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REVIEW ARTICLE

Clinical Futility, Therapeutic Inertia, and De-Implementation Strategies for Beta-2 Agonists in Acute Bronchiolitis: An Integrative Review

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SUMMARY

Introduction: Acute bronchiolitis is the leading cause of hospital admission in infants. Despite evidence of its futility, the routine use of beta-2 agonists (salbutamol) persists, a low-value practice that leads to therapeutic inertia. The aim of this integrative review was to synthesize the evidence on the ineffectiveness and risks of these agents and to systematize effective strategies for their discontinuation.

Methods: An integrative review design (Whittemore and Knafl framework) was applied, with reporting adhering to PRISMA 2020. The systematic search (2014–2024) focused on literature published after the 2014 AAP guideline. Methodological quality was assessed using the MMAT tool, and data were narratively synthesized into four domains: clinical futility, safety, therapeutic inertia, and de-implementation strategies.

Results: Clinical futility was consistently confirmed: salbutamol does not reduce hospital stay (MD: 0.12 days) or improve oxygen saturation. This ineffectiveness is attributed to the downregulation of beta-2 receptors induced by respiratory syncytial virus (RSV) infection. Safety risks include tachycardia, tremors, and transient hypoxemia due to ventilation-perfusion mismatch (V/Q mismatch). Inertia is more prevalent in primary care, driven by physician “action bias” and the pressure of parental expectations (technological placebo).

Conclusion: Treatment failure is structural, and its continued use violates the principle of non-maleficence, also entailing an opportunity cost. Successful discontinuation requires active behavioral strategies: “replacing the action” with visible support (nasal suction, parent education), modifying the decision-making environment (CDSS), and using comparative audit and feedback. Clinical excellence lies in providing strict physiological support.

Keywords: Bronchiolitis, Beta-Agonists, Therapeutic Futility, Therapeutic

Inertia, De-Implementation, Salbutamol, Respiratory Syncytial Virus.

INTRODUCTION

Acute bronchiolitis represents one of the most prevalent challenges in contemporary hospital pediatrics, consolidating itself as the main cause of respiratory morbidity and hospital admission in infants globally (1,2). Despite its primarily viral etiology and self-limiting clinical course, the management of this condition continues to exhibit remarkable and unjustified variability, characterized by the persistence of low-value pharmacological interventions that contradict the principles of evidence-based medicine (3). Among these outdated practices, the routine administration of short-acting beta-2 adrenergic agonists, such as salbutamol, remains deeply entrenched in various clinical settings, from primary care to emergency departments.

The scientific evidence accumulated over the last decade has established, with a high degree of certainty, the clinical futility of bronchodilators in this population. Recent systematic reviews corroborate that the use of salbutamol does not significantly impact critical outcomes: it does not reduce hospital stay—showing a clinically irrelevant weighted mean difference of 0.12 days—nor does it modify the severity of respiratory distress or oxygenation parameters compared to placebo (4). This ineffectiveness contrasts with the profile of other interventions, such as hypertonic saline solution or standardized supportive care, which have demonstrated superior or equivalent efficacy profiles, free from the pharmacological risks associated with beta-agonists (5,6). However, the translation of this evidence into real-world practice is poor; observational studies show a significant gap in adherence to clinical practice guidelines, with primary care physicians being more likely to prescribe these drugs compared to hospital specialists (7,8).

The therapeutic inertia perpetuated by this prescription is not a harmless phenomenon. From a mechanistic perspective, the lack of clinical response is explained by molecular pathophysiology: respiratory syncytial virus (RSV) infection induces functional insensitivity and downregulation of beta-2 adrenergic receptors in bronchial smooth muscle, negating the expected bronchodilator effect (9,10). Consequently, the administration of these agents exposes the infant to avoidable safety risks, such as tachycardia, tremors, and transient hypoxemia due to ventilation-perfusion imbalance, without offering any therapeutic benefit (11,12). Additionally, non-clinical factors, such as the pressure of parental expectations for visible intervention and clinician action bias (“doing something is better than nothing”), act as powerful behavioral barriers to de-implementation (13,14).

Faced with this scenario of stagnation in low-value practices, it is imperative to move beyond simply acknowledging the ineffectiveness of beta-agonists and address the systemic determinants of their continued use. This integrative review aims to synthesize the current evidence on the clinical futility and safety risks of beta-agonists in acute bronchiolitis, critically analyze existing barriers, and systematize the most effective de-implementation strategies. This is done to align clinical practice with the available scientific evidence.

