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ARTÍCULO ORIGINAL (Versión en inglés)

Modalidades de tratamiento respiratorio y su impacto en las exacerbaciones asmáticas agudas en pacientes con comorbilidades cardiovasculares

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Resumen

Las exacerbaciones agudas en pacientes con asma, especialmente en aquellos con enfermedad cardiovascular subyacente, plantean importantes desafíos clínicos debido a la compleja interacción entre los sistemas respiratorio y cardiovascular. Esta revisión sistemática, realizada de acuerdo con las directrices PRISMA, analiza cómo distintas estrategias de terapia respiratoria afectan la frecuencia y los desenlaces de estas exacerbaciones. Evaluamos estudios sobre tratamientos farmacológicos (como broncodilatadores y corticosteroides) y sobre intervenciones no farmacológicas avanzadas (incluida la ventilación no invasiva, la ventilación mecánica invasiva y el soporte vital extracorpóreo). La evidencia procedente de ensayos clínicos aleatorizados y estudios de cohorte sugiere que la ventilación no invasiva puede reducir las tasas de intubación en las exacerbaciones graves, mientras que el soporte vital extracorpóreo (ECLS) podría ser beneficioso en casos refractarios. Sin embargo, el conjunto global de evidencia sigue siendo limitado, con una notable variabilidad metodológica y una frecuente dependencia de análisis retrospectivos o post hoc. Se requiere con urgencia la realización de ensayos aleatorizados de gran tamaño y alta calidad centrados específicamente en pacientes asmáticos con comorbilidades cardiovasculares. La optimización de las estrategias terapéuticas en esta población podría mejorar los resultados clínicos y reducir la mortalidad asociada a las exacerbaciones agudas.

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Palabras clave: sistemas respiratorio y cardiovascular, pacientes con asma, broncodilatadores, corticosteroides

Summary

Respiratory treatment modalities and their impact on acute asthma exacerbations in cardiovascular comorbid patients

Acute exacerbations in asthma patients, especially those with underlying cardiovascular disease, pose major clinical challenges due to the complex interaction between the respiratory and cardiovascular systems. This systematic review, conducted according to PRISMA guidelines, examines how different respiratory therapy strategies affect the frequency and outcomes of these exacerbations. We evaluated studies on pharmacologic treatments (such as bronchodilators and corticosteroids) and advanced non-pharmacologic interventions (including non-invasive ventilation, invasive mechanical ventilation, and extracorporeal life support). Evidence from randomized controlled trials and cohort studies suggests that non-invasive ventilation can lower intubation rates in severe exacerbations, while extracorporeal life support (ECLS) may be beneficial in refractory cases. However, the overall evidence remains limited, with considerable methodological variability and frequent reliance on retrospective or post-hoc analyses. There is a clear need for large, high-quality randomized trials focused specifically on asthma patients with cardiovascular comorbidities. Refining therapeutic strategies in this population could improve clinical outcomes and reduce mortality associated with acute exacerbations.

Keywords: respiratory and cardiovascular systems, asthma patients, bronchodilators, corticosteroids

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Introduction

Asthma, a chronic lung disease marked by inflammation and airway narrowing, presents significant challenges to breathing. Symptoms such as frequent coughing, shortness of breath, chest tightness, and wheezing are common, yet their nonspecific nature can complicate distinguishing asthma from other respiratory conditions [1, 2, 3]. As a major global health concern, asthma contributes substantially to morbidity and healthcare costs, with an estimated €19 billion spent annually in Europe alone [4, 5, 6]. Moderate to severe exacerbations significantly increase both asthma-related and overall medical expenses [7]. The condition often emerges in childhood, driven by a complex interplay of genetic and environmental factors, particularly those related to atopy [1, 2, 3].

Exacerbations, characterized by rapidly worsening bronchial obstruction, manifest as intensified symptoms like chest tightness, coughing, wheezing, or shortness of breath [8, 9]. While some flare-ups resolve spontaneously or with treatment, systemic corticosteroids are often required for five to seven days [10]. Severe exacerbations, more common in poorly controlled asthma but possible even in mild or well-managed cases, may necessitate hospitalization and can be life-threatening [10, 11, 12, 13, 14, 15]. The Global Initiative for Asthma (GINA) evaluates asthma control using parameters such as daytime symptoms, activity limitations, nocturnal symptoms, rescue medication use, lung function, and exacerbation history, recommending tailored pharmacologic adjustments to optimize management [10].

Asthma frequently coexists with cardiovascular diseases, including heart failure, ischemic heart disease, and hypertension, particularly in older adults. These comorbidities can exacerbate asthma symptoms or complicate treatment, leading to poorer health outcomes. Effective asthma management relies on both pharmacological and non-pharmacological respiratory therapies to control symptoms and prevent exacerbations. However, cardiovascular comorbidities introduce complexities, necessitating careful evaluation of treatment impacts. While non-pharmacological interventions like ventilatory support and pulmonary rehabilitation show promise, their effects on patients with both asthma and cardiovascular disease remain underexplored.

