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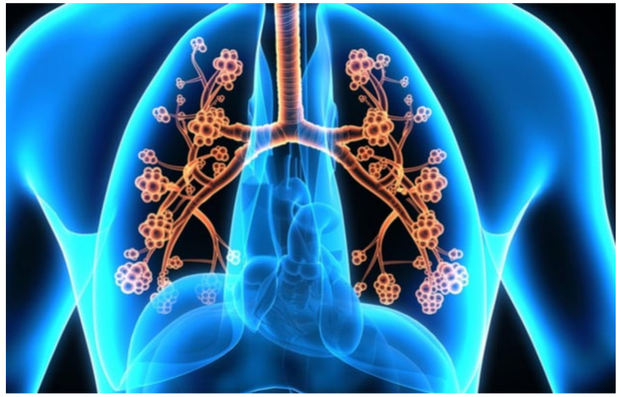
società italiana per le malattie respiratorie infantili

XXVIII CONGRESSO NAZIONALE SIMRI

Il respiro: scienza e terapia per la salute del bambino

Trattamenti biologici e terapie target nelle patologie respiratorie pediatriche



Meyer

Grazia Fenu
Broncopneumologia, AOU, IRCCS, Meyer
grazia.fenu@meyer.it

Ai sensi dell’Accordo Stato-Regione in materia di formazione continua nel settore “Salute” (Formazione ECM) vigente,

Dichiarazione sul Conflitto di Interessi

Il sottoscritto Grazia Fenu

in qualità di relatore

nell’ambito dell’evento XXVIII Congresso Nazionale SIMRI
Torino 10-12 Ottobre 2024

ai sensi dell’Accordo Stato-Regione in materia di formazione continua nel settore “Salute” (Formazione ECM) vigente,

Dichiara

che negli ultimi due anni ha avuto rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Boehringer-Ingelheim, Novartis, Sanofi

Trattamenti biologici e terapie target nelle patologie respiratorie pediatriche

Summary

Target therapy on …

- Severe Asthma (SA)
- Cistic Fibrosis (CF)
- childhood Interstitial Lung Disease (chILD)
- Bronchiolitis Obliterans Syndrome (BOS)/Bronchiolitis Obliterans (BO)

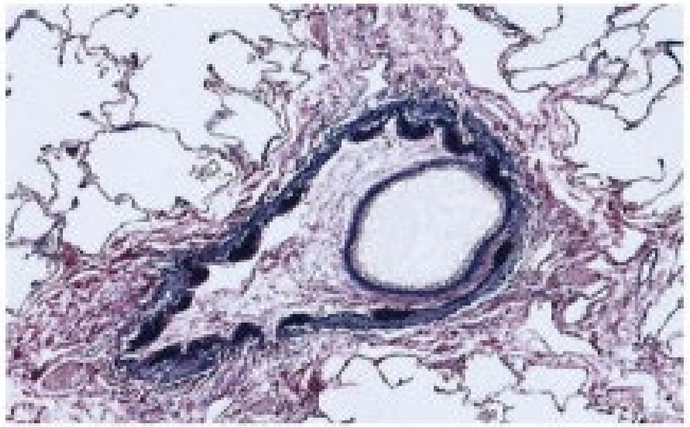
Bronchiolitis Obliterans (BO)

a rare chronic irreversible obstructive lung disease
leading to obstruction and/or obliteration of small airways

Bronchiolitis Obliterans (BO)

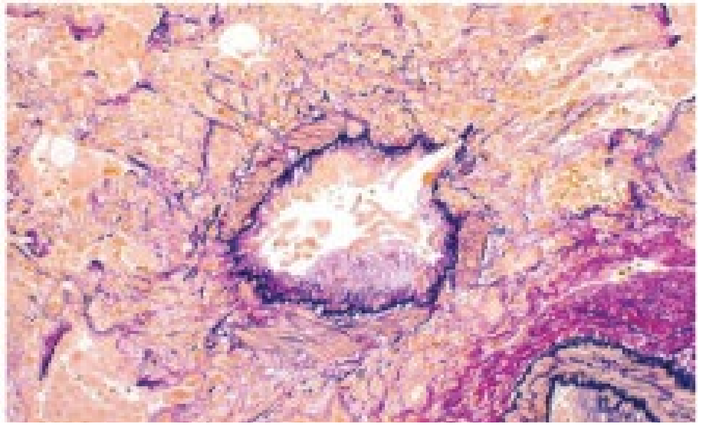
1. BO post-infettiva

chronic peri-bronchial inflammation
with focal bronchial obliteration



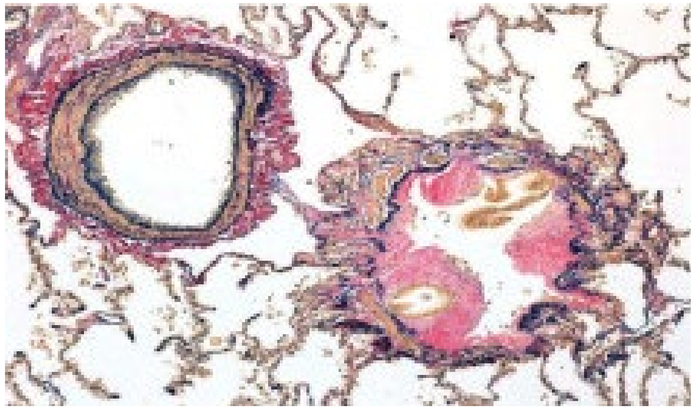
2. **BO post-trapianto del midollo o post trapianto di cellule staminali emopoietiche**

