HYPERTENSION PULMONAIRE

et

DEFICITS IMMUNITAIRES PRIMITIFS / ERREURS INNEES de l'IMMUNITE

Primary Immune Deficiencies / Inborn Errors Immunity (DIP/IEI)

Association Franco-Méditerranéenne de Pneumo-Cardiologie

A F M P

21ème Réunion 24-27 avril 2025

Bologne Italie

Pr Louis-Jean COUDERC

louisjean.couderc@gmail.com

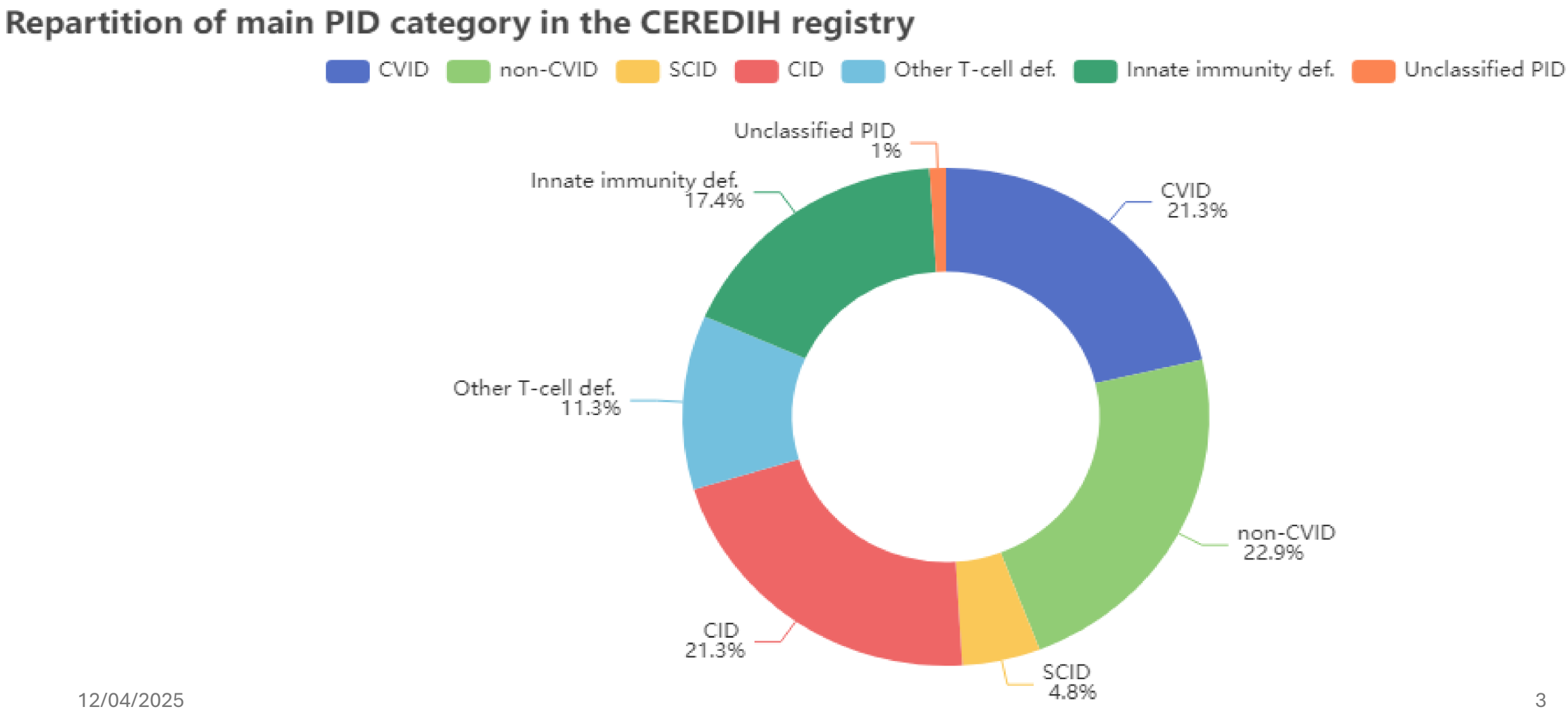
Hypertension Pulmonaire et DIP/IEI

Conflits d'intérêt

⇨ *en lien avec ce sujet :* aucun

⇨ *en général depuis 5 ans :* Air Liquide, Aria Médical, Novartis

Main PID category



Déficit Immunitaire Commun Variable : devenu un de vos connaissances!

