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EDITORIAL

What dangers does vaping pose to children's health?

Stamatoula Tsikrika¹, Des W Cox^{2,3,*} on behalf of the ERS tobacco control committee

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Dear Editor,

with great interest, we read the position statement from the Italian Pediatric Respiratory Society (SIMRI) entitled "Vaping as a new threat for respiratory health." This review comes at a pivotal moment as newer tobacco and nicotine products such as electronic cigarettes and tobacco heating products appear to be increasingly popular among teenagers and young adults.

Focused interventions at an early age, in addition to their preventive nature, aim to ensure the health of adolescents, in the sense that, while the health consequences of tobacco smoking in adults have been adequately investigated and recognised, the consequences of smoking and vaping during prepubescence and adolescence have been underestimated or partially studied.

According to the WHO, 37 million children aged 13–15 years use tobacco globally; the organisation emphasises that the rate of e-cigarette use among adolescents currently exceeds that of adults. Furthermore, the CDC has reported that the most common nicotine product among U.S. high school students is an e-cigarette with 7.8% admitting current use for the previous year, while at least 16,000 flavours have been recorded (1).

The scientific community is closely monitoring this global trend, recognising the health risks of nicotine that may lead to addiction and that young people are more likely to face significant challenges in overcoming addiction later in life. Co-optation of "harm reduction" by the tobacco industry lacks sufficient independent scientific evidence, while there is a looming risk that novel nicotine products may act as a Trojan horse, fostering nicotine addiction and normalizing smoking behaviour among youth. The official ERS statement on novel nicotine and tobacco products aligns with this perspective and is opposed to the rhetoric of 'harm reduction' (2). We appreciate the authors' efforts to shed light on the "anatomy" of electronic cigarettes, pod-mods, and heated tobacco products with or without nicotine, emphasising not only their basic operating characteristics but also making an extensive reference to the main irritant and toxic substances, which, according to current evidence, trigger inflammatory responses at both the airway and systemic levels. Many studies have shown that novel tobacco products may release varying concentrations of compounds, including formaldehyde, vegetable glycerin, acrolein, polycyclic aromatic hydrocarbons, sulphur compounds, metals such as lead, zinc, and significant levels of volatile organic compounds (VOCs), and aldehydes during mixing, heating, or evaporation of the liquid components. The effect of these substances may vary, depending on the frequency and duration of exposure.

Doi

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Recent data demonstrated a strong correlation between nicotine, vaping, and respiratory disorders. Primarily, vaping has been correlated with early impairment of lung function characterized by airway hyper-responsiveness, an increase of airway resistance (Raw) even in short-term exposure, impairment of innate immune and anti-viral defences, and severe acute or subacute respiratory illness such as EVALI (E-cigarette or Vaping Associated Lung Injury) and bronchiolitis obliterans syndrome or “popcorn workers” lung. Heated tobacco products influence the cardiovascular system, as their use increases the risk of hypertension, arrhythmias, and vascular endothelial dysfunction. Another study highlights the expression of anxiety symptoms and depression linked to vaping nicotine and tobacco heated products among teens and young adults, a situation that should be taken into consideration by parents and the school community (3).

Moreover, we would like to mention another emerging product, nicotine pouches, which has recently gained popularity across Europe. The intra-oral absorption of nicotine in varying contents and concentrations may impair oral health but may also have genotoxic and potentially oncogenic effects.

Of particular importance is the authors' reference to dual or triple users who not only failed to quit smoking but instead became trapped in addiction and continued gadget use, with the literature stating that dual users have a higher risk of cardiovascular disease and anxiety than cigarette-only smokers. The potential risks of bystanders' vaping exposure are not entirely clear, and limited scientific research is available; therefore, more studies are needed to investigate both short-, and long-term effects on vulnerable individuals such as children, pregnant women, the elderly, and people with chronic diseases. This may facilitate counselling and advocacy for a smoke-free future generation.

The authors discuss the potential dangers of vaping during pregnancy. Although there is a lack of studies on the impact of vaping on fetal development, SIMRI highlights several animal studies demonstrating the negative effects of nicotine on fetal lung growth as well as immune function development. There is sufficient concern from these studies to adopt the precautionary principle when it comes counselling expectant mothers on vaping during pregnancy. Some countries such as the

UK have taken a different approach and encourage expectant mothers who smoke tobacco products to swap to vaping. The World Health Organisation (WHO) strongly advises against vaping during pregnancy due to the potential harms of nicotine exposure to the developing foetus. Upcoming research studies will hopefully provide evidence for healthcare professionals on how best to counsel pregnant women on the potential harmful effects of vaping to their offspring (4).

The vaping industry have played a significant role in the rise of adolescent vaping. Vaping manufacturers have clearly deviated from promoting e-cigarettes as a tobacco cessation tool to a selling them as consumer products in recent years. The tactics employed are aimed at enticing adolescents and young adults to taking up vaping. Bright coloured packaging, flavours and sleek advertising on social media all have contributed to the explosion in adolescent vaping. In addition, vaping companies are often one step ahead of public health agencies as newer nicotine products are constantly emerging on the market. Rather than targeting ex-smokers who are hooked on tobacco products, vaping companies seek to recruit new consumers to the market.

The authors highlight that the developing brain is particularly susceptible to the dangers of nicotine addiction. The earlier a person starts vaping, the more likely they are to become addicted. SIMRI echo the concerns of many paediatric societies across the world that we are witnessing the dawn of a new generation of nicotine addicted teenagers. The progress made on decreasing tobacco smoking prevalence across many countries is in jeopardy as we now have evidence that teenagers who vape are more likely to start smoking tobacco products (5).

The authors propose a number of ways we can halt the increase in adolescent vaping. Increased physician awareness and counselling adolescent patients and their families on the potential dangers of vaping is clearly important. In addition, widespread public health campaigns will increase awareness on the facts about vaping rather than the mistruths being disseminated by vaping companies. Enforcement of age of sale bans and increased regulation of the sale of vaping products through legislation is urgently required. At EU level, there is significant inertia to introduce laws which would decrease the prevalence of adolescent vaping. It has

been left to individual countries themselves to bring in legislative measures. Such actions include an outright ban on all e-cigarettes, a ban on all e-liquid flavours apart from tobacco flavours and disposable vapes, restrictions on the marketing and advertising of vaping products as well as the introduction of plain packaging. Some countries have decided to introduce a combination of these legislative measures, and it remains to be seen which ones will prove most effective (6). Certainly, countries that do not act to curtail teenage vaping are placing their

population at risk of potential negative health effects in the future. Paediatric pulmonologists and respiratory societies such as SIMRI play an important advocacy role in calling on governments to regulate effectively on vaping, HTP and newer nicotine products.

In conclusion, SIMRI's position paper provides an important evidence-based update on newer nicotine products. The ten rules outlined provides an excellent road map for paediatricians to follow to protect children from the harms of vaping.

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RESEARCH ARTICLE

Digital Health Adoption in Pediatric Respiratory Care in Italy: A National Survey and Machine Learning-Based Clustering Analysis

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ABSTRACT

The integration of digital health technologies into pediatric respiratory care is growing, yet patterns of adoption and clinician readiness remain poorly understood. This study explores the integration of digital technologies in pediatric respiratory care through the first nationwide survey officially supported by the Italian Pediatric Respiratory Society (IPRS/SIMRI). Conducted in January 2025, the survey collected responses from 132 clinicians and aimed to identify distinct profiles based on digital technology use, competencies, and perceived barriers. Using Random Forest analysis and t-distributed Stochastic Neighbor Embedding, two main clusters emerged: “Users” (76.5%), primarily younger professionals working in tertiary settings and managing complex respiratory conditions, and “Non-Users” (23.5%), mainly older clinicians in primary or secondary care with no adoption of digital tools. The most commonly used technologies included electronic health records, telemedicine, and portable spirometry. Barriers reported by Users included lack of resources, high costs, and system complexity, despite a generally high level of digital skills. These findings provide a unique perspective on the current state of digital readiness and clinical integration in pediatric respiratory medicine. This nationwide survey is among the first to explore digital health adoption in pediatric respiratory care using machine learning techniques for pattern identification. Despite the limitations inherent to its cross-sectional design and possible self-selection bias, the study establishes a valuable foundation for developing targeted educational strategies, guiding health policy, and informing future longitudinal research.

IMPACT STATEMENT

This is the first study to provide a national overview of how pediatric respiratory clinicians in Italy engage with digital health technologies. By identifying distinct user profiles and mapping perceived barriers and benefits, the study highlights existing gaps in digital readiness and informs the development of targeted educational programs and infrastructure policies. These findings support a more equitable and effective integration of digital tools in pediatric respiratory care, aligning clinical innovation with real-world practice.

Doi

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KEY WORDS

Pediatric respiratory care; digital health; technology adoption; telemedicine; machine learning.

HIGHLIGHTS BOX

What is already known about this topic? Digital health tools, such as telemedicine and electronic health records, are increasingly used in pediatric medicine, but data on their adoption, perceived value, and barriers in pediatric respiratory care are limited. **What does this article add to our knowledge?** This study provides the first national overview of digital technology use in pediatric respiratory care, identifying two distinct clinician profiles, Users and Non-Users, and highlighting differences in age, care setting, clinical complexity, digital competencies, and perceived barriers. **How does this study impact current management guidelines?** By uncovering digital readiness gaps and the real-world use of technology, the findings support the need for targeted training and institutional investment. They inform future strategies aimed at integrating digital tools into routine pediatric respiratory care and aligning practice with innovation.

INTRODUCTION

The digital transformation of healthcare is rapidly reshaping the clinical landscape, offering new opportunities to improve diagnosis, monitoring, and treatment, particularly in chronic and complex conditions (1). In pediatric respiratory medicine, digital tools such as telemedicine, portable spirometry, electronic health records (EHRs), and remote monitoring systems have demonstrated growing potential to enhance continuity of care, reduce the burden of in-person visits, and support patient-centered approaches (2, 3).

In the field of pediatric respiratory medicine, where long-term follow-up, multidisciplinary collaboration, and real-time data are often essential, digital technologies could offer significant clinical and organizational benefits. However, while innovation continues to advance, the integration of such tools into daily practice remains uneven. Evidence on how clinicians actually use digital health solutions, which tools are most commonly adopted, and what barriers hinder their implementation is still limited, especially in the pediatric respiratory domain.

In Italy, the strategic push toward healthcare digitization has been strongly emphasized in recent years through the Piano Nazionale di Ripresa e Resilienza (PNRR), which promotes investments in telemedicine, health data infrastructure, and digital training for healthcare professionals (4, 5). At the international level, both the World Health Organization (WHO) and the European Respiratory Society (ERS) have highlighted the importance

of digital innovation in respiratory care and the need to address disparities in access and digital literacy (6-8). Yet, despite this growing attention, there is a lack of national-level data on how digital tools are actually being adopted in pediatric respiratory practice.

To address this gap, the present study reports the results of the first nationwide survey specifically designed to investigate these aspects, conducted by the Pediatric Digital Technologies for Respiratory Care (PeDiTCare) Study Group and officially endorsed by the Italian Pediatric Respiratory Society (IPRS/SIMRI). By offering a comprehensive, data-driven overview of clinicians' experiences, practices, and perspectives, this study aims to support the advancement of equitable, evidence-based digital transformation in pediatric respiratory care.

MATERIALS AND METHODS

Study Design and Objectives

This was a cross-sectional, observational study conducted through an anonymous online survey aimed at exploring the knowledge, use, and perceived value of digital health technologies among pediatric respiratory clinicians in Italy. The primary objective was to identify distinct clinician profiles based on patterns of digital technology adoption. Secondary objectives included assessing the clinical settings in which such technologies are used, the perceived benefits and barriers to their implementation, and the level of digital literacy among respondents.

Survey Development and Distribution

The survey was developed by the PeDiTCare Study Group and officially endorsed by IPRS/SIMRI. The questionnaire consisted of 23 items, organized into two sections: Section 1 collected demographic and professional data (age, gender, specialization, region of work, years of experience, and type of clinical setting); Section 2 explored awareness, access, and use of digital tools, perceived benefits, digital competencies, and barriers to implementation. The full English translation of the survey is available as Supplementary File 1. The survey was distributed in January 2025 via the IPRS/SIMRI national newsletter and hosted on the Google Forms platform. At the time of distribution, the society counted 986 active members (708 full members and 278 residents), resulting in a response rate of approximately 13.4%. Participation was voluntary, and completion time was approximately 10 minutes. Data collection was anonymous, and no identifiable personal information was requested. All responses were stored securely for statistical analysis.

Sample and Inclusion Criteria

All members of IPRS/SIMRI were eligible to participate. The society includes primarily pediatricians working in primary care, hospitals, and academic settings. Inclusion criteria required being a practicing clinician involved in pediatric respiratory care and completing the entire questionnaire. No incentives were offered.

Data Analysis and Statistical Methods

Descriptive statistics were used to summarize demographic and clinical characteristics, reporting frequencies and percentages for categorical variables, and mean $\pm$ standard deviation (SD) for continuous variables.

To identify patterns in digital technology use, we applied a Random Forest (RF) classification model (9), a non-parametric ensemble learning method that constructs multiple decision trees to enhance predictive accuracy and reduce overfitting. Model performance was evaluated using out-of-bag (OOB) error estimation (9) and standard classification metrics (accuracy, precision, recall, F1-score) (10).

To visualize the latent structure of the dataset and support cluster identification, we employed t-distributed Stochastic Neighbor Embedding (t-SNE), a dimensionality reduction technique designed to preserve local similar-

ities and reveal high-dimensional patterns in a low-dimensional space (11). The algorithm's hyperparameters, perplexity, learning rate, and number of iterations, were optimized using a greedy search strategy based on Kullback–Leibler divergence minimization (11).

The mathematical formulation of the RF and t-SNE models, including relevant equations and hyperparameter selection procedures, is provided in Supporting Information.

Ethical Considerations

Given the anonymous, voluntary nature of the survey and the absence of clinical or sensitive personal data, formal ethics committee approval was not required under current Italian regulations. All participants were informed about the aims of the study and provided implicit consent by completing the survey.

RESULTS

Study Population

The survey was completed by 132 clinicians actively engaged in pediatric respiratory care. The majority of respondents were under 40 years of age (59.1%) and female (68.1%). Most of respondents were pediatricians (54.5%), followed by residents in Pediatrics (33.3%), allergologists (6.1%), and pulmonologists (3.0%). Regarding professional experience, 56.1% had been practicing for 5–9 years, 33.3% for over 10 years, and 10.6% for fewer than 5 years. Respondents were geographically distributed across Italy, with 41.7% working in the South, 30.3% in the North, and 28.0% in Central regions. Clinical settings varied, with 37.1% employed in tertiary referral hospitals, 35.6% in primary care outpatient clinics, and 27.3% in secondary care centers. Hospital or university institutions were the most common workplaces (47.7%), followed by local hospitals (28.8%) and research institutes (17.4%). Detailed demographic and professional characteristics are reported in **Table 1**.

