Management and Long-Term Outcomes of Persistent Tachypnea of Infancy/ Neuroendocrine Cell Hyperplasia of Infancy

A European Multicenter Retrospective Study

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BACKGROUND: Persistent tachypnea of infancy (PTI), also known as neuroendocrine cell hyperplasia of infancy (NEHI), represents one of the most common childhood interstitial lung diseases. Despite its frequency, standardized management protocol is lacking, and long-term outcome data remain limited.

RESEARCH QUESTION: What treatment is used for patients with PTI/NEHI, how does clinical management vary across European countries, and what are the long-term outcomes in affected patients?

STUDY DESIGN AND METHODS: This was a European multicenter, retrospective, observational study. Clinical characteristics, therapeutic interventions, and long-term follow-up data were collected and analyzed. Treatment strategies were compared among countries that contributed at least 10 patients.

RESULTS: A total of 378 children (63.5% male [240 of 378]) from 73 centers across 17 countries were enrolled, with a median age at diagnosis of 9 months (interquartile range [IQR], 6-13 months). Therapeutic interventions included oxygen supplementation (75.9% [287 of 378]); inhaled bronchodilators, inhaled glucocorticoids, or both (62.4% [236 of 378]); systemic glucocorticoids (37.0% [140 of 378]); and nutritional support (33.8% [128 of 378]). Of the children who received oxygen therapy, 53.6% (154 of 287) were reported to have been weaned off, with a median age at weaning of 24 months (IQR, 16-36 months). Marked variability in treatment practices was observed across participating countries ($P < .05$). Longitudinal data were available for 48.9% of patients (185 of 378) with a median follow-up of 19 months (IQR, 16-57 months). The proportion of symptomatic children declined over time, with the most marked improvement observed at 4 years of age.

Resolution of imaging and pulmonary function abnormalities also was reported; however, a subset of patients continued to demonstrate persistent hypoxemia, crackles, and exercise intolerance, as well as abnormal imaging and pulmonary function test findings into adolescence.

INTERPRETATION: Our results show that significant differences in treatment strategies for PTI/NEHI were observed across European countries, highlighting the need for evidence-based guidelines. Although long-term prognosis generally is favorable, residual symptoms remain in some patients, warranting continued follow-up. CHEST 2026; ■(■):■-■

KEY WORDS: childhood interstitial lung diseases; neuroendocrine cell hyperplasia of infancy; persistent tachypnea of infancy

ABBREVIATIONS: chILD = childhood interstitial lung disease; GERD = gastroesophageal reflux disease; ILD = interstitial lung disease; IQR = interquartile range; LCI = lung clearance index; LUS = lung ultrasound; NEHI = neuroendocrine cell hyperplasia of infancy; PTI = persistent tachypnea of infancy; PNECs = pulmonary neuroendocrine cells.

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Take-Home Points

Research Question: What therapeutic interventions are used in persistent tachypnea of infancy (PTI)/neuroendocrine cell hyperplasia of infancy (NEHI) across Europe, and do these approaches differ among countries? What are the long-term outcomes in affected patients?

Results: Children with a diagnosis of PTI/NEHI most frequently receive oxygen supplementation, inhaled therapies, systemic glucocorticosteroids, and nutritional support. Treatment approaches vary across European countries. Longitudinal follow-up data indicate generally favorable outcomes, although some children continue to experience symptoms into adolescence.

Interpretation: A clear need exists for standardized, evidence-based recommendations to guide the management of PTI/NEHI.

Persistent tachypnea of infancy (PTI), also referred to as neuroendocrine cell hyperplasia of infancy (NEHI), is classified within the spectrum of childhood interstitial lung diseases (chILDs).[1,2] The reported prevalence of PTI/NEHI among cohorts with chILD varies widely, from 1.8% to 52.4%, depending on the population studied.[3-6] Clinical symptoms typically start in early infancy and are characterized by tachypnea, chest retractions, crackles on auscultation, hypoxemia, and failure to thrive.[1,7] Chest CT imaging reveals ground-glass opacities in the middle lobe, lingula, paramediastinal regions, or a combination thereof associated with areas of air trapping.[8] Diagnosis primarily is based on characteristic clinical features and typical CT scan findings, with lung biopsy reserved for atypical cases.[1,9] When performed, lung biopsy typically reveals normal or nearly normal lung parenchyma. Existing reports describe a variable excess in pulmonary neuroendocrine cells (PNECs) in distal bronchioles and alveolar ducts, reaching the diagnostic threshold (PNECs in $> 70\%$ of all bronchioles and $\geq 10\%$ PNECs in ≥ 1 bronchiole) in 36% to 100% of the patients who underwent biopsy.[7,10-12]

Despite being one of the more frequently diagnosed chILD entities, the management of PTI/NEHI lacks standardized guidelines. Supportive care, including supplemental oxygen and nutritional support, is used commonly. In some centers, additional interventions such as inhaled bronchodilators, inhaled or systemic glucocorticoids, long-term macrolide therapy, and hydroxychloroquine are used.[7,13-18] However, none of these treatments have been assessed in randomized controlled trials, and no consensus guidelines currently exist. Evidence from observational studies suggests that oxygen therapy and inhaled bronchodilators, alone or combined with inhaled glucocorticoids, may offer potential benefits in improving clinical outcomes.[16,18]