diffuse lung injury with organization
and constrictive bronchiolitis



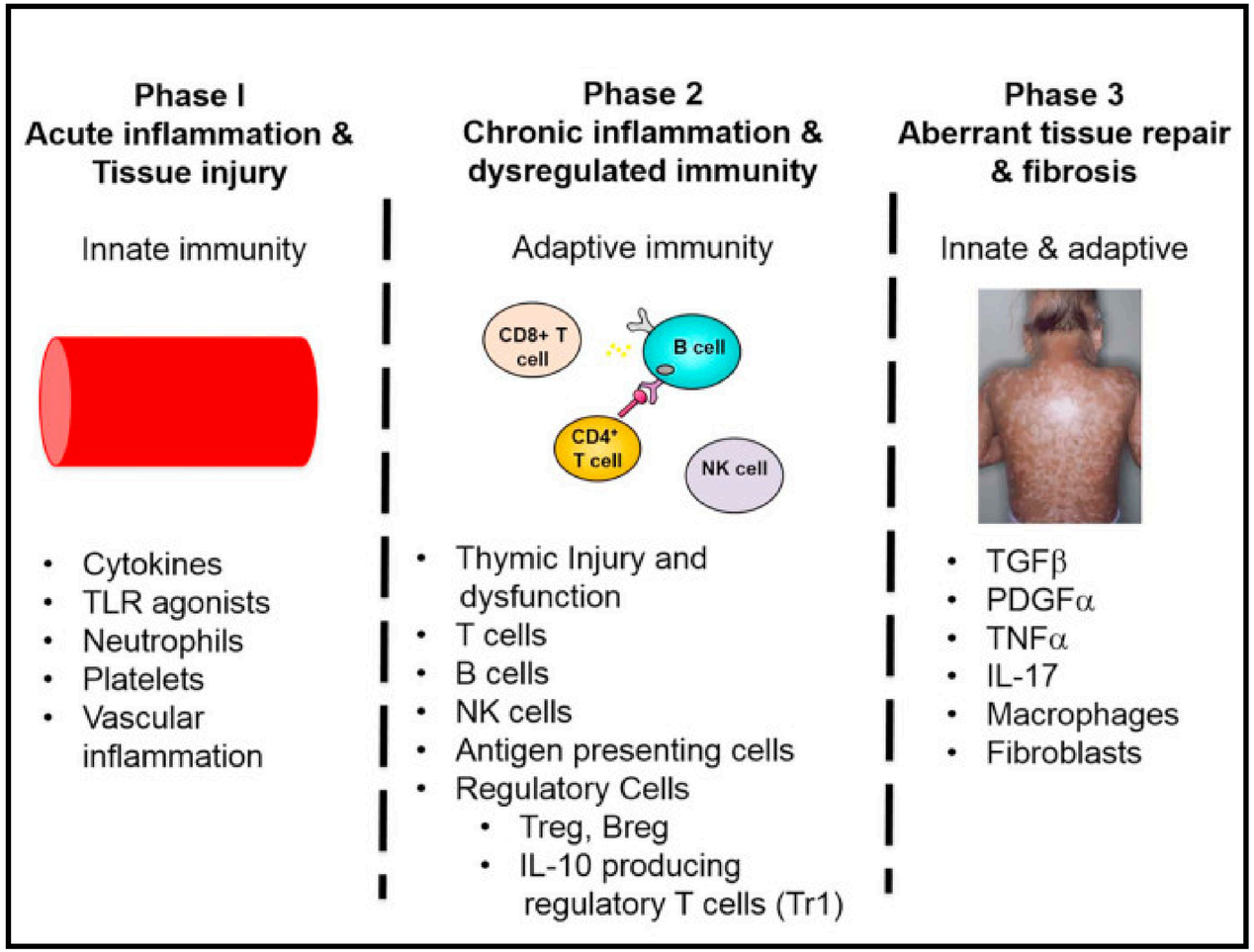
3. **BO post-trapianto del polmone**

appearances are of widespread and
severe obliterative bronchiolitis.



Graft-Versus-Host Disease (GVHD)

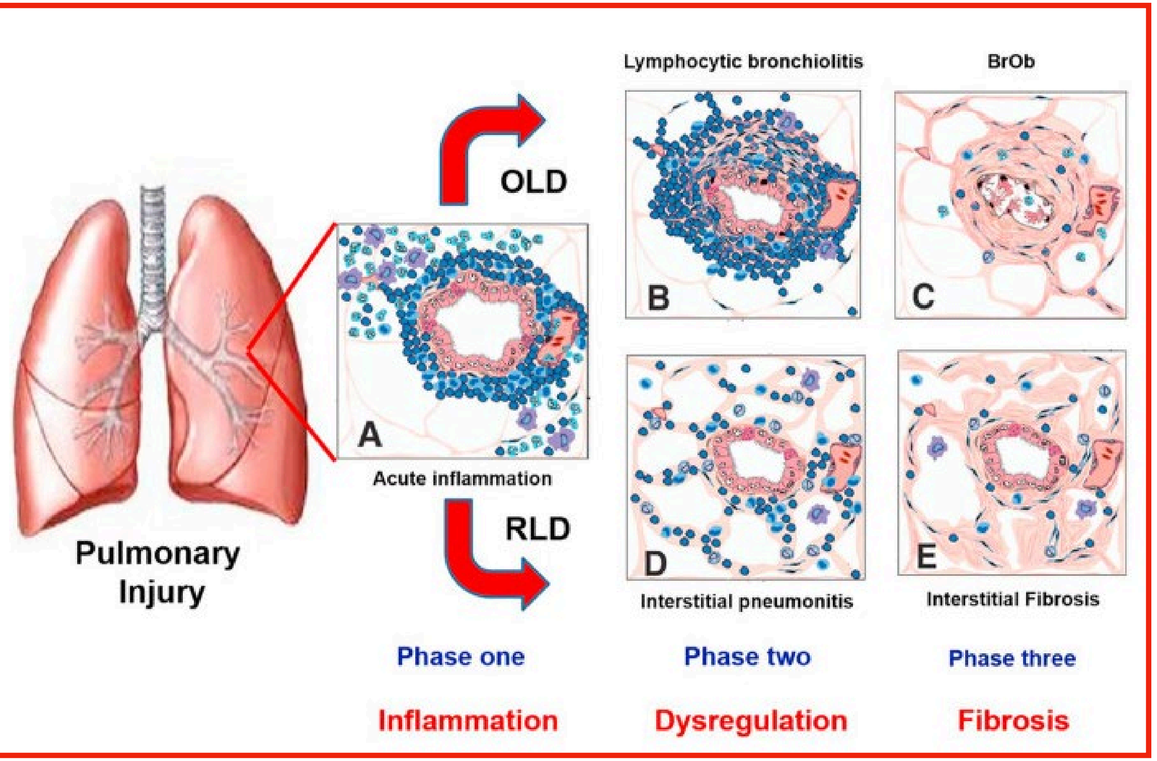
- What? Severe complication that can occur following (allogenic) hematopoietic stem cell transplantation
- When? Immunocompetent T lymphocytes from the donor graft recognize the recipient's tissues as foreign due to histocompatibility differences and initiate an immune response against them
- Who? T-cells play a major role in the initiation of GVHD, CD4+ T-helper 17 cells are likely involved
- Where? GVHD leads to tissue damage in various organs, and including the skin, gastrointestinal tract, liver, and lungs
- GVHD can manifest as acute or chronic forms



Cooke K R et al. Biol Blood Marrow Transplant. 2017 February; 23(2): 211–234. doi:10.1016/j.bbmt.2016.09.023

Bronchiolitis Obliterans Syndrome (BOS)

