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REVIEW ARTICLE

RSV bronchiolitis in infants: from pathomechanical obstruction to clinical stewardship and next-generation prophylaxis

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ABSTRACT

Respiratory Syncytial Virus (RSV) is the leading cause of bronchiolitis-related hospitalizations in infants, heavily burdening pediatric critical care during seasonal peaks. Despite established guidelines, a persistent gap remains between evidence-based recommendations and frontline prescribing practices. This review highlights that bronchiolar obstruction in RSV bronchiolitis is intrinsically mechanical. It arises from cytopathic necrosis of the ciliated epithelium, intraluminal cellular debris, altered mucus rheology driven by neutrophil extracellular traps (NETs), and submucosal edema, rather than reversible bronchospasm responsive to bronchodilators. The clinical consequences of this mechanical obstruction—dynamic hyperinflation, auto-positive end-expiratory pressure (auto-PEEP), ventilation-perfusion mismatch, and resorption atelectasis—are explained through the lens of respiratory mechanics. Furthermore, a phenotype-stratified approach is proposed to distinguish the classical RSV neutrophilic endotype from the Rhinovirus-associated type-2 inflammatory endotype, which carries a higher risk of recurrent wheezing and childhood asthma. Therapeutic interventions are critically appraised: the de-implementation of ineffective pharmacological treatments (bronchodilators, systemic corticosteroids, empirical antibiotics, and chest physiotherapy) is strongly advocated. Instead, supportive care, primarily high-flow nasal cannula therapy and targeted hydration to optimize mucus rheology, remains the cornerstone of management. For prevention, nirsevimab a long-acting monoclonal antibody targeting the pre-fusion RSV F glycoprotein at antigenic site represents a major advance in population-level passive immunoprophylaxis. Finally, a physiology-based clinical algorithm integrating severity triage, ventilatory support, and immunoprophylaxis is proposed to guide contemporary management.

Keywords: RSV bronchiolitis, nirsevimab, high-flow nasal cannula, de-implementation, respiratory mechanics, endotype, passive immunoprophylaxis.

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1. INTRODUCTION

Acute viral lower respiratory tract infections (aVLRTIs) in infancy, primarily bronchiolitis, remain a major global public health challenge. Annually, RSV-driven bronchiolitis is the leading preventable cause of unplanned hospitalizations in the first year of life, causing critical capacity strain in pediatric wards and intensive care units during winter peaks [1].

This seasonal pressure is particularly intense across the Middle East and North Africa (MENA) region, where systematic surveillance data indicate that RSV is detected in approximately 19.5% of young children presenting with acute lower respiratory tract infections, reflecting a substantial regional disease burden [2]. In North African settings, local observational data highlight that hospitalized infants exhibit a highly vulnerable profile, often presenting early in life, most frequently under 6 months of age and showing significant exposure to regional risk factors such as passive smoking and low rates of exclusive breastfeeding, which are strongly associated with increased clinical severity and prolonged hospital stays [3, 4].

Despite clinicians' familiarity with these seasonal surges, the underlying pathophysiology of bronchiolitis involves a complexity that routine prescribing habits often fail to address.

A well-documented gap persists between consensus guidelines and routine clinical practice. The overuse of bronchodilators, systemic corticosteroids, and empirical antibiotics in hospitalized infants remains pervasive [5,6].

This therapeutic deviation is highly pronounced in resource-constrained regional settings; clinical registry data from North Africa confirm that routine public practice frequently relies on inappropriate prescriptions, with antibiotics and systemic steroids administered to over half of hospitalized infants, often driven by diagnostic uncertainty, the co-management of suspected secondary bacterial infections, or family histories of atopy [7, 8].

At the root of this clinical inertia lies a fundamental misconception: the erroneous conflation of infantile bronchiolar obstruction with the reversible bronchospasm seen in atopic asthma. In reality, the obstructive process in RSV bronchiolitis is mechanical and structural, driven by the endoluminal accumulation of necrotic epithelial debris, fibrinous material, mucosal edema, and ciliary dysfunction [9]. This mechanistic distinction explains why pharmacological smooth muscle relaxation is ineffective, a conclusion consistently confirmed by multiple Cochrane meta-analyses [10].