The overall prognosis of PTI/NEHI is considered favorable compared with other chILD conditions.[19] Although the disease can impact quality of life significantly during infancy and early childhood, most affected children demonstrate gradual clinical improvement over time.[20] To date, there no cases of lung fibrosis, pulmonary hypertension, or mortality have been documented.[2] Nonetheless, some children continue to experience persistent respiratory symptoms and impaired pulmonary function into adolescence.[21,22] Longitudinal outcome data remain scarce because existing studies include a limited number of patients and have relatively short follow-up periods.[13,14,20,23] In this multicenter European study, we aimed to analyze treatment strategies, to compare clinical management approaches across participating countries for PTI/NEHI, and to assess the long-term outcomes among the affected children.

Study Design and Methods

Study Design and Data Collection

This was a multicenter, international, retrospective, observational study of patients with PTI/NEHI. Members of the European Respiratory Society Clinical Research Collaboration chILD-EU from 32 European countries who care for patients with chILDs were invited to contribute eligible individuals. Data were obtained from 2 sources: prospectively collected data in the web-based chILD-EU Registry (www.childeu.net) and datasheets completed by centers not using the registry.[24] The datasheet included demographic and clinical characteristics, details of the diagnostic approach (previously described),[9] treatment methods, and follow-up outcomes. Follow-up data were recorded at predefined time points ($\pm$ 3 months): 18 months and 2, 4, 6, 10, 14, and 18 years of age, with more frequent assessments during early childhood, when symptoms typically are most pronounced, and less frequent evaluations at older ages. Follow-up visits included

evaluation of clinical symptoms and results of CT imaging, lung ultrasound (LUS), and pulmonary function testing, if performed. Data were obtained from January 1, 2023, through December 31, 2023.

All data were collected anonymously. The Bioethics Committee of the Medical University of Warsaw, Poland, approved the study (Identifier: AKBE/91/2021). All participants included in the study via the chILD-EU Register consented therein, and the data merge was approved by the central ethics committee in Munich, Germany (Identifier: EK23-0962).

Study Population

Children with PTI/NEHI were included. Diagnosis was made at participating centers within a multidisciplinary evaluation in accordance with American Thoracic Society clinical practice guidelines, based on characteristic clinical features (persistent tachypnea, retractions, hypoxemia [oxygen saturation $<$ 92%], crackles, or a combination thereof) along with typical findings on chest CT imaging, which include the presence of ground-glass opacities in the middle lobe, lingula, or paramediastinal regions or a combination thereof.[7,25,26] Patients were eligible regardless of the time elapsed since diagnosis. Exclusion criteria included incomplete data on demographic and clinical characteristics, diagnostic procedures, or treatment methods (defined as $<$ 80% of required variables), as well as identification of a genetic variant indicative of an alternative diagnosis. For the longitudinal assessment, children with at least 1 predefined follow-up visit containing $\geq$ 80% of the required variables were included.

Variables

The definition of failure to thrive was based on BMI or weight below the fifth percentile on the World Health Organization centile charts. Based on the collected data, the NEHI clinical score proposed by Liptzin et al[27] was evaluated. Follow-up chest CT images were compared with baseline images and were categorized as follows: partial resolution (any reduction in ground-glass opacities), complete resolution (normal imaging findings), or progression (any increase in ground-glass opacities). LUS findings were classified as abnormal if $\geq$ 3 B-line artifacts per intercostal space were observed in conjunction with an irregular pleural line during longitudinal scanning. LUS findings were considered normal when $<$ 3 B-lines were present and no additional abnormalities were identified.

Pulmonary function testing results were interpreted using established reference standards.[28-30] Abnormal spirometry was defined as a z score of $<$ –1.645 for at least 1 of the following parameters: FVC, FEV_1, or FEV_1 to FVC ratio. In body plethysmography, abnormal findings included a z score of $<$ –1.645 for total lung capacity or a z score of $>$ 1.645 for specific airway resistance or the residual volume to total lung capacity ratio. Impulse oscillometry was considered abnormal if at least 1 of the following criteria was met: z score of $>$ 1.645 for resistance at 5 Hz, z score of $>$ 1.645 for resonant frequency, or z score of $<$ –1.645 for reactance at 5 Hz. The Lung Clearance Index (LCI), measured using nitrogen multiple-breath washout testing, was considered abnormal when values exceeded the upper limit of normal.[31] Diffusion capacity of the lungs for carbon monoxide was considered abnormal when the z score value was outside the range of $\pm$ 1.65.[32]

Statistical Analysis

Continuous variables were summarized as medians with interquartile ranges (IQRs), whereas categorical variables were presented as frequencies and percentages. Temporal trends in systemic glucocorticoid use were assessed using the Cochran-Armitage test. Comparisons between countries were performed using the Fisher exact test because of small sample sizes. All analyses were conducted using GraphPad Prism version 10.2.2 software (GraphPad Software), with a 2-tailed P value of $<$ .05 considered statistically significant.