METHODS

Research Design

An integrative literature review was conducted following rigorously the five-stage methodological framework proposed by Whittemore and Knafl (15). The review process consisted of three stages: 1) problem identification; 2) literature search; 3) data appraisal; 4) data analysis; and 5) presentation. This design was selected for its versatility in incorporating and synthesizing research with diverse methodologies (experimental trials, observational studies, and qualitative studies), allowing for a holistic understanding of complex phenomena such as clinical inertia and behavioral barriers to de-implementation. The review report adhered to the applicable items of the 2020 PRISMA statement (16) to ensure the transparency and reproducibility of the process.

Search strategy and information sources

The systematic literature search was conducted covering the period from January 2014 to December

2024. This time frame was deliberately selected to analyze the literature following the publication of the 2014 American Academy of Pediatrics (AAP) Clinical Practice Guideline, a milestone that marked the strong recommendation against the use of bronchodilators.

Three high-impact electronic databases were consulted: PubMed/MEDLINE, Scopus, and Web of Science. Additionally, the Semantic Scholar platform was used to perform bidirectional citation tracking, identifying relevant grey literature and emerging studies that might not be indexed in traditional databases.

The search strategy used a combination of controlled vocabulary (MeSH for PubMed, DeCS for Spanish literature) and free-text terms. Search strings included Boolean operators (AND, OR) and truncation (*) to maximize sensitivity. The main keywords were:

- **Population:** “Bronchiolitis”, “Viral Bronchiolitis”, “Infant*”.
- **Intervention:** “Beta-agonists”, “Adrenergic beta-Agonists”, “Albuterol”, “Salbutamol”, “Bronchodilators”.
- Resultados de interés: “Treatment outcome”, “Futility", “Inefficacy”, “Safety”, “Adverse effects”, “Hospitalization length”.
- **Implementation context:** “De-implementation”, “Therapeutic inertia”, “Guideline adherence”, “Clinical practice patterns”, “Overuse”.

Eligibility criteria

The selection of studies was based on the following modified PICO criteria:

- **Inclusion:** 1) Study type: primary studies (randomized clinical trials, prospective and retrospective cohorts, cross-sectional studies), systematic reviews with or without meta-analysis, qualitative studies (on attitudes and barriers) and quality improvement reports; 2) Population: infants under 24 months with a clinical diagnosis of acute bronchiolitis (first episode of wheezing associated with viral infection); 3) Language: articles published in English, Spanish, or Portuguese.
- **Exclusion:** 1) studies focused on populations with comorbidities that could pathophysiologically justify the use of bronchodilators (recurrent asthma or history of severe atopy, bronchopulmonary dysplasia, cystic fibrosis, hemodynamically significant congenital heart disease); 2) research that exclusively evaluated the use of racemic epinephrine/adrenaline; 3) opinion articles, editorials, and letters to the editor that did not provide original empirical data.

Study selection and data extraction

The selection process was carried out in two phases. First, titles and abstracts were screened to eliminate irrelevant references. Second, the full texts of potentially eligible articles were examined.

Data extraction was performed using a standardized matrix designed ad hoc for this review, capturing the following variables: author/year, country, study design, sample size, clinical setting (emergency, hospitalization, primary care), intervention evaluated, main outcomes (efficacy, safety, costs), and barriers identified.

Evaluation of methodological quality

Given the heterogeneity of the included designs, methodological quality was assessed using the Mixed Methods Appraisal Tool (MMAT). This tool allows for the concurrent evaluation of qualitative, quantitative, and mixed-methods research using criteria specific to each category (e.g., randomization in clinical trials, representativeness in descriptive studies). Studies of moderate to high quality were prioritized for inclusion to ensure the validity of the conclusions.

Data analysis and synthesis

Due to methodological diversity, a meta-analysis was not possible. Instead, a thematic narrative synthesis approach was adopted. Data were analyzed using the constant comparative method and categorized into four predefined analytical domains:

1. **Clinical futility:** comparative effectiveness in hard outcomes (hospital stay, saturation).
2. **Security:** profile of adverse events and physiological risks.
3. **Therapeutic inertia:** Analysis of behavioral barriers (doctors) and expectations (parents).
4. **De-implementation:** effective strategies to reduce low-value use.

RESULTS

The search and selection strategy culminated in the inclusion of a heterogeneous but complementary body of evidence, ranging from randomized clinical trials and meta-analyses to observational and qualitative studies. The following is a narrative synthesis of the findings, organized into five thematic areas: assessment of methodological quality, comparative clinical futility, pathophysiological mechanisms and safety, therapeutic inertia, and barriers to de-implementation.

