ISSN 3035-2134 | June 2026 Vol. 4, No. 2

Pediatric Respiratory Journal

Official Journal of the Italian Pediatric Respiratory Society

Official Journal of the Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili – SIMRI)

SIMRI società italiana per le malattie respiratorie infantili

via G. Quagliariello 27, 80131
Naples, Italy
Ph. 081 19578490
Fax 081 19578071
segreteria@simri.it
www.simri.it

edra MEDIA

Edra Media S.r.l.
Viale Forlanini, 21
20134 Milano, Italy
Ph. 0039 (0)2-88184.1
Fax 0039 (0)2-88184.301
www.edraspa.it

Vol. 4(2), 50-53, 2026

EDITORIAL

The Martoglio contribution to the Three T's: from molecular signaling to understanding inborn errors of immunity (IEIs) – a Sicilian view of information flow

Joseph A. **Bellanti** [1, 2, *]

* **Correspondence to:**
bellantj@georgetown.edu; ORCID: https://orcid.org/0000-0002-5038-7202

Doi
10.56164/PediatrRespirJ.2026.14

[1] Department of Microbiology-Immunology, Georgetown University Medical Center Washington DC, U.S.A.
[2] Department of Pediatrics, Georgetown University Medical Center, Washington DC, U.S.A.

INTRODUCTION

In this issue of the Pediatric Respiratory Journal, Bellanti introduces a practical framework – *Transduction, Transcription, and Translation ("the Three T's")* – to assist the pediatric pulmonary specialist in better understanding, classifying, diagnosing, and treating the inborn errors of immunity (IEIs) (1).

This Editorial uses the literary and cultural perspective, and the interpretive framework, of the Sicilian writer Martoglio as a conceptual lens through which to examine biologic signaling and the "Three T's" paradigm. By integrating narrative analogy with contemporary molecular immunology, the Editorial seeks to clarify how signaling specificity, timing, and transmission contribute to the understanding of Inborn Errors of Immunity (IEIs) and related pediatric respiratory disorders. The purpose is not to substitute metaphor for science, but rather to employ an interdisciplinary narrative structure as an educational tool that may enhance understanding of complex biologic communication systems for clinicians, trainees, and researchers.

This framework does not propose a new molecular pathway. Rather, it offers a synthesis – a way of understanding biologic signaling – not as a series of isolated steps, but as a coherent flow of information. In its simplest form, the concept is intuitive: cells capture signals, encode them, and execute them.

Cells perform three fundamental operations. They capture signals (transduction), encode those signals into an interpretable form (transcription), and execute them as functional outcomes (translation). A ligand binds to a receptor, initiating intracellular signaling; the signal is rewritten in the nucleus from DNA into messenger RNA; and finally, that message is translated into protein, producing a measurable biologic effect.

Clinical examples from inborn errors of immunity further illustrate the practical relevance of the 'Three T's' framework.' For example, autosomal recessive IFNAR1 deficiency (OMIM #618162) represents a defect in interferon receptor-mediated signaling in which impaired type I interferon signal transduction predisposes pediatric patients to severe viral respiratory infections despite otherwise intact cytokine production. In contrast, STAT1 loss-of-function mutations associated with Mendelian Susceptibility to Mycobacterial Disease (MSMD; OMIM #614889) may permit normal receptor engagement but impair downstream transcriptional activation required for interferon-γ-mediated host defense, resulting in increased susceptibility to mycobacterial and other intracellular infections.

 |

A FAMILIAR ANALOGY AT THE BEDSIDE CLARIFIES THIS PROCESS

Biologic signaling is often taught as molecular detail rather than as underlying logic. The Three-T framework restores that logic by emphasizing how cells convert signals into action.

Modern voice-activated systems follow the same sequence. When a spoken command turns on a bedside light, the system captures sound, encodes meaning, and executes an action. This parallel allows clinicians to reinterpret molecular biology as information flow rather than disconnected steps.

One might test this idea directly:

"ALEXA, turn on the light".

A bedside device receives the voice. The acoustic signal is captured, digitized, and interpreted; moments later, across the room, a light turns on, without any visible wire.

The correspondence is exact:

- Signal capture → Transduction
- Signal encoding → Transcription
- Physical action → Translation

Different substrates (molecules *versus* circuits), but identical logic.

WHY THIS MATTERS FOR PHYSICIANS

This analogy highlights several practical insights for the physician:

- Cells do not decide; they execute encoded instructions.
- AI-enabled systems similarly transform inputs into predefined outputs.
- Clinical reasoning itself follows this structure: signals are observed, interpreted, and acted upon.

Viewing biology through this lens strengthens both conceptual clarity and clinical reasoning.

Shown in **Figure 1** is a comparison of a bedside voice AI assisted communication system device that receives a voice. The acoustic signal is captured, digitized, and interpreted; moments later, across the room, a light is turned on, without any visible wire connecting the two. The system had received a signal, encoded its meaning, and executed an action.

The parallel was immediate:

- Signal capture → Transduction
- Signal encoding → Transcription
- Physical action → Translation

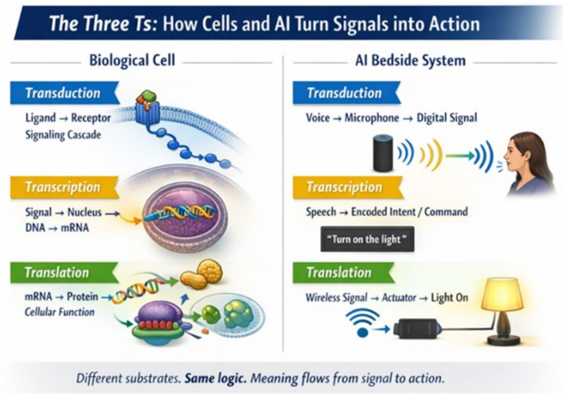

***Figure 1**. Schematic comparison of the 'Three Ts' in biological and AI systems.*

Both biological cells and AI-enabled devices process signals through three stages: transduction (signal capture), transcription (signal-associated genetic encoding) and translation (execution of action). Although the substrates differ, both systems share a common logic of information flow from signal to functional outcome.

Distinct substrates (molecules *versus* circuits), but a shared architecture of signal-to-action processing.

THE SICILIAN COUNTERPOINT

At first, the analogy appears straightforward. Yet its clarity invites scrutiny – particularly through the perspective of Nino Martoglio (1870-1921).

Martoglio, a Sicilian playwright and humorist, captured how ordinary people confront unfamiliar ideas. His characters are not naïve; they are rigorously practical. Faced with abstraction – wireless communication, invisible forces – they test it against lived experience.

Their reasoning is direct:

"Senti, caro cumpari…"

("Listen, my friend…")

THE MARTOGLIO CONTRIBUTION

Martoglio captured the tension between scientific abstraction and everyday intuition in his satirical dialect poem *Il Telefrico Senza Fili* ("the wireless telegraph") (2). Confronted with the idea that a message could travel invisibly through space, the listener asks:

"If it rains, does the message not get wet?"

The humor reflects a deeper conceptual challenge familiar to modern biology: signals transmit information without the physical transfer of substance. In biologic systems, as in wireless communication, information is captured, encoded, and translated into action through orga-

nized processes rather than visible material movement. As Martoglio concludes, the message arrives:
"Agghica asciuttu comu n'ossu e senza fili"
("Dry as a bone and without a wire")

RECONCILING INTUITION AND ABSTRACTION

The humor is immediate, but the question is precise. It reflects an intuitive expectation: that anything which travels must behave like matter – must have weight, occupy space, and be subject to the environment. Scientific systems operate differently. Signals are not substances: they are transformations of state.
In both biologic and engineered systems:

- A signal is captured
- Meaning is encoded
- Action is executed

Nothing travels as an object. Instead, information propagates through structured processes.
The Three-T framework makes this explicit, shifting attention from movement of matter to transformation of meaning.

IMPLICATIONS FOR MEDICINE AND TECHNOLOGY

For clinicians, this perspective reframes molecular biology as an information-processing system rather than a collection of pathways. Hormone signaling, immune activation, and neurotransmission all follow this logic (3-7). Modern AI-enabled systems – voice interfaces, smart devices, and cyber-physical systems – operate in the same way (8). The analogy is therefore more than rhetorical; both systems process information through staged transformations from signal detection to functional output. Understanding this parallel enhances both clinical reasoning and technological literacy.

CONCLUSIONS

Martoglio's character, confronted with these explanations, remains unconvinced.
The conclusion, for him, is inevitable:
"If there's no wire… it must be magic".
Yet this skepticism serves an important purpose. It exposes the persistent gap between formal explanation and human intuition.
We describe processes that defy expectation:

Signals without mass,
instructions without substance,
messages that travel –

and somehow –

Agghicanu asciuttu comu n'ossu
(they arrive dry as bones)

The Three-T framework offers one way to understand this logic.
Martoglio reminds us why such understanding is still necessary.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

The author declares no conflicts of interest.

Financial support

None.

Author contributions

JAB contributed entirely to the work.

Ethical approval

Human studies and subjects

N/A.

Data sharing and data accessibility

N/A.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

REFERENCES

1. Bellanti JA. Transduction, Transcription, and Translation: a practical framework for the pediatric pulmonary specialist for diagnosing and treating inborn errors of immunity. Pediatr Respir J. 2026;4(2):54-58. doi: 10.56164/PediatrRespirJ.2026.15.

2. Martoglio N. Centona. Catania: Di Mattei; 1899. “Il telefrico senza fili”, a satirical dialect poem on wireless communication. Available from: https://www.culturasiciliana.it/images/POETI-IMMAG/martoglio-centona.pdf.
3. Pirandello L. Six Characters in Search of an Author and Other Plays. New York: Penguin Classics; 1995.
4. Alberts B, Johnson A, Lewis J, Morgan D, Raff M, Roberts K, Walter P. Molecular Biology of the Cell. 6th ed. New York: Garland Science; 2015.
5. Lodish H, Berk A, Kaiser CA, Krieger M, Bretscher A, Ploegh H, Amon A, Martin KC. Molecular Cell Biology. 8th ed. New York: W.H. Freeman; 2016.
6. Russell SJ, Norvig P. Artificial Intelligence: A Modern Approach. 4th ed. Harlow, UK: Pearson; 2021.
7. Jurafsky D, Martin JH. Speech and Language Processing. 3rd ed. Stanford University; 2023. Available from: https://web.stanford.edu/~jurafsky/slp3/.
8. Lee EA. Cyber-physical systems—Are computing foundations adequate? Proc IEEE. 2008;96(1):75-82.

Vol. 4(2), 54-58, 2026

PERSPECTIVE

Transduction, Transcription, and Translation: a practical framework for the pediatric pulmonary specialist for diagnosing and treating inborn errors of immunity

Joseph A. **Bellanti** [1, 2, *]

[*] **Correspondence to:**
bellantj@georgetown.edu; ORCID: https://orcid.org/0000-0002-5038-7202

Doi
10.56164/PediatrRespirJ.2026.15

[1] Department of Microbiology-Immunology, Georgetown University Medical Center Washington DC, U.S.A.
[2] Department of Pediatrics, Georgetown University Medical Center, Washington DC, U.S.A.

KEY WORDS
Transduction; transcription; translation; inborn errors; immunity.

ABSTRACT

The expanding number of recognized inborn errors of immunity (IEIs), together with rapid advances in biologic, gene, and RNA-based therapies, has increased the diagnostic and conceptual complexity faced by practicing pediatric pulmonary specialists.

This article introduces a practical, biologically grounded framework – Transduction, Transcription, and Translation ("the Three T's") – to aid clinicians in understanding, classifying, and diagnosing IEIs.

The work is a conceptual synthesis of classic and contemporary IEIs based on the stage at which immune communication fails.

IEIs can be categorized as disorders of signal reception (Transduction), immune program selection (Transcription), or protein execution (Translation). Mapping disorders to this framework clarifies diagnostic reasoning and therapeutic implications.

In conclusion, the Three-T framework offers a clinically intuitive model for interpreting immune dysfunction and may facilitate the integration of emerging targeted therapies.

IMPACT STATEMENT

The "Three-T" framework provides pediatric pulmonary specialists with a practical conceptual model for localizing immune dysfunction in inborn errors of immunity. The model facilitates diagnostic reasoning and helps clinicians integrate emerging biologic, gene, and RNA-based therapies into clinical practice.

INTRODUCTION

In recent years, the field of clinical immunology has undergone a remarkable expansion. New inborn errors of immunity are described annually, and therapeutic options now include targeted biologics, small-molecule inhibitors, gene therapy, and RNA-based approaches (1-3). While these advances have transformed patient care, they have also created a growing challenge for the practicing pediatric pulmonary specialist: how to integrate molecular mechanism, clinical phenotype, and therapeutic strategy into a coherent diagnostic framework (4).

Traditional classifications of IEIs – based on affected cell lineages or immune pathways –remain valuable; however, they do not always provide clinicians with an intuitive way to localize where immune function fails. To address this need, I pro-

 |

pose a simple pedagogical model based on the fundamental flow of biological information.

Transduction → Transcription → Translation

The conceptual basis of the Three-T framework was introduced in earlier textbook work (5); however, it is not intended as a rigid or exhaustive classification system, but rather as a practical guide to aid clinical reasoning. This "Three-T" framework conceptualizes immunity as a process of communication, allowing the pediatric pulmonary specialist to ask a sequence of practical questions: "*Can the immune system hear the signal? Can it choose the correct response? Can it execute that response?*".

WHY A LANGUAGE-BASED MODEL MATTERS NOW

Advances in immunology increasingly manipulate information rather than cells or organs (6). Gene therapy edits genetic instructions, mRNA therapeutics deliver executable messages, and biologics block or amplify specific signals. In this context, IEIs are best understood not simply as missing components, but as failures in how immune information is received, interpreted, or executed. The Three-T framework aligns naturally with these developments by framing immunity as a communicative process, allowing the clinician to reason mechanistically while remaining grounded in clinical phenotype.

THE THREE T'S: THE GRAMMAR OF THE IMMUNE SYSTEM

All immune responses, whether innate or adaptive, follow a common informational pathway (**Figure 1**):

1) Transduction: extracellular signals are received by surface or intracellular receptors.

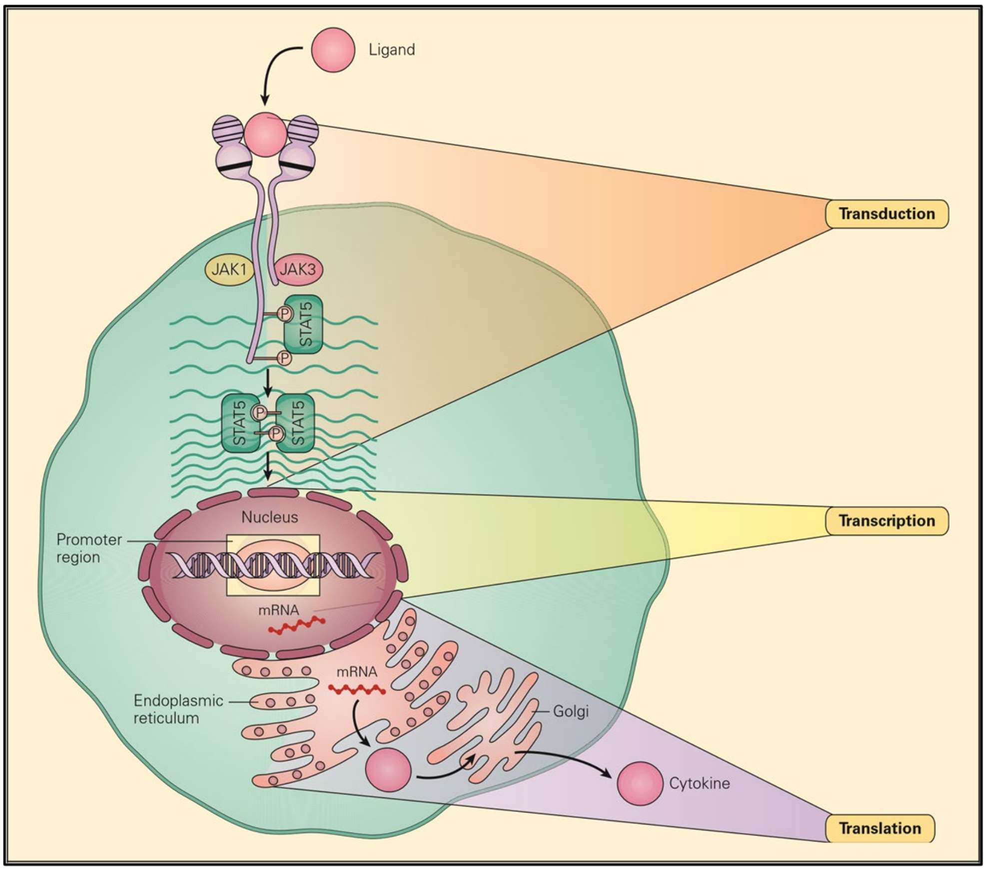

***Figure 1**. Schematic representations of the "Three Ts" of molecular signaling.*

Transduction: from the Latin transducere, meaning "to lead across". It is the process by which a signal is conveyed from outside the cell to its interior, initiating a cascade of molecular events. Transcription: from the Latin transcribere, "to write across". It occurs within the cell nucleus, where that signal is converted from DNA into a written molecular message: mRNA. Translation: from the Latin transferre, "to carry across". It interprets that message to produce the proteins that sustain every heartbeat, immune response, and act of cellular repair. (Reproduced with permission from Reference 5).

2) Transcription: intracellular signaling pathways activate nuclear programs that determine immune cell fate and function.
3) Translation: genetic instructions are converted into functional proteins that execute immune responses.

Failure at any of these stages produces characteristic clinical patterns. Framing IEIs within this sequence allows clinicians to localize immune dysfunction conceptually before identifying specific genetic defects.

TRANSDUCTION DEFECTS: WHEN THE IMMUNE SYSTEM CANNOT HEAR

Representative example: IFNAR2 deficiency

In disorders of transduction, immune signals are generated normally but cannot be received. IFNAR2 deficiency exemplifies this category. Despite normal production of type I interferons during viral infection, defective interferon receptor signaling prevents activation of antiviral programs. Clinically, this manifests as severe viral infections and intolerance to live viral vaccines. Conceptually, this represents immune deafness: the message exists, but the receiver is broken.

TRANSCRIPTION DEFECTS: WHEN THE WRONG IMMUNE PROGRAM IS WRITTEN

Representative examples: Activated PI3K-δ syndrome (APDS) and common variable immunodeficiency (CVID)

Transcription defects occur when immune signals are received but interpreted incorrectly. In APDS, gain-of-function mutations in PI3K signaling lead to constitutive pathway activation, resulting in immune dysregulation, lymphoproliferation, and allergic disease. The immune system repeatedly selects inappropriate transcriptional programs. Similarly, CVID often reflects impaired B-cell differentiation and class-switch recombination rather than absence of immune signals or proteins. These disorders represent immune misinterpretation: the signal is heard, but the wrong instructions are written.

TRANSLATION DEFECTS: WHEN IMMUNE EXECUTION FAILS

Translation defects are particularly familiar to allergist-immunologists and account for many classic IEIs. Examples include:

- Severe combined immunodeficiency (SCID): absence of functional immune cell output.
- X-linked agammaglobulinemia (XLA): failure to produce functional BTK protein, resulting in absent antibody production.
- Chronic granulomatous disease (CGD): nonfunctional NADPH oxidase despite intact transcription.
- Wiskott-Aldrich syndrome: defective cytoskeletal protein leading to impaired immune synapse formation.
- DOCK8 deficiency: failure to generate effective protein output from a large, complex gene.

In these disorders, immune intent exists, but execution fails – representing a loss of immune fluency.

THE THREE T'S AS A DIAGNOSTIC FRAMEWORK

Clinically, the Three-T model serves as a practical diagnostic framework rather than a rigid classification system. When faced with a patient with recurrent infection, immune dysregulation or allergy, the clinician may first ask:

- Transduction: are immune signals being received at all?
- Transcription: is immune decision-making biased or inappropriate?
- Translation: is the immune system capable of executing its intended response?

This approach localizes immune failure conceptually before molecular confirmation, guiding both diagnostic testing and therapeutic expectations.

THERAPIES MAP TO THE THREE T'S

The Three T's have relevance not only to diagnosis but also to therapy. Modern immunologic treatments act at distinct stages of immune communication, reinforcing the practical value of this framework for treatment selection (**Table 1**).

Integrating the framework: classic IEIs mapped to the Three-T hypothesis

Table 2 illustrates how selected classic and contemporary IEIs align naturally within the Three-T framework, providing a unifying visual model for diagnostic reasoning and teaching.

WHY TRANSLATION DEFECTS DOMINATE CLASSIC IEIS

Many of the IEIs most familiar to pediatric pulmonary specialist – SCID, X-linked agammaglobulinemia, chronic

Table 1. *Alignment of major immunologic therapies with the Three-T framework.*

Therapeutic Class	Example	Dominant T*
Biologics	Anti-cytokines, receptor blockade	Transduction
Small-molecule inhibitors	Tyrosine kinase inhibitors	Transcription
Gene therapy	mRNA, protein replacement	Translation

**Dominant T" refers to the primary molecular stage of the 'Three T's' targeted by the respective therapeutic class.*

Table 2. *Classic inborn errors of immunity mapped to the Three-T framework.*

IEI	Dominant T	Core Failure	Conceptual Label
IFNAR2 deficiency	Transduction	Signal not received	Immune deafness
APDS	Transcription	Constitutive signaling bias	Misinterpretation
CVID	Transcription	Faulty B-cell differentiation	Miswritten script
SCID	Translation	No immune output	Global loss of fluency
XLA	Translation	Absent BTK protein	Failed antibody translation
CGD	Translation	Nonfunctional enzyme	Silent execution
WAS	Translation	Cytoskeletal defect	Broken grammar
DOCK8 deficiency	Translation	Protein instability	Incomplete sentencing

granulomatous disease, and Wiskott-Aldrich syndrome – are disorders of translation. In these conditions, immune intent exists, but protein execution fails. In contrast, newly recognized IEIs increasingly affect immune sensing and transcriptional logic, reflecting advances in molecular diagnostics and population genetics. The Three-T framework naturally accommodates both, bridging classic teaching with contemporary discovery.