Results

Of the 397 patients with PTI/NEHI initially included in the study, clinical and treatment data were available for and analyzed in 378 individuals (representing 17 countries and 73 centers). Eighteen patients (4.5% [18 of 397]) were excluded because of incomplete data, and 1 patient was excluded after identification of a pathogenic *NKX2-1* variant (Fig 1).

Baseline demographic characteristics refer to the entire cohort of 378 patients; however, percentages were calculated based on the available data for each variable. Most patients were male (63.5% [240 of 378]), White (97.4% [340 of 352]), and born at term (90.3% [335 of 352]) with no significant perinatal complications. The median age at diagnosis was 9 months (IQR, 6-13 months). A total of 121 children (32.0% [121 of 378]) received a

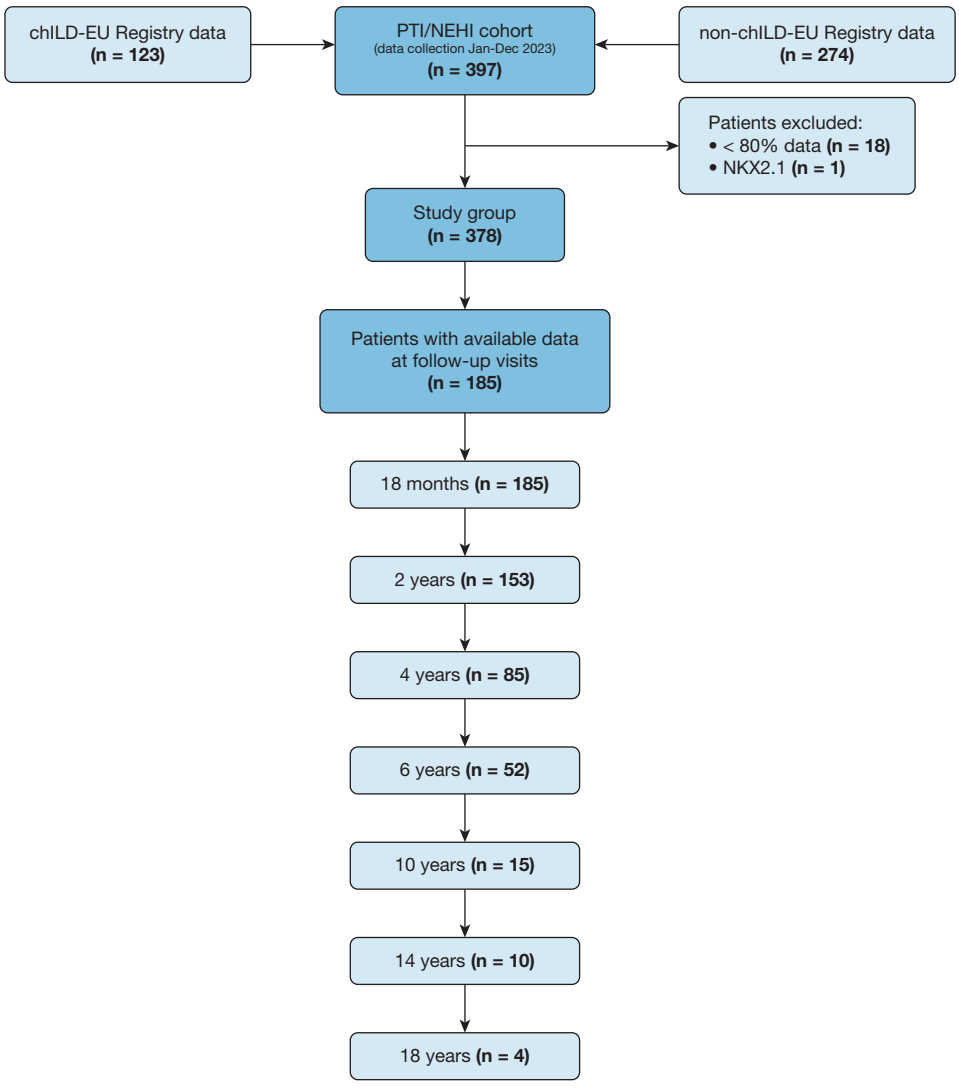

Figure 1 – *Study flowchart. chILD = childhood interstitial lung disease; NEHI = neuroendocrine cell hyperplasia of infancy; PTI = persistent tachypnea of infancy.*

diagnosis after 2020, 146 children (38.6% [146 of 378]) between 2015 and 2020, 72 children (19.0% [72 of 378]) between 2010 and 2014, and 39 children (10.3% [39 of 378]) between 2005 and 2009. Tachypnea (97.1% [367 of 378]), chest retractions (94.1% [348 of 370]), crackles (78.6% [291 of 370]), hypoxemia (75.9% [287 of 378]), and failure to thrive (45.9% [170 of 370]) were the most frequent baseline symptoms. Of the patients for whom the baseline NEHI clinical score could be calculated (with data available for all 10 components), most children (86.5% [193 of 223]) scored ≥ 7 points. The diagnostic evaluation and clinical findings of this cohort have been described previously.[9]

Ten treatment methods were administered within the study cohort and are summarized in Table 1. Oxygen supplementation was implemented in 287 patients (75.9% [287 of 378]). The median age at initiation was 6 months (IQR, 4-10 months). Of these patients, 154 children (53.7% [154 of 287]) were reported to have been weaned off, with a median age at weaning of 24 months (IQR, 16-36 months). The median duration of supplemental oxygen was 7 months (IQR, 7-30.5 months). One hundred forty children (37.0% [140 of 378]) were treated with systemic glucocorticoids, with a median age at treatment initiation of 9 months (IQR, 5-20 months). The median number of methylprednisolone pulses was 5 (IQR, 3-8.5 pulses), and the median duration of oral glucocorticoid therapy was 8 weeks (IQR, 4-40 weeks). A significant decreasing trend in systemic glucocorticoid use was observed across diagnosis periods ($z = -5.14$; $P < .001$).

