M. Iashvili Children's Central Hospital

Childhood Interstitial Lung diseases -

News and Emerging Treatments

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Childhood interstitial lung diseases (chILD) Is a large, heterogeneous group of rare disorders with significant morbidity and mortality.

ChILDs comprises more than 200 different conditions.

ChILDs are characterized by:

- Dyspnea and hypoxemia,
- Impaired gas exchange,
- Restrictive lung physiology,
- Diffuse lung parenchymal markings on chest imaging.

Disease can be presented in neonatal period, during childhood, or adolescence.

Diagnostic workup of childhood interstitial lung disease Nadia Nathan et al/ ERS CRC chILD-EU group European Respiratory Review 2023 32: 220188;

The term “interstitial” doesn‘t completely reflect the essence of disease.

Interstitial Lung Disease in Children Younger Than
2 Years/ P Spagnolo, A. Bush/Pediatrics . 2016 Jun;137(6)

Abnormalities are not limited to the lung interstation.

But comprises also alveoli, airways, lymphatic channels, pleura, blood vessels.

So, Terms - “Interstitial lung disease” and “Diffuse lung disease”- are synonyms.

Griese M, Seidl E, Bush A, tet al/ International management platform
for children’s interstitial lung disease (chILD-EU). Thorax. 2018;73(3):231–9.

A global prevalence of chILD is 1.6–46 case per million.

Torrent-Vernetta A, et al/ChILD-Spain Group. Arch Bronconeumol. 2022;58(1):22–9.

Interstitial lung disease (ILD) in children is approximately ten times rarer, 100 times less studied and published than adult ILD.

Griese M./ Eur Respir Rev. 2018;27(147):170100

The term ***chILD syndrome*** is used to case, suspected ILD, based on clinical and radiologic features. But a specific cause has not yet been established.

European Respiratory Review 2022 31: 210251P

Spagnolo, A. Bush Pediatrics 2016, vol.137 2016

Pathophysiology

Most ILDs share a common pathophysiologic feature:

- Persistent inflammation,
- Structural remodeling of the distal airspaces,
- Impaired gas exchange.
- At the same time healing processes of damaged tissue take place.

Fibroblasts play key role in lung remodeling by:

- Proliferation of fibroblasts, development of collagenous fibrosis,
- Blocked airways, collapsed alveoli, physiologic dysfunction.

Medscape Rebekah J Nevel, 2020
Selman M, et al Ann Intern Med. 2001 Jan 16. 134(2)

The classification system specifically for pediatrics:

- ✓ 0 to 2 years age - unique to infants and children;
- ✓ 2 to 16 years age - some forms of ILD are similar in children and adults.

Forms of chILD:

- ✓ Pulmonary-specific processes,
- ✓ Forms in association with a systemic disorder.

P Spagnolo, A Bush PEDIATRICS. 2016, vol.137 / European Respiratory Journal. 2016, 48

Interstitial lung disease in infancy and early childhood: a clinicopathological primer European Respiratory Review 31(163):210251 March 2022

The classification of chILD as proposed by the chILD-EU network Griese M, Irnstetter A, Hengst M, et al.

Categorizing diffuse parenchymal lung disease in children. Orphanet J Rare Dis 2015; 10

TABLE 1 Classification of children's interstitial lung disease (chILD) (modified after [3, 7])

ILD: more prevalent in infancy	
A1: diffuse development disorders	Acinar dysplasia Alveolocapillary dysplasia misalignment of pulmonary Congenital alveolar dyspl
A2: growth abnormalities	Alveolar simplification Chronic neonatal lung dise Bronchopulmonary dyspl Chromosomal alteratio
A3: specific entities of undefined aetiology	Pulmonary interstitial glycog Neuroendocrine hyperplasia o
A4: Surfactant dysfunction mutations and related disorders	Pulmonary alveolar protei Chronic pneumonitis of in Desquamative interstitial pne Nonspecific interstitial pneu
Ax: unclear respiratory distress syndrome in the mature neonate	
Ay: unclear respiratory distress syndrome in the almost mature neonate (30–36 weeks)	
ILD: not specific to infancy and childhood	
B1: ILD related to systemic disease processes	Storage disease Langerhans cell histiocyt Endogenous lipid pneum Immune-related disorde
B2: ILD of the normal host and due to exposures	Hypersensitivity pneumon Infection Aspiration pneumonia Eosinophilic bronchiolit
B3: ILD of the immunocompromised host	Infection Obliterative bronchiolitis/res allograft syndrome
B4: ILD with structural vascular changes	Pulmonary hypertensio Pulmonary veno-occlusive d

Lung developmental diffuse abnormalities, represent as **“typical” chILD and with bad prognosis are:**

- lung hypoplasia,

- chronic lung disease of prematurity (BPD).