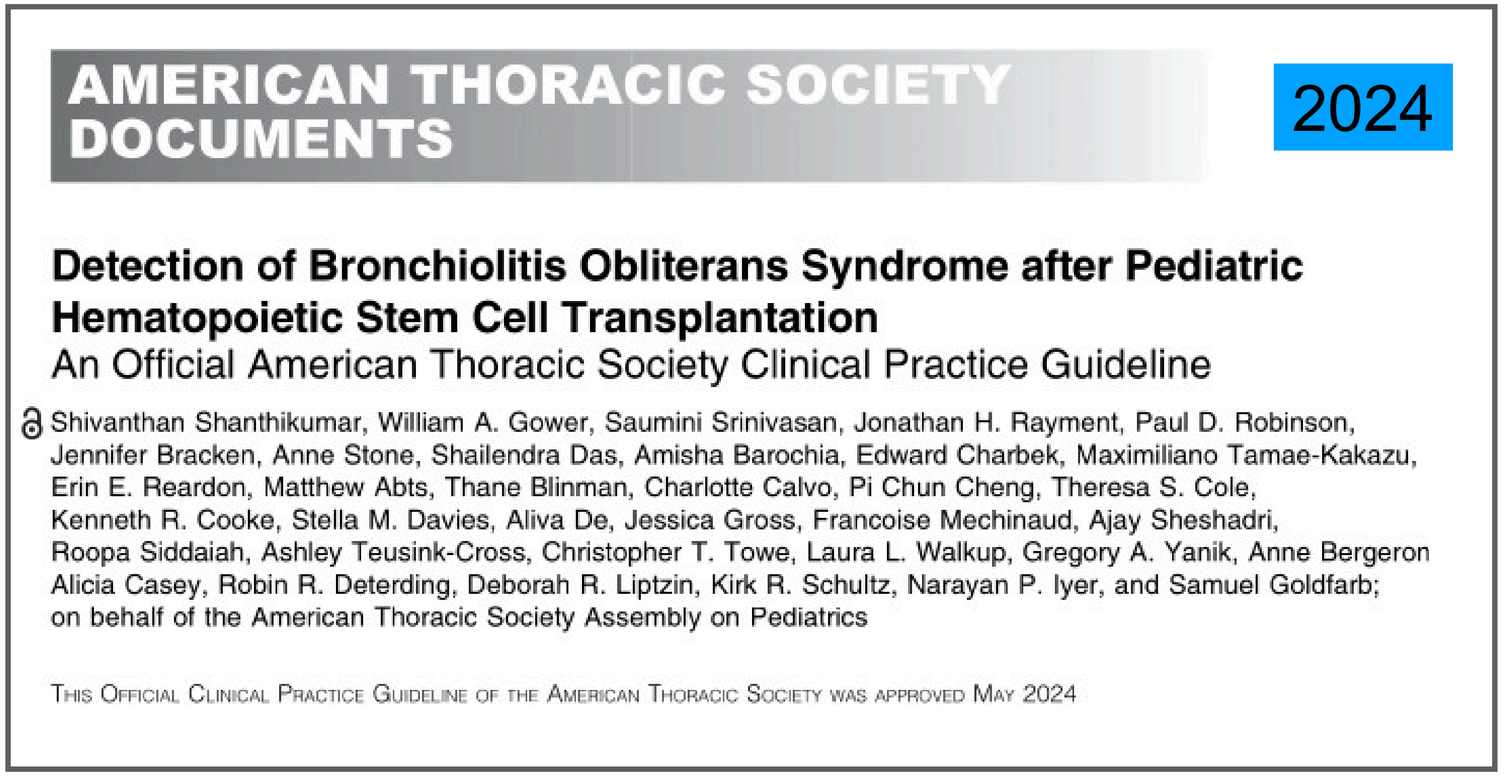
- A manifestation of chronic GVHD in the lung
- One of the most common pulmonary complications post Hematopoietic stem cell transplantation (HSCT)
- Prevalence: 4,5 to 8,3% in children post HSTC
- Progressive obstructive lung disease, which particularly affects the peripheral airways
- Signs and symptoms: dyspnea, wheeze and hypoxemia. In the early phases: asymptomatic, and detected only through PFT and CT!!!
- Is a diagnosis made on clinical features and these tools, but where a lung biopsy is performed (diagnosis confirmed), the term Bronchiolitis Obliterans (BO) is used.



Shantikumar S et al. Transplantation and Cellular Therapy 30 (2024) 760-769. doi.org/10.1016/j.jtct.2024.05.012

Cooke K R et al. Biol Blood Marrow Transplant. 2017 February; 23(2): 211–234. doi:10.1016/j.bbmt.2016.09.023

BOS post HSTC: ATS pediatric guidelines



AMERICAN THORACIC SOCIETY DOCUMENTS

2024

Detection of Bronchiolitis Obliterans Syndrome after Pediatric Hematopoietic Stem Cell Transplantation

An Official American Thoracic Society Clinical Practice Guideline

Shivanthan Shanthikumar, William A. Gower, Saumini Srinivasan, Jonathan H. Rayment, Paul D. Robinson, Jennifer Bracken, Anne Stone, Shailendra Das, Amisha Barochia, Edward Charbek, Maximiliano Tamae-Kakazu, Erin E. Reardon, Matthew Abts, Thane Blinman, Charlotte Calvo, Pi Chun Cheng, Theresa S. Cole, Kenneth R. Cooke, Stella M. Davies, Aliva De, Jessica Gross, Francoise Mechinaud, Ajay Sheshadri, Roopa Siddaiah, Ashley Teusink-Cross, Christopher T. Towe, Laura L. Walkup, Gregory A. Yanik, Anne Bergeron Alicia Casey, Robin R. Deterding, Deborah R. Liptzin, Kirk R. Schultz, Narayan P. Iyer, and Samuel Goldfarb; on behalf of the American Thoracic Society Assembly on Pediatrics

This Official Clinical Practice Guideline of the American Thoracic Society was approved May 2024

Shantikumar S et al. Am J Respir Crit Care Med Vol 210, Iss 3, pp 262–280, Aug 1, 2024

Bronchiolitis Obliterans Syndrome (BOS): PFT DIAGNOSIS

By the US National Institutes of Health

- BOS is diagnosed when all of the following criteria are met:

1. Airflow obstruction by FEV1/FVC <0,7 or 5th percentile of predicted

2. FEV1< 75% predicted with ≥ 10% decline in FEV1 within two years that does not correct with bronchodilators

3. Absence of respiratory tract infection

4. Evidence of air trapping either by PFT [residual volume (RV) >120% of predicted RV or RV/total lung capacity (TLC) above the 90th percentile or by expiratory computed tomography (CT)