Patterns of Digital Technology Use

Analysis of digital technology use revealed uneven adoption across the study population. The most frequently used tool was the electronic health record (EHR), reported by 18.9% of respondents. Telemedicine was used by 14.5%, followed by portable spirometry (11.8%). Home-based technologies such as home sleep studies and home ventilation monitoring were each used by

Table 1. Demographic and Professional Characteristics of the Study Sample: summary of age, gender, specialization, years of clinical experience, type of outpatient clinic, geographic distribution, and institutional setting for the 132 respondents included in the analysis.

	Total (N = 132)
Years of Professional Experience	
<5 years	14 (10.6%)
5 - 9 years	74 (56.1%)
>10 years	44 (33.3%)
Specialization	
Pediatricians	72 (54.5%)
Allergology	8 (6.1%)
Pulmonology	4 (3.0%)
Residents	44 (33.3%)
Unknown/Declined to answer	4 (3.0%)
Region of work	
North of Italy	40 (30.3%)
Center of Italy	37 (28.0%)
South of Italy	55 (41.7%)
Type of outpatient clinic	
Primary care	47 (35.6%)
Secondary care	36 (27.3%)
Tertiary Referral Hospitals	49 (37.1%)
Patients Seen per Month	
<10	19 (14.4%)
Between 10 and 20	17 (12.9%)
Between 20 and 50	48 (36.4%)
>50	47 (35.6%)
Unknown/Declined to answer	1 (0.8%)
Work Setting	
Hospital/University Institution	63 (47.7%)
Research Center/IRCCS	23 (17.4%)
Local Hospital	38 (28.8%)
Unknown/Declined to answer	8 (6.1%)

IRCCS: Scientific Institute for Research, Hospitalization and Health-care.

9.17% of respondents. In contrast, emerging technologies, including augmented reality, robotic rehabilitation, and digital twin platforms (defined as virtual models that integrate patient-specific data and computational simulations to predict disease trajectories and treatment responses) (12, 13), showed minimal uptake (0.3%). These frequencies are illustrated in **Figure 1**. Overall, respondents reported a preference for well-established technologies aimed at clinical documentation and

patient monitoring, whereas advanced or experimental tools were rarely used, likely due to limited availability, high costs, or lack of training.

Clustering of Respondents Based on Digital Engagement

Using t-distributed Stochastic Neighbor Embedding (t-SNE), two distinct clusters of respondents were identified based on digital tool usage and associated variables. Cluster 1 (Non-Users) comprised 23.5% of respondents (n = 31), while Cluster 2 (Users) included the remaining 76.5% (n = 101). The average probability of cluster assignment was higher among Users (0.694) than Non-Users (0.305), suggesting greater internal homogeneity in the digital adopter group. The two-cluster distribution and the visualization of respondent profiles are shown in **Figure 2**.

Cluster Characteristics

Non-Users were predominantly female (80.6%) and older, with 38.7% aged over 50. They were more commonly employed in primary (54.8%) or secondary (35.5%) care settings. In contrast, Users were younger (38.6% aged 30–39) and more frequently worked in tertiary hospitals (45.5%).

Non-Users primarily managed common conditions such as asthma (83.9%) and upper airway diseases (61.3%), with no reported use of digital tools in their clinical activities. Conversely, Users reported regular or occasional use of telemedicine (48.5%), EHRs (63.3%), portable spirometry (39.6%), and remote monitoring (27.7%). They were more likely to manage complex respiratory diseases, including bronchopulmonary dysplasia (36.6%), primary ciliary dyskinesia (39.6%), cystic fibrosis (22.7%), and chronic respiratory failure (33.6%).

Digital literacy was higher among Users, with 78.2% reporting proficiency in secure software use, 55.4% in digital communication, and 49.5% in telemedicine. Among Non-Users, such competencies were markedly lower or absent. The most frequently reported barriers among Users included lack of resources (52.4%), high system costs (40.5%), complexity of platforms (31.7%), and interpretability issues (33.7%). Connectivity challenges were also noted (21.8%).

Users identified several advantages associated with digital tools, including improved disease monitoring and adherence (70.3%), reduction in healthcare costs

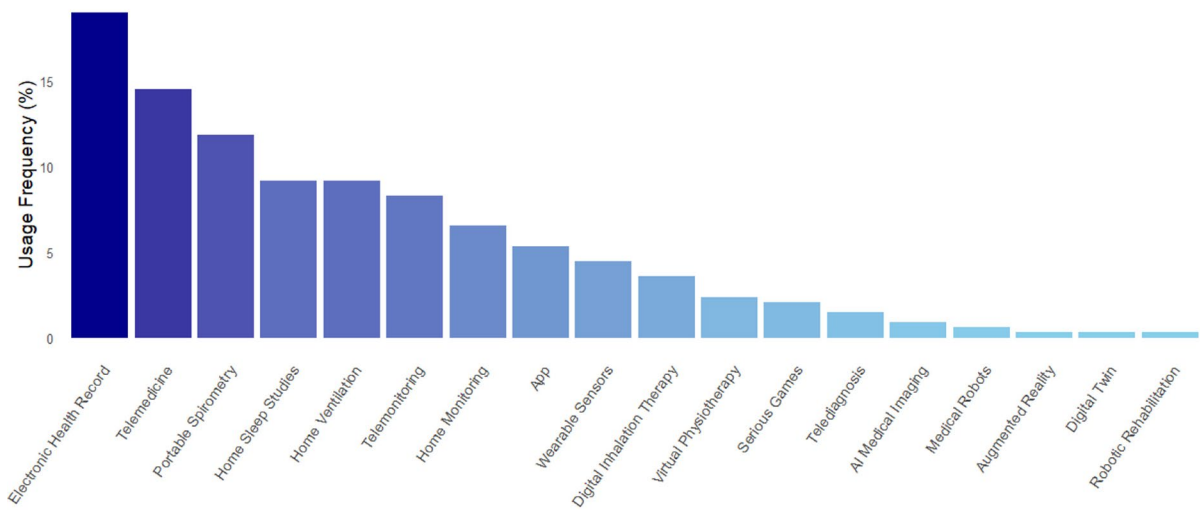


Figure 1. Frequency of Use of Digital Technologies in Pediatric Respiratory Care.



Figure 2. Clustering of Respondents Based on Digital Engagement and Technological Adoption. Two-dimensional representation of unsupervised clustering results visualized using t-distributed Stochastic Neighbor Embedding (t-SNE). Each point represents a clinician and is color-coded by cluster membership: Cluster 1 (Users, 76.5%) and Cluster 2 (Non-Users, 23.5%). Axes correspond to derived components capturing variation in digital engagement score and technological adoption index. The clear separation between clusters reflects distinct patterns of digital tool usage and associated clinical-demographic characteristics.

(49.5%), and the ability to deliver personalized care plans (34.7%). These benefits were not reported by Non-Users, likely due to their lack of direct experience with such technologies.

DISCUSSION

The results of the PeDiTCare national survey reveal a considerable heterogeneity in the integration of digital technologies among pediatric respiratory clinicians across Italy. While a significant proportion of respondents (76.5%) reported using digital tools to varying degrees in their clinical workflows, a notable minority (23.5%), referred to as the “Non-Users” cluster, declared that they neither have access to nor employ such tools in their daily practice. This discrepancy underscores a persistent digital divide within the Italian pediatric respiratory community, where innovation and traditional practice models coexist. Such divergence may stem from multiple interrelated factors, including disparities in institutional infrastructure, resource allocation, and organizational culture, as well as individual clinician readiness to embrace innovation. This aligns with international data suggesting that despite the growing availability of digital health tools, their implementation is not uniform and tends to lag in community and non-academic settings (6).

The analysis of demographic and professional variables within the survey sample provides compelling evidence that clinician characteristics and practice setting are key determinants of digital adoption. The “Non-Users” cluster was predominantly composed of older clinicians (with 38.7% aged over 50) and professionals working in primary or secondary care facilities (90.3% combined). In contrast, “Users” were significantly younger, with 38.6% aged 30–39, and more likely to work in tertiary referral hospitals (45.5%). These findings reinforce the idea that digital maturity is more pronounced in high-complexity clinical environments, where institutional investments in innovation, multidisciplinary collaboration, and access to technological infrastructure are more common. Moreover, generational factors likely play a role, with younger clinicians demonstrating greater digital literacy, flexibility, and comfort in using emerging technologies, an effect previously documented in digital adoption literature within the healthcare sector (14).

Another prominent pattern emerging from the survey is the co-occurrence of younger age, work in tertiary hospitals, and frequent management of complex respiratory diseases among clinicians in the ‘Users’ cluster. These variables are interrelated, as residents and early-career professionals are typically based in referral centers where technological infrastructures are more developed and where complex cases are more frequently seen. The “Users” cluster reported frequent management of severe and chronic respiratory conditions such as bronchopulmonary dysplasia (36.6%), primary ciliary dyskinesia (39.6%), cystic fibrosis (22.7%), and chronic respiratory failure (33.6%). These diseases often require close longitudinal follow-up, multidisciplinary coordination, and the collection of detailed physiological data, all of which are facilitated by the use of telemonitoring, portable spirometry, and electronic health records.

However, it is important to acknowledge that this association may reflect a confounding effect: younger clinicians, more digitally literate and receptive to innovation, are often based in tertiary hospitals, where both access to digital tools and exposure to complex cases are higher. Rather than implying a direct causal relationship between disease complexity and technology use, our findings suggest that digital engagement is primarily shaped by demographic and institutional characteristics of participants. Importantly, digital health solutions are not exclusive to high-complexity settings and could provide substantial benefits in managing common conditions such as asthma, particularly in primary care, where they may improve continuity, adherence, and self-management. Implementation strategies should therefore promote the use of digital tools across all care levels, not only in referral centers (15).

Beyond demographic and institutional factors, individual digital competencies also emerged as key elements influencing clinicians’ likelihood to adopt and effectively utilize digital health tools. In the “Users” group, respondents demonstrated high familiarity with secure software use (78.2%), digital communication platforms (55.4%), and key concepts related to data privacy (42.5%) and telemedicine (49.5%). These skills appear to form a foundational layer enabling the confident and effective use of digital solutions.

However, even among the digitally proficient, significant barriers to broader integration persist. The most fre-

quently reported obstacles included insufficient resources (52.4%), high system costs (40.5%), complexity of interfaces (31.7%), and issues related to data interpretability (33.7%). Connectivity problems were also cited (21.8%), especially in regions with limited digital infrastructure. It is worth noting that some reported barriers, such as “insufficient resources” and “high system costs,” may partially overlap and reflect the broader issue of structural underinvestment in digital infrastructure and support. These challenges are consistent with those described in other European studies, where lack of institutional support and fragmented digital ecosystems have been shown to hinder widespread adoption (16). The presence of such barriers, even among adopters, emphasizes the need not only for improved clinician training but also for structural reforms and investments at the healthcare system level. Personalized digital health can easily offer remote monitoring, especially when healthcare systems are overwhelmed and frequent follow-up visits are impractical. However, the healthcare sector is often slow to embrace change, and many technologies still need to be developed to a level of reliability suitable for clinical integration. For this reason, a collaborative approach is essential to fully harness the potential of digital health in pediatric respiratory care. Healthcare professionals, researchers, technology developers must work together to overcome challenges and ensure equitable access (15). This involves considering individual needs, providing continuous support, and addressing issues related to legal responsibility, workload, and training for healthcare providers. A cost-effective strategy could be to start with stand-alone digital interventions and then shift to integrated solutions with additional support if patients do not show improvement (17). The stratification of digital engagement observed in the study population has clear implications for both medical education and health policy. First, the evident gap in digital proficiency between clusters highlights the urgent need for structured digital health training across all levels of pediatric respiratory education, including continuing medical education programs. Targeted efforts should be directed toward clinicians in primary care and those with more years of professional experience, who may not have been exposed to formal digital training during their initial education. Second, policy-makers and institutional leaders must prioritize the

development of supportive infrastructures, both technological and organizational, to facilitate digital transformation. This includes ensuring equitable access to digital tools, interoperability of systems, and clear regulatory frameworks addressing privacy and ethical concerns. Without such systemic support, even the most motivated clinicians may face insurmountable obstacles to effective technology adoption.

A key strength of this study lies in its originality and institutional support. To our knowledge, this is the first national survey specifically designed to investigate the knowledge, use, and perceived impact of digital technologies in pediatric respiratory care. Its development and dissemination were officially supported by the IPRS/SIMRI through the PeDiTCare Study Group, underscoring the scientific relevance and timeliness of the topic. The survey addresses a significant gap in the literature and provides a foundational dataset that can inform future policy, clinical practice, and research initiatives in this evolving field. In addition, the use of advanced analytical approaches, including Random Forest models and unsupervised clustering through t-distributed Stochastic Neighbor Embedding (t-SNE), represents a novel methodological asset. These tools allowed us to explore latent profiles of technology adoption and to visualize complex multidimensional relationships in a clinician population, offering insights that go beyond conventional descriptive analysis.

Despite these strengths, certain limitations must be acknowledged. First, the cross-sectional design of the survey limits the ability to establish causal relationships between clinician characteristics and digital adoption behaviors. Second, as participation was voluntary and distributed through a scientific society newsletter (with a response rate of 13.4%), there is a risk of self-selection bias, whereby clinicians more interested or involved in digital health may have been more likely to respond. This should be considered when interpreting the generalisability of the findings. Third, the modest sample size, though representative of different geographic areas and care levels, may not capture the full diversity of clinical settings across the country.

Finally, although machine learning techniques offer advantages in exploratory data analysis, their interpretability and sensitivity to parameter tuning must be considered. Specifically, t-SNE is known to be influenced by

perplexity and learning rate choices and may obscure intermediate or hybrid user profiles. Future research with larger, longitudinally tracked cohorts and mixed-methods designs (including qualitative interviews or focus groups) could complement these findings and provide a more nuanced understanding of how digital health is transforming pediatric respiratory practice.

CONCLUSIONS

The integration of digital technologies into pediatric respiratory care represents a growing priority yet remains inconsistent across clinical settings and professional profiles. This study offers a timely contribution by mapping the current landscape of digital health use through a national survey supported by IPRS/SIMRI, shedding light on how clinicians engage with technological innovation in real-world practice. Rather than presenting a uniform picture, the findings reveal a stratified scenario, shaped by differences in experience, infrastructure, and clinical context. These insights call for a rethinking of implementation strategies, shifting from general promotion of digital tools to more targeted, needs-based approaches that consider existing disparities.