This systematic review investigates the impact of various respiratory therapy modalities on acute exacerbation rates in patients with asthma and pre-existing cardiovascular conditions. By addressing this knowledge gap, the review seeks to improve outcomes for this vulnerable population and inform therapeutic decision-making.

Methods

This systematic review evaluates the impact of respiratory therapy modalities on acute exacerbation rates in patients with asthma and cardiovascular comorbidities. A comprehensive literature search was conducted across PubMed, MEDLINE, EMBASE, and CINAHL, using keywords including "respiratory therapy," "asthma," "acute exacerbations," "cardiovascular diseases," "pulmonary rehabilitation," "oxygen therapy," and "comorbidities." Additional terms like "bronchospasm," "ventilatory support," and "systemic corticosteroids" were incorporated based on preliminary searches to enhance inclusivity. Boolean operators (AND, OR, NOT) refined the search strategy for each database. The search was restricted to peer-reviewed studies published within the last 10 years to ensure relevance and reflect recent advancements. Reference lists of included studies were manually reviewed to identify additional relevant research. The Cochrane Library and WHO Global Health Library were also searched for studies addressing respiratory therapy in patients with asthma and cardiovascular conditions. Reference management software facilitated duplicate removal, streamlining the review process.

Study selection

Inclusion criteria included: (1) studies evaluating respiratory therapy interventions (e.g., inhalation therapies, pulmonary rehabilitation, oxygen therapy) in patients with asthma and cardiovascular comorbidities (e.g., heart failure, ischemic heart disease, hypertension); (2) studies measuring exacerbation incidence, frequency, or severity; (3) peer-reviewed publications providing quantitative or qualitative data. Exclusion criteria encompassed studies focusing solely on non-respiratory interventions, non-exacerbation outcomes, single-comorbidity populations, or non-peer-reviewed publications like conference abstracts.

Data extraction

A standardized form captured study details, including author, publication year, population characteristics (sample size, demographics, comorbidities), intervention specifics, and outcomes (primary: exacerbation rates; secondary: hospitalization rates, therapy-related adverse events).

Quality assessment

Randomized controlled trials were assessed using the Cochrane Risk of Bias Tool (version 1), evaluating domains like sequence generation and blinding. Observational studies were evaluated with NIH quality assessment tools, addressing biases and confounders. Studies were rated as "good," "fair," or "poor" quality.

Study selection process

The search yielded 4,996 articles. After removing 1,509 duplicates, 3,487 titles and abstracts were screened, excluding 3,435 for irrelevance. Full-text screening of 52 articles led to 37 exclusions due to irrelevant outcomes, inappropriate designs, or insufficient comorbidity data. Six studies [16, 17, 18, 19, 20, 21, 22, 23] were included, as shown in the PRISMA flow diagram (Figure 1). Most studies were rated "fair" to "good" quality, with noted limitations considered in the analysis.

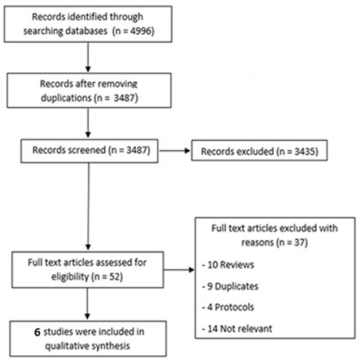

Figure 1: PRISMA flow diagram PRISMA: Preferred reporting items for systematic reviews and meta-analyses

In severe asthma exacerbations significantly affect cardiovascular health due to heart-lung interactions, such as increased venous return and elevated right ventricular afterload, potentially causing complications like pulsus paradoxus. Effective management requires monitoring both respiratory and cardiac parameters to reduce heart strain during attacks. Non-invasive ventilation (NIV) is a promising intervention for severe exacerbations, reducing the need for invasive mechanical ventilation and supporting respiratory and cardiovascular function. However, its long-term effectiveness and impact on mortality remain under investigation, with studies suggesting reduced intubation rates but inconclusive survival benefits.

In refractory cases, extracorporeal life support (ECLS), such as veno-venous extracorporeal membrane oxygenation (VV-ECMO), shows survival rates above 83% by oxygenating blood directly, bypassing compromised lungs. Risks like hemorrhagic complications necessitate careful patient selection. Pulmonary rehabilitation, incorporating exercise and education, helps manage comorbidities like cardiovascular disease, common in asthma and COPD, improving outcomes and reducing exacerbation frequency. Tailored programs for these comorbidities require further research.