Adding to this therapeutic challenge, the SARS-CoV-2 pandemic has disrupted endemic viral ecology. The temporary decline in population immunity during periods of social distancing led to a marked rebound in RSV transmission, characterized by off-season peaks of unusual severity [11,12]. Furthermore, the growing recognition of viral co-infections particularly RSV combined with Rhinovirus—adds clinical complexity by further amplifying inspiratory resistance and the mechanical work of breathing in vulnerable infants [13].

These evolving challenges require a shift in practice. The therapeutic focus must move away from ineffective pharmacological treatments and toward rational, physiology-driven supportive care: restoring airway patency, reducing the resistive ventilatory load, and maintaining systemic oxygenation until spontaneous mucociliary recovery occurs. Concurrently, the recent approval and broad deployment of nirsevimab, a long-acting monoclonal antibody targeting the pre-fusion conformation of the RSV F glycoprotein provides, for the first time, a highly effective tool for population-scale passive immunoprophylaxis, capable of profoundly altering the disease's epidemiological trajectory [14,15].

Resource constraints across the MENA region limit the routine deployment of costly preventive strategies. Care therefore remains centred on cost-effective supportive management, alongside targeted mitigation of established local risk factors, including passive smoke exposure, lack of exclusive breastfeeding, household overcrowding, and prematurity [16,17].

This review synthesizes mechanistic and clinical evidence to propose a rationalized management framework for RSV bronchiolitis. It critically examines the continued use of ineffective treatments and highlights the evidence for validated supportive interventions, culminating in a physiology-anchored clinical algorithm (Figure 1) to guide contemporary management.

2. PATHOPHYSIOLOGY: FROM VIRAL AGGRESSION TO MECHANICAL VENTILATORY FAILURE

Histopathological Substrate and Mucociliary Disruption

Understanding the consistent failure of empirical pharmacotherapy in RSV bronchiolitis requires a precise characterization of the tissue-level injury. In contrast to the eosinophilic, IgE-mediated inflammation seen in atopic asthma, RSV infection exerts a direct cytopathic effect on the pseudostratified ciliated columnar epithelium of the small airways[4]. Viral replication within infected cells induces the formation of multinucleated syncytia and causes extensive necrosis of ciliated epithelial cells. This cellular destruction leads to the functional collapse of the mucociliary escalator, the primary mechanical defense mechanism of the conducting airways.

Necrotic cellular debris progressively accumulates within the bronchiolar lumen, enmeshing with fibrin to form cohesive obstructive casts. Concurrent neutrophilic infiltration of the lamina propria adds a significant rheological burden: activated neutrophils produce neutrophil extracellular traps (NETs), releasing extracellular DNA strands that dramatically increase mucus viscosity and impair clearance [18]. Consequently, the pathological substrate is not simply excess mucus, but the formation of structured

intraluminal plugs that are inherently resistant to conventional suctioning and pharmacological mucolysis. Superimposed submucosal edema further narrows the already small bronchiolar lumen.

Two anatomical features specific to infants under six months of age amplify the clinical consequences of this obstructive process: first, according to the Hagen–Poiseuille law governing laminar flow, airway resistance is inversely proportional to the fourth power of the luminal radius. Therefore, even marginal reductions in bronchiolar caliber cause an exponential increase in the resistive load placed upon the infant's respiratory pump; second, the interalveolar communication channels, the pores of Kohn and canals of Lambert, are functionally immature at this developmental stage. This lack of collateral ventilation prevents alveolar gas exchange distal to the occluded bronchioles [19], meaning that complete airway occlusion inevitably leads to resorption atelectasis.

Respiratory Mechanical Consequences: Dynamic Hyperinflation and Ventilation-Perfusion Mismatch

The primary determinant of respiratory distress severity in RSV bronchiolitis is the pathological elevation of airway resistance (Raw), resulting from the combined effects of intraluminal plugging and mucosal edema. Partial bronchiolar obstruction acts as a unidirectional flow-limiting valve: active inspiratory efforts generate sufficient transpulmonary pressure gradients to draw air past partially occluded segments, but passive expiration is severely hindered by dynamic airway collapse and mucous plugs. This prolongs the expiratory time constant. Combined with infection-driven tachypnea, the expiratory time becomes insufficient for complete alveolar emptying between successive respiratory cycles [20].