As healthcare systems increasingly invest in digital transformation, aligning these investments with the realities of pediatric respiratory care will be essential. Moving forward, the integration of technological solutions should not be viewed merely as a matter of access, but as an evolving process that requires institutional support, continuous education, and a clear vision of digital health as an enabler of equity and quality in pediatric care.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest

The authors declare that they have no conflicts of interest relevant to the content of this article.

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Authors' contributions

AL, GF and SLG conceived and supervised the study, coordinated the development of the survey, and led the drafting of the manuscript. AP contributed to survey dissemination, data organization, and descriptive statistical analysis. AP performed the machine learning analysis and prepared the figures and supplementary material. VM, SM and RN assisted in interpreting clinical data and reviewing the manuscript critically for intellectual content. All authors contributed to the study design, revised the manuscript critically, and approved the final version. They all agree to be accountable for the integrity and accuracy of the work..

Ethical approval

Human studies and subjects

This study involved the voluntary and anonymous participation of clinicians through an online survey and did not include any collection of sensitive personal data or clinical information. In accordance with current Italian regulations, ethics committee approval was not required.

Animal studies

N/A.

Data sharing and data accessibility

The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to the nature of the survey and the anonymized dataset, no individual identifiable information is included. Data sharing will be considered for academic and research purposes in compliance with applicable data protection regulations.

Publication ethics

The authors declare that this manuscript is original, has not been previously published, and is not under consideration for publication elsewhere. All authors have approved the final version of the manuscript and agree with its submission to this journal.

The authors affirm that the work complies with the highest standards of research integrity. No data have been fabricated, manipulated, or falsified. The manuscript is free from plagiarism, and all sources and contributions have been appropriately acknowledged.

The authors confirm adherence to ethical principles regarding authorship, data transparency, and responsible communication of scientific results.

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REVIEW

Vaping as a new threat for respiratory health: a position statement from the Italian Pediatric Respiratory Society

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ABSTRACT

Electronic Nicotine Delivery Systems such as electronic cigarettes and heated tobacco products are more and more commonly used among youth worldwide. Even if such devices are proposed as a healthier alternative to conventional cigarettes smoking, many studies are reporting potential detrimental health effects both *in vitro* and in animals and humans. Regarding the lungs and airways, acute vape exposure causes mainly inflammation, bronchial hyperreactivity and reduced response to infections. The long-term effects of active and passive vaping are still largely unknown, but the presence of toxicants and carcinogens in vape suggest caution, especially when considering the first limited reports on increased risk of lung cancer. Second and third – hand exposure to vaping is likely to be harmful too, especially in childhood. Moreover, children and adolescents are at increased risk of addiction to nicotine, which is often present at high concentration in e-liquids and pod-mods. Notably, vape exposure may be harmful also during pregnancy, by contributing to preterm birth and low weight at birth. The Italian Pediatric Respiratory Society (SIMRI) has been involved and has proposed many different activities on smoking prevention in the last decades. In such a scenario, a group of SIMRI members proposed and obtained to create a Task Force with the goal of producing the first and up-to-date SIMRI recommendations on vaping, which are provided in this paper. To protect children and adolescents, SIMRI experts underline the need to educate paediatricians and families on this issue, to implement prevention campaigns, to ensure smoke-free and vaping-free environments and to reduce tobacco industry interference especially on social media.

IMPACT STATEMENT

SIMRI acknowledges that vaping represents a serious threat to respiratory health in children and adolescents and proposes ten recommendations to take action.

INTRODUCTION

The term “Electronic Nicotine Delivery Systems” (ENDS) includes many different electronic devices producing a visible aerosol called “vape” which delivers

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ABBREVIATIONS

CC = Combustion Cigarette/s

EC = Ecigarette/s

ENDS = Electronic Nicotine Delivery Systems

EVALI = E-cigarette or Vaping use Associated Lung Injury

HTP = Heated Tobacco Products

SIMRI = Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili)

US = United States

KEY WORDS

Children; e-cigarette; EVALI; heated tobacco products; vape.

nicotine without any combustion process (see glossary, **Table 1**). Electronic Cigarettes (EC) are the most common example of ENDS (1), appeared on the market in 2003 when the Chinese pharmacist Hon Lik proposed them as an alternative to traditional Combustion Cigarettes (CC). In 2006 EC arrived in Europe and the United States (US) and then spread worldwide, gaining increasing success. In 2014 new devices producing aerosol by heating tobacco sticks (HTP) appeared on the market, and they are now more and more commonly used, especially by young people. In 2023 vapers were around 80 million worldwide (2). In Italy, according to recent data from the Global Youth Tobacco Survey carried out by the “Smoke, Alcohol and Drug Observatory” within the Italian National Institute of Health, current and ever smokers are continuously reducing, with only 2% of adolescents using only CC. However, vaping has increased in 2023 by about 14%, with 1 adolescent out of 4 having used at least one tobacco product including ENDS. Vaping has already become the most

used tobacco product among adolescents in other countries such as the US (3, 4), where an estimated 1.6 million middle and high school students currently use EC (5). The widespread diffusion of EC is associated with a mistaken awareness that they are a healthier alternative to CC. On the contrary, direct and indirect exposure to the products of these devices is not free of risks so that the spreading of vaping especially among children and adolescents has become a significant public health problem, considering that it also facilitates nicotine addiction and transition to the use of CC (6). In the last few years, many scientists have become aware of the potential harms caused by vaping, and a growing number of studies showing such effects mostly *in vitro* and in animal models, but also in humans, have been published. The position statements and recommendations on vaping from the European Respiratory Society (7), the Forum of International Respiratory Societies (8), the European Board of Pediatrics (9) and American Academy of Pediatrics (10), tried to raise aware-

Table 1. Vaping glossary.

Cloud-chasing	Vapers use this technique to create different types of aerosol plume in a sort of competition.
Dripping	Vaping technique in which denser vape is generated by manually dripping e-liquids directly onto the heating coils.
Dual user	User of both electronic cigarettes and traditional combustion cigarettes.
E-Cigarette	Electronic devices that simulate the act of smoking by aerosolizing e-liquids instead of burning tobacco.
ENDS	“Electronic Nicotine Delivery Systems” is a generic term used to identify all electronic devices available to deliver nicotine without tobacco combustion.
EVALI	“ <i>E-cigarette or Vaping use-Associated Lung Injury</i> ” is an acute lung condition characterized by respiratory distress, abnormal chest CT, absence of signs of pulmonary infection or any other plausible diagnoses and a recent history of vaping. Some Authors proposed introducing also the term EVALD (“ <i>E-cigarette or Vaping use-Associated Lung Disease</i> ”) to underline that vaping may cause different types of lung disease and not only acute injury.
Heat-not-burn devices / Heated tobacco products	Electronic devices generating aerosol by heating up sticks of tobacco, without burning it.
Puff	The term refers to disposable and cheap electronic cigarettes resembling rechargeable pod-mods, the use of which is spreading among adolescents.
Stealth Vaping	The act of vaping in a discreet manner by using small quantities of vape or particularly small devices.
Triple user	Users of traditional combustion cigarettes together with electronic cigarettes and heated tobacco products.
Smoker	Traditional combustion cigarettes user.
Vape	The aerosol produced by ENDS which appears denser than that produced by combustion cigarettes. The act of inhaling and exhaling vape is known as “vaping”.
Vaper	Electronic cigarette user.

Table 2. SIMRI Call to action for pediatricians.**10 rules to protect our children from vaping exposure**

- 1 Pediatricians must be aware that mounting evidence shows that vaping threatens children's health and particularly respiratory health, in a similar way cigarettes do, and that they should routinely screen their patients and families for vaping.
- 2 Children and adolescents are at increased risk of addiction to nicotine and they should be protected from tobacco industry interference especially on social media.
- 3 First-hand exposure to vaping may cause acute and chronic lung damage, and respiratory symptoms such as cough, phlegm, dyspnea, wheezing and asthma exacerbations.
- 4 Second and third - hand exposure to vaping is likely to be harmful and should be avoided, especially in childhood.
- 5 Pregnant women must be routinely screened for vaping, and informed and counselled on the risks related to vaping during pregnancy.
- 6 Even if there is still no clear evidence on e-liquids and vaping carcinogenicity, following the precautionary principle it is strongly suggested to avoid any kind of exposure, especially if prolonged.
- 7 It is mandatory to ensure smoke-free and vaping-free environments, including indoor locations.
- 8 We suggest electronic nicotine delivery systems should be regulated as tobacco products, including bans on flavorings and on child-friendly packaging, which should be enforced.
- 9 Tobacco policy across Europe should be aligned with the objectives and political efforts promoted by the World Health Organization Framework Convention on Tobacco Control.
- 10 Urgent implementation campaigns to prevent the initiation of vaping among youth, including counselling plans focused on the risks of vaping in schools, which should be promoted locally and at a national level.

ness on the subject. The Italian Pediatric Respiratory Society (SIMRI), which is a partner of the Italian Pediatric Society, has been involved and has proposed many different activities on smoking prevention, including projects to make paediatricians part of the smoking cessation process and scientific events focused on vaping. In 2023 a group of SIMRI members proposed and obtained to create a Task Force with the goal of producing the first and up-to-date SIMRI recommendations on vaping, which are reported in **Table 2**. This paper outlines existing scientific data on EC and HTP, which was evaluated by searching relevant published studies in the MEDLINE/PubMed database in the last 10 years (the original search was run in March 2024 and updated in September 2024). The position statement was reviewed and approved by SIMRI executive committee in November 2024.

WHAT ARE E-CIGARETTES AND HEATED TOBACCO PRODUCTS?

EC are the most used ENDS: such devices are usually composed of three main components: an atomizer, a liquid storage unit, and a power source. The atomizer heats the e-liquid so that it can be vaporized and inhaled by the user. Four generations of EC are identifiable: the

first generation of EC looked like CC (the *cig-a-likes*), the second one are the so-called *vape-pens*, which have a refillable tank, while the third generation is represented by bigger devices allowing the user to customize voltage and wattage thus varying the temperature of the aerosol (the higher the temperature, the stronger the "hit" felt in the throat). The most recent EC are the *pod-mods*: these fourth EC generation devices resemble USB drives, are cheaper, easily conceivable and reusable, and are getting tremendous success among youth, especially the disposable ones. The pod-mods are particularly worrisome since they use nicotine salts with benzoic acid, which let the user inhale high quantity of nicotine in a short time, since they do not cause harshness or irritation (11, 12). E-liquids are composed mainly of solvents such as vegetable glycerin and propylene glycol, which produce the visible cloud while vaping, added with flavouring additives, which give vape a distinctive flavour. Nicotine is commonly found in e-liquids, even in those declared as nicotine-free, potentially in very high concentrations (up to 50 mg/mL). Notably, e-liquids may contain toxic and/or irritative substances, such as tobacco alkaloids and nitrosamines, volatile organic compounds, formaldehyde, acetaldehyde, acrolein, and metals (13). Heated Tobacco Products (HTP) are electric devices that produce aerosol by heating tobacco up to about 350°C.

Three main designs of HTP are available: i) electrically HTP (eHTP): vape is produced by heating a stick containing reconstituted tobacco and flavouring additives which must be inserted in the device by the user; ii) aerosol HTP: a warmed aerosol is passed through the tobacco sticks; iii) carbon HTP: vape is produced by heating a tobacco substrate through a smoldering carbon rod (14, 15). eHTP currently dominate the market. Increasingly available evidence shows that, even if the content of nicotine and toxicants in HTP vape seems to be lower than that in CC, the concentrations of some harmful constituents are higher in HTP than in CC, and several toxic compounds are uniquely present in HTP and not in CC smoke (16, 17).

NICOTINE AND EXPOSURE TO OTHER SUBSTANCES

The growing availability of different ENDS makes it difficult to clarify which substances such devices contain and deliver to the users, depending also on the user's vaping habits and device customization. However, some studies have already tried to shed light on the issue. Regarding e-liquids, their chemical composition may appear somehow simpler than that of CC and tobacco smoke, since the producers state that they contain the following four main components: i) nicotine, ii) vegetable glycerin, iii) propylene glycol, iv) flavourings (18). While a single CC contains about 10 mg of nicotine and delivers 1-2 mg when smoked, in e-liquids, the amount of nicotine is higher and varies between 15 and 50 mg/mL (with a limit of 20 mg/mL set by the Tobacco Products Directive in the European Union) (19) and the level of nicotine in vape in common conditions of use varies between 0.5 and 15 mg according to some studies performed via an automatic smoking machine using different EC (20, 21). As for pod-mods, a single pod may deliver in limited time about 15-30 mg of nicotine, with equivalence to 13-30 CC (22). Regarding vegetable glycerin and propylene glycol, these solvents are commonly used in the food and cosmetics industry and are included in the Food and Drug Administration *generally recognized as safe* list considering such use, but not inhalation. Notably, repeated inhalation of these molecules can be harmful, since they are hygroscopic and may irritate the bronchial mucosa, as demonstrated by the fact that cinema and theatre workers develop cough

and dyspnoea when repeatedly exposed to stage smoke (23). As for flavours, more than 15.000 different flavours are currently available on the market, to make EC more attractive and popular especially among young people (24), even if they can exert harmful pulmonary effects similar to some irritants that cause asthma or may represent allergens themselves (25, 26). Notably, the repeated inhalation of diacetyl, which gives vape the taste of butter/biscuits, has found to cause a bronchiolitis obliterans syndrome known as *pop-corn workers' lung* (27). The flavouring additives terpene and ethyl ester undergo decomposition after aerosolization with the production of reactive oxygen species and other chemical substances such as ketenes that induced lung damage even at low concentrations (28). Moreover, the heating and aerosolization at high temperatures of the e-liquids is associated with the degradation of other components and emission of potentially toxic and/or cancerogenic compounds such as carbonyl compounds (e.g., formaldehyde, acetaldehyde, and acetone), metals, and tobacco-specific nitrosamines (29), giving the aerosol a more complex chemical composition than the original e-liquid (**Table 3**). The aerosol generates particles of different sizes which allows their distribution in both the lower and upper airways (30, 31) and may cause inflammation on the respiratory mucosa (32-37). Also aerosol from HTP contains nicotine as well as many toxicants, some

Table 3. Main toxicant substances found in vape from e-cigarettes: even if the levels and numbers of substances are generally lower than those in smoke from conventional cigarettes, it is difficult to estimate the actual quantity of substances inhaled by the user, which depends on the device and related customization, vaping habits, composition of e-liquids, sticks or pod. Some of these toxicants have been found also in vape from heated tobacco products (13, 38).