Table 6. New Proposed Criteria for the Diagnosis of Pediatric Post-HSCT BOS

In children who can perform spirometry (GLI to be used at the reference equation for spirometry and plethysmography)
- Relative decline of FEV_1 percent predicted, compared to pre-HSCT baseline, by 15% which persists on two tests at least 2 wk apart

AND
- Supporting features (two or more of the following)
  - FEV_1/VC below lower limit of normal
  - Evidence of air trapping on expiratory CT
  - Evidence of air trapping on plethysmography (residual volume or residual volume/total lung capacity elevated above the upper limit of normal)
  - Lung clearance index >8.0
  - cGvHD (active or past history) in another organ

AND
- Persistence of suspicion of BOS after directed treatment or expected resolution of any identified infection. Assessment of infection should include investigations directed by clinical symptoms, such as chest radiographs, CT scans, or microbiologic cultures (sinus aspiration, upper respiratory tract viral testing, sputum culture, BAL)

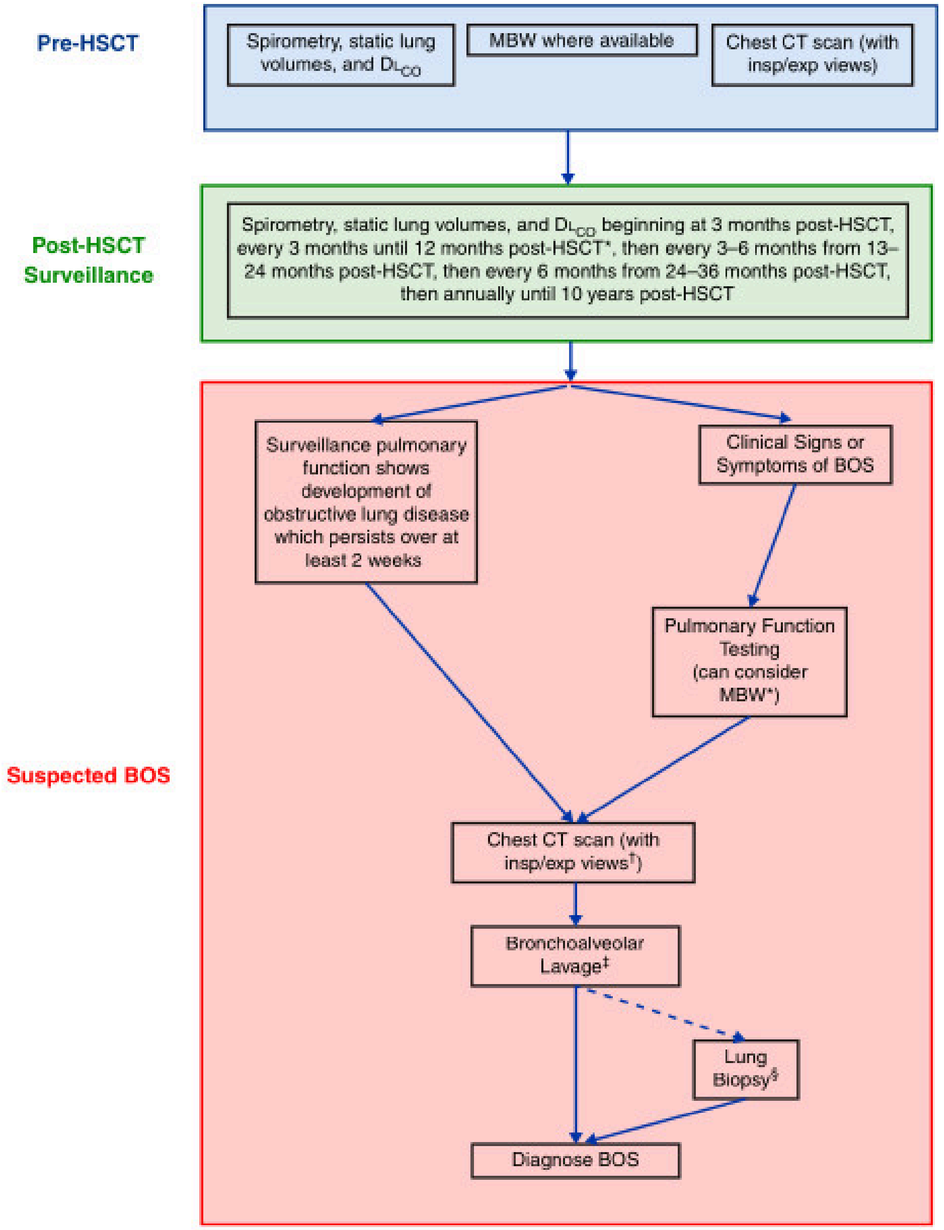
In children who cannot perform spirometry
- Clinical symptoms (e.g., wheeze, shortness of breath with activity)

AND
- Two or more of the following
  - Evidence of air trapping on expiratory CT
  - Lung clearance index >8.0
  - cGvHD (active or past history) in another organ

AND
- Persistence of suspicion of BOS after directed treatment or expected resolution of any identified infection. Assessment of infection should include investigations directed by clinical symptoms, such as chest radiographs, computed tomography (CT) scans, or microbiologic cultures (sinus aspiration, upper respiratory tract viral testing, sputum culture, BAL)

Shantikumar S et al. Am J Respir Crit Care Med Vol 210, Iss 3, pp 262–280, Aug 1, 2024