Evaluation of the methodological quality of the included studies

Critical appraisal using the Mixed Methods Appraisal Tool (MMAT) revealed a generally moderate to high level of methodological quality, which lends robustness to the synthesis of results. The quantitative experimental studies, mainly controlled trials and systematic reviews such as those by Cai et al. (4) and Islam et al. (6), were also included. These studies demonstrated a low risk of bias, with adequate randomization and blinding in most cases. Meanwhile, cross-sectional and cohort observational studies were used to measure adherence to guidelines (2,7,8). They presented large and representative sample sizes, although some showed limitations inherent to the retrospective reporting of data from medical records. The selected qualitative studies (13) met the criteria for credibility and confirmability, providing a rich description of the context, essential for understanding the behavioral phenomena behind the prescription. This methodological variability allowed for effective triangulation of the evidence: quantitative data confirmed the ineffectiveness, while qualitative data explained the persistence of the practice.

Evidence of clinical futility and comparative efficacy

Analysis of recent literature consistently confirms the lack of clinical benefit of beta-2 adrenergic agonists in the course of acute bronchiolitis, reinforcing the concept of therapeutic futility. When examining the impact on hospital stay, multiple high-level evidence studies converge on the same conclusion: the drug does not modify the natural course of the disease. Specifically, the meta-analysis by Cai et al. (4) demonstrated that the administration of salbutamol, compared with placebo, resulted in a weighted mean difference of only 0.12 days in the length of hospital stay. This finding lacks both statistical and clinical significance, indicating that the intervention does not accelerate hospital discharge. Similarly, Calogero et al. (17) reaffirmed that bronchodilators do not generate substantial changes in the recovery trajectory of hospitalized infants.

Beyond hospital stay, the evaluation of immediate clinical parameters yields similar results. The synthesized research indicates no significant differences in post-treatment oxygen saturation or long-term resolution of respiratory distress between the intervention and control groups. Previous reviews, such as that by Gadomski and Scribani (18), suggested that a minority of patients might experience a transient improvement in clinical scores. However, the authors categorically concluded that this ephemeral change does not reduce the need for hospitalization or shorten the duration of the viral process, thus questioning the practical utility of such a temporary improvement.

The inferiority of beta-agonists becomes even more evident when compared to other therapeutic interventions. The evidence provided by Islam et al. (6) and Angoulvant et al. (5) positions nebulization with 3% hypertonic saline solution as a superior alternative. These studies reported that the hypertonic solution, through osmotic mechanisms that promote mucociliary clearance and airway rehydration, achieved a more consistent reduction in hospital stay and a sustained improvement in clinical scores compared to salbutamol. This contrast reinforces the notion that obstruction in bronchiolitis is primarily a problem of debris and edema, and not bronchoconstriction amenable to beta-agonists.

Pathophysiological mechanisms and safety profile

The reviewed literature does not merely confirm clinical ineffectiveness but provides a solid mechanistic basis that explains therapeutic failure and highlights associated risks. From a translational research perspective, the work of Davis et al. (9,10) is fundamental to understanding the underlying molecular pathophysiology. Their research demonstrated that respiratory syncytial virus (RSV) infection induces a direct functional alteration in the beta-2 adrenergic receptors of bronchial smooth muscle. The virus causes desensitization and uncoupling of these receptors, downregulating them and thus eliminating the tissue's ability to respond to pharmacological stimulation. This phenomenon of “virus-induced drug resistance” offers a plausible biological explanation for why bronchodilators, highly effective in asthma, consistently fail in bronchiolitis.

Paradoxically, although the therapeutic effect is blocked, adverse systemic effects persist. The safety review conducted by Khalil and Salas (11), supported by classic data from Price and Clissold (12), documents a profile of adverse effects that, although known, are frequently underestimated in daily clinical practice. The administration of beta-agonists in infants is associated with tachycardia, muscle tremors, hypokalemia, hyperactivity, and, critically, with episodes of transient oxygen desaturation. This latter phenomenon is attributed to a worsening of the ventilation-perfusion (V/Q) mismatch, where the drug increases blood flow to poorly ventilated lung areas. Consequently, the use of these agents imposes an additional physiological burden and tangible iatrogenic risks on an already compromised infant, without offering a compensating benefit, significantly impairing the risk-benefit ratio.