Irritant/toxicant substances	Known carcinogens
Nicotine	Formaldehyde
Carbonyls	Butanone
Solvents (PG/VG)	Benzene
Flavourings	Acetaldehyde
Tobacco alkaloids	Benzopyrene
Tobacco specific nitrosamines	Acrolein
Volatile organic compounds	
Metals	
Microorganisms	
Carbon monoxide	Toluene
Tar	

of which are also found in traditional smoke, such as volatile organic compounds, polycyclic aromatic hydrocarbons, and carbon monoxide produced from pyrolysis and thermogenic degradation (38). It should be noted that HTP deliver at least 20 chemicals that are not present in CC and that could be toxic and harmful also (39).

ACUTE AND CHRONIC RESPIRATORY TOXICITY OF VAPING IN CHILDREN AND ADOLESCENTS

Health effects of acute and long-term exposure to vape from ENDS is currently being investigated. Some Authors reported that the acute lung toxicity of EC may be greater than that of CC and several studies have shown a concrete association between vaping and acute lung injury, current asthma, pulmonary haemorrhage and eosinophilic and lipoid pneumonia, even in adolescents (40, 41). A great concern was raised in 2019 after the spread of EVALI (*E-cigarette or Vaping use Associated Lung Injury*) among young adults and adolescents in the US, with 76% of the patients being <35 years of age and 15% <18 years of age, as reported by the Centers for Disease Control and Prevention (42). This condition includes non-specific symptoms such as shortness of breath, cough, fever and chills, vomiting and diarrhoea, headache, dizziness, and chest pain together with pulmonary opacities on radiography or CT and a history of vaping in previous 3 months, with no other causes (43-46): it should be noted that CT findings of EVALI show different degrees and stages of acute lung injury, with organizing pneumonia being the more common pattern (47). Notably, Corcoran *et al.* in their study reported seven EVALI cases in adolescents, five of which required supplemental and three of which showed reduced lung function after discharge despite resolution of symptoms, thus underlining the importance of respiratory follow-up for children and adolescents diagnosed with probable or confirmed EVALI (48). One case of EVALI was reported also in an Italian 15-year-old girl (49). The spread of EVALI seems to have been caused by vitamin E acetate, a substance used as a diluent and thickener in e-liquids containing tetrahydrocannabinol: unfortunately, when inhaled, vitamin E acetate interacts with phosphatidylcholine, altering surfactant and superficial tension, thus initiating alveolar inflammation (50, 51). However, vitamin E is not the only cause of EVALI, since more than 10%

of cases were reported in subjects who had used only ENDS products containing nicotine and no THC at all. In 2022, results from the PATH study (*Population Assessment of Tobacco and Health*) have shown that use of EC among healthy young adults is independently associated with the development of respiratory symptoms in general (52). As for children and adolescents, in the study by Zutrauen *et al.* 71 injury/illness cases of patients who presented to paediatricians for a harm related to the inhalation of vaping aerosols were analysed: 68% were aged 15 to 17 years; 54% presented with respiratory distress and 18% with symptoms of nicotine toxicity. Furthermore, the presence of respiratory distress was more likely associated with hospitalization or intensive care unit admission (53). Moreover, many studies on self-reported symptoms on adolescent vapers have been published: these are typically school-based data collections, mainly on high school students, which were carried out mostly in the United States but also in Asia and Canada. Taken together, these studies demonstrate increase odds of self-reported diagnosis of asthma by physicians and current asthma in the previous year in current EC users compared with never users, as well as increased odds of reporting asthma symptoms, chronic cough or phlegm, and/or bronchitis (54-59). In detail, the most reported respiratory symptoms are coughing, shortness of breath, throat irritation, chest pain, phlegm and wheezing (60, 61), and effects appear particularly prominent among individuals with a pre-existing history of bronchial asthma (62, 63). Some of these studies reported respiratory symptoms in adolescents exposed to second hand vaping at home. Notably, in 2022 Islam *et al.* demonstrated that second hand vape exposure was associated with increased risk of bronchitis symptoms and shortness of breath in a cohort of more than 2000 young participants (mean age 17,3 years) enrolled from schools in Southern California (64). It has been recently reported that second hand exposure to vaping can affect negatively asthma control in children (65). *In vivo* animal studies show potential also for third-hand exposure to vape (66). Even if studies are less numerous, acute lung injury and detrimental effect of second-hand exposure have been reported also for HTP (67-69).

The long-term effects of vaping exposure are still poorly known. However, there is already evidence on late onset

implications such as an increase in cardiopulmonary morbidities and potential detrimental effects in many other districts as well as increased risk of pulmonary, systemic and neoplastic illness in a similar way to CC (70, 71). Some studies have focused on the role of the single components of vape, demonstrating that vegetable glycerin, propylene glycol and flavourings are directly linked to lung function impairment (72). Additionally, it is well recognized the role of nicotine in increasing the permeability of primary lung microvascular endothelial cells, leading to the compromission of the endothelial cell barrier function (73). Moreover, molecular investigations underscore alterations in respiratory immune homeostasis attributed to chronic EC use, resulting in increased susceptibility to viral infections (74-77). It can be assumed that chronic, daily vape inhalation alters the inflammatory and immune status of the lungs, causing greater risk of infections and inflammatory disorders of the lungs, as well as significant decline in key spirometry parameters in vapers, but no data is available regarding childhood and adolescence (78). The cumulative effects in terms of oxidative stress, protease activity, inflammation, infection recurrency and DNA damage, collectively point to an elevated risk of asthma, COPD and lung cancer among EC users. This risk is corroborated by long-term exposure studies in mice, revealing the development of adenocarcinomas and bladder urothelial hyperplasia (79), nicotine-dependent airway changes comparable to cigarette-induced emphysema and COPD (80, 81), and persistent, widespread DNA damage in the lungs, heart, and bladder mucosa (82). Recently, in a case control study of 4975 lung cancer cases and 27294 controls without cancer, it was found that the risk of lung cancer among those who combined vaping with CC was 4-fold higher than for those who only smoked (83).

EFFECTS OF PRENATAL EXPOSURE TO VAPING

Women often think that the use of EC and HTP during pregnancy is harmless. A survey conducted in pregnant women showed that nearly 40% don't know that EC contain nicotine and 40-60% perceive them as safer than CC (84). Moreover, there are studies supporting the use of EC as a valuable option for pregnant smokers who cannot quit smoking (85). Nonetheless, most

authors as well as the World Health Organization warn against the risk of EC in pregnancy stating that no product containing nicotine is safe in pregnancy. So far, very little studies have been conducted in humans to evaluate the short and long-term effects of maternal vaping on offspring. A recent randomised control trial comparing EC and nicotine patches as strategies to quit tobacco smoking during pregnancy showed a similar safety profile of these products. However, it is important to highlight that the cessation rates were very low in both groups as a limitation (86). Nonetheless we need studies comparing EC with no tobacco-derived products to have reliable data on their safety. In this regard some recent data suggest that women vaping during pregnancy have a significantly higher risk of adverse perinatal outcomes, such as preterm birth (87, 88). Likewise, some recent studies suggested that also the use of HTP during pregnancy may be associated to preterm birth (89), low birth weight and hypertensive disorders of pregnancy (90). Moreover, a cross-sectional survey conducted in Japan showed an association between the use of HTP during pregnancy and an increased prevalence of allergy in the offspring (91). It should be noted that vaping can lead to blood nicotine levels like those associated with CC smoking (92): since animal studies proved that nicotine is the key mediator of the negative impact of in-utero tobacco smoke exposure on lung development, it is likely that similar detrimental effects can be caused by inhaling nicotine during pregnancy. Nicotine, in fact, affects offspring lung structure impairing alveolarization and reducing vessel density, and influences lung function causing a decrease in expiratory flow (93). Moreover, nicotine exposure during intrauterine life is associated with impaired function of alveolar macrophages and increased levels of oxidative stress (94). Furthermore, it should not be forgotten that exposure to vape during fetal life implies exposure to a mixture of other substances the effects of which on offspring are still largely unknown.

Studies in mouse models demonstrated that maternal vaping is associated with delayed embryo implantation, reduced birth weight, increased neurodevelopmental vulnerability and vascular dysfunction and can induce epigenetic reprogramming in offspring too (95, 96). As for the development of the lung, studies conducted in mice showed that intrauterine exposure to EC either

with or without nicotine can cause structural and functional lung abnormalities that persist into adulthood (97-99). At a molecular level, it has been demonstrated that EC vape exposure (with or without nicotine) leads to increased levels of factors associated with myogenesis and dysregulated extracellular matrix remodelling, processes that might predispose to chronic lung diseases later in life (100, 101). It has also been demonstrated that vaping exposure can lead to immune dysregulation in offspring persisting into adulthood (96). Finally, a recent study demonstrated that in utero mint-flavoured JUUL vaping exposure is associated with reduced offspring growth in a lamb model likely due to dysregulated expression of genes associated with hypoxia and oxidative stress which cause placental insufficiency. Moreover, increased lung inflammation in response to house dust mite was found, suggesting a possible association between maternal vaping and lifelong response to aeroallergens (102). In conclusion, although epidemiological studies on the effect on EC use during pregnancy on children's respiratory health are still scarce, considering the available evidence, it is mandatory that health care providers educate pregnant women about the risk associated with vaping (103).

VAPING USE IN CHILDHOOD AND ADOLESCENCE AND MARKETING STRATEGY OF ENDS

Despite being prosed as a smoking cessation device, a damage reduction strategy or a legal alternative where CC smoke is prohibited, EC have rapidly become the most common tobacco derived product used among youth (3-5, 104), with almost 5,9% of United States high school students currently vaping (5, 105) while in Europe, students as young as 11 years old tried EC at least once in 17 sites (106) and in Italy 20,2% of adolescents currently use EC and 14.3% currently use HTP (107). ENDS seem not to be a substitute for CC but rather a complementary product: almost all current smokers are triple users (CC + EC + HTP) or, sometimes, dual users (CC + EC) in this age group with a drastic increase of prevalence over the last two years. The reasons for this dramatic success must be sought in the widespread availability of ENDS together with their social acceptance and the attractive packaging of the products (108). Some of the products advertise their ability to be discreetly used: more than 60% of EC users declared to have *stealth*

vaped intended as used an EC in a public place where it was not approved and attempted to conceal EC use. Videos on the internet make demonstrate different techniques for producing vape by exhaling under clothing or into backpacks, often in the school setting (109). As expected, there is an association between social media use and increased risk of CC, EC, and dual use (109). Unfortunately, the adolescent brain is more susceptible to nicotine addiction: the effect is mediated by binding to the nicotine cholinergic receptor in the brain to release dopamine, which is involved in drug-induced reward and produces changes within the limbic and dopaminergic circuitry that underlies motivated behaviours, potentially enhancing the vulnerability to nicotine addiction (110). Therefore, adolescents may become easily addicted and may start also using CC (the *gateway effect*) (6). The main reasons for EC experimentation are curiosity, appealing flavours, and peer influences, while the top reasons for discontinuation were related to losing interest, perceiving EC as "uncool", and health concerns (111). Moreover, EC are perceived as less addictive and less harmful than CC and in adolescents. The worldwide spread of EC use is also due to aggressive marketing. Several studies have demonstrated the association between adolescent and young adults' exposure to EC marketing and their future vaping experimentation (112). EC companies base their marketing strategies on social media, working with celebrities and young influencers to promote their products with posts showing everyday activities and often concealing their commercial aim (113). Pricing strategies are also utilized by vaping industry to maintain existing customers but also to recruit new ones. Finally, social media is a powerful marketing tool because it lets companies learn about who interacts with their content and target consumers' specific demographic profiles (114). Another marketing tool that EC companies adopt is product placement in music videos that appear on popular platforms such as YouTube. This strategy that combines advertising and entertainment is known as "advertainment" and produces a positive attitude towards the product use (115, 116). Another strategy is the use of cartoon-based marketing to promote vape products, with many manufacturers using cartoons in their logo as a brand recognition strategy (117). The ENDS marketplace has also expanded in real shops, with thousands of new stores opening

in the last decade. These stores provide a social and interactive experience, where vape shop retailers act as consumer educators. Moreover, the store windows are designed to be colourful, attractive and eye-catching, showing price promotions, so even nonsmokers are exposed to vape products while walking about their daily activities. Vape shops and EC companies often sponsor social events where these devices can be tried for free, too, where branded merchandise is distributed to guests and there are often branded photos frames for taking pictures and selfies to post on social media. Marketing is also based on unproven and false claims. For instance, neither World Health Organization nor any scientific society have approved EC as a smoking cessation aid, EC companies still use smoking cessation as a marketing communication message. They also state that EC are cleaner and healthier because they don't produce second-hand smoke but only vapour, which is untrue. Health warnings are rare and written in small fonts, often placed at the bottom of the announce, within *terms and conditions*.

INTERVENTIONS FOR PREVENTING E-CIGARETTE USE AMONG CHILDREN AND ADOLESCENTS

Primary physicians' involvement is essential in screening, prevention and management of EC usage. Research from the US shows that in primary care settings, screening for vaping is not frequently undertaken: the most important reason is the lack of knowledge about ENDS and their risks (118), while awareness of the risk of EC in adolescents could increase through counselling actions by physicians. An important role should be given to the organization of public health education campaigns by institutions. Among the activities, it could be useful to distribute brochures to patients and their families on the health risks associated with vaping (119, 120). There are few data on the effectiveness of public health interventions. One trial demonstrated encouraging results from a text messaging campaign in the United States, and similar positive results have been seen in the past with text messaging aimed at smoking cessation (121). Moreover, EC apps dedicated to vaping cessation should be implemented since few are now available in contrast with many apps encouraging adolescent's EC use (122). Policy interventions should ban the use of cartoons and other strategies aimed at children and ado-

lescents as targets for EC marketing. In the last few years, the Food and Drug Administration issued warnings to companies regarding the advertising and distribution of EC young people, particularly through social media platforms (123) as well as to distribute ENDS resembling youth-appealing characters (124). The strict enforcement of bans on the sale of EC to minors and limiting their availability are essential as well as vaping in public places bans and stricter restrictions which are starting to be applied in many countries to face this new epidemic, together with increasing the minimum age of sale of EC and all tobacco products from 18 to 21. On the contrary, in other countries smoke-free laws were established before EC entered the market and therefore, they didn't mention EC at all (125).