- **Diminution du taux sérique de 2 isotypes d'immunoglobulines** avec un nombre normal ou faiblement abaissé de lymphocyte-B
- Plus de 60% des cas diagnostiqués à l'âge **adulte**
- Révélé dans 90% des cas par des infections broncho-pulmonaires et ORL à des germes usuels, mais à **rechute**
- Fréquence élevée(70%) de **complications non-infectieuses** ; au niveau respiratoire:

  dilatation des bronches⇨ immunoglobulines IV/SC

  pneumopathie interstitielle lymphoïde et/ou granulomateuse (GLILD) ⇨immunosuppresseurs

  asthme

Goussault H et al. Respir Res 2019 ; Cunningham-Rundles C et al. Blood 2009 ; Verma B et al. Lancet Respir Med 2015

Déficit Immunitaire Commun Variable

Onoletkova I et al. Orphanet J Rare Dis 2018

Table 1 The number of patients, registration rate, percentage of pediatric patients, follow-up period and mean monthly Ig dose per country

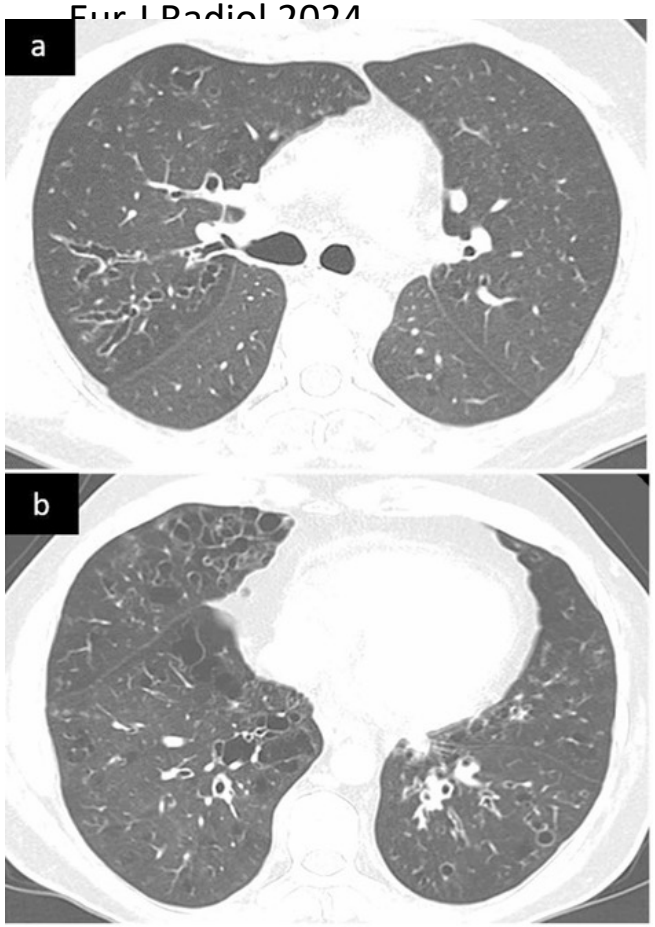
Country	Number of patients in the registry	Rate per 1 million of population	Percentage of patients diagnosed before 18 y.o.	Median (mean) follow-up period, years	Total person years	Percentage of patients with identified relative monthly Ig dose	Mean (SD) monthly Ig dose, mg/kg
Austria	5	0.6	80.0%	9.0 (10.6)	53	80%	450 (327)
Belarus	2	0.2	100%	3.0 (3.0)	6	N.A.	N.A.
Belgium	21	1.9	71.4%	6.0 (7.7)	162	61.9%	431 (110)
Czech Republic	90	8.6	30.0%	11.0 (12.1)	1093	80%	266 (146)
Egypt	4	0.5	100%	12.0 (10.3)	41	75%	300 (265)
Estonia	6	4.5	16.7%	6.5 (5.5)	33	100%	361 (70)
France	319	5.1	18.8%	6.0 (10.5)	3334	65.8%	538 (178)
Georgia	1	0.2	100%	5.0 (5.0)	5	100%	369 (—)
Germany	475	5.8	34.5%	7.0 (9.2)	4377	71.6%	385 (184)
Greece	34	3.1	76.5%	6.0 (9.3)	317	67.6%	544 (182)
Ireland	20	4.4	15.0%	15.5 (15.1)	302	50%	510 (68)
Italy	397	6.7	27.7%	7.0 (8.7)	3470	56.4%	405 (218)
Lithuania	4	1.3	0.0%	4.0 (6.5)	26	75%	380 (99)
Netherlands	183	11.0	38.3%	8.0 (9.9)	1803	56.3%	508 (214)
Poland	39	1.0	100%	5.0 (5.6)	218	100%	430 (142)
Russia	20	0.1	100.0%	6.0 (5.5)	110	90%	442 (146)
Serbia	11	1.5	81.8%	4.0 (5.5)	60	90.9%	400 (0)
Slovakia	13	2.4	84.6%	3.0 (5.5)	71	100%	392 (156)
Spain	258	5.5	24.4%	1.0 (3.4)	884	12.8%	412 (175)
Sweden	14	1.5	7.1%	8.0 (10.0)	140	78.6%	498 (221)
Switzerland	26	3.3	30.8%	7.0 (7.6)	197	69.2%	477 (287)
Turkey	75	1.0	76.0%	5.0 (5.6)	420	72%	472 (107)
U.K.	683	10.9	18.9%	7.0 (10.6)	7244	52.6%	528 (165)
Total/ overall	2700	3.9	30.5%	6.0 (9.0)	24,366	58.0%	454 (196)