CLINICAL IMPLICATIONS FOR THE PRACTICING PEDIATRIC PULMONARY SPECIALIST

The Three-T framework offers practical advantages:

- Guides diagnostic thinking before genetic testing.
- Clarifies why targeted therapies succeed or fail.
- Facilitates communication with patients and trainees.
- Bridges classic IEIs with modern gene and RNA therapies.

CONCLUSIONS

Inborn errors of immunity are not random failures of the immune system; they are failures of communication. By framing immune dysfunction as breakdowns in transduction, transcription, or translation, clinicians gain a practical and intuitive tool for diagnosis and education. As immunology advances, restoring immune meaning – rather than simply correcting components – may be the central therapeutic goal.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

The author declares no conflicts of interest.

Financial support

None.

Author contributions

JAB contributed entirely to the work.

Ethical approval

Human studies and subjects

N/A.

Data sharing and data accessibility

N/A.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

REFERENCES

1. Orange JS, Chinen J, Horner CC, Kobrynski LJ, Ballow M, Butte MJ, et al. Inborn errors of immunity practice parameter: Guidance from the Joint Task Force on Practice Parameters, the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI) and the Clinical Immunology Society (CIS). Ann Allergy Asthma Immunol. 2026;136(4):426-493. doi: 10.1016/j.anai.2025.10.026.
2. Poli MC, Aksentijevich I, Bousfiha AA, Cunningham-Rundles C, Hambleton S, Klein C, et al. Human inborn errors of immunity: 2024 update on the classification from the International Union of Immunological Societies Expert Committee. J Hum Immun. 2025;1(1):e20250003. doi: 10.70962/jhi.20250003.
3. Bellanti JA, Settipane RA. Essentials of an immunodeficiency primer: A practical reference for the allergist/immunologist and the allergy-immunology fellow-in-training (FIT). Allergy Asthma Proc. 2024;45(5):291-293. doi: 10.2500/aap.2024.45.240062.
4. Mersha TB, Afanador Y, Johansson E, Proper SP, Bernstein JA, Rothenberg ME, et al. Resolving Clinical Phenotypes into Endotypes in Allergy: Molecular and Omics Approaches. Clin Rev Allergy Immunol. 2021;60(2):200-219. doi: 10.1007/s12016-020-08787-5.
5. Bellanti JA (Ed). Immunology IV: Clinical Applications in Health and Disease. I Care Press, Bethesda, MD, 2012.
6. Bender MJ, Lucas CL. Decoding Immunobiology Through Genetic Errors of Immunity. Annu Rev Immunol. 2025;43(1):285-311. doi: 10.1146/annurev-immunol-082323-124920.

Vol. 4(2), 59-64, 2026

NARRATIVE REVIEW

Over-the-counter cough and cold medications in children: bridging the gap between evidence and clinical practice

Doi
10.56164/PediatrRespirJ.2026.09

Grigorios **Chatziparasidis** [1,*], Ioanna **Grivea** [2]

[*] Correspondence to:
gchatziparasidis@gmail.com; ORCID: https://orcid.org/0000-0003-4308-4710

[1] Department of Pediatric Pulmonology, Department of Pediatrics, University General Hospital of Larisa, Thessaly, Greece
[2] Department of Pediatrics, University General Hospital of Larissa, Thessaly, Greece

ABSTRACT

Over-the-counter cough and cold medications are widely used in children despite insufficient evidence of efficacy and well-documented safety concerns. This narrative review summarizes current evidence on pharmacological and non-pharmacological treatments for both acute and chronic cough in pediatric populations. Most over-the-counter medications, including antitussives, antihistamines, expectorants, and mucolytics, have not demonstrated superiority over placebo. In contrast, selected non-pharmacological interventions, such as honey and vapor rub, may provide modest symptomatic relief in specific age groups.

In chronic wet cough, cough suppression may be inappropriate, as it can delay the diagnosis and treatment of underlying conditions such as protracted bacterial bronchitis and bronchiectasis. Management should therefore prioritize etiological evaluation, caregiver education, and evidence-based interventions.

IMPACT STATEMENT

Over-the-counter cough medications in children lack consistent evidence of efficacy, with most pharmacologic agents performing no better than placebo while exposing children to potentially significant adverse effects. Chronic wet cough should not be suppressed, as it may represent an important clinical marker of underlying airway disease. At present, honey remains the only consistently supported symptomatic therapy for acute cough in children older than one year.

KEY WORDS
Pediatric cough; OTC medicines; antitussives; honey; herbal medications.

INTRODUCTION

Cough remains one of the most common reasons for pediatric consultation and a central challenge in everyday clinical practice. It accounts for approximately 4.7-23.3% of all pediatric primary care visits, particularly in younger children, emphasizing its substantial healthcare burden. A key distinction in pediatric cough is between acute and chronic presentations, as management strategies and clinical implications differ substantially. Acute cough is most commonly associated with upper respiratory tract infections, whereas chronic cough may reflect a broad spectrum of underlying conditions, including asthma, pertussis, and protracted bacterial bronchitis (PBB) (1).

The economic impact of over-the-counter (OTC) cough and cold medications is considerable, with annual revenue in the United States estimated at $10.3 billion despite limited supporting evidence (2). This discrepancy highlights a persistent gap between clinical evidence and real-world practice. Clinicians are frequently pressured to recommend symptomatic treatments, particularly by caregivers seeking rapid relief. Previous studies have shown that such expectations, combined with the lack of effective alternatives, contribute to continued prescribing practices despite guideline recommendations to the contrary (3).

This narrative review is based on a non-systematic literature search conducted using PubMed, Cochrane Library, and guideline databases (*e.g.*, CHEST, GINA). Relevant studies, systematic reviews, and guidelines published in English were selected based on clinical relevance to pediatric cough and over-the-counter treatments. Priority was given to high-quality evidence sources, including randomized controlled trials, meta-analyses, and international guideline recommendations.

ACUTE COUGH IN CHILDREN: EVIDENCE-PRACTICE GAP AND SAFETY CONSIDERATIONS

Available evidence consistently demonstrates a substantial discrepancy between the widespread use of OTC medications and their actual clinical efficacy. Although recent data suggest a modest reduction in acute cough frequency with dextromethorphan (4) these findings are not consistent with earlier pediatric studies. Paul *et al*. demonstrated that neither dextromethorphan nor diphenhydramine improved nocturnal cough frequency, severity, or sleep quality compared with placebo (5). The CHEST Expert Panel further concluded that no pediatric studies have demonstrated clinically relevant superiority of antitussives, antihistamines, decongestants or combination products over placebo (6).

Evidence supporting opioid antitussives is particularly limited. A Cochrane review identified no randomized controlled trials evaluating codeine in children, highlighting the absence of high-quality evidence for its use (7). Overall, systematic reviews consistently show that codeine, dextromethorphan, and hydrocodone do not provide clinically meaningful benefit compared with placebo (6, 8). In line with these findings, the American College of Emergency Physicians recommends prioritizing caregiver education rather than pharmacologic treatment (2).

Beyond the lack of efficacy, safety concerns are considerable. Dosing errors are common, particularly when household spoons are used, as these vary significantly in volume. The American Academy of Pediatrics reports increased error rates with such practices, compounded by caregiver misunderstanding of medication labels (9). Multi-symptom formulations further increase the risk of unintentional overdose, while dosing cups have been associated with higher error rates compared with oral syringes (9, 10).

Pharmacogenetic variability introduces additional risk, particularly with codeine. As a prodrug metabolized predominantly through CYP2D6, ultra-rapid metabolizers may develop life-threatening respiratory depression. This has led to strict regulatory restrictions, including contraindication in children under 12 years and in adolescents following tonsillectomy or adenoidectomy (11, 12). Dextromethorphan also carries risk, acting as N-Methyl-D-Aspartate (NMDA) receptor antagonist and potentially causing neuropsychiatric and neurological toxicity at high doses, including hallucinations, ataxia, and seizures (2, 13). Rare but severe cases of cerebellar toxicity (DANCE syndrome) have also been reported (14). Other OTC categories, including expectorants, mucolytics, and antihistamines, similarly lack convincing evidence of benefit. The CHEST Expert Panel found no evidence supporting their use in pediatric acute cough (5). A Cochrane review suggests minimal clinical benefit and potential harm, including paradoxical bronchorrhea in infants (15). Antihistamines have consistently failed to demonstrate superiority over placebo in randomized trials (2, 4, 16).

Given the combination of limited efficacy and potential harm, regulatory authorities have imposed restrictions. The FDA advises against use in children under 2 years, extended to under 4 years by manufacturers, while Health Ministry of Canada and the Medicines and Healthcare products Regulatory Agency in United Kingdom recommend avoidance in children under 6 years (2, 9, 17, 18). Professional bodies, including the American Academy of Pediatrics, similarly discourage use in young children (19).

NON-PHARMACOLOGICAL THERAPIES

In contrast to pharmacologic agents, certain non-prescription interventions appear to provide modest symptomatic benefit, likely through non-specific soothing mechanisms. The perceived effectiveness of many syrups may relate to their demulcent properties, as viscous solutions provide a protective coating of the pharyngeal mucosa and reduce cough receptor sensitivity (20). Sensory modulation also plays a role, with menthol activating Transient Receptor Potential Melastatin 8 (TRPM8) receptors to produce a cooling sensation that reduces cough perception (21, 22).

Among available options, honey has the most consistent evidence base. It has been shown to reduce cough frequency and improve sleep quality compared with placebo or no treatment (23, 24). Multiple subsequent studies have supported these findings (25, 26). From a practical perspective, administration of 2.5-5 mL of honey before bedtime may be beneficial in children older than one year; however, it is contraindicated in infants due to the risk of botulism (23).

Vapor rub preparations represent another intervention with evidence of benefit. In a randomized trial. Paul *et al*. demonstrated significant improvements in cough frequency, nasal congestion, and sleep quality compared with placebo and no treatment (27). However, the evidence is based on a single study with methodological limitations, including incomplete blinding (6). The proposed mechanism involves sensory counter-irritation, altering the perception of airflow and cough (2, 28).

CHRONIC WET COUGH

The clinical implications of cough extend beyond symptom control in chronic presentations, particularly in children with chronic wet cough. This condition, defined as a daily productive cough lasting more than 4 weeks, is a key clinical marker of underlying airway disease rather than a benign, self-limiting symptom. It is most commonly associated with protracted bacterial bronchitis and bronchiectasis and reflects ongoing lower airway infection (29). Importantly, wet cough serves a physiological role in airway clearance. SSuppression with antitussive agents may therefore be harmful, leading to retention of infected secretions and perpetuation of inflammation (18). CHEST guidelines explicitly advise against the use of cough suppressants in this context (30).

Increasing evidence supports a continuum from PBB to chronic suppurative lung disease and bronchiectasis when appropriate treatment is delayed (32). Prospective studies show that a proportion of children with PBB progress to bronchiectasis, particularly in the presence of recurrent episodes or persistent infection (33). The duration of wet cough correlates with disease severity, including radiological and inflammatory markers (31, 33).

A critical but often overlooked concept is the “opportunity cost” of symptomatic treatment. The use of OTC medications may create false reassurance, delaying appropriate investigation and treatment while the underlying disease progresses (18). Given that a significant proportion of children with chronic cough have serious underlying conditions, such delays may have long-term consequences (34).

Current guidelines emphasize an etiology-based approach. Initial antibiotic therapy is recommended, with escalation to further investigation if symptoms persist (29, 31). This approach is supported by randomized evidence demonstrating significant treatment benefit (35).

CHRONIC DRY COUGH

Chronic dry cough represents a heterogeneous clinical entity. Asthma and asthma-like conditions are among the most common causes (36). The Global Initiative for Asthma (GINA) 2025 guidelines highlight that cough-variant asthma may present with isolated cough, often with normal spirometry (37). However, asthma is also frequently overdiagnosed in this context, particularly in the absence of typical symptoms (38).

Somatic cough syndrome is another important consideration, characterized by suppressibility and variability. Management is primarily behavioral, and pharmacologic therapy is generally ineffective (39). The use of cough syrups in this setting may reinforce illness behavior and hinder effective treatment (26, 36).

Across chronic dry cough, OTC medications have consistently failed to demonstrate meaningful benefit (6). Current guidelines therefore recommend against their routine use, emphasizing instead a structured, diagnostic approach (29, 30).

CONCLUSIONS

The continued use of OTC cough medications in children reflects a persistent disconnect between clinical practice and evidence-based medicine. While cer-

Table 1. *Over-the-Counter cough medications in children: efficacy, risks, and recommendations.*

Category	Examples	Efficacy	Risks	Recommendation
Antitussives	Dextromethorphan, Codeine	No clinically meaningful benefit compared with placebo	CNS toxicity, respiratory depression (especially with codeine)	Not recommended
Antihistamines	Diphenhydramine	No benefit compared with placebo	Sedation, paradoxical excitation, dosing errors	Not recommended
Mucolytics / Expectorants	Acetylcysteine, Guaifenesin	Minimal or uncertain benefit	Worsening airway secretions in infants	Not recommended
Combination OTC products	Multi-symptom cough and cold syrups	No proven efficacy	Increased risk of overdose (acetaminophen toxicity), polypharmacy	Avoid
Honey	Natural product	Moderate evidence of symptom relief (nocturnal cough)	Risk of botulism in infants <1 year	Recommended in children >1 year
Topical vapor rubs	Menthol, camphor, eucalyptus	Symptomatic relief (improved sleep)	Skin irritation, accidental ingestion toxicity	May be considered with caution
Chronic wet cough	-	Cough suppression may be detrimental	Risk of disease progression (*e.g.* PBB, bronchiectasis)	Treat underlying cause (*e.g.* antibiotics)
Chronic dry cough	-	OTC medications ineffective	May reinforce cough hypersensitivity	Etiology-based diagnostic and therapeutic approach

OTC: over the counter; CNS: central nervous system; PBB: protracted bacterial bronchitis.

tain non-pharmacological interventions may provide modest symptomatic relief, most pharmacologic treatments offer no meaningful benefit and carry potential risks (**Table 1**).

More importantly, in chronic cough – particularly wet cough – symptom suppression may delay diagnosis and contribute to disease progression. Effective management requires a shift in focus from symptom control to identification and treatment of the underlying cause. Clinicians must balance caregiver expectations with evidence-based practice, adopting a strategy that validates concerns while redirecting care toward appropriate evaluation.

Ultimately, pediatric cough should not be viewed as a symptom to be suppressed, but as a clinical signal to be interpreted. Aligning clinical practice with this principle is essential to prevent avoidable long-term respiratory morbidity.

Future research should focus on age-specific, mechanism-based therapies targeting specific cough pathways, rather than non-specific symptomatic suppression.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

The authors declare no conflicts of interest.

Financial support

None.

Author contributions

GC: conceptualization, literature review, data curation, writing - original draft, writing - review & editing. IG: supervision, writing - original draft, writing - review & editing.

Ethical approval

Human studies and subjects

N/A.

Data sharing and data accessibility

N/A.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

REFERENCES

1. Bergmann M, Haasenritter J, Beidatsch D, Schwarm S, Hörner K, Bösner S, et al. Coughing children in family practice and primary care: a systematic review of prevalence, aetiology and prognosis. BMC Pediatr. 2021;21(1):260. doi: 10.1186/s12887-021-02739-4.
2. Lam SHF, Homme J, Avarello J, Heins A, Pauze D, Mace S, et al. Use of antitussive medications in acute cough in young children. J Am Coll Emerg Physicians Open. 2021;2(3):e12467. doi: 10.1002/emp2.12467.
3. Vogelberg C, Cuevas Schacht F, Watling CP, Upstone L, Seifert G. Therapeutic principles and unmet needs in the treatment of cough in pediatric patients: review and expert survey. BMC Pediatr. 2023;23(1):34. doi: 10.1186/s12887-022-03814-0.
4. Meeves SG, Cruz-Rivera M, Leyva RA, Wilson BL, Moreira SA, Gelotte CK, et al. Objective and self-reported evidence of dextromethorphan antitussive efficacy in children, aged 6-11 years, with acute cough due to the common cold. Pediatr Pulmonol. 2023;58(8):2229-2239. doi: 10.1002/ppul.26416.
5. Paul IM, Yoder KE, Crowell KR, Shaffer ML, McMillan HS, Carlson LC, et al. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. Pediatrics. 2004;114(1):e85-90. doi: 10.1542/peds.114.1.e85.
6. Malesker MA, Callahan-Lyon P, Ireland B, Irwin RS; CHEST Expert Cough Panel. Pharmacologic and Nonpharmacologic Treatment for Acute Cough Associated With the Common Cold: CHEST Expert Panel Report. Chest. 2017;152(5):1021-1037. doi: 10.1016/j.chest.2017.08.009.
7. Gardiner SJ, Chang AB, Marchant JM, Petsky HL. Codeine versus placebo for chronic cough in children. Cochrane Database Syst Rev. 2016;7(7):CD011914. doi: 10.1002/14651858.CD011914.pub2.
8. Taylor JA, Novack AH, Almquist JR, Rogers JE. Efficacy of cough suppressants in children. J Pediatr. 1993 May;122(5 Pt 1):799-802. doi: 10.1016/s0022-3476(06)80031-4.
9. Yin HS, Neuspiel DR, Paul IM, Franklin W, Tieder JS, Adirim T, et al. Preventing Home Medication Administration Errors. Pediatrics. 2021;148(6):e2021054666. doi: 10.1542/peds.2021-054666.
10. Balıkçı BB, Güneş Ü. Accuracy of liquid drug dose measurements using different tools by caregivers: a prospective observational study. Eur J Pediatr. 2024;183(2):853-862. doi: 10.1007/s00431-023-05293-6.
11. Tobias JD, Green TP, Coté CJ; Section On Anesthesiology And Pain Medicine; Committee On Drugs. Codeine: Time to Say “No”. Pediatrics. 2016;138(4):e20162396. doi: 10.1542/peds.2016-2396.
12. Gammal RS, Crews KR, Haidar CE, Hoffman JM, Baker DK, Barker PJ, et al. Pharmacogenetics for Safe Codeine Use in Sickle Cell Disease. Pediatrics. 2016;138(1):e20153479. doi: 10.1542/peds.2015-3479.
13. Paul IM, Reynolds KM, Kauffman RE, Banner W, Bond GR, Palmer RB, et al. Adverse events associated with pediatric exposures to dextromethorphan. Clin Toxicol (Phila). 2017;55(1):25-32. doi: 10.1080/15563650.2016.1240803.
14. Sharma S, Tiwari S, Saini L, Yadav T, Manjunathan S, Panda A, et al. Dextromethorphan-Associated Neurotoxicity with Cerebellar Edema Syndrome in Young Children: Neuroimaging Features. AJNR Am J Neuroradiol. 2025;46(2):390-394. doi: 10.3174/ajnr.A8455.
15. Chalumeau M, Duijvestijn YC. Acetylcysteine and carbocysteine for acute upper and lower respiratory tract infections in paediatric patients without chronic broncho-pulmonary disease. Cochrane Database Syst Rev. 2013;2013(5):CD003124. doi: 10.1002/14651858.CD003124.pub4.
16. De Sutter AI, Saraswat A, van Driel ML. Antihistamines for the common cold. Cochrane Database Syst Rev. 2015;2015(11):CD009345. doi: 10.1002/14651858.CD009345.pub2.
17. DeGroot J, Anderson LN, Chen Y, Birken CS, Parkin PC, Carsley S, et al. Mandatory labeling requirements and over-the-counter cough and cold medication use in early childhood. Can J Public Health. 2016;106(8):e477-82. doi: 10.17269/cjph.106.5148.
18. Clark G, Fitzgerald DA, Rubin BK. Cough medicines for children- time for a reality check. Paediatr Respir Rev. 2023;48:30-38. doi: 10.1016/j.prrv.2023.08.003.
19. Clebak KT, Partin MT, Borrero N. Oral Antihistamine/Analgesic/Decongestant Combinations for the Common Cold. Am Fam Physician. 2022;106(3):248-249.
20. Canning BJ, Chang AB, Bolser DC, Smith JA, Mazzone SB, McGarvey L, et al. Anatomy and neurophysiology of cough: CHEST Guideline and Expert Panel report. Chest. 2014;146(6):1633-1648. doi: 10.1378/chest.14-1481.
21. Plevkova J, Kollarik M, Poliacek I, Brozmanova M, Surdenikova L, Tatar M, et al. The role of trigeminal nasal TRPM8-expressing afferent neurons in the antitussive effects of menthol. J Appl Physiol (1985). 2013;115(2):268-74. doi: 10.1152/japplphysiol.01144.2012.
22. Bonvini SJ, Birrell MA, Smith JA, Belvisi MG. Targeting TRP channels for chronic cough: from bench to bedside. Naunyn Schmiedebergs Arch Pharmacol. 2015;388(4):401-20. doi: 10.1007/s00210-014-1082-1.
23. Oduwole O, Udoh EE, Oyo-Ita A, Meremikwu MM. Honey for acute cough in children. Cochrane Database Syst Rev. 2018;4(4):CD007094. doi: 10.1002/14651858.CD007094.pub5.
24. Ayazi P, Mahyar A, Yousef-Zanjani M, Allami A, Esmailzadehha N, Beyhaghi T. Comparison of the Effect of Two Kinds of Iranian Honey and Diphenhydramine on Nocturnal Cough and the Sleep Quality in Coughing Children and Their Parents. PLoS One. 2017;12(1):e0170277. doi: 10.1371/journal.pone.0170277.
25. Kuitunen I, Renko M. Honey for acute cough in children - a systematic review. Eur J Pediatr. 2023;182(9):3949-3956. doi: 10.1007/s00431-023-05066-1.
26. Cohen HA, Rozen J, Kristal H, Laks Y, Berkovitch M, Uziel Y, et al. Effect of honey on nocturnal cough and sleep quality:

a double-blind, randomized, placebo-controlled study. Pediatrics. 2012;130(3):465-71. doi: 10.1542/peds.2011-3075.