Bronchiolitis Obliterans Syndrome (BOS): DIAGNOSIS

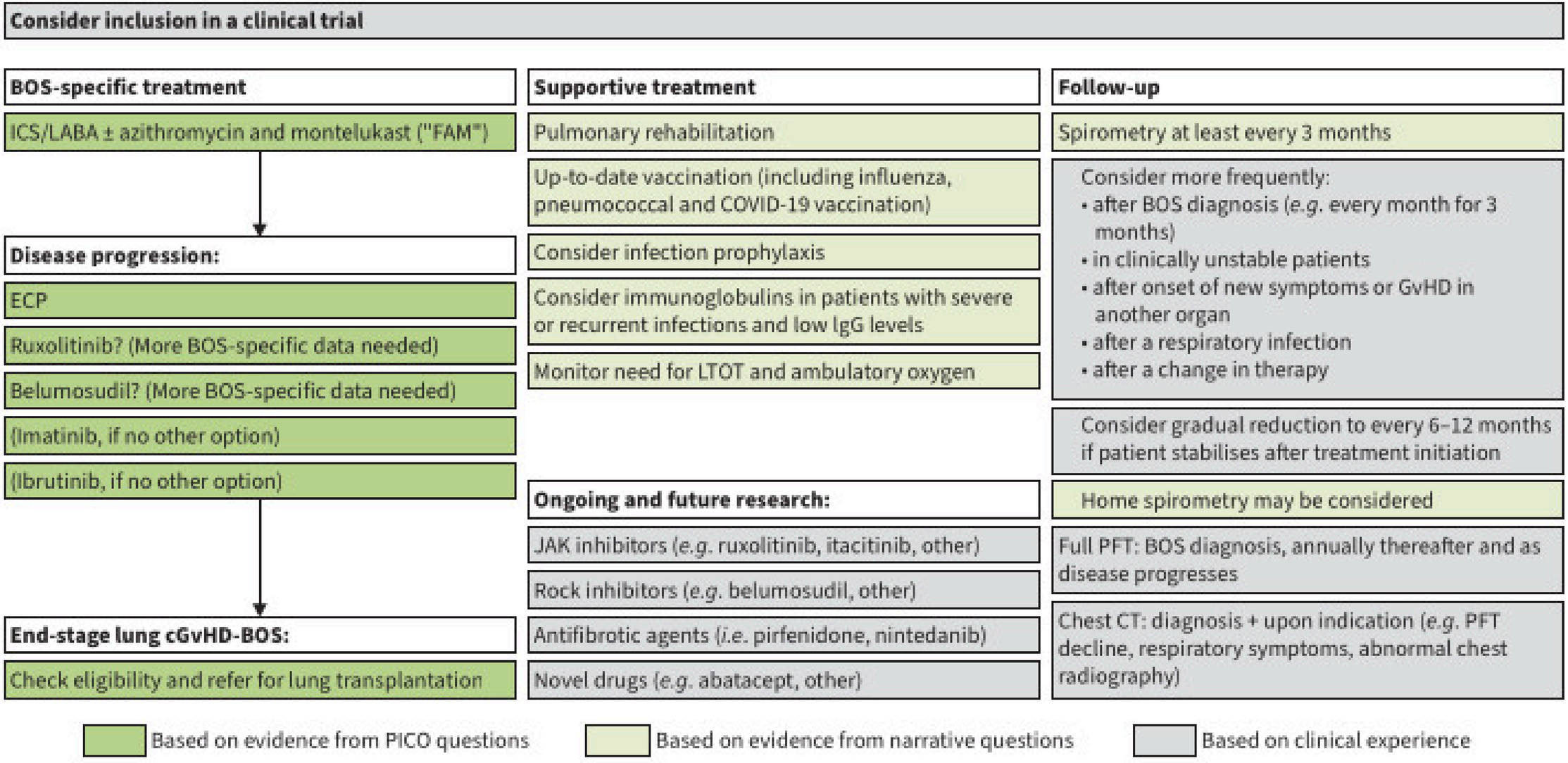


PFT timing in children

Months Post-HSCT	Recommended PFT Frequency
0–12 mo	Every 3 mo
13–24 mo	Every 3–6 mo
25–36 mo	Every 6 mo
⩾37 mo	Every 12 mo

Shantikumar S et al. Am J Respir Crit Care Med Vol 210, Iss 3, pp 262–280, Aug 1, 2024

Bronchiolitis Obliterans Syndrome (BOS): THERAPY



Bos S et al. ERS/EBMT clinical practice guidelines on treatment of pulmonary chronic graft-versus-host disease in adults.

Eur Respir J 2024; 63: 2301727.doi.org/10.1183/13993003.01727-2023

FAM = Fluticasone/Azithromycin/Montelukast

Biol Blood Marrow Transplant. 2016 April ; 22(4): 710–716. doi:10.1016/j.bbmt.2015.10.009.

phase II, single-arm, open label, multicenter study (NCT01307462)

FAM treatment for new onset bronchiolitis obliterans syndrome after hematopoietic cell transplantation

Kirsten M. Williams[1,2], Guang-Shing Cheng[3], Iskra Pusic[4], Madan Jagasia[5], Linda Burns[6], Vincent T. Ho[7], Joseph Pidala[8], Jeanne Palmer[9], Laura Johnston[10], Sebastian Mayer[11], Jason W. Chien[12], David A. Jacobsohn[1], Steven Z. Pavletic[2], Paul J. Martin[3], Barry E. Storer[3], Yoshihiro Inamoto[13], Xiaoyu Chai[3], Mary E.D. Flowers[3], and Stephanie J. Lee[3]

[1]Children's Research Institute, Children's National Health System, Washington, DC

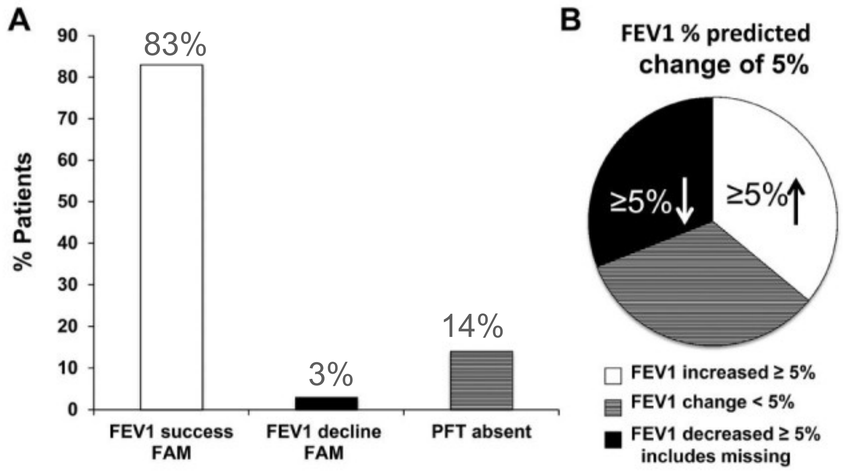
Fluticasone: Inhaled fluticasone propionate, 440 mcg twice a day (ages 12–99 years) or 220 mcg twice a day (ages 6–11 years).

Azithromycin: 250 mg orally for adults (19–99 years) and 5mg/kg orally (max 250mg) for children (6–18 years) taken three days per week was prescribed commercially.

Montelukast: 10 mg oral tablet nightly (14–99 years old) or 5 mg oral nightly (6–13 years old)

Highlights

- Bronchiolitis obliterans syndrome (BOS) after hematopoietic cell transplantation is a rare complication with high morbidity and mortality.
- This is a single arm, multicenter phase II study of 36 patients with newly diagnosed BOS treated with fluticasone propionate, azithromycin, and montelukast (FAM)
- FAM was well tolerated
- FAM with steroid pulse is associated with stable lung function and improved functional and patient-reported outcomes for most newly diagnosed patients with BOS



FAM stabilizes FEV1 in the majority of patients at 3 months

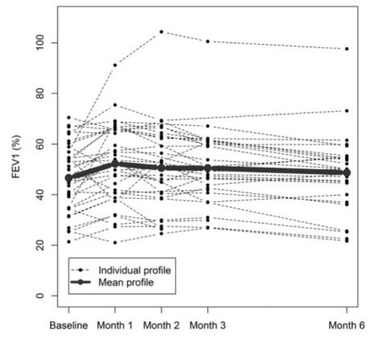


Figure 2. Trajectory of FEV1 over time after FAM exposure
Individual percent predicted FEV1 values are graphed as a function of time for each patient. The bold line represents the median of the cohort.