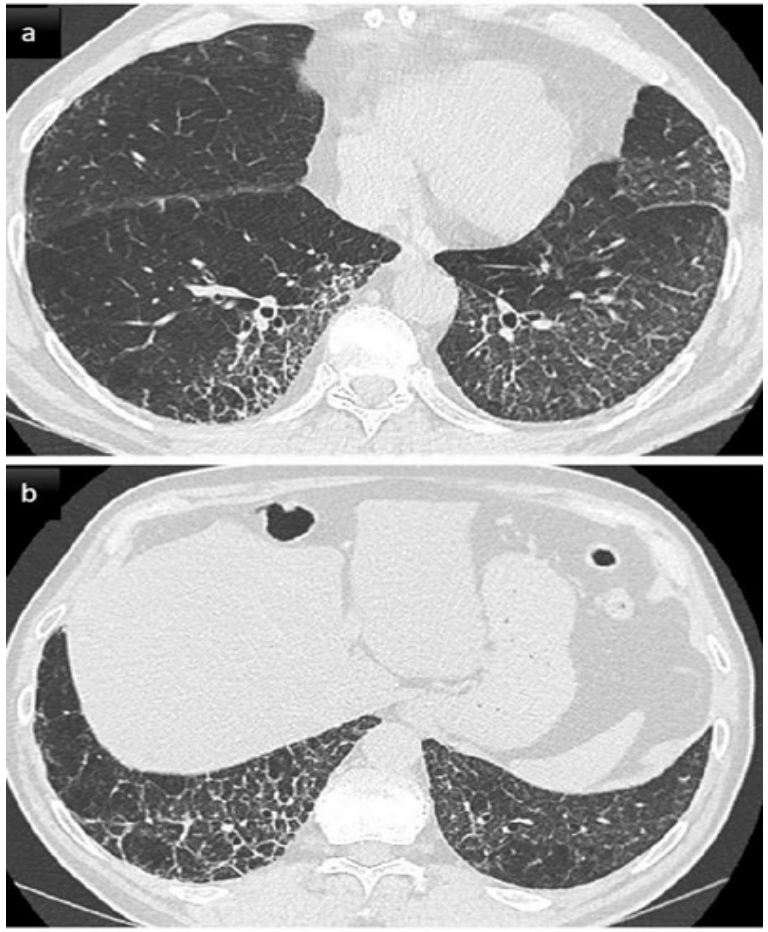
Ig immunoglobulin, *N.A.* data not available, *y.o.* years old

