respiratory failure: the HENIVOT randomized clinical trial. JAMA. 2021;325(17):1731-1743.

Grieco DL, Menga LS, Raggi V, Bongiovanni F, Anzellotti GM, Tanzarella ES, Bocci MG, Mercurio G, Dell'Anna AM, Eleuteri D, Berardi C, Maviglia R, Conti G, Antonelli M. Physiological comparison of high-flow nasal cannula and helmet noninvasive ventilation in acute hypoxemic respiratory failure. Am J Respir Crit Care Med. 2020;201(3):303-312.

Kang BJ, Koh Y, Lim CM, Huh JW, Baek S, Han M, Seo HS, Suh HJ, Seo GJ, Kim EY, Hong SB. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. Intensive Care Med. 2015;41(4):623-632.

Lemiale V, Dumas G, Demoule A, Pène F, Mayaux J, Kouatchet A, Seguin A, Nyunga M, Perez P, Argaud L, Reignier J, Papazian L, Rabbat A, Benoit D, Azoulay E. Performance of the ROX index to predict intubation in immunocompromised patients receiving high-flow nasal cannula for acute respiratory failure. Ann Intensive Care. 2021;11(1):17.

Lemiale V, Mokart D, Mayaux J, Lambert J, Rabbat A, Demoule A, Azoulay E. The effects of a 2-h trial of high-flow oxygen by nasal cannula versus Venturi mask in

immunocompromised patients with hypoxemic acute respiratory failure: a multicenter randomized trial. Crit Care. 2015;19:380.

Lemiale V, Resche-Rigon M, Mokart D, Pène F, Argaud L, Mayaux J, Guitton C, Rabbat A, Girault C, Kouatchet A, Vincent F, Bruneel F, Nyunga M, Meert AP, Benoit D, Papazian L, Demoule A, Chevret S, Azoulay E. High-flow nasal cannula oxygenation in immunocompromised patients with acute hypoxemic respiratory failure. Crit Care Med. 2017;45(3):e274-e280.

Lewis SR, Baker PE, Parker R, Smith AF. High-flow nasal cannulae for respiratory support in adult intensive care patients. Cochrane Database Syst Rev. 2021;3(3):CD010172.

Mauri T, Alban L, Turrini C, Cambiaghi B, Carlesso E, Taccone P, Bottino N, Lissoni A, Spadaro S, Volta CA, Patroniti N, Pesenti A. Optimum support by high-flow nasal cannula in acute hypoxemic respiratory failure: effects of increasing flow rates. Intensive Care Med. 2017;43(10):1453-1463.

Oczkowski S, Ergan B, Bos L, Chatwin M, Ferrer M, Gregoretti C, Heunks L, Frat JP, Longhini F, Nava S, Navalesi P, Uğurlu AO, Pisani L, Renda T, Thille AW, Winck JC, Windisch W, Tonia T, Boyd J, Sotgiu G, Scala R. ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. Eur Respir J. 2022;59(4):2101574.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

Perkins GD, Ji C, Connolly BA, Couper K, Lall R, Baillie JK, Bradley JM, Dark P, Dave C, De Soyza A, Dennis AV, Devrell A, Fairbairn S, Ghani H, Gorman EA, Green CA, Hart N, Hee SW, Kimbley Z, Madathil S, *et al.* Effect of noninvasive respiratory strategies on intubation or mortality among patients with acute hypoxemic respiratory failure and COVID-19: the RECOVERY-RS randomized clinical trial. JAMA. 2022;327(6):546-558.

Pitre T, Su J, Helmeczi W, Ortiz JR, Taljaard M, Vaillancourt C, Carrier FM, Duffett M, Lewis K, Zeraatkar D. Noninvasive oxygenation strategies in adult patients with acute hypoxemic respiratory failure: a systematic review and network meta-analysis. Chest. 2023;164(4):913-925.

Ranieri VM, Tonetti T, Navalesi P, Nava S, Antonelli M, Pesenti A, Grasselli G, Grieco DL. High-flow nasal oxygen for severe hypoxemia: oxygenation response and outcome in patients with COVID-19. Am J Respir Crit Care Med. 2022;205(4):431-439.

RENOVATE Investigators and the BRICNet Authors; Maia IS, Kawano-Dourado L, Tramujas L, de Oliveira NE, Souza RN, *et al.* High-flow nasal oxygen vs noninvasive ventilation in patients with acute respiratory failure: the RENOVATE randomized clinical trial. JAMA. 2025;333(10):875-890.

Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, García-de-Acilu M, Frat JP, Masclans JR, Ricard JD. An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Respir Crit Care Med. 2019;199(11):1368-1376.

Rochwerg B, Einav S, Chaudhuri D, Mancebo J, Mauri T, Helviz Y, Goligher EC, Jaber S, Ricard JD, Rittayamai N, Roca O, Antonelli M, Maggiore SM, Nava S, Navalesi P, Frat JP, Azoulay E. The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline. Intensive Care Med. 2020;46(12):2226-2237.

Rochwerg B, Granton D, Wang DX, Helviz Y, Einav S, Frat JP, Mekontso Dessap A, Mancebo J, Sklar MC, Azoulay E. High flow nasal cannula compared with conventional

oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis. Intensive Care Med. 2019;45(5):563-572.

Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

Tu G, He H, Yin K, Ju M, Zheng Y, Zhu D, Luo Z. High-flow nasal cannula versus noninvasive ventilation for treatment of acute hypoxemic respiratory failure in renal transplant recipients. Transplant Proc. 2017;49(6):1325-1330.

Wang Y, Ni Y, Sun J, Liang Z, Li H, Li J, Chen Y, Li X, Duan J. Use of high-flow nasal cannula for immunocompromised patients with acute respiratory failure: a systematic review and meta-analysis. J Intensive Care Med. 2020;35(11):1221-1229.

Xu XP, Zhang XC, Hu SL, Xu JY, Xie JF, Liu SQ, Liu L, Huang YZ, Guo FM, Yang Y, Qiu HB. Noninvasive ventilation in acute hypoxemic nonhypercapnic respiratory failure: a systematic review and meta-analysis. Crit Care Med. 2017;45(7):e727-e733.