In ICU settings, life-threatening exacerbations are treated with oxygen therapy, bronchodilators, corticosteroids, high-flow nasal oxygen (HFNC), or invasive mechanical ventilation (IMV) to stabilize respiratory status and prevent cardiovascular compromise. Evidence for advanced interventions like NIV and extracorporeal therapies is limited, requiring randomized controlled trials to establish efficacy. House dust mite sublingual immunotherapy (HDM SLIT) shows potential in reducing exacerbation severity in allergic asthma but has limited impact on health-related quality of life, needing further evaluation for long-term cardiovascular benefits.

Managing asthma with cardiovascular comorbidities demands an integrated approach, focusing on respiratory and cardiac health, personalized therapies like NIV or ECMO, and optimized ventilatory support. While these interventions are promising, high-quality studies are essential to confirm their safety and effectiveness in reducing exacerbations and improving outcomes.

Discussion

This systematic review highlights the significant role of respiratory therapy modalities in managing acute asthma exacerbations in patients with pre-existing cardiovascular conditions. Sublingual immunotherapy for house dust mite-induced allergic asthma demonstrated prolonged symptom control and improved health-related quality of life, particularly during moderate to severe exacerbations. Critical care interventions, including non-invasive ventilation (NIV), extracorporeal life support (ECLS), and pharmacologic management, showed efficacy in reducing the need for invasive mechanical ventilation and improving survival in refractory cases. For instance, NIV may lower intubation rates, which is critical given the high complication and mortality risks associated with invasive ventilation, as noted by Brenner et al. (2009) [24]. Pulmonary rehabilitation, while promising for COPD, requires adaptation for asthma

Table 1: shows the population sex and regional characteristics of the studies included in this systematic review. It provides details about the gender distribution within the study populations and the regions or countries where the studies were conducted, as outlined in the following

Paper	Population sex	Region
Andrew Briggs +4	Both Genders	Multinational European
Morgan Caplan +4	Not mentioned (the paper does not explicitly state the sex or gender distribution of the study population)	Multinational
Blanca Cárdaba +4	Not mentioned (the population sex is not mentioned in the paper)	Not mentioned (the paper does not explicitly state the region or country of the authors)
Shameek Gayen +7	mostly male	Not mentioned (the paper does not mention the specific region or country where the study was conducted)
Frits M E Franssen +3	82% male	Not mentioned (the paper does not specify the region or country where the research was conducted)
R H Dougherty Ãw +2	Both Genders, with a higher prevalence of asthma exacerbations in females compared to males	The paper appears to be a multinational or international review of asthma epidemiology and exacerbations, drawing from data and research across multiple countries, including the United States, United Kingdom, and New Zealand.

patients with cardiovascular comorbidities to maximize benefits.

Severe asthma exacerbations exacerbate airway hyperresponsiveness, bronchoconstriction, and dynamic hyperinflation, worsening respiratory mechanics [16]. Effective therapies, such as inhaled salbutamol combined with ipratropium bromide in severe cases, aim to reverse airway constriction and restore inspiratory and expiratory flows [22]. Beta-2-agonists, described by Misouri et al. [25], are recommended for their rapid action [22, 25]. Retrospective studies suggest NIV can improve outcomes by avoiding intubation, particularly in patients with cardiovascular comorbidities [26]. Understanding heart-lung interactions is crucial for tailoring treatments to optimize both respiratory and cardiovascular function.

This review uniquely synthesizes pharmacological and non-pharmacological interventions, emphasizing tailored care pathways for this underexplored population. However, limitations include a lack of specific data on asthma patients with cardiovascular comorbidities, methodological heterogeneity, reliance on post-hoc analyses, and inconsistent definitions of exacerbation severity. Despite these, the review's strengths lie in its comprehensive analysis of diverse therapies and detailed discussion of physiological implications, providing a robust basis for clinical decision-making.

In conclusion, while sublingual immunotherapy, NIV, ECLS, and pulmonary rehabilitation show promise, high-quality research is needed to define optimal treatment strategies. Future studies should focus on standardized outcome measures, cardiovascular monitoring, and tailored rehabilitation programs to improve care and reduce exacerbation burden in asthma patients with cardiovascular comorbidities.

Referencias bibliográficas

[1] Gershon, Andrea S., et al. "Asthma and Chronic Obstructive Pulmonary Disease (COPD) Prevalence and Health Services Use in Ontario Métis: A Population-Based Cohort Study." *PLOS ONE*, vol. 9, no. 4, 2014.

[2] Karahan, Serkan. "Asthma." *Chronic Disease Follow-Ups for Adults in Primary Care*, 2022.

[3] Porsbjerg, Celeste, et al. "Asthma." *The Lancet*, 2023.