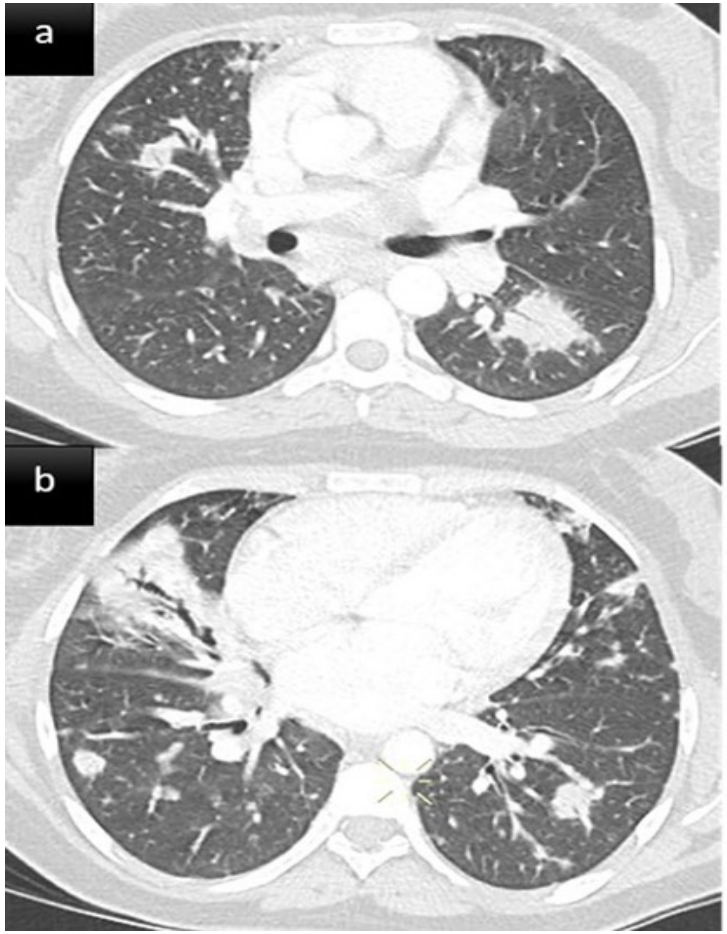
DICV: bronchectasies- GLILD

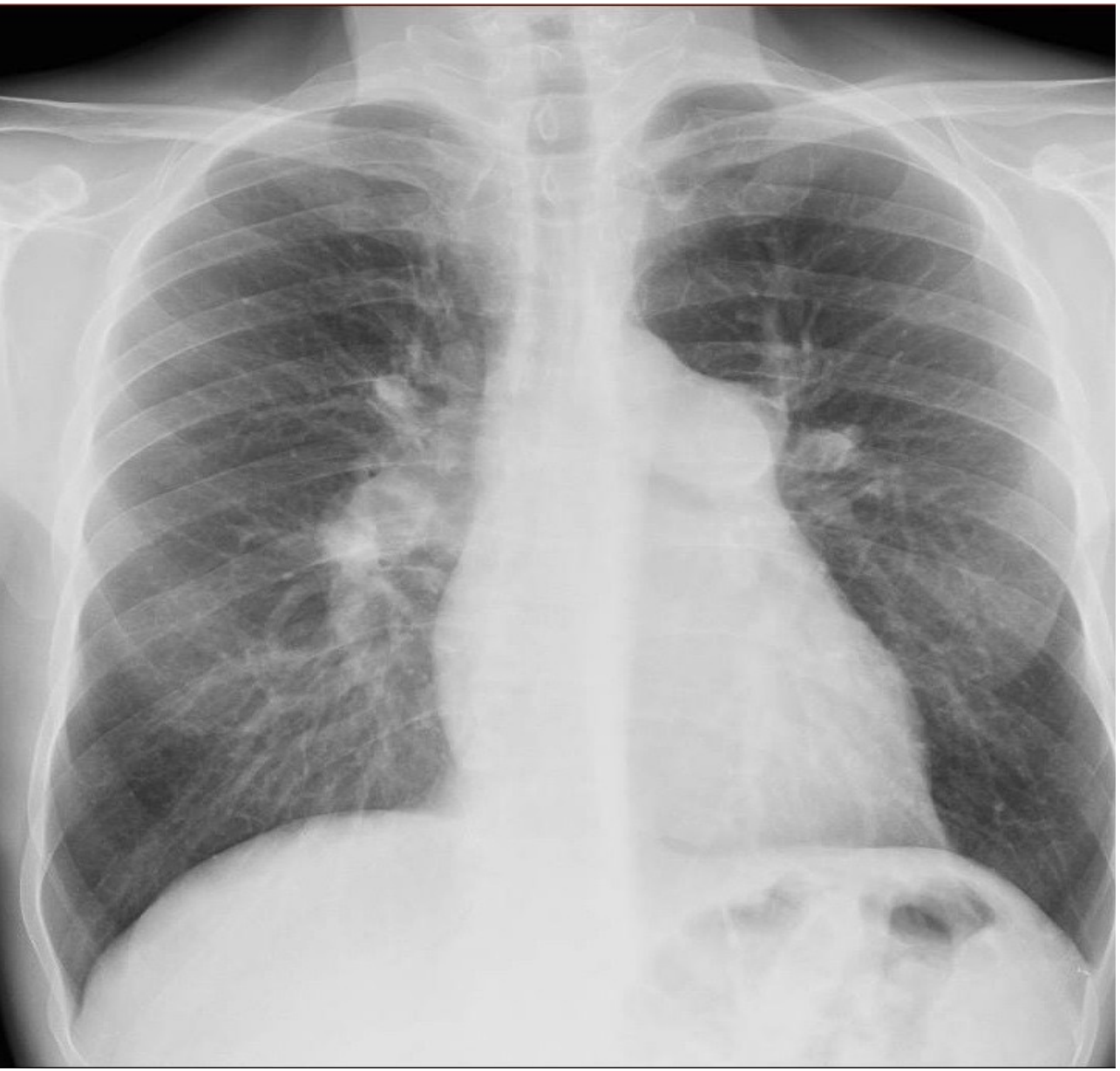
Grenier Ph et al.