TABLE 1] Treatment Ever Implemented in the Study Group (N = 378)

Treatment	No. (%)
Oxygen supplementation (hypoxemia < 92%)	287 (75.9)
At rest (daytime)	23 (6.1)
With sleep	250 (66.1)
During respiratory tract infections	14 (3.7)
Nutritional support	128 (33.8)
High-calorie diet	61 (16.1)
Gastrostomy	16 (4.2)
Nasogastric tube	13 (3.4)
Not specified	38 (10.1)
Inhaled treatment	236 (62.4)
Inhaled bronchodilators and inhaled glucocorticoids	188 (49.7)
Inhaled glucocorticoids	27 (7.1)
Inhaled bronchodilators	21 (5.6)
Systemic glucocorticoids	140 (37.0)
Methylprednisolone pulses[a]	66 (17.5)
Oral glucocorticoids	51 (13.5)
Oral glucocorticoids and methylprednisolone pulses	23 (6.0)
Long-term macrolide	75 (19.8)
GERD treatment	49 (12.9)
Hydroxychloroquine	29 (7.6)
Montelukast	14 (3.7)
IVIG	7 (1.8)
Immunosuppression[b]	7 (1.8)

Data are presented as No. (%) of patients with available data. GERD = gastroesophageal reflux disease; IVIG = IV immunoglobulin.
[a]Monthly 10-30 mg/kg for 3 days.
[b]Azathioprine, mycophenolate mofetil, cyclophosphamide, and methotrexate.

As shown in Figure 2, most children received between 1 and 3 therapeutic interventions, with a median of 2 interventions (IQR, 2-3 interventions). Significant differences were observed in the proportion of patients receiving therapies across countries (Fig 3). The highest median numbers of interventions per patient were recorded in France (median, 4 interventions [IQR, 3-5 interventions]) and Turkey (median, 3.5 interventions [IQR, 1.75-4.5 interventions]).

Follow-Up

Longitudinal follow-up data were available for 185 children (48.9% [185 of 378]) who had at least 1 predefined follow-up assessment (Fig 1). The number of patients declined across subsequent follow-up visits. The median follow-up duration was 19 months (IQR, 16-57 months). The proportion of children with symptoms declined over time, with the most marked improvement observed at 4 years of age (Fig 4). Nevertheless, abnormal findings persisted at later assessments, including both symptoms and imaging abnormalities. Among those who underwent pulmonary function tests, approximately one-third demonstrated abnormal spirometry results at 4 and 6 years of age, and nearly all showed abnormalities on body plethysmography at 6 years of age. These abnormalities gradually resolved during follow-up (Table 2). At the age of 4 years, 26 children underwent impulse oscillometry, with most demonstrating abnormal resonant frequency values (21 of 26 [80.7%]). Similar to spirometry and body plethysmography findings, these abnormalities tended to normalize over time. All 10 children in whom LCI was measured at 6 years of age showed abnormal results. Although abnormalities persisted during follow-up, LCI was assessed in only a few patients at later visits. At the age of 14 years, diffusion capacity of the lungs for carbon monoxide was evaluated in 5 patients; 3 patients showed abnormally elevated values, and 2 patients showed results within the normal range.

Discussion

This study revealed considerable heterogeneity in treatment strategies for patients with PTI/NEHI across European countries. Supportive measures (including oxygen supplementation and nutritional support), inhaled medications, and systemic glucocorticoids were the most commonly used interventions. Although longitudinal follow-up generally demonstrated favorable clinical outcomes, a proportion of patients continued to experience persistent PTI/NEHI-related symptoms into adolescence.

Given the absence of standardized management protocols for PTI/NEHI, clinical decisions primarily rely on general interstitial lung disease (ILD) guidelines and local clinical experience. Hypoxemia is a common clinical feature of PTI/NEHI, with desaturation episodes occurring predominantly during sleep, as shown in our study. In line with recommendations from the British Thoracic Society and the American Thoracic Society, supplemental oxygen should be provided in children with ILD to maintain oxygen saturation of ≥ 93%.[33,34] Ongoing monitoring, including nocturnal oximetry, is essential to adjust therapy and reduce the risk of complications associated with chronic hypoxemia.[16,33]