[4] Nathan, Robert A. "The Burden of Allergic Rhinitis." *Allergy and Asthma Proceedings*, 2007.

[5] Schatz, Michael. "A Survey of the Burden of Allergic Rhinitis in the USA." *Allergy: European Journal of Allergy and Clinical Immunology*, 2007.

[6] Bahadori, K., et al. "Economic Burden of Asthma: A Systematic Review." *BMC Pulmonary Medicine*, 2009.

[7] Ivanova, Julia I., et al. "Effect of Asthma Exacerbations on Health Care Costs among Asthmatic Patients with Moderate and Severe Persistent Asthma." *Journal of Allergy and Clinical Immunology*, 2012.

[8] Rochester, Carolyn L., et al. "An Official American Thoracic Society/European Respiratory Society Policy Statement: Enhancing Implementation, Use, and Delivery of Pulmonary Rehabilitation." *American Journal of Respiratory and Critical Care Medicine*, vol. 192, no. 11, 2015, pp. 1373–86.

Table 2: shows a summary of the study objectives, design, and discussions from the reviewed papers on asthma and respiratory interventions

Paper	Study objectives	Study design	Summary of discussion
Andrew Briggs +4	1) To investigate the duration of moderate and severe asthma exacerbations through analysis of patient electronic diaries 2) To derive utilities (patient preferences) for five asthma health states in order to measure the impact of asthma control and exacerbations on patients' health-related quality of life	The study design was a randomized, double-blind, placebo-controlled, multinational, multi-period clinical trial.	Moderate and severe asthma exacerbations have a significant and prolonged impact on lung function, symptoms, medication use, and quality of life, with severe exacerbations having a greater impact than moderate ones.
Morgan Caplan +4	- To explore the consequences of airway narrowing in the most severe form of acute asthma - To describe the cardio-pulmonary interactions that occur during spontaneous ventilation in acute asthma - To highlight the importance of understanding the intricate relationship between heart function and lungs in order to improve management of acute asthma	Not mentioned (the study design is not mentioned in the paper)	The key points from the discussion are that healthcare providers need to understand the complex interplay between the respiratory and cardiovascular systems in acute asthma, closely monitor cardiac parameters in high-risk patients, and that future research is needed to better elucidate the underlying mechanisms of the cardio-respiratory interactions in this disease.
Blanca Cárdaba +4	- Provide a comprehensive overview of the available treatments and the evidence for their use in intensive care for managing severe, life-threatening, and near-fatal asthma exacerbations in adults - Highlight the need for more multicenter trials to address clinical knowledge gaps in this area - Develop evidence-based intensive care guidelines for managing patients with life-threatening and near-fatal asthma exacerbations	Not mentioned (the study design is not mentioned in the paper)	The paper highlights the need for more research and evidence-based guidelines for the management of acute life-threatening and near-fatal asthma exacerbations in the intensive care unit, as current interventions lack strong clinical evidence to support their effectiveness.
Shameek Gayen +7	Not mentioned (the paper does not explicitly state any "study objectives")	The study design appears to be a retrospective observational analysis of data from the ELSO registry, as well as a review of smaller observational studies on the use of ECCO2R in asthma exacerbations. The paper does not mention any randomized controlled trials or other experimental study designs.	The summary of the discussion is that severe asthma exacerbations require a comprehensive understanding of the underlying pathophysiology and a multifaceted approach to management, including pharmacotherapy, ventilation strategies, and advanced supportive measures like extracorporeal life support, with some areas warranting further research.
Frits M E Franssen +3	- To review the current literature on the impact of comorbidities on pulmonary rehabilitation outcomes in COPD patients - To identify gaps in the current research and suggest areas for future study	Based on the information provided, this appears to be a review or commentary paper that summarizes existing literature on the impact of comorbidities on pulmonary rehabilitation outcomes in COPD patients, rather than a primary research study. The study design is predominantly retrospective, with one prospective study mentioned.	The impact of comorbidities on the outcomes of pulmonary rehabilitation in patients with COPD remains uncertain, as the current evidence provides contradictory results regarding the impact of specific comorbidities, while the potential benefits of pulmonary rehabilitation on the development and clinical course of comorbidities are largely unknown.
R H Dougherty Ãw +2	- Examine the epidemiologic features of acute asthma exacerbations - Summarize recent advances in the understanding of the clinical and biological features of asthma exacerbations - Review the potential mechanisms underlying the susceptibility of a subgroup of asthmatics to recurrent and severe exacerbations	Not mentioned (the paper does not explicitly state the study design, as it is a review article rather than a primary research study)	A better understanding of the biological mechanisms underlying the "exacerbation-prone" asthma phenotype, including deficient epithelial cell production of anti-viral type I interferons, will be important for developing more effective preventions and treatments to reduce the significant cost and morbidity associated with asthma exacerbations.

