edra ISSN 3035-2134 | June 2025 Vol. 3, No. 2

# Pediatric Respiratory Journal

Official Journal of the Italian Pediatric Respiratory Society

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

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EDITORIAL

# Why reduce the speed limit on the périphérique parisien? A Public Health and Environmental Necessity to protect children

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10.56164/PediatrRespirJ.2025.74

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The future of the Paris Ring Road, often referred to simply as the 'Périphérique Parisien', whose speed has been reduced from 70 to 50 km/h - effective since 1 October 2024 - by decision of the Paris City Council, deserves an in-depth discussion that goes beyond the controversy limited to the speed limit. Given the imperative need to reduce greenhouse gas emissions and adapt urban spaces to cope with climate change (1, 2), the project is intended to respect the universal commitment to tackling ecological responsibility and promoting sustainable urban development.

The Paris Ring Road is a 35-kilometre-long urban motorway that encircles Paris, roughly following the city's old fortifications. It is a crucial urban traffic artery, with daily traffic estimated at between 1.1 and 1.2 million vehicles, making it one of the busiest in Europe. Some stretches can exceed 250,000 vehicles a day at peak times. The areas around the Ring Road are densely urbanised, and mostly are considered 'social exclusion zones' due to the isolation caused by this infrastructure. Around 500,000 people live in the immediate vicinity of the Ring Road, where until October 2024 they were significantly exposed to significant noise and air pollution, Particulate Matter (PM) of 2,5 and 10 µm diameter respectively ($PM_{2.5}$ and $PM_{10}$) and nitrogen dioxide ($NO_2$). For the record, eight out of ten people living in the Greater Paris region close to the Ring Road are currently exposed to noise and air pollution that greatly exceeds World Health Organisation (WHO) recommendations.

***Figure 1***. *Périphérique Parisien (Paris Ring Road) in 2024.*

 

Among the exposed people, children should be a priority population when considering the impact of speed reduction on the Périphérique Parisien. Children are particularly vulnerable to air pollution due to their developing lungs and higher breathing rates (3). The Périphérique is a major source of air pollutants, like $NO_2$, $PM_{2.5}$, $PM_{10}$ and Black Carbon known as statistically linked to asthma, reduced lung function, and respiratory infections (4, 5). Several studies have shown that children living within 500 meters of major roads, like the Périphérique, are at higher risk of developing asthma due to consistent exposure to pollutants (6). Traffic noise is a known contributor to sleep disturbances, cognitive impairments, and stress in children (7).

For the time being, the impact of reducing the speed limit from 70 to 50 km/h is difficult to assess in terms of air and noise pollution. It is generally considered that reducing speed reduces fuel consumption and unit emissions of pollutants, although several other factors come into play (type and age of vehicles, gradient of the road, load, traffic flow, traffic conditions, etc.), making the relationship between speed and air pollution more complex. According to existing scientific evidence collected in a internal report by the French Agence de la Maîtrise de l'Energie (ADEME), a 20 km/h reduction from 70 km/h only marginally affects emissions of atmospheric pollutants. It is for speeds in excess of 90 km/h that the difference is statistically significant. Actually the average speed during the day on the Paris ring road is currently around 36 km/h (15-20 km/h during busy periods), well below the target limit. This has been the average for several years, characterized by significant air pollution and, in any case, by a failure to comply with the WHO standards. However, since the speed reduction air pollution has slightly diminished in some hot spots according to recent data that unfortunately have not yet been published in peer-reviewed journals. The situation is similar for noise, for which according to Bruit-Parif a reduction of two to three decibels maximum was observed, which is appreciable at night or certain weekends but not during the day. Such noise reductions are still insufficient to significantly improve the quality of life of local residents. A 2–3 dB drop in noise levels might be noticeable in very quiet environments, but it will not make a major difference in everyday loud settings like traffic noise or construction zones.

Although the immediate effectiveness of the speed reduction on the Round Ring is difficult to prove, its long-term benefits cannot be ignored and should play a decisive role in estimating the risks-benefits associated with the measure. First of all, the chronic health effects of air pollution arise not from extreme peaks but from continuous, long-term exposure to even moderate levels of pollutants (8). Chronic exposure can lead to cumulative damage over time, particularly affecting vulnerable populations like children, the elderly, and those with pre-existing conditions. Chronic exposure to environmental noise is increasingly recognized as a major public health issue, even at non-excessive levels. Unlike acute loud noises, which cause immediate hearing damage, long-term exposure to moderate noise levels can lead to physiological and psychological health effects over time (9).

In addition, in the longer term, other benefits affecting various aspects of urban life can be anticipated. Firstly, lower speeds reduce the severity of accidents and enable drivers to react more quickly in an emergency, thereby reducing the risk of serious collisions. The Atelier Parisien d'urbanisme (Apur) has foreseen changes in traffic and noise levels around the Ring Road since the speed limit was reduced to 50 Km/h in October. The number of accidents has fallen by 20%. In the long term, reducing speed helps to limit polluting gas emissions from vehicles. Less hard braking and acceleration reduces fuel consumption and abrasion and wear particles and, consequently, pollutant emissions. All in all, over the long term, a reduction in speed can help traffic flow more smoothly. Vehicles travelling at a constant speed, without jolts or traffic jams, and adopting a more regular driving style make it possible to better regulate the flow of traffic. This has a positive impact on greenhouse gas emissions, which are of vital importance in the context of anthropogenic climate change. Lastly, lower speeds also have repercussions on driving style, which once again has a significant impact on emissions of atmospheric pollutants, with a reduction of up to a factor of 4 in the case of nitrogen dioxides (NOx), according to IFPen (Institut Français du Pétrole Energies nouvelles, GECOAIR application). Reducing speeds should therefore be seen as an indirect approach to promoting a more responsible driving style, respectful of people exposed to pollution and health impacts from the Ring Road. All

these changes will have beneficial effects on the health of city dwellers, reducing chronic illnesses, especially respiratory and cardiovascular diseases, and improving their quality of life. Reducing speed also has positive effects on the protection of biodiversity and wildlife, by creating a more favourable environment for the coexistence of human infrastructures and natural ecosystems. In territorial terms, in the long term, slower and more regular traffic places less stress on road infrastructure (pavements, markings, etc.), which can reduce maintenance costs and extend the life of equipment. In addition, in the long term, as speeds fall, the width of the carriageway can be reduced to allow other vehicles to circulate (by including a protected bus lane, for example). In this context, a lane reserved for taxis and car-pooling can be maintained. In the very long term, we can also envisage putting vehicles at greater distances from each other, and planting trees that trap pollutants and therefore dilute them.

Overall, speed reduction on the Périphérique Parisien alone does not provide much information about the reduction in risks associated with human health. It is the combination of several advantages, belonging to the Ring Road exposome (all the environmental factors in the broad sense of the term that characterise it), that makes speed reduction a measure which, although sometimes unpopular at the outset, may prove to be beneficial to the quality of urban life in the long term. In this respect, from the epidemiological point of view, an experiment is needed to assess the short- and long-term effectiveness of this measure on markers linked to the health of Parisians. It is fair to say that these are just predictions and that they need to be confirmed. This is why, as scientists, we are asking for an experiment to be carried out under real-life conditions to measure changes in air quality, noise and traffic flow, and to identify changes in driving behaviour and mobility choices, etc. This would enable us to assess how all these changes impact on the health of local residents. Would there be fewer acute episodes of pollution-related illness? Fewer asthma attacks, fewer heart attacks, fewer attacks of multiple sclerosis, to name but a few? The data needed to answer these questions are readily available in France from various institutional stakeholders (Airparis, INERIS, Bruitparif, Sécurité Sociale, DGITM (Direction Générale des Infrastructures, des Transports et des Mobilités), OTM (Observatoire des Transports et de la Mobilité), etc.) and ready to be analysed. This should make it possible to sort things out.

To conclude, speed reduction on the Périphérique Parisien should not aim only to decarbonize traffic and reduce noise but also to foster a systemic transformation of mobility and land use by reducing speed and transforming modes of transport (10). This transformation represents a vision for a more resilient, equitable, and sustainable city. To this extent, it requires a far-reaching change that meets the global challenges of energy and land conservation, social and environmental justice, and metropolitan cohesion where children should constitute a priority population.

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RESEARCH ARTICLE

# Respiratory/allergic effects of indoor toluene exposure on Italian schoolchildren

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## ABSTRACT

The effects of indoor toluene on respiratory/allergic health in school children was assesed trhough questionnaire in 2284 schoolchildren ( mean age 10 years,59,9% males of eight italian cities). Measurements of pollutants were performed in 130 classrooms (44 schools). Toluene was measured by *Radiello*® passive diffusive samplers. The levels of indoor toluene were relatively low (mean 4.17 µg/m$^3$, median 2.70 µg/m$^3$). The prevalence of respiratory symptoms during the monitored week was 32.8% (16.8% at school), including 25.7% of dry cough (11.9% at school). Nasal and skin problems were reported by 73.3% (48.1% at school) and 31.6% (13.7% at school). Multiple logistic regression, accounting for center, sex, age, diagnosis/family history of asthma or rhinitis, passive smoking at home, levels of indoor particulate and carbon dioxide, indicated significant associations between toluene concentration and all considered respiratory/allergic symptoms. The strongest association regarded dry cough (OR 1.32, 95% CI 1.15-1.52) and dry cough at school (OR 1.51, 1.23-1.85). Although toluene levels in classrooms were relatively low, the exposure to this volatile organic compound is a risk factor for respiratory/allergic health of schoolchildren.

## HIGHLIGHTS BOX

**What is already known about this topic?** VOCs are ubiquitous in the environment and their concentration is consistently higher indoors than outdoors. VOCs indoor exposure is associated with general (such as headache and tiredness), irritant, respiratory, cardiovascular, neurological and carcinogenic effects. **What does this article add to our knowledge?** Evidence regarding the health effects of VOCs exposure in schools is still limited worldwide; our study showed that indoor toluene exposure, even at relatively low concentrations, is associated with respiratory/allergic symptoms in Italian schoolchildren. **How does this study impact current management guidelines?** This study highlights the importance of conducting further studies evaluating the health impact of exposure to VOCs in schools; public authorities should be aware of and intervene for abating this risk factor for children's health.

**Doi**

10.56164/PediatrRespirJ.2024.65

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**KEY WORDS**

*VOCs; toluene; schoolchildren; respiratory symptoms; allergic symptoms.*

 

## INTRODUCTION

Volatile Organic Compounds (VOCs) are a group of organic chemical pollutants that originate from both anthropogenic and biogenic sources. VOCs are ubiquitous in the environment since there are many sources (*e.g.*, traffic/industrial emissions, building/furnishing materials, arts/crafts materials, cleaning agents, and personal-care products). Concentrations of many VOCs are consistently higher indoors - up to ten times higher - than outdoors (1). Several studies have shown that indoor exposure to VOCs is associated with general (such as headache and tiredness), irritant, respiratory, cardiovascular, neurological and carcinogenic effects (2, 3).

Benzene, toluene, ethylbenzene and xylene (BTEX) are the most important toxic VOCs. Toluene is a clear, colorless liquid with a sweet, pungent odor. It can be released as a gas into the indoor air at room temperatures. Toluene can enter the indoor environments in vehicle exhaust or vapors from stored fuel. It is also a very good solvent, and it can dissolve many organic compounds. Indoor sources of toluene include building materials (*e.g.*, solvent/water-based adhesives, floor coverings, paint, chipboard), consumer and automotive products (*e.g.*, cleaners, polishes, adhesive products, oils, greases, lubricants), and environmental tobacco smoke (4). Exposure to toluene is generally via indoor air, through inhalation, and its average concentration can vary considerably.

It is known the role of indoor air pollution in affecting respiratory health in both children and adults (5). Even low concentrations of indoor pollutants may have adverse biological effects when exposures are prolonged (6). Even though health-related organizations have set standard limits as unhazardous levels (*e.g.,* Environmental Protection Agency, The European Union, The Standardization Administration of China), it has been observed that, within or even below these limits, constant exposure to these toxic chemicals is linked to adverse health effects. Concentrations below the VOCs reference values, including toluene, are associated with increased oxidative stress, a precursor mechanism of chronic diseases such as bronchitis, asthma, and loss of pulmonary function (7). Acute or chronic exposure to toluene vapor can irritate the mucous membranes of the upper respiratory tract (8). There is evidence on the association between occupational asthma and toluene exposure (9, 10), as well as between urinary metabolites of toluene and childhood asthma (11).

Children are most vulnerable to the ubiquitous pollution in their environment, and they do not always respond to pollutants as adults do. Children are frail during their growth and, because of their physical constitution and breathing rate relative to their body size, they are more susceptible to the health effects of air pollution than adults (12).

Children spend about 5-8 hours a day at school, thus the school ranks second after the home for the length of time spent indoors. Studies regarding the school environment and related health effects in children have been performed worldwide, including Europe (13-19). Most studies concern the effects of exposure to particulate matter (PM), nitrogen dioxide ($NO_2$), carbon dioxide ($CO_2$), mold/dampness, formaldehyde or total VOCs (8, 16, 17). There are very few studies on the association between indoor toluene in schools and respiratory/allergic symptoms in schoolchildren.

In the present study, we assessed how indoor toluene may affect respiratory health in schoolchildren.

## MATERIAL AND METHODS

### Study population

Data from the Italian project named 'Exposure to indoor pollutants: guidelines for the evaluation of risk factors in the school environment and definition of measures to protect the respiratory health of schoolchildren and adolescents' (*Indoor-School*), funded by the Center for Disease Control (CCM) of the Italian Ministry of Health, were analyzed (20).

The *Indoor-School* project (2011-2014) was conducted in eight Italian cities (Udine, Sondrio, Milan, Pisa, Rome, Bari, Cagliari, Palermo) in two phases (21). The project was developed considering possible geographic differences in the three Italian macro areas (North, Centre, South) (**Figure 1**). We present here data from the first phase (2011-2012), regarding 2285 schoolchildren (mean age 10.3 years., 50.8% males), 44 schools, and 130 classrooms.