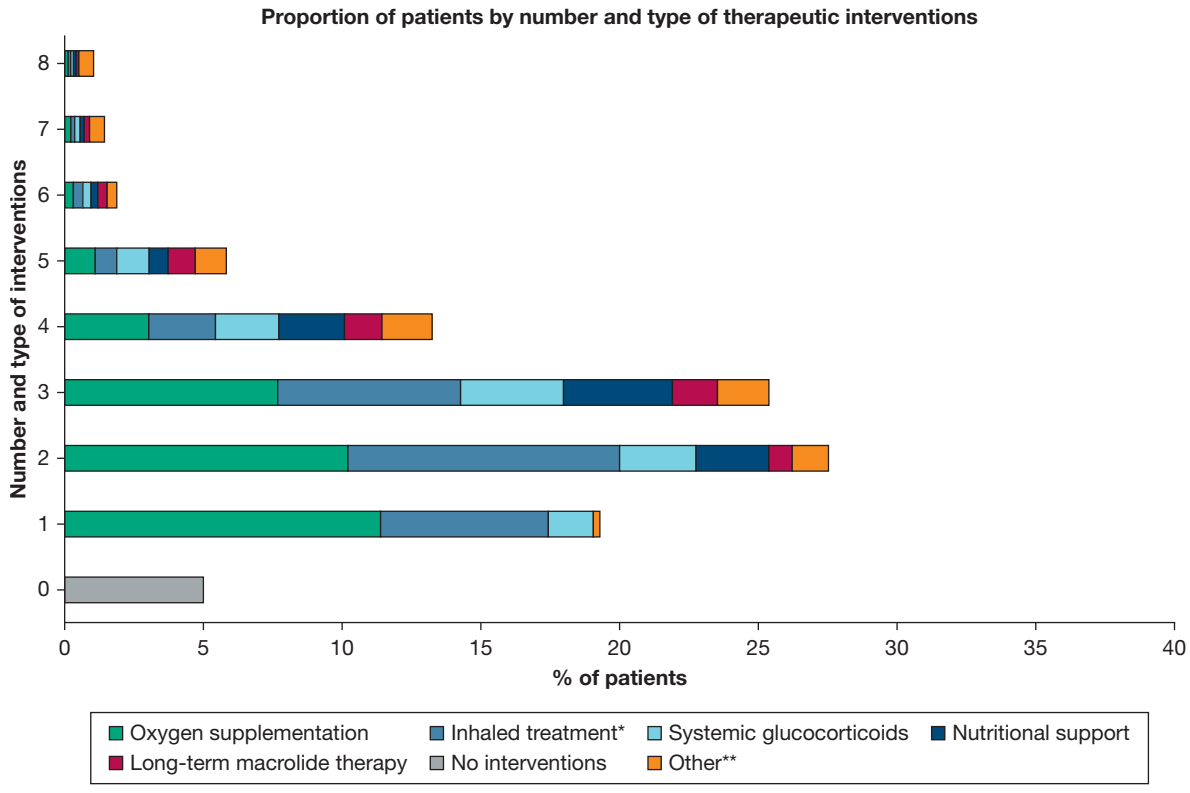

Figure 2 – *Bar graph showing the proportion of patients by number of therapeutic interventions, stratified by intervention type (no. 378).* [a]*Inhaled bronchodilators, inhaled glucocorticoids, or both.* [b]*Gastroesophageal reflux disease treatment, IV immunoglobulin, hydroxychloroquine, montelukast, or immunosuppression.*

In the present cohort, the median age at initiation of home oxygen therapy was 6 months, which is consistent with previous reports.[7,14-16] Oxygen was introduced when desaturation episodes were documented. Most children required oxygen supplementation during sleep, whereas only a few were dependent on oxygen throughout the day. At the time of data collection, approximately one-half of the cohort had been weaned from oxygen, with a median age of 24 months, consistent with findings from Gomes et al[14] and Balinotti et al.[15] Variation in the proportion of patients receiving oxygen therapy across countries likely reflected differences in the prevalence of hypoxemia, rather than disparities in clinical practice, because