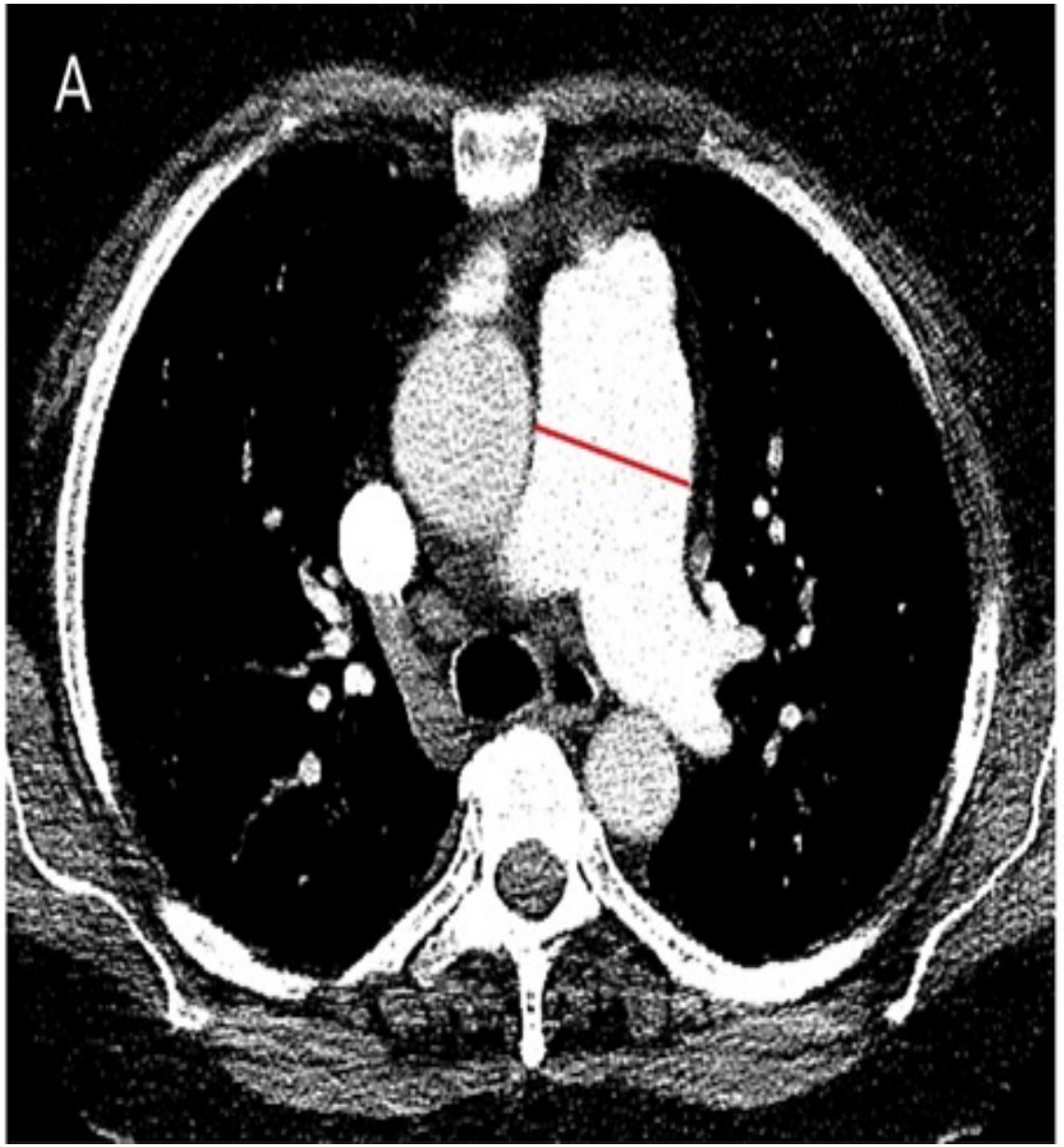
Eur J Radiol 2024







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DICV et Hypertension Pulmonaire

les premiers cas anecdotiques

2007 M-55 ans- diagnostic simultané HP sévère(mPAP 61 mm Hg ; RVP11 UW; mPCP 15 mm Hg) avec DICV (bronchectasies); ⇨iloprost inhalé.

2015 M- DICV 11ans; IgG +/-⇨ bronchectasies

24 ans : syndrome néphrotique ↦ amylose AA; HP ↦amylose pulmonaire; décès

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2020 M–DICV à 19 ans. 38 ans: IgG iv.

42 ans: HP (mPAP 54 mm Hg ;RVP 15 UW; DC 3,05 L/mn/m2)

44 ans :biopsie pulmonaire: GLILD (CPT 78%;DLCO48%) +remodelage vasculaire artériel et veineux⇨CS+ epoprostenol

F– DICV 27 ans ⇨ IgG

33ans:GLILD+ remodelage artériel avec prolifération intimale mais échocardio Nl

41 ans HP (mPAP 58mm Hg;RVP 9,2 UW;DC 4,02L/mn/m2; mPCP 9 mmHg)

⇨tadalafil+ambrisentan

Daniil Z et al. Eur J Intern Med 2007– Arslan S et al. J Clin Immunol 2015 – Huston J et al. Pulm Circ 2020

DICV et Hypertension Pulmonaire

caractéristiques cliniques

auteur/pays	Thoré P-2021-France	Parsons AJ -2025-USA
N -sex ratio H/F	10 1/9	5 1/ 4
Age (an) diagnostic		
DICV	31.5 (12-49)	41 (36-47)
HP	44 (20-69)	47 (39-58)
Délai (an) HP /DICV	10 (0-30)	6,5 (0-18)
Complications DICV		
GLILD	8	5
cytopénie	4	4
splénectomie	4	0
