



# Pediatric Respiratory Journal

Official Journal of the Italian Pediatric Respiratory Society

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

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Ludovico Baldessin

**EDITORIAL COORDINATOR**

Barbara Moret

**PUBLISHING EDITOR**

Elisa Grignani

editorialoffice@pediatric-respiratory-journal.com

**SALES**

dircom@lswr.it

Ph. 0039 (0)2-88184.404

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EDRA S.p.A.  
via G. Spadolini, 7  
20141 Milan, Italy  
Ph. 0039 (0)2-88184.1  
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## RESEARCH ARTICLE

# Experiences and opinions of cystic fibrosis patients and their families about their inability to access modulator treatments in Turkey: a qualitative study

Özge Keniş-Coşkun<sup>1,\*</sup>, Gürkan Sert<sup>2</sup>, Perihan Dikili<sup>3</sup>, Evrim Karadağ-Saygi<sup>1</sup>, Pinar Ergenekon<sup>4</sup>, Yasemin Gökdemir<sup>4</sup>, Ela Erdem-Eralp<sup>4</sup>, Bülent Karadağ<sup>4</sup>

**\* Correspondence to:**

ozgekenis@gmail.com. ORCID: <https://orcid.org/0000-0002-3004-1992>

**ABSTRACT**

Modulator drugs cannot be provided regularly to our patients because they are not reimbursed by the Ministry of Health in Turkey. Patients can access these drugs on a limited basis and with detrimental intervals after a series of legal processes. This study aimed to qualitatively investigate both the clinical effect of intermittent modulator therapy on patients, the difficulties in accessing the drugs, and opinions about the process. Our research was designed as qualitative. It included patients over the age of 18 diagnosed with cystic fibrosis who had access to modulator treatments through legal processes, who may or may not currently use the drugs, and caregivers of patients under the age of 18. A total of 3 patients, 5 caregivers and one attorney has been interviewed. Four themes have emerged from the analyses of patient interviews: before and after the modulator, receiving information about modulators, difficulties in obtaining the drug and hoping for a permanent solution. To the best of our knowledge, our country is the only place where they are obtained through legal processes on a semi-regular basis. This is detrimental for patient well-being and must be addressed immediately.

**HIGHLIGHTS BOX**

**What is already known about this topic?** Modulator drugs for cystic fibrosis are not still fully reimbursed in Turkey, causing problems in patient care. **What does this article add to our knowledge?** Currently, patients try to obtain these drugs through complicated legal process which causes unforeseen intervals in treatment and worsening of clinical conditions of the patients. **How does this study impact current management guidelines?** Urgent action is needed to end health inequality and improve drug access for all patients who are not currently have a constant access to modulator drugs.

**INTRODUCTION**

With the development and approval of treatments that modulate the Cystic Fibrosis Transmembrane Regulator (CFTR) gene by the Food and Drug Administration (FDA) in 2019, important progress was made in the treatment of patients

**Doi**

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<sup>1</sup> Department of Physical Medicine and Rehabilitation, School of Medicine, Marmara University, Istanbul, Turkey

<sup>2</sup> Department of Medical History and Ethics, School of Medicine, Marmara University, Istanbul, Turkey

<sup>3</sup> Health Sciences Institute, Marmara University, Istanbul, Turkey

<sup>4</sup> Department of Pediatric Pulmonology, School of Medicine, Marmara University, Istanbul, Turkey

**KEY WORDS**

*Cystic fibrosis; modulator drug; health inequity.*

with cystic fibrosis (CF) who are eligible to receive these drugs (1). These treatments can correct the protein synthesis disorder caused by the particularly common F508del mutation by improving the synthesis of the CFTR protein, thus significantly improving the function of the CFTR protein and the function of the sodium channel (2). Studies have shown that the use of modulator drugs provides clinically significant improvement in CF patients (3).

These treatments cannot be provided regularly to our patients because they are not reimbursed by the Ministry of Health in our country and are costly. However, after a series of legal processes, patients can access these drugs on a limited basis and with intervals that are detrimental to the treatment process. Despite the benefits provided by modulator drugs, these drugs are not yet included in the scope of reimbursement in Turkey. For this reason, individuals living with CF, who are medically thought to benefit from the drug and whose condition is determined by their health reports, cannot obtain modulator drugs within the scope of social security and have to apply for legal processes after documenting their improvements. There is no data in the world literature on intermittent use of modulator drugs in this way, and there is no data on the experiences of patients and families during this process. When talking about the obstacles in accessing medicine in rare diseases, it is pointed out that medicines are expensive and are often sold at prices that patients cannot pay. Although orphan drugs improve patients' health status and quality of life, the cost of these drugs limits patients' access to these drugs (4-6). Life-threatening health conditions and the lack of treatment alternatives can create an inelastic demand for orphan drugs, leading to high prices in a market where competition is already limited (6).

This study aimed to qualitatively investigate both the clinical effect of intermittent modulator therapy on pa-

tients, the difficulties in accessing the drugs, and opinions about the process.

## METHODS

Our research was designed as qualitative and was conducted between March 2023-December 2023. It was planned to include patients over the age of 18 diagnosed with cystic fibrosis who had access to modulator treatments through legal processes, who may or may not currently use the drugs, and caregivers of patients under the age of 18. Cystic Fibrosis Assistance and Solidarity Association facilitated the meetings. To gain insight about the legal processes of obtaining these drugs, one attorney was also interviewed. A questionnaire containing demographic and personal information, which the participants will fill out before the interviews, and semi-structured one on one interviews were used as data collection methods. The questions that are asked in the semi-structured interviews are given in **Table 1**.

Informed consent for participation in the study was obtained from participants before the interviews.

A descriptive case study approach with single in-depth interviews was employed. The descriptive case study approach was employed because we aimed to investigate a contemporary phenomenon in depth and within its real-life context, in which the boundaries between phenomenon and context were not clear and as investigators we had no control over events, as described by Yin (7, 8). Interviews were conducted using online platforms to decrease the risk of infection in these patients. The interviews were conducted by a researcher who is not working in the study clinic and not involved in the decision for modulator drugs and follow-up process and has a 15-year of experience in qualitative study interviewing. Observer notes were kept, and audio recordings were made during these interviews. The interview with each participant lasted

*Table 1. Questions of the semi-structured interview.*

### Semi-structured interview's questions

1. How did you first learn about the existence of modulator drugs?
2. Are you currently using your medication? When was the last time you used it? If you are not currently using it, how long have you been off it?
3. What is the most difficult aspect of obtaining your medication?
4. What are the differences you see when you compare your state of using the medication to your state of not using it?

approximately 50-60 minutes. After each interview, the voice recordings were converted into transcripts with notes taken and were coded independently by at least 3 researchers without waiting for the next interview (9). Conventional content analysis method is used for the data analysis of this qualitative study (10). A thematic map – a visual representation of the relationship between various codes – was employed in our study to organize the codes under categories and understand the relationship between various codes and categories and overarching themes (11, 12).

All interviews were audiotaped and transcribed and all participant identifiers were removed from transcripts. All Authors independently reviewed a selection of transcripts, familiarized themselves with the data, and generated initial codes using inductive coding. Codes were the starting points and the concepts in the transcripts about the experiences and perspectives of the participants. A new list of codes was produced, and each code included illustrative quotes. The codes generated from the data separately by the researchers were discussed together with the help of the clinical stories of the patients and the families to build categories at first. The codes are placed under the categories which were built after comparing, contrasting, combining, splitting, or renaming through consensus. After using discussions, analysis, matrices, and flowcharts to prompt deeper thinking, researchers described the related categories and put them together, and refined themes as the frame of the results (13). The themes were integrated into a meaningful conceptual framework to adequately tell the story of the data and answer the research questions. Excerpts from the data were used to support

the themes and illustrate patterns in the experiences of both the children and parents (14).

The themes were then reviewed to ensure that they adequately captured the details of all the coded transcripts. An effort was made to ensure that the themes were representative of the range of views expressed by all the participants and that the ideas from one participant or theme were not over-represented or under-represented (15).

## RESULTS

A total of 9 participants were interviewed. Their characteristics are given in **Table 2**.

### THEMES

In our study, four main themes were created as a result of the thematic analysis conducted in line with the questions asked to the participants. These are: 1) the situation before the modulator drug; 2) information about the modulator drug and access to the drug; 3) the situation after the use of the modulators; 4) the legal process and thoughts and recommendations for the authorities.

#### Before the modulator

Under this theme, the difficulties faced by the participants before using modulator drugs are included. The patients and parents stated that they had significant problems in performing daily living activities: «Before the medication, he wasn't active, (...) He was immobile because he couldn't breathe. He was sleeping a lot because his lungs were not working. He was out of breath the moment he walked (...) There was no water or food (patient 4)».

**Table 2.** The characteristics of the participants in the study.

Participant	Gender and age	Current FEV <sub>1</sub> level of the patient	Pre modulator FEV <sub>1</sub> level of the patient
Participant 1	female, 33	63%	55%
Participant 2	male, 36	44%	40%
Participant 3	male, 19	52%	48%
Participant 4 and Caregiver 1	female, 35	94%	94%
Participant 5 and Caregiver 2	female, 42	75%	65%
Participant 6 and Caregiver 3	male, 51	81%	67%
Participant 7 and Caregiver 4	female, 41	73%	53%
Participant 8 and Caregiver 5	female, 45	89%	85%

«I'm just going to sit at the table, mom», he says, «I can't expectorate my phlegm after the meal». He says, «Let's expel my phlegm thoroughly before the meal», and we try. Now he's really passing out thinking he's going to cough up phlegm (patient 1)».

Patients and their families were forced to live with above-normal restrictions in their home lives and stated these in their interviews: «Of course, we took it under more protection. After that we started paying attention to everything. We have been experiencing the pandemic for 6 years that people experienced in 2 years and a half. We do not receive many guests at our home. When we come out of the house, we change completely and take a shower. We do the same routine when my other two children come home from school (participant 4)».

«So, it is very difficult to accept the existence of the disease and to live with it. It was like we were in a bowl. «The people who come home should not have any diseases, that is, I do not meet with people who have the flu or something (patient 5)». Difficulties in the social life of the patient and his family: «He didn't go to nursery or school anywhere (patient 5)»; «He said he would not receive a high school education at home (patient 1)»; «So, we don't have the chance to have a social life anyway. We cannot even take two children to the wedding to prevent our children from getting infected. If we go alone. This time, we always have to leave it unfinished and come back because the child is left alone at home. It is necessary to follow his medications, he needs to do respiratory therapies. Unfortunately, it constantly reduces our quality of life because it is necessary to keep it under constant surveillance (patient 3)»; «The child was at home with his mother and father. He had an individual environment without much human contact, mostly with adults, not children (patient 5)»; «Before the medication, I could not go into crowded places. Because there are people who cough, sneeze, etc. I was more likely to stay at home and not be able to engage in social circles. When a person is masked like this, I don't hug or kiss him from afar (patient 7)».

The patients and parents stated that they had to endure frequent and long hospitalization periods for exacerbations, which disrupted the normal flow of their daily life: «The first 6 years were very difficult. There were constant hospitalizations. We were afraid of los-

ing him in intensive care twice. It was pseudomonas. Pseudomonas is our greatest enemy (patient 3)»; «I was in the hospital once a week and every 15 days (patient 1); «I didn't take my bag and ID when I went to the hospital. I was packing a small suitcase. I was leaving with that suitcase because I knew I wouldn't be able to come back (patient 4)».

### Getting informed about the modulators

After the participants obtain information from the association, the nurse or physician in the health institution or organization they apply to, about the existence of the drug, the benefits it will provide to the patient, and the possibility of accessing the drug through a lawsuit, they try to reach the attorneys interested in the subject. Participants stated that they were informed by the relevant health professionals about the reports and documents that needed to be submitted to the court and that they received support from these people regarding the documents.

A significant portion of the interviewees stated that they received their first information about the drug from a physician or nurse during hospitalization: «So, when the drug started coming out, they looked at our genes. Doctor, this medicine suits you», he said, «You know, file a lawsuit and get the medicine». «So, I said let me wait a little bit. Then, as I waited, it started to get worse. My bronchi are starting to burst or something. My cough started to get worse. I started vomiting blood. The doctor said, let's apply for medicine, come and use it, it will be good for you too. That's how we applied (patient 7)»; «When we contacted our nurses during the hospitalization, they gave directions: 'Actually, if your genetic result matches, you can do it'. We applied immediately. (patient 4); «How did I first find out? This is from our professors. They are already following the research beforehand. We were aware of the studies (patient 8); «We were in the hospital, while Dr. gave information about the medicine. We decided to apply (patient 2)».

Participants stated that physicians also provide information about modulator drugs from the patients' association. Individuals/families living with CF also stated that since the disease affects every moment of their lives, they actively use internet resources and follow foreign publications and opportunities in order to obtain information about developments and treatment opportunities. However, it appears that patients learn

about the modulator drug from social groups and social media: «In the association, in the family information meetings, in the information given by our professors, *etc.* We first learned about medicine when we were 3-4 years old, but our professors constantly said that there were studies, and this was good news for the future. We need to bring this to Turkey, we need to work for it (...) (patient 3)»; «I heard about a group of them via W...app. What did they say? Is it compatible or not? We looked and went to the nurses. From there, our nurses said: 'Let's see'. After that they said it is compatible with the medicine. How do we do it, how do we proceed? Thanks to our nurses who helped us, our doctors helped us (patient 1)»; «We are already connected to the association on Facebook. We were also following the processes regarding the drugs that were released. You know, abroad, long before this. Before modulator therapy was used in Turkey, we heard that it was happening abroad, that they had started it, their treatments, *etc.* We were getting excited too. We were following it to see if it would happen in Turkey as well (patient 6)»; «I first became aware of the modulator drug from international articles. I knew that such a medicine existed, but we were not old enough yet. When we reach the age of 6, our doctors already advise us to start this treatment. They said the mutations were compatible (patient 5)».

#### After the modulator

All participants stated that there was an improvement in the patient's health and a noticeable improvement in their quality of life after the modulator drug: «We see 98-99 when using medication. During the periods when we were not using medication, we were mostly hospitalized due to this low saturation. It drops as low as 92, when we are at home it is 95-96, but when we are on medication, we can see even 99%. But it drops a lot when there is no medicine (patient 4)»; «Since breathing becomes easier while using the medicine, both he feels more at ease. He's not having any trouble (patient 3)»; «Participants said that there were positive changes such as increased appetite, weight gain, and increase in physical activity along with relief in breathing. While using the medicine, he even eats his meals comfortably because he does not have phlegm and does not get stuck while eating. Weight gain is easy (patient 3)»; «So, I can say

that he may have been sick less than normal children while using (...) (patient 5)»; «So, you're getting a little more comfortable in terms of weight», «My cousins, brother, I saw you very well, you know (patient 8)».

Participants pointed out that the patient's adaptation to social life increased when using modulator drugs: «He went on trips with his uncle. He never stayed at home (patient 1)»; «Of course, after the modulator drug, he relaxed a lot, he can play with his friends», «He calls me home, makes me play, he becomes more social (patient 4)»; «Right now, M... is going to school while everyone is on holiday. They opened a special class for university preparation. He joined a group of 50 people and enjoys going back and forth (patient 3)»; «Their physical activity has increased. Most importantly, he started first grade. While using this medicine. We handled the school process very smoothly (patient 5)»; «At that time, my cousin was having an engagement party. It was a very closed, airless area. You know, I've never felt such a blockage, tightness, or cough. Other than that, in general, I don't cough at all at work (patient 8)». They stated that patients and their families felt psychologically relieved due to the benefits of the modulator drug: «We felt more relaxed as a family, both psychologically and physically. So, for example, when you send T... to school when it is not being used, will there be anyone sick in the classroom, will anyone sneeze, will anything happen? Will the child be infected with anything? You send it out of fear, but when you receive T..., we are like the same as the others (patient 5)»; «Yes, sir, it would mean the world to me for him to go somewhere alone. For the first time, we stayed away from our son for 15 days», «I have never been apart even for a day (patient 1)».

All of the interviewees stated that during periods when they could not access medicine due to the negativities experienced in the court and drug procurement processes. Their medical situation, which improved while using medication, became worse when they did not use medication. They experienced decrease in oxygen saturation, a decrease in physical activity in a short time, malnutrition, and weight loss: «When the medicine is finished and when the body starts to produce phlegm, it becomes difficult to breathe because it causes shortness of breath even from the food it eats due to the phlegm (H3)»; «When the medicine does not arrive,

after 20-25 days, their movements slow down and their steps slow down. Phlegm and cough begin (patient 2)».