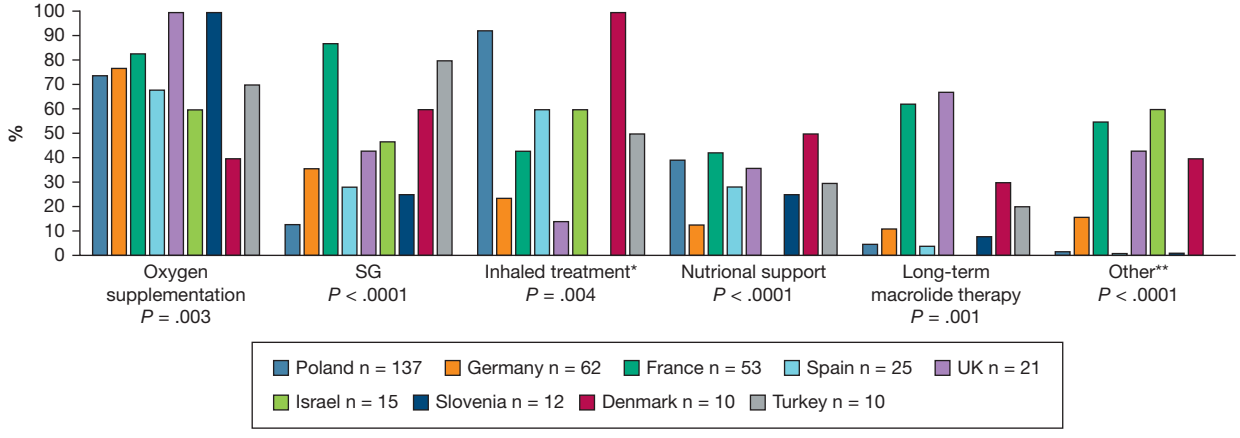

Figure 3 – *Bar graph showing a comparison of the most commonly used interventions among countries. The Fisher exact test was used for comparisons between countries; for all presented interventions, the differences were statistically significant (P < .05). SG = systemic glucocorticoids.* [a]*Inhaled bronchodilators, inhaled glucocorticoids, or both.* [b]*Gastroesophageal reflux disease treatment, IV immunoglobulin, hydroxychloroquine, montelukast, or immunosuppression.*

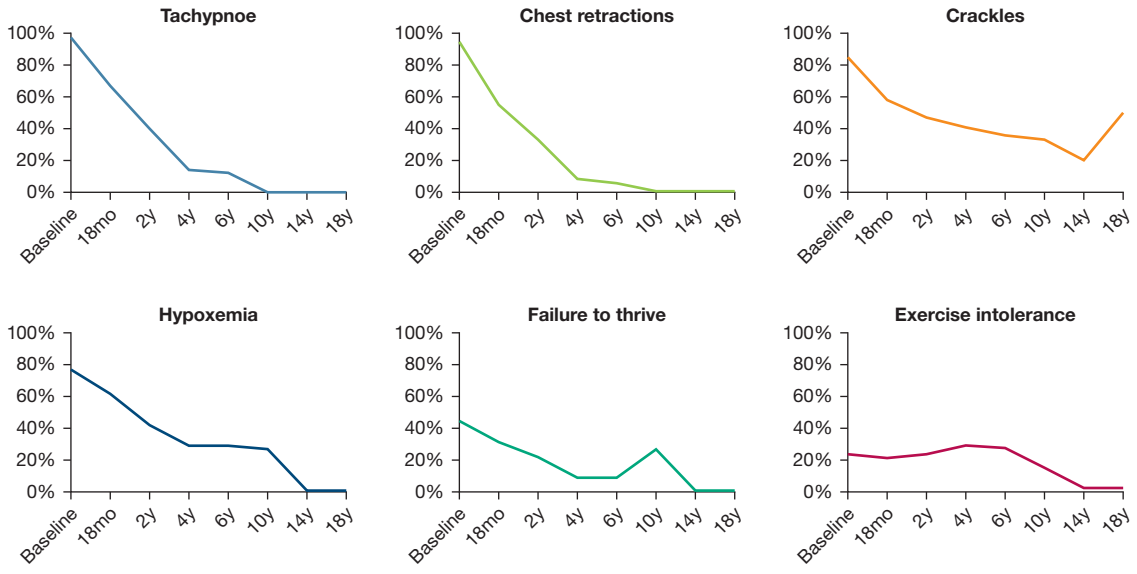

Figure 4 – *Line graphs showing the proportion of children with symptoms at baseline and at 7 follow-up visits.*

supplemental oxygen was administered uniformly when hypoxemia was identified.[9]

Nutritional support is essential in managing PTI/NEHI because of the elevated metabolic demand resulting from increased work of breathing and chronic respiratory distress.[35] In the entire cohort, 170 children had a diagnosis of failure to thrive at baseline; however, only 128 children received nutritional interventions. The frequency and type of support varied across countries. Most patients were managed with high-calorie diet, whereas a subset required enteral feeding via a nasogastric tube or gastrostomy. Because fewer children received nutritional support than were identified as experiencing failure to thrive, these findings suggest a potential underuse of dietary interventions. Adequate nutrition has been shown to have a positive influence on pulmonary function in other chronic lung diseases such as cystic fibrosis.[36] In PTI/NEHI, oxygen supplementation may reduce overall caloric requirements by decreasing the work of breathing, thereby supporting improved growth. Importantly, malnutrition may be associated with prolonged oxygen dependence.[16,37] Because malnutrition often develops during the early phase of the disease, when growth and neurodevelopment are most vulnerable, these findings underscore the importance of systematic nutritional assessment and timely intervention as integral components of comprehensive PTI/NEHI care.[35,37]

Inhaled therapies may play a role in the management of patients with PTI/NEHI. In a prospective observational study involving 31 patients, treatment with inhaled bronchodilators combined with inhaled glucocorticoids resulted in a significant reduction in tachypnea, chest retractions, and crackles, as well as improvement in pulmonary function test results. Although the study was nonrandomized and lacked a control group, the findings suggest a potential therapeutic benefit of inhaled agents.[18] In the present cohort, inhaled therapies were the most commonly used intervention after oxygen supplementation. Their use was almost universal in certain countries, such as Poland and Denmark, whereas it was not used at all in others, such as Slovenia. A survey-based study conducted in the United States reported frequent use of inhaled therapies in PTI/NEHI, with 60% of 40 patients receiving inhaled bronchodilators and 38% of patients treated with inhaled glucocorticoids.[16] The rationale for using bronchodilators in PTI/NEHI may be related to reports describing an increase in the number of pulmonary neuroendocrine cells in some patients, because these cells secrete vasoactive and bronchoactive mediators.[10]