### Environmental assessments

The project included indoor/outdoor environmental measurements (*i.e.*, temperature, relative humidity, $CO_2$, $PM_{2.5}$, $NO_2$, and VOCs). Measured VOCs were Ben-

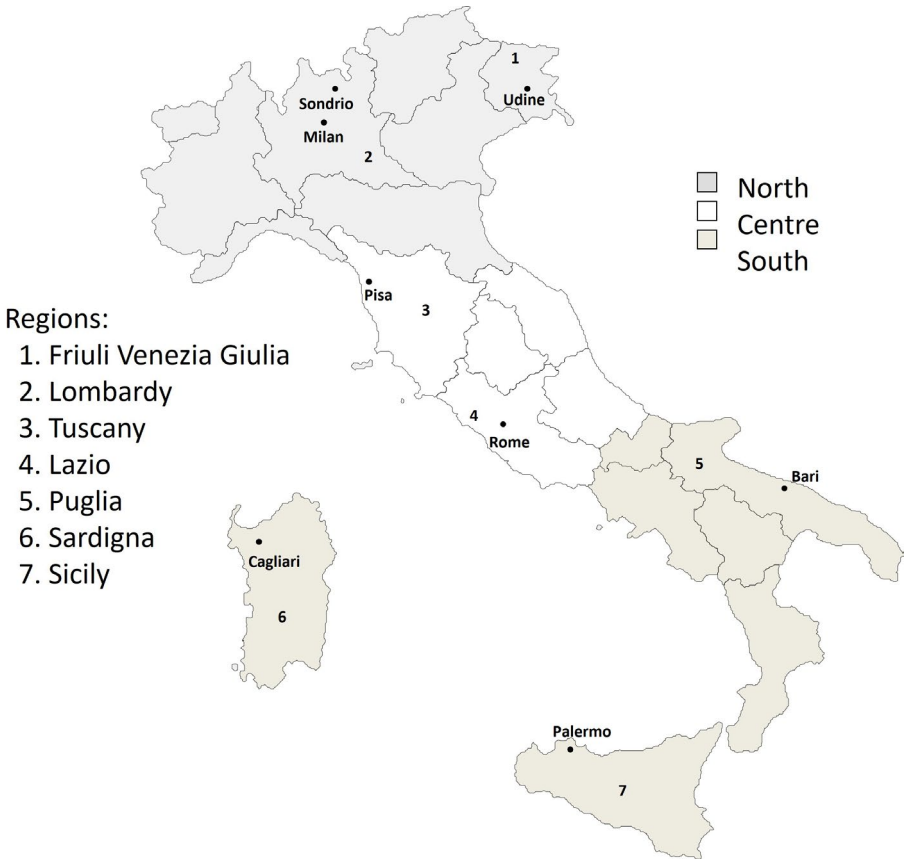


***Figure 1***. *Distribution of the investigated regions and participating cities throughout Italy.*

zene, Toluene, Ethylbenzene, Xylene (BTEX), and Formaldehyde. Indoor measurements were performed for one week in the classrooms, during normal activities (full classroom), and under representative conditions (same sampling points for all classrooms). In the same week, outdoor measurements were also carried out in the immediate vicinity of the school. The method was the same for all monitored schools. Toluene levels (μg/m$^3$) were measured by *Radiello*® passive diffusive samplers (ICS Maugeri, Italy) and high-performance liquid chromatography (HPLC) at the laboratory of 'Istituto Superiore di Sanità' (ISS), National Center for Research and Evaluation of Immunobiological Products (Rome). The VOCs were sampled by adsorption and extracted with carbon disulfide ($CS_2$) (2 mL and under stirring for approximately 30 minutes) and sent for HPLC analysis with a Flame Ionization Detector (FID).

$PM_{2.5}$ (μg/m$^3$) and $CO_2$ levels (part per million, ppm) were measured by means of direct reading analyzers (DustTrak for $PM_{2.5}$ and Q-track for $CO_2$) (22).

## Health assessments

Information on respiratory/allergic symptoms, during the monitored week, was collected through a questionnaire administered directly to the schoolchildren. We considered the following symptoms for analysis:

- respiratory symptoms (RSs) (Question: "In the past week, have you had dry cough or breathlessness with or without whistling/wheezing in the chest or whistling/wheezing in the chest?");
- nasal problems (NPs) (Question: "In the past week, have you had runny nose or itchy/irritated nose or stuffy nose or sneezing?");
- skin problems (SPs) (Question: "In the last week, have you had rashes/itching on hands/arms/face/neck or eczema?").

The answers to the questions were as follows: "Yes at home, yes at school, yes in other places, no". We considered presence/absence of symptoms in general, regardless of location, and specifically, while the children were at school.

### Potential confounders

Information on children's diagnosis of asthma/rhinitis, family history of asthma/rhinitis, allergy (hay fever, allergy to pollens/damp/mold/cat/dog), and exposure at home to second-hand smoke (SHS) was collected by a questionnaire filled in by the parents. The questionnaires were derived from previous questionnaires used in studies conducted among schoolchildren in Europe: "International Study of Asthma and Allergies in Childhood" (ISAAC) project (23), 'Health Effects of School Environment' (HESE) study (24), 'School Environment and Respiratory Health of Children' (SEARCH) study (25), and 'Schools Indoor Pollution and Health Observatory Network in Europe' (SINPHONIE) study (26). Moreover, we collected information on school characteristics through a questionnaire filled in by the principal.

***Table 1**. Characteristics of children.*

| | N (valid %) |
|---|---|
| Total sample: | 2285 |
| *Males* | 1161 (50.8) |
| City: | |
| *Udine* | 355 (15.5) |
| *Sondrio* | 76 (3.3) |
| *Milan* | 376 (16.5) |
| *Pisa* | 391 (17.1) |
| *Rome* | 343 (15.0) |
| *Bari* | 324 14.2) |
| *Cagliari* | 62 (2.7) |
| *Palermo* | 358 (15.7) |
| Age (years): *Mean ± SD (Median) [range]* | 10.3 ± 1.7 (10.0) [6-15] |
| Asthma/rhinitis diagnosis | 321 (15.4) |
| Asthma/rhinitis family history | 822 (38.6) |
| Allergy† | 299 (13.1) |
| Second-hand smoke at home | 446 (21.5) |

*† Including allergic cold, hay fever, allergy to pollens/damp/mold/cat/dog, confirmed by a physician*

The Indoor-School study protocol, participant information sheet, and consent form were locally approved by the Ethics Committee of each participating center, after the approval obtained by the Clinical Manager of the study from the Ethics Committee of the University Hospital P. Giaccone of Palermo (N. 5/2011, 18/5/2011).

### Statistical analysis

Statistical analyses were performed with the Statistical Package for Social Science (SPSS version 17). Used routines were frequency distributions, analysis of variance with post hoc Bonferroni and Waller-Duncan tests, non-parametric tests of Kolmogorov-Smirnov and Kruskal-Wallis. The association between symptoms and indoor toluene exposure was assessed by logistic regression analyses unadjusted and adjusted for city, gender, age, asthma/rhinitis diagnosis, family history of asthma/rhinitis, allergy, SHS exposure at home, and levels of indoor $PM_{2.5}$ and $CO_2$ as independent variables. Indoor toluene levels were not normally distributed and were log10-transformed for analyses. The significance level was set at 0.05.

## RESULTS

**Table 1** reports the characteristics of the sample. **Table 2** and **Figure 2** show the prevalence of symptoms considered. Any RSs were reported by 32.8% of the schoolchildren, with significantly higher prevalence in Bari (76.6%) and Cagliari (69.4%); 16.8% of children reported RSs at school, with the highest prevalence in Rome (28.6%). In particular, dry cough was present in 25.7 % of cases (11.9% at school), with significantly higher prevalence in Rome (40.5%, 24.8% at school). NPs were the most frequently reported (73.3%), with significantly higher prevalence in Palermo (84.8%); with regard to NPs at school, the prevalence was 48.1%, with the highest

***Table 2**. Respiratory/allergic symptoms reported by schoolchildren (N=2285) in the environmental monitored week.*

| | N (valid %) |
|---|---|
| Respiratory symptoms *(dry cough/breathlessness/wheezes)* | 749 (32.8) |
| at school | 385 (16.8) |
| Dry cough | 547 (25.7) |
| at school | 271 (11.9) |
| Nasal problems *(runny/dry nose)* | 1612 (73.3) |
| at school | 1100 (48.1) |
| Skin problems *(rashes/itching)* | 664 (31.6) |
| at school | 313 (13.7) |

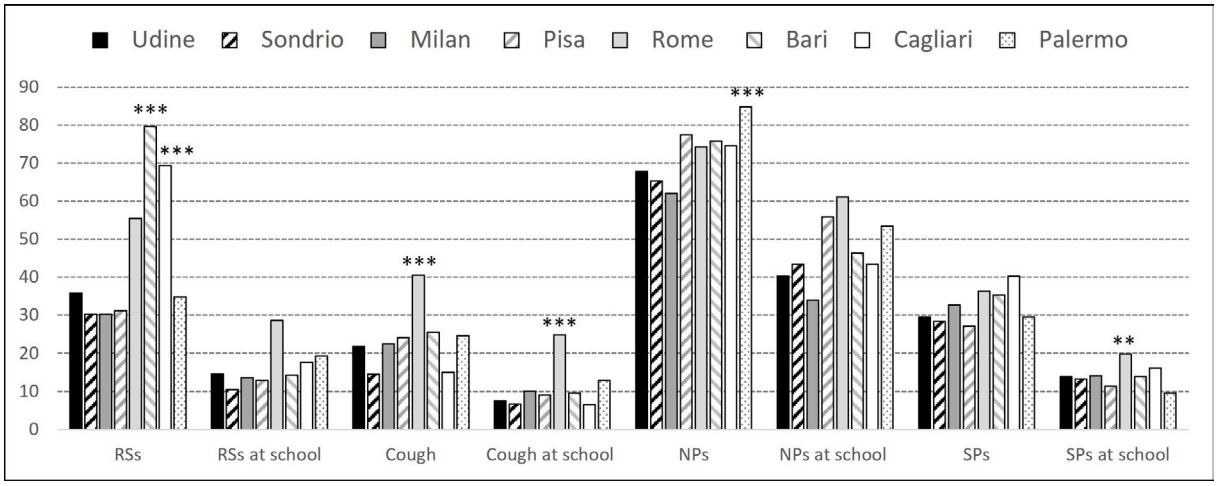


***Figure 2**. Percent prevalence of considered symptoms by city. RSs (Respiratory symptoms): dry cough/breathlessness/wheezes; NPs (Nasal problems): runny nose or itchy/irritated nose or stuffy nose or sneezing; SPs (Skin problems): skin rashes/itching. *** p <0.001; ** p = 0.01.*

value in Rome (61.2%). SPs were present in 31.6% of cases with the highest prevalence in Cagliari (40.3%), and 13.7% at school (19.8% in Rome).

SHS at home was reported by 21.5% of parents, with the highest prevalence in Rome (31.0%) and Palermo (27.4%), and the lowest in Udine (14.4%) and Milan (14.5%).

As regards toluene, indoor levels were relatively low (median value 2.70 μg/m$^3$) and showed a significant positive correlation with outdoor levels (Sperman's rho 0.74, p<0.001). Mean concentrations of toluene were more elevated indoors than outdoors (4.17 vs 3.94 μg/m$^3$) (**Table 3**).

There was a significant difference between centers (p < 0.001, by Kruskal-Wallis test), due to the highest concentrations in Rome and Milan (**Figure 3**). Indoor toluene was positively associated with vehicular traffic (p = 0.01 by Kruskal-Wallis test): median levels in schools located near roads with low, medium, and high/very high vehicular traffic were 1.35, 3.50 and 4.70 μg/m$^3$, respectively. Both bivariate and multiple regression analyses showed that indoor toluene was significantly related to all considered symptoms (**Table 4**). The strongest association was found with dry cough at school (odds ratio - OR 1.51, 95% confidence interval - 95% CI 1.23-1.85).

***Table 3**. Concentration of toluene inside the classroom, and outside the school in the environmental monitored week.*

| Region | City | Indoor toluene (μg/m$^3$) | | Outdoor toluene (μg/m$^3$) | |
|---|---|---|---|---|---|
| | | Mean ± SD | Median [range] | Mean ± SD | Median [range] |
| Friuli Venezia Giulia | Udine | 2.39 ± 2.44 | 1.85 [0.01-7.60] | 3.35 ± 5.03 | 1.85 [0.01-14.90] |
| Lombardy | Milan | 7.31 ± 5.62 | 5.70 [3.00-29.00] | 5.44 ± 1.69 | 5.10 [3.00-7.90] |
| | Sondrio | 0.99 ± 0.70 | 1.30 [0.01-1.70] | 0.01 ± 0.00 | 0.01 [0.01-0.01] |
| Tuscany | Pisa | 2.75 ± 2.48 | 1.35 [0.23-7.80] | 2.50 ± 2.51 | 1.45 [0.20-7.20] |
| Lazio | Rome | 12.40 ± 5.53 | 12.63 [3.14-26.33] | 11.75 ± 13.22 | 8.25 [3.80-44.0] |
| Puglia | Bari | 1.99 ± 3.30 | 0.01 [0.01-9.80] | 1.85 ± 3.64 | 0.01 [0.01-9.80] |
| Sardigna | Cagliari | 0.10 ± 0.24 | 0.01 [0.01-1.00] | 1.17 ± 1.27 | 1.01 [0.01-2.90] |
| Sicily | Palermo | 3.33 ± 2.06 | 3.40 [0.01-8.90] | 2.70 ± 1.99 | 2.55 [0.01-5.10] |
| Total | | 4.17 ± 5.17 | 2.70 [0.01-29.00] | 3.94 ± 6.35 | 2.40 [0.01-44.00] |

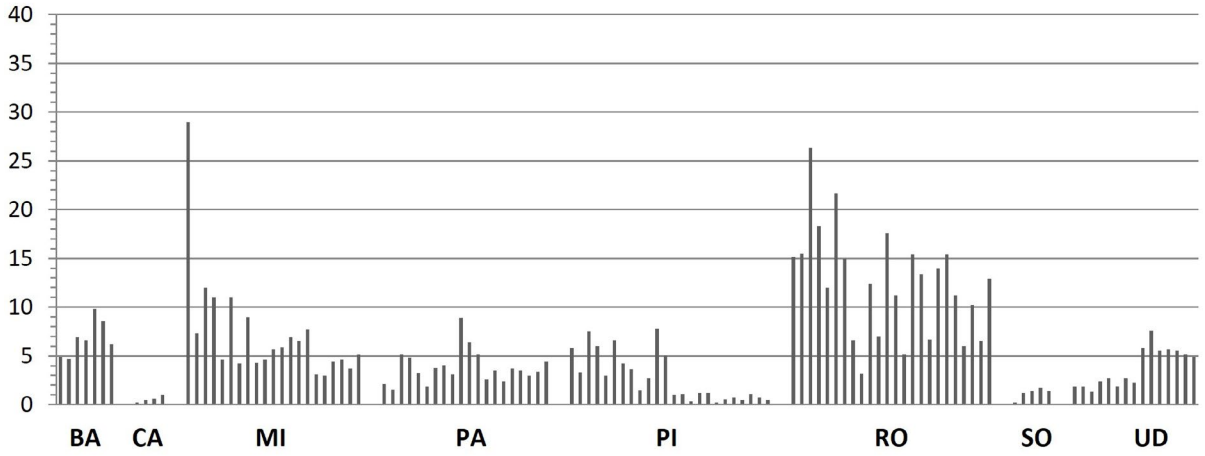


***Figure 3**. Levels of indoor toluene ((µg/m3) in the monitored classrooms, by city (Ba, Bari; CA, Cagliari; MI, Milan; PA, Palermo; PI, Pisa; RO, Rome; SO, Sondrio; UD, Udine).*

## DISCUSSION

Despite the magnitude of the school population, the state of knowledge regarding VOCs in schools, including their association with health outcomes in schoolchildren, is still limited worldwide. A reason might be that most epidemiological research on VOC exposure has focused on occupational exposure for workers, where the exposure concentrations are much higher than those in residences, office buildings, or schools. While high concentrations of toluene are known to affect multiple human organ systems, research concerning the influence of exposure to low concentrations of indoor toluene is scarce. Schoolchildren spend approximately six to eight hours per day in various school microenvironments. Therefore, assessing their air toxics exposure is important to formulate interventions and policies for a healthier environment.