This mechanism leads to progressive dynamic hyperinflation and the accumulation of intrinsic positive end-expiratory pressure (auto-PEEP). The infant is forced to breathe at elevated resting lung volumes, operating on the flat, upper portion of the respiratory system's pressure-volume curve where pulmonary compliance is markedly reduced. Consequently, each tidal breath requires disproportionate inspiratory muscular effort, causing an unsustainable increase in the work of breathing (WOB) and rapidly predisposing the infant to respiratory muscle fatigue [21].

Simultaneously, complete distal bronchiolar occlusion creates regions of absent ventilation with preserved perfusion. This true intrapulmonary shunt (V/Q = 0) generates refractory hypoxemia that typically does not respond to supplemental oxygen delivery alone [22]. This shunt-mediated physiology explains why merely increasing the fraction of inspired oxygen (FiO2) is inadequate in moderate-to-severe disease: alveolar recruitment and shunt reversal require the application of positive airway pressure capable of re-expanding collapsed lung units [23].

Clinical Endotype Stratification: Beyond the Diagnostic Label of Bronchiolitis

The broad clinical diagnosis of bronchiolitis encompasses at least two pathophysiologically and prognostically distinct endotypes that require clinical differentiation [24]. The classical RSV endotype is driven by neutrophil-dominant airway inflammation, direct cytopathic epithelial injury, and intraluminal cast formation. Its clinical course is dictated by the mechanical obstructive mechanisms described above, and recovery relies entirely on spontaneous mucociliary regeneration over a period of seven to fourteen days.

In contrast, rhinovirus-associated bronchiolitis, particularly involving Rhinovirus species A, follows a fundamentally different inflammatory pathway. Rhinovirus uses the cadherin-related family member 3 (CDHR3) receptor to breach the epithelial barrier without causing massive cytolysis. Instead, it triggers the potent release of epithelial-derived alarmins, including interleukin-33 (IL-33) and thymic stromal lymphopoietin (TSLP) [25]. This innate alarmin cascade activates a type-2 adaptive immune response marked by eosinophil recruitment and the production of IL-4 and IL-13, creating a bronchospastic phenotype closely resembling atopic asthma.

This endotypic distinction has major clinical implications. An infant presenting with Rhinovirus bronchiolitis, especially with a personal or family history of atopy, is not merely experiencing an isolated viral infection but likely the first event in a chronic recurrent wheezing trajectory [26]. This specific subpopulation requires closer pneumological follow-up and represents the target for emerging trials focused on alarmin blockade and Th2 pathway modulation[27]. **Importantly,** recognizing this Rhinovirus-driven, asthma-like endotype provides the only biologically plausible context in which corticosteroids might warrant further investigation; for the classical RSV-driven obstructive endotype, their ineffectiveness remains absolute.

3. DIAGNOSTIC RATIONALIZATION: THE IMPERATIVE OF RESTRAINT

Protecting the Infant from Iatrogenic Diagnostic Harm

Diagnostic restraint in bronchiolitis is not a passive omission but an active clinical responsibility. While the urge to perform extensive testing in a visibly distressed infant is understandable, routine investigations neither alter clinical management nor improve outcomes in uncomplicated cases.

Chest radiography is a prime example of a diagnostically misleading tool in this context [28,29]. The typical radiographic findings of RSV bronchiolitis bilateral hyperinflation, peribronchial thickening, subsegmental atelectasis, and scattered airspace opacities perfectly reflect the underlying mechanical obstruction. However, these expected viral features are frequently misinterpreted as bacterial consolidation, driving unnecessary and inappropriate antibiotic prescriptions. Therefore, chest radiography should be strictly reserved for cases of acute, unexpected clinical deterioration such as suspected pneumothorax or when alternative diagnoses like congenital heart disease must be ruled out. Similarly, routine blood tests, including full blood counts, C-reactive protein (CRP), and procalcitonin, offer no diagnostic or prognostic value in typical viral bronchiolitis and should be avoided [30]. As outlined in our proposed clinical algorithm (Figure 1), laboratory and radiological investigations should only be triggered by atypical presentations, failure to respond to supportive care, or strong suspicion of an alternative primary diagnosis.