Koucký V, Pohunek P, Vašáková M, Bush A. ERJ Open Res. 2021;7(2):00964–2020.

✓ **ILD related to the surfactant abnormalities:**

- surfactant genes mutations (SFTPB, SFTPC, ABCA3 and NKX2-1);

- pulmonary alveolar proteinosis genes (CSF2RA and CSF2RB);

Singh J, Jaffe A et al/ Eur J Pediatr. 2021;180(9):2711–21.

✓ Diseases with a better prognosis - neuroendocrine cell hyperplasia of infancy (persistent tachypnea of infancy).

Dervaux M, Thumerelle C, et al /Eur J Pediatr. 2023;182(2):949–56.

Recently ***classification system combining pediatric and adult lung ILDs was proposed***.

The system contains four main categories, almost similar to previous disorders:

1. lung-only (native parenchymal) disorders,
2. Systemic disease-related disorders,
3. Exposure-related disorders,
4. Vascular disorders.

Paediatr Drugs. 2024; 26(1): 19–30/Emerging Treatments of Childhood Interstitial Lung Disease/Bernardinello N, Griese M, Borie R, Paolo Spagnolo

Clinical manifestation

Varies by age.

There are two main clinical scenarios of chILD:

- ✓ Dramatic and progressive respiratory failure in the perinatal period,
- ✓ A slowly progressive disease.

- ✓ Clinical presentation - nonspecific, contributing to a poor recognition, delayed diagnosis.

It lead to significant remodeling of the lung and poor prognosis.

European Respiratory Review 2022 31: 210251

Clinical manifestations

In neonates, preterm and full term children:

- ✓ Persistent respiratory symptoms and signs - retractions, tachypnea, wheezing;

  Failure to thrive, pectus excavatum.

- ✓ An infant with an acute viral respiratory infection and more severe morbidity than would be expected.

- ✓ Prolonged respiratory-syncytial viral bronchiolitis.

- ✓ Other manifestations: hemoptysis, pulmonary hypertension.

Diagnostic workup of childhood interstitial lung disease Nadia Nathan et al/
ERS CRC chILD-EU group European Respiratory Review 2023 32: 220188

Extrapulmonary manifestations — particularly in older children

These include:

- Skin, eye, and nail findings,
- Anemia or pancytopenia,
- lymphadenopathy,
- Arthritis,
- Hepatosplenomegaly or splenomegaly.

The diagnosis should be suspected:

At least three of the following four conditions, for more than 4 weeks:

- ✓ Exercise intolerance, failure to thrive;
- ✓ Respiratory symptoms and signs: dyspnea, tachypnea, dry cough, crackles;
- ✓ Respiratory insufficiency - hypoxia/low oxygen saturation;
- ✓ Diffuse parenchymal lung abnormalities on chest imagens.

Nathan N, Griese M, et al/ERS CRC chILD-EU group/Diagnostic workup of childhood interstitial lung disease/Eur Respir Rev.2023;32(167).

The diagnostic investigation includes:

✓ Non-invasive tests:

- Chest imaging – radiography and computed tomography,
- Pulmonary function tests,
- Assessment of ventilation and oxygenation,

✓ Invasive procedures:

- Bronchoscopy, bronchoalveolar lavage;
- Lung biopsy.

✓ Genetic testing - improves diagnostic accuracy,

- Reduces the need for invasive diagnostic modalities.

Chest X-Ray

Shows hyperinflation, a fine to a coarse interstitial and alveolar pattern.

Semple TR, Ashworth MT, Owens CM. Interstitial lung disease in children made easier … well, almost. Radiographics 2017; 37: 1679–1703

In 10% to 42% of children with later proven chILD at initial radiograph appearances were normal.

Radiology Key/Fastest Radiology Insight Engine/2022, February

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During ILD secondary pneumothorax may occur in 12.9–20.2% of cases.