#### Legal processes and recommendations for authorities

Since CF modulator drugs are not produced domestically and are not covered by reimbursement, patients file lawsuits with the Social Security Institution (SSI) to access the drug. All of the interviewees who participated in our study were patients or their relatives who had access to medicine by applying to the judiciary. The legal process of one participant was concluded in his favor, and the process of the others is still ongoing. According to the data we obtained from the interviewees, patients generally resort to litigation in line with the information of healthcare professionals and carry out the processes with attorneys specialized in healthcare law: «We reached (the attorney) from Ankara. He guided us. You will prepare the following documents and send them to us. We went to the notary. We gave him power of attorney, then he filed the lawsuit (patient 6)». They specifically stated that it takes a long time for the payment of the medicine to depend on the court decision. One participant made a comparison with a drug within the scope of payment: «So normally, let me tell you in comparison to medicine. At least the doctor writes the prescription directly, and we inform the pharmacy of the prescription. And what happens is that the delivery time for the medicine is 4-6 weeks, during which time the medicine comes to me. But after we get the prescription written, we provide SSI documents. SSI is given by court decision, and these are examined. These then go to the Turkish Association of Pharmacists, where they are reviewed and ordered again, and this process inevitably takes a long time. Since it was taken by judicial decision, it is not within the scope of payment. The process is getting slower (patient 5)». The interviewees pointed out that many documents had to be prepared before starting the litigation process and that the patient had to have some examinations re-done. The interviewees also stated that healthcare professionals provide support with the necessary documents when initiating the legal process: «We photocopied our file (in the hospital), no matter how long we had been treated there at that time, our entire file (in the hospital) was around 600 pages, and we turned it into a file and handed it over. They were also present-

ed to the court (patient 6)»; «During the court process, they asked us for (the patient's) disability report and documents. Of course, they asked for additional examinations, eye examination, sweat tests, stool tests. They asked for our routine medical check-up, that is, our cystic fibrosis hospital doctor, diagnoses and lung function tests. We prepared these. Then as I remember. Yes, we sent an attorney to an attorney one on one. We waited, we waited for a long time (patient 4)». Some of the participants said that the courts issued an interim injunction at the beginning of the trial, ensuring that the cost of the medicine was paid to the patient. However, during this process, participants also pointed out that there were interruptions in access to medicine due to court decisions and other procedures: «We waited, we waited for a long time. We even got rejected. We objected again and received a rejection. We applied again and had trouble in court, but it did not come directly. You know, we applied right away, but it didn't come right away. It took almost 9 months for us to gain indefinite time in court. We won it back. But before that, for the third month, our medication was indefinite (patient 4)».

Before starting the modulator drug, all examinations are performed again, and the drug is started to be used with the approval of the doctors. One month after using the medication, the tests are repeated and sent to the court. These tests are repeated every three months to prove the effectiveness of the drug: «When the drugs start arriving, examinations are renewed every 3 months. How did this happen with drugs? The hospital prepares a report saying that the child is feeling better or something like that. We photocopy those hospital files 3-4 times. We send it to an attorney every 3 months with the epicrisis report and expert decision. Then the attorney applies to the court on our behalf. And after 3 months, the medicine comes again. It always takes 3 months. At these intervals, usually every 3 months, 3 boxes of medicine come to us. We renew the tests not as soon as they arrive, but before the first box is finished. Because it takes a long time for the documents to come out. Then we send it to the Court. After these cases, we got hopeful (patient 2)».

Although patients have access to modulator drugs during the trial, they are concerned that the case may end against them: «Yes, we are supplying the medicine

right now, but they have come up with a different process related to the litigation process. In other words, we won the big case, but now our files are in appeal, so when the appeal is rejected, you will apply to the Constitutional Court. You have to go one step further, but of course there will be times when we will be without medication during this process. There will be times when our child may deteriorate rapidly. Their concerns are definitely high (patient 5)»; «After winning another case, an injunction decision is taken, which is confusing. You take the dose for 3 months. You can object the decision. Meanwhile, if the injunction is lifted, the litigation process becomes longer. You request again as the case continues. For example, if you run out of medicine between the hearing and the date when the injunction order is lifted, you cannot take the medicine (patient 8)». One interviewee stated that after the lawsuit was filed during the legal process, they went drug-free for a period after using it regularly for nine months: «I don't remember what the problem was exactly. We were without medication for almost three months. We had one hospitalization in those three months. Afterwards, we live, of course, we can go without medication for a week or 10 days, of course we experience problems. But this one week and 10 days may seem too short for others, but as soon as we stop taking the drug, we go back to the old situation (patient 4)».

Participants are of the opinion that the legal process is quite detailed and long due to the procedures. Interviewees pointed out the difficulties in accessing medicine in a timely manner while the judicial process continues: «Taking the drug by judicial decision is a really bad thing. We receive our right to health, that is, one of our medicines, by a judicial decision, and inevitably, the drugs taken by judicial decision are more stuck in the procedure. So, for example, we apply to SSI. Then, the delivery of these documents from TEB is delayed and SSI first reviews the court decisions. The period after that is really challenging and prolongs our access to medicine (patient 5)»; «We apply while taking the medicine for a month. We are left with 2 months of medication. Are we supposedly told to have 4 or 6 weeks? It's been 6 weeks for me and I'm still waiting for it to arrive. We always wander around in such uncertainty, that is, in such chaos regarding medicine. Let's see, there's a cycle going on saying 'Let's hope our

children are well'. Let's see what happens (patient 1)»; «The most challenging thing is that it does not reach us quickly. Thanks to our attorneys, they can reach us, but I wish we had not gone to the attorney and the state would have reimbursed us and all children would have benefited. Nobody hears our children's voices anyway. Let me say as a state. Our doctors are trying hard, and they are very caring (patient 2)»; «In our first attempt were rejected. We had a hard time accepting that decision. We have waited for so long. Then we used the medication for 2 months. Then we faced with a third rejection (patient 4)».

However, some interviewees also pointed out that the process of drug procurement has accelerated with the increase in the number of cases. He emphasized that the institutions responsible for this issue also gained experience: «I used one dose; it made a difference. I waited another month and a half for the second doses. I don't know, there was a problem here and there, there weren't many people filing lawsuits back then. You know, this case process was not widely spread. For example, medicines are now becoming easier to obtain. I am waiting very little; we are waiting for a maximum of 10 days (patient 7)».

Doctors and patients have developed some solutions to overcome the difficulties they experience when they cannot access medicine through the legal process and are left without medication. In order not to lose the duration of the drug's effect, they use it in half doses or every other day: «So, the doctors said to use the medicine in the morning and evening, never in half. That's how they made me use it. But many patients, those who are followed up from other hospitals; you know, when the medicine is almost finished, they break it in half and take it. But I don't do anything like that. At least, I say, I can take it in the evening and morning, but the effects still remain. Also, during the waiting period, I started to give the nebulized medications even more (patient 7)».

## DISCUSSION

In this study, we aimed to document the hardships that the patients face during the obtaining of modulator drugs in a country that does not reimburse this treatment. For this purpose, we interviewed a variety of patients and their parents that have been through this process. To increase diversity, we tried to include both

adult patients that are handling their own process and parents who care for and handle for these processes. We reached the patients with the help of the patients' association that are helping the patients guide through these processes and we included patients that have been through this process both just once and a couple of times to diversify the statements.

The patient association makes significant contributions to ensuring individuals' right to access health and the right to be informed about innovations by informing patients about new drugs and developments regarding the treatment of the disease by physicians and nurses. It is important for an association whose all activities can be audited, with the support of physicians who are experts in their fields, to inform patients and their relatives about scientific developments, treatment-related developments, and the current stages of research by experts and competent people, so that patients are not misinformed, have unfounded hopes, are not abused, and are not directed to unnecessary demands. The fact that the interviewees participating in the research were informed about issues such as the fact that the drug will not produce the same results for every patient and that the drug cannot be used in every patient and age also suggests that education and information are beneficial. Main challenge that the patients face is the interruptions during the obtaining of the drug due to complicated legal processes. If the lawsuit regarding the payment of drugs is filed with a request for injunction, the judge may decide to use the drug as a precaution. In this case, shortly after the case is filed, the Social Security Institution begins to pay for the drug purchased. However, a significant risk that this decision poses for the family is that the Social Security Institution may overturn the decision in the appeals court. Then until the case is concluded, the institution will not pay for the medicines the patient.

The scope of interim injunction decisions may also vary. For example, a decision may be made to use a three-month dose of the same modulator drug. In this case, the patient also needs a judicial decision to pay for each subsequent three-month dose. This situation causes consequences such as interruption of the use of doses. In these cases, the health of a patient whose treatment is going well may deteriorate again. Sometimes, the judiciary imposes a precautionary measure

for the use of the drug as long as the case continues. In this case, since only applying to the institution for payment is sufficient to pay for the medicine, fewer problems are encountered in timely access to the medicine. The attorney said that in both cases, procedures were restarted a month after the first dose was used so that an application could be made to the court or institution to ensure that the social security institution paid for the next dose. The attorney stated that patients or their families who do not want to take the risks of injunction, can also choose to file the case without requesting injunction. If this method is used, the patient will have to wait for the end of the case to be paid for the medicine, which can be very long.

In this study, patients are caregivers clearly stated that using modulator drugs have improved their quality of life and their trajectories significantly, which is also supported by quantitative data. They also stated that every interval causes significant decrease in their quality of life and nullifies the progress made during the use of the drugs. In this context, it should be accepted that access to medicine through litigation causes significant problems in the patient's access to medicine and in time. It is important to take the necessary steps to ensure patients' access to drugs with proven effectiveness and to include the drugs within the scope of reimbursement. The fact that patients who are not informed about these drugs, even if they have knowledge, are not informed about how to access these drugs, or cannot access support, cannot access the medicine will also cause violations in terms of the right to fair and equal access to healthcare services. Most modern societies consider it an ethical obligation to provide patients with access to medicines for the prevention and treatment of serious and life-threatening diseases (6). The fact that the medicine needed by a child living with a rare disease is not covered by social security is against all international agreements and national legislation in which the right to life is accepted as a fundamental right. In this context, it is not controversial that access to preventive, therapeutic and diagnostic products and services for individuals living with rare diseases is related to the right to life and health recognized by international agreements and domestic legislation of countries (6). Therefore, it is imperative for the health authorities in Turkey and all countries

that are not currently reimbursing these medications to start reimbursing them as soon as possible.

## CONCLUSIONS

There is an urgent need for modulator costs and reimbursement policies to be revised for patients with CF in Turkey, because we are losing precious time for all CF patients. The current system is not sustainable, causes significant time losses in patients' care and hinders some patients from accessing the drugs.

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## COMPLIANCE WITH ETHICAL STANDARDS

### Conflict of interests

The Authors have declared no conflict of interests.

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### Author contributions

Literature search, data analysis, writing and editing of the manuscript: OCK, GS, PD, EKS, PE, YG, EEE, BK. Data acquisition: OCK, GS and PD.

### Ethical approval

#### Human studies and subjects

Informed consent for participation in the study was obtained from participants before the interviews and the research has been performed according to the standards of 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 correspond to the real.

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## RESEARCH ARTICLE

# Lung function trajectories in asthmatic children after the onset of omalizumab

Claire Le Thai<sup>1</sup>, Plamen Bokov<sup>2</sup>, Bruno Mahut<sup>3</sup>, Christophe Delclaux<sup>2</sup>, Nicole Beydon<sup>1,4,\*</sup>

**\* Correspondence to:**

nicole.beydon@aphp.fr, ORCID: <https://orcid.org/0000-0002-6417-382X>

**ABSTRACT**

Children with severe asthma are at risk of long-term lung function impairment. In those receiving biologic treatments such as omalizumab (OZ), the medium-term evolution of lung function has shown variability.

In this retrospective single-center study, we recorded data, including lung function, from asthmatic children who started on OZ between 2012 and 2015, with at least two follow-up visits over a period of no less than two years. We determined the course of forced expiratory volume in 1 s expressed as percentage predicted (FEV<sub>1</sub>%) in each patient by constructing the annual slope and testing the significance of its trend (positive = improvement, negative = loss, or null). Pre-bronchodilator (pre-BD) and post-BD FEV<sub>1</sub>% slopes were determined.

The 71 children included (55 male, 57 atopic) had been started on OZ at a mean age of 11.7 (2.9), when the mean dose of inhaled corticosteroids treatment (ICS) was 1245 (856) µg/day. Asthma disease was poorly or partially controlled in 37 and 24 children, respectively. During the follow-up (mean 5.7 (2.1) years), the majority of children did not modify their pre-BD or post-BD FEV<sub>1</sub>% slopes (59, 83%, 95% CI: 72%-91%, and 57, 80%, 95% CI: 69%-89%, respectively). Meanwhile, clinical asthma control significantly improved ( $P < 0.0001$ ) and the ICS dose significantly decreased to 906 (649) µg/day ( $P = 0.01$ ).

In conclusion, the real-life long-term evolution of lung function in children with severe asthma started on OZ is stable. This is accompanied by improved clinical asthma control and a reduction in the burden of ICS treatment.

**HIGHLIGHTS BOX**

**What is already known about this topic?** Omalizumab improves clinical symptoms of asthma in children, but consistent improvement in lung function has not been persistently observed. **What does this article add to our knowledge?** We demonstrate that in children with improved asthma symptoms after starting omalizumab, lung function does not significantly change despite a reduction in inhaled corticosteroid dosage. **How does this study impact current management guidelines?** Physicians managing children on omalizumab treatment must closely monitor lung function, including bronchial responsiveness, while reducing treatment to ensure there is no impairment during therapy.

**Doi**

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<sup>1</sup> Laboratory of Physiology - Respiratory function tests and somnology, AP-HP, Armand Trousseau Hospital, University of Sorbonne, Paris, France

<sup>2</sup> Pediatric Physiology Service, AP-HP, Sorbonne, Paris, France, INSERM, Robert Debré University Hospital, Paris, France

<sup>3</sup> La Berma Clinic, Antony, France

<sup>4</sup> University of Sorbonne, INSERM, U934, Centre de Recherche Saint Antoine, Paris, France

**KEY WORDS**

*Pediatric asthma; spirometry; bronchodilator; biologics.*

## INTRODUCTION

Asthma is the most common chronic disease in children, with a prevalence of 11%-13.7% in those over 6 years old in our country (1). However, only 5% of children with asthma experience severe asthma (2).

Severe asthma is defined by asthma which requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy (3). Children with severe asthma are prone to more symptoms and frequent exacerbations, which have an established deleterious effect on lung function (4). The challenges in treating these children are to decrease symptoms and exacerbations and preserve their lung function. In a cohort of children followed for asthma of various levels of severity, it has been found that over 10 years, 28% of cases had a decrease in lung function, as assessed by a significant negative slope of their Forced Expiratory Volume in 1 second ( $FEV_1$ ) over time (5).

The recent availability of biologics, such as omalizumab (OZ), to treat severe asthma in children has shown positive effects in the rate of hospitalizations and the dose of ICS (decrease), as well as in asthma control and lung function (improvement) (6). However, the outcomes of randomized controlled trials conducted in highly selected and closely monitored patients are not always similar to those measured in real-life settings. The few studies exploring the long-term lung function outcomes (1 to 3 years) in children receiving OZ have failed to constantly detect an improvement in  $FEV_1$ , Forced Vital Capacity (FVC), and their ratio (2, 7-10). This is an important issue, as physicians following these children need to know what lung function evolution is to be expected. In this retrospective study, we evaluated a cohort of children routinely tested for lung function in the same laboratory using standardized procedures, before and at least twice after the start of OZ, to determine the proportion of children who had a significant change in  $FEV_1$ .

## MATERIALS AND METHODS

### Study design

We designed a retrospective single-center study at Armand Trousseau Hospital in Paris, France, involving

children who had been started on OZ between 2012 and 2015 for moderate to severe uncontrolled asthma. The decision to start OZ was made after a multidisciplinary discussion.

The criteria for initiating OZ treatment in asthmatic children at our institution are as follows: exclusion of differential diagnoses, management of modifiable factors and comorbidities, use of a high daily dose of ICS (based on age and medication, as outlined by Global Initiative for Asthma (GINA, [ginasthma.org](http://ginasthma.org))), completion of patient therapeutic education, presence of positive TH2 inflammatory markers, and symptomatic asthma with a high annual dose of oral corticosteroids and/or uncontrolled asthma symptoms at each visit.