Table 3: shows a summary of the recommendations, discussions, and conclusions from the reviewed papers on asthma and respiratory interventions

Paper	Recommendation	Summary	Conclusions
Andrew Briggs +4	Not mentioned (the paper does not provide any explicit recommendations, but does suggest several areas for future research that could be considered recommendations)	The paper reports the duration of moderate and severe asthma exacerbations in patients with house dust mite induced allergic asthma and the impact of these exacerbations on patients' quality of life.	The conclusions state that moderate and severe house dust mite-induced allergic asthma exacerbations have a longer-lasting impact on patients than previously appreciated, with effects seen up to 14 days before and 28 days after the peak of the exacerbation. Both moderate and severe exacerbations lead to decreased health-related quality of life, with severe exacerbations having a greater impact on lung function, symptoms, medication use, and sleep compared to moderate exacerbations.
Morgan Caplan +4	1. Use non-invasive positive pressure ventilation cautiously, as its role is not yet clearly defined. 2. Limit invasive mechanical ventilation to patients with life-threatening prognosis, as it is associated with high mortality and can lead to hemodynamic instability. 3. If using invasive mechanical ventilation, the goal should be to ensure oxygenation while minimizing the risk of hyperinflation, which can negatively impact the cardiovascular system. Reducing tidal volume and lengthening expiratory time are recommended methods to achieve this.	The paper provides a comprehensive review of the cardiorespiratory interactions that occur in acute asthma, particularly during severe exacerbations, and how these interactions can impact cardiac function and lead to the development of pulsus paradoxus.	1) Asthma has significant cardiovascular effects due to heart-lung interactions, and healthcare providers need to consider both respiratory and hemodynamic aspects in managing acute asthma. 2) Close monitoring of cardiac parameters is crucial in high-risk asthma patients to optimize treatment. 3) Future research is needed to better understand the complex heart-lung interactions in asthma, as it remains a life-threatening condition.
Blanca Cárdaba +4	The key recommendation from the paper is that major respiratory and intensive care societies should consider patients with life-threatening and near-fatal asthma exacerbations as an "orphan disease" and address the urgent research needs in this area, as there is a significant lack of high-quality evidence to support the effectiveness of many interventions commonly used in the ICU setting for these patients.	The paper provides a comprehensive overview of the management of acute life-threatening asthma exacerbations in the intensive care unit, highlighting the lack of high-quality evidence to guide specific interventions beyond standard guidelines and the need for further research and evidence-based guidelines in this area.	1) There is a lack of high-quality evidence supporting the effectiveness of various advanced interventions used to manage life-threatening and near-fatal asthma exacerbations in the ICU. 2) Current guidelines do not adequately address the management of this patient population, and an evidence-based approach is needed to evaluate these interventions. 3) Major medical societies should prioritize research on the management of severe, life-threatening asthma exacerbations, as this patient population is currently underserved.
Shameek Gayen +7	1) Optimize pharmacologic and ventilation strategies to treat underlying bronchospasm 2) Consider using NIV, which may be associated with lower rates of intubation and mortality 3) Consider using VV-ECMO in severe, refractory cases, which has been associated with high survival rates	This paper provides a comprehensive review of the critical care management of severe asthma exacerbations, including pathophysiology, pharmacologic management, ventilation strategies, and advanced non-pharmacologic techniques.	Managing airway hyperresponsiveness, bronchoconstriction, and dynamic hyperinflation is critical for optimal severe asthma exacerbation care. Mechanical ventilation, if excessive, risks complications; controlled hypoventilation and extended expiratory time are essential. Refractory cases may need advanced support like ECLS, paralysis, Heliox, buffer solutions, or inhaled anesthetics despite optimal pharmacotherapy. Close monitoring and deep physiological understanding ensure effective, safe management of critically ill asthmatics.
Frits M E Franssen +3	1) Pulmonary rehabilitation staff should be trained to recognize and manage common comorbidities in COPD patients. 2) Pulmonary rehabilitation staff should be able to provide advice to patients on managing their comorbidities, recognize signs of disease destabilization, and refer patients to other specialists as needed. 3) Pulmonary rehabilitation programs should include patient education on managing common comorbidities, with targeted goals and monitoring for these conditions.	The paper provides a comprehensive overview of the prevalence and impact of comorbidities in patients with COPD, as well as the potential role of pulmonary rehabilitation in managing these comorbidities, and concludes that more research is needed to optimize pulmonary rehabilitation for COPD patients with specific comorbidities.	1) Comorbidities are common in COPD patients referred for pulmonary rehabilitation, but the impact of comorbidities on pulmonary rehabilitation outcomes is unclear. 2) While the total number of comorbidities may not affect pulmonary rehabilitation, specific types of comorbidities like cardiovascular, metabolic, and psychological conditions may impact certain outcomes. 3) The impact of pulmonary rehabilitation on the development and course of comorbidities is not well understood, and future research should focus on optimizing pulmonary rehabilitation programs to address specific comorbidities in COPD patients.
R H Dougherty Áw +2	Not mentioned (the paper does not provide any explicit "recommendations" or recommendations section)	The paper provides an overview of the epidemiology, biology, and characteristics of the "exacerbation-prone" phenotype of asthma, which is responsible for the majority of the cost and morbidity associated with asthma.	1) Asthma exacerbations are a major public health burden, with a minority of "exacerbation-prone" asthmatics responsible for the majority of healthcare costs. 2) The "exacerbation-prone" phenotype is characterized by factors like smoking, non-compliance, comorbidities, and psychosocial factors. 3) Intrinsic host factors, such as deficient antiviral responses, may contribute to the "exacerbation-prone" phenotype, and further research in this area is needed to develop new preventions and treatments.