CONCLUSIONS

The members of SIMRI's Task force on vaping, based on the current available evidence, acknowledge that ENDS represent a serious threat to respiratory health in children and adolescents and propose ten recommendations to take action, which are provided in **Table 2**. While limiting the spread of ENDS among children and adolescents seems very difficult, we believe that each pediatrician should screen for vaping and might contribute to educate parents and children on the subject. Schools and organization should also be involved, and it is desirable that more restrictive laws will be approved soon to reduce the places where to use ENDS. Our goal should be to pursue breathing clean air and preventing or stopping all tobacco and nicotine product use, and not to replace one harmful tobacco/nicotine product with another one.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have no conflict of interests relevant to this article to disclose.

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Author contributions

MEDC, MG, SLG conceptualized the study, drafted the initial manuscript, reviewed the literature and critically revised the final manuscript. ABe, ABo, SC, MF, AK, CM, RN, DR contributed to the review of the literature and data collection and drafted parts of the initial manuscript. All authors proposed, discussed and approved the final ten recommendations. All authors read, critically reviewed and approved the final manu-

script as submitted and agree to be accountable for all aspects of the work.

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REVIEW

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

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Supplementary Table 1 can be found at: <https://www.pediatric-respiratory-journal.com/>

ABSTRACT

Croup, also known as acute laryngotracheobronchitis, is common in the first years of life and is mainly caused by respiratory viral infections leading to laryngeal edema with subsequent onset of hoarseness, barking cough and stridor. Although most of the cases are classified as mild, some patients may show severe respiratory distress requiring up to intensive care. Moreover, even mild and moderate cases result in a high rate of pediatric emergency departments visits since croup symptoms, often occurring at night, can be frightening for caregivers. Treatment of pediatric croup is based on corticosteroids administration, with the addition of inhaled epinephrine in severe cases. However, croup management is still highly heterogeneous worldwide due to the paucity of dedicated randomized controlled trials. This statement outlines the most recent evidence supporting the use of corticosteroids and epinephrine in the treatment of croup in childhood and reports the recommendations for optimal treatment from the Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili - SIMRI).

IMPACT STATEMENT

Systemic corticosteroids represent the first-line treatment for managing croup in childhood, with the addition of inhaled epinephrine in severe cases. However, management of this condition is heterogeneous worldwide due to the lack of evidence-based guidelines and paucity of dedicated randomized clinical trials. This statement outlines the evidence supporting the use of corticosteroids and epinephrine in the treatment of croup in childhood and reports the recommendations of the Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili - SIMRI) in treating this condition. The statement will have a significant role in improving croup treatment at least at a national level.

INTRODUCTION

Croup, also known as acute laryngotracheobronchitis, is a prevalent respiratory condition in young children. It is a frequent cause for pediatric healthcare visits, accounting for approximately 15% of all respiratory-related healthcare visits in this age group. Croup typically leads to obstructions in the upper airways, character-

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KEY WORDS

Children; inhaled corticosteroids; larynx; laryngotracheobronchitis; respiratory infections.

ized by distinctive symptoms including hoarseness, a barking cough, stridor and/or noisy breathing. Children may also experience difficulty with inhalation and varying degrees of respiratory distress that can worsen rapidly (1). While usually self-limiting, croup places a significant burden on healthcare resources due to frequent doctor visits, emergency room use, and occasional hospitalization in a small proportion of cases. This condition predominantly occurs during the fall and winter months, affecting boys more often than girls (ratio of 1.5:1). Although most common between six months and three years of age, with peak incidence at two years, croup can affect children up to 6 years old, and even younger infants in rare cases (2). In children <2 years the majority of cases (around 85%) are classified as mild, potentially to be managed at home by educating parents or through greater access to primary care (3). Less than 5% of children with croup require hospitalization, and only 1-3% need intubation. The prognosis is generally favorable, with a mortality rate of less than 0.5%, even in intubated patients (4). Recurrent croup, defined as more than two episodes per year, should be viewed as a potential indicator of an underlying airway abnormality. This could be structural, as seen in children with a history of intubation or prematurity, or inflammatory, as in cases with a history suggestive of asthma or gastroesophageal reflux. Such cases warrant further investigation to identify the underlying cause (5, 6).

Before the 20th century, the term “croup” was mainly used to refer to diphtheria, while viral infections are currently the most common cause, identified in up to 80% of patients, and triggering inflammation and swelling in the subglottic region and laryngeal mucosa, leading to respiratory difficulties and stridor. Parainfluenza viruses are implicated in 75% of cases, with human parainfluenza virus 1 being the most frequent. Other viral causes include influenza A and B, adenovirus, respiratory syncytial virus, rhinovirus, and enterovirus (7). Nowadays, croup is rarely caused by bacteria such as *Mycoplasma pneumoniae* and *Corynebacterium diphtheriae* (8). Notably, croup can be caused also by SARS-CoV-2 (9, 10). Viral croup usually presents with 12-72 hours of low-grade fever and a runny nose. The progressive narrowing of the larynx results in stridor, hoarseness and a barking cough, often accompanied by an increased respiratory rate and chest retractions. Symptoms may worsen

with emotional distress, are often more pronounced at night (11) and typically resolve spontaneously within 48 hours to one week. Diagnosis is primarily based on clinical findings so that diagnostic testing is usually unnecessary. A blood count can help differentiate viral croup from bacterial causes of stridor (like epiglottitis, peritonsillar abscess, or retropharyngeal abscess), with lymphocytosis suggesting a viral etiology. Viral cultures and rapid antigen tests may be considered if initial treatment fails. Imaging is not routinely recommended, since only in 50% of cases croup exhibits the “steeple sign” on X-rays, indicative of glottic and subglottic narrowing (12, 13). Computed tomography of the neck may be reserved for cases with suspected abscess, tumor, or foreign body aspiration. Laryngoscopy can be considered to confirm the diagnosis in atypical presentations (2, 14). As a matter of fact, other conditions can cause acute and recurrent stridor in children, so that differential diagnosis is of particular importance in such cases (6, 15, 16). Differentiating croup from epiglottitis is critical, as the treatment and prognosis for these conditions differ significantly due to the potential for rapid deterioration in epiglottitis. Although epiglottitis can also present with cough, fever, and difficulty breathing, it is more likely to manifest initially with a sore throat (17). Management of croup is based on its severity. A number of different scores have been used to classify the severity of disease in patients with croup. The most commonly used scoring system is the Westley Croup Score (WCS) which is based on the assessment of the following clinical signs: level of consciousness, cyanosis, stridor, air entry, and retractions. The sum of the partial scores related to each clinical sign allows us to classify croup into mild, moderate, and severe according to a total score of ≤ 2 , 3 to 7 and 8 to 11, respectively. A condition of impending respiratory failure is identified when the total score is ≥ 12 (**Table 1**) (18, 19). Another croup scoring system is the Taussig Croup Score which relies on five components such as cyanosis, air entry, retractions, level of consciousness, and stridor, for a maximum of 15 points. A higher score represents a more abnormal clinical examination (20) (**Table 1**).

METHODOLOGY

This position paper was developed by a panel of experts identified by SIMRI Executive Committee during the

Table 1. Most commonly used clinical scores to classify the severity of croup.**1a. Westley Croup Score (WCS):** A total score of ≤ 2 indicates mild, 3-7 moderate, 8-11 severe croup, ≥ 12 impending respiratory failure (18, 19).

SCORE				
ITEM	0			5
LEVEL OF CONSCIOUSNESS	Normal (including sleep) ☐			Disoriented ☐
CYANOSIS	None ☐		Cyanosis with agitation ☐	Cyanosis at rest ☐
STRIDOR	None ☐	When Agitated ☐	At rest ☐	
AIR ENTRY	Normal ☐	Decreased ☐	Markedly decreased ☐	
RETRACTIONS	None ☐	Mild ☐	Moderate ☐	Severe ☐

1b. Taussig Croup Score. A higher score (up to a maximum of 15 points) indicates a more abnormal clinical examination (20).

SCORE				
ITEM	0	1	2	3
SKIN COLOUR	Normal ☐	Dusky ☐	Cyanotic in room air ☐	Cyanotic on 30% oxygen ☐
AIR ENTRY	Normal ☐	Mildly decreased ☐	Moderately decreased ☐	Substantially decreased ☐
RETRACTIONS	None ☐	Mild ☐	Moderate ☐	Severe ☐
CONSCIOUSNESS	Normal ☐	Restless ☐	Lethargy (depressed) ☐	Obtunded ☐
STRIDOR	None ☐	Mild ☐	Moderate ☐	Severe or absent in the presence of severe obstruction ☐

XXVIIIth SIMRI national congress held in Turin in October 2024: the panel includes pediatric pulmonologists and researchers with proved experience in the field and in active clinical practice, who were asked to propose and produce position statements on cornerstone subjects in Pediatric Pulmonology, to improve the management of the most common respiratory conditions in our country. Considering the lack of national guidelines and the heterogeneous data available on management of croup in Italy, the panel proposed to develop a position paper on

this condition. Following approval by SIMRI Executive committee, a conference call was held in November 2024 to disclosure potential conflicts of interest, assign tasks and settle the timing of the project. Moreover, four main subjects regarding croup were identified, which include: role of 1) systemic corticosteroids, 2) inhaled corticosteroids, 3) inhaled epinephrine, 4) outdoor cold air/room temperature exposure and Heliox. At least two panelists performed a systematic literature review in December 2024 for each item, including all relevant publications in

English from PubMed, EMBASE, Cochrane Database of Systematic Reviews, Web of Science, and in January 2025 a list of recommendations was provided and collegially discussed. In February 2025 the first draft of the position statement was submitted to SIMRI Executive Committee and SIMRI Advocacy Committee: after appropriate review, the final version of the statement was completed in March 2025 and received formal approval before submission.

TREATMENT OF CROUP

Role of systemic corticosteroids

Efficacy of corticosteroids compared to placebo

Since their introduction in the clinical practice in the 90s to treat croup, corticosteroids (CS) have rapidly become the cornerstone of the management of this condition (21), which should be guided by illness severity. The use of CS is supported by their anti-inflammatory properties, which decrease capillary dilation and permeability, reducing the swelling of the laryngeal mucosal, improving the respiratory effort and facilitating air entry into the airways (5). However, data is limited, with a few Randomized Controlled Trials (RCT) evaluating different therapeutic approaches to croup in childhood. Dexamethasone is the most studied systemic steroid for the treatment of croup, being a long-acting steroid requiring less frequent dosing (onset of action in 30-60 minutes, peaking after 6-12 hours and lasting up to 36-72 hours), with a 25 times greater potency than short-acting products. The traditional dosage for croup management is 0.6 mg/kg. It can be administered via parental, oral or nebulized routes, with the oral one preferred due to its ease of use and patient tolerance (22). The most recent Cochrane systematic review on glucocorticoids for the treatment of croup in children confirms their mainstay role for reducing symptoms of croup at two hours, shortening hospital stays, and reducing the rate of return visits or (re)admissions. Across various levels of croup severity, various delivery methods of glucocorticoids (intramuscular, intravenous, oral, or inhaled) proved to be effective (23). The review included 45 RCTs conducted between 1964 and 2021 and involving 5888 pediatric inpatients and outpatients diagnosed with croup (23), showing that the administration of any CS was followed by 1) a greater reduction in croup score at 2, 6, and 12 hours after treatment; 2)

a decreased rate of return visits or hospital (re)admissions; and 3) shorter hospital stays when compared to placebo. However, there was no reported difference between CS and placebo in the use of additional treatment such as antibiotics, epinephrine, supplementary steroids, or tracheal intubation (23).

Dexamethasone vs other corticosteroids

When considering different systemic CS, betamethasone shows a similar profile as dexamethasone in terms of onset of action, half-life and anti-inflammatory properties. Nevertheless, only a single RCT has compared dexamethasone to betamethasone, showing that dexamethasone resulted in a greater reduction in croup score after two (SMD -0.62, 95% CI -1.17 to -0.06; $P = 0.03$; 1 RCT, 52 children; low-certainty evidence) and six hours (SMD -0.67, 95% CI -1.23 to -0.11; $P = 0.02$; 1 RCT, 52 children; low-certainty evidence), while no difference in the rate of re-examinations between groups was found (24). In this study, patients were randomized to receive either a high dose of intramuscular dexamethasone (26 patients, 0.6 mg/kg) or oral betamethasone (26 patients, 0.4 mg/kg) and those treated with dexamethasone exhibited a higher risk of requiring epinephrine (24). However, this result may have been influenced by a higher mean croup score at baseline in the dexamethasone group, despite random assignment. As for prednisone and prednisolone, these are considered as viable options in several studies, despite their palatability: data from the four available studies comparing oral dexamethasone to prednisolone show no superior efficacy for dexamethasone in reducing WCS at 2 and 6-hour post-treatment (25-27). Nevertheless, dexamethasone reduced return visits and hospital (re) admissions for croup when used in Emergency Departments (ED) or hospital settings, while no significant difference has been observed between dexamethasone and prednisolone regarding the use of additional epinephrine, or length of in the ED and hospital stay (25-28). Dexamethasone is associated with a lower need for supplemental CS compared to prednisolone (22, 25) (**Suppl tab. 1**).

Dexamethasone dosage and administration route

Comparison between oral and intramuscular administration route of dexamethasone at the same dosage (0.6 mg/kg) reveals no difference in the rate of return visits or admissions to the hospital, or the need for addi-

tional treatments such as epinephrine, antibiotics, supplementary steroids, or intubation (22, 29, 30). Focusing on the dosage, 0.6 mg/kg of dexamethasone reduces croup severity at 24 hours, if compared to the dosage of 0.15 mg/kg, but no significant changes in severity of WCS are observed between these doses at 2, 6, and 12 hours. In addition, no difference between dexamethasone doses is recorded in terms of return visits or (re) admissions, ED or hospital length of stay, or requirement for additional treatments (epinephrine, additional steroids, or tracheal intubation) (25, 27, 30-33). Based on the above analysis, dexamethasone, at any dosage (both 0.6 mg/kg and 0.15 mg/kg) and administered via any route (both oral and intramuscular), appears to be effective in the treatment of viral croup. However, given the comparable efficacy across doses and to minimize potential side effects, a lower dose of 0.15 mg/kg of dexamethasone may be considered as an alternative to the standard 0.6 mg/kg dose (22, 33), but more studies are needed to support this strategy. Notably, no significant adverse events have been reported in patients treated properly with systemic CS, confirming their safety profile, and supporting their prescription in croup (22) (**Suppl tab. 1**).