Systemic glucocorticoids also were administered commonly; their use varied considerably among countries, ranging from 0% to 87% of patients (Fig 2). This practice likely reflects the general ILD treatment protocols recommended by both European and North American societies, which advocate for a trial of systemic corticosteroids in most patients with chILD.[26,38] The rationale for corticosteroid use in PTI/NEHI may be based on isolated reports describing airway inflammation in affected patients.[39,40] However,

TABLE 2] Symptoms and Results of Diagnostic Tests of the Follow-Up Group at Baseline and at 7 Follow-Up Time Points

Visit	Follow-Up Group Baseline	18 Mo	2 Y	4 Y	6 Y	10 Y	14 Y	18 Y
Symptoms								
No.	185	185	153	85	52	15	10	4
Tachypnoea	180 (97)	125 (67)	62 (40)	12 (14)	7 (13)	0	0	0
Retractions	174 (94)	101 (55)	50 (33)	8 (9)	3 (6)	0	0	0
Crackles	157 (85)	107 (58)	72 (47)	35 (41)	19 (36)	5 (33)	2 (20)	2 (50)
Hypoxemia	141 (76)	113 (61)	64 (42)	25 (29)	15 (29)	4 (27)	0	0
Failure to thrive[a]	83 (45)	57 (31)	33 (22)	8 (9)	4 (8)	4 (27)	0	0
Exercise intolerance[b]	41 (22)	35 (19)	34 (22)	23 (27)	13 (25)	2 (13)	0	0
Mean no. of symptoms (per patient)	4.2	2.9	2.0	1.3	1.2	1	0.2	0.5
Chest CT imaging								
No.		11	12	8	10	4	2	0
Similar		4 (36)	3 (25)	0	2 (20)	0	1 (50)	0
Partial resolution		7 (64)	6 (50)	4 (50)	4 (40)	3 (75)	0	0
Complete resolution		0	1 (8)	4 (50)	4 (40)	1 (25)	1 (50)	0
Progression		0	2 (17)	0	0	0	0	0
Lung ultrasound								
No.		48	46	24	14	3	2	2
Normal findings		3 (6)	6 (13)	2 (8)	3 (21)	0	0	1 (50)
Abnormal findings		45 (94)	40 (87)	22 (92)	11 (79)	3 (100)	2 (100)	1 (50)
Spirometry								
No.		0	0	23	39	15	8	4
Normal findings		0	0	15 (65)	27 (69)	14 (93)	8 (100)	4 (100)
↓ FVC		0	0	8 (35)	10 (26)	1 (7)	0	0
↓ FEV_1		0	0	6 (26)	10 (26)	2 (5)	0	0
↓ FVC to FEV_1 ratio		0	0	0	2 (5)	0	0	0
Body plethysmography								
No.		0	0	0	6	6	6	4
Normal findings		0	0	0	1 (17)	3 (50)	6 (100)	4 (100)
↑sRaw		0	0	0	5 (83)	3 (50)	0	0
↑RV to TLC ratio		0	0	0	5 (83)	1 (17)	0	0
↓TLC		0	0	0	0	0	0	0

Data are presented as No. or No. (%). RV = residual volume; sRaw = specific airway resistance; TLC = total lung capacity; ↑ = > 1.645 *z* score; ↓ = < −1.645 *z* score.

[a]Weight, BMI, or both less than 5th percentile on World Health Organization growth charts.

[b]Reported by parents or patient.

these findings are inconsistent, because other studies have not demonstrated significant inflammatory changes.[41,42] In the present cohort, the high frequency of systemic glucocorticoid use may reflect in part the inclusion of children who received a diagnosis in the early 2000s. Systemic glucocorticoids were administered more often to children who received a diagnosis in the early 2000s. Over the past 2 decades, growing

knowledge of the disease has influenced treatment practices, leading to a decline in systemic steroid use.[2,7] Given the young age at which PTI/NEHI typically is diagnosed, the potential adverse effects of prolonged systemic steroid use are of particular concern.[43,44] Moreover, the clinical benefit of systemic glucocorticoids remains unproven.[13,14,25] Berteloot et al[45] even suggested that a marked clinical response to steroids might indicate an alternative or coexisting diagnosis. In the absence of strong evidence supporting their efficacy in PTI/NEHI, and considering the potential for significant side effects, the use of systemic glucocorticoids remains controversial. To evaluate the usefulness of systemic corticosteroids in PTI/NEHI, a prospective clinical trial (Efficacy of Methylprednisolone Pulses in Neuroendocrine Celles Hyperplasia of Infancy: An Early Phase Study [CoritcoNEHI])[46] is currently underway in France.

Other pharmacologic therapies, including long-term macrolides, hydroxychloroquine, and immunosuppressive agents, also were reported, albeit infrequently and with significant variation among participating countries. No evidence is available to suggest that any of these treatments are effective in PTI/NEHI; their use likely reflects extrapolation from therapeutic approaches used in other forms of ILD.[47] These practices further highlight the urgent need for evidence-based, disease-specific guidelines to inform the management of this rare condition.