According to other authors, we found that indoor toluene was the predominant compound within the measured BTEX (mean concentrations were 4.16, 1.00, 1.13, 0.19 µg/m$^3$ for toluene, benzene, xylene, and ethylbenzene, respectively), and it was more elevated indoors than outdoors (26-28), indicating a double origin in indoor levels (original sources and penetration from outdoors). Indeed, we found a significant positive correlation between indoor and outdoor toluene

***Table 4**. Crude and adjusted associations between indoor toluene and respiratory/allergic symptoms.*

| | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|
| Dry cough/breathlessness/wheezes | **1.19 (1.10-1.29)** | **1.16 (1.03-1.29)** |
| Dry cough/breathlessness/wheezes at school | **1.20 (1.08-1.33)** | **1.26 (1.08-1.46)** |
| Dry cough | **1.24 (1.12-1.37)** | **1.32 (1.15-1.52)** |
| Dry cough at school | **1.40 (1.22-1.61)** | **1.51 (1.23-1.85)** |
| Nasal problems | **1.03 (1.00-1.13)** | **1.15 (1.03-1.29)** |
| Nasal problems at school | **1.08 (1.01-1.17)** | **1.17 (1.06-1.30)** |
| Skin rashes/itching | 1.03 (0.95-1.12)† | **1.17 (1.04-1.31**) |
| Skin rashes/itching at school | **1.11 (1.00-1.24)** | **1.21 (1.03-1.40)** |

*Odds Ratio (OR) and 95% Confidence Interval (CI) for toluene log-unit increment. Analyses accounted for city, gender, age, asthma/rhinitis diagnosis, asthma/rhinitis familiarity, allergy, second-hand smoke at home, indoor PM2.5 (log unit increment), and indoor CO2 (100 ppm increment).*
*† Borderline significant.*

in the study sites. Our results confirm the difference in the concentration of toluene between the schools located in areas with high traffic density and school located in areas with low vehicular traffic (12). It is not surprising that the highest levels of exposure happen in schools in Rome, near roads with medium (50%) or heavy/very heavy traffic (50%). Children attending near-road schools are more sensitive to the deleterious effects of these air toxics, thus the role of school location in children's air pollution exposure is a growing policy issue (29).

The mean indoor toluene level in our classrooms (4.17 $\mu g/m^3$) was lower than those found by Sofuoglu et al. in Turkish primary schools (18.70 $\mu g/m^3$) (28), by Martins et al. in Portugal (20.70 $\mu g/m^3$) (27), by Norbäck et al in Malaysian schools (12.3 $\mu g/m^3$) (8), and remarkably by Kim et al in Korea (81.17 $\mu g/m^3$) (30). Conversely, the median concentration (2.70 $\mu g/m^3$) was very similar to that found in the schools of the "School Health Initiative: Environment, Learning, and Disease" (SHIELD) study, performed in Minnesota (2.5 $\mu g/m^3$) (31).

With regard to adverse health effects, we found significant positive association of respiratory symptoms, nasal and skin problems with toluene exposure at school. The Agency for Toxic Substances and Disease Registry (ATSDR) (32) indicates in 1 ppm the minimal risk level for chronic exposure to toluene for the general population, which corresponds to 265 $\mu g/m^3$. Thus, the levels measured in our classrooms were low. However, our results suggest the lack of a real threshold below which there are no effects of toluene exposure on children's health. As mentioned, children are more vulnerable and susceptible to air pollution than adults.

Kim et al., in Korea, reported that schools with many students having allergic rhinitis symptoms had higher concentrations, almost double for toluene ($p = 0.02$), compared to schools where fewer students had allergic rhinitis symptoms (30). Similarly, we found significantly higher levels of toluene for schoolchildren with allergy (including hay fever) than for those without allergy.

Most studies on the effects of toluene exposure in children report associations with asthma or reduced lung function (11, 27, 33). Indeed, in our study we found that toluene exposure was associated with typical asthma symptoms, such as dry cough, shortness of breath, and chest wheezing.

## CONCLUSIONS

Our study points out that toluene exposure at school, even at relatively low concentrations, is associated with respiratory/allergic symptoms in Italian schoolchildren. Further studies evaluating both toluene and other VOCs should be conducted in schools in order to clarify the underlying mechanisms of the adverse respiratory/allergic impacts.

Public authorities should be aware of and intervene to avoid this risk factor in order to protect children's health.

## COMPLIANCE WITH ETHICAL STANDARDS

### Conflict of interest

The authors have no financial or non-financial interests to disclose.

### Financial support

This work was supported by Center for Disease Control (CCM) of the Italian Ministry of Health (Indoor-School project, Id. N°: 13).

### Author contributions

SB, GV contributed to the study conception, design and data interpretation. Material preparation, data collection and analyses were performed by MS, GS, SM, IS, AA, PS. The first draft of the manuscript was written by MS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

### Ethical approval

*Human studies and subjects*

The Indoor-School study protocol, participant information sheet, and consent form were locally approved by the Ethics Committee of each participating centre, after the approval obtained by the Clinical Manager of the study from the Ethics Committee of the University Hospital "P. Giaccone" of Palermo (N. 5/2011, 18/5/2011).

*Animal studies*

N/A.

### Data sharing and data accessibility

The data presented in this manuscript are available on request from the Corresponding Author.

### Publication ethics

*Plagiarism*

All original studies are cited as appropriate.

*Data falsification and fabrication*

All the data corresponds to the real.

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REVIEW

# Eight common mistakes pediatricians should avoid that hinder antimicrobial immune defenses: strategies for boosting protective immunity

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10.56164/PediatrRespirJ.2024.61

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## ABSTRACT

Antimicrobials and vaccinations are vital tools in the fight against infections and in supporting the immune system. Over recent years, significant improvements in life expectancy have been attributed to better access to antimicrobials. However, the increasing threat of antimicrobial resistance has become one of the leading causes of death globally. Vaccinations remain the cornerstone of preventive strategies. In addition to them, other preventive measures, such as handwashing, mask use, physical distancing, and proper nutrition, play crucial roles in reducing infection spread. Nutritional interventions that offer immunomodulatory and antioxidant effects should also be considered in conjunction with these strategies to enhance immune defenses further.

This paper aims to highlight common mistakes pediatricians should avoid that may hinder immune defenses and exacerbate the risk of viral and bacterial infections. By identifying and correcting these errors, pediatricians can improve patient outcomes, reduce the burden of disease, and promote more robust immune development in children.

## IMPACT STATEMENT

This article aims to underline the crucial role of pediatricians in preventing recurrent respiratory infections in children and their sequelae, through diet and lifestyle suggestions, pollution prevention, vaccines and conscious use of antitussives, antipyretics and inhaled steroids.

## ABBREVIATIONS

COVID-19: COronaVIrus Disease 19
MDI: Mental Development Index
aHR: adjusted Hazard Ratio
CI: Confidence Interval
aOR: adjusted Odd Ratio
ARI: Acute Respiratory Infections
HR: Hazard Ratio
COPD: Chronic Obstructive Pulmonary Disease
RSV: Respiratory Syncytial Virus
Th2: T Helper 2
TRPA-1: Transient Receptor Potential Ankyrin-1

## KEY WORDS

*Immunity; infections; children; prevention; lifestyle.*

## INTRODUCTION

Antimicrobials and vaccinations are vital tools in the fight against infections and in supporting the immune system. Over recent years, significant improvements in life expectancy have been attributed to better access to antimicrobials, particularly in low -and middle- income countries (1). However, the increasing threat of antimicrobial resistance jeopardizes these gains, as it has become one of the leading causes of death globally, with the highest burden in low-resource settings. Immunizations, which remain the cornerstone of preventive strategies, have successfully utilized diverse technologies such as inactivated, attenuated, nucleic acid, and viral vector-based vaccines (2). These innovations have led to

the development of highly effective and safe products. For instance, during the COVID-19 pandemic, vaccinations are estimated to have prevented around 14.4 million deaths globally (3).

Despite these advances, vaccine-preventable diseases still affect millions of individuals, particularly in regions like Europe (4).

In addition to vaccines, other preventive measures -such as handwashing, mask use, physical distancing, and proper nutrition- play crucial roles in reducing infection spread (5). These measures gained widespread recognition during the COVID-19 pandemic, as they demonstrated their efficacy in mitigating viral transmission (6). Nutritional interventions that offer immunomodulatory and antioxidant effects should also be considered in conjunction with these strategies to enhance immune defenses further.

This paper aims to highlight common mistakes pediatricians should avoid that may hinder immune defenses and exacerbate the risk of viral and bacterial infections. By identifying and correcting these errors, pediatricians can improve patient outcomes, reduce the burden of disease, and promote stronger immune development in children.

## MULTI-SYSTEMIC AND PROLONGED CONSEQUENCES OF AIRWAY INFECTIONS

Viral and bacterial infections of the airways that occur during childhood pose a relevant individual and social burden, and may impair health across the lifespan. Recurrent respiratory infections during the early years of life may have potential adverse effects both on the nervous and the respiratory systems. For instance, infants who suffer from bronchiolitis and, in the following months, from recurrent wheezing may experience early cognitive deficits. It has been shown that the cognitive status of children at the age of 3 years, assessed with the Bayley Mental Development Index (MDI), was inversely correlated with the number of wheezing days experienced during the first 24 months of life ($r = -0.13$, $p = 0.007$). Compared to healthy children, those who suffered from wheezing during the first year of life showed a 2-point MDI deficit (beta coeff. = -2.31, 95% CI: -4.63 to 0.02), and those with persistent wheezing (both first and second year) even had a 4-point deficit (beta coeff. = -4.41, 95% CI: -8.27 to -0.55) (7).

Cognitive impairment may be related to decreased respiratory function, leading to fluctuating oxygen delivery and consequent oxidative stress (8), which can be worsened by exposure to passive smoking (7) and the possible use of paracetamol for concomitant febrile respiratory infections (9). These co-existing factors may impair brain development during its rapid growth phase. Interestingly, optimal selenium levels favor adequate cognitive function at 18 months of age during pregnancy (10), while recurrent episodes of virus-induced wheezing in the first years of life are associated with selenium and zinc deficiency (11), and low vitamin D levels (12). Pneumonia-related hypoxia (13) and uncontrolled inflammation (14) can activate microglial cells, contributing to subsequent cognitive impairment and dementia (15).

In adults as well as in the elderly, a respiratory problem, such as pneumonia requiring hospitalization, is associated with a 53% higher incidence of cognitive impairment and dementia compared with the general population (adjusted hazard ratio (aHR) 1.53, CI 95% 1.46-1.61) The highest risk was observed within the first year after hospitalization (aHR 1.89, 95% CI 1.75-2.05), and the effect was stronger in individuals aged 45-60 years (aHR 2.10, 95% CI 1.56-2.82) (16). Surprisingly, the risk was lower for subjects over 80 years old (aHR 1.67, CI 95% 1.43-1.95). Still, is known that healthy aging is associated with a more remarkable ability to defend against oxidative stress and a well-balanced immune system response (17).

In addition to potential adverse effects on the nervous system, recurrent respiratory infections during the first years of life can both damage the airways and contribute to the development of chronic respiratory disease. A prospective study of 5197 children demonstrated that respiratory tract infections in the first three years of life are associated with an increased risk of asthma development by age 10 years (OR 1.79, 95% CI 1.19 -2.59) (18). Furthermore, a dose-response effect has been proven in children with nine or more ARIs/year that had a higher risk of asthma by the age of 7 years compared to infants from 0 to 23 months with fewer than five acute respiratory infections (ARIs)/year, (aOR 7.20; CI 95% 2.49-20.88). In children with subsequent asthma development, the mean duration of ARIs was longer, and the severity was higher compared to controls (19), thus reflecting a more unbalanced immune response. Although this

may partly be attributed to airflow limitation with intermittent hypoxia, it is noteworthy that in the same study most ARIs occurred without wheezing (19). Indeed, in another cohort of children followed from birth to 7 years of age, the frequent referral for major respiratory problems in the first three years of life was more predictive of asthma development at seven years of age ($p < 0.0001$) rather than the finding of wheezing at medical evaluation ($p = 0.05$) (20). However, it is essential to remember that detecting wheezing by clinical examination seems insufficiently accurate (21). Consequently, relying solely on this sign, without objective assessment of flow limitation (22), could result in medical undertreatment, of both bronchial obstruction and the pathogenetic mechanisms underpinning asthma, such as inflammation and oxidative stress (23). It has been demonstrated that early airway infections are associated to changes in endothelial cell physiology, such as increased vascular permeability, thereby causing bronchial wall edema (24). These changes contribute to bronchial hyperresponsiveness and reduced lung function, and could be ascribed to increased inflammatory responses (25) and oxidative stress. A longitudinal study of the "British Cohort" (26) - 17.198 infants born in a specific week of the year 1946 in England, Scotland, and Wales, followed until adult age -provided evidence that participants who had experienced a lower respiratory tract infection during early childhood had a higher risk of dying from respiratory disease before they turned 73, compared to control (HR 1-93, 95% CI 1-10- 3-37; $p = 0.021$) (27), regardless of socioeconomic position, childhood household overcrowding, birth weight, gender, and adult cigarette smoking. These deaths represented one-fifth of all deaths in this cohort (27). Impaired lung function is likely to link early childhood infections and respiratory mortality in adults and should be a clear reminder for pediatricians of their own essential role in prevention (28). Identifying young children affected by lower airway infections, actively optimizing their health, and protecting airway development could be a way to disrupt the tracking of respiratory health impairment in childhood until adulthood. Remarkably, being born with smaller airways represents both a risk factor for the onset of bronchiolitis, recurrent wheezing during viral respiratory infections (29-31), as well as for the development of asthma in children and chronic obstructive bronchitis in adults (32). Moreover, reduced respiratory function in adults is associated with increased mortality. This stresses the importance of adopting preventive measures in the early years of life, during pregnancy (33), and perhaps even before conception (34, 35), and is a further reminder that prevention should be started but should not be limited to pediatric age.

## EIGHT MISTAKES TO AVOID

### 1. Ignoring Environmental Impacts

Air pollution causes millions of deaths annually (36), contributing to adverse respiratory outcomes like asthma, reduced lung function, and COPD (37). Children are particularly vulnerable to the detrimental effects of air pollution. Due to various physiological-behavioral factors, they run a higher risk of outcomes such as acute respiratory infections, asthma, and reduced lung function. The risk varies in different geographical regions, depending on the source of air pollution, the duration of exposure, and the concentration of pollutants (38). Factors such as prenatal and childhood exposure to parental smoking can exacerbate these outcomes (39, 40). Emerging pollutants like microplastics are also harmful, leading to inflammation and other adverse effects on the respiratory system (41-43).