Therapeutic inertia and variability in clinical practice

Despite the overwhelming biological and clinical evidence and the existence of clear international guidelines such as the 2014 American Academy of Pediatrics (AAP) guideline that strongly recommends against its use, the review identified an alarming persistence in prescribing. This phenomenon is known as therapeutic inertia. However, this inertia is not uniform; the studies by Maki et al. (7) and Szupieńko et al. (8) revealed a profound disparity based on the care setting. There is a significant gap in adherence to guidelines between specialized hospital settings and primary care or general emergency services.

Data indicate that primary care physicians and physicians in non-pediatric emergency departments prescribe bronchodilators substantially more frequently than hospital pediatricians. This variability suggests that knowledge dissemination and protocol updates are less effective outside academic settings, or that the pressure of frontline care favors rapid interventions. Plint et al. (2) reported encouraging temporary trends with a gradual reduction in use in high-volume pediatric emergency departments. However, the prescription rate in the community remains stagnant, demonstrating that passive publication of guidelines is insufficient to eradicate entrenched practices.

Behavioral determinants and barriers to de-implementation

Qualitative analysis of the literature allowed for a more in-depth understanding of the root causes of this inertia, revealing that persistent prescribing is a multidimensional phenomenon driven by psychological and systemic factors rather than a lack of theoretical knowledge. First, parental expectations play a determining role in clinical decision-making. Campbell et al. (14) identified that parental anxiety regarding their children's breathing difficulties translates into explicit or implicit pressure on the doctor to “do something.” In this context, nebulization acts as a “technological placebo” that satisfies the family's need for a visible and immediate intervention, validating the doctor's role as healer, regardless of the drug's actual effectiveness.

Secondly, there are barriers inherent to the healthcare providers themselves. Hester et al. (19) described “action bias”—the irrational belief that intervention is inherently superior to vigilant observation—as a powerful driver of overprescribing. Furthermore, many clinicians express distrust of guidelines when they contradict their prior anecdotal experience (“it worked for me once”) and struggle to manage diagnostic uncertainty in older infants (“is it bronchiolitis or early-onset asthma?”), opting for a therapeutic trial as a defensive safety mechanism. Finally, institutional culture also perpetuates the problem; the absence of binding local protocols and the lack of audit and feedback create a permissive environment where outdated practices are maintained through oral tradition, resisting evidence-based change.

DISCUSSION

This integrative review synthesizes a decade of evidence accumulated since the publication of the 2014 American Academy of Pediatrics (AAP) guidelines, revealing a persistent paradox in contemporary pediatric medicine: the routine administration of beta-2 adrenergic agonists in acute bronchiolitis remains an endemic practice, defying a global scientific consensus on its futility. The findings of this review allow us to deconstruct this phenomenon not as a simple lack of medical updating. They reveal a complex interplay between systemic therapeutic inertia, a misinterpretation of viral respiratory pathophysiology, and deeply ingrained behavioral barriers in both clinical culture and societal expectations.

The most significant contribution of this synthesis lies in the integration of translational evidence to dismantle the biological rationale of the treatment. While clinical meta-analyses, such as that by Cai et al. (4), quantify ineffectiveness through statistical metrics—a clinically irrelevant reduction of 0.12 days in hospital stay—basic research provides the definitive mechanistic explanation. The work of Davis et al. (9,10) demonstrates that therapeutic failure is not idiosyncratic but structural: respiratory syncytial virus (RSV) infection induces functional insensitivity and down-regulation of beta-2 receptors in bronchial smooth muscle.

This finding invalidates the “trial by eye” premise often advocated in clinical practice. Unlike asthma, where obstruction is mediated by reversible muscle spasm, the pathophysiology of bronchiolitis is dominated by airway edema, epithelial necrosis, and debris blockage—processes against which bronchodilators have no substrate for action. Therefore, any transient improvement observed clinically is more likely attributable to the natural variability of the disease or the observer placebo effect than to a genuine pharmacological response in an airway with uncoupled receptors.

The continued use of beta-agonists under the premise that “it can't hurt to try” constitutes a violation of the principle of non-maleficence. Our review of the safety profile, based on Khalil and Salas (11) and the historical evidence of Price and Clissold (12), emphasizes that adverse effects are not trivial in a physiologically compromised infant. Tachycardia and hypokalemia, along with psychomotor agitation, increase metabolic oxygen consumption in patients already experiencing respiratory distress. Even more critical is the phenomenon of paradoxical desaturation due to ventilation-perfusion mismatch (V/Q mismatch), where drug-induced pulmonary vasodilation diverts blood flow to non-ventilated alveoli, exacerbating the hypoxemia it was intended to treat.