Gastroesophageal reflux disease (GERD) is a common comorbidity in patients with PTI/NEHI, with reported prevalence ranging from 28% to 51%.[27,48] In a survey-based study by Nevel et al,[16] approximately one-third of patients received treatment for GERD. In the present cohort, GERD treatment was administered in 13% of patients. Given the established association between GERD and worsening symptoms in ILD, this comorbidity warrants further investigation.[49] Prospective, controlled studies are needed to characterize better its role in PTI/NEHI.

Follow-Up

Currently, no universally accepted protocols exist regarding the recommended frequency of follow-up visits or the types of routine testing in PTI/NEHI. Since the initial description of the disease > 2 decades ago, longitudinal observation of an increasing number of patients has become possible.[7] Clinical symptom monitoring remains the cornerstone of follow-up. Although most children with PTI/NEHI exhibit gradual clinical improvement over time, the disease course can vary. In the present cohort, tachypnea and chest retractions typically resolved by school age; however, a subset of patients demonstrated persistent features such as crackles, oxygen desaturation, or failure to thrive into adolescence. These findings are consistent with previous reports: Lukkarinen et al[13] described symptoms persisting to 5 years, whereas Gomes et al[14] noted continued improvement beyond 2 years of age, with chest retractions and hyperinflation present beyond 8 years of age. Popler et al[50] further documented exertional dyspnea persisting into adulthood. The cause and pathophysiologic characteristics of PTI/NEHI remain poorly understood. Therefore, it is unclear whether persistent symptoms reflect a more severe disease phenotype, arise from coexisting comorbidities that prolong the clinical course, or instead represent distinct, still-unidentified disease processes. These observations underscore the need for ongoing clinical monitoring beyond early childhood and highlight an important area for future research.

In addition to symptom monitoring, pulmonary function testing may play a valuable role in the long-term follow-up of PTI/NEHI. These tests are noninvasive, reproducible, and, particularly in the case of impulse oscillometry, feasible even in young children. Characteristic findings in PTI/NEHI include peripheral airway obstruction and air trapping.[17,21,51] Our data confirm similar functional abnormalities, most of which tended to improve over time. However, LCI remained abnormal in some patients despite resolution of clinical symptoms, suggesting persistent subclinical small airways involvement. LCI may offer greater sensitivity than spirometry for detecting residual disease.[52,53] When used in combination, LCI and spirometry provide a practical, noninvasive strategy for longitudinal monitoring in children with PTI/NEHI.

Given concerns about radiation exposure, routine follow-up imaging with chest CT imaging is not recommended and should be reserved for patients with clinical deterioration or persistent symptoms. As a result, longitudinal radiologic data remain limited, and the decision to obtain further imaging typically is based on clinical indications, rather than standardized protocols. In the present cohort, follow-up chest CT scans were performed in only a minority of patients. Notably, despite overall clinical improvement, persistent radiologic abnormalities were observed in some individuals. Similarly, LUS abnormalities were identified in adolescents. Because LUS findings may

correlate with CT scan-based severity, it is reasonable to assume that radiologic changes might have been present in patients who did not undergo follow-up CT imaging.[54] These observations suggest that LUS may serve as a valuable, noninvasive tool for longitudinal monitoring of disease activity in PTI/NEHI.

Study Limitations

This study has several limitations. First, patient enrolment was based on voluntary clinician participation, resulting in disproportionate representation across countries and creating potential for selection bias. The uneven geographic distribution of patients also may reflect underlying influences such as ethnicity, genetic background, or local environmental exposures, although these factors remain uncertain. Second, because of its retrospective design, some clinical data were incomplete. Longitudinal follow-up was not available for all patients at the predefined time points, primarily because of young patient age or loss to follow-up. Consequently, it is not possible to determine whether patients who were lost to follow-up became asymptomatic or if the information is simply missing. This limitation affects our ability to characterize long-term outcomes fully. In addition, parameters were not assessed continuously, but rather only during scheduled follow-up visits, resulting in further gaps in the data set. Third, because of the observational design, treatment decisions were not standardized and reflect local practices, so these data should not be interpreted as evidence of efficacy or as uniform recommendations. Finally, follow-up CT scans were evaluated by radiologists at the participating centers, and possible variability in radiologic interpretation across sites represents an additional limitation.

Despite these limitations, this study presents the most comprehensive analysis of treatment strategies in the largest cohort with PTI/NEHI reported to date. It also provides the most robust longitudinal clinical data set available in the literature.

Interpretation

Management of PTI/NEHI varies considerably across Europe, highlighting the lack of standardized, evidence-based protocols for this rare condition. Supportive measures and inhaled therapies remain the most commonly used interventions. Systemic glucocorticoid therapy also is relatively frequent; however, its use declined over time. Although most children demonstrate gradual clinical improvement, a subset experience persistent respiratory symptoms, growth impairment, or functional abnormalities that extend into adolescence or beyond. These findings underscore the importance of long-term follow-up. Pulmonary function tests and LUS may provide useful, noninvasive methods for longitudinal assessment in these patients. Despite broad collaboration within the European network, not all centers were able to contribute patients, reflecting the inherent challenges of conducting research in rare diseases. Overall, our report underscores the need for well-designed studies to establish standardized management protocols for PTI/NEHI.

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