27. Paul IM, Beiler JS, King TS, Clapp ER, Vallati J, Berlin CM Jr. Vapor rub, petrolatum, and no treatment for children with nocturnal cough and cold symptoms. Pediatrics. 2010;126(6):1092-9. doi: 10.1542/peds.2010-1601.
28. Paul IM. Therapeutic options for acute cough due to upper respiratory infections in children. Lung. 2012;190(1):41-4. doi: 10.1007/s00408-011-9319-y.
29. Chang AB, Oppenheimer J, Irwin. Managing Chronic Cough as a Symptom in Children and Management Algorithms: CHEST Guideline and Expert Panel Report. Chest;2020;158(1):303-329. doi: 10.1016/j.chest.2020.01.042.
30. Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):260S-283S. doi: 10.1378/chest.129.1_suppl.260S.
31. Chang AB, Bush A, Grimwood K. Bronchiectasis in children: diagnosis and treatment. Lancet. 2018;392(10150):866-879. doi: 10.1016/S0140-6736(18)31554-X.
32. Wurzel DF, Marchant JM, Yerkovich ST, Upham JW, Petsky HL, Smith-Vaughan H, et al. Protracted Bacterial Bronchitis in Children: Natural History and Risk Factors for Bronchiectasis. Chest. 2016;150(5):1101-1108. doi: 10.1016/j.chest.2016.06.030.
33. Chang AB, Oppenheimer JJ, Weinberger MM, Rubin BK, Grant CC, Weir K, et al. Management of Children With Chronic Wet Cough and Protracted Bacterial Bronchitis: CHEST Guideline and Expert Panel Report. Chest. 2017;151(4):884-890. doi: 10.1016/j.chest.2017.01.025.
34. Sonoda K, Nayak R. Chronic Cough: Evaluation and Management. Am Fam Physician. 2024;110(2):167-173.
35. Marchant JM, Petsky HL, Morris PS, Chang AB. Antibiotics for prolonged wet cough in children. Cochrane Database Syst Rev. 2018;7(7):CD004822. doi: 10.1002/14651858.CD004822.pub3.
36. Chang AB, Oppenheimer J, Weinberger M, Grant CC, Rubin BK, Irwin RS, et al. Etiologies of Chronic Cough in Pediatric Cohorts: CHEST Guideline and Expert Panel Report. Chest. 2017;152(3):607-617. doi: 10.1016/j.chest.2017.06.006.
37. Reddel H, Bateman E, FitzGerald G, Bacharier L, Bonini M, Bourdin A, et al. 2025 Global Strategy for Asthma Management and Prevention.Global Initiative for Asthma. 2025. Available from: https://lms.iapnrc.com/cms/images/GINA-Strategy-Report_2025-WEB-WMS-1_compressed.pdf.
38. Kennedy AA, Anne S, Hart CK. Otolaryngologic Management of Chronic Cough in School-aged Children: A Review. JAMA Otolaryngol Head Neck Surg. 2020;146(11):1059-1064. doi: 10.1001/jamaoto.2020.2945.
39. Vertigan AE, Murad MH, Pringsheim T, Feinstein A, Chang AB, Newcombe PA, et al. Somatic Cough Syndrome (Previously Referred to as Psychogenic Cough) and Tic Cough (Previously Referred to as Habit Cough) in Adults and Children: CHEST Guideline and Expert Panel Report. Chest. 2015;148(1):24-31. doi: 10.1378/chest.15-0423.

NARRATIVE REVIEW

Evaluation of chronic cough in children: a practical approach

Adil **Khan,** Sami L. **Bahna** *

* **Correspondence to:**

Sami.bahna@lsuhs.edu; ORCID: https://orcid.org/0000-0003-2113-1870

Doi

10.56164/PediatrRespirJ.2026.10

Allergy and Immunology Section, Department of Pediatrics, Louisiana State University Health in Shreveport, Louisiana, U.S.A.

ABSTRACT

Cough is one of the main causes of seeking medical care worldwide. Cough that persists for more than a few weeks is very tasking to the patient and family, both financially and psychosocially. The latter is particularly notable when cough is chronic (> 8 weeks) and the patient is a child.

Whereas acute cough in children is mostly caused by an infection, chronic cough can have numerous respiratory tract and extra-respiratory causes and mechanisms. An early recognition of the underlying cause would lead to early and precise treatment that, in some cases, may require multiple medical consults. Towards such an objective, this article is designed to provide a practical, easy-to-follow guideline for evaluating chronic cough in children.

A skillful medical history-taking of the present illness, past history, family history, and environmental history, followed with a comprehensive physical examination can provide very valuable clues for selecting supportive, cost-effective investigative tests. In addition to the currently available standard evaluation tests, technological advances are leading to the recent development of practical devices for objective assessment of cough characteristics which in turn enhance precise evaluation.

IMPACT STATEMENT

This article provides an easy-to-follow practical approach for evaluation of chronic cough in children. It should facilitate early identification of the underlying cause, prescribing the appropriate management, and limiting the illness' negative impact.

KEY WORDS

Childhood chronic cough; chronic cough causes; cough characteristics; radiologic findings in cough; cough assessment devices.

INTRODUCTION

Cough is basically an innate reflex that acts as a defense mechanism – primarily to clear the respiratory tract of excessive mucus or to expel a foreign body. Healthy children normally cough several times a day with an average of 11 times a day; more in cold weather than on warm days (1). However, cough can be a symptom of illness and a potent method of spreading respiratory infections. It is one of the most common reasons for seeking medical care worldwide and contributes substantially to the healthcare costs. It accounts for 4.7% to 23.3% of all reasons for pediatric primary care visits (2). Apart from the financial burden, the psychosocial effects of chronic cough in children, compared to adult patients, impact family dynamics and peer relationships differently.

DEFINITION AND CLASSIFICATION

Cough from acute respiratory infection usually resolves within a few weeks. Chronic cough in children is generally defined as a cough persisting for more than 4 weeks (3, 4). According to these guidelines, the pediatric population is generally defined as pre-pubertal children younger than 14 years. In contrast, the British Thoracic Society defines chronic cough in children as a cough lasting for more than 8 weeks (5), which is similar to adults, but this cut-off is considered too long in children (6, 7). The etiologies and clinical characteristics of cough in children differ substantially from those in adults (4, 8, 9). The differential diagnosis of cough in young children is distinct from older children and adults. Cough may be classified in different ways, *i.e.*, according to its mechanisms, characteristics, causes, or as non-specific *vs* specific. Non-specific cough is typically dry with a normal chest X-ray (CXR) and spirometry; it mostly follows a respiratory viral infection and resolves spontaneously without serious sequelae. Specific cough may be wet or dry and is associted with abnormal findings by lung auscultation and/or CXR, along with other symptoms such as dyspnea, hemoptysis, recurrent pneumonia, swallowing problems, or failure to thrive.

The objective of this review is to provide a practical approach for evaluating chronic cough in children. Awareness of the various causes is crucial for conducting an appropriate evaluation, including medical history-taking, physical examination, and selection of diagnostic procedures and laboratory tests. To enhance the usefulness of this article in clinical practice, more information is presented in simplified tables in lieu of long texts.

CAUSES OF CHRONIC COUGH

The underlying causes of chronic cough can be simply divided into respiratory and extra-respiratory (**Table 1**) – a broad spectrum reflecting the marked heterogeneity of cough phenotypes. Furthermore, cough can be stimulated or provoked by a large number of mechanical, thermal, chemical, and inflammatory mediators (**Table 2**). Such agents act through different complex pathophysiological mechanisms and pathways (10, 11). According to a review by Rubin (12), chronic cough in children is often preceded by viral respiratory infection. Protracted bacterial bronchitis is one of the most common causes of persistent wet cough in young children. Gastroesophageal reflux rarely causes chronic cough in children. Also, isolated-cough-variant asthma without objective airway findings appears to be rare in children. Chronic purulent cough should prompt evaluation for bronchiectasis, immune deficiency, aspiration, cystic fibrosis, or ciliary dyskinesia. Functional cough disorders include psychogenic cough, habit cough, and cough associated with secondary gain – which can be hard to differentiate from each other; psychologic consult would help in diagnosis and management.

EVALUATION OF CHRONIC COUGH IN CHILDREN

Multiple guidelines and diagnostic algorithms for the evaluation of chronic cough have been published (1, 3, 9, 13-18). We present a simplified yet comprehensive guideline that is easy to follow and applicable in clinical practice.

Table 1. *Causes of chronic cough.*

Respiratory tract	Extra-respiratory
Upper: disorders of nose, sinuses, pharynx, larynx, ear canal **Lower:** trachea, bronchi, lungs, pleura	**Cardiovascular:** heart failure, vascular rings, anomalies of large blood vessels **Neuromuscular:** swallowing disorders **Gastroesophageal:** gastroesophageal reflux, diaphragmatic hernia **Medications:** angiotensin-converting enzyme inhibitors; cytotoxic drugs **Functional:** Psychogenic, habitual, secondary gain

Table 2. *Cough stimuli.*

Mechanical	Thermal	Chemical	Mediators
Mucus Foreign body Instrumentation Inflation/deflation	Cold air Hot air Cold water ingestion	Capsaicin Citric acid Osmotic agents Tobacco smoke	Histamine Bradykinin Prostglandin-F2α

Appropriate evaluation starts with a thorough skillful medical history-taking followed by a comprehensive physical examination with emphasis on, but not limited to, the respiratory tract. According to the information gathered from these two procedures, a differential diagnosis that guides the selection of appropriate diagnostic procedures and laboratory tests can be formulated.

MEDICAL HISTORY

It cannot be overemphasized that a skillful history-taking plays a pivotal role in the assessment of chronic cough in children (9, 19, 20). Medical history should include the present illness history, past history, family history, and environmental history. Since in most cases the information is obtained through the parents, a special skill is required on the part of the health provider, parents may not volunteer important information unless specifically prompted.

Present illness history

Information-gathering should begin with the cough's onset and its circumstances. Onset during early infancy may be related to prematurity, congenital malformations, neonatal illness, interventions, conditions predisposing to aspiration, or chronic pulmonary disease such as bronchopulmonary dysplasia (BPD) or cystic fibrosis. A sudden onset of cough while playing with small toys or eating should raise suspicion of foreign body aspiration or a tracheoesophageal fistula. The cough should be assessed in terms of its initial characteristics, course over time, triggers, exacerbating factors, and associated symptoms such as fever, night sweats, dysphagia, and weight loss. Hemoptysis may suggest foreign body aspiration, bronchiectasis, tuberculosis, lung abscess, hemosiderosis, heart failure, neoplasm, vascular lesions, endobronchial lesions, and clotting disorders. Obtaining information on current or past medication can be valuable in knowing the response to past therapies or as potential cause – a dry cough may develop after prolonged asymptomatic use of angiotensin-converting enzyme (ACE) inhibitors. Information on the characteristics of cough can provide valuable clues to the underlying etiology (21) (**Table 3**).

Past medical history and comorbidities

Past medical history should be evaluated for perinatal history, including prematurity, neonatal illnesses, interventions, and BPD. In addition, a history of severe respiratory infections like pertussis and adenoviral bronchiolitis should be taken into consideration. A recent case-control study (22) revealed that children with chronic cough exhibited higher rates of allergic diseases compared to controls: allergic rhinitis was present in about 75% *vs* 24%, food allergy in 60% *vs* 28%, and eczema in 55% *vs* 31%.

Family history

Information should be obtained regarding a family history of illness, particularly chronic cough and atopy, especially asthma. A family history of allergy was noted in 72% of children with chronic cough *vs* 28% in children without cough (22). Chronic cough in a family member may lead to the development of habit cough in a child. Tobacco smoking by household members can be a pri-

Table 3. *Cough characteristics may point to the underlying cause.*

Cough Characteristic	Possible Underlying Condition
Honking, not during sleep, stops upon request	Psychogenic, habit, secondary gain
Nocturnal	Postnasal drip (Upper airway cough syndrome), asthma, allergens in bed
Post-exercise	Asthma, cough-dominant asthma
Environmental exposure	Respiratory allergy
Associated with stridor	Laryngeal obstruction, foreign body, pertussis
Spasmodic, inspiratory whoop	Pertussis
Staccato	Chlamydia pneumonia
Brassy, barking	Croup, laryngitis, tracheitis, tracheomalacia
Productive, purulent sputum, worse in morning	Immunodeficiency, foreign body, cystic fibrosis, bronchiectasis, ciliary dyskinesia

Modified from (21).

mary or a major contributory factor. The family dynamics may not only contribute to exacerbation of the child's cough but can also be the cause of psychogenic cough.

Environmental history

Environmental exposures should be explored, including indoor, outdoor, and geographic factors (23-26). Indoor exposures include allergens such as pets, mold, and dust mites, as well as irritants such as tobacco smoke, wood burning stoves, fumes, and cleaning chemicals. Outdoor exposures may include pollens, mold, and nearby industrial pollution. Geographical and endemic factors should also be considered, particularly exposure to parasitic and fungal infections. Compared with children without cough, children with chronic cough had higher exposure to household smoking (55% *vs* 21%) and mold (29% *vs* 7%) (22).

PHYSICAL EXAMINATION

Children with chronic cough should undergo a comprehensive physical examination, starting with the general appearance, vital signs, and main body systems, particularly the respiratory and the cardiovascular systems (**Table 4**). Physical findings can point to possible underlying causes of cough (**Table 5**). External ear examination may reveal a foreign body which may be as small as a tiny piece of paper or a hair lodged against the tympanic membrane, inducing reflex cough through stimulation of the auricular branch of the vagus nerve (27). Failure to thrive may point to cystic fibrosis or other chronic pulmonary diseases. Dyspnea, tachypnea, cyanosis, or finger clubbing typically indicate chronic airway obstruction, substantial pulmonary parenchymal disease, or cardiac disease. On lung auscultation, crepitations suggest alveolar secretion whereas localized decreased breath sounds indicate consolidation or atelectasis. Skillful chest percussion may reveal areas of lung consolidation, cavitation, or pleural effusion.

LABORATORY INVESTIGATIONS

A vast array of laboratory tests is available for a comprehensive evaluation of chronic cough. Multiple factors should be taken into consideration including availability, the child's age, and cost. They can be broadly classified into two main groups: initial basic tests and additional selected tests (**Table 6**).

Table 4. *Physical examination in chronic cough.*

Vital signs: temp, respiratory rate, heart rate, blood pressure, weight, height.
General: halitosis, obesity, cyanosis, digital clubbing, lymphadenopathy.
Cough: characteristics (**Table 3**).
ENT: deformities, nasal obstruction, rhinorrhea, tonsillar/adenoid hypertrophy, postnasal drip, foreign body in ear canal.
Chest: deformity, tachypnea, retractions, accessory muscle use, hyperinflation, lung auscultation, chest percussion.
Heart: murmurs, cardiomegaly, *situs inversus*.
Neuromuscular: swallowing disorders.

Table 5. *Significance of physical findings in subjects with chronic cough.*

Physical finding	Possible underlying condition
Failure to thrive	Cystic fibrosis, other chronic pulmonary disease
Tachypnea or dyspnea	Substantial airway or pulmonary parenchymal disease
Cyanosis	Chronic airway or parenchyma disease, cardiac disease
Digital clubbing	Suppurative lung disease, cyanotic heart disease
Lymphadenopathy	Neoplastic disease, tuberculosis
Chest wall deformity	Any chronic airway or parenchymal disease
Lung auscultation	Wheeze, rhonchi, crepitations, decreased breath sounds
Chest percussion	Consolidation, cavitation, pleural effusion
Cardiac abnormalities	Associated airway abnormalities, cardiac failure
Neuromuscular disease	Aspiration lung disease

Adapted from (1); (9); (13); (21).

Table 6. Tests for evaluation of chronic cough.

Initial basic tests	Additional selected tests	
Complete blood count with differential Chest radiograph (CXR) Sinus X-ray or computed tomography (CT) Spirometry: Flow-volume loop Pre- / post-bronchodilator Pre- / post-exercise	Chest radiograph (CXR) specific views Chest high resolution computed tomography (HRCT) PPD or QuantiFERON Cystic fibrosis (sweat/genetic) Allergy evaluation Immunodeficiency evaluation	Nasal brush biopsy Bronchial challenge Rhinolaryngoscopy Bronchoscopy Bronchial or lung biopsy Esophageal pH monitoring

Initial basic tests

A routine complete blood count (CBC) may suggest infection or reveal anemia, eosinophilia or cytopenia that warrant further investigation. Radiologic imaging of lungs and paranasal sinuses can reveal important findings. Common chest radiograph (CXR) abnormal findings and their potential clinical significance are presented in **Table 7**.

Spirometry (with flow-volume loop), including pre- and post-bronchodilator or exercise testing can help assess airway obstruction and reversibility. A concave expiratory flow-volume curve is suggestive of asthma, whereas a flat inspiratory loop would indicate an extra-thoracic airway obstruction such as inducible laryngeal obstruction (vocal cord dysfunction). It is important to note that normal CXR and/or spirometry findings do not exclude the need for further pulmonary investigation. A study showed that the use of CXR and spirometry in initial evaluation of children with chronic cough showed specificities of 93% and 94% respectively, but their sensitivities were only 19% and 17% (28).

Radiologic imaging of the paranasal sinuses may include a Waters' view X-ray, but CT scan, if feasible, has better sensitivity and specificity for revealing abnormalities. Expertise is needed in interpreting sinus imaging because some findings may be transient or not clinically relevant (3). Initial signs of sinus pneumatization are noted at birth for the maxillary and ethmoid, at 9 months for the sphenoid, and after the age of 5 years for the frontal (29). For practical purposes, the maxillary and ethmoid sinuses can be radiologically visualized in young infants, the sphenoids become apparent at 3-5 years, and the frontals at 7-12 years (30-32).

Additional selected tests

Additional diagnostic tests should be individualized and judiciously selected (**Table 6**). In some cases, certain CXR views may be needed such as decubitus for pleural effusion or films during inspiration *versus* expiration for localized airway obstruction. In screening for tuberculosis, to differentiate between infection and immunity, interferon-gamma release assays, such as QuantiFER-

Table 7. Clinical significance of chest X-ray abnormal findings.

Abnormal finding	Possible clinical significance
Peribronchial accentuation	Chronic asthma, cystic fibrosis, chronic bronchitis
Peribronchial accentuation with macro-nodularity or railroad sign	Bronchiectasis
Asymmetry in aeration or vascular markings	Partial airway obstruction
Right middle lobe infiltrate	Atelectasis from mucus plugging or foreign body
Pleural effusion or pneumothorax	Parenchymal lung disease
Hilar lymphadenopathy	Tuberculosis, fungal infection, sarcoidosis, neoplasm
Large heart or pulmonary artery	Heart failure, pulmonary hypertension
Shifted cardiac shadow	Substantial atelectasis
Right-sided heart	*Situs inversus*, ciliary dyskinesia
Multiple lung infiltrates	Milk-induced pulmonary disease (Heiner syndrome) (**Table 8**)

Modified from (21).

***Table 8**. Milk-induced chronic pulmonary disease (Heiner syndrome).*

Chronic or recurrent lower respiratory symptoms, often associated with upper respiratory and GI symptoms and failure to thrive. Cow's milk is the most common, but not the only, causative food.
CXR may show patchy infiltrates, localized atelectasis, consolidation, peribronchial infiltrate, hilar lymphadenopathy, pleural thickening, or reticular density.
CBC may show eosinophilia and/or iron deficiency anemia.
High titers of serum IgG antibodies (precipitins) to multiple cow's milk protein fractions.
Pulmonary hemosiderosis in severe cases.
Symptoms begin to improve within several days after dietary elimination, but radiologic improvement may take several weeks.

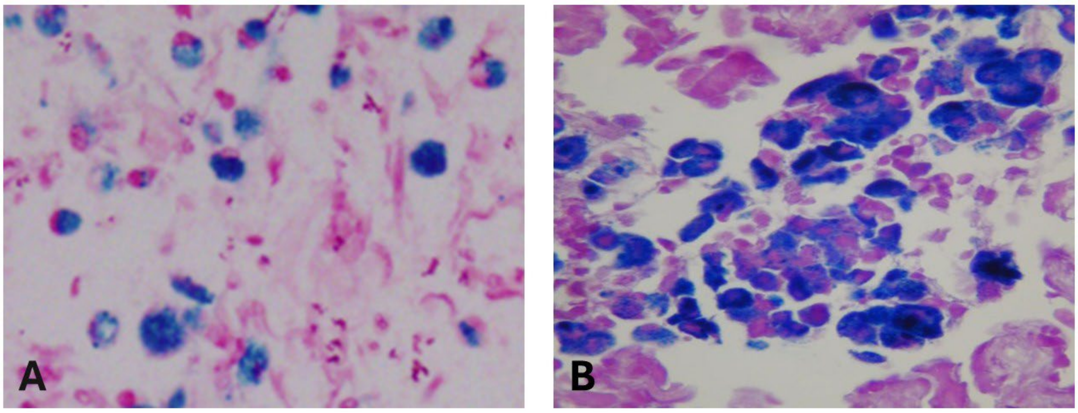

***Figure 1**. Iron-laden macrophages (Prussian blue stain) in bronchoalveolar lavage (**A**) and in lung biopsy (**B**) from 2 children with Heiner syndrome with pulmonary hemosiderosis.*

ON-TB or T-SPOT.TB, are preferred over the tuberculin Mantoux skin test (33).