Leukotrienes?

- immune target with good biologic rationale in BOS after HCT
- have been implicated in lung transplant BOS, similar in pathology, radiography, clinical presentation and progression to BOS after HCT. *[Philit F et al. Post-transplant obstructive lung disease ("bronchiolitis obliterans"): a clinical comparative study of bone marrow and lung transplant patients. Eur Respir J. 1995;8(4):551–558]*
- In a murine model, BOS was abrogated in leukotriene knock-outs and T cell leukotriene receptor expression was higher in BOS BAL.*[Medoff BD, Seung E, Wain JC, et al. BLT1-mediated T cell trafficking is critical for rejection and obliterative bronchiolitis after lung transplantation. J Exp Med. 2005;202(1):97–110]*
- are pro-fibrotic, activating fibroblasts and boosting collagen deposition.[Wilborn J et al. Constitutive activation of 5-lipoxygenase in the lungs of patients with idiopathic pulmonary fibrosis. J Clin Invest. 1996;97(8):1827–1836].
- promote and perpetuate inflammatory responses, inducing immune cell activation, promotion of T cell survival, chemotaxis, and enhancing antigen presentation, all of which could propagate alloimmunity in BOS.

[*Prinz I, et al. The type 1 cysteinyl leukotriene receptor triggers calcium influx and chemotaxis in mouse alpha beta- and gamma delta effector T cells. J Immunol. 2005;175(2):713–719]* .

[Okunishi K et al.A novel role of cysteinyl leukotrienes to promote dendritic cell activation in the antigen-induced immune responses in the lung. J Immunol. 2004;173(10):6393–6402].

- inhibition with montelukast had shown benefit in other forms of GvHD without undue toxicity.

Montelukast

Transplant Cell Ther. 2022 May ; 28(5): 264.e1–264.e9. doi:10.1016/j.jtct.2022.01.021.

Prospective phase II trial of montelukast to treat bronchiolitis obliterans syndrome after hematopoietic cell transplant and investigation into BOS pathogenesis

Kirsten M. Williams[1], Steven Z. Pavletic[2], Stephanie J Lee[3], Paul J Martin[3], Don E Farthing[4], Frances T. Hakim[4], Jeremy Rose[4], Beryl L Manning-Geist[5], Juan C. Gea-Banacloche[6], Leora E. Comis[7], Edward W. Cowen[8], David G. Justus[9], Kristin Baird[10], Guang-Shing Cheng[11,3], Daniele Avila[2], Seth M. Steinberg[12], Sandra A. Mitchell[13], Ronald E. Gress[4]

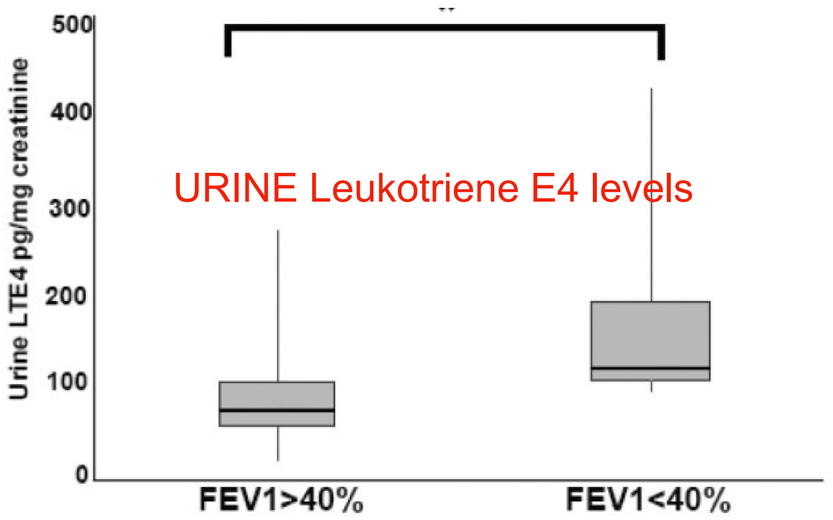


Figure 3: Leukotriene E4 levels in urine at baseline association with FEV1 severity
Median twenty-four hour LTE4 levels (y-axis) are shown as box plots for mild/moderate FEV1% predicted at baseline (>40%, GVHD lung score 1 (FEV1 60-74%, n=5), GVHD score 2 (FEV1 40-59%, n=12)) compared to severe (GVHD score of 3 (n=6), FEV1<40%, x-axis), *p=0.026.

Highlights

- Montelukast safely stabilized the majority of patients with established BOS post HCT.
- Improvement in symptoms, function, and good 2-year survival occurred in responders.
- Our data suggest that leukotrienes play a role in BOS disease after HCT.

ECP = ExtraCorporeal Photopheresis

Transfusion and Apheresis Science 63 (2024) 103990
Contents lists available at ScienceDirect
Transfusion and Apheresis Science
journal homepage: www.elsevier.com/locate/transci
2024

Check for updates

Treatment of acute and chronic graft-versus-host disease with extracorporeal photopheresis: Update of best practice recommendations from Italian Society of Hemapheresis and Cell Manipulation (SIdEM) and the Italian Transplant Group for Bone Marrow Transplantation, Hematopoietic Stem Cells and Cell Therapy (GITMO)

Anna Colpo [a,*], Monia Marchetti [b], Irene Bianco [c], Fabio Cruciani [d], Francesco Ipsevich [e], Mauro Montanari [f], Maria Teresa Lupo Stanghellini [g], on behalf of the Italian Society of Hemapheresis and Cell Manipulation (SIdEM) and the Italian Transplant Group for Bone Marrow Transplantation, Hematopoietic Stem Cells and Cell Therapy (GITMO)

una terapia immunomodulatoria:
raccolta dei globuli bianchi del paziente, poi sottoposti ad una terapia attivata dai raggi Uva prima di essere rinfusi.
Studi clinici ed evidenze di real-world hanno confermato l'efficacia e la sicurezza della fotoferesi per il:
-trattamento della GVHD;
-del linfoma cutaneo a cellule T;
-del rigetto post trapianto di organo solido

AIM:

to define uniform criteria for the application of ECP in adult and pediatric patients affected by GVHD throughout the national territory, in line with international guidelines, in maintaining of high standards of safety for patients and quality of the procedures provide.