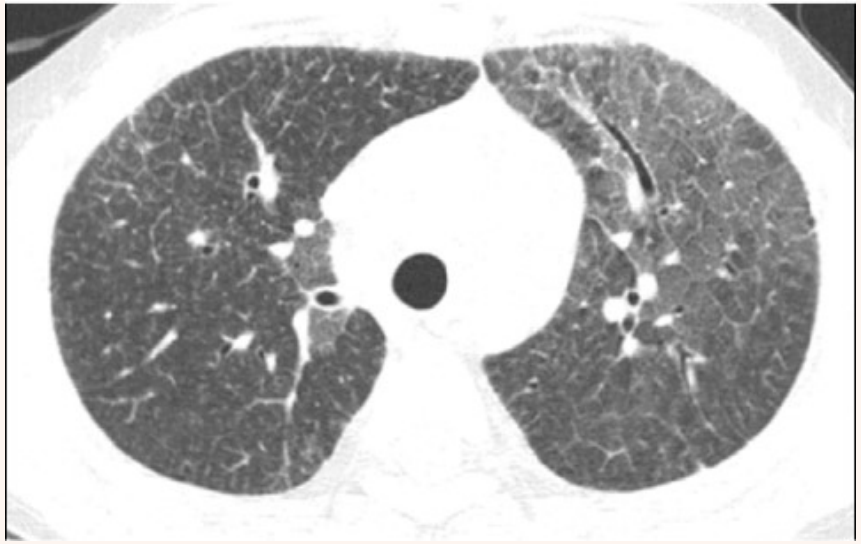
Treatment of secondary pneumothorax with interstitial lung disease.
Takuya Watanabe, Masayuki Tanahashi,et al J Thorac Dis. 2022 May; 14(5): 1393–1400.

The CT scan will allow to confirm ILD and to identify the ILD pattern.

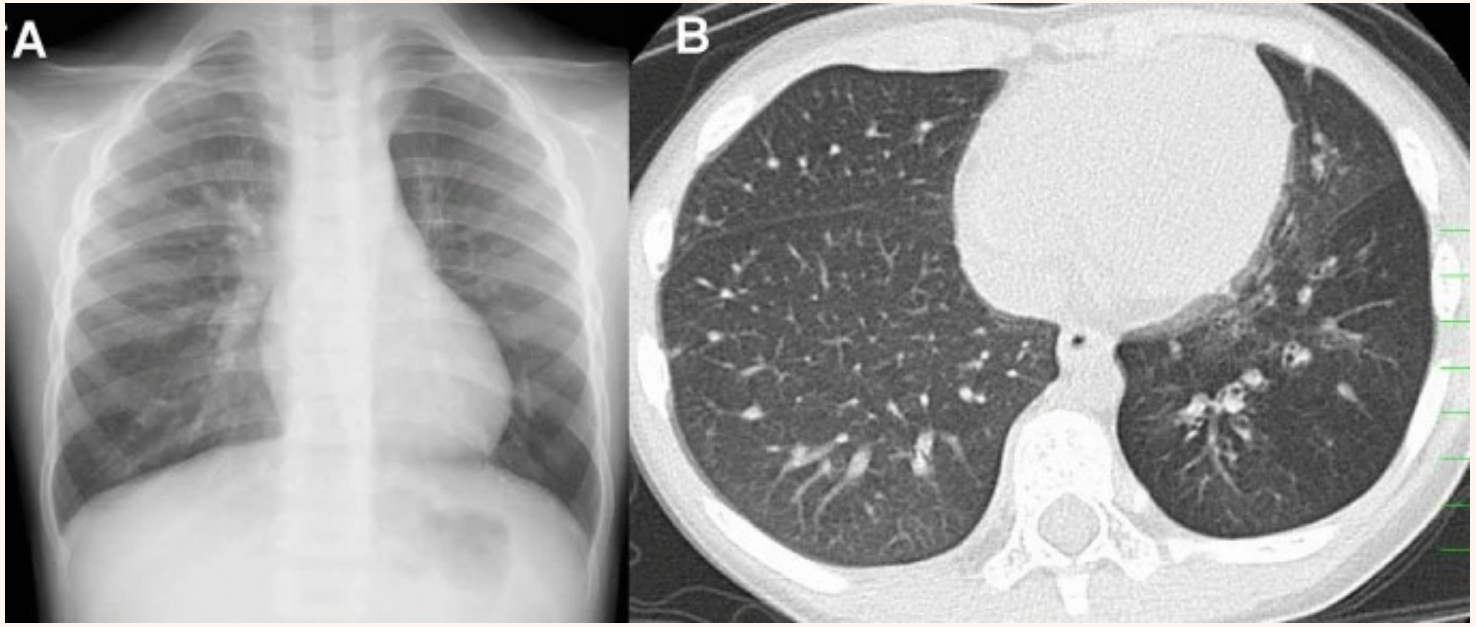
HRCT demonstrates damage of the lung architecture:

- linear and ground-glass opacities,
- hyperinflated or hyperlucent areas,
- consolidations,
- bronchovascular interstitium and of the interlobular septal thickening,
- nodules, traction cysts and bronchiectasis, mosaic changes.

Their association, distribution and extent presents signs of lung fibrosis.