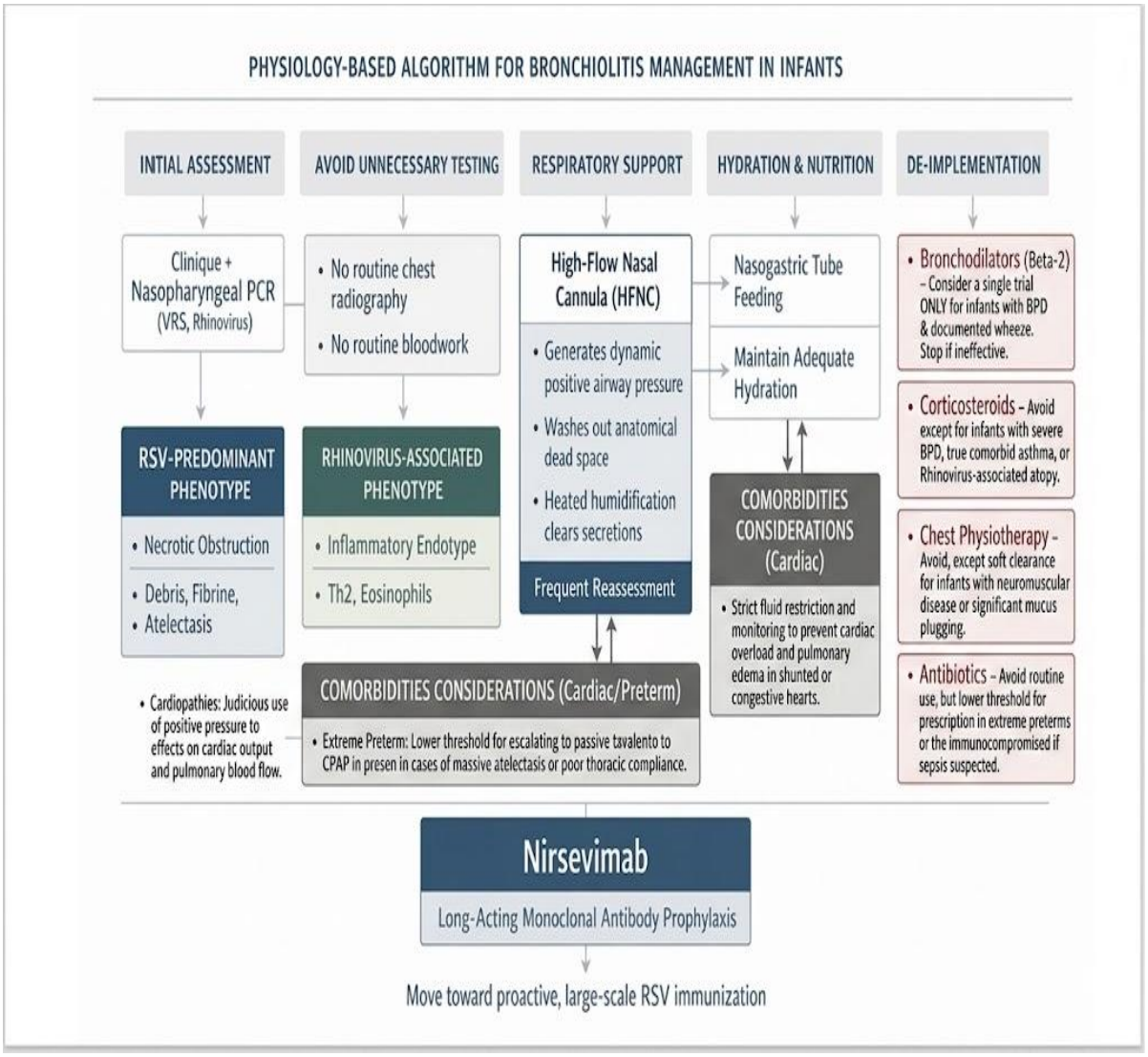

Figure 1. Physiology-based algorithm for bronchiolitis management. This framework prioritizes clinical and metabolic stability, shifting the focus from empirical therapy toward a precision-based approach. Initial triage integrates respiratory assessment with the immediate identification of high-risk cohorts, such as infants with congenital heart disease, extreme prematurity, or chronic lung disease. Management centers on targeted supportive care, primarily high-flow nasal cannula (HFNC) and enteral hydration; however, fluid volumes and positive pressure must be carefully titrated in cardiac or shunted phenotypes to avoid complications. Diagnostic tests and pharmacological interventions—including bronchodilators, steroids, and antibiotics—are strictly de-implemented in uncomplicated cases, though they may be individualized for atypical presentations or specific chronic conditions. Molecular phenotyping differentiates between the necrotic-obstructive RSV endotype and the Th2-driven inflammatory profile typical of Rhinovirus. Finally, universal prophylaxis with nirsevimab completes this strategy, moving the clinical paradigm from reactive crisis management toward proactive primary prevention.