### Subjects

Inclusion criteria were a typical clinical history of asthma symptoms with, at least once, a bronchial obstruction showing a significant reversibility on the lung function test. The children must have had at least three spirometry during the follow-up (the first one just before or within 3 months after OZ treatment onset). Non-inclusion criteria were a less-than-2 year of period of OZ treatment or a lack of clinical data on asthma control.

### Data collection

Once the patient was included, we recorded anthropometric data, history of atopy and of asthma, previous lung function tests, allergenic sensitization, asthma comorbidities, and treatment before OZ start. Lung function tests included forced spirometry performed at baseline and 20-minute post-bronchodilator (BD) (400  $\mu$ g of salbutamol administered via a metered dose inhaler through a spacer device) using a bodyplethysmograph (BodyBox<sup>®</sup>, Medisoft<sup>™</sup>, Sorinnes, Belgium) that was calibrated daily, in accordance with current international recommendations at the time of the test (11). In practice, after entering the patient's age, sex and height into the software, the patient was fitted with a nose clip and connected to the mouthpiece. The patient then performed a deep inspiration followed by a forced exhalation through the pneumotachograph. At least three tests were conducted to obtain at least two reproducible maneuvers, both at baseline and after bronchodilation, from which the best FVC and  $FEV_1$  values were recorded. Post-bronchodilation reversibility in FVC or

FEV<sub>1</sub> was considered significant if it reached at least 12% of the baseline value. The results were expressed as z-scores and percentages predicted according to the Global Lung Initiative reference values (12).

We recorded annual visits, including clinical assessments and lung function tests contained in the patient's electronic records. Asthma control over the past four weeks was assessed using the four-question tool recommended by GINA: 1) were daytime asthma symptoms present more than twice a week? 2) was there any night waking due to asthma? 3) was a short-acting beta-adrenergic reliever used for symptoms more than twice a week (excluding reliever taken before exercise)? 4) was there any activity limitation due to asthma? Patients with all negative responses were considered to have good asthma symptom control, those with one or two positive responses had partial asthma symptom control, and those with three or four positive responses had poor asthma symptom control. Patients and their family were informed about the potential use of their data in a retrospective study and provided consent. The study was approved by the Institutional Review Board of the French Société de Pneumologie de Langue Française (CEPRO 2024-043).

### Statistical analysis

To study the course of FEV<sub>1</sub>% overtime, we determined for each patient the slope of the annual change in FEV<sub>1</sub> percent predicted using standard least squares linear regression models and performed Pearson test to classify the slope (significant when  $P < 0.05$ ). The slope was deemed as positive (improvement in lung function) when the slope was significantly positive, and negative (loss or insufficient growth of lung function) when the slope was significantly negative. When Pearson test P-value was not significant, the slope was considered null (stable lung function).

Results were numbers (percentages, %) for categorical data, and mean (standard deviation, SD) or median (25<sup>th</sup>-75<sup>th</sup> percentiles) according to the normality or not of their distribution. Between-group comparisons were performed using the student test or the Mann-Whitney U test. Categorical variables were compared using the Chi-square test or the Fisher exact test. Only children with a baseline lung function recorded before the start of OZ were included in the lung function comparisons,

while the construction of FEV<sub>1</sub>% trajectories also included those whose first lung function was recorded within 3 months after the start of OZ.

Results with a P-value  $< 0.05$  were considered as significant. Statistical analyses were performed using GraphPad Prism® (v 6.07, Boston, MA) and Octave.

## RESULTS

Among the 104 patients identified as having started OZ during the study period, 71 fulfilled the inclusion criteria (**Figure 1**). The study population included 55 male and 16 female patients. A family history of atopy was present in 41 patients (58%). Personal atopic

**Table 1.** Lung function before onset of OZ and at last visit in 71 study patients.

	Before OZ	Last visit
Age, years	10.5 (2.6)	16.6 (2.1)
Height, cm	141.6 (16)	169.1 (12.2)
Asthma symptom control		
Good	2	39*
Partial	24	28
Poor	37	4
Daily dose, µg/day beclomethasone-equivalent	1245 (856)	906 (649)**
<b>Baseline spirometry</b>		
FEV <sub>1</sub> (L)	1.77 (0.57)†	3.22 (0.68)
FEV <sub>1</sub> (%predicted)	87.2 (15.9)	88.5 (14.5)
FEV <sub>1</sub> (z-score)	-1.07 (1.32)	-0.94 (1.25)
FVC (L)	2.42 (0.81)	4.30 (1.02)
FVC (%predicted)	102.6 (14.1)	103.0 (13.3)
FVC (z-score)	0.19 (1.17)	0.20 (1.15)
FEV <sub>1</sub> /FVC	0.74 (0.11)	0.77 (0.13)
FEV <sub>1</sub> /FVC (z-score)	-1.80 (1.25)	-1.72 (1.27)
<b>Post-bronchodilator spirometry</b>		
FEV <sub>1</sub> (L)	2.01 (0.61)†	3.36 (0.8)
FEV <sub>1</sub> (%predicted)	95.6 (13.7)	95.2 (13.8)
FEV <sub>1</sub> (z-score)	-0.33 (1.15)	-0.37 (1.19)
FVC (L)	2.53 (0.82)	4.28 (1.0)
FVC (%predicted)	104.2 (13.1)	102.8 (12.8)
FVC (z-score)	0.33 (1.08)	0.19 (1.11)
FEV <sub>1</sub> /FVC	0.81 (0.09)	0.84 (0.08)
FEV <sub>1</sub> /FVC (z-score)	-0.97 (1.23)	-0.89 (1.20)

OZ: Omalizumab; FEV<sub>1</sub>: Forced Expiratory Volume in 1 s; FVC: Forced Vital Capacity. Results are mean (SD) or number; †: in 67 patients before OZ treatment. Different from before OZ; \*  $P < 0.0001$ ; \*\*  $P = 0.01$ .

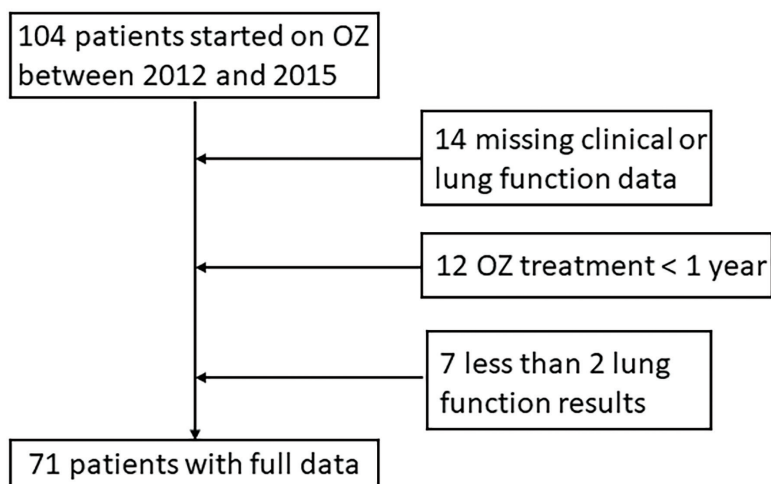


Figure 1. Participant flow chart. OZ: Omalizumab.

conditions were documented as follows: atopic dermatitis in 36 patients (51%), rhino-conjunctivitis in 59 patients (83%), and food allergy in 23 patients (32%). The age at asthma onset was under 3 years for 44 patients (62%), between 3 and 6 years for 10 patients (14%), and after 6 years for 6 patients (8%). The mean (SD) age at the start of OZ treatment was 11.7 (2.9) years. All but two patients received a high dose of ICS, with a mean (SD) daily dose of 1245 (856)  $\mu\text{g}$  in beclomethasone equivalents.

Age, asthma control, lung function and treatment on the first and last visit (before and last follow-up after OZ onset) are shown in **Table 1**. Mean (SD) follow-up was 5.7 (2.1) years, with a maximum of 9.8 years.

Asthma control significantly improved, and ICS dose significantly decreased with OZ treatment, but  $\text{FEV}_1$  z-score did not change between measurements at baseline and at last OZ treatment visit.

The majority of patients did not modify their slope of  $\text{FEV}_1\%$  (null slope in 59 (83%, 95% CI: 72%-91%) for pre-BD  $\text{FEV}_1$ ; 57 (80%, 95% CI: 69%-89%) for post-BD  $\text{FEV}_1$ ) (**Table 2**). In **Figure 2** shows the individual significant positive and negative  $\text{FEV}_1\%$  slopes for pre-BD (**Figure 2A**) and post-BD (**Figure 2B**) among all the  $\text{FEV}_1\%$  predicted values recorded. The slope of pre-BD and post-BD  $\text{FEV}_1\%$  was significantly positive in 8 and 3 patients, respectively, and negative in 4 and 11 patients, respectively. No patient exhibited a discrepancy

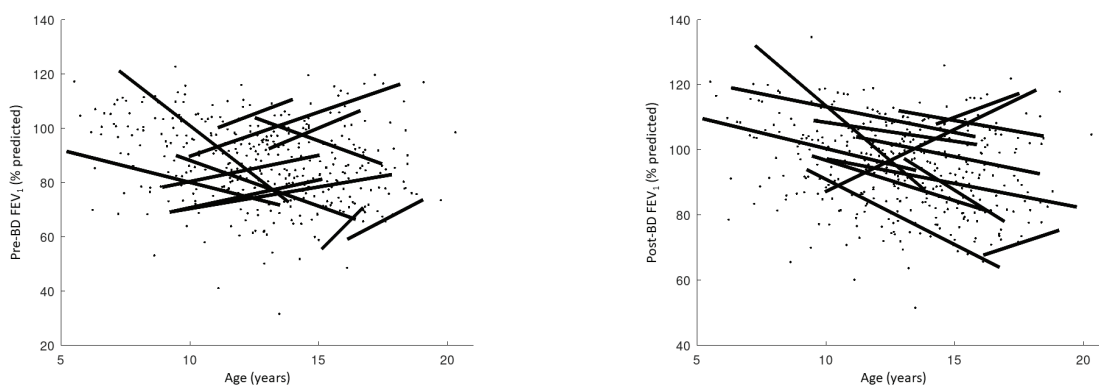


Figure 2. (a) Pre-bronchodilator  $\text{FEV}_1$  measured in 71 before and after omalizumab onset; (b) post-bronchodilator  $\text{FEV}_1$  measured in 71 before and after omalizumab onset. The dots represent pre-bronchodilator  $\text{FEV}_1$  (a) and post-bronchodilator  $\text{FEV}_1$  (b) measurements expressed as percentage predicted and performed in all the study patients. Only the significantly positive ( $n = 8$ , **Figure 2a**,  $n = 3$ , **Figure 2b**) and negative ( $n = 4$ , **Figure 2a**,  $n = 11$ , **Figure 2b**) slopes are represented by solid lines.  $\text{FEV}_1$ : Forced expiratory volume in 1 second.

**Table 2.** Lung function across the three groups of patients according to the pre-bronchodilator FEV<sub>1</sub>% slope.

	Positive slope	Null slope	Negative slope
Number of patients	8	59	4
Sex Male/Female	5/3	46/13	4/0
Duration of OZ treatment (years)	5.3 (2.2)	5.0 (4.6)	7.5 (2.6)
<b>Results at OZ onset</b>			
Age (years)	11.6 (2.8)	10.3 (2.4)	9.0 (3.4)
Height (cm)	144.9 (9.5)	141.8 (16.0)	134.0 (22.3)
<b>Baseline spirometry</b>			
FEV <sub>1</sub> (L)	1.64 (0.47)	1.80 (0.56)	1.68 (0.96)
FEV <sub>1</sub> (%predicted)	73.6 (16.2)	88.5 (15.4)	94.8 (9.2)
FEV <sub>1</sub> (z-score)	-2.18 (1.30)	-0.96 (1.28)	-0.36 (0.7)
FVC (L)	2.29 (0.46)	2.45 (0.84)	2.11 (1.14)
FVC (%predicted)	90.9 (15.7)	103.9 (13.7)	107.1 (3.1)
FVC (z-score)	-0.82 (1.34)	0.31 (1.13)	0.54 (0.24)
FEV <sub>1</sub> /FVC	0.72 (0.14)	0.75 (0.10)	0.79 (0.09)
FEV <sub>1</sub> /FVC (z-score)	-2.00 (1.65)	-1.79 (1.22)	-1.47 (0.99)
<b>Post-bronchodilator spirometry</b>			
FEV <sub>1</sub> (L)	1.86 (0.43)	2.04 (0.62)	2.05 (0.97)
FEV <sub>1</sub> (%predicted)	83.4 (14.6)	97.8 (12.9)	101.3 (7.2)
FEV <sub>1</sub> (z-score)	-1.39 (1.23)	-0.19 (1.08)	0.13 (0.55)
FVC (L)	2.40 (0.53)	2.55 (0.85)	2.42 (1.11)
FVC (%predicted)	95.0 (19.1)	105.6 (11.9)	106.3 (3.6)
FVC (z-score)	-0.48 (1.58)	0.45 (0.98)	0.50 (0.27)
FEV <sub>1</sub> /FVC	0.78 (0.12)	0.81 (0.09)	0.84 (0.08)
FEV <sub>1</sub> /FVC (z-score)	-1.31 (1.61)	-0.94 (1.18)	-0.60 (1.25)

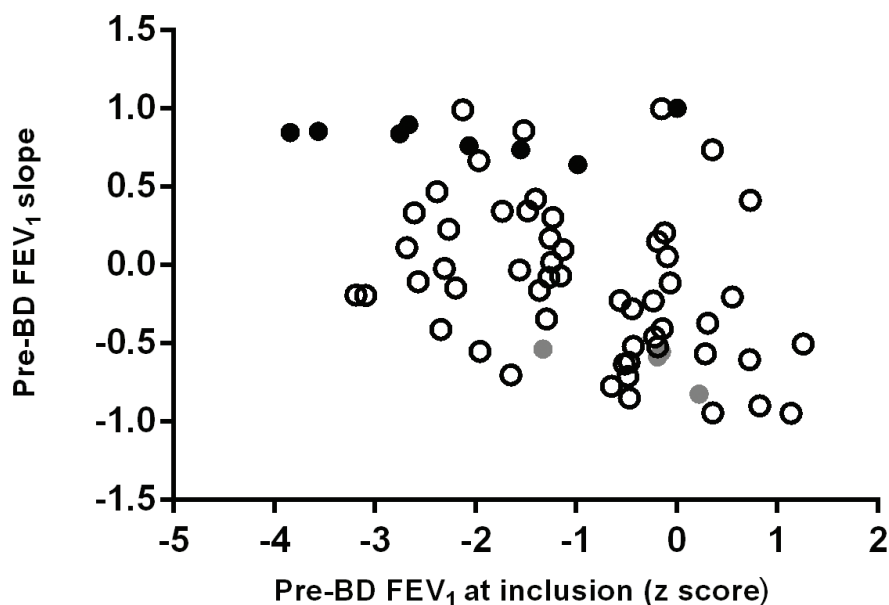
OZ: Omalizumab; FEV<sub>1</sub>: Forced Expiratory Volume in 1 s; FVC: Forced Vital Capacity. Results are mean (SD) or number.

between a positive pre-BD FEV<sub>1</sub>% slope and a negative post-BD FEV<sub>1</sub>% slope, or vice versa. In the largest group of 11 patients with a significant negative post-BD FEV<sub>1</sub>% slope, only three also had a negative pre-BD FEV<sub>1</sub>% slope. The post-treatment clinical asthma control was similar in these three children compared to the eight children with a null pre-BD FEV<sub>1</sub>% slope (totally controlled in three and six children, respectively, partially controlled for the two remaining children).

There was no relationship between the FEV<sub>1</sub> outcome and the personal history of atopy or the amount of ICS received before OZ treatment. **Figure 3** describes the distribution of FEV<sub>1</sub>% slopes according to baseline lung function. A positive FEV<sub>1</sub>% slope was more frequently observed in children with low baseline z-score of FEV<sub>1</sub>.

## DISCUSSION

In this retrospective single-center study on lung function trajectories in asthmatic children after the onset of OZ, we found that in 83% of cases, the slope of pre-BD FEV<sub>1</sub>% was null, despite significant improvement in asthma symptom control and reduction in ICS dosage. The real-life evolution of lung function in children after the onset of OZ treatment has been scarcely evaluated, with conflicting results. The two studies in which FEV<sub>1</sub> did not improve were based on small populations (n = 14 and 17) and, therefore, may lack statistical power (7, 9). The two largest studies (n = 48 and 78) finding a statistical improvement in FEV<sub>1</sub> evaluated the change in lung function over a relatively short period (6 and 12 months) compared to the usual duration of OZ treatment (2, 10). However, none of these studies eval-



**Figure 3.** Distribution of pre-bronchodilator FEV<sub>1</sub>% slopes according to FEV<sub>1</sub> at inclusion. Black circles represent patients with a positive slope, open circles represent patients with null slope, grey circles represent patients with a negative slope.

uated the slope of FEV<sub>1</sub>% after OZ onset. In our study, FEV did not improve significantly after at least 2 years of follow-up (Table 1), consistent with the progression of individual FEV<sub>1</sub>% slopes. Indeed, we found that, in most cases, the slope of FEV<sub>1</sub>% was not significant, with no difference between pre- and post-BD results.