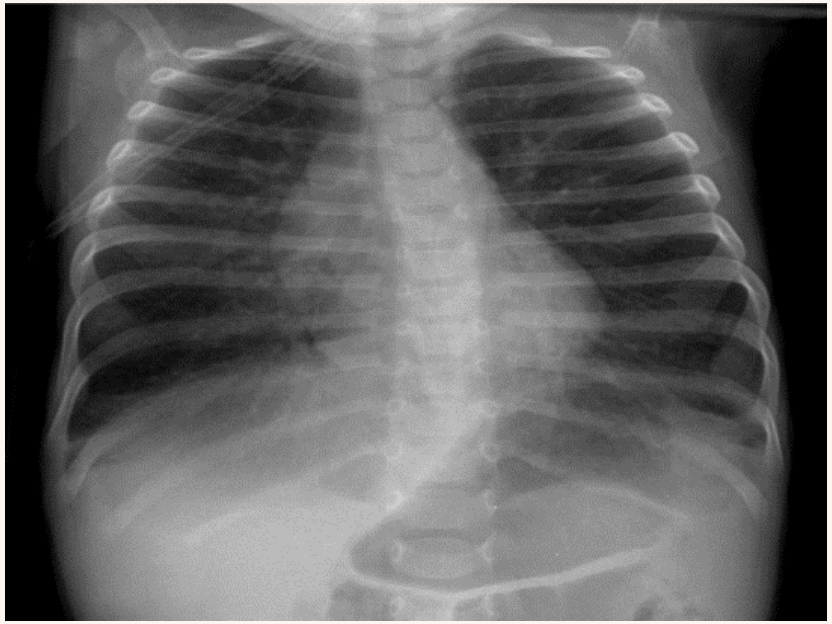


HRCT - A fine reticular pattern of septal thickening and ground – glass opacification in the left lung in a child with nonspecific interstitial pneumonia.



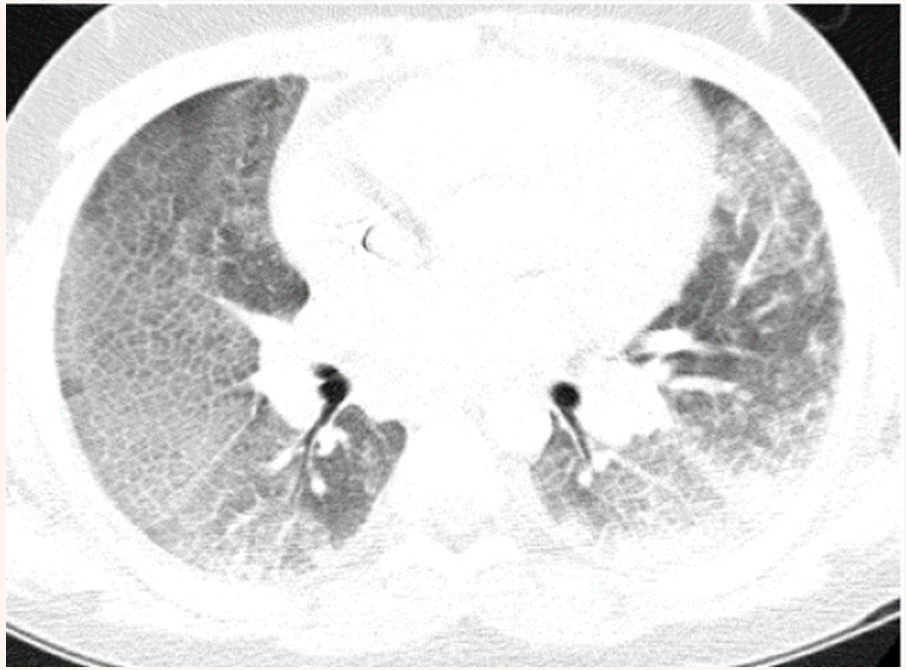
A 4-year-old girl with a history of adenovirus pneumonia.

A. CXR shows lucent lung and thick interstitial markings
B. CT revealed generalized hyperlucency with attenuated vascular shadows and bronchial wall thickening



A. The CXR of a 9-month-old infant with neuroendocrine cell hyperplasia of infancy. Pulmonary hyper-expansion.

This can be misattributed to reactive airways disease or bronchiolitis.



B. CT scan – “crazy paving”, mosaic and ground – glass appearance.

EU collaboration - developed a Delphi consensus process with the aim of harmonizing treatment protocols for a chILD.

Bush A, Cunningham S, de Blic J, et al. European protocols for the diagnosis and initial treatment of interstitial lung disease in children. Thorax. 2015;70:1078–84.

In this regard, some drugs used for chILD derive from the treatment of adult disease.

Deterding RR, DeBoer EM, et al . Am J Respir Crit Care Med. 2019;200(10):1219–27.

Treatment

Corticosteroids, hydroxychloroquine, and azithromycin are the most common pharmacological treatments for chILD.

Dinwiddie R, Sharief N, Crawford O. Idiopathic interstitial pneumonitis in children: a national survey in the United Kingdom and Ireland. Pediatr Pulmonol. 2002;34(1):23–9.