Suspicion of pertussis requires confirmation with PCR testing. In screening for cystic fibrosis, genetic testing for CFTR gene mutations is superior to sweat chloride testing (34). Screening for primary ciliary dyskinesia can be by electron microscopy examination of respiratory tract brush biopsy or by genotyping for mutations in the PCD gene, but normal finding does not exclude the disease (35). For bronchial hyperresponsiveness, mannitol challenge is preferred over methacholine (36). A suspicion of Heiner syndrome (**Table 8**) would be supported by a high serum titer of IgG antibodies to cow milk proteins (37, 38); the presence of iron-laden macrophages in bronchoalveolar lavage or lung biopsy would indicate pulmonary hemosiderosis (**Figure 1**).

ADVANCED TOOLS FOR ASSESSING COUGH CHARACTERISTICS

Recent years have witnessed the development of many new methods and devices for objective assessment of cough frequency, intensity, and reflex sensitivity (**Table 9**). They were initially developed primarily for research studies. Most of these tools are expensive and require specific expertise for administration and interpretation, and so far, have shown varying degrees of correlation with subjective assessment. Several devices have been adapted for easy clinical use. Selected devices will be briefly mentioned here; details are available in other publications (39-43).

Several ambulatory cough frequency monitors are available; the most commonly used are VitaloJAK and Leicester Cough Monitor. Others are Hull Automatic Cough Counter, LifeShirt, Cayetano Cough Monitor, LR102, and PulmoTrack-CC. Cough intensity can be assessed with measuring the expiratory flow rate, electromyogram activity of respiratory muscles, and cough sound amplitudes. For assessing the cough reflex sensitivity, capsaicin and citric acid have been used for controlled inhalation challenge tests. More recently, there has been an increased focus on advanced technology to develop wearable, low-cost, real-time, and patient-

Table 9. *Advanced tools for assessing cough characteristics (40-48).*

Device	Use
VitaloJAK and Leicester Cough Monitor; Hull Automatic Cough Counter; LifeShirt; Caytano Cough Monitor; Pulmo Track-CC	Ambulatory monitors for objective cough frequency assessment
Expiratory flow rate, electromyogram activity of respiratory muscles, and cough sound amplitude	Objective assessment of cough intensity
Capsaicin and citric acid inhalation challenge	Controlled inhalation challenge tests for assessing cough reflex sensitivity
Hyfe Cough Monitor	AI-powered smartwatch device for passive, continuous, real-world cough monitoring
Smartphone-based cough detection systems	Smartphone sound recording, detect and classify cough in noisy environments, can distinguish dry from wet cough
LEOSound system	Automated lung sound monitor using ambient microphone and bio-acoustic sensors attached to the trachea and back
Wearable collar cough counter	Compact wearable microphone paired with a Bluetooth-enabled tablet app for real-time, long-term cough counting

friendly devices for the acquisition and automatic assessment of cough sounds.

The Hyfe Cough Monitor is a smartwatch-based system, which is connected to its software application. It is an artificial intelligence-powered cough detection system designed to passively and continuously monitor cough in real-world conditions. In a multicenter observational study, the results of the Hyfe Cough Monitor wrist-worn device were compared with manually counted coughs; it demonstrated high sensitivity (90.4%), a low false positive rate (~1.03/hour), and a very strong correlation (r = 0.99) between its automated counts and manual count (44).

Hoyos-Barcelo *et al*. (45) proposed a smartphone-based cough detection system which can classify cough in a noisy environment with 88.94% sensitivity and 98.64% specificity. Similarly, Kvapilova *et al*. (46) used continuous smartphone sound recordings combined with machine learning algorithms to measure cough frequency and distinguish between dry and wet cough, with reported sensitivity and specificity of 88% and 86% respectively.

The LEOSound-system is an automated lung sound monitor, functioning as a “long-term stethoscope”. It can continuously record lung sounds using an ambient microphone and three small bio-acoustical sensors. One of the sensors is attached to the patient’s trachea and the other two to the back (47). In children, the sensitivity of cough detection was 89% and its specificity was 99%, with a strong correlation (r = 0.85) with subjective measures (48).

Another wearable portable automatic cough counting device containing acquisition and reception software has been recently developed (43). It includes a small microphone connected to a controller, Bluetooth module, and software that enables real-time cough counting. The cough sensor is designed to be worn on the body (*e.g*. on the collar near the mouth) and paired with a host tablet app for long-term monitoring. It has the advantages of denoising and high degrees of accuracy, sensitivity, and specificity at 93.24%, 97.58%, 86.97%, respectively. In comparison to other devices which are often larger, stationary and require offline processing, this system is compact, wearable, and suitable for daily long-term use. With the continued advances in technology, more advanced devices for objective cough monitoring are expected in the coming years.

ACKNOWLEDGEMENTS

The authors thank David A. Kaufman, MD, for reviewing the manuscript and providing valuable editorial revisions.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

The authors declare no conflicts of interest.

Financial support

None.

Author contributions

Both authors shared equally in the conceptualization, writing and reviewing of the manuscript.

Ethical approval

Human studies and subjects

N/A.

Data sharing and data accessibility

N/A.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

REFERENCES

1. Shields MD, Doherty GM. Chronic cough in children. Paediatr Respir Rev. 2013;14(2):100-5; quiz 6, 37-8. doi: 10.1016/j.prrv.2012.05.002.
2. Bergmann M, Haasenritter J, Beidatsch D, Schwarm S, Hörner K, Bösner S, et al. Coughing children in family practice and primary care: a systematic review of prevalence, aetiology and prognosis. BMC Pediatr. 2021;21(1):260. doi: 10.1186/s12887-021-02739-4.
3. Chang AB, Oppenheimer JJ, Irwin RS. Managing Chronic Cough as a Symptom in Children and Management Algorithms: CHEST Guideline and Expert Panel Report. Chest. 2020;158(1):303-29. doi: 10.1016/j.chest.2020.01.042.
4. Marchant JM, Chang AB, Kennedy E, King D, Perret JL, Schultz A, et al. Cough in Children and Adults: Diagnosis, Assessment and Management (CICADA). Summary of an updated position statement on chronic cough in Australia. Med J Aust. 2024;220(1):35-45. doi: 10.5694/mja2.52157.
5. Shields MD, Bush A, Everard ML, McKenzie S, Primhak R. BTS guidelines: Recommendations for the assessment and management of cough in children. Thorax. 2008;63(Suppl 3):iii1-iii15. doi: 10.1136/thx.2007.077370.
6. Marchant JM, Masters IB, Taylor SM, Cox NC, Seymour GJ, Chang AB. Evaluation and outcome of young children with chronic cough. Chest. 2006;129(5):1132-41. doi: 10.1378/chest.129.5.1132.
7. Chang AB, Robertson CF, Van Asperen PP, Glasgow NJ, Mellis CM, Masters IB, et al. A multicenter study on chronic cough in children: burden and etiologies based on a standardized management pathway. Chest. 2012;142(4):943-50. doi: 10.1378/chest.11-27258.
8. Chang AB. Cough: are children really different to adults? Cough. 2005;1:7. doi: 10.1186/1745-9974-1-7.
9. Masson V, Kier C, Chandran L. Cough Conundrums: A Guide to Chronic Cough in the Pediatric Patient. Pediatr Rev. 2022;43(12):691-703. doi: 10.1542/pir.2021-005398.
10. Rouadi PW, Idriss SA, Bousquet J, Laidlaw TM, Azar CR, Al-Ahmad MS, et al. WAO-ARIA consensus on chronic cough - Part 1: Role of TRP channels in neurogenic inflammation of cough neuronal pathways. World Allergy Organ J. 2021;14(12):100617. doi: 10.1016/j.waojou.2021.100617.
11. Rouadi PW, Idriss SA, Bousquet J, Laidlaw TM, Azar CR, Al-Ahmad MS, et al. WAO-ARIA consensus on chronic cough - Part II: Phenotypes and mechanisms of abnormal cough presentation - Updates in COVID-19. World Allergy Organ J. 2021;14(12):100618. doi: 10.1016/j.waojou.2021.100618.
12. Rubin BK. Chronic cough in childhood. Pediatr Respir J. 2022;1(0):25-30. doi: 10.56164/PediatrRespirJ.2022.01.
13. Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):260S-83S. doi: 10.1378/chest.129.1_suppl.260S.
14. Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Domingo Ribas C, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J. 2020;55(1):1901136. doi: 10.1183/13993003.01136-2019.
15. Marseglia GL, Manti S, Chiappini E, Brambilla I, Caffarelli C, Calvani M, et al. Chronic cough in childhood: A systematic review for practical guidance by the Italian Society of Pediatric Allergy and Immunology. Allergol Immunopathol (Madr). 2021;49(2):133-54. doi: 10.15586/aei.v49i2.44.
16. Mukerji SS, Yenduri NJS, Chiou E, Moonnumakal SP, Bedwell JR. A multi-disciplinary approach to chronic cough in children. Laryngoscope Investig Otolaryngol. 2022;7(2):409-16. doi: 10.1002/lio2.778.
17. Chang AB, Oppenheimer JJ, Dunlap W, Lieberman JA, Irwin RS. Yardstick for managing cough, part 2: In children. Ann Allergy Asthma Immunol. 2023;130(5):681-9. doi: 10.1016/j.anai.2023.01.026.
18. Irwin RS, Oppenheimer JJ, Dunlap W, Lieberman JA, Chang AB. Yardstick for managing cough, part 1: In adults and adolescent patients older than 14 years of age. Ann Allergy Asthma Immunol. 2023;130(3):379-91. doi: 10.1016/j.anai.2022.12.008.
19. Kantar A, Marchant JM, Song WJ, Shields MD, Chatziparasidis G, Zacharasiewicz A, et al. History Taking as a Diagnostic Tool in Children With Chronic Cough. Front Pediatr. 2022;10:850912. doi: 10.3389/fped.2022.850912.
20. Peek R, Walker L, Singleton R. Chronic cough in preschool aged children. BMJ. 2024;386:e079747. doi: 10.1136/bmj-2024-079747.
21. Acosta R, Bahna SL. Chronic cough in children. Pediatr Ann. 2014;43(8):e176-e183. doi: 10.3928/00904481-20140723-07.
22. Zheng K, Wang Q, Tang L, Chen X. Pediatric chronic cough: Allergies, environmental factors, and asthma-as-

sociated inflammation. J Asthma. 2025;62(11):1939-49. doi: 10.1080/02770903.2025.2537406.

23. Ciprandi G, Caimmi D, Miraglia Del Giudice M, La Rosa M, Salpietro C, Marseglia GL. Recent developments in United airways disease. Allergy Asthma Immunol Res. 2012;4(4):171-7. doi: 10.4168/aair.2012.4.4.171.
24. Maio S, Baldacci S, Carrozzi L, Pistelli F, Simoni M, Angino A, et al. 18-yr cumulative incidence of respiratory/allergic symptoms/diseases and risk factors in the Pisa epidemiological study. Respir Med. 2019;158:33-41. doi: 10.1016/j.rmed.2019.09.013.
25. 25 . Cilluffo G, Ferrante G, Fasola S, Malizia V, Montalbano L, Ranzi A, et al. Association between Asthma Control and Exposure to Greenness and Other Outdoor and Indoor Environmental Factors: A Longitudinal Study on a Cohort of Asthmatic Children. Int J Environ Res Public Health. 2022;19(1):512. doi: 10.3390/ijerph19010512.
26. Viegi G, La Grutta S. Passive smoke exposure as an intergenerational risk factor for lung health. Thorax. 2026;81(2):103-4. doi: 10.1136/thorax-2025-223508.
27. Dicpinigaitis PV, Kantar A, Enilari O, Paravati F. Prevalence of Arnold Nerve Reflex in Adults and Children With Chronic Cough. Chest. 2018;153(3):675-9. doi: 10.1016/j.chest.2017.11.019.
28. Marchant JM, Masters IB, Taylor SM, Chang AB. Utility of signs and symptoms of chronic cough in predicting specific cause in children. Thorax. 2006;61(8):694-8. doi: 10.1136/thx.2005.056986.
29. Adibelli ZH, Songu M, Adibelli H. Paranasal sinus development in children: A magnetic resonance imaging analysis. Am J Rhinol Allergy. 2011;25(1):30-5. doi: 10.2500/ajra.2011.25.3552.
30. Scuderi AJ, Harnsberger HR, Boyer RS. Pneumatization of the paranasal sinuses: normal features of importance to the accurate interpretation of CT scans and MR images. AJR Am J Roentgenol. 1993;160(5):1101-4. doi: 10.2214/ajr.160.5.8470585.
31. Wolf G, Anderhuber W, Kuhn F. Development of the paranasal sinuses in children: implications for paranasal sinus surgery. Ann Otol Rhinol Laryngol. 1993;102(9):705-11. doi: 10.1177/000348949310200911.
32. Lee S, Fernandez J, Mirjalili SA, Kirkpatrick J. Pediatric paranasal sinuses-Development, growth, pathology, & functional endoscopic sinus surgery. Clin Anat. 2022;35(6):745-61. doi: 10.1002/ca.23888.
33. Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis. 2017;64(2):e1-e33. doi: 10.1093/cid/ciw694.
34. Anton-Paduraru DT, Azoicai AN, Trofin F, Mindru DE, Murgu AM, Bocec AS, et al. Diagnosing Cystic Fibrosis in the 21st Century-A Complex and Challenging Task. Diagnostics (Basel). 2024;14(7):763. doi: 10.3390/diagnostics14070763.
35. Goutaki M, Shoemark A. Diagnosis of Primary Ciliary Dyskinesia. Clin Chest Med. 2022;43(1):127-40. doi: 10.1016/j.ccm.2021.11.008.
36. Leung SSY, Tsang HSL, Chan J, Kui OYH, Zeng P, Cheung YT, et al. Evaluation of bronchial hyperresponsiveness in asthmatic paediatric patients using mannitol challenge test - Impacts of body mass index. Ann Med. 2025;57(1):2468262. doi: 10.1080/07853890.2025.2468262.
37. Moissidis I, Chaidaroon D, Vichyanond P, Bahna SL. Milk-induced pulmonary disease in infants (Heiner syndrome). Pediatr Allergy Immunol. 2005;16(6):545-52. doi: 10.1111/j.1399-3038.2005.00291.x.
38. Arasi S, Mastrorilli C, Pecoraro L, Giovannini M, Mori F, Barni S, et al. Heiner Syndrome and Milk Hypersensitivity: An Updated Overview on the Current Evidence. Nutrients. 2021;13(5):1710. doi: 10.3390/nu13051710.
39. Hunt J. Exhaled breath condensate pH assays. Immunol Allergy Clin North Am. 2007;27(4):597-606; vi. doi: 10.1016/j.iac.2007.09.006.
40. Cho PSP, Birring SS, Fletcher HV, Turner RD. Methods of Cough Assessment. J Allergy Clin Immunol Pract. 2019 Jul-Aug;7(6):1715-1723. doi: 10.1016/j.jaip.2019.01.049.
41. Hall JI, Lozano M, Estrada-Petrocelli L, Birring S, Turner R. The present and future of cough counting tools. J Thorac Dis. 2020;12(9):5207-23. doi: 10.21037/jtd-2020-icc-003.
42. Zhang M, Sykes DL, Brindle K, Sadofsky LR, Morice AH. Chronic cough-the limitation and advances in assessment techniques. J Thorac Dis. 2022;14(12):5097-119. doi: 10.21037/jtd-22-874.
43. Wang Y, Yang K, Xu S, Rui S, Xie J, Wang J, et al. An automatic cough counting method and system construction for portable devices. Front Bioeng Biotechnol. 2024;12:1477694. doi: 10.3389/fbioe.2024.1477694.
44. Chaccour C, Sanchez-Olivieri I, Siegel S, Megson G, Winthrop KL, Botella JB, et al. Validation and accuracy of the Hyfe cough monitoring system: a multicenter clinical study. Sci Rep. 2025;15(1):880. doi: 10.1038/s41598-025-85341-3.
45. Hoyos-Barcelo C, Monge-Alvarez J, Pervez Z, San-Jose-Revuelta LM, Casaseca-de-la-Higuera P. Efficient computation of image moments for robust cough detection using smartphones. Comput Biol Med. 2018;100:176-85. doi: 10.1016/j.compbiomed.2018.07.003.
46. Kvapilova L, Boza V, Dubec P, Majernik M, Bogar J, Jamison J, et al. Continuous Sound Collection Using Smartphones and Machine Learning to Measure Cough. Digit Biomark. 2019;3(3):166-75. doi: 10.1159/000504666.
47. Koehler U, Hildebrandt O, Weissflog A, Zacharasiewicz A, Sohrabi K, Koehler N, et al. LEOSound - A new device for long-term recording of wheezing and cough in pediatric and adult patients with asthma (during sleep). Clin Investig. 2018;8(3):103-7. doi: 10.4172/clinical-investigation.1000135.
48. Urban C, Kiefer A, Conradt R, Kabesch M, Lex C, Zacharasiewicz A, et al. Validation of the LEOSound®monitor for standardized detection of wheezing and cough in children. Pediatr Pulmonol. 2022;57(2):551-9. doi: 10.1002/ppul.25768.

 Vol. 4(2), 74-85, 2026

RESEARCH ARTICLE

Who talks to adolescents about e-cigarettes? Attitudinal profiles among Italian pediatricians

Stefania **Roncaglia** [1,§], Alessandra **Pandolfo** [2,3,§,*], Maria Elisa **Di Cicco** [4], Stefania **La Grutta** [2,#], Michele **Ghezzi** [1,#]

* **Correspondence to:**
alessandra.pandolfo@ift.cnr.it; alessandra.pandolfo@unipa.it;
ORCID: https://orcid.org/0009-0006-1852-8622

Doi
10.56164/PediatrRespirJ.2026.08

[1] Department of Pediatrics, Buzzi Children's Hospital, Milan, Italy
[2] Institute of Translational Pharmacology (IFT), National Research Council (CNR), Palermo, Italy
[3] Department of Economics, Business and Statistics (dSEAS), University of Palermo (UNIPA), Palermo, Italy
[4] Section of Pediatrics, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[§] Joint first authorship
[#] Joint senior authorship

ABSTRACT

E-cigarette use among adolescents is rising rapidly, yet heterogeneity in pediatricians' knowledge, risk perception, and counselling practices remains poorly characterized. This study aimed to identify distinct attitudinal profiles among Italian pediatricians and to determine the variables that most strongly discriminate between them. A cross-sectional anonymous online survey was distributed between April and October 2025 via the Italian Pediatric Respiratory Society (IPRS/SIMRI) national newsletter. The questionnaire covered demographic characteristics, smoking habits, knowledge of e-cigarettes, risk perception, clinical practices, and counselling behaviors. Latent class analysis (LCA) with an expectation-maximization algorithm was applied to 250 completed responses. Models with two to six classes were compared using AIC, BIC, entropy, and the Lo-Mendell-Rubin likelihood ratio test. The three-class solution provided the best balance between fit and parsimony (lowest BIC); however, entropy values were uniformly low (<0.05), indicating limited separation between classes, so the resulting profiles should be interpreted as broad, partially overlapping tendencies rather than sharply distinct groups. Class 1 (≈25%) tended to include senior pediatricians (mean age >60 years), with a pattern of more conservative attitudes and lower engagement in e-cigarette counselling. Class 2 (≈39%) showed tendencies toward mid-career practitioners reporting greater confidence and openness in discussing e-cigarettes with patients. Class 3 (≈36%) was more frequently composed of early-career pediatricians who tended to underestimate e-cigarette risks and reported lower counselling self-efficacy. Years of practice (importance = 1.00) and age (0.86) were the strongest class discriminators, followed by communication behaviors and risk perception variables. Italian pediatricians appear to cluster along three career-stage-related attitudinal tendencies regarding e-cigarettes, though the low entropy indicates these groupings are partially overlapping rather than rigid categories. These findings support the development of differentiated, career-stage-tailored educational interventions to strengthen counselling capacity across the pediatric workforce.

KEY WORDS
Adolescents; e-cigarettes; pediatricians; latent class analysis; risk perception.

 |

HIGHLIGHTS BOX

What is already known about this topic? E-cigarette use among adolescents is rising rapidly; pediatricians are expected to counsel on this issue, but their knowledge and attitudes vary substantially by professional setting and career stage. **What does this article add to our knowledge?** Applying latent class analysis to a national survey of 250 Italian pediatricians, this study identifies three career-stage-defined attitudinal profiles; professional experience and age are the strongest discriminators of e-cigarette knowledge and counselling behavior. **How does this study impact current management guidelines?** The three-class structure suggests a single educational intervention is insufficient; differentiated, career-stage-tailored training is needed to align all pediatricians with AAP, EAP, and SIMRI counselling recommendations on e-cigarettes.

INTRODUCTION

The use of electronic cigarettes (e-cigarettes) among adolescents has grown sharply over the past decade, raising serious concerns for public health. Global estimates counted approximately 68 million e-cigarette users in 2020 and around 80 million by 2023, with higher prevalence in high-income countries (1). In Italy, the proportion of adolescents aged 11-17 who reported e-cigarette use more than doubled between 2014 and 2018, rising from 9.1% to 18.3% (2, 3). E-cigarettes are increasingly used alongside conventional cigarettes (CC) and heated tobacco products (HTP), with many adolescent users reporting concurrent use of two or more products (2).