One of the challenges is to define the significance of FEV<sub>1</sub>% change over time. The wide range of definitions used in the literature to define significant variations in FEV<sub>1</sub> needs to be addressed, especially in children, in whom lung growth prevents comparisons between absolute values of FEV<sub>1</sub> or FVC. One recent proposal is the use of the conditional change score for FEV<sub>1</sub> (13). This score has the advantage of taking into account the age of the subject, the natural variability of FEV<sub>1</sub> in healthy subjects and the interval between the two measurements. Using a methodology similar to ours for calculating individual slopes of FEV<sub>1</sub>% in asthmatic adolescents and adults (standard least-squares linear regression models), Delinger *et al.* defined the significance of changes as severe decline (>2% loss/year); mild decline (>0,5-2,0% loss/year); no change (0,5% loss/year to <1% gain/year); and improvement (≥1% gain/year) (14). On the other hand, we chose to use a statistical test (Pearson's) to determine the significance of the individual slopes. Using this method-

ology, Mahut and colleagues previously showed in a study of 295 asthmatic children not receiving OZ treatment, each with at least 10 spirometry tests, that 28% exhibited a negative FEV<sub>1</sub>% slope, while 69% had a null slope (5). This proportion of asthmatic children losing lung function over time was the same as that observed in the CAMP study (28% versus 26%) (15). Our study therefore shows that children receiving OZ experienced less lung function loss than those not receiving this treatment (5, 15).

The second important factor to consider in our population is that ICS dosage significantly decreased in the children receiving OZ treatment, likely because of clinical improvement in their asthma. This can be seen as a positive effect of OZ on lung function, even though most children had a null FEV<sub>1</sub>% slope. However, data on ICS treatment doses should be interpreted with caution, as treatment compliance has been found to be low in this population. In 79 asthmatic adults treated with OZ, after 2 years of treatment, low compliance with ICS treatment was noted in 40 patients (taking less than 80% of the ICS prescribed), 26 of whom took less than 50% of the prescribed dose of ICS (16). These non-compliant patients showed greater improvement in asthma control and quality of life, which could explain lower treatment adherence.

The last finding related to lung function was that children with a positive pre-FEV<sub>1</sub>% slope tended to have a low z-score of FEV<sub>1</sub> at inclusion, while the few ones with negative slope had a higher z-score of FEV<sub>1</sub> at inclusion (**Figure 3**). This result is consistent with the study by Mahut and colleagues, where significantly higher baseline FEV<sub>1</sub> in children with a negative slope was accompanied by a higher FEV<sub>1</sub>/FVC ratio, which should serve as a warning sign when treating these patients (5). There were too few patients with a negative pre-BD FEV<sub>1</sub>% slope to perform statistical analysis in our study, and we cannot infer from our results why children with higher baseline FEV<sub>1</sub>/FVC values would be likely to decline further.

The trend indicating a higher frequency of negative slopes for post-BD FEV<sub>1</sub>% compared to pre-BD FEV<sub>1</sub>% slopes (11 *versus* 3) should not be overinterpreted, given the small sample size and the retrospective nature of the study. But eight of these patients had a null pre-BD FEV<sub>1</sub>% slope. This may indicate a poor prognosis associated with initially high bronchial responsiveness to bronchodilators (large post-BD FEV<sub>1</sub> change) in some patients. This should be examined in more detail, as the follow-up of the Dunedin cohort has shown that relapses, persistence, or severity of symptoms were more common among those exhibiting the greatest responsiveness to bronchodilators (17, 18).

Our study has many limitations because of its retrospective design. We excluded 33 children from the study: 12 were ineligible due to discontinuation of OZ treatment at the six-month visit because of lack of efficacy, and 21 did not meet the inclusion criteria for clinical and lung function follow-up. Of these, 14 were alternately followed in the hospital and in private practice (missing data), and seven were unable to perform sufficiently reliable spirometry. These exclusions are not expected to introduce bias, as neither the physician's location nor the patient's inability to complete spirometry at certain visits corresponds to any specific lung function pattern. We were unable to record treatment compliance, but in this real-world study, it is likely that some patients did not take the full dose of their treatment, particularly those who experienced significant improvements in asthma control and quality of life. In our study, children with a negative FEV<sub>1</sub>% slope had a similar asthma control to that of the rest of the population and may therefore have been

similarly compliant. However, there is no solid evidence supporting the notion that ICS treatment can prevent lung function decline in asthmatic children (15).

This is a single-center study, so our results may differ from other centers. However, patients are referred from all over the district to decide whether to initiate OZ treatment and most of them benefit from joint follow-up by their local carers and our severe asthma clinic. The advantage of this single-center study is that lung function tests were performed using the same machines and methodology by a team of trained technicians adhering to international recommendations. Furthermore, all lung function test results were consistently reported in a single database.

## CONCLUSIONS

The real-life evolution of lung function in asthmatic children treated with OZ is stable in most cases, which contrasts with the observed improvement in clinical symptoms. However, we also found a less frequent significant loss of lung function compared to previous reports on children with asthma of varying severity who were not receiving OZ (5, 15).

The potential decrease of bronchodilator responsiveness in some patients with a negative post-BD FEV<sub>1</sub>% slope, in conjunction with the clinical and functional evolution, would be better studied in a systematic prospective study.

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† Sadly, Hélène Morsy passed away during this study.

## COMPLIANCE WITH ETHICAL STANDARDS

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The Authors have declared no conflict of interests.

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**Author contributions**

CLT and NB designed the study and recorded the data. PB, BM and CD performed the slopes calculation and statistics. CLT, PB and NB drafted the manuscript. BM and CD made important comments on the manuscript. All Authors gave approval of the final version.

**Ethical approval***Human studies and subjects*

the study received the approval of the Institutional Review Board of the French Société de Pneumologie de Langue Française (CEPRO 2024-043).

*Animal studies*

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 correspond to the real.

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## REVIEW

# Childhood interstitial lung disease

Elias Seidl

**Correspondence to:**Elias.Seidl@kispi.uzh.ch. ORCID: <https://orcid.org/0000-0001-6610-3756>**Doi**

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Division of Respiratory Medicine,  
University Children's Hospital Zurich,  
Zurich, Switzerland**ABSTRACT**

Childhood interstitial lung disease (chILD) is a non-specific umbrella term encompassing a broad spectrum of over 200 rare respiratory pediatric disorders. These disorders mainly affect the lung parenchyma leading to impaired alveolar gas exchange. The clinical presentation is usually non-specific. Most commonly, patients present with tachy-/dyspnea, crackles, hypoxemia, and/or dry cough. Clinicians should be familiar with these disorders as they are associated with high morbidity, mortality, healthcare resource utilization as well as medical costs. Different diagnostic tools are available, while treatment options are limited. Growing data and knowledge of pathogenetic genetic variants as well as pathophysiological models increase therapeutic options for personalized treatments in chILD.

**IMPACT STATEMENT:** chILD is a large group of rare, chronic and complex disorders of variable pathology. This brief review highlights current knowledge in the field of chILD to assist clinicians with diagnostic approach and guide their treatment decisions.

**INTRODUCTION**

Childhood interstitial lung disease (chILD) is a non-specific umbrella term encompassing a broad spectrum of over 200 separate respiratory disorders (1). The aim of this review is to give an overview about chILD to help clinicians in their diagnostic approach and guide treatment decisions.

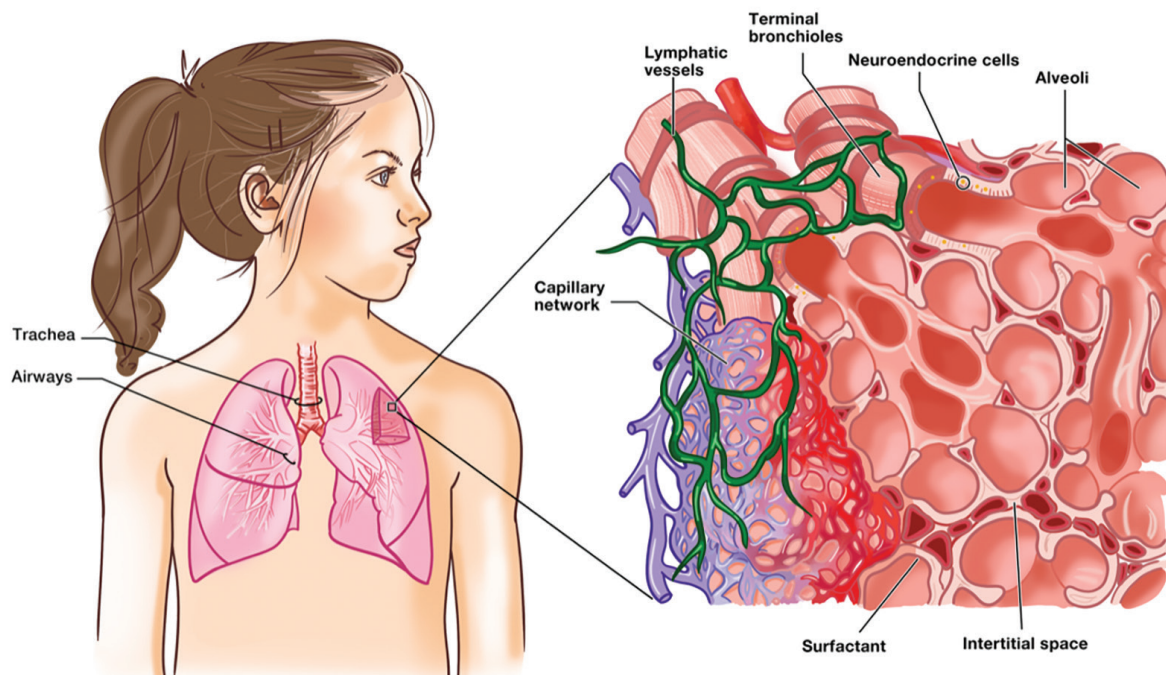
**What is chILD?**

The acronym chILD encompasses a broad group of rare respiratory diseases that are usually separated from other diseases including airway disorders, pleural disorders, neoplasm, and gross structural abnormalities (**Table 1**). In childhood, the term "interstitial lung disease" may be misleading as not only the interstitial space, but also the surfactant homeostasis, capillary network, lymphatic vessels, terminal bronchioles, neuroendocrine cells and alveoli may be affected (**Figure 1**).

Therefore, other generic terms including diffuse parenchymal lung disease (DPLD), childhood diffuse interstitial lung disease, children's interstitial lung disease, interstitial lung disease in infancy, children's interstitial and diffuse lung disease, or chronic interstitial lung disease in children have been introduced. In affected children, efficient gas exchange is impaired, but the clinical presentation is non-specific (**Figure 2**). The earliest clinical presentation is unexplained respiratory distress after birth. Further clinical features include tachy-/dyspnea, (dry) cough, hypoxemia, fine crackles (crepitations), wheezing, hemoptysis, ex-

**KEY WORDS**

*Childhood interstitial lung disease; children's interstitial lung disease; rare disease.*



**Figure 1.** Normal lungs. The umbrella term *chILD* not only includes diseases that affect the interstitial space but also the surfactant hemostasis, capillary network, lymphatic vessels, terminal bronchioles, neuroendocrine cells, and alveoli (image adapted from National Health Lung, and Blood Institute. *Interstitial Lung Diseases. Childhood Interstitial Lung Disease* (66)).

**Table 1.** Etiologic classification of *chILD* as used in the *chILD* EU register ([www.childeu.net](http://www.childeu.net)) (1). The disorders are divided into four categories (1) lung-only/native parenchymal disorders, (2) systemic disease-related disorders, (3) exposure-related disorders and (4) vascular disorders. Specifiers and subcategories are used to describe the different disease characteristics.

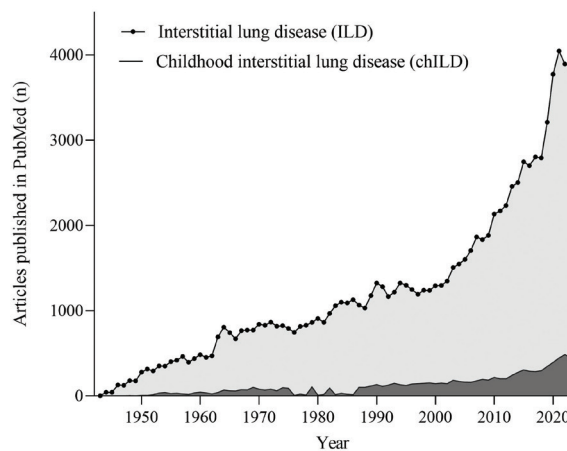
Category	Specifier	Subcategories (examples)
Lung-only/native parenchymal disorders	Developmental conditions manifesting in infancy	A1- Diffuse developmental disorders (ACD, acinar dysplasia, CAD) A2- Growth abnormalities deficient alveolarization (related to preterm birth, associated with diaphragmatic hernia, associated with oligohydramnios) A3- Infant conditions of undefined etiology (PTI, NEHI, PIG) A4- related to alveolar surfactant region (CPI)
	All ages	NSIP, DIP, LIP, PAP, genetic surfactant protein deficiencies.
Systemic disease-related disorders	Immuno-competent	Lane-Hamilton syndrome, EGPA, Hermansky-Pudlak syndrome
	Immuno-deficient	COPA syndrome
	Transplanted	CLAD
Exposure related disorders	Immune dysregulated	STING associated vasculopathy, interferonopathy
	Non-infectious	HP, drug induced interstitial lung disease, radiation pneumonitis
Vascular disorders	Infectious	Postinfectious constrictive bronchiolitis
		DAH, pulmonary capillary hemangiomatosis, VOD

ACD: Alveolar Capillary Dysplasia; CAD: Congenital Alveolar Dysplasia; CLAD: Chronic Lung Allograft Dysfunction; CPI: Chronic Pneumonitis of Infancy; DAH: Diffuse Alveolar Hemorrhage; DIP: Desquamative Interstitial Pneumonia; EGPA: Eosinophilic Granulomatosis with Polyangiitis; HP: Hypersensitive Pneumonitis; LIP: Lymphocytic Interstitial Pneumonia; PAP: Pulmonary Alveolar Proteinosis; PTI: Persistent Tachypnea of Infancy; NEHI: Neuroendocrine Hyperplasia of Infancy; NSIP: Nonspecific Interstitial Pneumonia; PIG: Pulmonary Interstitial Glycogenosis; VOD: Vena Occlusive Disease.

ercise intolerance, digital clubbing, subcostal retractions, chest wall deformities (*i.e.*, *pectus excavatum*, *pectus carinatum*), pulmonary hypertension and failure to thrive/ weight loss (2, 3). None of these clinical symptoms are specific to chILD, and there is a broad overlap to the clinical presentation of children with other respiratory conditions. Before suspecting chILD, a variety of diagnoses need to be excluded (*e.g.*, pulmonary infections with different pathogenic agents, cystic fibrosis, primary ciliary dyskinesia, congenital or acquired immunodeficiencies, recurrent aspirations, structural airway abnormalities, sleep disorder breathing or bronchopulmonary dysplasia). Importantly, also congenital heart defects may mimic chILD (4). The interest in chILD has increased in recent years (Figure 3), leading to the development of large national and international registries, including chILD-EU in Europe ([www.childeu.net](http://www.childeu.net)), RespiRare in France ([www.respifil.fr](http://www.respifil.fr)), The Children's Interstitial and Diffuse Lung Disease Research Network (ChILDRN) in the USA ([www.child-foundation.org](http://www.child-foundation.org)), and chILDRN in Australia and New Zealand ([www.lungfoundation.com.au](http://www.lungfoundation.com.au)).