Less frequently used medications include azathioprine, cyclophosphamide, and colchicine.

Seidl E, Schwerk N, et al chILD EU collaborators, Griese M. Acute exacerbations in children's interstitial lung disease. Thorax. 2022;77(8):799–804.

Intravenous pulse – therapy with methylprednisolone (10–30 mg/kg) is used in critical patients.

Desmarquest P, et al /Chronic interstitial lung disease in children: response to high-dose intravenous methylprednisolone pulses. Pediatr Pulmonol. 1998;26(5):332–8

Specific therapies with plausible effect:

- ✓ Biologics i.e. rituximab,
- ✓ Immunomodulatory therapies in connective tissue disorders,
- ✓ Stem cell transplantation.
- ✓ For some conditions surfactant replacement therapy may be beneficial but it requires more studies.

Seidl E et al/Pediatr Pulmonol. 2022;57(1):273–7.

Specific therapies with plausible effect:

✓ Whole lung lavage is the standard treatment in pulmonary alveolar proteinosis,

Bush A, Pabary R. Pulmonary alveolarproteinosis in children. Breathe (Sheff). 2020;16(2
)

✓ Two drugs, used in adult ILDs, with antifibrotic effects - pirfenidone and nintedanib, nintedanib showed similar pharmacokinetics and safety as in adults.

King TE Jr / Engl J Med. 2014;370(22):2083–92.

✓ Ivacaftor and genistein, approved for CF, in patients carrying ABCA3 genetic variants.

Li Y, Seidl E, Thorax. 2023;78(6):587–95.

Recently, a multicenter, study investigated the role of baricitinib

Kanazawa N, Ishii T/Pediatr Rheumatol Online J. 2023;21(1):38

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STING- associated vasculopathy is a genetic autoinflammatory disease secondary to Interferon Genes activation.

The disease generally has a neonatal or infantile onset.

Liu Y, Jesus AA, al Activated STING in a vascular and pulmonary syndrome. N Engl J Med. 2014;371(6):507–18.

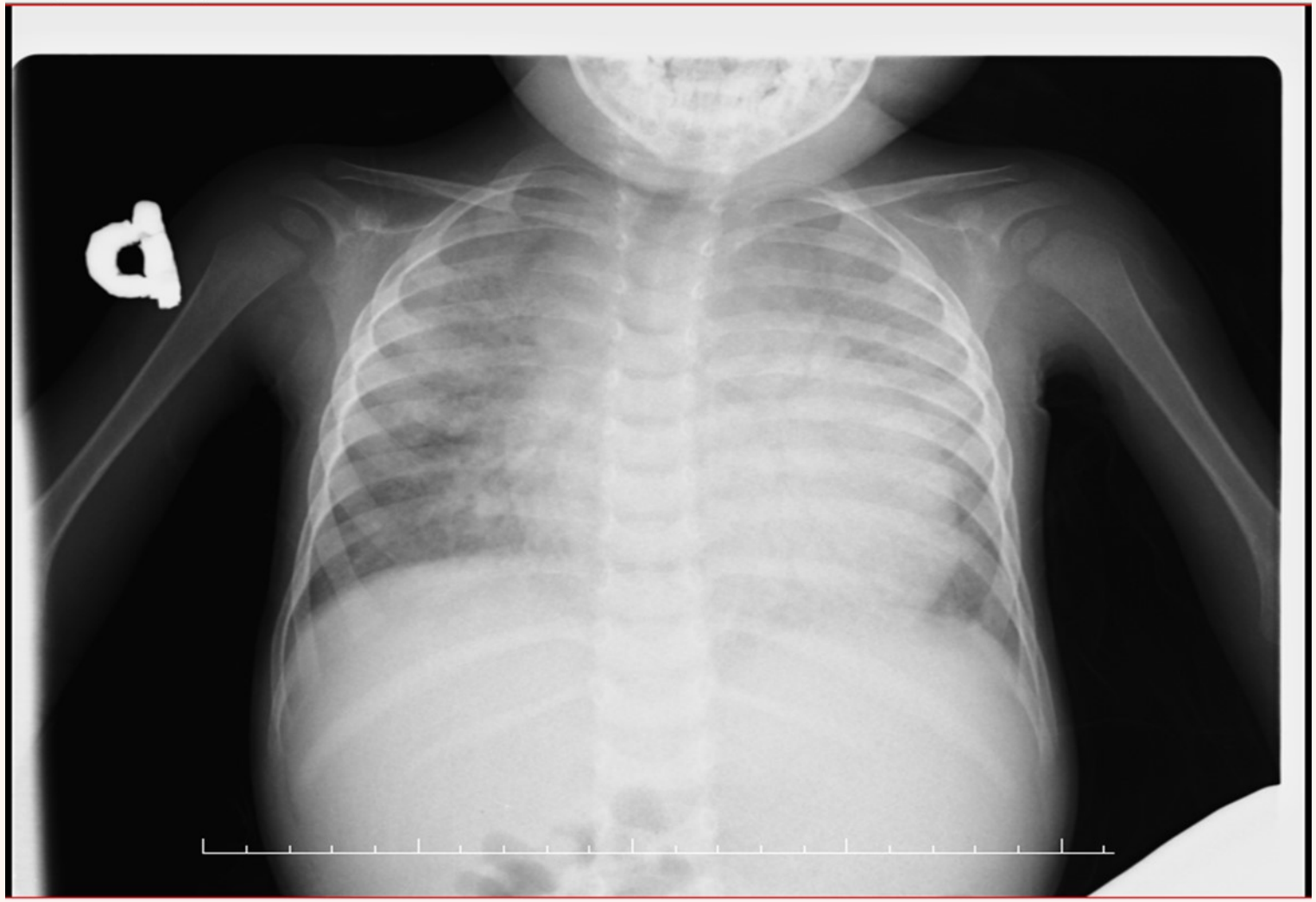
COPA syndrome is a rare, genetic autoimmune disorder (that is caused by dysfunctional coatomer associate protein subunit alpha (COPα).