4. THERAPEUTIC STRATEGY: SUPPORTING THE RETURN TO PHYSIOLOGICAL HOMEOSTASIS

The therapeutic framework for RSV bronchiolitis is built upon a single, fundamental principle: supportive care remains the sole evidence-based intervention. The clinician's role is not to attempt the pharmacological reversal of the airway obstruction which is structurally fixed during the acute phase but rather to preserve the infant's cardiorespiratory reserve. The ultimate goal is to sustain adequate gas exchange until the natural, spontaneous restoration of mucociliary function occurs [24].

Ventilatory Support: Biomechanical Optimization

Maintenance of adequate oxygenation, targeting a peripheral oxygen saturation (SpO2) above 90–92% in previously healthy infants, constitutes the primary clinical endpoint of ventilatory intervention [31]. Escalation of respiratory support should be guided by serial clinical assessment of work of breathing, rather than by SpO2 thresholds in isolation.

High-flow nasal cannula (HFNC) therapy has become the cornerstone of moderate-to-severe bronchiolitis management in the contemporary era. Delivered at flows typically approximating 2 L/kg/min, HFNC exerts its therapeutic effect through three discrete and complementary mechanisms: generation of low-level dynamic positive end-expiratory pressure that mechanically splints the collapsible small airways; washout of anatomical dead-space carbon dioxide that reduces the ventilatory burden; and delivery of actively heated and humidified inspired gas that attenuates evaporative desiccation of airway secretions, thereby improving secretion fluidity and facilitating mucociliary transport [32].

While the clinical effectiveness of HFNC is well-substantiated, systematic re-evaluation of ongoing need is mandatory to avoid unnecessary hospitalization prolongation [27]. The treating clinician must possess the clinical acumen to identify and act upon resolution of increased work of breathing, recognizing that premature escalation and prolonged continuation are both harmful. Non-invasive continuous positive airway pressure (CPAP) and invasive mechanical ventilation constitute escalatory options in the subset of infants progressing to respiratory failure, as guided by the clinical algorithm in Figure 1.

Hydration and Nutritional Support: The Rheological Imperative

Systemic hydration is a direct pathophysiological intervention rather than a supportive adjunct [33]. Tachypnea-driven insensible water loss combined with fever-mediated evaporation accelerates dehydration, which increases mucus viscosity and hinders secretion clearance. This bidirectional relationship between hydration status and airway patency creates a vicious cycle that requires active correction.

The enteral route via nasogastric or orogastric tube is preferred. It maintains the metabolic and immunological benefits of enteral nutrition while reducing the aspiration risk associated with oral feeding in tachypneic infants [34,35]. However, fluid administration must be meticulously titrated against the severity of respiratory effort. A respiratory rate exceeding 70 breaths per minute represents a critical physiological threshold where the coordination of the suck-swallow-breath cycle is fundamentally disrupted, making oral intake hazardous and substantially increasing the risk of aspiration pneumonia. In such cases of extreme tachypnea, nasogastric tube feeding is mandated [36]. Furthermore, if gastric distension further compromises diaphragmatic excursion, temporary parenteral hydration should be initiated to prioritize respiratory mechanics.

Therapeutic De-implementation: Abandoning Ineffective Interventions

The evidence base for bronchiolitis management is defined as much by what it advises against as by what it supports. Systematic reviews have consistently shown that several entrenched interventions lack efficacy and may even cause harm [37].

Beta-2 agonists (albuterol/salbutamol) act by relaxing peribronchial smooth muscle. However, this cellular target is anatomically underdeveloped in the infant airway. More importantly, smooth muscle relaxation cannot reverse the underlying structural and necroinflammatory endoluminal obstruction [38]. Consequently, multiple randomized controlled trials have confirmed the complete absence of clinical benefit from bronchodilators in RSV bronchiolitis.

Similarly, systemic and inhaled corticosteroids offer no reduction in viral replication, symptom severity, or length of hospital stay. Instead, they needlessly expose the infant to immunosuppression during an active viral infection [39]. Furthermore, manual chest physiotherapy (percussion or vibration) once a standard of care is now explicitly contraindicated during the acute phase. It is mechanically ineffective for clearing small airways, increases infant agitation and metabolic demand, and raises the risk of gastroesophageal reflux and aspiration [44].