### Why is chILD important?

For chILD, the overall mortality is suspected to be around 15%, with deaths within the first six months of life being most common (5, 6). A recent study analyzed health-care resource utilization and costs for

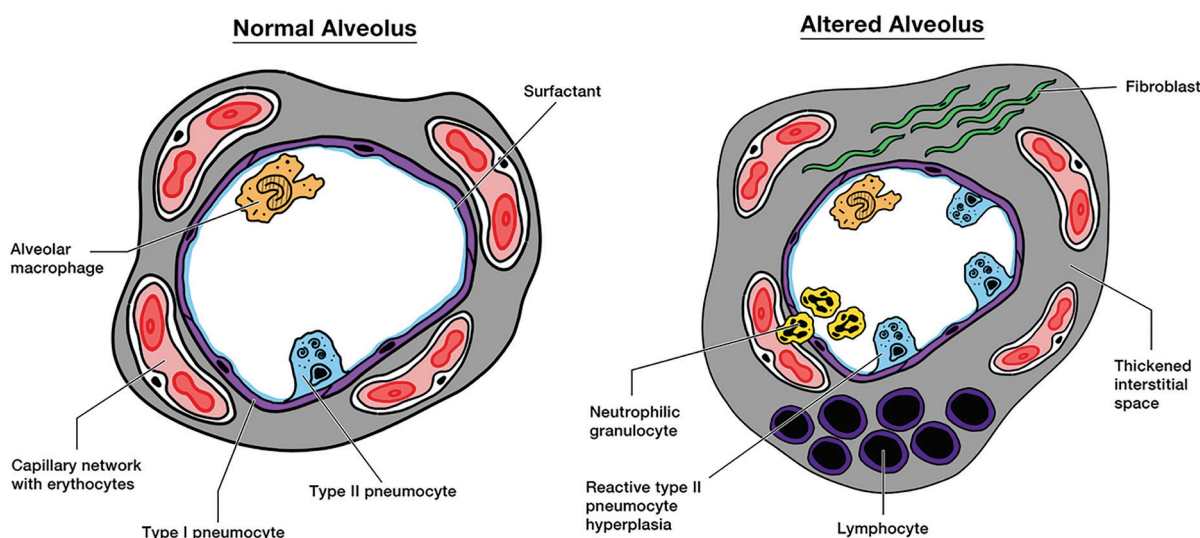


**Figure 3.** Number of publications available on PubMed with 'interstitial lung disease' (light grey) and 'childhood/ children interstitial lung disease' (dark grey) between 1940 and 2023.

chILD across different European countries. Patients at young age presented with extraordinarily high health-care costs, which were mostly caused by high hospitalization rates (7). Also, health-related quality of life (HrQoL) is significantly impaired in chILD compared to healthy children (8, 9). Further studies are needed to assess how these factors can be influenced and HrQoL improved.

### Why is it hard to diagnose chILD?

As chILD is rare, most pediatric pneumologists will only see a few cases in their working life. Prevalence rates



**Figure 2.** (a) Normal alveolus with Type II pneumocytes (blue) synthesizing and secreting surfactant. A small space between type 2 pneumocytes (light purple), the alveolar walls, blood vessels, and erythrocytes allow good gas exchange; (b) an altered alveolus may contain increased granulocytes (yellow; acute inflammation). Lymphocytes (dark purple; chronic inflammation) may infiltrate the interstitium, while Type II pneumocyte hyperplasia, interstitial edema, and fibrosis (green) thicken the interstitium leading to impaired gas exchange (image adapted from (20)).

of chILD have been reported to be between 3.6 and 46.5/1,000,000 in United Kingdom/Ireland (10) and Spain, respectively (11). The annual incidence rates have been calculated to be 1.3/1,000,000 in Germany (5), 3.1/1,000,000 in Denmark (12) and 8.2/1,000,000 in Spain (11). In contrast to that, interstitial lung diseases in adults are more common, less diverse, have been studied more intensively and are therefore better understood than chILD (**Figure 3**) (13, 14). Over ten different classifications for chILD have been proposed (1). Most classifications are based upon histopathology entities, which has limitations particularly in relation to histopathological findings are overlapping with entities caused by gene mutations (3). The ability of clinicians to categorize a working diagnosis in the most commonly used classification system (15, 16) needs structured training for correct disease allocation (17). The most recently proposed classification offers an easy memorable, etiologic based system (1). Disorders are divided into four different categories: lung only (native parenchymal) disorders, systemic disease related disorders, exposure related disorders and vascular disorders. Specifiers and subcategories allow to describe the different disease characteristics (**Table 1**). The etiologic approach helps harmonizing the pediatric and adult classification, and lumps disorders with similar diagnostic and therapeutic principals.

#### What are the diagnostic tools for chILD?

For children with suspected chILD, it is recommended determining a specific chILD diagnosis to enhance clinical decision making regarding specific treatment options.

##### Imaging

For patients with suspected child, high-resolution computed tomography (HR-CT) scans of the chest are the first-line investigation (4, 18, 19). The most common findings associated with chILD are noduli, ground-glass opacities (GGO), consolidation, septal thickening hyperinflation, air trapping, (traction-) bronchiectasis, or mosaic perfusion. Of note, protocols for optimization of image quality are crucial as approximately 30% of external recordings from the Kids Lung Registry were of poor image quality (20). When describing HR-CT scanning results, it is recommended to use terms in accordance with the glossary of terms for thoracic imaging as suggested by the Fleischner Society (21,

22). In chILD, the presence and absence of specific HR-CT findings may lead to a specific pattern, e.g., 'Neuroendocrine hyperplasia of infancy/NEHI-Pattern' (GGO located in the middle lobe, lingula, and the parahilar/paramediastinal distribution without other major abnormalities (23, 24), 'crazy paving pattern' (GGO in concert with septal thickening), and 'Fibrosis' (reticular opacities, traction bronchiectasis, architectural distortion, honeycombing, cystic lucency) (25). In most cases, however, the picture remains non-specific. Thus, HR-CT scanning results are helpful to diagnose chILD, but mostly unsuitable for identifying a specific etiology (19). Data on magnetic resonance imaging (MRI) findings in chILD are scarce. MRI has been reported to detect consolidation as well as interstitial thickening, while septal thickening, GGO, nodules and cystic lesions might be missed (26, 27). Until more studies on the interpretation of lung MRI scanning results are available, the clinical utility of MRI remains limited. At initial evaluation, MRI studies may be performed as add-on to HR-CT scanning, whereas it is more commonly used for follow-up evaluation. Lung ultrasound may be a promising diagnostic tool as a recent controlled prospective study performed in children with the specific chILD diagnosis (persistent tachypnea of infancy (PTI)/neuroendocrine hyperplasia of infancy (NEHI)) demonstrated a close correlation between the presence and features of B-lines (28).

##### Bronchoscopy

Bronchoscopy including bronchoalveolar lavage (BAL) is mostly performed to exclude pulmonary infections or other diagnoses, like structural airway abnormalities or recurrent aspirations. Findings leading to a specific chILD diagnosis are rare but are known to be reported in pulmonary hemorrhage syndromes, pulmonary alveolar proteinosis, eosinophilic lung disease, and hypersensitivity pneumonitis (3).

##### Histopathology

The analysis of lung tissue is reported to be the gold standard to establish a specific chILD diagnosis (17, 29). Lung tissue can be obtained via open, video-assisted thoracic surgery or less invasive cryobiopsies, the latter being a rather new diagnostic tool available for children. Two recent studies investigating cryobiopsies in children reported that the intervention was safe while

maintaining high diagnostic yield (30, 31). Of note, trans-bronchial biopsies are not recommended to perform because the samples are usually too small not containing a sufficient quantity of lung parenchyma to analyze. The current Standard Operating Procedure of the chILD EU register recommend the biopsy to be performed prior to commencing treatment, to be performed in centers with expertise in processing the biopsy. Also, the sample should yield at least 20 x 15 x 10 mm, while the tip of the lobes should be avoided. Electron microscopy is important for the diagnosis of some conditions and therefore to be collected (32). The lung tissue should be evaluated by a pathologist specialized in chILD.

### Genetics

Due to recent developments in capability, processing time and fees, testing for pathogenic genetic variants has become increasingly important. Genetic analysis is recommended for all pediatric patients with chILD as specialized treatment is available for certain diseases. Although disease-causing mutations are considered common in chILD, currently pathogenic variants were identified in only 20% of patients with chILD (17). Most genetic centers offer gene panels or whole exome sequencing to scan for the most common pathogenic variants. For correct interpretation of testing results, the analysis should be carried out by specialized genetics centers.

### Multi-disciplinary team

In contrast to children, when diagnosing adult interstitial lung diseases, multi-disciplinary teams (MDTs) are standard for some time (33). Comprehensive consideration of all available data concludes with the most precise diagnosis (34). Before coming up with a final working diagnosis, the goal is to ensure adherence to diagnostic standards and exclusion of differential diagnoses. The chILD EU register implemented an expert board for peer-review respiratory pediatricians, pediatric radiologists, geneticists and pathologists (17). Of note, even with intensive investigations and a thorough evaluation, in 10-30% of cases no specific diagnosis was found (35).

### What are the treatment options for chILD?

There is no specific therapy that is approved for chILD, yet (36). The clinical care of patients with chILD is mainly based on supportive measures including supplement-

tal oxygen/ invasive or non-invasive ventilation, specific nutritional support and respiratory physiotherapy (3, 4). Respiratory infections are the main driver of acute pulmonary exacerbation in chILD and lead to increased morbidity/mortality, persistent lung function decline and impaired HrQoL (37). However, there are no studies that systematically investigate what preventive measures in chILD are beneficial. Pharmacological treatment for chILD is mainly based on anecdotal evidence and small case collections. Most commonly used are glucocorticosteroids, hydroxychloroquine, and azithromycin, of which only the clinical effect of hydroxychloroquine has been systematically evaluated recently (38). While including only a small study population, one double-blind, randomized, placebo-controlled trial showed no efficacy of the treatment besides being well tolerated (39). Another double-blind, randomized, placebo-controlled trial in patients with chILD and fibrosis on chest HR-CT reported an acceptable safety and tolerability for the antifibrotic drug nintedanib (40). There were no statistical differences between the placebo and nintedanib group on pulmonary function testing results or peripheral oxygen saturation at rest, however, the study was not powered to assess efficacy.

Pulmonary alveolar proteinosis (PAP) is a specific chILD diagnosis that is associated with impaired removal of surfactant (41) due to a variety of different underlying mechanisms including genetic defects in the surfactant metabolism, impaired function as well as reduction of alveolar macrophages or autoantibodies that block GM-CSF signaling (42-44). Whole lung lavage (WLL) is the standard treatment for PAP feasible for stabilizing the clinical condition until a specific treatment is available, even over a longer period (45). Depending on the underlying cause, specific treatment option for PAP may include hematopoietic stem cell transplantation (46), oral methionine supplementation (47), atorvastatin (48), recombinant and exogenous GM-CSF (49), aerosolized GM-CSF (50, 51), or rituximab (52-54).

For surfactant protein dysfunction caused by genetic defects in ABCA3, promising *in vitro* results have been published regarding variant-specific small molecules including ivacaftor, genistein and cyclosporine A (55-57). While no reports about the clinical use of ivacaftor and genistein have been published, a patient with chILD caused by systemic lupus erythematosus was

successfully treated with cyclosporine A in combination with prifinidone (58). A recent observational analysis showed a positive effect of inhaled glucocorticosteroids and bronchodilators on the diseases severity and pulmonary function testing results in symptomatic children with PTI/NEHI (59). Preliminary data have also been published about the clinical use of baricitinib in STING-associated vasculopathy with onset in infancy (SAVI) (60) and COPA syndrome (61), for which ruxolitinib may also be beneficial (62).

For patient with severely impaired pulmonary function who do not respond to therapy, lung transplantation is a treatment option, which has been successfully performed in infants and young children with genetic disorders of surfactant metabolism (63). One infant with chILD related to ABCA3 gene mutation was successfully treated receiving a living donor lobe transplant (64), while the first ABO-incompatible lung transplantation was performed in an infant with surfactant protein B deficiency (65). Good short- and long-term outcome of children and adolescents following lung transplantation were published recently, reporting a 5-year graft and patient survival of 72% and 79%, respectively (63).

## SUMMARY

chILD is a rare group of respiratory rare respiratory disorders that typically present with non-specific clinical features. Clinicians should be familiar with these disorders as they are associated with high morbidity, mortality and healthcare resource utilization. The diagnosis and classification are challeng-

ing, while treatment options are limited. Growing data and knowledge of pathogenetic genetic variants as well as pathophysiological models increase therapeutic options for personalized treatments in chILD. Multi-center collaboration is the key for further research to improve the care for our patients.

## COMPLIANCE WITH ETHICAL STANDARDS

### Conflict of interests

The Author has declared no conflict of interests.

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### Author contributions

Conceptualization, methodology, writing the original draft, review and editing: ES.

### 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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## REVIEW

## Lung malformations: predicting respiratory distress at birth

Ernst Eber

## Correspondence to:

ernst.eber@medunigraz.at. ORCID: <https://orcid.org/0000-0001-7628-030X>**ABSTRACT**

A number of classifications and nomenclatures have been suggested for lung malformations based on the heterogeneous appearances of these abnormalities, and “congenital thoracic malformation” has been recommended as an umbrella term for the whole spectrum of developmental lung and thoracic abnormalities. With the implementation and improvement of prenatal ultrasound examinations it appears that the incidence of lung malformations has risen over the last decades. In developed countries, the vast majority of lung malformations are detected in prenatal screening programmes. Clinical features of lung malformations vary widely. The majority of fetuses have a good outcome, with typically less than 20% of neonates presenting with early life manifestations including neonatal respiratory distress and respiratory insufficiency. Respiratory distress at birth is predicted by size, not the type of a lung malformation. Studies on the natural history of prenatally detected lung malformations have shown that many lesions decrease in size over time; even full prenatal regression of malformations has been described. A number of variables have been investigated as potential predictors of neonatal respiratory distress and early surgery. The most extensively studied parameter is the congenital pulmonary airway malformation (CPAM) volume ratio (CVR), which represents a volumetric index of mass size allowing for comparisons of fetuses at different gestational ages. In addition, other ultrasound and magnetic resonance imaging (MRI) derived measurements such as maximal (cyst) volume, mass to thorax ratio, observed to expected normal fetal lung volume, fetal cardiac axis, and cardiac position have been investigated. CVR has been associated with the development of hydrops, neonatal respiratory distress in both term and preterm infants, and the need for respiratory support within 24 hours after birth. While consensus on a cut-off value is lacking, it appears that a CVR at presentation of <0.40 is associated with favorable outcomes. However, a low CVR does not completely rule out respiratory problems after birth. A multidisciplinary approach to the management of fetuses and infants with lung malformations is important, and fetuses at risk should be delivered at specialized tertiary care centers with a neonatal intensive care unit and pediatric surgical expertise to ensure optimal clinical outcomes.

**IMPACT STATEMENT:** A congenital pulmonary airway malformation volume ratio (CVR) at presentation of <0.40 has been associated with favourable outcomes.

**Doi**

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Division of Pediatric Pulmonology and Allergology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Steiermark, Austria

**KEY WORDS**

*Lung malformations; congenital thoracic malformations; prenatal ultrasound examinations; natural history; clinical features.*

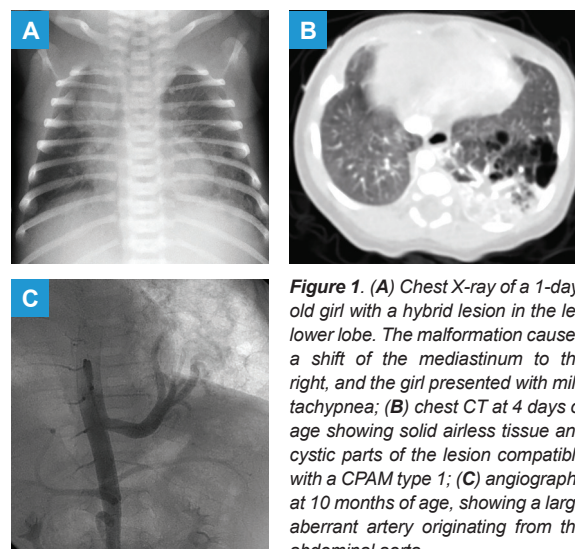
## NOMENCLATURE

The term ‘congenital thoracic malformation’ (CTM) has been recommended as an umbrella term for all congenital lung and thoracic malformations (1). It comprises a spectrum of developmental abnormalities, including pulmonary parenchymal lesions such as congenital cystic adenomatoid malformation (CCAM) or congenital pulmonary airway malformation (CPAM), extra- and intralobar bronchopulmonary sequestration, and congenital lobar and segmental emphysemas, as well as less frequent abnormalities such as bronchogenic and foregut duplication cysts (2, 3).