Ruxolitinib

Bone Marrow Transplant. 2019 July ; 54(7): 1158–1160. doi:10.1038/s41409-019-0450-3.

Ruxolitinib is an effective steroid sparing agent in children with steroid refractory/dependent bronchiolitis obliterans syndrome after allogenic hematopoietic cell transplantation

Michelle Schoettler[1], Christine Duncan[1], Leslie Lehmann[1], Elissa Furutani[1], Meera Subramaniam[2], Steven Margossian[1]

[1]Boston Children's/Dana Farber Cancer and Blood Disorders Center, Boston, MA, USA

[2]Department of Pulmonology, Boston Children's Hospital, Boston, MA, USA

- JAK1/2 inhibitor
- Potent anti-inflammatory
- FDA approved to treat acute GVHD in adults
- To treat chronic GVHD is also described in adults
- Report of use in children are rare

Single center experience of pediatric patients with steroid refractory-BOS, treated with Ruxolitinib

Conclusion: we describe 5 pediatric and young adult patients with SR-BOS treated with ruxolitinib.

Ruxolitinib was steroid sparing in all 4 patients with an evaluable response; 3 were able to stop steroids, and 1 weaned significantly.

Responses occurred early, and the medication was well tolerated with minimal side effects.

Further prospective studies are needed to evaluate the role of ruxolitinib in children with cGVHD, particularly BOS.

- **There is only one case report of ruxolitinib use in a child for cGVHD published in abstract form.** [*Karras N et al. Ruxolitinib in a pediatric patient with chronic Gvhd. Biol Blood Marrow Transplant. 2017;23:S236].*
- **A case series of ruxolitinib use in children for aGVHD reported a response rate of 45%. However, 13/13 children experienced toxicities, highlighting the need for determining the maximum tolerated dose in pediatrics.** [*Khandelwal P et al. Ruxolitinib as salvage therapy in steroid-refractory acute graft-versus-host disease in pediatric hematopoietic stem cell transplant patients. Biol Blood Marrow Transplant. 2017;23:1122–7].*

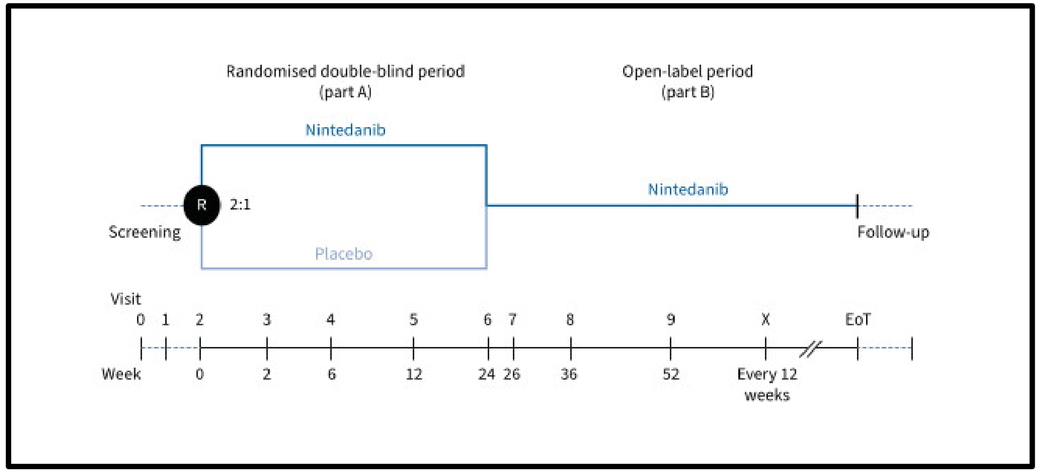
This cohort was comprised of children who weighed >40 kg, allowing adult FDA approved dosing. Perhaps this explains the discrepancies in toxicities reported in the two cohorts.

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
R. DETERDING ET AL.

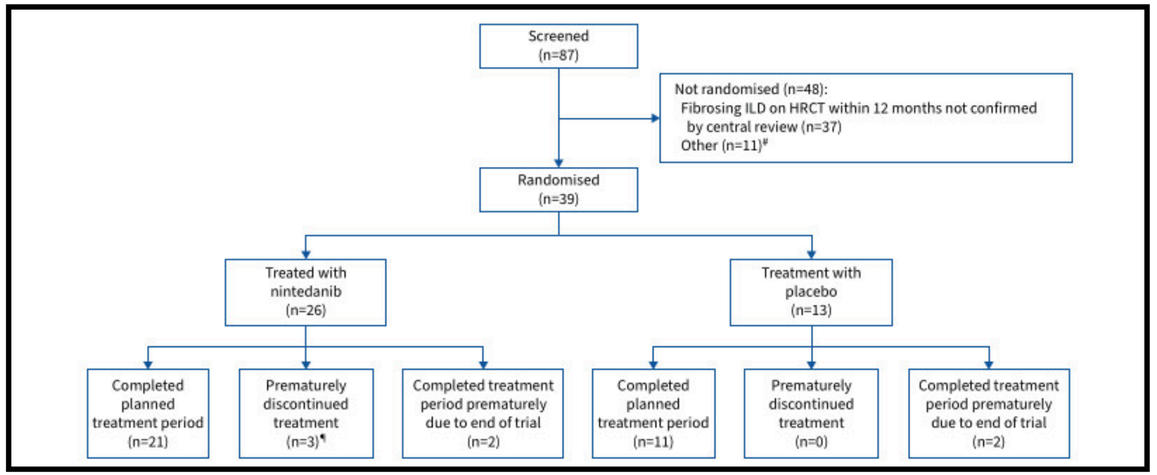
Nintedanib in children and adolescents with fibrosing interstitial lung diseases

Robin Deterding[1,2,15], Lisa R. Young[3,15], Emily M. DeBoer[1,2], David Warburton[4,5], Steven Cunningham[6], Nicolaus Schwerk[7], Kevin R. Flaherty[8], Kevin K. Brown[9], Mihaela Dumistracel[10], Elvira Erhardt[11], Julia Bertulis[11], Martina Gahlemann[12], Susanne Stowasser[13] and Matthias Griese[14] for the InPedILD trial investigators[16]

an intracellular inhibitor of tyrosine kinases that inhibits processes fundamental to the progression of pulmonary fibrosis