hypertension portale	6	3

Thoré P et al. J Clin Immunol 2021 Parsons AJ et al. Pulm Circ 2025

DICV et Hypertension Pulmonaire

caractéristiques fonctionnelles et hémodynamiques

auteur/pays	Thoré P-2021-France	Parsons AJ -2025-USA
EFR		
S. obstructif	0 /10	1/4
S. restrictif	1/ 10	2/4
DLCO %	46 % (n=9)	35,7% (n=4)
Cathétérisme cardiaque droit		
N	10	5
mPAP mm Hg	41,5 (35-64)	56 (42-79)
mPCP mmHg	8,7 (3-14)	12 (2-20)
DC L/mn	5,04 (3,4- 7,03)	3,32 (2,8- 4,3)
RVP Wood units	7,6 (4,7-14,2)	11,3 (7,6-14)

DICV et Hypertension Pulmonaire

Evolution et traitements

auteur/pays	Thoré P-2021-France	Parsons AJ -2025-USA
PDE5i	5	
+ CS	1	
PDE5i+ERA	2	4
+ CS	1	
évolution (mois)	24,5 (3-105)	
vivant/décédé	9/1	5/0
	stabilité	aggravation
transplantation		
TBP-Foie		2 + 1 inscrit
TBP		1 + 1 inscrit

DICV et Hypertension Pulmonaire

Les messages pour la maison ….et le cerveau

- Fréquence élevée= 0,37% des DICV = 400 fois plus fréquente que dans la population générale

  Humbert M et al. Am J Respir Crit Care Med 2006
- Prédominance féminine
- Survenue tardive , environ 10 ans après le diagnostic de DICV
- Fréquence de l'association avec une GLILD
- Abaissement disproportionné de la DLCO
- Rôle de l'hypertension portale ⇨ recherche systématique
- Rajouter l'hypertension pulmonaire dans les complications non-infectieuses des malades avec DICV