Finally, antibiotic therapy should be strictly reserved for cases with objective evidence of a concurrent bacterial infection. Bronchiolitis is fundamentally a viral disease, with true bacterial co-infection occurring in less than 10% of cases. Crucially, fever alone even high-grade does not justify antimicrobial use without clear clinical or microbiological proof of a bacterial source [41].

5. PREVENTION: NIRSEVIMAB AND THE PASSIVE IMMUNOPROPHYLAXIS PARADIGM

The development of nirsevimab has reshaped RSV prophylaxis. The RSV fusion (F) glycoprotein is a homotrimeric class I viral fusion protein essential for viral entry. Upon activation, it undergoes a conformational transition from a metastable pre-fusion state to a highly stable post-fusion hairpin structure, a rearrangement that drives the fusion of the viral envelope with the host cell membrane.

Nirsevimab is a recombinant human IgG1 monoclonal antibody featuring a YTE-modified Fc region that extends its serum half-life to approximately 70 days, ensuring clinical protection for an entire 5-month RSV season following a single dose. The antibody binds with nanomolar affinity to antigenic site , a highly conserved epitope located at the apex of the pre-fusion F trimer that becomes sterically inaccessible in the post-fusion state [42]. By engaging this specific epitope, nirsevimab blocks the conformational rearrangement required for fusion peptide insertion, locking the F protein in its pre-fusion state and preventing viral entry before intracellular replication occurs.

Preventing the primary infection of the bronchiolar epithelium halts the downstream cytopathic cascade: syncytium formation, ciliated cell necrosis, intraluminal debris accumulation, and NET-driven mucus viscosity [43]. Consequently, mucociliary clearance remains intact, bypassing the mechanical obstruction, dynamic hyperinflation, auto-PEEP, and shunt-mediated hypoxemia that characterize severe disease.

Large-scale randomized controlled trials confirm that nirsevimab drastically reduces RSV-attributable hospitalizations in both healthy term and vulnerable preterm infants [11,12]. Integrating universal seasonal prophylaxis into national immunization programs shifts the management of RSV bronchiolitis from futile reactive treatments to population-level primary prevention.

However, implementation within resource-constrained MENA settings faces major barriers. Prohibitive procurement costs represent the primary deterrent to large-scale rollout. These financial hurdles are compounded by gaps in diagnostic infrastructure particularly the reliance on PCR-based surveillance stringent cold-chain requirements, and the logistical precision required to time seasonal immunization campaigns, complicating operational integration across the region.

6. CONCLUSION

The management of RSV bronchiolitis in infancy has shifted from empirical pharmacological interventions toward a strict adherence to respiratory physiology. Because mucosal edema and the mechanical accumulation of necrotic epithelial debris cannot be acutely reversed by current drugs, primary management must focus on maintaining physiological homeostasis. This approach requires ensuring adequate gas exchange, optimizing secretion rheology to facilitate clearance, and resisting the pressure to over-prescribe driven by institutional habits or parental anxiety. In this framework, therapeutic restraint represents evidence-based judgment rather than clinical inaction. Contemporary management relies on two strategic pillars. The first is the transition toward early molecular phenotyping. Rapid nasopharyngeal multiplex PCR allows clinicians to distinguish the classic neutrophilic obstructive endotype of RSV from the alarmin-driven, Type-2 inflammatory endotype often associated with Rhinovirus. This differentiation has clinical implications: the latter carries a higher risk of recurrent wheezing and childhood asthma, requiring structured pulmonary follow-up extending beyond acute hospitalization. The second pillar is the implementation of universal seasonal immunoprophylaxis with nirsevimab. By preventing viral entry and preserving mucociliary architecture, this intervention redefines the seasonal epidemiology of the disease. However, long-term success depends on viral evolutionary dynamics. The selection pressure exerted by the mass administration of monoclonal antibodies necessitates vigilant molecular surveillance. The emergence of viral escape mutants specifically through amino acid substitutions at the conserved antigenic site could compromise neutralization efficacy in future seasons. Consequently, the convergence of precision phenotyping and high-efficacy prophylaxis transforms bronchiolitis from a seasonal crisis managed with ineffective reactive treatments into a predictable condition addressed through proactive, scientifically grounded strategies that must adapt to the potential for viral resistance.

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