### 2. Using a Presumptive Approach for Vaccinations

A participatory approach in discussing vaccinations, especially during pregnancy and early infancy, reduces vaccine hesitancy (44). To promote adherence to vaccinations against diseases like pertussis, influenza, and RSV infection during pregnancy and early life is crucial, and necessitates of a close collaboration between pediatricians, neonatologists and obstetricians (45).

### 3. Not Promoting Breastfeeding

Breastfeeding reduces the severity of RSV bronchiolitis, hospitalization duration, and the risk of SARS-CoV-2 infection in infants. Encouraging exclusive breastfeeding is essential for infant health (46, 47).

### 4. Neglecting Maternal Diet

A diet rich in fruits and vegetables during pregnancy and breastfeeding promotes early acceptance of these foods in infants (48). This contributes to reduced risks of food allergies, atopic dermatitis, asthma, and improved lung and immune system development in children (49-51).

### 5. Failing to Warn Against Smoking During Pregnancy

Maternal smoking, including vaping, is a leading cause of abnormal lung development, resulting in increased respiratory diseases like asthma in children. Nicotine is harmful to fetal lung development, and exposure to secondhand smoke should be strongly discouraged (52-54).

### 6. Suppressing the cough reflex

Cough is a natural defense mechanism, and suppressing it can be harmful, especially in cases of infection (55). While cough suppressants act on neural pathways, they do not address underlying inflammation (56). Natural anti-inflammatory substances should be preferred (57).

### 7. Overuse of paracetamol for fever

Fever is a critical defense mechanism against infections (58, 59). Overuse of paracetamol, especially during pregnancy and infancy, has been linked to the development of asthma (60, 61). The summary of evidence linking, with a causality ratio (60), the use of paracetamol with the onset of asthma is summarized in Table 1 (**Table 1**) (61). Paracetamol depletes antioxidants and disrupts immune balance, prolonging infections (62) and increasing allergy risks (63, 64).

### 8. Over-reliance on steroids a panacea

Although effective for certain respiratory conditions, steroids are often overprescribed for treating cough and infections (65). Moreover, they do not address the root causes of diseases like asthma and can worsen oxidative stress (66), leading to diminished efficacy and increased reliance on higher doses, thus contributing to long-term health risks.

## CONCLUSIONS

Respiratory infections in early life and childhood, if recurrent and/or particularly severe, can have repercussions on the nervous system, ranging from a slight reduction in cognitive abilities in children to dementia in the elderly. The pathogenesis of these diseases can be attributed to oxidative stress and uncontrolled inflammatory response. Other consequences of early respiratory infections, including the development of asthma and allergies at a young age and COPD in the elderly, may recognize the same pathogenetic mechanism. Prevention should begin before conception and continue during pregnancy and in the early years of life through a diet rich in antioxidants and anti-inflammatory substances and by avoiding common mistakes that may hinder antimicrobial immune defenses.

***Table 1**. Summary of evidence identifying a causal relationship between the use of paracetamol and the development of asthma according to Bradford Hill criteria (61).*

| | |
|---|---|
| **Effect strength** | Increased risk of asthma up to 2.1 (exposure to paracetamol in utero) |
| | Up to 7,3 (use of paracetamol in infancy or childhood) |
| | And up to 2,9 (use of paracetamol in adults) |
| **Dose-response** | Described for exposure to paracetamol in utero, childhood and adults |
| **Coherence/coherence** | Consistency between different studies in various age groups and populations worldwide |
| | Moderate consistency with some studies reporting a lack of effects, biases and/or confounders |
| **Exposure before response** | Observed in studies on exposure to paracetamol in utero |
| | And in adulthood |
| **Biological plausibility** | Increased oxidant-induced inflammation, potentially increased Th2 response, and stimulation of the transient receptor ankyrin 1 (TRPA-1) |
| **Removal of exposure prevents the disease** | Not yet reviewed |
| **Specificity** | No increased risk of asthma associated with aspirin or other nonsteroidal anti-inflammatory drugs |
| **Temporal association** | International trends of increasing use of paracetamol and increasing prevalence of asthma |

## COMPLIANCE WITH ETHICAL STANDARDS

### Conflict of interests

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

### Funding

No external funding.

### Author contributions

VH, CB and GF: conceptualized the study, drafted the initial manuscript, reviewed the literature and critically revised the final manuscript.

MP, GF, LT, GP and LP actively participated in critically reviewing the manuscript.

All Authors read and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

### Ethical approval

*Human studies and subjects*

N/A.

*Animal studies*

N/A.

### Data sharing and data accessibility

Data are available upon motivated 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 correspond to the real.

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POSITION PAPER

# Position Paper on short-acting beta-2 agonists for acute wheezing episodes in children aged below 6 years. A statement proposed by the Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili, SIMRI) Asthma Committee and approved by the SIMRI Advocacy Council and Executive Committee

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## ABSTRACT

The term 'wheeze' denotes a common clinical sign observed in various respiratory obstructive diseases among pediatric patients. It affects approximately one out of every three children under the age of three. In children aged below 6 years, viral respiratory tract infections commonly trigger the episode of wheeze, although some children may wheeze in response to other triggering factors. Short-acting beta-2 agonists, that proved to be a safe and wieldy drug, represent the first-line treatment for managing acute wheezing attacks in preschoolers, regardless of the severity of wheezing.

Their bronchodilator action is established within 5 minutes and lasts for 4-6 hours. This statement outlines the role, the mechanisms of action and side effects of short-acting beta-2 agonists and reports the recommendations of the Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili, SIMRI) in treating acute wheezing episodes in children younger than 6 years.

## IMPACT STATEMENT

SABA, that proved to be a safe and wieldy drug, represents the first-line treatment for managing acute wheezing attacks in preschoolers. This statement outlines the role, the mechanisms of action and side effects of short-acting beta-2 agonists in children aged under 6 years.

## INTRODUCTION

The term 'wheeze' denotes a common clinical sign observed in various respiratory obstructive diseases among pediatric patients (1). It affects approximately one out of every three children under the age of three (2). We distinguish 'wheeze' that refers to a sign identified by healthcare professionals and 'wheezing' that describes symptoms reported by the patient or caregiver. During chest auscultation of a patient with wheezing, a characteristic musical, high-pitched, and continuous sound is observed (3). This sound, provoked by airway obstruction regardless of the underlying etiol-

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10.56164/PediatrRespirJ.2024.67

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**KEY WORDS**

*Short-acting beta-2 agonists; wheezing; children.*

 

ogy and mechanism, arises from the limitation and turbulence of airflow at the site of airway constriction and varies based on the degree of obstruction.

Airway narrowing in patients experiencing wheezing can stem from several underlying mechanisms, including: 1) congenital abnormalities; 2) smooth muscle constriction; 3) extrinsic or intrinsic compression; 4) mucosal swelling and mucus accumulation in the airway.

Given the different possible mechanisms involved, it is not surprising that wheezing is observed in various diseases with differing etiologies, such as asthma, cystic fibrosis, bronchiolitis, as well as bronchomalacia, endobronchial masses, aspirated foreign bodies, vascular rings (4, 5).

The features of the sound produced during airway narrowing depend on the level and severity of obstruction. Wheezing, as an indication of intrathoracic airway obstruction, typically manifests during the expiratory phase, although it may also occur during inspiration in cases of severe obstruction (1). When wheeze arises from the obstruction of larger airways, the sound is transmitted uniformly throughout the lung and is termed 'monophonic'. Conversely, obstruction of smaller airways results in 'polyphonic' sounds due to variable obstruction occurring at different sites within the lung (1).

Wheeze is categorized as mild, moderate, or severe based on the degree of airflow limitation. This categorization takes into account the presence or absence of respiratory distress signs (such as nasal flaring, prolonged expiration, tachypnoea, and intercostal muscle engagement) and the association with red flag signs (including desaturation, cyanosis, inability to speak, and confusion) (6).

Various types of wheezes can be identified based on the onset time and duration of signs and symptoms. The unexpected and sudden onset in an otherwise healthy patient defines 'acute wheeze', while experiencing two or more episodes within a six-month period defines 'recurrent wheeze' (5). In both cases, wheeze is a very common clinical issue which most practitioners must face.

***Figure 1***. *10 rules on short-acting beta-2 agonists (SABA) for acute wheezing episodes in children aged below 6 years.*

Pediatricians must be aware that wheeze is caused by airway obstruction, arises from the limitation and turbulence of airflow at the site of airway constriction and varies based on the degree of obstruction.

SABA promote the release of the bronchial muscles, increasing the caliber of the bronchi and bronchioles aimed at reducing resistance within the airways.

Prolonged exposure to the SABA desensitizes β2 receptors through a downregulation mechanism. Corticosteroids, reverse β2 receptors downregulation.

SABA exert the bronchodilator action from 5 minutes, up to 4-6 hours.

The most reported side effects of SABA are tachycardia and tremors.

SABA are considered the first-line treatment for managing acute wheezing attacks, regardless the severity of wheezing.

pMDI with a spacer is the preferred strategy through which administering such drugs, while nebulizers are considered an alternative option.

Young children can use spacers of all size, but a lower volume spacer is preferred in very young patients; priming is not necessary; a single pMDI actuation should be delivered immediately after having shaked the inhaler; inhalation should start as soon as possible after actuation; when a mask face is used, it must be fitted tightly around the child's mouth and nose; caregivers should ensure that the valve is moving while the child is breathing through the spacer; plastic spacers should be washed weekly with detergent, without rinsing, and allowed to air dry, to reduce static charge and increase lung delivery.

The initial dose of SABA in children aged below 6 years is two puffs of salbutamol (100 mcg per puff) (2.5 mg salbutamol solution using a nebulizer) or equivalent; however, in severe acute attacks six puffs should be administered. If symptoms persist after the initial treatment, a further administration of SABA may be repeated at 20-minute intervals for an hour. Further SABA, i.e. additional 2-3 puffs up to a total of 10 puffs per day or additional 2.5 mg salbutamol via nebulizer up to a total of five administrations per day, should be given each hour if symptoms persist or recur.

The combination of low doses of inhaled corticosteroids whenever SABA is used should be considered, including in patients with not sufficient evidence to start a daily corticosteroid controller.

In children aged below 6 years, viral respiratory tract infections are commonly the *primum movens* of wheezing (episodic viral wheeze), although some children may wheeze in response to other triggering factors (multiple-trigger wheeze) (1).

Although microbiologic diagnostic tests are rarely performed in clinical practice (particularly in an outpatient setting) (7), Respiratory Syncytial Virus (RSV), Rhinovirus (RV), human Bocavirus, Metapneumovirus, Parainfluenza virus, Influenza virus, Adenovirus and Coronavirus are frequently involved in starting the inflammatory response in the airways (8).

Inflammation causes cellular infiltration of the peribronchiolar tissue, oedema of the bronchioles, mucus overproduction, and inefficient mucous clearance. These factors collectively contribute to varying degrees of airway obstruction, bronchospasm and air trapping.

This statement outlines the role of short-acting beta-2 agonists (SABA) in treating acute wheezing episodes in children younger than 6 years.

## MECHANISMS OF SHORT ACTING β 2 AGONISTS

Since their introduction in clinical practice in 1968 (9), β2 agonists have been widely used to treat acute episodes of bronchoconstriction caused by asthma as well as other respiratory diseases. The β2 agonists are bronchodilator drugs acting on β2-adrenergic receptors (β2-AR) (G-protein-coupled receptors) present on bronchial smooth muscles. They are also called β2-mimetics (10). The stimulation of β2-AR, activating adenyl cyclase and producing an increase in intracellular cyclic adenosine 3′,5′-monophosphate (cAMP), leads to smooth muscle relaxation and inhibition of smooth muscle contraction in the airways (11). They can promote the release of the bronchial muscles, increasing the caliber of the bronchi and bronchioles aimed at reducing resistance within the airways (12). More precisely, the activation of these receptors leads to a decrease in the levels of calcium ions (Ca++) in the cells of the bronchial smooth muscle. Calcium ions are responsible for bronchoconstriction; therefore, it is clear how a reduction in their concentration can favor the reverse process, i.e. bronchodilation. Therefore, β2 agonists, as agonists of the β2-AR, stimulate them and induce bronchodilation.

The β2AR-mediated vasorelaxation, and potentially bronchodilation, decline with age due to decreased affinity for agonists, sub- optimal receptor signaling and reduced cAMP production (13). Prolonged exposure to the agonist desensitizes G-protein-coupled receptors through a downregulation leading to a net loss of receptors after hours of agonist exposure. The receptors can only be replaced by re-synthesis of new receptors through transcription of the β2AR-gene (14, 15). It takes hours to days to overcome downregulation. Corticosteroids increase β2AR-gene transcription and regulate both the number of receptors and the coupling to adenylate cyclase, reversing β2AR downregulation (14).

The pharmacologic actions of β2 agonists differ mainly with respect to their potency due to relative binding affinities and duration of action based on their ability to be retained in the lung tissue. The drugs belonging to the class of β2-AR agonists can be divided into three groups depending on their duration of action: 1) short-acting β2-agonists (SABA): the bronchodilator action is established within 5 minutes, and they have a duration of action of 4-6 hours. Salbutamol belongs to this category; 2) long-acting β2-agonists (LABA): these drugs are used primarily to prolong the control of symptoms of asthma. They have a slow onset of action (20-30 minutes), but the bronchodilation they induce lasts 8-12 hours. LABA has larger side chains, which make them more lipophilic, thereby increasing lung retention, giving them a longer duration of action. This category includes salmeterol and formoterol. Formoterol is moderately lipophilic with most of the inhaled dose being retained in cell membranes and gradually released. Some molecules remain in the aqueous phase outside the cells allowing immediate interaction with β2-receptors and thus, a rapid effect (16); and 3) ultra long-acting β2-agonists (ultra-LABA): the bronchodilator action lasts 24 hours allowing for a single daily administration. Abediterol, indacaterol, olodaterol and vilanterol belong to this category of drugs (17,18).

Formoterol is a full agonist at the β2-receptor and results in more than 80% of maximal β2-receptor activation, on the other hand, salmeterol and salbutamol are partial agonists at the β2-receptor and therefore they do not result in maximal bronchodilation (16).

While salbutamol is one of the most effective and safest drugs available, currently included in the World Health Organization list of essential drugs (19), it may cause

adverse effects mostly by stimulating extra-respiratory β2-receptors found in the vessels, heart, muscles, brain, and liver. Side effects depend on the dosage (they are not very common at recommended doses) and the route of administration. They are more frequent when salbutamol is administered intravenously or orally. Nebulized administration is a safer option, achieving high drug concentrations and faster bronchodilation effect in the airways while minimizing systemic absorption (17, 19). The most reported side effect is tachycardia with or without palpitations, which is more common when salbutamol is administered by an inhaler, due to the inhaled portion rather than the swallowed one (20). Tachycardia is caused by direct stimulation of β receptors in the atria and ventricles, some of which are β2, but this effect is transient and usually not life threatening. Moreover, tachycardia may be caused by the response to vasodilation caused by stimulation of β-receptors in the vessels (20). Also, angina and arrhythmias have been reported, especially in those with severe hypoxemia and hypokalemia. As a matter of fact, salbutamol may cause or worsen hypokalemia, especially at high doses administered intravenously or by nebulizer, due to stimulation of intracellular accumulation of potassium in the skeletal muscle (21). Due to such effect, salbutamol has been used to treat hyperkalemia in intensive care units in both adults and children.