Role of inhaled corticosteroids

Inhaled CS have long and effectively been used in croup management, since high doses of inhaled CS may have a faster anti-edema effect than systemic CS, estimated in minutes more than hours, which is due to their “membrane” or “non-genomic” effect: CS bind an endocellular receptor determining an increase in smooth muscle tone of the laryngeal and bronchial vessels, with consequent vasoconstriction and reduction of local oedema (the so-called *bleaching effect*) (34). Such an effect is particularly pronounced for budesonide, which is therefore the most studied and used nebulized CS to treat croup in childhood, at least in Italy (35, 36). When nebulized, budesonide shows onset of action in 30-60 minutes, peaking after 1-2 hours, and a single dose of 2 mg has been shown to be effective in all grades of severity, with a marked reduction of symptoms in the first 24 hours (22). Nebulization should always be the preferred route for inhalation therapy in croup, since it allows that most of the drug settle in the upper airways, while pressurized metered dose inhalers are not recommended

since most of their molecules reach the lower airways (34, 37, 38). In the recent Cochrane review on the role of CS in pediatric croup, only 4 RCT comparing inhaled budesonide and systemic dexamethasone have been included in the meta-analysis, despite their heterogeneity: all the studies showed efficacy of budesonide over placebo at all levels of severity (patients with WCS ≥ 3 , with one study excluding patents with score >6), but dexamethasone was slightly superior to budesonide in improving symptoms scores at 6 and 12 hours and reducing the risk of additional treatment with epinephrine, while there was no significant difference in return visits or readmission rates as well as length in hospital/ED stay (22) (**Suppl tab. 1**). Notably, two of these studies compared inhaled budesonide (1 or 4 mg) to intramuscular dexamethasone (0.6 mg/kg) (39, 40) while the other two compared inhaled budesonide (2 mg) with oral dexamethasone (0.6 mg/kg) (41, 42). Taken together, these data suggest that nebulized budesonide can be administered as an alternative for children who do not tolerate oral drugs or considering availability, cost and ease of administration of other oral CS, and as an alternative to intramuscular dexamethasone too. As for the use of budesonide as a combination therapy with dexamethasone, only two RCT have been performed, showing conflicting results, with one reporting no benefit in adding 2 mg inhaled budesonide to a single oral dose of 0.15 mg/kg dexamethasone (43) and the other reporting clinically significant faster response when added to a single oral dose of 0.6 mg/kg dexamethasone (44). Treatment with budesonide was found to be safe, with only one case of oral thrush in the budesonide group in the study by Klassen *et al.* (42). Studies are too scarce to determine which is the best dose for budesonide, but in most of the studies evaluating such molecule 2 mg was the chosen dosage. As for other CS, we found 2 RCT on beclomethasone dipropionate and fluticasone propionate respectively. In the first one, the administration of 200 mcg via metered dose inhaler and spacer was found as effective as a single dose of 0.6 mg/kg intramuscular dexamethasone to treat mild to moderate croup (45), while in the second one, 2000 mcg of fluticasone propionate administered with metered dose inhaler and spacer showed no therapeutical effect in a small group of children hospitalized with moderate croup (46).

Role of nebulized epinephrine

Nebulized epinephrine (also known as adrenaline) has become a standard treatment for moderate to severe croup, since it decreases mucosal oedema through vasoconstriction by stimulating α -adrenergic receptors in subglottic mucous membranes (2). The clinical effect starts at 30 min, is sustained for at least 1 h, but disappears after 2 h. Both racemic epinephrine (that is composed of equal ratio of L-epinephrine and D-epinephrine) and L-epinephrine have been studied in croup. In 2013 a Cochrane systematic review evaluated the efficacy and safety of nebulized epinephrine versus placebo in children with croup (47). The review evaluated six studies including 183 participants with moderate to severe croup. Nebulized epinephrine (racemic epinephrine in five studies, L-epinephrine in one study) was associated with higher croup score improvement at 30 minutes, but not two- and six-hours post-treatment and significantly shorter hospital stay than placebo. In one small study (28 participants, average age of 11 months) comparing racemic and L-epinephrine (0.5 ml of 2.25% and 5 ml of 1:1000 dilution, respectively), no difference in croup score was found after 30 minutes, while after two hours, L-epinephrine showed significant score reduction (48) (**Suppl tab. 1**). Eghbali *et al.* in 2016 demonstrated that nebulized L-epinephrine (0.5 mg/kg/dose, maximum dose: 5 ml) in addition to a single dose of intramuscular dexamethasone (0.6 mg/kg, maximum dose: 8 mg) reduced mild and moderate symptoms of croup more effectively over time without cardiac side effects (49). Epinephrine should be administered in addition to glucocorticoids in children with moderate to severe croup at a dose of 0.25-0.5 mL/kg (1:1000) plus 3 ml saline via nebulizer. However, evidence on the optimal dosage is limited. Children who received epinephrine should be observed for at least 2 hours (even if the optimal duration of the observation has not been established yet) to evaluate symptoms relapse as the effect of epinephrine wanes (50). The risk of a rebound was disavowed because studies demonstrated that no children was clinically worse hours after epinephrine administration and the relapsed symptoms were less marked in children who received also CS (51). Repeated doses are associated with a low increase in heart rate for up to 60 min after treatment. Pallor was also noted in some trials. Epinephrine can be repeated every 2 hr in case of

severe upper airway obstruction, but the patient should be continuously electrocardiographic monitored (2). Ventricular tachycardia with a small myocardial infarct in a child with an anatomically normal heart with normal coronary circulation who required multiple doses of nebulized racemic epinephrine to treat severe croup has been reported anecdotically (52). The only relative contraindication for nebulized epinephrine is ventricular outflow tract obstruction (53).

Role of outdoor cold air/room temperature exposure and Heliox

Exposure to cold air and Heliox have been studied to treat croup, but these treatments are not universally applicable or as robustly effective as CS. An open-label, single-center RCT recently evaluated the therapeutic effects of exposure to cold outdoor air for 30 minutes in 118 children (aged 3 months to 10 years) with croup symptoms with WCS >2, suggesting that brief exposure to cold air (temperature below 10°C), can alleviate the severity of croup symptoms of moderate intensity. In this study the effectiveness of such treatment was comparable to the administration of a single 0.6 mg/kg dose oral dexamethasone, particularly when considering the improvement or resolution of symptoms 60 minutes after treatment (54). Heliox is a biologically inert, colourless, odourless, and non-combustible gas mixture of helium and oxygen (at 70:30 or 80:20 ratio), with lower density than air (helium is in place of nitrogen) or oxygen. Heliox should decrease airflow turbulence due to its reduced density but has a limitation due to the low fractional concentration of oxygen which should be considered in case of hypoxia. A Cochrane review on Heliox for croup in children included 3 RCT (91 children aged 6 months – 4 years) conducted in ED and concluded that it may not be more effective than 30% humidified oxygen for children with mild croup but may be beneficial in the short term for children with moderate croup treated with dexamethasone. In the study by Weber *et al* (55), the effect of Heliox was found to be similar to 100% oxygen given with one or two doses of epinephrine (1:1000, 0.5 mL/kg, max 5 mL). Adverse events were not reported, but it is unclear if these were monitored in the included studies. Further Heliox versus standard treatment RCT are certainly needed to understand the role of Heliox in moderate-severe croup (19).

TREATMENT OF CROUP IN REAL LIFE: WHAT DOES SIMRI SUGGEST?

Treatment of croup is highly heterogeneous at a world level, due to the paucity of studies supporting the preferred CS molecule, route of administration, and dosage. To our knowledge, no guidelines are available so far, but only clinical practice algorithms. In Italy, a recent online survey administered to a sample of primary care and hospital-based pediatricians (326 and 323 participated, respectively) showed extensive use of inhaled CS (mostly budesonide) for mild and moderate croup as well as of nebulized epinephrine for mild cases. As for systemic CS, the most prescribed was oral betamethasone, both in ED and as a short course home therapy. The Authors found also a relatively poor application of the WCS to assess disease severity, especially among primary care physicians (35). The same research group conducted an observational, retrospective cohort study by reviewing the medical records of more than 650 patients discharged with a diagnosis of croup from two Italian pediatric ED (82%, 16% and 1.9% had mild, moderate or severe croup respectively), confirming that inhaled CS were prescribed in more than 54% of cases (budesonide was the only inhaled CS prescribed), while oral CS were given to 35.8% patients (betamethasone in more than 90% of cases; in 75.7% of cases at 0.1 mg/kg). Almost all patients received a prescription for home therapy for a few days (mostly inhaled budesonide, often associated with oral betamethasone). However, no difference was found in terms of hospitalization rates,

return visits rates and length of hospital stay among the different treatment groups (36). Even if croup is usually mild and responds to both inhaled and oral CS in most cases, a more unified approach and adequate management should be sought, especially in our country, since it has been estimated that the high rate of home therapy prescription costs our national health system ten times more than providing the single-shot CS administration in the ED (36). Taking all this into consideration and the available evidence, we suggest implementing the use of CS in the ED and outpatient services in case of mild or moderate croup (**Table 2**). Oral dexamethasone should be preferred at the dose of 0.6 mg/kg, until further studies prove that lower dosages could be equally effective. When dexamethasone is not available or difficult to administer, oral betamethasone or prednisolone could be considered as a second option on a case-by-case basis, but it is difficult to state at what dosage so far. Other alternatives to the single oral dose of CS are 2 mg of nebulized budesonide or intramuscular administration of dexamethasone (0.6 mg/kg). Combination therapy with budesonide and dexamethasone may be beneficial but data are too limited to suggest such treatment, which should be avoided so far. Nebulized epinephrine should be administered in severe cases in association with CS. Heliox and cold air may be useful in croup treatment.

SIMRI advocates for improved management of croup, including in mild cases, emphasizing the importance of enhancing prescription practices to ensure greater

Table 2. SIMRI recommendations for the treatment of croup in children.

CRITICAL POINTS BASED ON EVIDENCE FROM THE LITERATURE

Croup should be diagnosed clinically and its severity assessed through scoring systems.

The preferred single dose of oral CS should be of dexamethasone (0.6 mg/kg; 0.15 may be effective) *.

As for alternative treatments, nebulized budesonide (2 mg) or intramuscular administration of CS (dexamethasone, 0.6 mg/kg) are feasible

Other systemic CS could be used when dexamethasone is not available or not easy to administer.

Nebulized epinephrine (0.25-0.5 mL/kg (1:1000), max 5 mg) must be administered in combination with systemic CS in severe cases.

Cold air exposure is beneficial; Heliox, where available, could be useful to treat pediatric croup.

WHAT NOT TO DO IN CLINICAL PRACTICE

Combination therapy of inhaled and systemic CS.

Home therapy (limited exception on a case-by-case basis).

*In Italy, tablets and drop formulations are available.

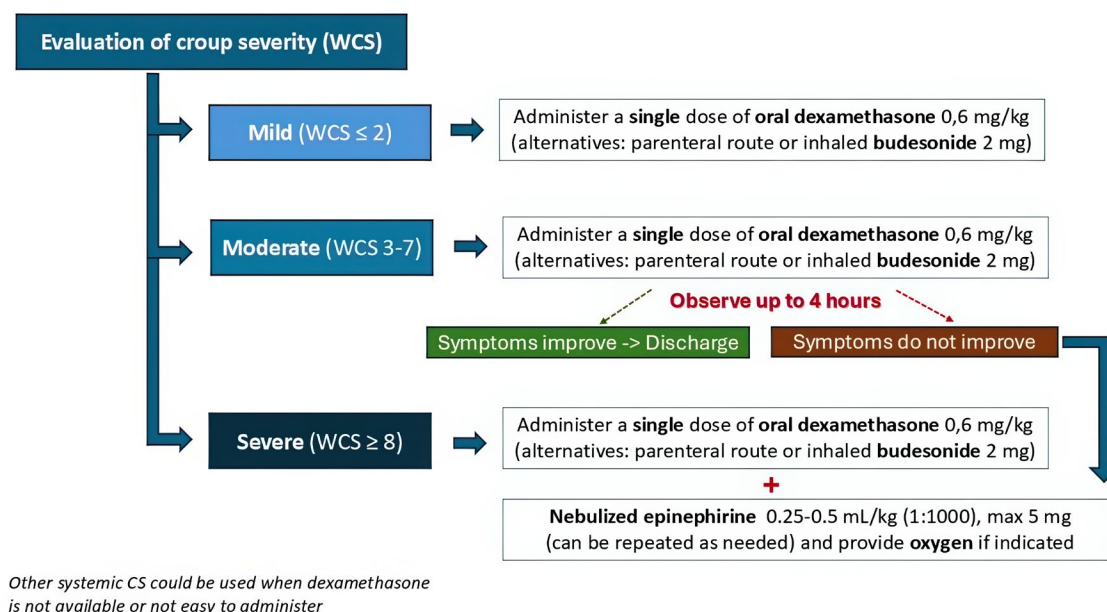


Figure 1. Algorithm for initial management of croup in the ED or primary care.

safety, appropriateness, and to reduce the economic impact of prescribing errors. SIMRI encourages adherence to current guidelines and recommendations, both in primary care and emergency department settings and remains committed to supporting this effort by offering ongoing residential and online training programs. We also strongly advocate for the need for more RCT on a large number of patients.

CONCLUSIONS

Despite being a very common condition among young children, croup continues to be heterogeneously treated worldwide. Treatment of pediatric croup should be based on a single dose of systemic corticosteroid, with inhaled budesonide as an alternative, with the addition of inhaled epinephrine in severe cases (**Figure 1**). SIMRI advocates for the need of dedicated pediatric RCT in order to evaluate whether other approaches may be feasible.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have no conflict of interests relevant to this article to disclose.

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Author contributions

MEDC and SLG conceptualized the study; MEDC, GFen, GFer, RN, FP and SLG drafted the initial manuscript, reviewed the literature and critically revised the final manuscript. 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.

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BRIEF REPORT

Multifrequency oscillometry for evaluating pediatric patients with exercise-induced symptoms

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ABSTRACT

Forced oscillometry (FOT) is valuable for assessing Exercise-Induced Bronchoconstriction (EIB) and bronchodilator response, but newer reference values for comparable FOT devices remain underutilized.

To compare FOT and spirometry parameters after exercise testing and bronchodilation in children reporting exercise-induced symptoms.

We measured Resistance (Rrs), its Frequency dependence (Fdep 5-19), and reactance (Xrs) at 5, 11, and 19 Hz during inspiration and expiration in 35 patients (ages 6-16). Spirometry, FeNO, blood eosinophils, and skin-prick tests were also assessed. After treadmill exercise, spirometry was repeated at 1', 5', 10', 15', and 20', and FOT at 3' and 18'. EIB was defined by a $\geq 10\%$ drop in FEV₁, and bronchodilation was evaluated 15' post-salbutamol.

Fourteen patients with EIB exhibited lower functional values and higher inflammatory indices. Post-exercise, these patients had significant increases in Rrs z-scores and Fdep 5-19, along with decreases in Xrs compared to non-EIB patients. FOT changes correlated with the drop in FEV₁ and FEF₂₅₋₇₅. Bronchodilation was reflected in Rrs at 5 Hz and Xrs across all frequencies.