COPA syndrome can affect multiple organs, especially the lungs, joints, and kidneys.

Kumrah R, Mathew B, et al. Genetics of COPA syndrome. Appl Clin Genet. 2019;8(12):11–8.

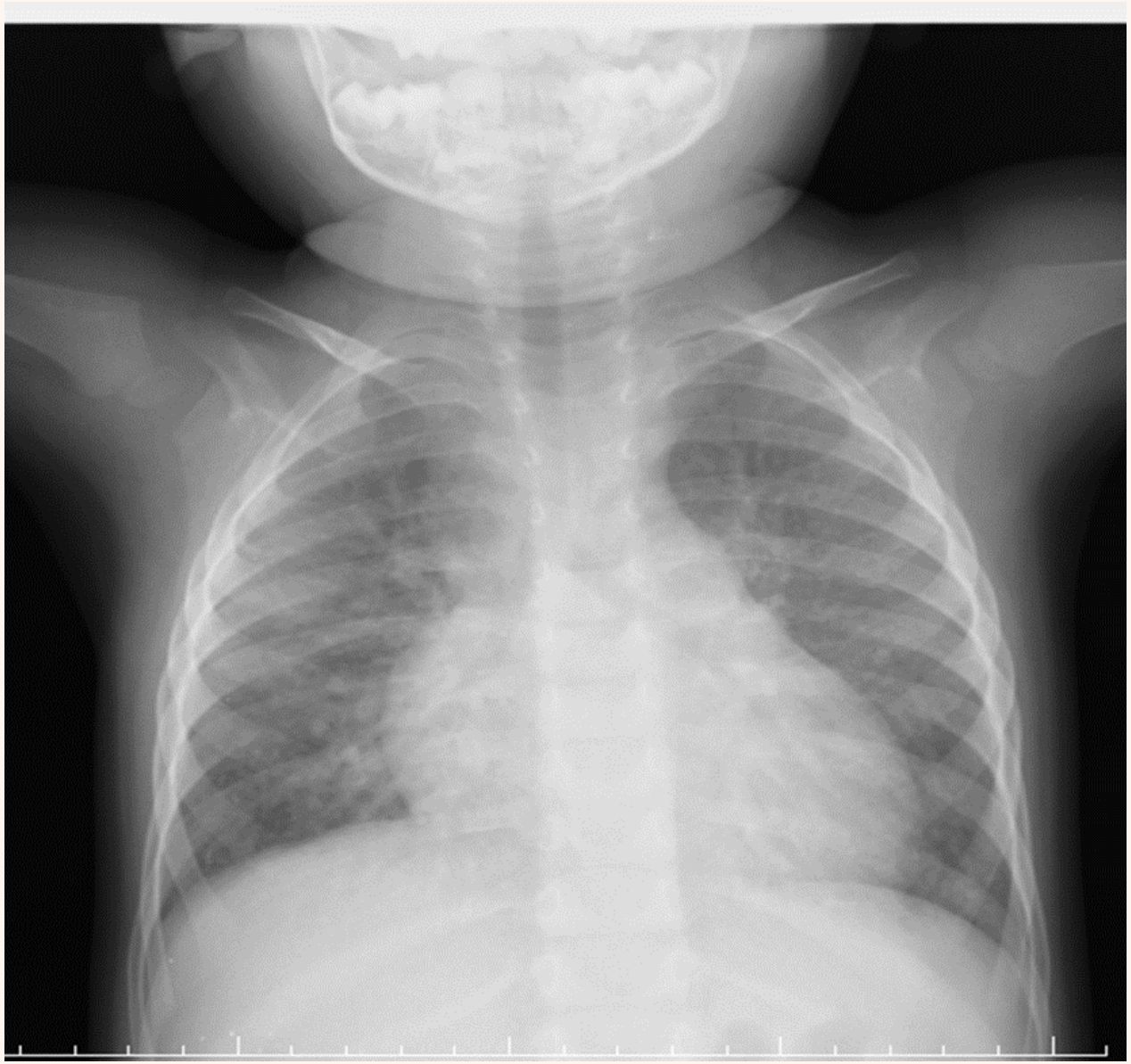
The JAK, a Janus kinase (JAK)-1/2 inhibitors - baricitinib and ruxolitinib have recently been suggested for patients with COPA syndrome.