Tremor is another common adverse effect of salbutamol which seems to be caused by direct stimulation of β-receptors on the skeletal muscle or may be correlated with hypokalemia (22).

Among side effects, even respiratory symptoms might be reported, including chest heaviness and paradoxical bronchoconstriction (23). Finally, β2-receptors stimulation in the liver causes glycogenolysis and increase in blood sugar levels (24) and in the nervous system, it may cause hallucinations and anxiousness (25, 26). To our knowledge, there are few data on the incidence of salbutamol's systemic side effects, especially in childhood (27-29). Notably, a recent systematic review and meta-analysis evaluated the risk of cardiovascular system adverse events in salbutamol users showing that the only reported cardiovascular system adverse event in 2097 subjects was tachycardia or palpitations, and its pooled incidence was 16% (95%CI: 11% - 22%) (30).

## SHORT-ACTING β2-AGONISTS: ACTION PLAN IN WHEEZING CHILDREN AGED BELOW 6 YEARS

SABA is considered the first-line treatment for managing acute wheezing attacks in preschoolers, regardless the severity of wheezing (31). Oral administration of bronchodilators is not recommended; indeed, delivery by inhalation achieves high concentration in the airways, more rapid onset of action, and fewer systemic adverse effects. Spacers (with mask in the first 3 years of life or mouthpiece in children aged 3 years and over) are the preferred device through which administering such drugs, while nebulizers are considered an alternative option (32). In particular, SABA should be administered via a pressurized metered-dose inhaler (pMDI) with a spacer in mild-to-moderate attacks or via nebulization driven by oxygen in severe attacks. For most children pMDI plus spacer is the preferred choice as it is more efficient and faster than a nebulizer for drug delivery; moreover, the use of nebulizers can be associated with spreading of infectious particles, so local infection control measures must be followed (33). Noteworthy, correct inhalation technique and education are essential, when using a spacer. Most children aged 3 years and older can use a mouthpiece. Treatment must be administered during quiet awake breathing, due to the risk that no medication will be deposited in the lower airways during crying or sleep (34). The only possible inhalation technique in infants and preschoolers is tidal breathing. The number of breaths required to empty the spacer depends on the child's tidal volume, volume of the spacer, and dead space; however, usually 5-10 breaths per actuation are considered sufficient. The optimal use of spacers is crucial to deliver an efficient treatment. Therefore, it should be considered that:

- young children can use spacers of all size, but a lower volume spacer (< 350 ml) is preferred in very young patients;
- priming of the spacer by firing waste puffs is not necessary (since even 15 waste puffs would not affect significantly the half-life of the drug in the spacer) (35);
- a single pMDI actuation should be delivered at a time, after shaking the inhaler; multiple actuations before inhalation may dramatically reduce the amount of medication inhaled;
- inhalation should start as soon as possible after actuation, which should be delivered when the child is ready, and the spacer is in the mouth;

– when a mask face is used, it must be fitted tightly around the child's mouth and nose;
– caregivers should ensure that the valve is moving while the child is breathing through the spacer;
– plastic spacers should be washed weekly with detergent, without rinsing, and allowed to air dry, to reduce static charge and increase lung delivery.

The initial dose of SABA in children aged below 6 years is two puffs of salbutamol (100 mcg per puff) or equivalent; however, in severe acute attacks six puffs should be administered (36). When using a nebulizer, a dose of 2.5 mg salbutamol solution is recommended. If symptoms persist after the initial treatment, a further administration of SABA may be repeated at 20-minute intervals for an hour. Further SABA, i.e. additional 2-3 puffs up to a total of 10 puffs per day or additional 2.5 mg salbutamol via nebulizer up to a total of five administrations per day, should be given each hour if symptoms persist or recur. Importantly, patients must be admitted to hospital if: 1) they require more than 10 puffs or more than four administrations of 2.5 mg salbutamol via nebulizer in 3-4 hours; 2) they are unresponsive to 6 puffs of SABA (2 puffs, repeated 3 times) or to 2.5 mg salbutamol via nebulizer repeated 3 times for more than 1-2 hours; 3) they show persistent tachypnoea despite 3 administrations of SABA, regardless of other clinical signs of improvement (33).

Given the risks of only SABA-based treatment, the combination of low doses of inhaled corticosteroids (ICS) whenever SABA is used should be evaluated, even in patients with not sufficient evidence to start a daily controller (33, 37). Indeed, the frequent use of SABA can lead to increased inflammation, bronchial hyperreactivity and reduced bronchodilation capacity; it can also mask the worsening of symptoms (38).

An educational program should be provided to caregivers of wheezy children aged below 6 years. This program should include training on correct inhalation technique and a written action plan. The action plan should cover how to recognize symptoms, administer medications and when and how to seek medical assistance, including urgent hospital treatment (33).

## CONCLUSIONS

Pediatricians often face wheezing in children aged under 6 years. Viral respiratory tract infections, allergens, exercise, or crying may suddenly trigger unexpected acute episodes with a wide range of severity. Increasing evidence supports early airway remodeling in recurrent preschool wheezing. SABA, that proved to be a safe and wieldy drug, represents the first-line treatment for managing acute wheezing attacks in preschoolers, regardless the severity of wheezing. The bronchodilator action is established within 5 minutes and lasts for 4-6 hours. In recurrent wheezing children aged below 6 years, the Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili, SIMRI) recommends a starting dose of two puffs of salbutamol (100 mcg per puff) that can be repeated every 20 minutes for an hour and anyhow 4-5 times a day during acute wheeze episodes. SABA via nebulization at a dose of 2.5 mg driven by oxygen should be used during severe attacks. Low doses of ICS whenever SABA is used should be prescribed.

## COMPLIANCE WITH ETHICAL STANDARDS

### Conflict of interests

The Authors have declared no conflict of interests.

### Financial support

There was no institutional or private funding for this article.

### Authors' contributions

Conceptualization and study design: RN, GF, GF, MEDC, FP, SLG. Drafting of the manuscript: RN, GF, GF, MEDC, FP; Supervision of the project, and final approval of the version to be submitted: RN, GF, GF, MEDC, FP, SLG. All Authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

### Ethical approval

*Human studies and subjects*

N/A.

*Data sharing and data accessibility*

The Authors confirm that the data supporting the findings of this study are available within the article.

### 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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BRIEF REPORT

# Respiratory outcome of infants with or without documented wheezing during bronchiolitis

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## ABSTRACT

The presence of wheezing during bronchiolitis may be associated with recurrent episodes of wheezing and asthma.

The objectives were to assess the inter-observer agreement of wheezing recorded by a digital stethoscope during a bronchiolitis and to assess whether the identification of wheezing was associated with an increased incidence of recurrent wheezing at three years and asthma at six years.

Two hundred and seventy infants (<2 years) with bronchiolitis were included, while follow-up data at 3 and 6 years were available for 144 (33 had definite wheezing during bronchiolitis: 23%) and 112 (28 had definite wheezing during their bronchiolitis: 25%) children, respectively.

The overall agreement percentage between the two raters for wheezing (249 infants were available for the two raters) was 71%, with a free-marginal kappa of 0.42 (95% CI [0.31, 0.53]), which is a moderate agreement. The prevalence of definite (two observers) wheezing was 58/270 (21%) that was associated with tobacco exposure and, at 3 years of age, with more respiratory episodes and asthma medications while it was not associated with asthma at 6 years.

In conclusion, the agreement over wheezing during bronchiolitis is moderate, but it ought to be diagnosed since it is associated with recurrent respiratory episodes (wheezing).

## IMPACT STATEMENT

The formal identification of wheezing during a bronchiolitis episode is associated with recurrent episodes of respiratory episodes.

## INTRODUCTION

Acute viral bronchiolitis is one of the leading causes of lower respiratory tract infection and hospitalization in the first 12-24 months of life (1, 2). Studies report that 17-60% of children with bronchiolitis might develop recurrent wheezing in the years following their initial admission to hospital (2). Severe bronchiolitis (*i.e.*, bronchiolitis requiring hospital admission) has been associated with an increased risk of asthma, with 30%-50% developing asthma by 5 years of age (3).

Four phenotypes of bronchiolitis have been identified in a multicenter study (4). Overall, in this study 64% of the infants exhibited wheezing, and the presence or absence of wheezing was a variable that allowed for the differentiation of the

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10.56164/PediatrRespirJ.2025.73

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**KEY WORDS**
*Wheezing; bronchiolitis; asthma; interobserver agreement; auscultation.*

phenotypes (4). In another multicenter study, wheezing was associated with the use of albuterol among infants hospitalized for bronchiolitis (5).

Thus, the formal identification of wheezing during bronchiolitis may have both immediate and long-term consequences, and one may wonder whether the presence of wheezing may increase the risk of recurrent wheezing within the first 3 years of life and the risk of asthma at 6 years.

This issue deserves to be evaluated because the identification of wheezing requires auscultation skills, which not all non-physician providers may have (6, 7).

The objectives of our study were to assess the inter-observer agreement of respiratory sounds recorded by a digital stethoscope and to assess whether the identification of wheezing was associated with an increased incidence of recurrent wheezing at three years of age and asthma at six years of age.

## METHODS

This trial (WheezOut: ClinicalTrials.gov Identifier: NCT04811248) is the follow-up study of the WheezSmart trial (ClinicalTrials.gov Identifier: NCT02897960) devoted to recording respiratory sounds in in infants with acute respiratory symptoms (using both a smartphone and a digital stethoscope). For the WheezOut study, only children from one center (Robert Debré hospital) were followed up. The study complied with STROBE statement for observational studies.

Ethical approval was obtained from the Comité de Protection des Personnes SUD-EST IV (ID-RCB: 2020 – A01482-37). The parents were informed of the collection of prospective data for research purposes, and they could request that their child be exempted in accordance with French law (observational non-interventional study).

All infants (younger than 2 years) referred to the emergency department for acute respiratory symptoms and diagnosed by the attending physician as having bronchiolitis (as defined by the American Academy of Pediatrics (8)) were enrolled during one bronchiolitis season (10/26/2016 to 04/28/2017) and were followed up by telephone.

In the emergency room, the following data were recorded by the physician: sex, age, pulsed saturation in the room air, and presence of wheezing upon auscultation. The physician also recorded respiratory sounds using a digital stethoscope (Littman™ 3200 Digital Electronic Stethoscope) that has been demonstrated to be more sensitive than clinician auscultation in detecting wheezing (9). Since these data were acquired at the initial evaluation of the infant, the need for hospitalization was not recorded. All recordings obtained with the stethoscope were classified by two physicians (PB and CD) who identified instances of wheezing, rhonchus and coarse crackles. These two physicians assessed their skills using the Reference Database of Respiratory Sounds (https://www.ers-education.org/e-learning/reference-database-of-respiratory-sounds/wheezes/).

### Telephone interviews at 3 and 6 years of age

The questions that were recorded when the child was three years of age are described in **Table 1**. The eight questions from the wheezing module for 6-7-year-olds from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire were recorded when the child was six years of age (10) and are described in **Table 2**.

### Statistical analysis

Results were expressed as a mean ± SD or median [25$^{th}$; 75$^{th}$ percentile] depending on the distribution of the variable or as a proportion, with a 95% confidence interval (CI) for the main results. Categorical variables were compared using Fisher's exact test and continuous variables using the Mann Whitney test. A p value $< 0.05$ was deemed significant. All statistical analyses were performed with StatView 5.0 software (SAS Institute, Cary, NC, United States). To evaluate the inter-observer agreement, Randolph's free-marginal multirater kappa with 95% CIs was calculated (11). The kappa values were interpreted as follows: 0-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial, and 0.80-1.0 almost perfect agreement (12).

## RESULTS

Two hundred-and-seventy infants with bronchiolitis were included in the winter sample of 2016-2017. When they were three years of age, 144 families responded to the telephone interview; at 6 years of age, 113 families responded. In total, data at 3 and 6 years of age were available for 112 children (one family responded only when their child was 6 years of age, no data at three years of age).

***Table 1.*** *Characteristics at three years of age.*

| Characteristic | Wheezing at inclusion, n = 33 (23%) | No wheezing at inclusion, n = 111 (77%) | P value |
|---|---|---|---|
| Gestational age, weeks | 39 [38; 40] | 40 [38; 40] | 0.325 |
| Pregnancy smoking, n (%) | 6 (18) | 8 (7) | 0.089 |
| Sex: female, n (%) | 12 (36) | 43 (39) | 0.841 |
| $SpO_2$ at inclusion, % | 98 [96; 99] | 98 [96; 99] | 0.967 |
| Respiratory episodes # before 3 years of age | | | |
| Number | 3 [2; 4] | 1 [1; 3] | <0.001 |
| Hospitalized, n | 0 [0; 1] | 0 [0; 1] | 0.349 |
| Respiratory episodes (≥3) before 3 years of age, n | 18 (55) | 46 (41) | 0.167 |
| Asthma treatment*, n | 23 (70) | 47 (42) | 0.009 |
| Wheezing at cold, n | 18 (55) | 54 (49) | 0.692 |
| Wheezing at laughing/crying, n | 5 (15) | 12 (11) | 0.541 |
| Wheezing at exercise, n | 2 (6) | 12 (11) | 0.523 |
| Night awaking, n | 7 (21) | 33 (30) | 0.384 |
| Family asthma, n | 13 (39) | 42 (38) | >0.999 |
| Maternal asthma, n | 5 (15) | 18 (16) | >0.999 |
| Family allergy, n | 9 (27) | 43 (39) | 0.303 |
| Passive smoking, n | 22 (67) | 47 (42) | 0.014 |

*#: these respiratory episodes were either diagnosed as bronchiolitis by a doctor or associated with possible wheezing necessitating hospitalization and/or nebulized treatment and/or respiratory therapist intervention.*
**: fluticasone; budesonide; beclomethasone; salbutamol.*

***Table 2****. Core questionnaire according to wheezing at six years of age in the 112 children who were also assessed at three years of age.*

| Characteristic | Whole population n = 112 | Wheezing at inclusion n = 28 (25%) | No wheezing n = 84 (75%) | P value |
|---|---|---|---|---|
| Ever wheezing, n (%) | 67 (60) | 18 (64) | 49 (58) | 0.659 |
| Wheezing in last year, n (%) | 17 (15) | 2 (7) | 15 (18) | 0.126 |
| wheezing attacks: none/1-3/4-12/>12, n | 51/13/3/0 | 16/1/1/0 | 35/12/2/0 | 0.220 |
| sleep awaking: never/<1/≥1 per week, n | 62/1/4 | 18/0/0 | 44/1/4 | 0.371 |
| speech limitation, n | 3 | 0 | 3 | 0.558 |
| Ever asthma, n (%) | 40 (36) | 11 (39) | 29 (35) | 0.655 |
| Wheezing at exercise last year, n (%) | 6 (5) | 0 (0) | 6 (7) | 0.334 |
| Cough at night last year, n (%) | 37 (33) | 8 (29) | 29 (35) | 0.647 |
| Characteristics at three years of age | | | | |
| recurrent respiratory episodes, n | 49 (44) | | | |
| asthma treatment, n | 56 (50) | | | |
| wheezing at exercise, n | 11 (10) | | | |
| family allergy, n | 42 (37) | | | |

When comparing the characteristics of these 112 infants at the time of inclusion as compared to the 158 infants whose families did not respond to a telephone interview, the presence of definite (see below) wheezing at the time of inclusion (28/112 *vs*. 30/158) and the proportion of infants who already had repeated respiratory episodes (25/112 *vs*. 34/158) were not significantly different (p = 0.236 and p = 0.875, respectively).