Risk perception is a key driver of this trend. Studies conducted in Europe, North America, and India consistently show that a substantial proportion of adolescents consider e-cigarettes safer than CC, perceive the aerosol as harmless water vapor, and underestimate the addictive potential of nicotine (4-6). This distorted risk perception is reinforced by targeted marketing, social media exposure, and the wide availability of flavored products designed to appeal to young users (7). Available evidence documents associations between e-cigarette use and respiratory symptoms, airway inflammation, nicotine dependence, and, via the gateway effect, subsequent initiation of conventional smoking (4, 8-15).

In 2018, the Forum of International Respiratory Societies issued a position statement specifically addressing electronic cigarette use in youths, recommending that these products be regulated as tobacco products and their sale barred to minors worldwide (16).

Pediatricians are well positioned to address this issue. They maintain regular contact with children, adolescents, and their families, and are expected to screen for tobacco and nicotine use, provide counselling, and promote risk awareness (17-19). The American Academy of Pediatrics recommends universal screening and preventive counselling on e-cigarette use for both patients and parents (17); the European Academy of Pediatrics has similarly issued specific guidance for clinical practice (18). More recently, the Italian Pediatric Respiratory Society (SIMRI) published a comprehensive position statement outlining ten recommendations to protect children from vaping exposure (19), whose relevance for clinical practice has been underlined in an accompanying editorial (20).

Yet the international literature documents considerable heterogeneity in pediatricians' knowledge and attitudes towards e-cigarettes. Surveys conducted in Jordan, Poland, Turkey, and the United States report that many physicians lack adequate training on e-cigarettes during their undergraduate education, source information primarily from non-scientific channels, and show ambivalence about whether to recommend e-cigarettes as a harm-reduction strategy (21-23). These knowledge gaps may limit the quality of counselling provided and reduce practitioners' confidence in discussing e-cigarettes with patients (21-23). E-cigarettes are not currently recognized by the FDA or WHO as smoking cessation tools, given insufficient evidence (24-26), and this ambiguity appears to compound clinical uncertainty.

Against this background, characterizing the heterogeneity within the Italian pediatrician workforce is a necessary step towards designing targeted educational interventions. A previous Italian study by Cilluffo *et al*. applied latent class analysis to a nationally distributed survey of pediatricians within the GARD-Italy Demonstration Project, identifying three distinct profiles of barriers and incentives for smoking cessation counselling (27). Building on this methodological approach, the present study used latent class analysis (LCA) to identify distinct knowledge and attitudinal profiles among Italian pediatricians, and to determine which variables most strongly discriminate between groups.

MATERIALS AND METHODS

Study design and objectives

This cross-sectional observational study was conducted via an anonymous online survey to investigate the awareness among Italian pediatricians of the respiratory health risks associated with electronic cigarettes. The primary objective was to identify distinct profiles based on knowledge of e-cigarettes. The secondary objective was to identify the variables that best discriminate between the identified groups.

Survey development and distribution

A 27-item questionnaire was designed and distributed via the SIMRI national newsletter. The questionnaire was organized into three sections. The first collected the pediatrician's professional profile. The second addressed personal smoking habits. The third investigated knowledge, risk perception, awareness of key concepts (*e.g.*, the "gateway" effect), opinions on regulatory policies, perceived training, and how pediatricians discuss e-cigarettes with children, adolescents, and families. The survey was administered on Google Forms from April to October 2025. Participation was voluntary and took about 5 minutes. All responses were collected anonymously and stored securely for analysis.

Data analysis and statistical methods

We used descriptive statistics to summarize the participants' demographic and clinical characteristics. We reported the frequencies and percentages for categorical variables and mean ± standard deviation (SD) for continuous variables. Before the latent class analysis, respondents with more than 30% missing values across the indicator set were excluded from the modelling sample; for the remaining respondents, residual missing values were imputed using the median for ordinal and continuous variables and the mode for categorical variables.

Overview of latent class analysis

Latent class analysis is a form of finite mixture modelling that identifies unobserved subgroups within a population based on patterns of responses to categorical indicators (4). The underlying assumption is that the observed distribution of responses arises from a mixture of a finite number of latent classes, each characterized by distinct conditional response probabilities (4). Unlike traditional cluster analysis, which relies on distance metrics, LCA is model-based and provides statistical fit indices for determining the optimal number of classes (4). Once the model is fitted, posterior probabilities quantify each respondent's likelihood of belonging to each class. Individuals are usually assigned to the class with the highest posterior probability, although membership remains probabilistic (4).

Estimation via the expectation-maximization algorithm

Parameter estimation in LCA was conducted using the Expectation-Maximization (EM) algorithm. The EM algorithm is an iterative procedure designed to find maximum likelihood estimates in models with unobserved variables (5). Starting from random initial values for the class proportions and item-response probabilities, the algorithm alternates between two steps:

1) E-step: Given current parameter estimates, the posterior probability that each respondent belongs to each latent class is computed.
2) M-step: Parameters are updated by maximizing the expected complete-data log-likelihood with respect to the class membership probabilities computed in the E-step (5).

Each iteration increases the likelihood, guaranteeing convergence to a local maximum (5). In this study, the EM algorithm was implemented in Python 3.11 using the numpy and scipy.stats libraries (custom code, available from the corresponding author upon reasonable request). For each candidate model, initial class proportions and class-specific item-response probabilities were drawn at random from a Dirichlet distribution with uniform concentration parameters ($\alpha = 1$). The EM updates continued until the absolute change in the log-likelihood between successive iterations fell below a tolerance of 1 × 10^{-6} or a maximum of 200 iterations was reached, whichever occurred first. Each candidate *K-class* model (*K* = 2-6) was fitted with a single Dirichlet-based random initialization and its log-likelihood, AIC, BIC, entropy and LMR-LRT p-value were stored for subsequent model comparison.

Model specification

Let *J* be the number of indicators and *K* the number of latent classes. For individual *i*, the joint probability of responses x_{ij} and class membership c_i is

$$p(x_{i,1},\ldots, x_{iJ}, c_i = k) = \pi_k \prod^{J}_{j,1} p_{jk}(x_{ij})$$

where π_k is the prior probability of belonging to class *k* (with $\sum^{k}_{k,1} \pi_k = 1$) and $p_{jk}(\cdot)$ is the class-specific probability distribution for indicator *J*. During the E-step, the posterior membership probability for class k is computed via Bayes' rule using current parameters. In the M-step, updated π_k values are obtained by averaging the posterior membership probabilities across individuals, and $p_{jk}(x)$ are updated by the expected relative frequencies of response categories within each class.

Determining the number of latent classes

Models with two to six latent classes were fitted. Model fit and parsimony were compared using several criteria:

1) Bayesian Information Criterion (BIC): as outlined by Nylund-Gibson *et al*., the BIC is one of several information criteria used to evaluate LCA models; it penalizes model complexity and recommends selecting the model with the lowest BIC (28). In practice, researchers may plot BIC values across different class solutions and look for an “elbow” where adding further classes yields diminishing reductions in BIC (28).
2) Entropy: it measures the certainty of classification; values near zero indicate that individuals have similar posterior probabilities across classes, whereas values approaching one denote clear separation. Low entropy across all models suggests overlapping response patterns.
3) Lo-Mendell-Rubin adjusted likelihood-ratio test (LMR-LRT): this test compares a model with *K* classes to a model with *K-1* classes; a significant P-value suggests that the *K-class* model provides a significantly better fit. Nylund-Gibson *et al*. noted that if the P-value is non-significant, the simpler model is preferred (28).
4) Akaike Information Criterion (AIC): although not explicitly discussed in the document, AIC is another information criterion computed as *-2×log likelihood+* × *d*, where *d* is the number of estimated parameters. Lower AIC values indicate better trade-off between fit and complexity. Both AIC and BIC were used to rank models.

The BIC indicated that the three-class solution achieved the best balance between fit and parsimony, despite the five-class model having a slightly lower AIC. Entropy values were uniformly low (<0.05), indicating that the classes are not sharply distinct; however, the three-class model still offered interpretable groupings.

Variable importance

To assess the discriminative power of each indicator, a variable importance metric was computed. For each variable *j*, the analysis calculated the maximum difference between the highest and lowest conditional response probabilities across classes. Formally,

$$Importance(j) = max_k (max_x p_{jk}(x) - min_x p_{jk}(x))$$

where $p_{jk}(x)$ denotes the probability of responding *x* to indicator *j* given class *k*. Variables with larger importance values exhibit greater variability in response probabilities across classes and thus better discriminate between latent groups. For example, the discretized years of practice variable showed the highest importance (1.00), while age and several items related to discussing electronic cigarette use with patients also ranked highly.

RESULTS

Study population

The survey was completed by 250 Italian pediatricians. The majority of respondents were over 40 years of age (55.2%) and female (80.4%). Most of the sample had been practicing for over 10 years (57.2%), 20.0% had been practicing for 5-10 years, 18.8% had been practicing for less than 5 years, and 4.0% prefer not to answer. Participants were geographically located throughout Italy, with 67.2% working in the North, 19.6% in the South, and 13.2% in Central Italy. Work contexts ranged widely: most of the sample worked as Primary Care Pediatricians (42.0%) or in Pediatric Specialty Hospitals (42.0%), while the remainder worked as Local Pediatricians (2.8%) or in General Hospitals (13.2%), consistent with **Table 1**. In the Italian National Health Ser-

***Table 1**. Demographic characteristics and lifestyle of the pediatricians.*

	Total (n = 250)
Age, mean (± SD)	45.42 (± 12.32)
Gender	
Female, n (%)	201 (80.4%)
Male, n (%)	49 (19.6%)
Years of professional experience	
< 5 years, n (%)	47 (18.8%)
5 - 10 years, n (%)	50 (20.0%)
10 - 15 years, n (%)	27 (10.8%)
15 - 20 years, n (%)	22 (8.8%)
≥ 20 years, n (%)	94 (37.6%)
Prefer not to answer, n (%)	10 (4.0%)
Region of work	
North of Italy, n (%)	168 (67.2%)
Center of Italy, n (%)	33 (13.2%)
South of Italy, n (%)	49 (19.6%)
Work setting	
Primary care pediatricians, n (%)	105 (42.0%)
Local pediatricians, n (%)	7 (2.8%)
General hospital, n (%)	33 (13.2%)
Pediatric specialty hospital, n (%)	105 (42.0%)
Conventional cigarette smoker	
Yes, n (%)	6 (2.4%)
No, n (%)	217 (86.8%)
Ex-smoker, n (%)	27 (10.8%)
E-cigarette smoker	
Yes, n (%)	9 (3.6%)
No, n (%)	239 (95.6%)
Ex-smoker, n (%)	2 (0.8%)
Both smoker	
Yes, n (%)	0 (0.0%)
No, n (%)	247 (98.8%)
Ex-smoker, n (%)	3 (1.2%)

vice, Primary Care Pediatricians (Pediatri di Famiglia) are individually assigned to children aged 0-14 years and serve as their principal healthcare provider, delivering routine care, preventive visits, and first-line management of acute and chronic conditions. Local Pediatricians (Pediatri Territoriali), by contrast, are employed by the Local Health Authority (ASL) and operate within community health services, where they focus on developmental screening, vaccination programmes, school health activities, and public health interventions rather than individual patient follow-up. The demographic characteristics and smoking lifestyle of the pediatricians are shown in **Table 1** and **Table 2**.

Model selection and fit criteria

The latent class analysis was executed using an expectation-maximization (EM) algorithm that alternated between estimating posterior class membership probabilities for each individual and updating the class-specific item-response probabilities until convergence. Models with two to six latent classes were fitted, and their relative adequacy was assessed using Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), entropy, and the Lo-Mendell-Rubin likelihood ratio test (LMR-LRT). These fit statistics balance model complexity against goodness of fit and can suggest the most plausible number of classes when interpreted jointly.

Table 3 summarizes the model fit indices reported in the document. The BIC reached its minimum with the three-class model, whereas the AIC continued to decrease slightly until the five-class solution. Entropy values were uniformly low (<0.05), signaling that the separation between latent classes was modest. The LMR-LRT P-values were significant for transitions from two to three classes and from four to five classes but not for the other comparisons. Taken together, these criteria led the authors to select the three-class solution, prioritizing parsimony and interpretability over marginal improvements in AIC.

Figure 1 visualizes the AIC and BIC trajectories across the models. The plot shows a pronounced decrease in AIC up to five classes but a sharp inflection in BIC at three classes. The low entropies across all solutions caution that even the selected model likely features overlapping response patterns, and class assignments should be interpreted probabilistically rather than deterministically.

Class proportions and profiles

The chosen three-class model yielded the following class membership proportions: Class 1 – 63 respondents (≈25%), Class 2 – 97 respondents (≈39%) and Class 3 – 90 respondents (≈36 %). These proportions indicate that no single latent class dominates the sample; instead, the distribution is relatively balanced, allowing meaningful comparison across groups. Posterior probabilities of class membership were used to assign individuals to classes for descriptive purposes, though

Table 2. *Demographic characteristics by smoke habits [n (%)].*

	Conventional cigarette smoker	E-cigarette smoker	Both smoker
Years of professional experience			
< 5 years	1 (16.7%)	1 (11.1%)	0 (0%)
5 - 10 years	1 (16.7%)	2 (22.2%)	0 (0%)
10 - 15 years	0 (0%)	3 (33.3%)	0 (0%)
15 - 20 years	0 (0%)	0 (0%)	0 (0%)
≥ 20 years	4 (66.7%)	2 (22.2%)	0 (0%)
Prefer not to answer	0 (0%)	1 (11.11%)	0 (0%)
Work Setting			
Primary care pediatricians	1 (16.7%)	0 (0%)	0 (0%)
Local pediatricians	0 (0%)	0 (0%)	0 (0%)
General hospital	2 (33.3%)	3 (33.3%)	0 (0%)
Pediatric specialty hospital	3 (50%)	6 (66.7%)	0 (0%)
Region of Work			
North of Italy	4 (66.7%)	4 (44.4%)	0 (0%)
Center of Italy	0 (0%)	0 (0%)	0 (0%)
South of Italy	2 (33.3%)	5 (55.6%)	0 (0%)
Gender			
Female	4 (66.7%)	5 (55.6%)	0 (0%)
Male	2 (33.3%)	4 (44.4%)	0 (0%)

Table 3. *Model fit statistics for latent class solutions.*

Numbers of classes	AIC	BIC	Entropy	P-value LMR-LRT
2	9,968.31	10,556.39	0.0360	-
3	9,613.39	**10,497.28**	0.0373	0.0000
4	10,010.63	11,190.32	0.0021	1.0000
5	**9,466.36**	10,941.85	0.0356	0.0000
6	9,580.17	11,351.47	**0.0436**	0.9953

The numbers in bold represent the AIC, BIC, and entropy values used to determine the correct number of classes identified by the model. For AIC and BIC, the lowest value returned by the model should be used; for entropy, the highest value should be used.

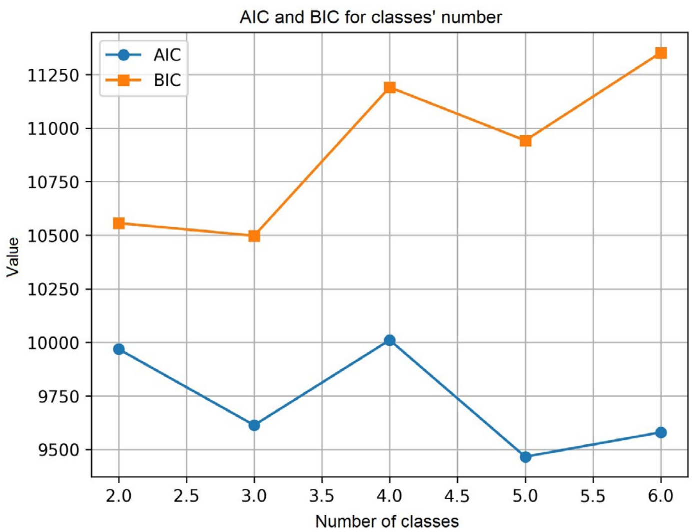

Figure 1. *AIC and BIC values plotted against the number of latent classes.*

While AIC suggests improved fit up to five classes, BIC reaches its minimum at three classes, favoring parsimony.

the low entropy implies that some individuals had similar probabilities across multiple classes.

Class 1 tended to include the most senior and experienced pediatricians, with class-conditional probabilities that most strongly distinguished this group from the others on seniority-related indicators. On average, respondents assigned to this class had a mean age exceeding 60 years and had worked in the profession for over three decades. On indicators related to cigarette smoking, the class-conditional probabilities showed a relative concentration of the few respondents who smoked traditional cigarettes. Respondents in this class had a lower probability of reporting exposure to educational material on electronic cigarettes and showed a higher class-conditional probability of being less inclined to initiate discussions about e-cigarette use with adolescent patients. Taken together, the response pattern of this class is consistent with a generally more conservative stance towards reduced-risk nicotine products and potentially more limited exposure to contemporary cessation strategies, though individual members may depart from this overall pattern.

Class 2 was more frequently composed of mid-career pediatricians around their early forties, with approximately 13.5 years of professional experience. On the counselling-related indicators, their class-conditional response probabilities were consistent with greater confidence in discussing electronic cigarettes with patients and reported more frequent engagement in conversations about e-cigarette use during adolescent consultations. On risk-perception items, class-conditional probabilities showed a relatively higher likelihood of viewing electronic cigarettes as potentially useful for smoking cessation, while still acknowledging their risks. This mixed pattern of openness and caution is suggestive, rather than definitive, of more nuanced attitudes within this group and should be read in light of the overall low entropy.

Class 3, the youngest group, showed a relative concentration of early-career pediatricians with a mean age under 40 years and less than a decade of practice. Although they were closer in age to many adolescent patients, they reported lower confidence in discussing electronic cigarette issues and tended to perceive these devices as less harmful than traditional cigarettes. Overall, the response pattern in this class is consistent with a combination of youth, limited experience and lower perceived risk, and points to a possible gap in training rather than to a sharply bounded subgroup; it nevertheless supports the potential value of targeted educational interventions for early-career pediatricians.

The narrative profiles above provide qualitative interpretation of the quantitative findings. They should, however, be viewed in light of the overall low entropy, which signifies that class differences are subtle rather than stark. Individual pediatricians may share characteristics of more than one class, and the classes should be considered as conceptual guides rather than rigid categories.

Model fit indices

Beyond the AIC and BIC, we obtained entropy and LMR-LRT P-values for each model. Entropy measures the certainty with which individuals can be assigned to latent classes, with values close to one indicating clear separation. In this analysis, entropy ranged between 0.0021 and 0.0436 across models with two to six classes (**Table 2**). Such low values suggest that the posterior membership probabilities were diffuse: respondents often had comparable probabilities of belonging to multiple classes. This result emphasizes that the latent structure explains only a small portion of the variability in response patterns and underscores the importance of reporting uncertainty when classifying individuals.

The Lo-Mendell-Rubin (LMR) likelihood ratio test compares models with k and $k - 1$ classes to determine whether adding another class significantly improves fit. According to **Table 3**, the P-value for the transition from two to three classes was 0.0000, indicating a significant improvement in fit. Conversely, the P-value for the transition from three to four classes was 1.0000, suggesting no meaningful improvement; for the transition from four to five classes the P-value was 0.0000, but the subsequent comparison to six classes yielded 0.9953, indicating again no significant improvement. These alternating results align with the contradictory signals from AIC and BIC, highlighting how the choice of model requires balancing statistical criteria with interpretability. Ultimately, the three-class solution provided a parsimonious representation that captured the major differences in the sample without overfitting.

Variable importance and discriminative power

To identify which variables most strongly differentiated between latent classes, the authors calculated, for the selected three-class model, the maximum difference in conditional response probabilities across classes for each variable. This statistic indicates how much the probability of a given response differs between the class with the highest probability and the class with the lowest probability for that response. Variables with larger differences possess greater discriminative power and thus contribute more to defining the latent structure.