Additionally, an ethical and economic dimension emerges: the opportunity cost. The investment of nursing and physician time in administering futile therapies displaces attention from validated supportive interventions, such as adequate nutrition and hydration. The comparative evidence from Islam et al. (6) suggests that, if a nebulized intervention is to be performed, 3% hypertonic saline solution offers superior biological plausibility in addressing the rheological problem of mucus, making the continued choice of salbutamol over more effective options represent a form of financial and logistical toxicity for health systems.

Analysis of variability in practice reveals a profound ecological disparity. The studies by Maki et al. (7) and Szupieńko et al. (8) highlight that therapeutic inertia is not evenly distributed; it is significantly more prevalent in primary care and general emergency departments than in specialized pediatric hospitals. This gap suggests that the academic setting acts as an “immune system” against low-value practice, thanks to peer supervision, structured ward rounds, and binding protocols.

In contrast, the primary care physician often operates in isolation and faces greater diagnostic uncertainty—the difficulty of phenotypically distinguishing between pure viral bronchiolitis and the first episode of virus-induced wheezing in an atopic patient. Faced with this uncertainty, and under the direct pressure of parental anxiety documented by Campbell et al. (14), clinician is vulnerable to “action bias” (7,19). The prescription then becomes a defensive tool to manage uncertainty and satisfy the human need to “do something,” transforming the drug into an anxiolytic for the parents and the doctor, rather than a treatment for the child.

The evidence analyzed indicates that the passive dissemination of clinical practice guidelines is an insufficient strategy for eradicating ritualized medical practices. Successful de-implementation requires a shift from theoretical education to active behavioral intervention. The most promising strategies identified do not simply seek to prohibit drug use but rather to replace the ritual of prescribing. This involves “replacing the action,” redirecting the imperative to intervene toward visible and effective care, such as standardized nasal suctioning and intensive education for parents about the natural history of the disease, which has been shown to reduce the demand for medications.

Furthermore, modifying the decision-making environment through electronic decision support systems (CDSS) that require explicit justification for prescribing to children under 24 months introduces a necessary “cognitive friction” to break the prescribing automatism. Finally, audit and feedback, where physicians are exposed to their usage rates compared to their peers, appeals to professionalism and intrinsic competitiveness to align practice with evidence. This proves to be one of the most powerful tools for overcoming clinical inertia.

This review presents distinctive methodological strengths that bolster its conclusions. First, the adoption of Whittemore and Knafl's integrative framework allowed for the effective triangulation of quantitative efficacy data with qualitative findings on behavioral barriers and mechanistic translational evidence. This holistic approach overcomes the limitations of traditional systematic reviews focused solely on numerical outcomes, offering a causal explanation for the inertia phenomenon. Second, the temporal restriction to the period after 2014 ensures that the analysis reflects contemporary clinical practice following the issuance of the most influential de-implementation guidelines, avoiding contamination with data from outdated historical practices. Finally, the rigorous quality assessment using the MMAT tool ensures that inferences are derived exclusively from evidence with proven internal validity.

However, the findings should be interpreted within the context of certain limitations. There is inherent heterogeneity in the operational definitions of "bronchiolitis" (e.g., first episode vs. recurrent wheezing) and "respiratory distress" among the primary studies, introducing clinical variability that complicates direct synthesis. Furthermore, a predominant geographical bias is identified; most of the literature on behavioral barriers and parental expectations comes from high-income healthcare systems in North America and Europe. This could limit the transferability of the psychosocial findings to resource-constrained settings or divergent doctor-patient cultural dynamics, where the determinants of prescribing may differ.

In conclusion, a rigorous synthesis of the current evidence establishes an unequivocal mandate for the deprescribing of beta-2 adrenergic agonists in acute bronchiolitis. The futility of these agents is not an accidental statistical finding but rather the predictable consequence of a viral pathophysiology that disables the target drug receptors. The perpetuation of their use cannot be justified under principles of beneficence or safety, given the iatrogenic risk profile and the opportunity cost they represent. Eradicating this low-value practice requires going beyond the simple dissemination of guidelines to implement multimodal strategies that address the behavioral determinants of prescribing and offer safe alternatives for managing family anxiety. In the management of bronchiolitis, the evidence dictates that clinical excellence lies not in the addition of pharmacological interventions but in the ability to provide strict physiological support, allowing the self-limiting course of the disease to resolve without iatrogenic interference.

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Conflicts of interest

The authors declare no commercial conflicts of interest.

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