### Interrater agreement for respiratory sounds

The overall agreement percentage between the two raters for wheezing (249 infants were available for the two raters) was 71.08%, with a free-marginal kappa of 0.42 (95% CI [0.31, 0.53]), which is a moderate agreement. The prevalence of definite (two observers) wheezing was 58/270 (21%), and the prevalence of possible wheezing (at least one observer) was 151/270 (56%).

The overall agreement percentage between the two raters for rhonchus (241 infants were available for the two raters) was 71.78%, with a free-marginal kappa of 0.44 (95% CI [0.32, 0.55]), which is a moderate agreement. Finally, the overall agreement percentage between the two raters for coarse crackles (254 infants were available for the two raters) was 84.65%, with a free-marginal kappa of 0.69 (95% CI [0.60, 0.78]), which is substantial. The prevalence of possible crackles was 58/271 (21%).

### Interview at three years of age

**Table 1** shows the results of the interview according to the presence of definite wheezing at the time of inclusion. Children with wheezing at the time of inclusion, as compared to those without wheezing, were more frequently exposed to tobacco smoke (22/33 *vs*. 47/111, p = 0.014), had more respiratory episodes during infancy (3 episodes [2; 4] *vs*. 1 [1; 3], p < 0.001), and received asthma medication more frequently (23/33 versus 47/111, p = 0.009).

### Interview at six years of age (core questionnaire wheezing module for 6-7-year-olds)

The results of the eight questions are provided in **Table 2**. Overall, 67/112 (60%, 95% CI [50, 69]) of the children who had at least one case of bronchiolitis experienced wheezing or whistling in the chest in the past. Cases of wheezing were logically associated with asthma diagnoses: 34/40 *vs*. 33/72 (p < 0.001).

An asthma diagnosis (ever asthma in **Table 2**, n = 40/112, 36%, 95% CI [27, 45]) was mainly related to the recurrent wheezing phenotype: 31/49 versus 9/63 (p < 0.001). Asthma at 6 years of age (wheezing in the last year, **Table 2**: 17/112, 15%, 95% CI [9, 23]) was associated with wheezing during exercise at 3 years of age (4/11 versus 7/101, p = 0.002) and with a family history of allergies (21/42 *vs*. 21/70, p = 0.044) but not with the early wheezing criteria (either recurrent respiratory episodes: 10/17 *vs*. 39/95, or asthma treatment before 3 years of age: 12/17 *vs*. 44/95, p = 0.174 and p = 0.065; respectively).

Asthma at 6 years of age was not associated with the presence of wheezing at the initial auscultation (**Table 2**).

## DISCUSSION

This prospective study, which included infants referred to the emergency department, demonstrates that the identification of wheezing at auscultation during a bronchiolitis episode was associated with tobacco exposure, recurrent wheezing, and asthma treatment at three years of age, but not with asthma at six years of age.

The first important issue is whether our population is representative of infants with bronchiolitis. The observed rate of infants with bronchiolitis and subsequent recurrent wheezing in the first three years of age (64/144, 44%) is within the expected range (2). The rate of 6-year-old children with wheezing during the last year (17/112, 15%; 95% CI: 9 to 23%) is consistent with the rate of 12.5% of recurrent wheezing in the fifth year of life among infants hospitalized for respiratory syncytial virus (13).

To the best of our knowledge, no previous study has evaluated the benefit of the identification of wheezing during bronchiolitis. Since the presence of wheezing may help to define bronchiolitis phenotypes (4), it was important to assess inter-observer agreement. Elphick et al. investigated the validity and reliability of computerized acoustic analysis in the detection of abnormal respiratory noises in 102 infants and showed that the level of agreement between observers concerning the presence of wheezing was poor for both examinations with a stethoscope and acoustic analysis (14). Our results are consistent with those of Liu *et al*., who found a weighted kappa of 0.43 for the auscultation of children with asthma or bronchiolitis (7). Overall, these results support the argument for the use of auscultation by digital stethoscopes or digital wheeze detectors, which are more sensitive in detecting wheezes (9, 15), and even artificial intelligence in order to diagnose respiratory sounds (16).

Our main result is the demonstration that definite wheezing upon auscultation is associated with respiratory prognoses, namely repeated respiratory episodes and asthma treatment at 3 years of age. The fact that wheezing was associated with exposure to parents' tobacco use is consistent with the demonstrated risk of the increased incidence of wheezing due to this exposure (17).

Our study has limitations due to its design. Only half of the families were available for a telephone interview when their child was three years of age, and this percentage decreased to ~ 40% at six years of age. Recurrence of respiratory episodes (necessitating hospitalization and/or nebulized treatment and/or respiratory therapist intervention), a more stringent criterion than recurrent wheezing, was retrospectively recorded (at three

years of age: telephone interview) and a recall bias cannot be eliminated. Furthermore, rhinovirus-induced bronchiolitis has more strongly been associated with the risk of developing wheeze and childhood asthma than respiratory syncytial virus (18), which was not recorded. Finally, no assessment of lung function was obtained, which is also a limitation, even if lung function parameters obtained from impulse oscillometry and asthma probability are belonging to independent dimensions of the wheezing disease (19), confirming that there is a paucity of evidence to guide clinicians in selecting diagnostic tests for recurrent or persistent wheezing (20).

In conclusion, the identification of wheezing during bronchiolitis is associated with recurrent respiratory episodes (wheezing) at three years. This result supports a plea for the use of digital stethoscopes with artificial intelligence in order to detect pathologic pediatric breath sounds.

## COMPLIANCE WITH ETHICAL STANDARDS

### Conflict of interests

The Authors have declared no conflict of interests.

### Financial support

There was no institutional or private funding for this article.

### Ethical approval

*Human studies and subjects*

Ethical approval was obtained from the Comité de Protection des Personnes SUD-EST IV (ID-RCB: 2020 – A01482-37). The parents were informed of the collection of prospective data for research purposes, and they could request that their child be exempted in accordance with French law (observational non-interventional study).

### 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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BRIEF REPORT

# National survey in pediatric patients on Long-Term Home Oxygen Therapy

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10.56164/PediatrRespirJ.2024.68

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## ABSTRACT

This study aims to describe current prescriptive practices regarding home long-term oxygen therapy (LTOT) in Italian pediatric population. The Chronic Respiratory Insufficiency and Long-Term Ventilation Study Group produced a survey that was sent to the referents of the Italian Society of Infantile Respiratory Diseases and of the Italian Society of Neonatology. Forty-two responses were collected from different centers: 32 (76%) participants declared to be LTOT prescribers. Of these, 8 (25%) reported following more than 30 patients, 3 (9%) between 20-30 patients, 9 (28%) between 10-20, 12 (37%) less than 10 patients. Twenty (63%) use blood gas test to decide starting LTOT, 7 (22%) use daytime and/or night-time oximetry, 5 (16%) use both. Twenty-two (69%) prescribe high-flow oxygen (HFNC), of which 8 (36%) to more than 5 patients/year and 14 (64%) to less. Patients receiving HFNC suffer from bronchopulmonary dysplasia (10/26, 38%), neurological disease (6/26, 23%), interstitial disease (6/26, 23%), oncological disease (2/26, 8%) or cystic fibrosis (2/26, 8%).
Results show that pediatric patients on LTOT are fewer than adult ones; most are infants with bronchopulmonary dysplasia or children with neurological disabilities, reflecting the increasing reality of medically complex children. Most prescribers use blood gas tests to initiate LTOT, despite the availability of less invasive methods such as oximetry. The data collected will prove to be useful to produce official recommendations to standardize LTOT indications, devices and therapeutic purposes.

## IMPACT STATEMENT

There is a need for standardization of prescriptive practices for home long-term oxygen therapy (LTOT) in Italian pediatric population; the creation of a national dataset could be useful for this aim.

**KEY WORDS**
*LTOT; HFNC; long-term ventilation; chronic respiratory insufficiency; guidelines; survey.*

## BACKGROUND

Long-term oxygen therapy (LTOT) provides support for children experiencing chronic hypoxemia due to various causes, including chronic neonatal lung disease (CNLD), cystic fibrosis (CF), interstitial lung disease (ILD) and neurodisability (1). Despite the heterogeneous and distinct nature of pediatric chronic respi-

ratory conditions, guidelines and diagnostic criteria are frequently borrowed from adult protocols, primarily centered on patients with chronic obstructive pulmonary disease (COPD) (2, 3). A multidisciplinary panel assembled by the American Thoracic Society (ATS) recently issued valuable clinical recommendations for home oxygen therapy tailored to pediatric chronic lung diseases and pulmonary vascular diseases (4). However, authors emphasized the scarcity and low quality of available evidence in particular about the pediatric population, with limited data about implementation, efficacy, monitoring, and discontinuation of LTOT across various age groups and clinical conditions. Given the potential harms and costs, it is essential to obtain data on the number of children receiving home oxygen therapy and their characteristics. In fact, only a few national experiences have been reported, providing prevalence rates of children undergoing LTOT. Balfour-Lynn and colleagues aggregated data from a cross-sectional survey and a dedicated database in England and Wales (5). They estimated a prevalence of 1.08 per 1000 in the first year of life and 0.33 per 1000 in children older than one year of age, with chronic neonatal lung disease (CNLD) being the primary cause, followed by neurodisability (5). Other prevalence studies of national registers from Scandinavian countries dealt with pediatric population only partially and are more than twenty years old (6-8).

The Study Group "Chronic Respiratory Failure and Long-Term Ventilation" within the Italian Society of Pediatric Respiratory Disease (Società Italiana per le Malattie Respiratorie Infantili, SIMRI) conducted a research project to offer an overview of the Italian scenario and lay the foundation for future implementation projects.

## METHODS

The Study Group "Chronic Respiratory Failure and Long-Term Ventilation" devised a survey questionnaire through a multistage process. A task force of four pediatric pulmonologists within the Study Group formulated the study protocol, identifying various aspects of interest for each center, including: geographic location, medical subspecialties of the prescriber, number of patients cared for at each center, diagnostic tools utilized, oxygen delivery devices and monitoring methods employed, clinical conditions, and follow-up procedures. The task force formulated a questionnaire which underwent revision by the Study Group in two dedicated meetings. A final version was subsequently approved by the entire Study Group.

The survey questionnaire was distributed via email invitation, along with a link to an online platform, to regional representatives of SIMRI and SIN (Italian Society of Neonatology), starting from July 10th, 2023. We selected the regional representatives with the aim of giving the most complete national picture and of avoiding specialty-based sampling bias.

Following a second email reminder, responses received up to June 1st, 2024, were assessed.

Dichotomous and categorical variables were presented as numerical values and percentages. Most of the percentages represent the distribution across prescribing centers, with any exceptions to this explicitly noted. Continuous variables were reported as either the mean and standard deviation (SD) if normally distributed, or as the median with the first and third quartiles if not normally distributed. The normality of the data was evaluated both visually and through the Shapiro-Wilk test.

## RESULTS

Email invitations were sent to 200 SIMRI and SIN representatives between July 2023 and June 2024. Forty-two centers (21%) replied; 32 centers (32/40, 76% of the participating centers) reported prescribing LTOT. Ten centers (10/42, 24%) participated in the survey as non-prescribing centers: 3 Tertiary referral Pediatric Hospitals, 3 Neonatology Units and 6 Secondary Pediatric hospitals.

Eight centers (25% of the prescribing centers) reported following more than 30 patients in LTOT, three centers (9%) between 20 and 30 patients, 9 centers (28%) between 10 and 20 and 12 centers (37%) less than 10 patients (**Figure 1**).

Regarding the start of LTOT, 20 centers (20/32, 63%) reported using blood gas test (BGT). Seven centers (7/32, 22%) used daytime and/or nighttime pulse oximetry (**Figure 2**) and five used both (5/32, 16%).

## EQUIPMENT

All but one center prescribed liquid oxygen; 28 centers (28/32, 87%) prescribed oxygen gas and 22 centers (22/32, 69%) oxygen concentrators. Twenty-two prescribing centers (22/32, 69%) prescribe high-flow oxy-

gen, of which 8 (8/22, 36%) to more than five patients/year and the remaining (14/22, 64%) to less than five patients/year.

Patients receiving high-flow oxygen therapy were: patients with bronchopulmonary dysplasia (10/26, 38%), neurological disease (6/26, 23%), interstitial disease (6/26, 23%), oncological disease (2/26, 8%) or cystic fibrosis (2/26, 8%).