Maglione PJ et al. Ann Allergy Asthma Immunol 2021

DICV et Hypertension Pulmonaire
Mécanismes physiopathologiques

- Probablement multifactoriels:
  -infiltration inflammatoire des parois vasculaires pulmonaires
  -insuffisance respiratoire chronique (GLILD, bronchectasies)
  -hypertension portale
  -compression vasculaire / fibrose médiastinale (sarcoidose-like)
  -facteurs génétiques

  ⇨ classe 5 «mal connu ou multi-factoriel »

  Oui, Mais ?

Table 1. Current clinical classification of pulmonary hypertension, adapted from [1].

Group 1: Pulmonary arterial hypertension (PAH)
1.1 Idiopathic
1.1.1 Non-responders at vasoreactivity testing
1.1.2 Acute responders at vasoreactivity testing
1.2 Heritable
1.3 Associated with drugs and toxins
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
1.6 Persistent PH of the newborn
Group 2: PH associated with left heart disease
2.1 Heart failure:
2.1.1 with preserved ejection fraction
2.1.2 with reduced or mildly reduced ejection fraction
2.2 Valvular heart disease
2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
Group 3: PH associated with lung diseases and/or hypoxia
3.1 Obstructive lung disease or emphysema
3.2 Restrictive lung disease
3.3 Lung disease with mixed restrictive/obstructive pattern
3.4 Hypoventilation syndromes
3.5 Hypoxia without lung disease (e.g., high altitude)
3.6 Developmental lung disorders
Group 4: PH associated with pulmonary artery obstructions
4.1 Chronic Thromboembolic Pulmonary Hypertension (CTEPH)
4.2 Other pulmonary artery obstructions
Group 5: PH with unclear and/or multifactorial mechanisms
5.1 Hematological disorders
5.2 Systemic disorders
5.3 Metabolic disorders
5.4 Chronic renal failure with or without hemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis

- Kularante F et al. J Cardiovas Dev Dis 2024

DICV et Hypertension Pulmonaire

aspect histologique

Parsons AJ et al.