Table 4 lists the nine variables with the highest discriminative importance. The duration of professional practice variable ("How long have you been doing your profession?") achieved the maximum possible importance value (1.00), confirming that seniority is the principal

***Table 4**. Top nine discriminative variables in the three-class model.*

Variable	Importance
How long have you been doing your profession?	1.00
Age	0.86
During conversations with patients, discuss the topic of e-cigarette smoking?	0.70
As a healthcare professional, do you feel confident discussing issues related to e-cigarettes with patients?	0.64
E-cigarettes are less dangerous than traditional cigarettes?	0.53
In your clinical practice, have you ever encountered and/or confirmed adverse events related to active smoking of e-cigarettes?	0.50
Have you ever asked your patients and/or their families if they smoke e-cigarettes?	0.50
The risk of chronic lung disease is lower for e-cigarettes than for traditional cigarettes?	0.45
What kind of structure do you work in?	0.44

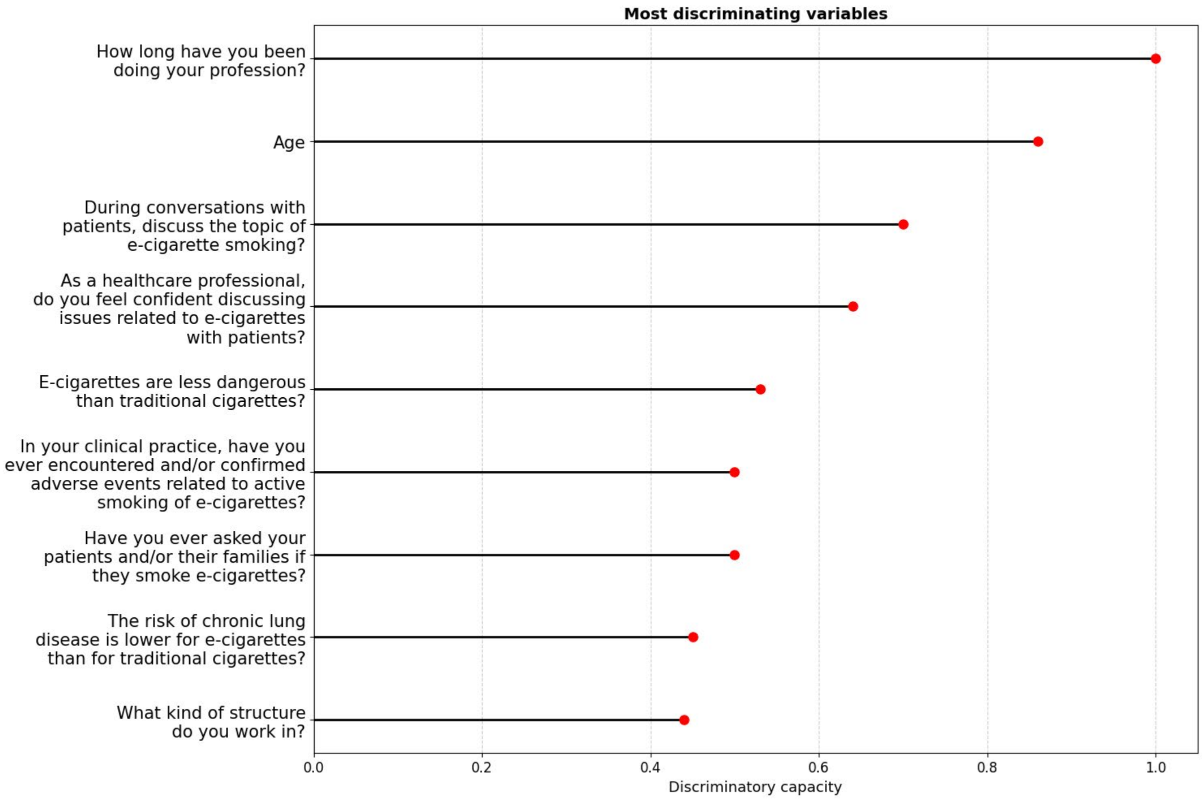

***Figure 2**. Plot of the top nine variables contributing to class discrimination.*

The horizontal axis displays the discriminative importance, defined as the maximal difference in conditional response probabilities across classes. Larger values indicate greater separation.

driver of class separation. Age was also highly discriminative (importance = 0.86), consistent with the strong correlation between age and years in practice. Variables related to discussing electronic cigarette use with adolescents and confidence in addressing e-cigarette issues with patients ranked prominently, indicating that communication behaviors and self-efficacy contribute to class differences beyond mere demographics. Perceptions of the relative safety of electronic *versus* traditional cigarettes and experiences with adverse events also appeared among the top discriminators. Conversely, variables relating to the clinical setting ("What kind of structure do you work in?") had lower, though still meaningful, discriminative values.

These results, visualized in **Figure 2**, show that both demographic variables (age and years of practice) and attitudinal variables (perception of harm and communication practices) shape the latent grouping of pediatricians. The high importance of professional experience underscores how exposure to clinical practice and continuing education shapes practitioners' confidence and behavior regarding electronic cigarette counselling.

DISCUSSION

Before interpreting the three-class solution, it is important to emphasize that entropy values across all models were uniformly low (<0.05). Posterior membership probabilities were therefore diffuse, many respondents had comparable probabilities of belonging to more than one class, and the three classes should be read as broad, partially overlapping attitudinal tendencies rather than as sharply bounded, mutually exclusive subgroups. The class-specific profiles described below and their discussion in terms of age, experience, counselling behavior and risk perception thus refer to differences in class-conditional response probabilities, not to deterministic descriptions of individual pediatricians.

The combined evidence from model fit statistics, class profiles and variable importance analysis suggests that latent heterogeneity among the surveyed pediatricians is driven primarily by age and professional experience, with attitudinal and behavioral variables playing secondary but still meaningful roles. The relatively balanced class sizes mean that interventions aimed at improving knowledge and counselling practices could be tailored to specific career stages. For instance, senior pediatricians (Class 1) may benefit from updated training materials and guidance on the evolving evidence around electronic cigarettes to overcome conservative biases. Mid-career practitioners (Class 2) already display a proactive stance but could be supported with formalized communication strategies to ensure consistent messaging. Early-career pediatricians (Class 3) may require foundational education that addresses both the risks and potential cessation benefits of electronic cigarettes and builds confidence in discussing these topics with patients and families.

The low entropy values across all models highlight an important methodological caveat: the latent classes identified are not sharply delineated. This could reflect genuine complexity in pediatricians' attitudes, with many holdings nuanced or ambivalent positions that do not align neatly with distinct categories. It may also indicate that additional variables not captured in the questionnaire (*e.g.* exposure to specific training modules, institutional policies, or personal experiences with nicotine cessation) play a role in shaping attitudes. Future research could incorporate more granular measures of education and training, as well as longitudinal designs, to examine how attitudes towards emerging nicotine products evolve over time.

The findings of the present study align with and extend those reported in the international literature on healthcare providers' knowledge and attitudes towards electronic cigarettes. Surveys conducted in Jordan, Poland, and Turkey consistently documented substantial gaps in physicians' training on e-cigarettes, with many practitioners relying on non-scientific sources of information and holding ambivalent views on the role of these products in smoking cessation (21-23). The profile of Class 1 in our sample, characterized by greater clinical experience, lower engagement in e-cigarette counselling, and a more conservative stance towards reduced-risk nicotine products, is consistent with the pattern observed by Mohammad *et al.* among Jordanian physicians, where longer time since graduation was associated with lower confidence in discussing e-cigarettes with patients (21). Similarly, the ambivalence towards harm-reduction strategies observed in Class 2 mirrors findings by Tanriover *et al.* among Turkish family physicians, approximately half of whom considered e-cigarettes a viable cessation tool despite limited supporting evidence (23). The relatively higher engagement of mid-career practitioners in e-cigarette counselling in our sample is also broadly consistent with the pattern reported by Zgliczyński *et al*. in Poland, where younger physicians showed greater familiarity with e-cigarettes and greater willingness to discuss them with patients (22). Compared with these international surveys, the present study adds methodological value by applying latent class analysis rather than descriptive comparisons, enabling the identification of distinct attitudinal subgroups rather than aggregate means. This approach reveals heterogeneity that univariate analyses might obscure and provides a basis for profiling physicians in need of targeted educational intervention. The observation that Class 3, the youngest practitioners, reported lower perceived risk from e-cigarettes is consistent with evidence that younger cohorts have greater exposure to industry marketing and social-media content promoting e-cigarettes as safe alternatives (4, 7), and underscores the importance of integrating evidence-based e-cigarette content into undergraduate and postgraduate medical training. The current position statements from the American Academy of Pediatrics, the European Academy of Pediatrics, and the Italian Pediatric Respiratory Society all recommend systematic screening and counselling on tobacco and nicotine use (17-19); our results suggest that achieving this standard will require differentiated educational strategies across career stages.

Limitations

Like any study, this one has limitations worth acknowledging. Distribution through the IPRS/SIMRI newsletter may have introduced self-selection bias, potentially overestimating engagement with e-cigarette issues. The cross-sectional design prevents causal inference between career stage, knowledge, and counselling behavior; longitudinal studies would be needed to assess how attitudes evolve over time. Self-reported data carry an inherent risk of social desirability bias, particularly for items on clinical practice and perceived competence. Low entropy values in the latent class analysis suggest the findings reflect broad tendencies rather than mutually exclusive categories. The overrepresentation of northern Italy (67.2%) limits generalizability across different healthcare contexts. Future research should include general practitioners, adolescent medicine specialists, and school health professionals.

CONCLUSIONS

This study provides a novel characterization of Italian pediatricians' knowledge, attitudes, and counselling practices regarding electronic cigarettes. Applying LCA to a nationally distributed survey of 250 practitioners, we partially overlapping profiles structured primarily along the dimension of professional experience: senior pediatricians with conservative and less engaged stances (Class 1), mid-career practitioners exhibiting greater openness and counselling confidence (Class 2), and early-career pediatricians with lower perceived risk and reduced self-efficacy in discussing e-cigarettes with patients (Class 3). Years of practice and age were the strongest discriminators between classes, followed by communication behaviors and risk perceptions, confirming that career stage is a central axis of heterogeneity in this professional group.

These findings may carry direct implications for the design of continuing medical education programmes. The three-class structure suggests that a single, undifferentiated educational intervention is unlikely to be adequate. Senior pediatricians may require targeted updates on emerging evidence regarding e-cigarette harms and the current regulatory and clinical guidance issued by the American Academy of Pediatrics, the European Academy of Pediatrics, and the Italian Pediatric Respiratory Society (17-19). Early-career practitioners, despite their proximity in age to the adolescent populations they serve, appear to underestimate e-cigarette risks and lack confidence in counselling, a gap that should be addressed through dedicated content in undergraduate and postgraduate medical curricula. Mid-career pediatricians, while more proactive, would benefit from structured communication tools to ensure that the information conveyed to patients and families is consistent, evidence-based, and aligned with current clinical recommendations. Given the continued rise in e-cigarette use among Italian adolescents (2, 6), strengthening the capacity of pediatricians across all career stages to screen, counsel, and refer is an urgent public health priority.

Future research should replicate this profiling approach in larger and more geographically representative samples, incorporate objective measures of knowledge alongside self-reported attitudes, and examine the extent to which targeted educational interventions shift practitioners between attitudinal classes over time. Extending the analysis to general practitioners, school health professionals, and adolescent medicine specialists would broaden the evidence base and support the development of coordinated, multi-professional strategies for reducing youth e-cigarette initiation in Italy.

ACKNOWLEDGEMENTS

The authors wish to thank the Italian Pediatric Respiratory Society (IPRS/SIMRI) for facilitating the distribution of the survey through its national newsletter, and all the Italian pediatricians who gave their time to participate in the study.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

The authors declare no conflicts of interest.

Financial support

None.

Author contributions

SR, AP, SLG, MG: conceptualization. SR, AP: data curation, visualization, writing – original draft. AP: formal analysis. SR, AP, MEDC: investigation. SR, AP, SLG, MG: methodology. SLG, MG: project administration, supervision. SR, AP, MEDC, SLG, MG: writing – review & editing.

Ethical approval

Human studies and subjects

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. In accordance with Italian law (Legislative Decree 211/2003 and subsequent amendments), studies based exclusively on anonymous questionnaires administered to healthcare professionals, involving no intervention, no collection of biological samples, and no processing of sensitive personal data, are exempt from formal ethical committee review. Participation in the survey was entirely voluntary. No personally identifiable information was collected at any stage of the study. Completion and submission of the questionnaire were considered to constitute implicit informed consent to participate. All data were stored securely and used solely for the purposes of this research.

Data sharing and data accessibility

The data presented in this study are not publicly available due to privacy and confidentiality constraints. The survey was conducted anonymously, and respondents were assured that their responses would not be shared beyond the research team. Data may be made available upon reasonable request to the corresponding author, subject to applicable data protection regulations.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

REFERENCES

1. Jerzyński T, Stimson GV, Shapiro H, Król G. Estimation of the global number of e-cigarette users in 2020. Harm Reduct J. 2021;18(1):109. doi:10.1186/s12954-021-00556-7.
2. Tarasenko Y, Ciobanu A, Fayokun R, Lebedeva E, Commar A, Mauer-Stender K. Electronic cigarette use among adolescents in 17 European study sites: findings from the Global Youth Tobacco Survey. Eur J Public Health. 2022;32(1):126-32. doi:10.1093/eurpub/ckab180.
3. Simpson EEA, Davison J, Doherty J, Dunwoody L, McDowell C, McLaughlin M, et al. Employing the theory of planned behaviour to design an e-cigarette education resource for use in secondary schools. BMC Public Health. 2022;22(1):276. doi:10.1186/s12889-022-12674-3.
4. Pepper JK, Brewer NT. Electronic nicotine delivery system (electronic cigarette) awareness, use, reactions and beliefs: a systematic review. Tob Control. 2014;23(5):375-84. doi: 10.1136/tobaccocontrol-2013-051122.
5. Khambayat S, Jaiswal A, Prasad R, Wanjari MB, Sharma R, Yelne S. Vaping among adolescents: an overview of e-cigarette use in middle and high school students in India. Cureus. 2023;15(5):e38972. doi: 10.7759/cureus.38972.
6. Gorini G, Gallus S, Carreras G, De Mei B, Masocco M, Faggiano F, et al. Prevalence of tobacco smoking and electronic cigarette use among adolescents in Italy: Global Youth Tobacco Surveys (GYTS), 2010, 2014, 2018. Prev Med. 2020;131:105903. doi: 10.1016/j.ypmed.2019.105903.
7. Mantey DS, Cooper MR, Clendennen SL, Pasch KE, Perry CL. E-cigarette marketing exposure is associated

with e-cigarette use among US youth. J Adolesc Health. 2016;58(6):686-90. doi: 10.1016/j.jadohealth.2016.03.003.

8. U.S. Department of Health and Human Services. E-cigarette use among youth and young adults: a report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention; 2016.
9. Mendelsohn CP, Hall W. What are the harms of vaping in young people who have never smoked? Int J Drug Policy. 2023;117:104064. doi: 10.1016/j.drugpo.2023.104064.
10. Cherian C, Buta E, Simon P, Gueorguieva R, Krishnan-Sarin S. Association of vaping and respiratory health among youth in the Population Assessment of Tobacco and Health (PATH) study wave 3. Int J Environ Res Public Health. 2021;18(15):8208. doi: 10.3390/ijerph18158208.
11. Wang MP, Ho SY, Leung LT, Lam TH. Electronic cigarette use and respiratory symptoms in Chinese adolescents in Hong Kong. JAMA Pediatr. 2016;170(1):89-91. doi: 10.1001/jamapediatrics.2015.3024.
12. McConnell R, Barrington-Trimis JL, Wang K, Urman R, Hong H, Unger J, et al. Electronic cigarette use and respiratory symptoms in adolescents. Am J Respir Crit Care Med. 2017;195(8):1043-9. doi: 10.1164/rccm.201604-0804OC.
13. Alnajem A, Redha A, Alroumi D, Alshammasi A, Ali M, Alhussaini M, et al. Use of electronic cigarettes and secondhand exposure to their aerosols are associated with asthma symptoms among adolescents: a cross-sectional study. Respir Res. 2020;21(1):300. doi: 10.1186/s12931-020-01569-9.
14. Cho JH, Paik SY. Association between electronic cigarette use and asthma among high school students in South Korea. PLoS One. 2016;11(3):e0151022. doi: 10.1371/journal.pone.0151022.
15. England LJ, Bunnell RE, Pechacek TF, Tong VT, McAfee TA. Nicotine and the developing human: a neglected element in the electronic cigarette debate. Am J Prev Med. 2015;49(2):286-93. doi: 10.1016/j.amepre.2015.01.015.
16. Ferkol TW, Farber HJ, La Grutta S, Leone FT, Marshall HM, Neptune E, et al. Electronic cigarette use in youths: a position statement of the Forum of International Respiratory Societies. Eur Respir J. 2018;51(5):1800278. doi: 10.1183/13993003.00278-2018.
17. Section on Tobacco Control. Clinical practice policy to protect children from tobacco, nicotine, and tobacco smoke. Pediatrics. 2015;136(5):1008-17. doi: 10.1542/peds.2015-3108.
18. Bush A, Lintowska A, Mazur A, Hadjipanayis A, Grossman Z, del Torso S, et al. E-cigarettes as a growing threat for children and adolescents: position statement from the European Academy of Paediatrics. Front Pediatr. 2021;9:698613. doi: 10.3389/fped.2021.698613.
19. Di Cicco ME, Ghezzi M, Beni A, Borghi A, Carraro S, Ferraro M, et al. Vaping as a new threat for respiratory health: a position statement from the Italian Pediatric Respiratory Society. Pediatr Respir J. 2025;3(3):112-25. doi: 10.56164/PediatrRespirJ.2025.76.
20. Tsikrika S, Cox DW; on behalf of the ERS Tobacco Control Committee. What dangers does vaping pose to children's health? Pediatr Respir J. 2025;3(3):100-2. doi: 10.56164/PediatrRespirJ.2025.73.
21. Mohammad H, Nassrawin S, Alhyasat A, AlMuhaissen S. Physicians, pharmacists, and dentists' knowledge and attitudes toward the use of electronic cigarettes. Clin Epidemiol Glob Health. 2023;24:101443. doi: 10.1016/j.cegh.2023.101443.
22. Zgliczyński WS, Jankowski M, Rostkowska O, Gujski M, Wierzba W, Pinkas J. Knowledge and beliefs of e-cigarettes among physicians in Poland. Med Sci Monit. 2019;25:6322-30. doi: 10.12659/MSM.916920.
23. Tanriover O, Hidiroglu S, Ay P, Cook RL. Do family physicians perceive electronic cigarette use as a harm reduction strategy for smokers? A survey from Istanbul. Prim Health Care Res Dev. 2022;23:e15. doi: 10.1017/S1463423622000056.
24. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. N Engl J Med. 2019;380(7):629-37. doi: 10.1056/NEJMoa1808779.
25. Chan GCK, Stjepanović D, Lim C, Sun T, Shanmuga Anandan A, Connor JP, et al. A systematic review of randomized controlled trials and network meta-analysis of e-cigarettes for smoking cessation. Addict Behav. 2021;119:106912. doi: 10.1016/j.addbeh.2021.106912.
26. Hussain S, Shahid Z, Foroozesh MB, Sofi U. E-cigarettes: a novel therapy or a looming catastrophe. Ann Thorac Med. 2021;16(1):73-80. doi: 10.4103/atm.ATM_190_20.
27. Cilluffo G, Ferrante G, Cutrera R, Piacentini G, Bignamini E, Landi M, et al. Barriers and incentives for Italian paediatricians to become smoking cessation promoters: a GARD-Italy Demonstration Project. J Thorac Dis. 2020;12(Suppl 2):S165-83. doi: 10.21037/jtd-gard-20-003.
28. Nylund-Gibson K, Garber AC, Carter DB, Chan M, Arch DAN, Simon O, et al. Ten frequently asked questions about latent transition analysis. Psychol Methods. 2023;28(2):284-300. doi: 10.1037/met0000486.

Vol. 4(2), 86-95, 2026

POSITION PAPER

Position paper on aerosol therapy in childhood: a statement proposed by the SIMRI Asthma Committee and approved by the SIMRI Advocacy Council and Executive Committee

Grazia **Fenu** [1,*], Maria Elisa **Di Cicco** [2],
Giuliana **Ferrante** [3], Raffaella **Nenna** [4], Federica **Porcaro** [5], Stefania **La Grutta** [6],
SIMRI Advocacy Council [†] and Executive Committee [‡]

[*] **Correspondence to:**
grazia.fenu@meyer.it; ORCID: https://orcid.org/0000-0002-4360-8417

Doi
10.56164/PediatrRespirJ.2026.11

[1] Pulmonology Unit, Department of Pediatrics Specialties, Meyer Children's Hospital, IRCCS, Florence, Italy
[2] Department of Clinical and Experimental Medicine, Section of Pediatrics, University of Pisa, Pisa, Italy
[3] Pediatric Division, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Verona, Italy
[4] Department Maternal Infantile and Urological Sciences, Sapienza University of Rome, Rome, Italy
[5] Pediatric Pulmonology and Cystic Fibrosis Unit, Respiratory Research Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
[6] National Research Council (CNR), Institute of Translational Pharmacology (IFT), Palermo, Italy
[†] Giampaolo **Ricci**, Sabrina **Di Pillo**, Paola **Di Filippo**, Barbara **Madini**, Sergio **Ghirardo**, Laura **Petrarca**, Alessandra **Boni**, Valentina **Fainardi**, Marina **Attanasi**
[‡] Stefania **La Grutta**, Enrico **Lombardi**, Giovanni **Pompeo Ciccarone**, Amelia **Licari**, Sara **Manti**, Raffaella **Nenna**, Giuseppe Fabio **Parisi**, Nicola **Ullmann**, Pierluigi **Vuilleumier**

ABSTRACT

Aerosol therapy represents a cornerstone in the management of respiratory diseases in pediatric patients. By enabling the direct delivery of medications to the airways, this modality ensures a rapid onset of action while minimizing systemic side effects. It is particularly valuable in the treatment of conditions commonly affecting children, such as recurrent wheezing, asthma, and croup, as well as orphan or complex diseases including cystic fibrosis, primary ciliary dyskinesia (PCD), and post-infectious bronchiectasis.

In pediatric practice, aerosol therapy offers several advantages, including improved therapeutic efficacy at lower doses and superior tolerability compared with systemic administration. However, the clinical effectiveness of this intervention is contingent upon multiple factors, such as the patient's age and degree of cooperation, respiratory pattern, and the appropriate selection and correct utilization of inhalation devices. Consequently, comprehensive education for both caregivers and healthcare professionals is essential to optimize therapeutic delivery and clinical outcomes. Overall, aerosol therapy is a safe, effective, and widely used strategy in pediatric respiratory management, contributing significantly to symptom control and quality of life in both acute and chronic conditions.

This statement summarizes current evidence and presents the official recommendations of the Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili – SIMRI) to guide best practices for aerosol therapy throughout childhood.

IMPACT STATEMENT

This statement optimizes pediatric aerosol therapy by promoting evidence-based indications and appropriate delivery devices, thereby enhancing clinical efficacy, reducing unnecessary healthcare costs, and minimizing caregiver burden in respiratory disease management.

KEY WORDS
Aerosol therapy; nebulizer; pMDI; dry powder inhaler; pediatrics.