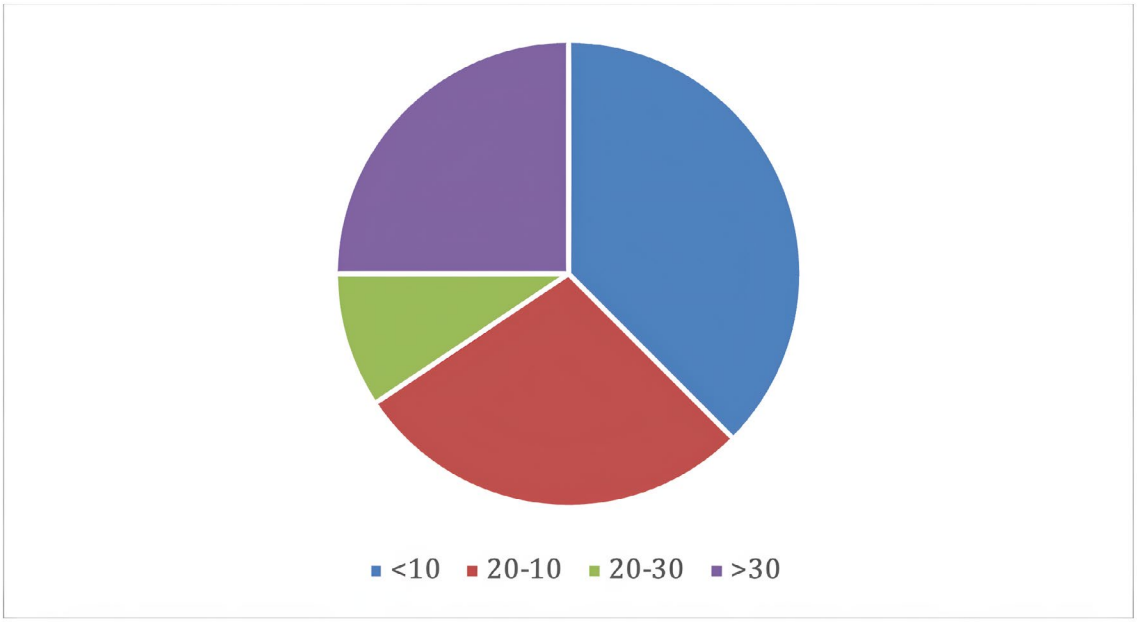


***Figure 1***. *Numbers of patients in LTOT followed by prescribing centers.*

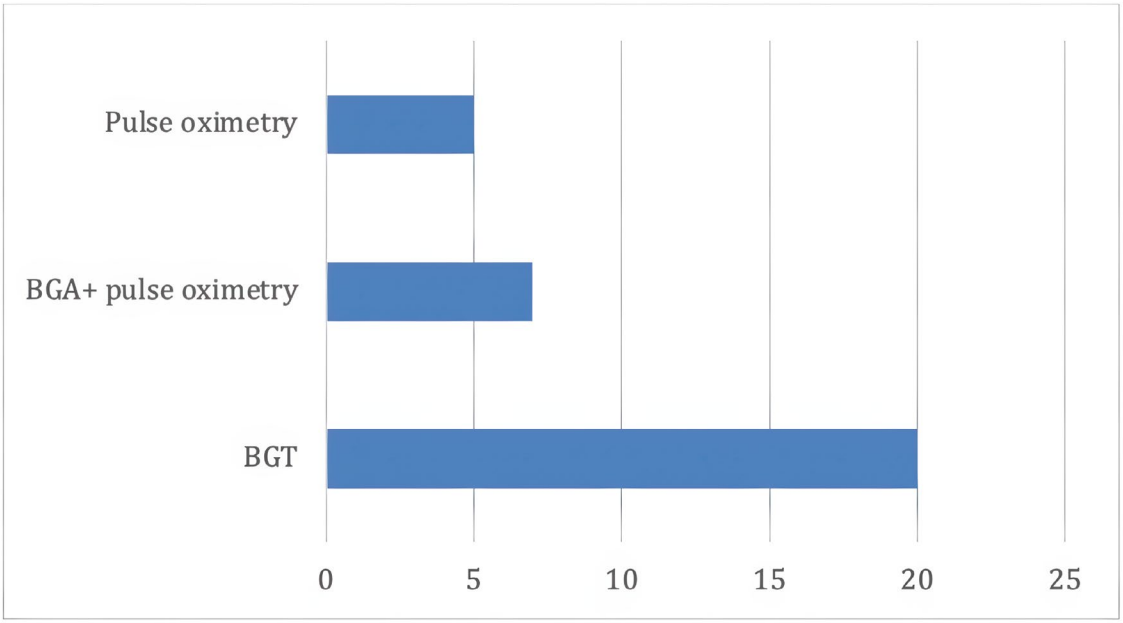


***Figure 2***. *Diagnostic tests. BGT = Blood Gas Test.*

## DISCUSSION

The last twenty years have been characterized by a profound change in the landscape of pediatric patients with respiratory insufficiency and complex clinical needs (9), with a remarkable increase in the number of these patients. Despite the relative availability of data on non-invasive ventilation, our study represents the first report on long-term oxygen therapy (LTOT) in the pediatric population published in the last twenty years and the very first in Italy. There is only one European survey that analyzed the pattern of LTOT prescriptions in children (5).

Similar to non-invasive ventilation, the availability of LTOT is scattered throughout the territory of Italy, with most centers reporting the care of only a few dozen patients. Available recommendations on LTOT are based on poor data quality (10). Regarding prescriptions, the ATS task force recommend pulse oximetry to define hypoxemia; surprisingly, in our report almost all the centers (87%) based LTOT prescriptions on arterial blood gas test, even if it is neither practical nor reliable for routine assessment in pediatric patients due to factors such as crying, procedural pain, and technical challenges.

On the other hand, overnight pulse oximetry was reported to be available for outpatient assessment and monitoring, but its use to prescribe LTOT appears to be limited to a few centers (26%). We consider it a rather contradictory approach, that could be due to adult guidelines where measurement of arterial PaO2 is critical for oxygen therapy.

The use of pulse oximetry is cost-effective and non-invasive, whereas blood gas analysis is painful, often inaccurate when performed during crying, and therefore limited to the intensive care setting. Given that pulse oximetry is a painless, accurate, and non-invasive method for diagnosing hypoxemia in children, we fully support its use, instead of the blood gas test, as the preferred diagnostic tool.

This recommendation is backed by other guidelines about hypoxemia and by the fact that the use of BGT is increasingly limited even in acute settings, with a preference for using the peripheral oxygen saturation to the fraction of inspired oxygen ratio (SpO2/FiO2) instead of the arterial oxygen tension to the fraction of inspired oxygen ratio (PaO2/FiO2). This shift in approach is highlighted in the latest update regarding pediatric acute respiratory distress syndrome (PARDS) guidelines (11).

Moreover, the use of pulse oximetry perfectly aligns with the philosophy of telemedicine and home monitoring, as it is easily implementable in various settings and has been integrated into medical practice for several years now (12).

Similar to the findings of Balfour-Lynn and colleagues, LTOT prescriptions were primarily given to children with BPD. Prescriptions of LTOT for BPD are followed by those for patients with neurodisability (5). If this finding was once considered surprising, it is no longer so nowadays, given the increasing number of children with neurodisability observed over the past decades. In such patients, the clinical rationale of LTOT is not always clearly evident. Actually, in such patients, LTOT may be prescribed to enhance the quality of life of patients and their families rather than to reach saturation targets. In such a setting oxygen may be necessary exclusively during intercurrences and exacerbations. This approach is supported also by the British Thoracic Society (BTS) guidelines referring to these aspects with the term “special situation” (13).

Our research has several limitations. Despite invitations to all the representative members of the two societies, only a small proportion of members responded. Consequently, we can offer only a partial picture derived from results potentially contaminated by respondent bias.

About 50% of responses resulted from centers located in Northern Italy and data from some central regions are missing. Nevertheless, we still got response from 8 centers (8/32, 25%) located in Southern Italy and from 8 centers (8/32, 25%) in Central Italy.

The lack of data for some smaller regions in central Italy may be due to the actual absence of prescribing centers. Moreover, given the phenomenon of healthcare migration, many patients travel to larger centers in neighboring regions (14).

Furthermore, we did not collect data regarding clinical conditions or comorbidities nor patients’ age or SpO2 measurements as well. Lastly, we did not provide any information about discontinuation.

We hope this research raises awareness and interest in pediatric pulmonologists in order to pave the way for a national dataset. Further data collection is warranted based on a more comprehensive survey and involving oxygen providers. Future efforts of the Study Group will be directed towards standardization in providing LTOT,

promoting non-invasive assessment and monitoring and optimizing the care of children with respiratory conditions on a more general perspective.

## COMPLIANCE WITH ETHICAL STANDARDS

### Conflict of interests

The Authors have declared no conflict of interests.

### Financial support

There was no institutional or private funding for this article.

### Ethical approval

*Human studies and subjects*

The study followed the ethical standards established in the Declaration of Helsinki.

*Animal studies*

N/A.

### Data sharing and data accessibility

Data are available upon motivated 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

# Pneumomediastinum and pneumorrhachis. Rare complications in pediatric age: case report and its management

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## ABSTRACT

Pneumomediastinum (PM) is an unusual and rare event in children. It is usually secondary to alveolar rupture in the pulmonary interstitium, followed by dissection of gas towards the hilum and mediastinum. Many events can lead to alveolar rupture, but the most common trigger factors in children are asthma and upper airway infections. Extremely rare is pediatric PM related to cardiac diseases, lung diseases such as pneumothorax, pulmonary embolism, thoracic traumatism, central airway perforation or digestive tract perforation and foreign body aspiration. The clinical diagnosis is based on the concomitant presence of chest pain, dyspnea, and subcutaneous emphysema that may affect face, neck and chest. In severe cases, pneumomediastinum may lead to a cardiac tamponade, induced by an increase in pressure in the mediastinal compartment to develop a severe obstacle venous flow back to the heart or in case of bacterial over-infection PM can lead to a mediastinitis. The diagnosis is confirmed by chest radiography and/or chest computerized tomography (CT). In most patients the air in the mediastinal compartment is slowly reabsorbed by neighbors' tissues, favoring the spontaneous resolution of this condition. This process is also favored by the inhalation of high concentrations of low flow oxygen. In most cases conservative treatment such as bed rest and analgesics led to a rapid resolution of PM. The invasive surgical approach is necessary only in selected cases. It's important to identify and treat all the possible underlying causes (if identified) and predisposing factors should be identified and controlled to prevent recurrence of PM. The combination of pneumomediastinum with pneumorrhachis (PR) rarely occurs in children. The present case report describes the presence of pneumomediastinum, subcutaneous emphysema, and pneumorrhachis in a child who had a history of persistent dry cough. A 9-year-old male child presented to our emergency service with respiratory distress, persistent dry cough, neck and chest pain. A chest X-ray and CT were performed and showed extensive pneumomediastinum with subcutaneous emphysema in neck area with no pneumothorax and concomitant air was in vertebral canal in the epidural space. Both clinical presentation and instrumental exams were consistent with those reported in the literature. The patient received noninvasive monitoring, analgesia, low flow oxygen, nebulized bronchodilators, intravenous steroids, and intravenous empiric antibiotics. This case highlights how PM and PR can be successfully managed conservatively and how an early diagnosis and management of the underlying cause is essential and important.

## ABBREVIATIONS

PM: pneumomediastinum
CT: computerized tomography
SPM: spontaneous pneumomediastinum
PR: pneumorrhachis
PRIST: Paper RadioImmunoSorbent Tes

## KEY WORDS

*Pneumomediastinum; asthma; children; subcutaneous emphysema; pneumorrhachis.*

 

## IMPACT STATEMENT

Asthma represents a significant health problem worldwide, and epidemiological studies in the last few decades have consistently shown a marked increase in childhood asthma prevalence. Asthma is infact recognized as the most common chronic disease in children with major public health consequences, including high morbidity and mortality in severe cases. Although asthma is recognized as the most common chronic disease in children, issues of underdiagnosis and undertreatment persist. Asthma treatment is based on a stepwise approach.

Furthermore while many official documents are present regarding asthma treatment, much less explored are all therapeutic options for related complications.

This manuscript highlights some rare and atypical complications of asthma exacerbations. Although these complications are typically benign and can resolve with supportive measures, severe cases can lead to acute airway compromise. This case also shows the importance of the knowledge of all therapeutic options but also the management of complication even if these are very rare and atypical and unusual.

## INTRODUCTION

Pneumomediastinum consists in the presence of free air within the mediastinum. Pneumomediastinum can be divided into spontaneous pneumomediastinum (SPM) without any obvious primary source and into secondary or traumatic pneumomediastinum with mediastinal organ injury or other known events such as trauma, surgery or medical procedures (1). Alveolar rupture leads to air infiltration along the bronchovascular sheath with free air finally reaching the mediastinum (2). Furthermore, if the air travels along tissue planes and spreads through the neck, face, abdomen or even the limbs, it can lead to subcutaneous emphysema. When the presence of air is in the spinal canal, we can observe pneumorrhachis (PR). The air may spread through fascial planes from the posterior mediastinum, through the neural foramina, and into epidural space. PR is usually asymptomatic and improves spontaneously.

Pneumorrhachis is characterized by the presence of air within the spinal canal. The air may spread along fascial planes from the posterior mediastinum, through the neural foramina, and into epidural space. PR is usually asymptomatic, doesn't tend to migrate and it is generally regarded as a self-limited and relatively benign process. Early diagnosis and management of the underlying cause it is essential. The causes of PR can be divided into iatrogenic, non-traumatic and traumatic. It is an exceptional but eminent radiographic finding, accompanied by different etiologies and possible pathways of air entry into the spinal canal. Since PR is usually asymptomatic, it is often a radiographic diagnosis and not a clinical one (3).

In the pediatric age the most frequent cause of PM is asthma and airway infection. PR associated with asthma is extremely rare in pediatric age and only very few cases are reported in the literature (4).

We describe the case of a pediatric patient with pneumomediastinum, subcutaneous emphysema and pneumorrhachis associated with asthma.

## CASE PRESENTATION

A 9-year-old boy was admitted to the emergency department with a persistent dry cough, dyspnea and severe chest/neck pain, no fever reported. The family story show that the mother as an allergic rhinitis with sensitization to Olea Europea. In the personal story was reported birth term, hyperreactive airways with multitrigger wheezing since the first year of life. The adenotonsillectomy was performed at 4 years of life. Not referred to allergic sensitizations. No trauma referred. No additional comorbidities were present. At first clinical evaluation the patient was not well appearing, with signs of respiratory distress. Body temperature was normal, 35 breaths/min, 115 beats/min, sat O2 97% with low flow oxygen 1-2L/min, normal blood pressure for age, absence of cyanosis, normal peripheral perfusion. Auscultation of his chest revealed pathological sounds: reduced vesicular breath sound and bilateral wheezing and inspiratory substernal retraction. Normal heart sounds. Subcutaneous emphysema on the right and left side of his neck and upper chest was detected. Blood exams were performed: arterial hemogasanalysis: pH 7.40, pCO2 42