Table 4: shows a summary of the main findings, methodologies, and details about the population and participants from the reviewed papers

Paper	Main findings	Methodology	Population	Details about the participants, such as sample size, age range, gender distribution, or comorbid conditions.
Andrew Briggs +4	Moderate and severe house dust mite-induced allergic asthma exacerbations increase symptoms, medication use, and reduce lung function for up to 14 days before and 28 days after peak events. Severe exacerbations more significantly impair health-related quality of life than moderate ones.	The MT-04 phase III trial's post-hoc analysis examined moderate and severe asthma exacerbation duration and health-related quality of life impact. Patient diaries informed duration; EQ-5D-3L and AQL-5D questionnaires calculated utilities for five asthma health states. Regression analysis predicted disutility of health state transitions.	Patients with house dust mite induced allergic asthma	The study included 742 participants, with 485 receiving the active treatment and 257 receiving placebo. The participants had partly controlled asthma at the start of the study, but the paper does not provide details on the age range, gender distribution, or other comorbid conditions of the participants.
Morgan Caplan +4	Acute asthma exacerbations impact the cardiovascular system via heart-lung interactions, increasing venous return, right ventricular afterload, and ventricular interdependence. Inspiratory pleural pressure drops cause pulsus paradoxus, reflecting airway obstruction severity. Bronchodilators and positive pressure ventilation improve respiratory mechanics and cardio-pulmonary interactions by reducing pleural pressure variations.	Not mentioned (the paper does not describe a specific methodology, as it is a review article that discusses the existing literature on cardio-respiratory interactions in acute asthma)	The population in this paper consists of patients with asthma, specifically those experiencing acute exacerbations or "life-threatening asthma", which may include both pediatric and adult patients.	Not mentioned (the paper does not mention any details about the participants, such as sample size, age range, gender distribution, or comorbid conditions)
Blanca Cárdaba +4	Managing life-threatening asthma exacerbations in the ICU is challenging, with an unclear pathway. Evidence for interventions like non-invasive ventilation, intravenous bronchodilators, and extracorporeal therapies is limited. Large randomized trials are needed to evaluate their efficacy and impact on invasive ventilation and mortality.	Not mentioned (the paper does not describe a specific study methodology, as it is a narrative review article that aims to provide a comprehensive overview of the available treatments and the evidence for their use in intensive care for patients with acute life-threatening asthma exacerbations)	The population in this paper is patients with acute life-threatening and near-fatal asthma exacerbations who are admitted to the intensive care unit (ICU).	Not mentioned (the paper does not provide any details about the participants in the studies it references, such as sample size, age range, gender distribution, or comorbid conditions)
Shameek Gayen +7	Severe asthma exacerbations, including near-fatal cases, have high morbidity and mortality, with complex pathophysiology complicating mechanical ventilation. Despite optimal management, ICU mortality is 8%, indicating a need for advanced therapies like VV-ECMO, which offers over 83% survival but risks hemorrhagic complications.	This paper is a review article that does not describe a specific study methodology. Instead, it provides a comprehensive overview of the critical care management of severe asthma exacerbations, covering the pathophysiology, pharmacologic management, ventilation strategies, and use of advanced therapies like extracorporeal life support.	The population in this paper is critically ill adult patients with severe asthma exacerbations, including those with near-fatal asthma (NFA).	Not mentioned (the paper does not provide any details about the participants, such as sample size, age range, gender distribution, or comorbid conditions)
Frits M E Franssen +3	Over 50% of COPD patients referred for pulmonary rehabilitation have at least one comorbidity. The impact of comorbidities on rehabilitation outcomes is unclear, with conflicting study results. Specific comorbidities may affect program adherence and outcomes.	Not mentioned (the paper does not describe a specific methodology, but rather provides a review of the current literature on comorbidities in copd patients and the impact of comorbidities on pulmonary rehabilitation outcomes)	The population in this paper is patients with chronic obstructive pulmonary disease (COPD) who are referred for pulmonary rehabilitation.	32% of COPD patients have one comorbidity, 39% have two or more. Cardiovascular disease risk is 2-3 times higher than in age-matched controls. Skeletal muscle dysfunction and fat-free mass loss affect 10-15% of mild-to-moderate and up to 50% of severe COPD patients. Study details on sample size, age, and gender are lacking.
R H Dougherty Âw +2	Asthma exacerbations drive significant US healthcare costs, with 15 million outpatient visits, 2 million ER visits, and 500,000 hospitalizations yearly. "Exacerbation-prone" asthmatics face recurrent risks from extrinsic (smoking, non-compliance, comorbidities) and intrinsic (impaired antiviral interferon production) factors.	Not mentioned (the paper does not describe a specific methodology, but rather provides a review of the epidemiology and biology of acute asthma exacerbations)	The paper discusses the epidemiology of asthma and asthma exacerbations in general, rather than focusing on a specific population. It provides statistics on the global prevalence of asthma, the prevalence in the United States, and the higher risk of exacerbations among certain racial/ethnic groups.	Asthma affects 22.2 million Americans (7.7%). Ages 35-54 account for 31.7% of hospitalizations. Children/adolescents have the lowest mortality (0.02%), elderly the highest (1.9%, >75). Females face more exacerbations and double the hospitalization risk than males. Study details on sample sizes, ages, genders, and comorbidities are limited.