Frémond ML, Nathan N. COPA syndrome, 5 years after: where are we? Jt Bone Spine. 2021;88(2): 105070.



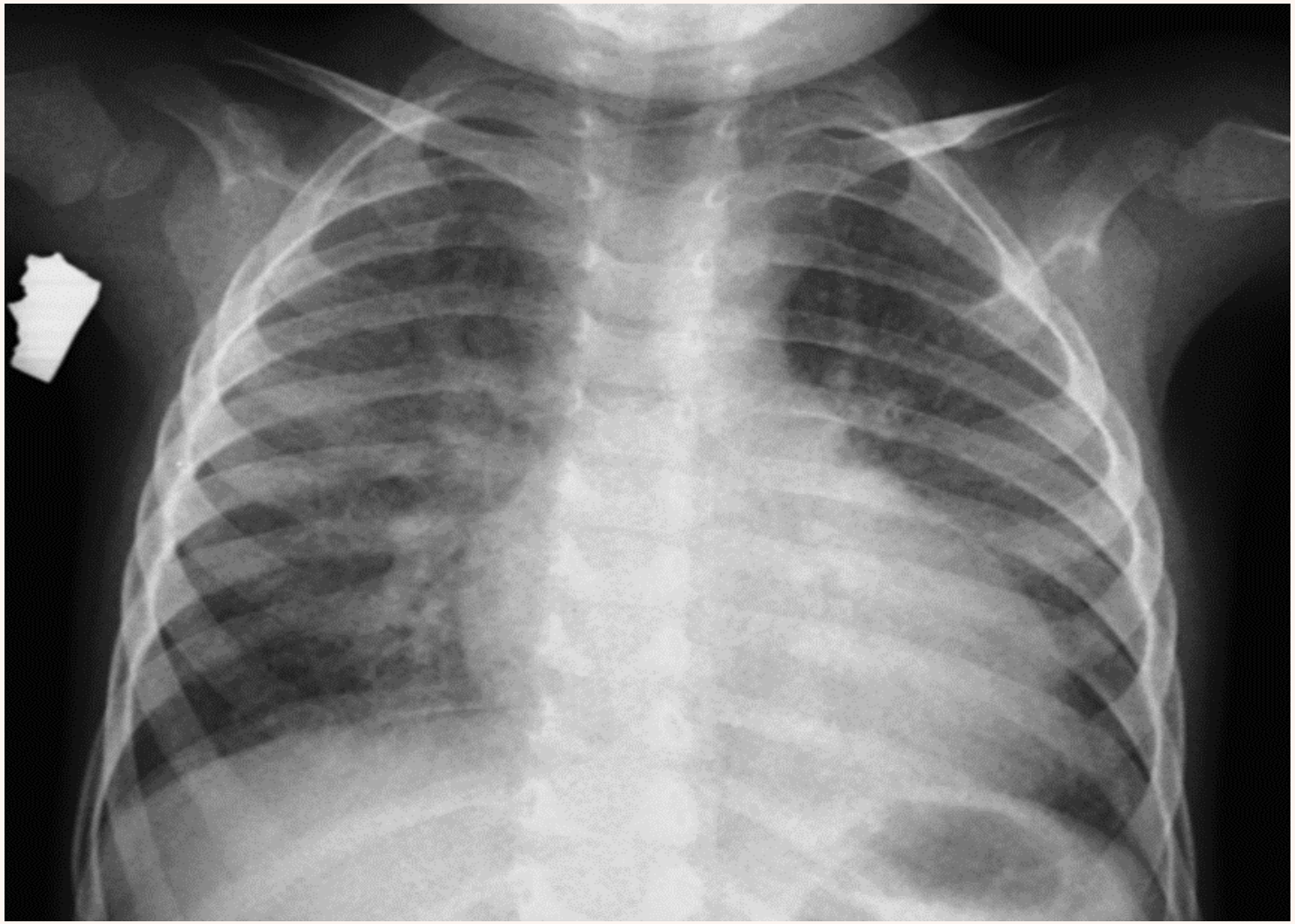
04.05.18

X-ray - On the right side hyperlucency, both sides ground glass opacification, amplified interstitial markings, bilateral infiltrations, cardio-thoracic index – 0,65