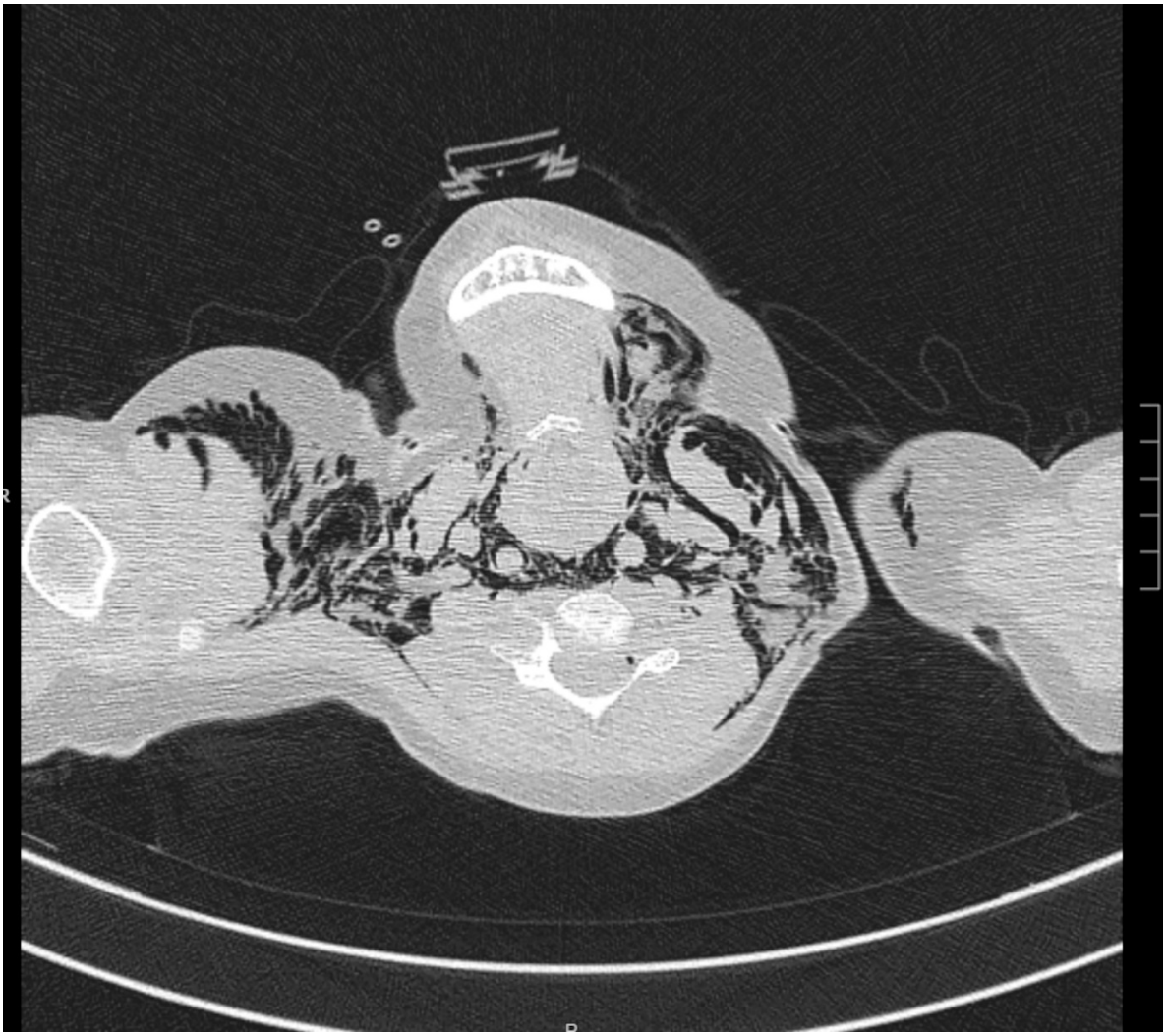

***Figure 1***. *CT shows the presence of air in all compartments of the neck.*

mmHg, pO2 59 mmHg, HCO3 24 mmol/l, normal C reactive protein; normal renal, hepatic function tests and electrolyte levels. Hemoglobin 12.7 g/dl; white blood cell count 16.4 × $10^3$/μL; neutrophil count 47.7%; lymphocyte count 40.4%, monocyte count 9.8% platelet count 410 × $10^3$/μl. A chest X-ray showed extensive pneumomediastinum with subcutaneous emphysema in supraclavicular and neck area with no pneumothorax. Chest computerized tomography (CT) was performed and revealed the presence of air in all compartments of the neck: both in the visceral compartment (retropharyngeal area, carotid area and submandibular area) and in the non-visceral ones, in the supra, infra and subhyoid bilaterally moreover at the level of the masticatory space and infratemporal fossa. Air was even in the supra and infraclavicular areas, axillary muscles, subcutaneous adipose tissue and on the anterior chest wall. Severe mediastinal emphysema was appreciable in all recesses of the mediastinum and between the chest wall and the pericardium with a slight compression of mediastinum structures.

Air was also appreciable in the retrocrural area and in the left posterior extrapleural space, between the erector spinae muscles and the subcutaneous adipose tissue. Air was also detected in vertebral canal in the epidural space, predominantly left approximately at C6, C7, D1, D2 and D3 (**Figures 1**, **2, 3**).

The patient was admitted and received noninvasive monitoring, analgesia, low flow oxygen (1-2 l/min) for 4

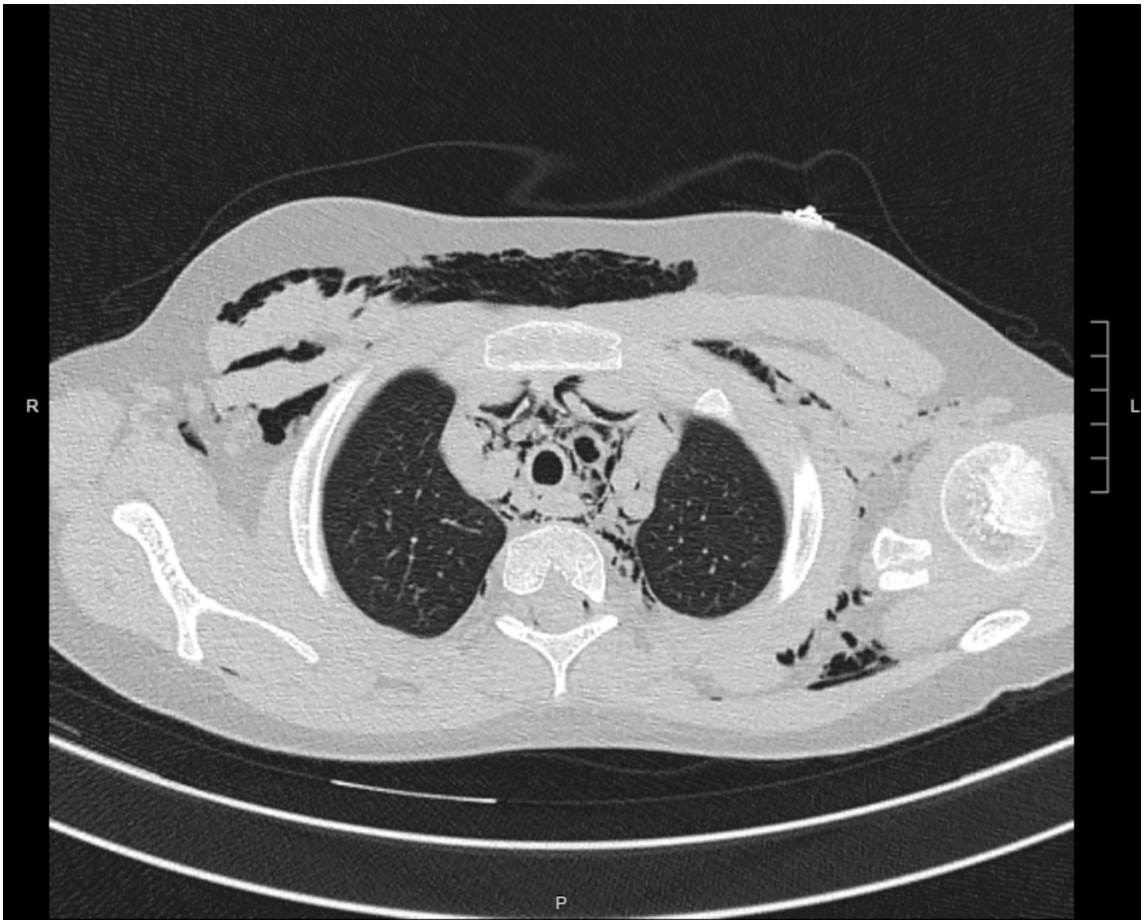


***Figure 2**. CT shows the presence of air in all recesses of the mediastinum and in vertebral canal in the epidural space.*

days, nebulized bronchodilators (salbutamol and ipratropium), intravenous steroids, and intravenous empiric antibiotics for preventing mediastinitis.

Cardiological consult was performed without pathological results. Neurological consult was performed to exclude neurologic involvement related to compressive events. Sputum analysis and culture was performed to exclude lower respiratory tract infections. Also, SARS-CoV-2 infection was excluded performing oropharyngeal swab and IgM and IgG against SARS-CoV-2 were absent. Normal dosage of alpha1 antitrypsin. Serological tests for the detection of *Mycoplasma Pneumoniae*, *Chlamydia Pneumoniae* and *Bordetella Pertussis* infection were normal. Immunological evaluation excluded congenital and acquired immunodeficiency.

Paper Radio Immunosorbent Test (PRIST) and ImmunoCap ISAC assay documented serum total IgE levels (575 kU/l) and positivity of specific IgE for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* (Der p1 1.00 kU/l and Der p 2 0.48 kU/l) and *Cynodon dactylon* (nCyn d 1 0.67 kU/l).

After 72 hours, a chest X-ray showed a reduced amount of gas in the neck and mediastinum but persistence of gas into medullary space without clinical neurological signs and symptoms. He continued noninvasive monitoring, analgesia, low flow oxygen (1-2 l/min), inhaled nebulized bronchodilators (salbutamol and ipratropium), intravenous steroids, and intravenous empiric antibiotics (Cefotaxime and Clarithromycin). He showed a progressive improvement during hospitalization and was discharged on day 12. It was prescribed therapy at discharge included fluticasone dipropionate 125 µg twice daily with spacer, home environmental interventions and he advised not to perform extreme physical activity to avoid barotrauma.

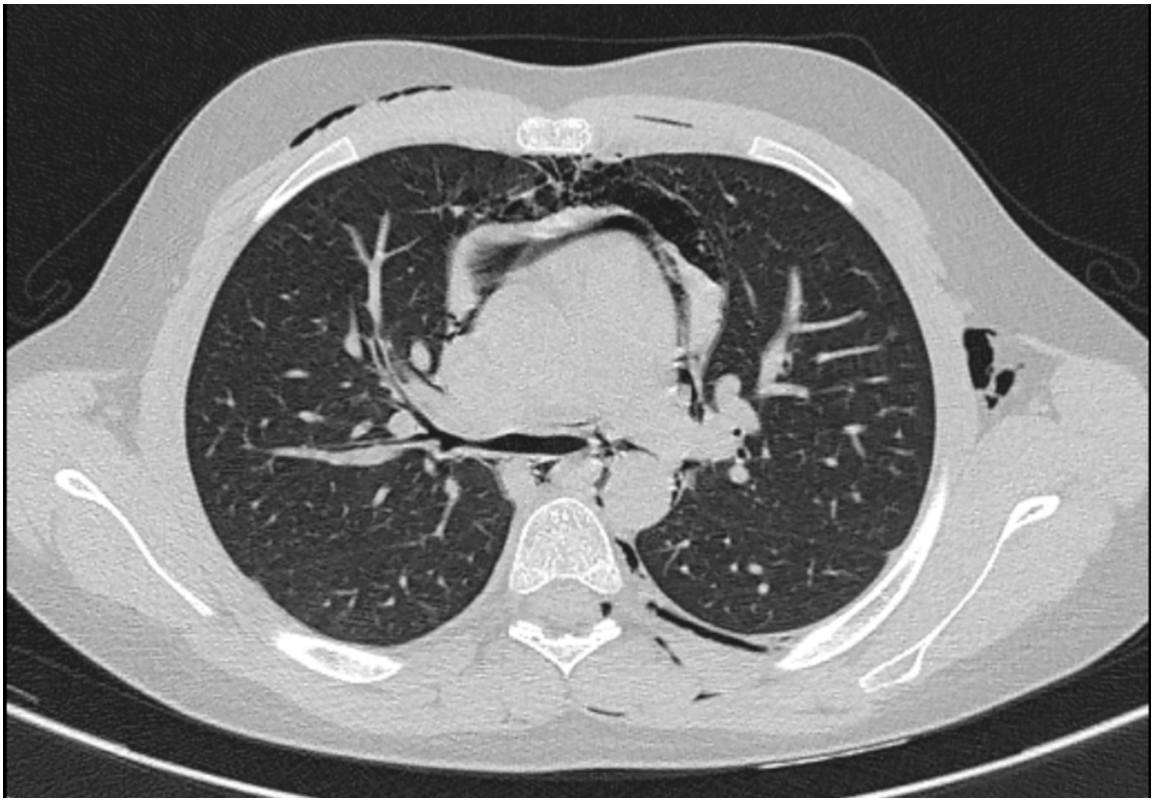

***Figure 3**. CT shows the presence of air in vertebral canal in epidural space.*

## DISCUSSION

PM is an uncommon disease in pediatric age that usually shows a self-limited and not complicated course. It should be treated conservatively unless a complication requires using invasive procedures (5). Asthma exacerbation and lower airway infection appear to be the most frequent risk factors for PM (6). PM and PR have already been described as potential complications of virus infections, also in healthy children. Common flu virus infection also can cause pneumothorax, pneumomediastinum, subcutaneous emphysema and pneumorrhachis in a healthy child (7). Most cases appear to occur in teenagers and no obvious differences in incidence have been reported between the sexes. The probable reason of the major incidence in teenagers is described in many manuscripts and some authors reported that their mediastinal tissue is looser than adults, who have a fibrosed sheath that make air migration more difficult (8).

The clinical diagnosis is based on the association of chest pain, dyspnea, and subcutaneous emphysema that may affect face, neck and chest. Chest X-ray is increasingly being replaced by CT to confirm diagnosis. Lateral neck X-ray appear to be useful only in doubtful cases before CT exam (9).

Therapy was mainly based on supportive care, bed rest, low flow oxygen therapy, analgesics, steroids, and bronchodilators. Oxygen therapy has been recommended in most previous reports because it is considered that the consumption of oxygen increases the diffusion pressure of nitrogen in the interstitium, promoting absorption of free air in the mediastinum. Many studies report the use of empirical antibiotics to prevent possible infection such as mediastinitis even if it remains debatable whether antibiotic treatment is essential. Since PM may occur in asthmatic children, it's very important to obtain control of asthma. Clinical course in reported cases has been generally favorable with spontaneous resolution being achieved after hospital admission and supportive care. Since asthma and upper and lower air infections are being described as the most common causes of PM it is very important to detect allergies, to detect viral and/or bacterial infections. Alpha1-antitrypsin deficiency

screening has been recently recommended in patients with PM for differential diagnosis purposes (10).

A rare complication associated with pneumomediastinum is pneumorrhachis (PR) that consists in the presence of air within the spinal canal. It can be classified into internal or intradural and external or epidural. The causes of PR can be divided into iatrogenic, nontraumatic and traumatic (11). Although PR is usually asymptomatic and improves spontaneously, early diagnosis and management of the underlying cause is essential and important.

Most cases of epidural space pneumorrhachis are usually benign and improve spontaneously when the underlying cause is treated. In our case, pneumorrhachis almost disappeared without any intervention after ten days. Rarely, symptomatic PR with neurological deficits has been reported. Our case report represents an extremely rare case of pneumorrhachis secondary to pneumomediastinum with bronchial asthma in pediatric age. Spontaneous resolution occurs in most cases of epidural space pneumorrhachis, which allows conservative management in this benign occurrence (12).

## ACKNOWLEDGEMENTS

We would like to thank our patient, his parents and radiologists for their collaboration.

## COMPLIANCE WITH ETHICAL STANDARDS

### Conflict of interests

The Authors declare that they have no competing financial interests.

### Financial support

The authors declare they have not received financial support.

### Authorship

Each Author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. All Authors approved the final manuscript.

### Authors' contributions

Wrote the manuscript: AF and GC; contributed to the discussion: FF, MO and LT; collected the references: NZ, VA and MC. Reviewed the manuscript: FF, MO and LT. Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. All authors read and approved the final manuscript.

### Ethical approval

*Human studies and subjects*

The manuscript was written according to Good Clinical Practice and compliance with the Declaration of Helsinki with successive amendments.

*Animal studies*

N/A.

### Data sharing and data accessibility

The data presented in this manuscript are available on request from the Corresponding Author.

### Publication ethics

*Plagiarism*

All original studies are cited as appropriate.

*Data falsification and fabrication*

All the data corresponds to the real.

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