Table 5: shows a summary of the intervention types, comparators, outcomes measured, and limitations from the reviewed papers

Paper	Intervention Type	Comparator	Outcomes Measured	Limitations
Andrew Briggs +4	The intervention type in this study was a house dust mite sublingual immunotherapy (HDM SLIT) tablet, with two different doses (6 SQ-HDM or 12 SQ-HDM) compared to a placebo.	The comparator in this study was the placebo group.	1) The duration of moderate and severe asthma exacerbations 2) The impact of those exacerbations on patients' health-related quality of life (HRQoL) through utility values	1) The definition of moderate exacerbations was novel and may have limited applicability in clinical practice 2) The trial design led to a relatively small number of exacerbations, preventing analysis of the impact of repeated exacerbations on HRQoL 3) The analysis did not account for the timing between exacerbation occurrence and AQLQ assessment 4) Most of the analyses were conducted post-hoc rather than being prespecified
Morgan Caplan +4	Not mentioned (the paper does not describe any specific intervention type)	Not mentioned (the paper does not mention a specific comparator group)	Not mentioned (the paper does not report any specific outcomes measured in a study)	The paper does not explicitly state any limitations, but acknowledges that the precise underlying mechanisms for pulsus paradoxus in acute asthma remain subject to ongoing research, and that the role of non-invasive positive pressure ventilation in acute asthma still needs further clarification.
Blanca Cárdaba +4	The main intervention types discussed in the paper are oxygen therapy, bronchodilators, corticosteroids, magnesium sulfate, non-invasive ventilation, invasive mechanical ventilation, extracorporeal carbon dioxide removal, extracorporeal membrane oxygenation, mucolytics, and helium-oxygen mixtures.	1) Conventional oxygen therapy vs. high-flow nasal oxygen (HFNC) 2) Non-invasive ventilation (NIV) vs. HFNC 3) NIV vs. standard care	Not mentioned (the paper does not report on specific outcomes measured in a study, but rather provides a narrative review of the available treatments and evidence for managing acute life-threatening and near-fatal asthma exacerbations in the intensive care unit)	1) It is a narrative review, which has inherent methodological constraints compared to a systematic review. 2) The studies included had significant heterogeneity in terms of study type, population, and interventions, limiting the ability to draw firm conclusions.
Shameek Gayen +7	The "Intervention Type" in this paper is a comprehensive review of the critical care management of severe asthma exacerbations, including pharmacologic interventions, ventilatory interventions, and advanced supportive measures such as extracorporeal life support.	Not mentioned (the paper does not appear to report on a specific study with a comparator group)	Not mentioned (the paper does not report any specific outcomes that were measured)	The main limitations of this review are the lack of large, prospective, randomized trials evaluating the use of non-invasive ventilation (NIV) and extracorporeal CO2 removal (ECCO2R) in the management of severe asthma exacerbations. The authors acknowledge that while these interventions show promise, more research is needed to fully evaluate their efficacy and optimal implementation.
Frits M E Franssen +3	Pulmonary rehabilitation	Not mentioned (the paper does not mention a "comparator" group)	The key outcomes measured in the studies reviewed were dyspnea, health status, exercise capacity, and functional performance.	Previous studies used medical records to identify comorbidities without confirming diagnoses or assessing severity. No prospective studies compare pulmonary rehabilitation outcomes in COPD patients with versus without comorbidities. Few studies adapt rehabilitation programs to target comorbid conditions or use them as primary outcomes. The long-term impact of pulmonary rehabilitation on comorbidity development and progression in COPD remains unstudied.
R H Dougherty Ãw +2	Not mentioned (the paper does not describe any specific intervention or study design)	Not mentioned (the paper does not appear to describe a specific comparator group)	1) Symptoms like shortness of breath, cough, and wheezing 2) Decreases in lung function as measured by spirometry and peak flow 3) Number of exacerbations requiring oral corticosteroids 4) Incidence of near-fatal asthma events	Not mentioned (the paper does not mention any limitations)