The original Stocker classification distinguished three CCAM types, 1, 2, and 3: in the ‘macrocytic type’ 1) one or more large cysts predominate; the ‘microcytic type’ 2) consists of numerous small cysts; and the ‘solid type’ 3) is characterized by a mass of airless tissue (4). Subsequently, Stocker proposed a new name for these lesions – CPAM – and also the rarer types 0 and 4: type 0 is a tracheobronchial defect (also known as acinar dysplasia), characterized by firm small lungs with a bronchial airway; type 4 is an entirely alveolar defect at the lung periphery (5). Of the five types, only types 1, 2, and 4 are cystic, and only types 1, 2, and 3 are adenomatoid. **Table 1** summarizes the characteristics of this classification.

However, the nomenclature of lung malformations is quite confusing (1). A number of classifications and nomenclatures have been suggested, based on the heterogeneous appearances of the malformations (5-7). The

term ‘hybrid lesion’ refers to a CTM with anatomical and/or histological overlap between a CCAM and a bronchopulmonary sequestration, such as a lesion with an abnormal blood supply and a histological appearance compatible with CCAM (**Figure 1A, B, C**). CTMs presumably share a common embryological origin and represent a spectrum of abnormalities of fetal lung development with significant overlap, and airway obstruction *in utero* might result in defective lung development, with different patterns of lung malformations according to the level, timing, and degree of the obstruction (7). While there is histological evidence for an association of peripheral bronchial atresia or stenosis with all types of CTMs, mode and timing of these incidents are unclear (8, 9).



**Figure 1.** (A) Chest X-ray of a 1-day-old girl with a hybrid lesion in the left lower lobe. The malformation caused a shift of the mediastinum to the right, and the girl presented with mild tachypnea; (B) chest CT at 4 days of age showing solid airless tissue and cystic parts of the lesion compatible with a CPAM type 1; (C) angiography at 10 months of age, showing a large aberrant artery originating from the abdominal aorta.

**Table 1.** Classification of congenital pulmonary airway malformations according to Stocker (1, 5).

Type	Incidence	Cyst size	Histology
0	Rare		Complete failure of development beyond the pseudo-glandular stage (acinar dysplasia); lethal.
1	Common	Large cysts (>2 cm), can be multiple	Pseudostratified ciliated columnar epithelium, intermixed with rows of mucous cells.
2	Common	Multiple small cysts, sponge-like	Dilated bronchiole-like structures, intermixed with simplified alveolar parenchyma; occasionally striated muscle.
3	Rare	Solid	Bronchiolar structures separated by small air spaces with cuboidal lining, resembling late fetal lung.
4	Rare	Large cysts	Peripheral and thin-walled cysts, lined by alveolar or bronchiolar epithelial cells upon loose mesenchymal tissue.

## EPIDEMIOLOGY

In 1979, the European Community established the European Surveillance of Congenital Anomalies (EUROCAT), with the aim to establish a network of population-based registers for the epidemiological surveillance of congenital anomalies (10). This network consists of 43 registries in 23 countries and covers approximately 30% of the European birth population. However, in most cases the individual registers are regional and not national, which is likely to affect robustness of the data. In past years, the reported incidence was around 4/10,000 live births for all CTMs and around 1/10,000 live births for CCAMs, respectively (10). The reported incidence of bronchopulmonary sequestrations ranges between 1 and 6% of all CTMs. It appears that the incidence of CTMs has risen over the last decades, partially explained by the implementation and improvement of prenatal fetal ultrasound examinations (11). For low- and middle-income countries there is a lack of epidemiological data.

## PRENATAL DETECTION AND POSTNATAL EVALUATION

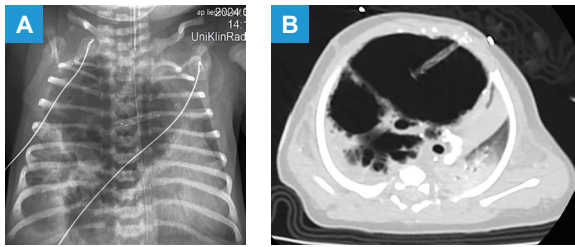
In developed countries, more than 90% of lung malformations are detected in prenatal screening programmes. Many of these lesions will have regressed and some even disappeared on postnatal ultrasound and chest X-ray examinations. Vanishing lung lesions late in gestation have been reported to be associated with a low CCAM or CPAM volume ratio (CVR), a volumetric index of mass size allowing for comparisons of fetuses at different gestational ages, and microcystic disease (12). Postnatal evaluation including ultrasound with Doppler, chest X-ray, and chest computed tomography (CT) scan with intravenous contrast or magnetic resonance imaging (MRI) is required in all children with prenatally detected CTMs. These investigations are intended to characterise the malformation, its vascularity, and whether a communication with the tracheo-bronchial tree is present. Chest CT angiography in the first year of life is considered the gold standard for specifying CTM characteristics (13); in asymptomatic children it is usually performed in the second half of the first year of life. However, while clinicians often try to make a pathological diagnosis on imaging, modalities including ultrasound, CT and MRI all have some level of discrepancy with pathology (14, 15). To rule out a

foregut communication, an esophageal contrast study may be necessary. Further, all children should be evaluated for associated congenital disorders, in particular cardiac anomalies (2).

## CLINICAL FEATURES AND COMPLICATIONS

Clinical features of CTMs vary widely. *In utero*, large lesions may compress the ipsilateral lung and via mediastinal shift also the contralateral lung, resulting in lung hypoplasia. Compression of the esophagus may lead to polyhydramnios, and the resulting distension of the uterus may induce premature labor. Impairment of venous return and hydrops may bring about fetal or neonatal death. However, treatment *in utero* is only required in a minority of fetuses, with interventions such as maternal steroid administration, puncture or shunting of macrocystic masses, alcohol embolization or lasering of a feeding vessel, lobectomy via hysterotomy for more solid masses, and resection while on placental circulation. A fetal hydrothorax or pleural effusion may be treated with thoraco-amniotic shunting. Fetal therapy requires the expertise of a highly skilled multidisciplinary team (1, 2). The majority of fetuses with CTMs have a good outcome with typically less than 20% of neonates presenting with early life manifestations including respiratory distress and respiratory insufficiency, cardiovascular overload, or pneumothorax (**Figure 2A, B**) (1, 16, 17). However, primarily asymptomatic neonates may develop complications at any age from infancy to adulthood; the exact incidence of complications and the natural history of different types of CTMs are largely unknown. Complications include infection (recurrent localized pneumonia, lung abscess, empyema), hemoptysis, pneumothorax (due to cyst rupture), compression of neighbouring structures (airways, esophagus), sudden respiratory compromise, and cardiovascular symptoms or high output cardiac failure (if there is a large systemic arterial blood supply) (1, 3, 18-23).

In addition, relationships between CTMs and malignancies have repeatedly been reported. These include pleuropulmonary blastoma (typically, preschool children are affected) and bronchioloalveolar carcinoma (the mean age for this complication appears to be young adulthood) (24-26). In a series of prenatally detected, asymptomatic cystic malformations almost a quarter demonstrated either subclinical infection or malignancy (27).



**Figure 2.** (A) Chest X-ray and (B) chest CT of an intubated 38-week gestational age boy with a CPAM type 1 demonstrating very large cysts, which compressed the surrounding lung tissue and caused a shift of the mediastinum to the left, and the remnant of a thoraco-amniotic shunt. The boy presented with severe respiratory distress and respiratory insufficiency immediately after birth.

### NATURAL HISTORY OF PRENATALLY DETECTED CTMS

There is still a shortage of prospective studies on the natural history of prenatally detected CTMs. Many lesions decrease in size over time, but for the individual malformation the growth process is unpredictable. Hydrops is associated with an extremely high risk of fetal or neonatal death, but an initially large lesion does not necessarily correlate with a poor prognosis (2).

Crombleholme *et al.* introduced CVR as a sonographic indicator of fetuses at risk for hydrops who require close ultrasound observation and possible fetal intervention. They controlled for fetal gestational age by dividing the volume of the malformation by the head circumference ( $CVR = L \times W \times H \times 0.52 / \text{head circumference}$ ). Thus, CVR allows direct comparisons of fetuses at different gestational ages and serial measurements of the lung malformation in the same fetus normalized to head circumference, to determine progression or regression of the malformation (28).

Riley *et al.* from the same center performed a retrospective review of the pre- and postnatal courses of 103 fetuses with an intralobar ( $n = 44$ ) or extralobar ( $n = 59$ ) bronchopulmonary sequestration managed at their institution. They found that most extralobar (71%) and intralobar (94%) sequestrations decreased in size or became isoechoic from initial to final evaluation. The peak lesion size occurred at 26 to 28 weeks gestation (29).

Delacourt *et al.* conducted a nationally representative, multicenter, prospective cohort study including 579 ultrasound examinations in 176 pregnant women with a diagnosis of congenital pulmonary malformations. Several ultrasound examinations performed between diag-

nosis and delivery included CVR measurements, with changes in CVR modelled as a function of gestational age, overall and separate for cystic/mixed vs. hyperechoic malformations. Further, the association between CVR and signs of compression during pregnancy was examined (30). They found a statistically significant decrease in CVR with increasing gestational age, with a different pattern of change according to the phenotype of the malformation at the first ultrasound examination. While cystic/mixed malformations were characterized by a steady decrease in CVR with increasing gestational age, hyperechoic malformations showed an initial increase in CVR up to 27 weeks of gestation, followed by a subsequent decrease. For cystic/mixed malformations, peak CVR values were predicted as early as 21-22 weeks, compared to 25-26 weeks for hyperechoic malformations. The authors speculated that this difference might be the result of different pathophysiological mechanisms or differences in the timing of occurrence of different types of malformations. Further, CVR measured at the first ultrasound examination was found to be strongly associated with the odds of subsequent compression (30).

### PREDICTION OF RESPIRATORY DISTRESS AT BIRTH

In the last 20 years, a number of variables have been investigated as potential predictors of neonatal respiratory distress and early surgery, with CVR being the most extensively studied parameter.

In a retrospective single center study, Hellmund *et al.* evaluated the potential of prenatal sonographic findings as risk parameters for adverse outcome or need for intervention in fetuses with a CPAM (31). The Authors performed measurements of CVR, mass to thorax ratio (MTR), and observed to expected lung to head ratio (o/e LHR) and correlations to fetal or neonatal morbidity and mortality, and/or need for prenatal intervention. They came to the conclusion, that CVR and MTR are able to identify fetuses at risk, and that the o/e LHR is less sensitive than the other two parameters.

Similarly, in a retrospective single center study Girsén *et al.* evaluated the utility of fetal lung mass imaging for predicting neonatal respiratory distress by analysing the initial as well as maximal lung mass volume and CVR determined by sonography and MRI (32).

They reported the strongest predictors of respiratory distress to be maximal volume  $>24.0 \text{ cm}^3$  by MRI and maximal volume  $>34.0 \text{ cm}^3$  by sonography.

In another retrospective single center study of children with prenatal diagnosis of a lung malformation, Gerall *et al.* assessed fetal ultrasound and MRI parameters including maximal CVR, absolute cyst volume, and observed to expected normal fetal lung volume (o/e NFLV) (33). They found a correlation between postnatal respiratory symptoms and ultrasound based, but not with MRI derived measurements.

Further, Tuzovic *et al.* again in a retrospective study set out to assess the performance of the fetal cardiac axis (CA) and/or cardiac position (CP) versus the CVR in predicting any and severe neonatal respiratory morbidity in fetal congenital lung malformations (34). They reported an abnormal CA and/or CP to have a higher sensitivity for any respiratory morbidity compared to the CVR (with cut-off values of 0.5 and 0.8, respectively) both before 24 weeks and between 24 and 32 weeks.

### CPAM VOLUME RATIO (CVR)

In the early years of this millennium, reported threshold values of CVR ranged between 1.6 and 2.0 (28, 35, 36). Ehrenberg-Buchner *et al.* conducted a retrospective review of 64 fetal lung lesions managed at a single fetal care referral center. Ultrasound data were correlated with perinatal outcomes (37). Among 60/64 fetuses without hydrops, the CVR was the only variable that was significantly associated with respiratory compromise and the need for lung resection at birth. Based on a maximum CVR  $>1.0$ , the sensitivity, specificity, positive predictive value, and negative predictive value for respiratory morbidity were 90%, 93%, 75%, and 98%, respectively.

Ruchonnet-Metrailler *et al.* investigated cases with prenatal diagnosis of hyperechoic and/or cystic lung lesions from RespiRare, the French prospective multicenter registry for liveborn children with rare respiratory diseases and sought correlations between prenatal parameters and neonatal respiratory outcome (16). Twenty-two out of 89 children had abnormal breathing at birth, and severe respiratory distress was observed in 12 neonates. While respiratory distress was significantly associated with mediastinal shift, polyhydramnios, ascites, maximum prenatal malformation area, and

maximum CVR, severe respiratory distress was best predicted by polyhydramnios, ascites, or a CVR  $>0.84$ . By way of contrast, Costanzo *et al.* in a retrospective, single center study of 70 prenatally diagnosed fetuses with pulmonary malformations referred to their center reported the presence of fetal complications and a CVR  $>1.6$  as predictors of respiratory distress at birth and of the need for early surgery (38).

More recently, Kane *et al.* performed a retrospective cohort study of all pregnancies with a prenatal diagnosis of an isolated fetal echogenic lung lesion managed at their referral center between 2005 and 2015 (39). In 65 cases (four with hydrops), they found a CVR at presentation of  $<0.45$  to be associated with favorable outcomes.

In the same year, Eyerly-Webb *et al.* in a retrospective multicenter study used serial measurements to create estimated growth curves of fetal CVR for both asymptomatic and symptomatic neonates with lung malformations, in order to investigate whether a discriminant prognostic model could accurately predict which fetuses will require invasive respiratory support at delivery (40). Sixteen out of 147 neonates required postnatal invasive respiratory support. Fetal CVR growth curves showed different growth patterns for asymptomatic vs. symptomatic neonates; CVR was significantly higher in symptomatic neonates, and values peaked at around 25 weeks' gestation in asymptomatic neonates.

In another retrospective single center study, Peters *et al.* analyzed prenatal, perinatal and postnatal data from fetuses with a lung malformation (41). Fourteen out of 80 fetuses required respiratory support on the first postnatal day, and 17 required surgery within 2 years. The Authors found a CVR at  $25 + 0$  to  $29 + 6$  weeks predictive of the need for respiratory support, with a cut-off value of 0.39. However, they also showed that even full prenatal regression of a malformation does not rule out respiratory problems after birth. Altogether, there was only low concordance between the prenatal appearance of the malformations and the postnatal type.

Delacourt *et al.* utilized a prospective population-based nationally representative cohort to develop a simple prognostic model for predicting the risk of neonatal respiratory distress in preterm and term infants with lung malformations (42). They used CVR measured at diagnosis and the highest CVR measured as main

predictive variables. Sixty-seven out of 383 neonates had respiratory distress. For term infants, the most parsimonious model included the highest CVR measured as the only predictive variable. The probability of neonatal respiratory distress increased linearly with increasing maximum CVR and remained below 10% for a maximum CVR <0.4. For preterm infants, maximum CVR and gestational age were found to be predictors of neonatal respiratory distress.

## CONCLUSIONS

A minority of fetuses present with a neonatal respiratory distress and respiratory insufficiency. Respiratory distress at birth is predicted by size, not the type of a lung malformation. Several parameters have been investigated as potential predictors of neonatal respiratory distress and/or early surgery. The most commonly used parameter CVR among others has been associated with neonatal respiratory distress and early need of respiratory support. In recent years, a CVR at presentation of <0.40 has been associated with favorable outcomes. Importantly, prenatal regression of a lung malformation or a low CVR do not rule out respiratory problems after birth. The value of other sonography or MRI-derived parameters in individualized risk assessment to guide decisions is being discussed. A multidisciplinary approach to the management of lung

malformations is key, and fetuses at risk should be delivered at specialized tertiary care centers to ensure best possible clinical outcomes.

## COMPLIANCE WITH ETHICAL STANDARDS

### Conflict of interests

The Author has declared no conflict of interests.

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### Author contributions

EE wrote the manuscript.