Trial design



Disposition of patients during the double-blind period

Eur Respir J 2023;61: 2201512

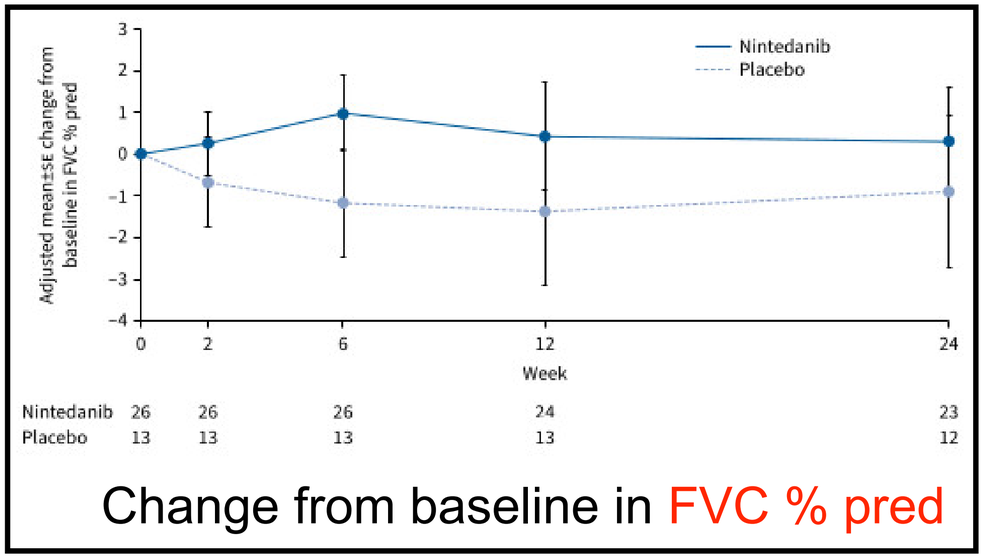
TABLE 1 Dosing and dose adjustments

Weight bin	Weight range, kg	Dose, mg twice daily	Capsule strength, mg	Reduced dose, mg twice daily	Capsule strength for reduced dose, mg
1	13.5[#]– <23.0	50	25 (2×)	25	25 (1×)
2	23.0– <33.5	75	25 (3×)	50	25 (2×)
3	33.5– <57.5	100	100 (1×) or 25 (4×)	75	25 (3×)
4	⩾57.5	150	150 (1×) or 25 (6×)	100	100 (1×) or 25 (4×)

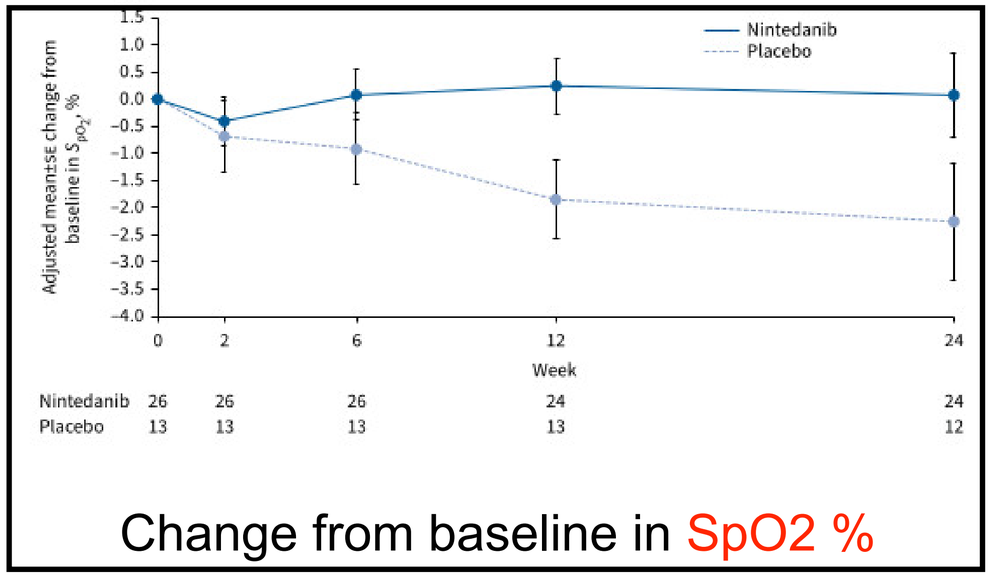
[#]: patients with weight <13.5 kg were excluded from the trial.

Adverse event

	Nintedanib (n=26)	Placebo (n=13)
Any adverse event(s)	22 (84.6)	11 (84.6)
Most frequent adverse event(s)[#]		
Diarrhoea	10 (38.5)	2 (15.4)
Vomiting	7 (26.9)	3 (23.1)
Dental caries	7 (26.9)	3 (23.1)
Nausea	5 (19.2)	3 (23.1)
Abdominal pain	5 (19.2)	3 (23.1)
COVID-19	5 (19.2)	1 (7.7)
Headache	3 (11.5)	1 (7.7)
Pyrexia	3 (11.5)	1 (7.7)
Rhinitis	3 (11.5)	0
Tooth impacted	2 (7.7)	2 (15.4)
Fatigue	2 (7.7)	2 (15.4)
Faeces soft	1 (3.8)	2 (15.4)
Oropharyngeal pain	1 (3.8)	2 (15.4)
Epistaxis	0	2 (15.4)
Radiography limb abnormal	0	2 (15.4)
Adverse event(s) leading to discontinuation	2 (7.7)[¶]	0
Serious adverse event(s)[+]	2 (7.7)[§]	1 (7.7)[f]
Required or prolonged hospitalisation	2 (7.7)	0
Other medically important serious event	0	1 (7.7)
Fatal or life-threatening	0	0



Change from baseline in FVC % pred



Change from baseline in SpO2 %

Eur Respir J 2023;61: 2201512

Conclusions: Bronchiolitis Obliterans Syndrome (BOS)

- Bronchiolitis obliterans (BO) is a rare chronic irreversible obstructive lung disease leading to obstruction and/or obliteration of small airways
- 3 separate BO clinical entities: post-infectious BO (PIBO), BO post lung transplantation and BO after bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (HSCT)
- Although lung biopsy remains the gold standard to diagnose BO, PIBO can be diagnosed on history, clinical, physiological and radiological findings
- Post transplantation the non-histological diagnosis is termed Bronchiolitis Obliterans Syndrome (BOS)
- HRCT is the imaging method of choice
- Further studies of BAL analysis might identify biomarkers used to predict and diagnose BOS, or to assess treatment response
- Treatment: anti-inflammatory and anti-fibrosis
- Further research is crucial to explain the exact mechanisms of BO and to develop new treatment options

Good collaboration hematology-respiratory department

GRAZIE!


World Asthma Day
• May 7, 2024 •
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ASTHMA EDUCATION EMPOWERS
Information is Key
SIMRI
società italiana per le malattie respiratorie infantili
Broncopneumologia
Pulmonary Unit