Multifrequency FOT effectively detects airway changes, with low frequencies key for EIB assessment and the 5-19 Hz range essential for bronchodilation evaluation.

IMPACT STATEMENT

Z-scored values and changes from device-appropriate reference points allow multifrequency FOT to detect airway alterations during EIB and bronchodilation.

INTRODUCTION

Exercise limitations are a common concern among pediatric patients in pulmonary clinics. Some children experience symptoms exclusively during exercise, while others have broader, recurrent respiratory symptoms, affecting their participation in sports and psychosocial well-being (1). Diagnosing Exercise-Induced Bronchoconstriction (EIB) through exercise testing, particularly in suspected asthma cases, aids in diagnosis and guides clinical management (2).

KEY WORDS

Oscillometry; exercise-induced bronchoconstriction; bronchodilation; respiratory symptoms; children.

Spirometry is often used to assess bronchial response after exercise (3). However, it requires forced breathing maneuvers, which may be challenging for young children. Moreover, forced expiratory maneuvers may induce bronchial relaxation in sensitive individuals, especially those with asthma, potentially skewing results (4). The Forced Oscillation Technique (FOT) offers an advantage as it is measured during normal breathing, providing reliable and repeatable data even in young children. FOT records respiratory impedance (Zrs), which consists of resistance (Rrs) and reactance (Xrs) (5). Modern devices can assess these parameters at multiple frequencies, allowing for the calculation of Frequency dependence (Fdep) and separate analyses of Rrs and Xrs during inspiration and expiration (5, 6).

Pediatric studies have shown FOT's utility in assessing EIB and bronchodilator response (BDR) (4-10). However, variation in devices, techniques, and patient populations, along with a lack of normative values, limits comparison between studies. Recently, we demonstrated that Rrs and Xrs z-scores derived from new predicted values at 8 Hz were useful in assessing EIB in children with exercise-induced symptoms (10). We hypothesized that using multifrequency z-scores could provide additional insights into EIB and BDR evaluation, potentially revealing changes that a single frequency module might miss. This study compares multifrequency FOT and spirometry parameters after exercise testing and bronchodilation in children with Exercise-Induced Symptoms (EIS).

MATERIALS AND METHODS

Subjects

This report is part of an ongoing study investigating the effects of exercise on FOT variables. Thirty-five outpatients (ages 6-16) attending our pediatric pulmonology unit at Sant'Andrea Hospital in Rome were consecutively enrolled if they reported EIS, with or without an asthma diagnosis. Participants were excluded if they had a respiratory infection in the past 4 weeks, required corticosteroids, Montelukast, or antihistamines within 10 days, or used beta-2 agonists in the last 6-12 hours. Additional exclusions included poor disease control, baseline FEV₁ <80%, poor cooperation, suspected exercise-induced laryngeal obstruction, or other exercise limitations (10). Parents provided informed consent, and the hospital's Ethical Review Board approved the study.

Study design

All assessments were completed in a single session. Parents answered a respiratory health questionnaire, and children underwent a medical exam, Skin Prick Tests (SPTs), Blood Eosinophil Counts (BECs), FOT, FeNO measurement, baseline spirometry, and an exercise challenge.

Measurements

Inflammatory biomarkers

SPTs assessed sensitization to common inhaled and food allergens, with positive and negative controls. A reaction ≥ 3 mm was considered positive. BECs were measured, and FeNO levels were assessed using triplicate single-breath maneuvers with constant expiratory pressure (11).

Oscillometry

Multifrequency FOT was conducted at 5, 11, and 19 Hz using a Resmon Pro Full device. Baseline measurements were performed in triplicate, with inspiratory and expiratory Rrs and Xrs values expressed as z-scores based on recent reference values (12).

Spirometry

Spirometry was performed according to ATS/ERS guidelines (13), with FEV₁ and other parameters expressed as percentages of predicted values (14).

Exercise testing

The exercise challenge involved running on a treadmill at 6 km/h with a 10% incline until the target heart rate ($220 - \text{age}$) was reached (15). Post-exercise spirometry was repeated at 1, 5, 10, 15, and 20 minutes, and FOT was performed at 3 and 18 minutes. The bronchodilator response was assessed after administering albuterol. EIB was defined as a $\geq 10\%$ fall in FEV₁ from baseline (2, 3, 15), with changes in Rrs and Xrs calculated similarly.

Statistical analysis

Continuous variables were expressed as means $\pm$ SD. The Mann-Whitney U test was used for unpaired comparisons, and the χ^2 test with Fisher's correction for categorical variables. Spearman's rank correlation coefficients assessed correlations. Significance was set at $p < 0.05$.

RESULTS

The 35 subjects (age 6-16, M/F: 21/14) completed all measurements. EIB was observed in 14 (40%) sub-

Table 1. Main characteristics of patients with exercise-induced symptoms (EIS).

	Non-EIB (n = 21)	EIB (n = 14)	P value
Gender (M/F)	11/10	10/4	0.260
Ages, years	11.5 ± 2.9	10.6 ± 2.7	0.377
Height, cm	148.7 ± 18.2	145.3 ± 16.6	0.662
BMI percentile	64.2 ± 36.6	77.9 ± 21.5	0.479
Asthma, n (%)	4 (19.0)	8 (57.1)	0.031
Therapy last 12 months, n (%)			
-Antileukotrienes	3 (14.3)	8 (57.1)	0.011
-Antihistamines	7 (33.3)	11 (78.6)	0.015
-Inhaled corticosteroids	16 (76.2)	13 (92.9)	0.366
Inflammatory biomarkers			
Atopy, n (%)	12 (57.1)	13 (92.9)	0.028
Blood eosinophils, %	4.2 ± 2.6	7.9 ± 5.2	0.077
FeNO, ppb	12.8 ± 11.8	31.9 ± 24.3	0.002
Baseline lung function			
FEV1%	107.5 ± 14.5	95.0 ± 10.5	0.013
FEV1/FVC (%)	89.5 ± 8.1	83.1 ± 6.6	0.012
FEF25-75%	104.0 ± 26.0	80.7 ± 16.6	0.013
zs-R5i	0.52 ± 0.93	1.28 ± 1.44	0.121
zs-R5e	0.91 ± 0.95	1.40 ± 1.25	0.312
zs-X5i	-0.23 ± 1.03	-0.83 ± 0.92	0.099
zs-X5e	-0.33 ± 1.45	-1.42 ± 1.31	0.017
zs-R5t	0.75 ± 0.91	1.39 ± 1.28	0.121
zs-X5t	-0.24 ± 1.11	-1.16 ± 0.93	0.012
zs-Fdep5_19	-0.02 ± 1.22	0.79 ± 1.14	0.080
Post-exercise changes			
Fall FEV1 (%)	-4.9 ± 3.0	-24.1 ± 13.6	<0.001
Fall FEF25-75 (%)	-12.6 ± 10.9	-39.9 ± 17.1	<0.001
Rise zs- R5i	0.10 ± 0.82	1.79 ± 2.33	0.010
Rise zs- R5e	0.14 ± 0.93	1.21 ± 2.02	0.138
Fall zs-X5i	-0.12 ± 1.16	-1.49 ± 1.82	0.007
Fall zs-X5e	-0.21 ± 1.33	-2.81 ± 4.85	0.138
Rise zs-R5t	0.12 ± 0.80	1.47 ± 2.22	0.086
Fall zs-X5t	-0.08 ± 1.06	-2.32 ± 3.57	0.059
Rise zs-Fdep5_19	0.14 ± 0.80	1.60 ± 1.71	0.007
Post-bronchodilator changes			
D FEV1 (%)	5.9 ± 6.7	25.1 ± 18.3	<0.001
D FEF25-75 (%)	17.3 ± 24.4	64.6 ± 44.1	<0.001
Dzs-R5t	-0.74 ± 1.01	-2.33 ± 2.14	0.008
Dzs-X5t	0.29 ± 0.78	2.09 ± 3.21	0.012
Dzs-R11t	-0.84 ± 0.92	-1.58 ± 1.28	0.055
Dzs-X11t	0.33 ± 0.51	2.46 ± 2.94	<0.001
Dzs-R19t	-0.86 ± 1.03	-0.89 ± 0.90	0.711
Dzs-X19t	0.45 ± 0.94	1.88 ± 1.75	0.002
Dzs- Fdep5_19	-0.04 ± 0.66	-2.00 ± 2.11	<0.001

EIB: exercise-induced bronchoconstriction. Inspiratory, expiratory, and total resistance (R), and reactance (X) at 5, 11, and 19 Hz (e.g., R5i, R5e, R5t, X5i, X5e, X5t). Less relevant results for baseline and post-exercise frequencies (11 and 19 Hz) are not reported.

jects, with higher atopic inflammation and lower baseline lung function than those without EIB. Low baseline z-scores of expiratory Xrs at 5 Hz better distinguished EIB patients (**Table 1**).

Post-exercise, inspiratory Rrs and Fdep 5_19 z-scores increased, and Xrs z-scores decreased more in EIB patients than those without EIB. Bronchodilator responses included reductions in Rrs and increases in Xrs across all frequencies and respiratory phases. Changes in these z-scored FOT parameters correlated with percent changes in FEV₁ and FEF₂₅₋₇₅ ($r = 0.58$ to 0.76 , $p < 0.001$ for all). After exercise, Fdep 5_19 increased inversely with FEV₁, while Xrs decreased in direct correlation with the reduction in FEF₂₅₋₇₅ (**Figure 1, A, B**). Conversely, after bronchodilation, Fdep 5_19 decreased as FEV₁ increased, and Xrs increased in direct correlation with the improvement in FEF₂₅₋₇₅ (**Figure 1, C, D**).

DISCUSSION

Our preliminary study shows that multifrequency FOT and spirometry are useful for evaluating airway narrow-

ing due to exercise and bronchodilation in children with Exercise-Induced Symptoms (EIS). Rather than overlapping, the results of these tests appear complementary. FOT is more effective than spirometry in identifying responses to bronchial challenges and bronchodilator responsiveness (6). This suggests a clinical role in asthma diagnosis, assessing disease control, and integrating with other biomarkers for phenotyping and monitoring patients with obstructive diseases. These include early-onset conditions such as those associated with prematurity or congenital abnormalities, comorbidities like obesity, and upper airway dysfunction. Other potential applications include reducing infectious exposure in pulmonary function laboratories by avoiding high aerosol-generating maneuvers and enabling home monitoring (16). However, FOT devices remain costly, challenging to interpret, and require further standardization, including device-specific and multiethnic reference values, before they can be widely adopted.

As expected, EIB was frequently associated with asthma and atopic inflammation, even among patients on anti-in-

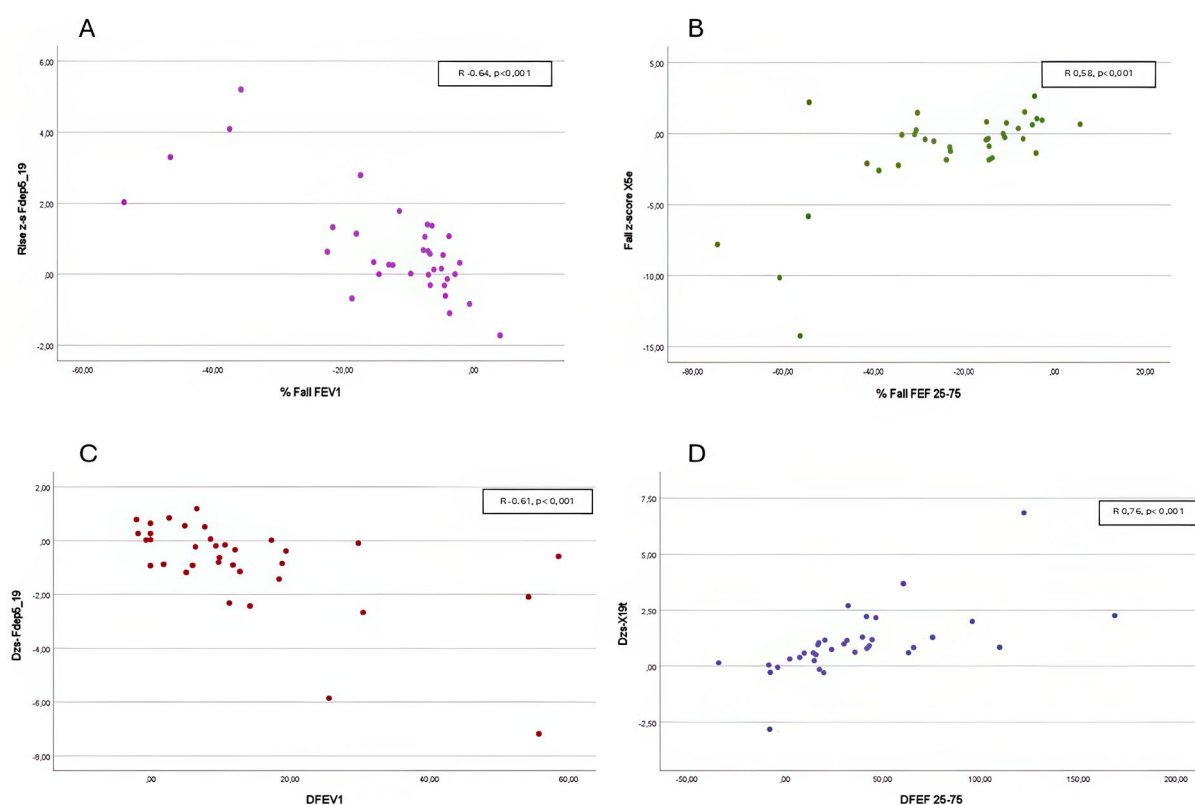


Figure 1. Correlations of post-exercise (**A, B**) and post-bronchodilator changes (**C, D**) in FOT parameters with respective changes in FEV₁ and FEF₂₅₋₇₅.

flammatory therapy. Baseline spirometry and low-frequency baseline Xrs, rather than Rrs, distinguished children with EIB. Xrs becomes more negative at frequencies below 8-10 Hz in response to peripheral airway obstruction and gas trapping (17). Therefore, low Xrs z-scores could help identify children prone to EIB alongside spirometry and inflammatory biomarkers.

Our findings support the use of post-exercise changes in low-frequency inspiratory Rrs and Xrs for assessing EIB (4, 7, 10), consistent with our previous reports on changes in z-scores of 8-Hz Rrs and Xrs (10). Additionally, increased zs-Fdep 5_19 helped identify EIB, as this parameter reflects heterogeneous airway obstruction (6). High frequencies (11 and 19 Hz) poorly discriminated EIB, suggesting they are less suitable for pediatric airway assessment.