### 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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## REVIEW

# State of the art of research in pediatric pulmonology

Susanna A. McColley\*

**\* Correspondence to:**

mccolleysusanna@gmail.com. ORCID: <https://orcid.org/0000-0003-0842-728X>

**Doi**

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Feinberg School of Medicine, Northwestern University, Chicago, USA

**ABSTRACT**

Despite high global prevalence, morbidity, and economic impact, respiratory disease research has long had disproportionate investment compared to disease burden. This is especially true for pediatric respiratory diseases that are leading causes of childhood morbidity and mortality. Nevertheless, advances in science, technology and research study design have increased opportunities for efficiency, effectiveness and global representation in research. This review presents evolving research approaches and technologies, emphasizing strategies to improve accessibility, inclusion, generalizability, rigor, and reproducibility.

**IMPACT STATEMENT:** This review can impact the design and implementation of childhood respiratory disease research through enhancing knowledge of new study designs and technologies, increasing access to and generalizability of studies.

**INTRODUCTION**

Respiratory disorders are major contributors to childhood morbidity and mortality worldwide (1). These include high-prevalence diseases such as viral, bacterial and mycobacterial infections, asthma, and obstructive sleep apnea; rare genetic disorders such as cystic fibrosis and diffuse lung diseases; and respiratory complications of neuromuscular, hematological, oncological and rheumatological disorders. There is ongoing, disproportionately low investment in respiratory disease research (2), compounded by low investment in pediatric research (3), even in high income countries. There are also many barriers to the conduct of clinical research across fields. Nevertheless, international collaborations, new approaches to clinical study design, and new technologies are increasingly being applied to improve understanding of and advance therapeutics for pediatric respiratory disorders.

Many conferences and journals include 'best of' or 'year in review' presentations or papers in a given calendar year. This review will instead focus on new and evolving research approaches and technologies, highlighting recent articles of interest to the pediatric respiratory research community. Throughout, there will also be a focus on inequities in opportunity to participate in and benefit from research advances.

**KEY WORDS**

*Clinical research; clinical trials; study design; digital technology; pediatric respiratory disease.*

### INTERNATIONAL COLLABORATIONS, NETWORKS, AND METHODOLOGIES ADVANCE UNDERSTANDING AND GLOBAL REPRESENTATION

As of July 2024, an estimated 5.4 billion people have internet access, representing just over 67% of the world's population (4). Expanded connectivity and advances in computing have allowed increased collaboration, crossing borders and time zones, and application of sophisticated methods in quantitative sciences, including biostatistics and epidemiology. This presents opportunities for international collaborations, data harmonization and methodological standardization that enhance transparency, generalizability, rigor and reproducibility of research findings.

A 2024 study of the global burden of respiratory syncytial virus (RSV) in preterm infants and young children exemplifies use of international collaborations and advances in technology and analysis (5). This sophisticated systematic review and meta-analysis of aggregated and individual participant data, registered in PROSPERO, the International prospective register of systematic reviews (6), included investigators from two global networks and was written by an author team from China, the United Kingdom, Europe, Africa and the United States. Combined aggregated data from studies published between January 1995 and December 2021 and individual participant data from the Respiratory Virus Global Epidemiology Network on respiratory infectious diseases were included. Methods, including meta-regression and two-stage metanalysis, allowed sophisticated estimates of global RSV acute lower respiratory infection morbidity, mortality and risk factors for hospitalization. Among important findings are that, in 2019, an estimated 1,650,000 (uncertainty range [UR] 1,350,000-1,990,000) children under 2 years of age were diagnosed with RSV; 533,000 (UR, 385,000-730,000) were hospitalized, and 26,760 (UR, 11,190-46,240) with preterm birth died. One in 4 hospitalized infants were preterm, and early preterm infants and children had higher hospitalization rates. In-hospital mortality was not different between infants born preterm compared to those born at any gestational age. Risk factors for RSV acute lower respiratory infection were mostly perinatal and sociodemographic, and risk factors for severe outcomes were mostly underlying medical conditions.

While this study confirms many previously identified risk factors for RSV hospitalization and death, the description of the contemporary global magnitude, severity and risk factors is both novel and timely. Recent advances in RSV prevention, including RSV vaccines for pregnant people (7) and monoclonal antibody administration to infants <8 months of age (8), have potential to markedly reduce infant and early childhood morbidity and mortality from acute lower respiratory infections. How quickly these advances will reduce the heavy toll of RSV disease is, however, dependent on an adequate supply, global distribution, and ability of public health and health care systems to deliver these preventive therapies at the right time. Implementation of RSV prophylaxis using the monoclonal antibody, nirsevimab, in the US was hampered by shortages in 2023. Furthermore, disparities in availability and acceptance were evident across pediatric practices in the state of Massachusetts (9), whose child health system performance is among the highest in the nation (10). The availability of data on worldwide incidence, morbidity and mortality is essential for industry leaders, governments and health care systems to create pathways to access to apply these scientific advances to benefit children across geographies.

### ADVANCES IN CLINICAL STUDY DESIGN TO PROMOTE EFFICIENCY, ACCESS AND GENERALIZABILITY

Delays from scientific discovery to new treatments (11), and from efficacy trials to effective implementation (12), are well described, and include specific challenges for pediatric trials (**Table 1**). Participants in clinical trials often do not reflect the general population of people with, or at risk for, diseases, including children, people from minoritized groups, and people who live in remote or rural regions (13). There are evidence-based approaches to enhancing representative study recruitment (14) for both observational and interventional research. New study designs (**Table 2**), approaches, and technologies can overcome longstanding barriers to efficiency, access and inclusion, accelerating research processes, reducing study participant burden, and aiding generalizability of findings by using data from large, geographically distributed populations.

Table 1. Barriers to conduct of pediatric clinical trials.

Barrier	Example(s)
Caregiver consent and child assent	Caregiver concerns about safety Caregiver and child aversion to study procedures (e.g., phlebotomy)
Ethical and regulatory considerations for vulnerable population	More protections increase time needed for regulatory and ethics committee approvals
Eligibility criteria	Strict inclusion and exclusion criteria limit availability of participants and generalizability
Awareness	Caregivers and may not be aware of clinical trials or why they are needed
Accessibility	Trial sites are often in large urban areas that are difficult for many families to access
Communication	Study materials and consent/ assent documents may be difficult for caregivers and children to understand Study staff and investigators may have difficulty communicating in plain language
Language	Materials and consent/assent may not be available in all languages spoken by potential participants
Logistics	Caregiver responsibilities and child school attendance can make traveling to study sites infeasible
Incentives and reimbursement	Financial constraints and ethical considerations may make incentives and reimbursements inadequate to account for time and lost income for caregivers

Table 2. Advances in study design and enabling technologies.

New study designs	Benefits	Caveats and risks
Real-World Evidence	Uses data from existing records/registries Clinical characteristics and treatment responses from in larger, more heterogeneous populations	Data may not include representative populations
Decentralized studies	Study procedures performed at home increase recruitment and retention	Internet service and device availability vary geographically and by household resources
Adaptive trial designs	Trial parameters can be adjusted based on interim results without compromising study integrity	Increased complexity May introduce bias if not carefully designed
Participant-centric trial design	Involving participants and their families in study design can improve acceptability of the ultimate protocol, enhancing recruitment	Requires time and resources Patient and family preferences may not align with regulatory requirements
<b>Enabling technologies</b>		
Artificial Intelligence and Machine Learning	Supports identification of eligible study participants, identification of physiologic and laboratory predictors of disease/disease severity, and analysis of large datasets	Bias in data sources, data entry or algorithms may reduce performance and/or result in inequitable disease or disease severity prediction
Digital tools	Portals and applications provide secure, easily accessible platforms for informed consent, interactions with study staff, and entry of participant/ caregiver reported outcomes	Internet access and digital literacy vary between and within regions

**REAL-WORLD EVIDENCE**

Real-world evidence (RWE) studies are being increasingly used to characterize disease and effectiveness of treatment in children (14). Rather than collect-

ing data prospectively, RWE studies electronic health records, registries, and other data collected without specific attention to hypotheses or observing natural history. Study designs using RWE include observa-

tional studies to describe phenotypes, single-arm trials that use RWE as a proxy for a control group, as in studies of therapies for very rare diseases that extend new therapies to children based on adult clinical trial data, or when controlled, randomized efficacy trials are limited in size.

An outstanding 2024 study of children with asthma represents the power of RWE in disease phenotyping. Nearly 30,000 children from in a Danish nationwide database were studied to explore how routinely collected clinical data could be used for clinical phenotyping and risk assessment (15). Elevated blood eosinophils and elevated total- or specific-IgE were associated with asthma exacerbations and higher asthma severity, respectively. Children with both these laboratory findings, in utero tobacco exposure, and severe viral infections were at the highest risk of any adverse asthma outcome. These findings can be applied to clinical practice and can also aid in developing therapeutic clinical trials by guiding inclusion criteria and/or risk stratification.

An important caveat in interpreting RWE studies is understanding how the population from whom data were derived are similar, or different, from a population that may benefit from study findings, whether for clinical care or design of clinical trials. Ancestry, environment, rates of child poverty, access to and quality of health care vary by country, region, and demographics influence incidence and prevalence of disease and contribute to disease severity. While race and ethnicity are sociopolitical constructs, children of minoritized race or ethnicity have worse outcomes across acute and chronic diseases in the US and other countries. For example, there is clear evidence that poorer quality in health care delivery is a major contributor to adverse outcomes in minoritized US children (16). Even the mandatory and highly comprehensive Danish National Child Health Register used for the above-referenced study has missing data, to which ethnic background or socio-economic disparities may contribute (17). Although RWE study protocols can be replicated in any region where electronic health data are available, the proportion of children with a disease who have data, and how data are entered and analyzed can limit generalizability of findings (18). Thus, RWE studies, while efficient, useful and relatively inexpensive, should be interpreted in the context of these limitations.

## DECENTRALIZED STUDY DESIGNS

Clinical research is hampered by accessibility to study sites posed by distance, costs of transport, and other factors such as missed school for children and missed work for parents. Studies that are decentralized, either wholly or in part, are an important solution to enhance enrollment and representative participation. During restrictions imposed to reduce COVID-19 exposure, many trials originally designed to have study procedures at health care or research facilities made rapid adaptations to offsite procedures and remote study visits, conducted by telephone or videoconference (telehealth visits) (19). One such clinical trial is especially memorable to the author. The extension trial of elexacaftor/tezacaftor/ivacaftor for children with cystic fibrosis (CF), homozygous or heterozygous for the F508del CFTR variant, and 6-11 years old was rapidly decentralized during the COVID-19 pandemic (20). Study medication was delivered to the homes of enrolled children, clinical samples were collected in homes or local laboratories, and some clinical assessments (e.g., sweat chloride) were missed. Despite these challenges, most participants remained enrolled, the trial was completed, and the medication has become available in countries whose health care systems have adequate resources.

An important paper describing incidence and symptoms of long COVID was published in 2024, demonstrating how a large prospectively enrolled cohort from a single center can be retained in a low burden, partly decentralized, longitudinal study (21). The investigators recruited a cohort of children, up to age 13, who had been seen at the hospital Emergency Department, admitted to the hospital, or seen by an external pediatrician over the course of ~4 years. Baseline, 3- and 6-month assessments were conducted in person, and those who had returned to pre-COVID health were subsequently assessed by telephone. Among 1319 children referred, 98.6% received follow-up at 3 months, 97.9% at 6 months, and 85.6% at 12 months, and 82.2% at 24 months. Even at 36 months, when the majority had recovered, retention was 66.2%. This allowed thorough evaluation of diagnosis of long COVID incidence, using published definitions, and clinical course of those who met diagnostic criteria. Findings were important for both health care practitioners and

public health leaders. These include a high prevalence of persistent symptoms and long COVID, present in ~23% of children at 3 months and continuing at 36 months in some, demographic and clinical predictors of long COVID, variation in long COVID associated with specific variants, emergent autoimmune disorders, and the protective effects of vaccination.

It is unlikely that this study will be fully replicated in other regions, given expansion of COVID-19 vaccines to younger children and ongoing variant shifts. The implications of the study are critically important for primary care physicians and pediatric subspecialists, providing insights into natural history and setting a stage for clinical trials to prevent or alleviate long COVID. Furthermore, this example of a rapidly designed and implemented prospective study, with low participant burden, can be replicated or applied to other emerging diseases.

### ADAPTIVE CLINICAL TRIAL DESIGNS

Adaptive clinical trials (22) allow modifications of trial parameters, such as drug dose, participant selection, or measurements based on prespecified interim results. This allows trial adjustments without compromising study integrity. To date, adaptive trial designs have not been widely used in pediatric respiratory disease. For example, a recent systematic review of adaptive trial designs in pediatric critical care reported that only 3% of reported trials conducted between 1986 and 2021 used an adaptive design (23). However, adaptive trial designs are in progress or planned for studies of childhood respiratory disorders. These include the Precision Medicine in Severe Asthma study (24), which has enrolled adolescents and adults and uses an adaptive design to test novel interventions in biomarker-defined subgroups of severe asthma. Another trial in progress is the Pragmatic Adaptive Trial for Respiratory Infection in Children (PATRIC) study (25). In addition to generating important new knowledge, these studies may serve as examples for future adaptive trials of pediatric respiratory disorders.

### PATIENT-CENTRIC TRIAL DESIGNS

Nearly 1 in 5 pediatric clinical trials fail to enroll enough participants. A potential solution to this per-

sistent problem is to involve children and their caregivers in the design of study protocols. A 2023 report described lessons learned and recommendations from a collaboration between two European Innovative Medicines Initiative Innovative Health Initiative projects, conect4children and European Patient-Centric Clinical Trial Platforms (26). The groups conducted advice meetings that included experts in relevant scientific disciplines and clinical study design. Children (referred to as patients in this report) and caregivers affected by relevant diseases advised on scientific feasibility and acceptability of the proposed study design, or acceptability alone. Patients and caregivers gave feedback in groups or in interviews. Positive outcomes included synergy between investigators and patients/caregivers that generated unique inputs and insights, balancing scientific feasibility with acceptability, and generating culturally relevant information by engaging patients/caregivers from different countries. Social benefits were derived from participation in groups, but not interviews. Limitations included that some topics are less suitable for discussion, that patients/caregivers may be afraid to speak up in the presence of experts, and that patient/caregiver input may not be fully considered. Study protocol changes included changes in eligibility criteria and including patient reported outcome measures in composite study endpoints.

### ENABLING TECHNOLOGIES

#### Artificial intelligence and machine learning

Artificial intelligence (AI) and machine learning are technologies that allow computers to perform tasks that otherwise require human intelligence. Artificial intelligence is a broad term to describe use of machine-based learning and algorithms, while machine learning describes automated changes in programs or algorithms based on exposure to data to improve performance over time (27). These technologies are applied in many industries for customer service, targeted advertising, process automation, analytics, and other business functions. In medicine, AI and machine learning are being increasingly used for diagnostic and prognostic prediction, monitoring and medication management (27). Data may be derived from electronic health records, medical devices, or applications

for non-medical devices, as applied to detect atrial fibrillation from a widely available 'smart watch' (28). A 2023 article demonstrated applications of machine-learning trained devices to aid diagnosis of pediatric lung disease (29). Electronic stethoscope recordings were recorded during routine clinical care by pediatric pulmonologists and labeled as normal, crackles, or wheezing, based on the examiner's findings. Models were trained to differentiate normal vs. abnormal, crackles vs. wheezing, normal vs. crackles, and crackles vs. wheezing. A prospective validation showed that the machine learning breath sound classification model performance was high, was lower than pediatric specialist performance, but was better than non-pediatric physician performance, except for practice. This technology could potentially be deployed for more rapid assessment of children with respiratory symptoms during viral respiratory outbreaks.

A 2024 article described development of a mechano-acoustic sensor for accurate cough detection in children with cystic fibrosis (30). This study adapted technology from a previously described sensor (31) and studied children with CF who had brief, protocolized study visits in which they coughed, talked, ate, drank, and moved; in clinic during visits, including pulmonary function testing; and for longer periods while stable and during pulmonary exacerbations. Machine learning algorithms accurately detected cough and vital signs, and quantified reduction in cough with resolution of pulmonary exacerbation. Such technology could be deployed to monitor children with CF at home, or as a clinical trial endpoint.

Another 2024 article described development of a machine-learning strategy to diagnose obstructive sleep apnea syndrome (OSAS) in children (32). Children with symptoms of OSAS had clinical evaluations, standardized questionnaires, and physical assessments, including neck, waist and hip circumference. A machine learning algorithm was trained based on clinical evaluation and polysomnography findings. Machine learning selected 47 clinical features associated with apnea-hypopnea index (AHI)>5 and 31 features associated with AHI>10. Linear discriminant analysis using these features had sensitivity of 44% and specificity of 90% for detecting OSAS, performing better than the questionnaire alone.