[9] Celli, Bartolome R., et al. "An Official American Thoracic Society/European Respiratory Society Statement: Research Questions in COPD." *European Respiratory Journal*, 2015.

[10] Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention (2016 Update).* Guía GINA Actual, 2016.

[11] Mroczek, Bożena, et al. "The Influence of Asthma Exacerbations on Health-Related Quality of Life." *Advances in Experimental Medicine and Biology*, 2015.

[12] Reddel, Helen, et al. "Differences between Asthma Exacerbations and Poor Asthma Control." *The Lancet*, 1999.

[13] Pauwels, Romain A., et al. "Early Intervention with Budesonide in Mild Persistent Asthma: A Randomised, Double-Blind Trial." *The Lancet*, vol. 361, no. 9363, 2003, pp. 1071–76.

[14] Nasser, Sami. "An Imperfect 'PAST': Lessons Learned from the National Review of Asthma Deaths (NRAD) UK." *Respiratory Research*, 2016.

[15] Bateman, Eric D., et al. "Can Guideline-Defined Asthma Control Be Achieved? The Gaining Optimal Asthma Control Study." *American Journal of Respiratory and Critical Care Medicine*, 2004.

[16] Gayen, Sanchari, et al. "Critical Care Management of Severe Asthma Exacerbations." *Journal of Clinical Medicine*, vol. 13, 2024.

[17] Talbot, Thomas, et al. "Management of Acute Life-Threatening Asthma Exacerbations in the Intensive Care Unit." *Applied Sciences*, vol. 14, no. 2, 2024.

[18] Franssen, F.M.E., and Carolyn L. Rochester. "Comorbidities in Patients with COPD and Pulmonary Rehabilitation: Do They Matter?" *European Respiratory Review*, vol. 23, no. 131, 2014, pp. 131–41.

[19] Pankratov, E.L. "On Model of Spatio-Temporal Distribution of Blood in a Cardiovascular System." *Trends in Clinical and Medical Sciences*, vol. 4, no. 1, 2025, pp. 1–5. Published 26 May 2025.

[20] Briggs, Andrew, et al. "The Impact of Moderate and Severe Asthma Exacerbations on Quality of Life: A Post Hoc Analysis of Randomised Controlled Trial Data." *Journal of Patient-Reported Outcomes*, vol. 5, no. 1, 2021.

[21] AlMalmi, Mohammed Abdul Qader. "Mobile Teledermatology Update: Clinical Case Presentations." *Trends in Clinical and Medical Sciences*, vol. 4, no. 1, 2025, pp. 6–12. Published 29 July 2025.

[22] Caplan, Michael, and Omran Hamzaoui. "Cardio-Respiratory Interactions in Acute Asthma." *Frontiers in Physiology*, vol. 14, 2023.

[23] Dougherty, Robert H., and John V. Fahy. "Acute Exacerbations of Asthma: Epidemiology, Biology and the Exacerbation-Prone Phenotype." *Clinical and Experimental Allergy*, vol. 39, no. 2, 2009, pp. 193–202.

[24] Brenner, Barry, et al. "Intubation and Mechanical Ventilation of the Asthmatic Patient in Respiratory Failure." *Proceedings of the American Thoracic Society*, vol. 6, no. 4, 2009, pp. 371–79.

[25] Misuri, Gianfranco, et al. "Respiratory Muscle Overloading and Dyspnoea during Bronchoconstriction in Asthma: Protective Effects of Fenoterol." *Pulmonary Pharmacology & Therapeutics*, vol. 10, no. 5–6, 1997, pp. 299–304.

[26] Althoff, Michael D., et al. "Noninvasive Ventilation Use in Critically Ill Patients with Acute Asthma Exacerbations." *American Journal of Respiratory and Critical Care Medicine*, vol. 202, no. 11, 2020, pp. 1520–30.