Post-bronchodilator responses showed improved airway patency through a reduction in Rrs and an increase in Xrs, independent of frequency or respiratory phase. Limitations of this study include the small sample size and lack of healthy controls, but it represents the first phase of ongoing research in a clinical setting. Future studies could help validate our findings in specific pediatric groups experiencing exercise-induced symptoms. For example, establishing cut-offs for FOT indices in response to exercise and bronchodilators in asthmatic children with varying levels of disease control and exploring their applicability in other respiratory conditions. In conclusion, multifrequency FOT effectively evalu-

ates airway changes. Low frequencies during inspiration best reflect EIB, while a broader 5-19 Hz range captures bronchodilation.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Ethical approval

Human studies and subjects

The study adhered to the ethical standards established in the Declaration of Helsinki; participants gave written consent before enrollment.

Data sharing and data accessibility

The respiratory sound database is available for researchers upon request to the Corresponding Author.

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.

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CASE REPORT

Severe uncontrolled asthma with biologic therapy in a pediatric patient. The role of fungal sensitization, a case report

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ABSTRACT

We present the case of M., a girl followed by our Center since 2020 for severe asthma. After an initial positive response to Mepolizumab, she experienced multiple asthma exacerbations with poor response to conventional therapies, increased IgE levels, peripheral eosinophilia, and new sensitization to *Aspergillus*, raising suspicion of Allergic Bronchopulmonary Aspergillosis (ABPA). Consequently, Mepolizumab was discontinued. However, due to insufficient diagnostic criteria to confirm ABPA, she was ultimately diagnosed with Severe Asthma with Fungal Sensitization (SAFS).

Her environmental history revealed significant mold exposure at home. Following environmental remediation and the initiation of Dupilumab therapy, she showed clinical improvement.

IMPACT STATEMENT

This case report underscores the diagnostic and therapeutic challenges of managing Severe Asthma with Fungal Sensitization (SAFS) in pediatric patients. By highlighting the role of environmental mold exposure and the clinical benefit of Dupilumab after Mepolizumab failure, the report emphasizes the importance of comprehensive environmental assessment and personalized biologic therapy. It contributes to the growing understanding of SAFS and supports the consideration of alternative biologics in children with uncontrolled asthma and fungal sensitization, even in the absence of clear ABPA criteria.

INTRODUCTION

Severe Asthma with Fungal Sensitization (SAFS) is a complex and challenging subtype of asthma, characterized by an exaggerated immune response to fungal antigens, leading to exacerbations and poor symptom control. Although the association between asthma and fungal sensitization has long been recognized, its pathophysiology remains incompletely understood, and diagnosis is complicated by overlapping symptoms with other forms of severe asthma. The identification and management of SAFS are further hindered by the lack of standardized diagnostic criteria and variability in patient responses to treatment.

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ABBREVIATIONS

ABPA: Allergic Bronchopulmonary Aspergillosis

SAFS: Severe Asthma with Fungal Sensitization

LABA: long acting beta-adrenoceptor agonists

ACT: Asthma Control Test

BAL: bronchoalveolar lavage

KEY WORDS

Severe Asthma; biologic therapy; Dupilumab; SAFS; ABPA.

Severe asthma in pediatric patients presents a significant clinical challenge, as it is associated with frequent exacerbations and the need for intensive therapies. Allergic Bronchopulmonary Aspergillosis (ABPA) is a rare but potentially serious complication of allergic asthma, often linked to environmental mold exposure. However, not all diagnostic criteria for ABPA are always met, making it crucial to consider an alternative condition: Severe Asthma with Fungal Sensitization (SAFS). This clinical entity was first described in a 2006 publication, which explored the relationship between fungal sensitization and severe asthma symptoms, distinguishing SAFS as a separate clinical condition from ABPA (1-2). This case report aims to provide insight into the diagnostic challenges and management of SAFS by presenting a novel case that highlights its unique clinical features and treatment response. The significance of this case lies in its contribution to the growing body of literature on SAFS, offering new perspectives on patient management, diagnostic approaches, and therapeutic options. By discussing this case, we hope to enhance awareness of SAFS, improve its clinical recognition, and optimize diagnostic and treatment strategies for affected patients.

CLINICAL CASE

Asthma diagnosis and severe disease course

M. was born in 2013 at term via cesarean section. She has a family history of asthma and inhalant allergies. At the age of three, after entering preschool, she began experiencing frequent episodes of asthma-like bronchitis with significant bronchospasm, requiring repeated courses of oral corticosteroids and inhaled bronchodilators. These episodes had no clear seasonal pattern and were associated with both daytime and nighttime cough, limiting her daily activities.

In 2017, she was diagnosed with asthma and started on inhaled corticosteroids, with minimal benefit.

In 2018, skin prick tests were negative except for mild sensitization to cat epithelium.

In 2020, she was referred to our Pulmonology Department for further evaluation.

Despite escalating inhaled corticosteroids to high doses (fluticasone 500 mcg/day) combined with a long-acting β_2 -agonist (LABA) as a second controller, she continued to require frequent courses of oral corticosteroids.

Throughout the year, she experienced approximately five acute exacerbations requiring oral corticosteroids and one severe attack necessitating oxygen therapy in the emergency department. Following these episodes, leukotriene receptor antagonist therapy was introduced. However, even after six months, disease control remained poor, with an Asthma Control Test (ACT) score frequently around 16.

Spirometry could not be performed at the time due to pandemic-related restrictions in accordance with recommendations from the Italian Pediatric Respiratory Society (3).

Laboratory investigations revealed:

- WBC 9200/mm³;
- eosinophils 550/mm³;
- elevated total IgE at 2065 IU/ml;
- specific IgE for: *Dermatophagoides pteronyssinus* 1.34 IU/ml; *Dermatophagoides farinae* 1.24 IU/ml; Cat dander 2.44 IU/ml; for Dog dander >100 IU/ml;
- alpha-1-antitrypsin levels, sweat tests, serologies for major respiratory pathogens, and screening for celiac disease were normal.

Biological Treatment and Disease Progression

Due to a poor response to conventional therapy, the patient was diagnosed with severe asthma and started on biological therapy. In March 2021, Mepolizumab (40 mg subcutaneously every four weeks) was initiated alongside background therapy with fluticasone-salmeterol (25/125 mcg, two puffs twice daily) and a leukotriene antagonist. Symptoms improved rapidly within a month. Follow-up assessments showed a stable ACT score of 24, indicating good asthma control. No acute respiratory symptoms occurred, either at rest or during physical activity.

However, spirometry showed mild obstruction with a positive bronchodilation test even after three and six months of therapy:

Pre-B:

- FEV1: 1.35 L (89%);
- FVC: 1.62 L (95%);
- FEV1/FVC: 83.58 (93%);
- MEF: 75-25 (64%).

Post-B:

- FEV1: 1.53 L (101%);
- FVC: 1.73 L (102%);

- FEV1/FVC: 88.46 (98%);
- MEF: 75-25 (87%).

During monthly check-ups, laboratory parameters improved within three months: total IgE levels decreased to 1817 IU/ml, and eosinophils dropped to 50/mm³.

Given the stable clinical condition, the fluticasone-salmeterol dosage was reduced to one puff twice daily, while leukotriene antagonist therapy was continued.

Worsening asthma disease control

However, in December 2022, total IgE levels increased again to 3368 IU/ml, while eosinophils remained stable at 50/mm³.

In March 2023, M. experienced her first asthma exacerbation without clear signs of infection, requiring a course of oral corticosteroids. The ACT score dropped to 13, and she reported episodes of dyspnea requiring inhaled bronchodilators.

Spirometry revealed an obstructive pattern:

Pre-B:

- FEV1: 1.42 L (83%);
- FVC: 1.62 L (84%);
- FEV1/FVC: 87.76 (98%);
- MEF: 75-25 (67 %).

Post-B:

- FEV1: 1.68 L (99%);
- FVC: 1.71 L (89%);
- FEV1/FVC: 98.79 (110%);
- MEF: 75-25 (110%).

In June 2023, due to persistent symptoms and worsening lung function despite good compliance with maximal therapy and repeated courses of oral corticosteroids, a chest CT was performed but showed no abnormalities. Given the poor efficacy of Mepolizumab, biological therapy was discontinued in August 2023.

At reevaluation in October 2023, total IgE levels exceeded 5000 IU/ml, with eosinophilia (360/mm³) and an exhaled FENO of 75 ppb.

Skin prick tests revealed new sensitization to *Aspergillus*, with weakly positive specific IgE for *Aspergillus fumigatus* and *Alternaria*.

Blood tests evaluated specific IgE levels as follows:

- *Aspergillus fumigatus*: f2 0.14 kU/L, f4 0.24 kU/L, f6 0.11 kU/L;
- *Alternaria*: 0.15 kU/L.

Specific IgG antibodies for *Aspergillus fumigatus* were negative.

Environmental Exposure and SAFS Diagnosis

She underwent bronchoscopy with Bronchoalveolar Lavage (BAL) to detect fungal hyphae. The results were negative for bacterial and fungal cultures, bacterial PCR, and mycobacteria.

During hospitalization, the patient reported significant improvement in dyspnea and fatigue, raising suspicion of an environmental exposure at home. A further review of her history revealed that her home had been severely infested with mold for years, with visible growth covering the walls of her bedroom. While the specific mold species were not initially identified, the persistent dampness suggested the presence of *Aspergillus* and *Alternaria*, both commonly associated with allergic airway diseases. The family had attempted multiple remediation efforts, including commercial antifungal treatments, but structural issues in the home prevented complete resolution. Their residence, located in a historic building, suffered from severe rising dampness, making eradication of the mold nearly impossible.

The patient's clinical improvement during hospitalization and after relocating to a different sleeping area

Table 1. Comparison between ABPA and SAFS criteria with our clinical case.

Criteria	ABPA	SAFS	Patient Findings
Central bronchiectasis	Present	Absent	Absent
Specific IgE for <i>Aspergillus fumigatus</i>	High	Low or absent	Low
Total IgE levels	>500 IU/mL	Elevated	>5000 IU/mL
Recurrent pulmonary infiltrates	Present	Absent	Absent
Asthma severity	Variable	Severe, steroid-dependent	Severe, steroid-dependent
Response to antifungal therapy	Often beneficial	Not always effective	Not tested

further supported the role of environmental exposure in her disease progression. Based on her clinical presentation and laboratory findings, allergic bronchopulmonary aspergillosis (ABPA) was suspected. However, due to the absence of full ABPA diagnostic criteria, she was instead diagnosed with Severe Asthma with Fungal Sensitization (SAFS) (Table 1).

Distinguishing between SAFS and ABPA can be challenging, as can selecting the most appropriate treatment. Given the patient's condition, Dupilumab therapy was initiated, leading to sustained clinical improvement.

DISCUSSION

We presented a case of severe asthma under biological treatment with worsening disease control. Given the high total IgE levels, weakly positive specific IgE for *Aspergillus fumigatus*, and a positive skin prick test, an initial diagnosis of ABPA was suspected.

The diagnosis of ABPA requires a series of criteria, including:

- presence of high risk conditions such as persistent severe asthma or cystic fibrosis;
- elevated total IgE levels (>500 IU/ml);
- presence of specific IgE and IgG against *Aspergillus fumigatus* (M. only had weakly positive specific IgE but skin prick test were positive for *Aspergillus fumigatus*);
- eosinophilia (present in M.);
- chest X-ray or CT showing evidence of transient pulmonary infiltrates or central bronchiectasis (absent in M.);
- expectoration of mucus plugs with pulmonary eosinophilia (4) (absent in M.).

Although M. had elevated total IgE levels and sensitization to *Aspergillus fumigatus*, other key criteria for ABPA, such as structural lung alterations, infiltrates, or bronchiectasis, were absent.

Additionally, during hospitalization, her symptoms significantly improved simply by removing her from the mold-infested home environment an outcome more consistent with chronic allergenic exposure rather than an invasive lung disease like ABPA.

Since the diagnostic criteria for ABPA were not fully met, SAFS was considered the more appropriate diagnosis. Her clinical presentation aligned more closely with SAFS, characterized by severe asthma poorly controlled with

standard therapy, high total IgE levels, and fungal sensitization without structural lung changes.

Currently, scientific literature lacks well-defined, evidence-based guidelines for SAFS treatment. Management typically involves minimizing environmental exposure to fungal allergens alongside optimized pharmacological therapy, such as corticosteroids or biologics when available (5).

While immediate relocation was not feasible, every effort was made to reduce mold exposure. Given M.'s prolonged corticosteroid use, alternative therapies were also considered.

During Mepolizumab treatment, she initially showed a good clinical response, with significant reductions in total IgE and eosinophils. However, despite nearly three years of therapy, full lung function recovery was not achieved an outcome previously noted in the literature (6). As disease control worsened and the response to Mepolizumab declined, the treatment was discontinued.

Although evidence on Dupilumab for SAFS is limited, studies have demonstrated its effectiveness in severe eosinophilic asthma, reducing corticosteroid dependence and improving quality of life (7-9).

Dupilumab targets the IL-4 and IL-13 pathways, which play a central role in Th2-driven inflammation in severe asthma and allergic diseases. Unlike other biologics, it has been shown to reduce corticosteroid dependence and improve lung function, particularly in patients with allergic sensitization.

Given the patient's high total IgE and fungal sensitization, it was deemed the most appropriate option compared to alternative biologics targeting eosinophils alone. Other options, such as Omalizumab, were considered but deemed less suitable due to the extreme IgE levels, which exceeded standard dosing recommendations.

Therefore, Dupilumab was chosen as an alternative biologic therapy.

CONCLUSIONS

The management of SAFS remains challenging due to the lack of standardized guidelines. Current recommendations emphasize environmental control, aggressive asthma management, and the use of biologics when appropriate. Studies suggest that Dupilumab may pro-

vide significant benefits for patients with severe allergic asthma, including those with fungal sensitization. However, the role of antifungal therapy in SAFS remains controversial, as its efficacy is not well established in the absence of ABPA.

This case highlights the importance of obtaining a thorough environmental history when asthma is poorly controlled, conventional therapy proves ineffective, or socio-economic and environmental risk factors are present. A precise evaluation of ABPA criteria in severe asthma is essential, as is considering SAFS in the differential diagnosis.

Future research is needed to establish definitive treatment protocols, but emerging evidence supports the use of targeted biologic therapy in cases like ours.

By presenting this case, we aim to contribute to the growing body of literature on SAFS, raise awareness of its clinical presentation, and improve diagnostic and treatment approaches for affected patients.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Ethical approval

Human studies and subjects

Not applicable for this case.

Data sharing and data accessibility

The respiratory sound database is not available for researchers.

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.

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