### Digital tools to facilitate communication and collect study data

Digital tools, including applications for portable devices and participant portals, are increasingly used for communication with research participants (or their proxies) and to collect participant-reported information, including participant (*i.e.*, patient) reported outcome measures. A 2021 paper described how the Asthma Research in Children and Adolescents (ARCA) cohort was developed (33). Children aged 6-16 who had persistent asthma were eligible for enrollment. Parents/proxy, children, and adolescents submitted information related to asthma control on a smartphone application. Data was sent to pediatricians through a portal that displayed color-coded in the familiar 'traffic light' system of green, yellow and red to indicate asthma control. High usability scores were found across age groups. The smartphone application was subsequently used in a prospective observational study that assessed longitudinal associations between inhaler adherence and technique and asthma control (34). This study demonstrated the associations between adherence, symptom control and health-related quality of life, and associations between inhaler technique and health-related quality of life.

### SUMMARY AND CONCLUSIONS

Advances in connectivity, study design, and technologies have great potential to increase and enhance research in childhood respiratory disorders. Improving access to technology, including child and caregiver perspectives in study designs, and increasing awareness and accessibility of clinical research are essential to advance health and health equity in respiratory and other childhood diseases. Researchers should consider new study designs, technologies and approaches that increase collaboration between investigators, awareness of research opportunities by caregivers and health care providers, and reduced burden to participants and caregivers.

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## COMPLIANCE WITH ETHICAL STANDARDS

### Conflict of interests

The Author has declared no conflict of interests.

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### Author contributions

SAM wrote the article.

### Ethical approval

N/A.

### Data sharing and data accessibility

Data are available upon motivated request to the Corresponding Author.

### Publication ethics

#### Plagiarism

The Author declares 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. The development of this manuscript was aided by ChatGPT through the Chat Smith application. All language is original and attributable to the author.

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## BRIEF REPORT

## E-cigarettes and health: segmentation of risk awareness with latent class analysis

Stefania Roncaglia<sup>1</sup>, Giulia Bertolucci<sup>2</sup>, Alessandra Pandolfo<sup>3,4</sup>, Alessandra Beni<sup>2</sup>, Giulia Grillo<sup>1</sup>, Stefania La Grutta<sup>3</sup>, Michele Ghezzi<sup>1</sup>, Maria Elisa Di Cicco<sup>2</sup>

**Correspondence to:**

st.roncaglia@gmail.com. ORCID: <https://orcid.org/0009-0008-8807-8158>

**ABSTRACT**

Electronic cigarette (e-cig) use, especially among young people, has become widespread. The aim of this study was to use Latent Class Analysis (LCA) to identify and categorize distinct groups of individuals based on their awareness of the health risks and characteristics of e-cigs. We administered a questionnaire to 83 participants, with an average age of 27.22 years, that included 83 questions on different aspects of e-cigs, including composition, health effects and risk perceptions. Only 23 questions were considered suitable for analysis. We found that the probability of belonging to the 'Low awareness' class is higher than the 'High awareness' class. We observed that there is a distinction between subjects with Low and High awareness about the risks of e-cigs, this is observed as the response probability of the 'High Awareness' class is greater than that of the 'Low Awareness' class. Among those who were surveyed, only 55.4% had a high awareness of the risks of e-cigs.

**IMPACT STATEMENT:** Our study shows a significant lack of awareness among young people regarding the risks associated with e-cigarettes.

**INTRODUCTION**

Electronic cigarettes (ECs or e-cigs) deliver nicotine by simulating traditional smoking, without burning tobacco (Electronic Nicotine Delivery Systems - ENDS). They also include pipes, cigars and electronic hookahs, as well as devices that heat tobacco without burning it (Heat-not-burn tobacco products). ECs generally consist of an atomizer that allows the so-called e-liquid to be raised to high temperatures, generating vapor ('vape'), which is then inhaled. The main components of the solution are solvents (propylene glycol, vegetal glycerin), variously associated with water, flavoring agents and nicotine. ECs were introduced to the market in Europe in 2006 and in the United States in 2007. According to data from the Global Youth Tobacco Survey, in Italy the prevalence of EC users in the 11-17 age group more than doubled from 2014 to 2018 (from 9.1% to 18.3%), with 2 times more use in males than females (1, 2). The use of e-cigs has spread widely in recent years as an alternative to traditional smoking, but awareness of the health risks associated with their use varies widely among individuals.

**Doi**

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<sup>1</sup> Department of Pediatrics, Buzzi Children's Hospital, Milan, Italy

<sup>2</sup> Outpatient Clinic of Pediatric Pneumology and Allergology, Unit of Pediatrics, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

<sup>3</sup> Institute of Translational Pharmacology (IFT), National Research Council (CNR), Palermo, Italy

<sup>4</sup> Department of Economics, Business and Statistics (dSEAS), University of Palermo (UNIPA), Palermo, Italy

**KEY WORDS**

*Electronic cigarette (e-cig); awareness; health risks; Electronic Cigarette Attitudes Survey (ECAS); Adolescent E-Cigarette Consequences Questionnaire (AECQ); vaping.*

## OBJECTIVES

The objective of this study was to investigate the knowledge, and the risk perceptions attributed to ECs among adolescents and their parents. Utilizing Latent Class Analysis (LCA), we aimed to identify and categorize distinct classes of individuals based on their awareness of health risks and characteristics of ECs by analyzing responses from an online questionnaire. LCA enables the detection of hidden patterns within the data, allowing for a more refined categorization of risk awareness levels among participants. This methodological approach facilitates a deeper understanding of how different segments of the population perceive the risks associated with ECs, which is crucial for developing targeted public health strategies and interventions. By uncovering these latent classes, the study contributes to the existing literature on ECs risk perception and provides valuable insights for policymakers and health professionals.

## METHODS

From October 2023 to June 2024 an anonymous online questionnaire was administered to patients older than 12 years of age who were referred to the Pediatric Pneumology outpatient clinics of the Unit of Pediatrics at Pisa University Hospital and Buzzi Hospital in Milan, Italy, and their parents. The questionnaire consisted of three sections: i) knowledge about the risks related to ECs, ii) 'Adolescent E-Cigarette Consequences Questionnaire' (AECQ) for expectations about the use of ECs and iii) the 'Electronic Cigarette Attitudes Survey' (ECAS) related to attitude toward ECs.

In this study, LCA was employed to uncover underlying response patterns among individuals regarding health risk awareness and characteristics of e-cig. LCA is a statistical methodology that identifies unobserved subgroups within a population based on responses to observed variables, enabling the classification of respondents into distinct latent classes reflecting varying levels of awareness and perceptions.

The analysis utilized the poLCA package (3) in R statistical software version 4.4. The poLCA package estimates latent class models by maximizing the log-likelihood function with respect to the mixing proportions  $p_r$  and the class-conditional probabilities  $\pi_{jrk}$ . The log-likelihood function is defined as:

$$\ln L = \sum_{i=1}^N \ln \left( \sum_{r=1}^R p_r \prod_{j=1}^J \prod_{k=1}^K (\pi_{jrk})^{Y_{jrk}} \right)$$

Where  $J$  denotes polytomous categorical variables (manifest variables), each containing  $K_j$  possible outcomes for individuals  $i=1, \dots, N$ . The indicator  $Y_{jrk}$  equals 1 if respondent  $i$  selects the  $k$ -th response to the  $j$ -th variable, and 0 otherwise. The class-conditional probability  $\pi_{jrk}$  represents the likelihood that an observation in class  $r=1, \dots, R$  produces the  $k$ -th outcome on the  $j$ -th variable, while  $p_r$  indicates the mixing proportions of the latent classes. The poLCA package leverages the iterative Expectation-Maximization algorithm to estimate the model parameters, allowing for the inclusion of cases with missing observations on the manifest variables. Within this framework, all associations among the included variables are attributed entirely to distinct subpopulations known as latent classes, wherein the variables are assumed to be independent (4).

Variable selection for LCA was performed to identify variables that contribute significant clustering information and to eliminate those that are redundant or uninformative.

LCA estimates two key parameters: the proportion of respondents in each latent class (prior probabilities of class membership) and the response probabilities within each class (item response probabilities). These parameters allow for the updating of prior probabilities into posterior probabilities for each respondent, given their observed response patterns (5). Consequently, respondents were probabilistically ranked and assigned to the most likely latent class.

Data were collected through a comprehensive questionnaire consisting of 83 questions addressing various aspects of e-cigs, including composition, health effects, and risk perception. Multiple LCA models were fitted by varying the number of latent classes ( $K$ ) from one to five. The Bayesian Information Criterion (BIC) was employed to determine the optimal number of classes, with a lower BIC indicating a better model fit (6). For the optimal model, the estimated probabilities of positive responses were examined, and the classes were labeled accordingly.

Each subject's posterior probabilities of class membership were calculated, assigning them to the class with the highest probability. The overall classification accuracy was assessed by averaging the highest

**Table 1.** Distribution of positive responses in the whole sample and by class of membership.

Questions	All simple	All awareness	High awareness	p-value
1. The use of e-cigs can facilitate smoking cessation.	42 (50.6)	21 (63.6)	19 (43.2)	0.107
2. How familiar do you think you are with e-cigs?	54 (65.1)	16 (48.5)	34 (77.3)	0.015
3. Is the e-cigs safe in pregnancy?	47 (56.6)	14 (42.4)	28 (63.6)	0.105
4. Can the substances in e-cigs cause cancer and other disease?	67 (80.7)	25 (75.8)	37 (84.1)	0.396
5. Exposure to secondhand smoke from electronic cigarettes is not dangerous to children.	41 (49.4)	15 (45.5)	23 (52.3)	0.647
6. E-cigs are a device that aerosolizes flavored water, so they are safe: do you agree?	32 (38.6)	11 (33.3)	19 (43.2)	0.480
7. The long-term consequences of direct and passive exposure to e-cig aerosol have not been extensively studied. How much do you agree with this statement?	45 (54.2)	17 (51.5)	24 (54.5)	0.821
8. E-cigs deliver less nicotine than regular cigarettes.	57 (68.7)	20 (60.6)	33 (75.0)	0.218
9. In the long run, using an e-cig is cheaper than buying packs of regular (combustible) cigarettes. How much do you agree with this statement?	43 (51.8)	12 (36.4)	28 (63.6)	0.022
10. E-cig can be purchased by anyone, even children. How much do you agree with this statement?	23 (27.7)	6 (18.2)	15 (34.1)	0.195
11. To protect the health of the people I live with, it is enough to smoke on the terrace or outdoors. How much do you agree with this statement?	25 (30.1)	11(33.3)	14 (31.8)	1.000
12. Are you familiar with tobacco heating devices? (e.g., IQOS)?	34 (41)	1 (3.0)	32 (72.7)	<0.001
13. Can tobacco warming devices (e.g., IQOS) be addictive?	45 (54.2)	0 (0.0)	40 (90.9)	<0.001
14. Tobacco warming devices (e.g., IQOS) can help smokers quit smoking.	35 (42.2)	1 (3.0)	33 (75.0)	<0.001
15. Tobacco heater devices (e.g., IQOS) are less harmful to health than traditional cigarettes.	20 (24.1)	0 (0.0)	20 (45.5)	<0.001
16. Have you ever tried, or would you be willing to try to quit smoking ST and/or EC?	17 (20.5)	8 (24.2)	7 (15.9)	0.396
17. E-cigs help concentration.	34 (41)	11 (33.3)	21 (47.7)	0.247
18. E-cigs are bad for your lungs.	75 (90.4)	26 (78.8)	44 (100.0)	0.002
19. Most popular people smoke e-cigs.	59 (71.1)	24 (72.7)	30 (68.2)	0.802
20. A person has more control over the ingredients of an e-cigs (e.g., nicotine content) than a regular cigarette (fuel).	32 (38.6)	10 (30.3)	21 (47.7)	0.161
21. E-cigs are less harmful than regular (combustible) cigarettes.	28 (33.7)	15 (45.5)	8 (18.2)	0.013
22. The convenience of smoking e-cigs in more places (indoors) than regular (combustible) cigarettes are attractive.	28 (33.7)	14 (42.4)	13 (29.5)	0.335
23. In the long run, using e-cigs is cheaper than buying packs of regular (combustible) cigarettes.	66 (79.5)	30 (90.9)	31 (70.5)	0.045

posterior probabilities across all subjects, known as the assignment probability. Class-specific classification accuracies were also derived as conditional averages of these assignment probabilities, providing insight into the reliability of class assignments. Subjects with an assignment probability of at least 0.90 were considered to be classified with high certainty. Statistical analyses adhered to a significance threshold of  $p \leq 0.05$ .

## RESULTS

Out of a sample of 83 participants with an average age of 27.22 years and 52% male, only 23 of the 83 survey questions were found to correctly identify the two knowledge profiles.

As depicted in **Table 1**, the probability of participants belonging to the 'Low Awareness' class is higher than that of the 'High Awareness' class, indicating a prevalent lack of awareness about the risks associated with e-cigarette use.

**Figure 1** further highlights a distinction between subjects with differing awareness levels; specifically, the response probabilities of the high awareness group (represented by the green class) are lower than those of the low awareness group (represented by the pink class). The survey results revealed that only 55.4% of participants had a high awareness of the risks posed by e-cigarettes.

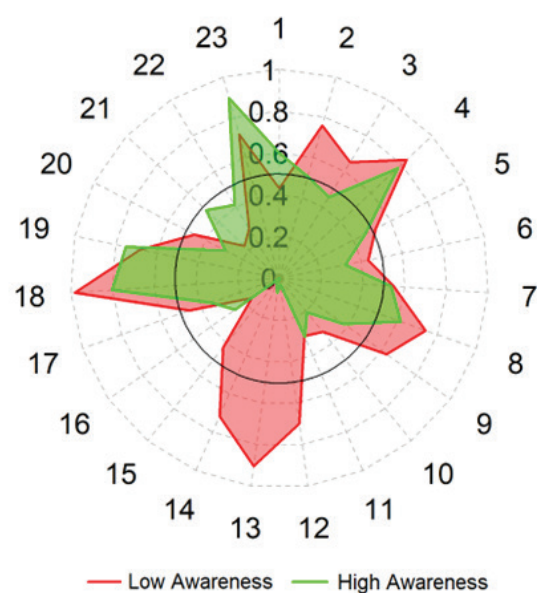
## DISCUSSION

Our findings align with the recorded increase in current e-cigarette users and are consistent with previous studies conducted in other countries, which have also reported low levels of awareness regarding e-cigarette risks in both adolescents and their parents (7, 8). The long-term low awareness may lead to e-cigarette use and later in life to development of respiratory and cardiovascular problems, such as cough, wheeze, asthma and atherosclerosis, and to the increased risk of cancer (9). In addition, nicotine exposure in young age interferes with brain development and predisposes to having other addictions to substances in the future (10). We believe that low awareness among teens can trigger a vicious cycle, whereby teens risk using e-cigarettes, thus setting a bad example in turn for other young people. Through counseling services

offered by pediatricians and primary care physicians, awareness of the risks and dangers of e-cigarette use can be markedly increased (11). In the field of public health, studies such as ours can persuade policymakers to invest more in awareness campaigns targeting the specific needs of young people. Educational interventions, like school-based programs, could help increasing awareness and reducing the prevalence of e-cigarette use in young people (12). One of the limitations of our study is that it studied a selected sample, as it consists of patients and their relatives referred to the outpatient pulmonology and allergology clinic. In fact, this sample is likely to be more sensitized to the issue of smoking due to the disease. Applying the LCA to a larger and more diverse sample may allow to organize a more targeted and detailed awareness campaign.

## CONCLUSIONS

Our study reveals a significant lack of awareness among young people regarding the risks associated with vaping. The rapid proliferation of e-cig use among youth has reached epidemic proportions, thus necessitating immediate action to address this public health concern. Increased education and regulation are urgently needed to mitigate the potential long-term health consequences.



**Figure 1.** Radar chart of the probability of belonging to the latent classes based on the affirmative answer to the question.

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## COMPLIANCE WITH ETHICAL STANDARDS

### Conflict of interests

The Authors have declared no conflict of interests.

### Financial support

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### Author contributions

The Authors confirm contribution to the manuscript as follows. Paper conception and design: GM, DME, RS, BG and BA; data collection: GM, RS, GG, BG and BA; data interpretation: PA, MG, RS, DME and GLS; draft manuscript preparation: GM, RS and PA; critical

revision: LGS, GM and DME. All Authors reviewed the manuscript and approved its final version.

### Ethical approval

#### Human studies and subjects

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

### Data sharing and data accessibility

Material and further inquiries can be directed 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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