INTRODUCTION

Aerosol therapy constitutes a cornerstone of pediatric respiratory medicine, providing an efficient route for the targeted delivery of pharmacological agents to the air-

 |

ways while limiting systemic exposure. It plays a pivotal role in the management of conditions such as recurrent wheezing, asthma, croup, cystic fibrosis (CF), and other obstructive airway diseases in the pediatric population. However, despite decades of clinical application, the practice of aerosol therapy in childhood remains highly variable. Discrepancies in device selection, inhalation techniques, and clinical protocols continue to impact therapeutic outcomes across different age groups and healthcare settings (1).

Pediatric patients exhibit unique physiological and developmental characteristics that influence aerosol delivery and lung deposition. Compared with adults, children possess smaller airway calibers, higher respiratory rates, and variable inspiratory flow patterns, all of which affect the distribution and deposition efficiency of inhaled particles (2). In infants and preschool-aged children, limited cooperation and suboptimal inhalation coordination often necessitate caregiver intervention and the use of dedicated interfaces, such as valved holding chambers (VHCs) with face masks (3). Consequently, age-specific strategies are essential to ensure optimal drug delivery, treatment adherence, and therapeutic efficacy (4).

Technological advancements have broadened the range of delivery systems available for pediatric aerosol therapy (5). These include pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and various nebulizer platforms. Each device has distinct aerosol-generation mechanisms, output rates, and performance profiles that dictate its suitability for specific patient cohorts and clinical scenarios. Nevertheless, current evidence documents frequent inconsistencies in device utilization, cleaning, and maintenance, which may lead to suboptimal drug deposition and an increased risk of infection (1).

Education and practical training remain fundamental determinants of successful aerosol therapy. Research consistently demonstrates that the implementation of correct techniques and regular reinforcement can significantly enhance pulmonary deposition, symptom control, and overall disease management (6, 7). However, a substantial proportion of healthcare professionals responsible for prescribing inhalation devices may lack adequate training in device-specific administration techniques (8).

Structured and consistent educational programs are equally vital for caregivers. Regular competency assessments, practical demonstrations, and feedback sessions are instrumental in maintaining correct inhalation practices, thereby mitigating the long-term variability observed in clinical outcomes and maximizing treatment efficacy. Despite the existence of various national and international guidelines, a single, universally accepted protocol for aerosol therapy across all pediatric age groups remains elusive. Disparities in recommendations concerning device selection, pharmacological agents, and delivery techniques contribute to clinical uncertainty and heterogeneous care (9). This lack of harmonization underscores the imperative for an updated, evidence-based consensus that integrates contemporary research findings with practical, age-appropriate guidance.

The objective of this position paper is to establish a scientifically grounded and clinically coherent framework for the use of aerosol therapy in childhood. By synthesizing current evidence on aerosol delivery systems, pharmacological principles, and patient-specific determinants of response, this document seeks to define unified standards to enhance the effectiveness, safety, and appropriateness of treatment. The standardization of pediatric aerosol therapy practices is expected to improve individual clinical outcomes, facilitate equitable access to high-quality respiratory care, and promote cost-effective management strategies on an international scale.

METHODOLOGY

Panel composition and scope

This position paper was commissioned by the Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili – SIMRI). A panel of experts, comprising pediatric pulmonologists and researchers with extensive clinical and academic expertise, was convened during the XXIX SIMRI National Congress (Verona, September 2025). The primary objective was to establish evidence-based recommendations to standardize aerosol therapy practices in the pediatric population, thereby addressing the current lack of national guidelines and the heterogeneity of clinical approaches within Italy.

Literature search strategy and evidence selection

The panel identified three core thematic areas: 1) pathophysiology of pulmonary deposition; 2) device characteristics and common technical mistakes; and 3) disease-specific pharmacological applications and patient-related factors. A comprehensive, non-systematic literature review was performed by pairs of experts for each thematic area. Electronic searches were conducted across PubMed, EMBASE, the Cochrane Database of Systematic Reviews, and Web of Science for articles published between January 2005 and December 2025. Search strings included combinations of the terms "aerosol therapy", "nebulizer", "pMDI", "spacer", "dry powder inhaler", and "pediatrics", with filters applied for English and Italian languages. Priority was given to meta-analyses, systematic reviews, and international guidelines (*e.g.*, GINA, GOLD, ERS).

Consensus process and development of recommendations

Following the literature review, a series of preliminary statements was drafted. In January 2026, a consensus-building process was facilitated through structured teleconferences. Any discrepancies were resolved through collegial discussion until a 100% consensus was achieved for each recommendation. The strength of each recommendation was graded based on a simplified Evidence-Based Medicine (EBM) framework, categorized as follows:

- Grade A: supported by high-quality evidence (meta-analyses or randomized controlled trials).
- Grade B: supported by moderate-quality evidence (observational studies or non-randomized trials).
- Grade C: expert opinion (based on panel consensus in the absence of high-level evidence).

Review and approval

The final draft underwent a two-stage internal peer-review process, conducted by the SIMRI Executive Committee and the SIMRI Advocacy Committee in March 2026. The final manuscript received formal approval on March 26, 2026.

THREE THEMATIC AREAS

Pathophysiology of pulmonary deposition

An "aerosol" is defined as a system composed of liquid droplets or solid particles small enough to remain suspended in the air (10).

In the context of aerosol therapy, these particles serve as carriers for pharmacological agents delivered locally to the respiratory tract, with the primary objective of targeting bronchial and pulmonary diseases. This route of administration facilitates targeted drug delivery, ensures a rapid onset of action, enhances therapeutic efficacy, and reduces systemic adverse effects due to localized deposition and lower systemic absorption.

However, the overall effectiveness of aerosol therapy is contingent upon several determinants, including: 1) the physical and chemical characteristics of the aerosolized drug; 2) patient-specific respiratory parameters (such as inspiratory flow, inspiratory volume, end-inspiratory breath-holding, and coordination between inhalation and drug delivery); 3) the anatomical features of the airways, including mucociliary clearance, airway geometry, and pathological conditions; and 4) the adequacy of the administration technique (10).

Drug delivery by inhalation is primarily achieved via nasal or oral routes, with oral inhalation providing superior efficiency for particles around 5 µm in diameter (11).

The therapeutic outcome depends not only on the pharmacological properties of the drug but also on the proportion and location of particle deposition within the airways. The principal factors influencing deposition include: 1) aerosol properties such as size, shape, density, electrical charge, and hygroscopicity; 2) inhalation dynamics, including inspiratory flow rate, tidal volume, and breath-holding; and 3) physiological conditions such as mucociliary clearance and airway geometry, which vary with age, sex, and disease state (12-14).

Three predominant mechanisms govern particle deposition within the respiratory tract: 1) inertial impaction; 2) gravitational sedimentation; and 3) Brownian diffusion (15, 16).

Inertial impaction occurs predominantly for particles ≥ 5 µm that are unable to follow airflow changes at high velocity, resulting in deposition within the oropharyngeal and upper bronchial regions. This phenomenon provides the rationale for using VHCs or spacers with pMDIs, which allow for the deceleration of the aerosol plume. It should be noted that aerosol particles and droplets acquire an electrostatic charge through contact or friction for solids, and through spraying for liquids when the device is activated. In addition, most spacers are manufactured from plastic materials and can accumulate electrostatic charge on their surface during use. The resulting effect is a reduction of available drug aerosol for inhalation and a shorter aerosol half-life within the spacer (17). Although measures exist to reduce electrostatic charge, the development and use of antistatic devices is highly advantageous.

Gravitational sedimentation affects particles between 0.5 μm and 5 μm that reach the distal bronchi and alveoli, where reduced airflow allows deposition under the influence of gravity. The efficiency of this process increases with particle size and residence time and is enhanced by an end-inspiratory breath-hold. This principle underlines the use of pMDIs and DPIs. With pMDIs, the generation of a fine aerosol independent of inspiratory effort, combined with slow and deep inhalation followed by breath-holding, maximizes the time for sedimentation of fine particles in the peripheral lung. In DPIs, gravitational sedimentation plays a less significant role during the initial aerosolization phase, as rapid and forceful inhalation promotes the impaction of particles in the oropharynx. However, it becomes important for the deposition of respirable particles (2-5 μm), particularly during the breath-holding phase after inhalation (18).

Brownian diffusion dominates for particles < 0.5 μm and results from random molecular collisions that drive particles to deposit diffusively along bronchiolar and alveolar surfaces (15).

A key determinant of particle behavior is the aerodynamic diameter (19). In this regard, the mass median aerodynamic diameter (MMAD) in aerosol therapy is defined as the aerodynamic diameter at which 50% of the total mass of aerosol particles consists of particles smaller than this diameter, and 50% consists of particles larger than this diameter (20). By combining geometric diameter and density, the MMAD represents a crucial parameter determining the inhalability of a particle. Particles with lower density exhibit smaller aerodynamic diameters and can therefore penetrate deeply into the lung regions (21). Consequently, the selection of MMAD should be tailored to the disease, target site, and therapeutic goal. Particles with an MMAD of 1-3 μm achieve optimal deposition in both central and peripheral airways, while particles with an MMAD of 3-5 μm are more suitable for targeting central airways, and those with an MMAD < 1 μm may reach the alveoli and are therefore useful for systemic drug delivery. Accordingly, larger MMADs are utilized with traditional nebulizers to treat the upper airways, whereas medium-to-small MMADs, such as those produced by pMDIs, are preferred for the lower airways (20).

Despite technological advances in inhaler design, only approximately 20% of the delivered dose typically reaches the lungs, while the remaining fraction deposits in the oropharyngeal cavity and is swallowed (22). The fraction absorbed systemically may induce extrapulmonary side effects; however, these effects are often mitigated by extensive first-pass hepatic metabolism, as observed with inhaled corticosteroids (22).

Device characteristics and common mistakes

Technological advancements in aerosol delivery systems have progressively enhanced the efficiency, precision, and clinical applicability of inhaled therapies in pediatric respiratory care (23). Currently, most guidelines recommend pMDI as the first-line topical treatment for lower airways diseases in childhood (**Table 1**). These portable, multi-dose, manually operated devices generate aerosolized medication using a high-pressure propellant that forces a mixture through an atomizing nozzle, independently of the patient's inspiratory effort. pMDIs are characterized by reproducibility of the delivered dose but should be used with a spacer or valved holding chamber to increase the fraction of the dose reaching the lungs, since the particles are released at very high speed (approximately 130 km/h) and may otherwise impact the pharyngeal walls (24).

***Table 1**. Main technical characteristics of delivery devices.*

Device type	Mechanism	Target Age group	Key technical feature
pMDI + Spacer	Pressurized metered-doseinhaler	All ages (gold standard < 5 years)	Portable, high lung deposition, no coordination needed with spacer
DPI	Patient's inspiratory flow	Children > 5-6 years	No propellants; required high peak inspiratory flow
Jet nebulizer	Compressed air/oxygen	Neonates / Severe distress	Can deliver high doses: commonly used for upper airway treatment; noisy and requires a power source
Vibrating mesh	High-frequency vibration	Chronic patients / Neonates	Silent, minimal residual volume, preserves drug integrity

DPIs do not require spacers and are therefore often preferred by adolescents. However, their clinical effectiveness may be limited by high aerosol deposition in the upper airways due to the relatively large aerodynamic diameter of emitted particles; consequently, rinsing the mouth after the inhalation is recommended (25, 26) (**Table 1**).

Soft mist inhalers deliver medication as a fine mist form, allowing a reduction in drug deposition in the upper airways. However, these devices are currently available only for tiotropium with or without olodaterol, and their use in children remains limited (27).

As for traditional nebulizers, which may also be used to treat upper airways conditions, jet nebulizers are the most widely used (**Table 1**).

These devices nebulize both solutions and suspensions through the Venturi effect. Ultrasonic nebulizers, in contrast, aerosolize only solutions via vibration of piezoelectric crystals. Although relatively quiet and efficient, they are unsuitable for many inhaled medications that are formulated as suspensions. Mesh nebulizers, employing a vibrating mesh containing thousands of microscopic openings, provide improved efficiency and are widely used for aerosolized antibiotics, however, they remain costly (28) (**Table 1**).

Breath-actuated nebulizers are aerosol delivery devices designed to release medication only during inhalation, rather than continuously generating aerosol. This mechanism reduces drug waste and limits dispersion of medication into the surrounding environment: however, these devices are not widely available worldwide.

Considering the differences between aerosol therapy devices, physicians should select the most appropriate device for each patient. Moreover, inhaled treatments are effective only when medications reach the intended target site; therefore, families and patients should receive adequate training in the correct use of these devices. Unfortunately, poor inhaler technique is common among children and adolescents. Younger children may be unable to inhale deeply or hold their breath for several seconds without exhaling. In addition, some parents administer aerosol therapy when their children are sleeping or crying, despite the fact that both situations markedly reduce the dose of medication reaching the lower airways (29) (**Table 2**).

It is also important to remember that many mistakes are commonly made while using aerosol therapy devices: as an example, most pMDIs contain suspensions and need to be shacked just before every single actuation, but many patients forget to do so (30). Moreover, even if spacers with a facemask reduce the dose at the target, they should be used for pMDIs in younger children who cannot use a mouthpiece, and a good seal of the mask on the face should be warranted (31) (**Table 2**).

Notably, DPIs can be used without a spacer, but require the patient to prepare the dose and exhale completely before inspiration, which should be deep and forceful enough to produce a turbulent flow capable of disaggregating the drug when meeting the resistance of the device's internal structure, thus producing an aerosol (**Table 1**). Therefore, most children are unable to use such devices.

***Table 2**. Common mistakes in pediatric aerosol therapy.*

Type of Mistake	Description	Clinical impact
The "Crying and/or sleeping child"	Administering aerosol therapy while the child is crying and/or is sleeping	Massive reduction in lung deposition (most drug remains in the throat)
Failure to shake the pMDI	Administering aerosol therapy with pMDI containing drugs in suspension without shaking the pMDI well before every single actuation	Variability in delivered dose
Poor mask seal	Gap between the mask and the child's face	Up to 50-80% of the medication is lost to the environment
"Blow-by" technique	Holding the mask / tube near the face without contact	Ineffective delivery; negligible drug reaches the lower airways
Inadequate cleaning	Failing to wash / dry the nebulizer kit after use	Risk of bacterial colonization and respiratory infections (*e.g.*, Pseudomonas)
Nasal breathing	Using a mask for older children who should use a mouthpiece	The nose acts as a filter, trapping most of the drug before it reaches the lungs

Another significant mistake is failing to maintain proper hygiene and cleanliness of the devices used. This can lead to bacterial colonization of the airways, such as *Pseudomonas aeruginosa*, a germ that is difficult to eradicate (31) (**Table 2**).

The environmental impact of inhaler devices has become a significant consideration in respiratory medicine. pMDIs utilize hydrofluoroalkane (HFA) propellants, which are potent greenhouse gases. In contrast, DPIs have a significantly lower carbon footprint (32).

However, in pediatric populations – particularly infants and young children – clinical efficacy must remain the priority. Since many children under the age of 6 cannot achieve the inspiratory flow required for DPIs, pMDIs with spacers remain the first-line recommendation for this age group. We advocate for a "clinically-led" approach where the most sustainable device is chosen only if it is appropriate for the child's age, coordination, and clinical status.

Disease-specific pharmacological applications and patient-related factors

Aerosol therapy in children encompasses a broad range of pharmacological agents selected according to the underlying respiratory conditions and individual patient needs. It is indicated in numerous pediatric respiratory disorders (**Table 3**).

Among its primary applications is the management of asthma, particularly during acute exacerbations, in which inhaled short-acting β2-agonists (SABA), such as salbutamol constitutes the cornerstone of rapid bronchodilation (33, 34) and are therefore considered as the first-line therapy for acute asthma attacks. When administered in combination with anticholinergic bronchodilators, most notably ipratropium bromide, SABA demonstrate enhanced efficacy, especially in mild to moderate or moderate to severe asthma attacks, reducing symptom burden and hospital admission rates (33). For maintenance therapy in children older than 4 years of age, long-acting β2-agonists (LABA) may be delivered via inhalation in combination with inhaled corticosteroids (ICS), such as fluticasone and budesonide. ICS represent the most effective maintenance therapy for persistent asthma in children owing to their potent anti-inflammatory activity on airway mucosa. In case of poor control despite optimized ICS-LABA therapy, the addition of a long-acting muscarinic antagonist (LAMA), such as tiotropium bromide, may provide further improvement in symptoms and lung function in children older than 6 years.

Additionally, aerosol therapy plays a role in recurrent wheezing: the clinical response to inhaled salbutamol therapy at home during the acute episode together with the response to a therapeutic trial of ICS, constitutes one of the three diagnostic criteria used to support early asthma diagnosis in children under 6 years of age (33).

In bronchiolitis, the use of aerosolized hypertonic saline has been investigated for its potential to reduce the duration of hospitalization; however, the most recent guideline updates conclude that current evidence does not support its routine use (35). In contrast, aerosol therapy remains a cornerstone of treatment for croup. Nebulized budesonide, used as a second line after systemic corticosteroids or as an alternative when the latter are not available or are difficult to administer, and nebulized epinephrine, a non-selective adrenergic agonist with potent vasoconstrictive activity, provide rapid but temporary relief from upper airway obstruction and represent well-established approach for moderate to severe cases (36, 37).

Nebulized epinephrine is often used in the management of acute laryngospasm or post-extubation stridor, to reduce airway edema (38).

Aerosolized hypertonic saline (3-7%) is widely used in conditions associated with impaired mucociliary clear-

***Table 3**. Examples of indications and pharmacological inhaled treatments.*

Condition / disease	Main drug class	Specific examples	Therapeutic goal
Asthma / wheezing	Inhaled corticosteroids (ICS)	Fluticasone, Budesonide	Reduce airway inflammation
Acute exacerbations	Short-Acting Beta-Agonists (SABA)	Salbutamol (Albuterol)	Rapid bronchodilation
Croup	Sympathomimetics Inhaled corticosteroids	Nebulized Epinephrine Nebulized Budesonide	Reduce subglottic edema reduce airways inflammation
Cystic fibrosis / PCD/post-infectious bronchiectasis	Mucolytics / antibiotics	Dornase alfa / tobramycin	Clear mucus and treat infection

ance (39). In CF, it is often combined with dornase alfa, a recombinant DNase that decreases mucus viscosity by cleaving extracellular DNA from neutrophils. Dornase alfa remains a mainstay of airway-clearance therapy, consistently demonstrating improvements in lung function and reductions in exacerbation frequency (40, 41). Inhaled antibiotics, such as tobramycin, aztreonam lysine, and colistin, are central to the management of chronic *Pseudomonas aeruginosa* infection in CF, allowing the delivery of high local concentrations while minimizing systemic toxicity. Although primarily indicated for CF, these agents may also be considered for selected multidrug-resistant respiratory infections in non-CF patients under specialized supervision (40, 41). Similar therapeutic principles apply to children with PCD and in those with post-infectious bronchiectasis, in whom aerosolized mucolytics and saline solutions support airway clearance. In conditions shared by CF and PCD, namely bronchiectasis and chronic *Pseudomonas aeruginosa* colonization, emerging evidence, largely derived from adult trials, supports the use of inhaled antibiotics (42).

Regarding preterm infants with a history of bronchodysplasia, there are no robust data on the chronic use of bronchodilators, nor on the efficacy of other aerosol therapy modalities for airway clearance in this population (43). Overall, the selection of aerosolized medication is informed by disease mechanism, guidelines-based recommendations, and patient-specific factors such as age, coordination abilities, and comorbidities. In certain infectious conditions such as bacterial pneumonia, aerosolized antibiotics are not considered first-line treatments, but may be used selectively for infections caused by multidrug-resistant pathogens under specialist supervision (44). Finally, aerosol therapy is routinely used for airway humidification and secretion management in children with tracheostomies or neuromuscular diseases associated with ineffective cough, thereby supporting airway hygiene and reducing respiratory morbidity (22).

Study limitations

This position paper has several limitations that should be acknowledged. First, while the literature review was comprehensive and covered major international databases, it was not conducted as a formal systematic review (PRISMA). Therefore, selection bias cannot be entirely excluded. Second, many recommendations are based on a consensus of experts (Grade C evidence) or extrapolated from international guidelines, due to the relative scarcity of high-quality randomized controlled trials specifically conducted on the Italian pediatric population. In **Table 4**, we report only recommendations with level A or B. Lastly, while we provide a standardized framework, the choice of aerosol device remains highly dependent on individual patient adherence and local availability of medications.