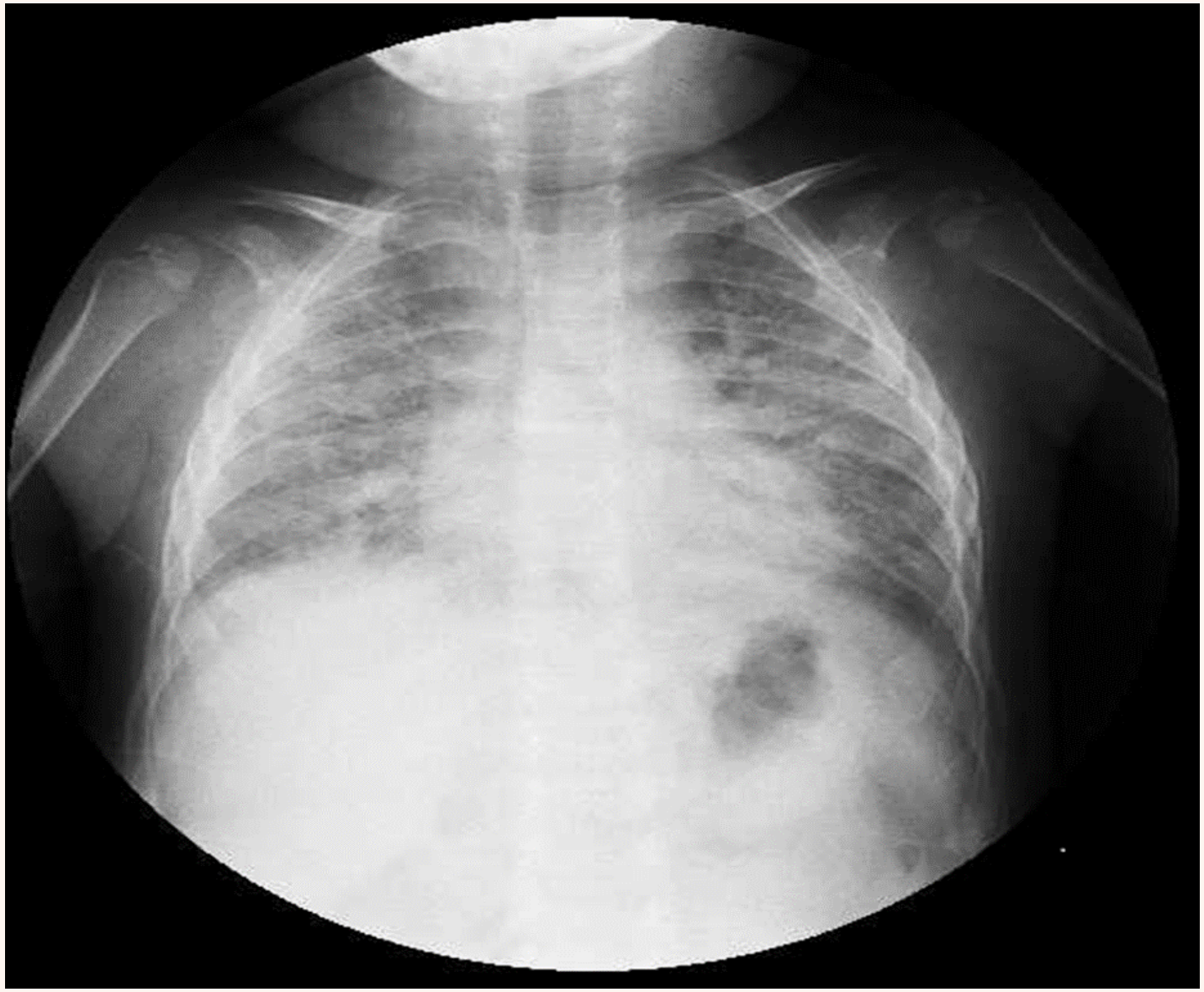


17.07.18

Bilateral amplified interstitial picture, reticular – nodular changes, ground glass opacification improved, parenchymal changes, cardio-thoracic index – 0,62



06.05.21
On the right side perihilar ground-glass opacification, amplified interstitial markings, enlarged cardial borders.



06.05.23
Diffuse fibrosis, ground-glass opacification, air- bronchogramm on the left side, enlarged cardiac borders.

Thank you for your attention!