SIMRI RECOMMENDATIONS (TABLE 4)

Aerosol therapy represents a fundamental component in the management of selected pediatric respiratory diseases; however, its use must be grounded in evidence-based indications and delivered using appropriate techniques to ensure clinical effectiveness. Current recommendations consistently support the use of aerosol therapy primarily for conditions characterized by lower airway obstruction, most notably asthma and recurrent wheezing, while discouraging its routine use in upper respiratory tract infections or uncomplicated viral illness, for which no meaningful clinical benefit has been demonstrated, with the exception of croup (36, 37). In infants and young children with bronchiolitis, both international and national intersociety recommendations, including those endorsed by the Italian Pediatric Respiratory Society (SIMRI/IPRS), strongly advise against the routine use of nebulized bronchodilators, corticosteroids, or other aerosolized medications. These interventions have not demonstrated improvements in clinically relevant outcomes and may contribute to unnecessary healthcare costs and caregiver burden (45, 46). Supportive care therefore remains the standard management in this population (12). For asthma management, aerosol therapy is recommended as the preferred route for the administration of bronchodilators and ICS, owing to its rapid onset of action and favorable safety profile. pMDIs used in combination with VHCs or spacers are recommended as first-line delivery systems in children of all ages, including preschoolers, as they provide drug deposition comparable to or superior to nebulizers while reducing treatment time and systemic exposure (33, 47). Nebulizers should be reserved for severe exacerbations or for children who are unable to effectively use an pMDI with spacer. The choice of interface is critical for effective aerosol delivery. A well-fitting face mask is recommended in infants and toddlers, whereas a mouth-

Table 4*. SIMRI recommendations in pediatric aerosol therapy.*

	SIMRI Recommendations	LoE*
1	Target lower airway obstruction, such as asthma or recurrent wheezing, rather than routine upper respiratory infections (except for croup).	A
2	Avoid routine aerosol use for bronchiolitis, as bronchodilators and corticosteroids do not improve clinical outcomes in these cases.	A
3	Prioritize pMDIs with spacers/holding chambers for all ages when treating the lower airways, as they are as effective as nebulizers but faster and with fewer side effects.	A
4	Reserve nebulizers for severe exacerbations, for children who cannot effectively use a pMDI with a spacer, or when treating croup.	B
5	Ensure a well-fitting face mask for infants and toddlers to maximize drug delivery and minimize ocular/skin deposition.	B
6	Transition to a mouthpiece in older children (usually > 5 years) to minimize drug loss and deposition on the face.	B
7	Strictly avoid the “blow-by” technique, as it results in negligible medication reaching the lungs.	A
8	Avoid DPIs (Dry Powder Inhalers) under age 5–6, as young children often lack the inspiratory flow required to use them effectively.	B
9	Do not use saline or mucolytics routinely, as there is a lack of robust evidence regarding their clinical efficacy, with the exception of specific conditions such as CF and PCD.	A
10	Provide regular education and reassessment of the inhalation technique to caregivers and patients to ensure therapeutic success.	A

**LoE (Level of Evidence): A: High-quality evidence (RCTs/Meta-analyses); B: Moderate-quality evidence; C: Expert Opinion/Consensus.*

piece is preferred in older children to minimize drug loss and facial deposition. The use of “blow-by” techniques is strongly discouraged, as it results in negligible pulmonary drug deposition (47). DPIs are generally not recommended in children under 5-6 years of age because of inadequate inspiratory flow generation. However, DPIs are less polluting; therefore, we prefer HFA pMDIs with a lower environmental impact (32). Regarding pharmacological agents, intersociety consensus documents involving SIMRI/IPRS support the use of ICS as maintenance therapy in children with persistent asthma and selected wheezing phenotypes, with dosing tailored to age and disease severity (48). In children with croup, the use of budesonide, particularly when delivered via jet nebulizers rather than ultrasonic nebulizers, is recommended as a second line to the administration of systemic steroids or as an alternative in case of unavailability of the first (37). Conversely, the routine use of nebulized saline or mucolytics lacks robust evidence of clinical efficacy and should not be considered standard care outside specific well-defined indications (47, 48).

CONCLUSIONS

The selection of an appropriate aerosol delivery device is a critical determinant of therapeutic effectiveness in pediatric respiratory care. When used correctly, all major aerosol delivery devices demonstrate comparable efficacy; however, their real-world performance varies substantially according to patient- and context-specific factors (**Table 1** and **Table 2**). Device choice should therefore be individualized, taking into account the child’s age, physical and cognitive abilities, coordination skills, availability of the prescribed medication in specific formulations, ease of use of the aerosol therapy device, the required administration time and the environmental setting in which the therapy is delivered.

Across all guidelines, structured caregiver and patient education is emphasized as an essential component of effective aerosol therapy. Proper instruction on device assembly and use, regular reassessment of inhalation technique, and systematic monitoring of adherence are essential to optimizing drug delivery, minimizing treatment failure and ensuring sustained clinical benefit (33).

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

The authors declare no conflicts of interest.

Financial support

None.

Author contributions

GFen, SLG: conceptualization. GFen, MEDC, GFer, RN, FP, SLG: writing – original draft, writing – review & editing. The members of SIMRI Advocacy Council and Executive Committee contributed to drafting the paper based on their expertise on the subject. All authors discussed and approved the final recommendations. All authors read, critically reviewed and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethical approval

Human studies and subjects

N/A.

Data sharing and data accessibility

N/A.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

REFERENCES

1. DiBlasi RM. Clinical Controversies in Aerosol Therapy for Infants and Children. Respir Care. 2015;60(6):894-914; discussion 914-6. doi: 10.4187/respcare.04137.
2. Berlinski A. Pediatric Aerosol Therapy. Respir Care. 2017;62(6):662-677. doi: 10.4187/respcare.05298.
3. Berlinski A. Aerosol Delivery Challenges and Strategies for Pediatric Asthma. Respir Care. 2025;70(6):721-734. doi: 10.1089/respcare.12626.
4. Berlinski A, von Hollen D, Hatley RHM, Hardaker LEA, Nikander K. Drug delivery in asthmatic children following coordinated and uncoordinated inhalation maneuvers: a randomized crossover trial. J Aerosol Med Pulm Drug Deliv. 2017;30(3):182-189. doi: 10.1089/jamp.2016.1337.
5. O'Neil JA, Villasmil-Urdaneta LA. A path forward in the development of new aerosol drug delivery devices for pediatrics. Respir Med. 2023:211:107210. doi: 10.1016/j.rmed.2023.107210.
6. Volerman A, Kan K, Carpenter D, Press VG. Strategies for Improving Inhalation Technique in Children: A Narrative Review. Patient Prefer Adherence. 2021:15:665-675. doi: 10.2147/PPA.S267053.
7. Capanoglu M, Misirlioglu ED, Toyran M, Civelek E, Kocabas CN. Evaluation of inhaler technique, adherence to therapy and their effect on disease control among children with asthma using metered dose or dry powder inhalers. J Asthma. 2015;52(8):838-45. doi: 10.3109/02770903.2015.1028075.
8. Alismail A, Song CA, Terry MH, Daher N, Almutairi WA, Lo T. Diverse Inhaler Devices: A Big Challenge for Health-Care Professionals. Respir Care. 2016;61(5):593-9. doi: 10.4187/respcare.04293.
9. Chang AB, Fortescue R, Grimwood K, Alexopoulou E, Bell L, Boyd J, et al. European Respiratory Society guidelines for the management of children and adolescents with bronchiectasis. Eur Respir J. 2021;58(2):2002990. doi: 10.1183/13993003.02990-2020.
10. Douafer H, Andrieu V, Brunel JM. Scope and limitations on aerosol drug delivery for the treatment of infectious respiratory diseases. J Control Release. 2020:325:276-292. doi: 10.1016/j.jconrel.2020.07.002.
11. Lippmann M, Albert RE. The effect of particle size on the regional deposition of inhaled aerosols in the human respiratory tract. Am Ind Hyg Assoc J. 1969;30(3):257-75. doi: 10.1080/00028896909343120.
12. Cheng YS. Mechanisms of pharmaceutical aerosol deposition in the respiratory tract. AAPS PharmSciTech. 2014;15(3):630-40. doi: 10.1208/s12249-014-0092-0.
13. Hickey AJ. Controlled delivery of inhaled therapeutic agents. J Control Release. 2014;190:182-8. doi: 10.1016/j.jconrel.2014.05.058.
14. Carvalho TC, Peters JI, Williams III RO. Influence of particle size on regional lung deposition-what evidence is there? Int J Pharm. 2011;406(1-2):1-10. doi: 10.1016/j.ijpharm.2010.12.040.
15. Verma RK, Ibrahim M, Garcia-Contreras L. Lung anatomy and physiology and their implications for pulmonary drug delivery, Pulmonary Drug Delivery, 2015, pp. 1-18.
16. O'Riordan TG, Smaldone GC, Aerosol deposition and clearance, Murray and Nadel's Textbook of Respiratory Medicine, Elsevier, 2016, pp. 168-183. e162.
17. Lip Kwok PC. Electrostatics of Pharmaceutical Aerosols for Pulmonary Delivery. Curr Pharm Des. 2015;21(27):3945-54. doi: 10.2174/1381612821666150820110407.
18. Dolovich MB, Dhand R. Aerosol drug delivery: developments in device design and clinical use. Lancet. 2011;377(9770):1032-45. doi: 10.1016/S0140-6736(10)60926-9.
19. Bisgaard H, O'Callaghan C, Smaldone GC. Drug Delivery to the Lung. New York: Marcel Dekker; 2002. p. 162.
20. Finlay WH, Darquenne C. Particle Size Distributions. J Aerosol Med Pulm Drug Deliv. 2020;33(4):178-180. doi: 10.1089/jamp.2020.29028.whf.
21. Alharbi AS, Yousef AA, Alharbi SA, Al-Shamrani A, Alqwaiee MM, Almeziny M, et al. Application of aerosol therapy in respiratory diseases in children: A Saudi expert consensus. Ann Thorac Med. 2021;16(2):188-218. doi: 10.4103/atm.atm_74_21.
22. Strong P, Ito K, Murray J, Rapeport G. Current approaches to the discovery of novel inhaled medicines. Drug Discov Today. 2018;23(10):1705-1717. doi: 10.1016/j.drudis.2018.05.017.
23. Stein SW, Thiel CG. The History of Therapeutic Aerosols: A Chronological Review. J Aerosol Med Pulm Drug Deliv. 2017;30(1):20-41. doi: 10.1089/jamp.2016.1297.

24. Dolovich MB, Dhand R. Aerosol drug delivery developments in device design and clinical use. Lancet. 2011;377(9770):1032-45. doi: 10.1016/S0140-6736(10)60926-9.
25. Atkins PJ. Dry powder inhalers: an overview. Respir Care. 2005;50(10):1304-12.
26. Laube BL, Janssens HM, de Jongh FHC, Devadason SG, Dhand R, Diot P, et al. What the pulmonary specialist should know about the new inhalation therapies. Eur Respir J. 2011;37(6):1308-31. doi: 10.1183/09031936.00166410.
27. Komalla V, Wong CYJ, Sibum I, Muellinger B, Nijdam W, Chaugule V, et al. Advances in soft mist inhalers. Expert Opin Drug Deliv. 2023;20(8):1055-1070. doi: 10.1080/17425247.2023.2231850.
28. Troy M, Van Vleet J, Tashkin D, Barjaktarevic I. Recent advances predict a bright future for nebulizers. Curr Opin Pulm Med. 2023;29(2):123-132. doi: 10.1097/MCP.0000000000000941.
29. Esposito-Festen J, Ijsselstijn H, Hop W, van Vliet F, de Jongste J, Tiddens H. Aerosol therapy by pressured metered-dose inhaler-spacer in sleeping young children: to do or not to do? Chest. 2006;130(2):487-92. doi: 10.1378/chest.130.2.487.
30. Hatley RH, Parker J, Pritchard J N, von Hollen D. Variability in Delivered Dose from Pressurized Metered-Dose Inhaler Formulations Due to a Delay Between Shake and Fire. J Aerosol Med Pulm Drug Deliv. 2017;30(1):71-79. doi: 10.1089/jamp.2015.1284.
31. Samady W, Rodriguez VA, Gupta R, Palac H, Karamanis M, Press VG. Critical Errors in Inhaler Technique among Children Hospitalized with Asthma. J Hosp Med. 2019;14(6):361-365. doi: 10.12788/jhm.3195.
32. Woodcock A, Beeh KM, Sagara H, Aumônier S, Addo-Yobo E, Khan J, et al. The environmental impact of inhaled therapy: making informed treatment choices. Eur Resp J. 2022;60(1):2102106. doi: 10.1183/13993003.02106-2021.
33. Global Initiative for Asthma Global Strategy for Asthma Management and Prevention (2025 update). Available from: https://ginasthma.org/wp-content/uploads/2025/05/GINA-Strategy-Report_2025-WEB-WMS.pdf. Accessed: March 28, 2026.
34. Nenna R, Fenu G, Ferrante F, Di Cicco ME, Porcaro F, La Grutta S. Position Paper on short-acting beta-2 agonists for acute wheezing episodes in children aged below 6 years. A statement proposed by the Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili, SIMRI) Asthma Committee and approved by the SIMRI Advocacy Council and Executive Committee. Pediatr Respir J. 2025;3(2):74-80. doi: 10.56164/PediatrRespirJ.2024.67.
35. Manti S, Stain O, Orfeo L, Midulla F, Marseglia GL, Ghizzi C, et al. UPDATE- 2022 Italian guidelines on the management of bronchiolitis in infants. Ital J Pediatr. 2023;49(1):19. doi: 10.1186/s13052-022-01392-6.
36. Bjornson CL, Johnson DW. Croup. Lancet. 2008;371(9609):329-39. doi: 10.1016/S0140-6736(08)60170-1.
37. Di Cicco ME, Fenu G, Ferrante G, Nenna R, Porcaro F, La Grutta S. Italian Pediatric Respiratory Society (SIMRI) position paper on treatment of croup in childhood: an expert group statement approved by SIMRI Advocacy Council and Executive Committee. Pediatr Respir J.2025;3(3):126-135. doi: 10.56164/PediatrRespirJ.2025.75.
38. McCall JE, Fischer CG, Schomaker E, Young JM. Laryngeal mask airway use in children with acute burns: intraoperative airways management. Paediatr Anaesth. 1999;9(6):515-20. doi: 10.1046/j.1460-9592.1999.00407.x.
39. Wark P, McDonald VM, Smith S. Nebulized Hypertonic Saline in Cystic Fibrosis. Cochrane Database Syst Rev. 2023;6(6):CD001506. doi: 10.1002/14651858.CD001506.pub5.
40. Stanford G, Morrison L, Brown C. Nebulizer system for drug delivery in cystic fibrosis. Cochrane Database Syst Rev. 2023;11(11):CD007639. doi: 10.1002/14651858.CD007639.pub3.
41. Elborn J. Cystic fibrosis. Lancet. 2016;388(10059):2519-2531. doi: 10.1016/S0140-6736(16)00576-6.
42. Haworth CS, Shteinberg M, Winthrop K, Barker A, Blasi F, Dimakou K, et al. Inhaled colistimethate sodium in patients with bronchiectasis and Pseudomonas aeruginosa infection: results of PROMIS-I and PROMIS-II, two randomised, double-blind, placebo-controlled phase 3 trials assessing safety and efficacy over 12 months. Lancet Respir Med. 2024;12(10):787-798. doi: 10.1016/S2213-2600(24)00225-X.
43. Cristea AI, Ren CL, Amin R, Eldredge LC, Levin JC, Majmudar PP, et al. Outpatient Respiratory Management of Infants, Children, and Adolescents with post-prematurity Respiratory Disease: An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2021;204(12):e115-e133. doi:10.1164/rccm.202110-2269ST.
44. Hakamifard A, Torfeh Esfahani AA, Homayouni A, Khorvash F, Ataei B, Abbasi S. Comparing inhaled colistin with inhaled fosfomycin/tobramycin as an adjunctive treatment for ventilator-associated pneumonia: An open-label randomized controlled trial. Clin Respir J. 2023;17(4):295-302. doi: 10.1111/crj.13594.
45. American Academy of Pediatrics (AAP). Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis. Pediatrics. 2014;134(5):e1474-502. doi: 10.1542/peds.2014-2742.
46. National Institute for Health and Care Excellence (NICE). Bronchiolitis in children: diagnosis and management. NICE guideline NG9, 2015.
47. American Association for Respiratory Care (AARC). Aerosol Therapy in Pediatrics. Respiratory Care. 2015;60(6):e95-e118.
48. Duse M, Santamaria F, Verga MC, Bergamini M, Simeone G, Leonardi L, et al. Intersociety consensus for the use of inhaled corticosteroids in infants, children and adolescents with airway diseases. Ital J Pediatr. 2021;47(1):97. doi: 10.1186/s13052-021-01013-8.

Vol. 4(2), 96-97, 2026

OBITUARY

Henry Levison, a Giant of Pediatric Respiratory Medicine

Fernando Maria **de Benedictis** [1, 2, *]

***Correspondence to:**
pediatria@fmdebenedictis.it

[1] Puer Foundation Trust, Ancona, Italy
[2] Pediatric Clinic, University of Perugia Medical School, Perugia, Italy

Henry Levison ("Henry" for his pupils), one of the universally recognized Fathers of Pediatric Respiratory Medicine, died on June 6, 2025, in Toronto, Canada, at the age of 94.

He graduated at the Royal College of Surgeons, Dublin. After working as a physician in a kibbutz in the north of Israel for a few years, he came to appreciate his lack of knowledge in pediatrics and moved first to complete a residency in general pediatrics at the Michael Reese Hospital, Chicago, and then to Boston Children's Hospital where he was introduced to respiratory physiology by Dr. Clement Smith.

In the early 1960's, he was a Fellow at Sick Children Hospital, Toronto. His intellectual talent soon became apparent, resulting in pioneering work in mechanical ventilation of premature newborns with respiratory distress syndrome along with Maria Delivoria-Papadopoulos, under the supervision of neonatologist Dr. Paul Swyer. Together with Blair Fearon, Otolaryngologist, they were among the first to intubate and ventilate premature infants. Henry's interest in respiratory physiology prompted him to spend a training period in one of the greatest centers of this specialty, Winnipeg, Manitoba, under Dr. Rubin Cherniak.

When he returned to SickKids, in 1966, he joined Dr. Charlie Bryan, an authority in the field of physiology, to create a leading center for studying respiratory physiology in childhood. The role of precision in measurements of respiratory function and gas exchange was of paramount importance to improve understanding of how the lung works in normal children and in those with respiratory diseases.

Soon after, he was inspired to establish one of the first Pulmonary Function Laboratories for children. Recognizing the importance of precise reference values, he performed pulmonary function tests on thousands of children, producing the widely used "Weng and Levison" normal standards. During the 1970s and 80s, under his direction, the laboratory at SickKids became an internationally recognized research and training center for many young pediatric pulmonologists; among Italians, Alberto Andreoli, Attilio Boner, Fernando Maria de Benedictis, Giovanna De Castro, and Luigi Mappa. New pulmonary techniques and fundamental studies on airway reactivity were developed, resulting in numerous publications. Henry also emphasized robust study design, aiming for at least 100 subjects per trial – a standard humorously dubbed the "Levison Unit" before power calculations became common practice.

In 1978, he became Director of the Cystic Fibrosis Clinic at SickKids, a role he held until 1995. He pioneered a multidisciplinary approach, assembling pulmonologists, physiotherapists, gastroenterologists, nutritionists, psychologists, nurses, and family counselors, and along with Dr. Douglas Crozier revolutionized CF care, including high-fat, high-calorie diets, achieving the world's best CF survival rates in Toronto. He also initiated the Toronto CF database with biostatistician Mary Corey, a landmark resource that enabled longitudinal studies, genotype-phenotype correlations, and contributed to the cloning of the CF gene. Recognizing the need for adult care, he laid the foundation for adult CF clinic transition programs in North America.

From 1984 to 1994, he led the Division of Chest Diseases at SickKids, which became a global reference center for pediatric respiratory research. Clinical studies on asthma, cystic fibrosis, bronchiolitis, croup, pneumonia, and primary ciliary dyskinesia established the role of pharmacologic therapies. His landmark work on asthma pathology first identified inflammation as a central feature, paving the way for anti-inflammatory treatments that transformed asthma care. During this period, he published extensively in top international journals and had an unparalleled influence on pediatric respiratory medicine worldwide. Collaborating with other Canadian leaders, he also secured recognition of Pediatric Respiratory Medicine as a Royal College subspecialty.

In 1989-1990 he spent his sabbatical year at University of Perugia, Italy. During this period, he was able to create a new scientific consciousness between pediatric respirologists by transferring enthusiasm, passion and desire for scientific evidence, and was invited to give lectures at the main national universities.

Throughout his career, Henry brought a paradigm shift that guided his research and defined the field of pediatric pulmonology. His studies advanced our understanding of childhood respiratory diseases, often challenging dogma with his legendary principle "*Make things simple!*". His leadership, team building, foresight, and contagious enthusiasm inspired a generation of young researchers. Henry was tireless, often arriving early in the morning and studying the latest scientific literature before his academic activities. Renowned for his incredible memory, clarity of thought, and insistence on evidence – earning him the nickname "guru of skepticism" – he demanded data before accepting new ideas. This rigor instilled confidence in his collaborators while teaching them to recognize when evidence was lacking. Despite his strictness, he was deeply respectful, warm, and humble, valuing contributions from everyone, from chief executives to the greenest medical students. Behind his occasional outspokenness, he radiated kindness and integrity.

At meetings, he was a respected speaker. He had an extraordinary ability when presenting data, even the most complex ones, and was unique in openly answering questions to which he did not know the answer ("*I don't know!*"). Such intellectual honesty was an expression of knowledge, not of ignorance, and this is patrimony of great minds only.

Henry was a man of eclectic tastes. He loved classical music, arts and reading. Those who visited his apartment were able to appreciate thousands of books, vinyl albums and CD, and an extensive collection of drawings including works by Matisse and Picasso. In sports, he supported the Toronto Blue Jays baseball team.

Henry's legacy lies in the number of trainees who graduated under his leadership and mentorship over the years. They are now spread across the globe, many in academical positions or successful careers themselves continuing the work he helped to inspire. Between them, Gerard Canny, Fernando Maria de Benedictis, Khoulood Fakhoury, Dennis Gurwitz, Meyer Kattan, Alan Isles, Thomas Keens, Eitan Kerem, Thomas Kovesi, Ian McLusky, Christopher Newth, Hugh O'Brodovich, Linda Pedder, Constantine Petrou, Joe Reisman, Joseph Rivlin, Colin Robertson, Renato Stein, and Elvan Tabachnik.

Apart from respiratory diseases, many of those who had the privilege of working with him learned so much outside of medicine from his personality. An episode may characterize the essence of his human value. Once, when asked about his greatest professional satisfaction, he said: "All my pupils did well". That was Henry.

MEDIA

SIMRI
società italiana per le malattie respiratorie infantili

www.pediatric-respiratory-journal.com