Pulm Circ 2025

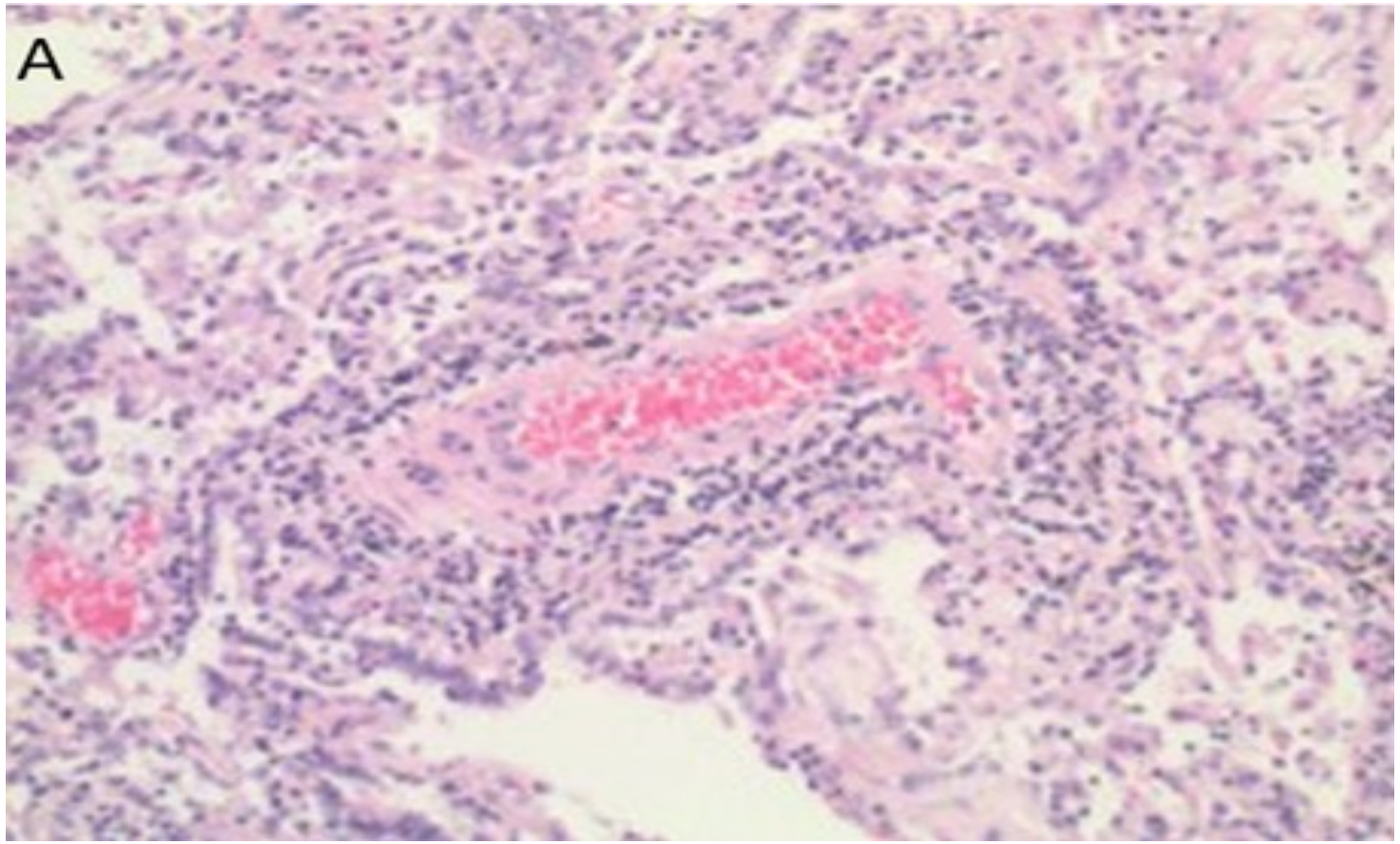


TABLE 13 Phenotypic features associated with pulmonary arterial hypertension mutations

Gene	Pulmonary hypertension phenotypic association	Putative molecular mechanism	Inheritance pattern	Potential distinguishing clinical and examination features	Investigations	Populations	Reference
BMPR2	Heritable and idiopathic PAH	Haploinsufficiency	Autosomal dominant	No specific or diagnostic clinical features described	No discriminative investigations described	Paediatric and adult	[152]
ATP13A3	Heritable and idiopathic PAH	Unknown	Autosomal dominant	No specific or diagnostic clinical features described	No discriminative investigations described	Adult	[149]
AQP1	Heritable and idiopathic PAH	Unknown	Autosomal dominant	No specific or diagnostic clinical features described	No discriminative investigations described	Adult	[149]
ABCC8	Heritable and idiopathic PAH	Haploinsufficiency	Autosomal dominant	No specific or diagnostic clinical features described	No discriminative investigations described	Adult	[153]
KCNK3	Heritable and idiopathic PAH	Haploinsufficiency	Autosomal dominant	No specific or diagnostic clinical features described	No discriminative investigations described	Adult	[154]
SMAD9	Heritable and idiopathic PAH	Haploinsufficiency	Autosomal dominant	No specific or diagnostic clinical features described	No discriminative investigations described	Adult	[155]
Sox17	Heritable and idiopathic PAH Congenital heart disease	Unknown	Autosomal dominant	No specific or diagnostic clinical features described	No discriminative investigations described	Paediatric and adult	[149]
CAV1	Heritable and idiopathic PAH Lipodystrophy	Gain of function; dominant negative	Autosomal dominant	Deficiency of subcutaneous adipose tissue	Fasting triglyceride and leptin levels	Paediatric and adult	[156]
TBX4	Heritable and idiopathic PAH Small patella syndrome (ischiopatellar dysplasia) Parenchymal lung disease Bronchopulmonary dysplasia Persistent pulmonary hypertension of the neonate	Unknown	Autosomal dominant	Patellar aplasia Skeletal abnormalities, in particular pelvis, knees, and feet	Skeletal X-rays: pelvis, knees, and feet CT chest: diffuse parenchymal lung disease	Paediatric and (less commonly) adult	[149, 157]
EIF2AK4	Pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis	Loss of function	Autosomal recessive	Distal phalangeal clubbing	Reduced DLCO CT chest: interlobular septal thickening and mediastinal lymphadenopathy, and centrilobular ground-glass nodular opacities	Adult	[158]
KDR	Heritable and idiopathic PAH	Loss of function	Autosomal dominant	No specific or diagnostic clinical features described	Possible reduced DLCO	Older-onset adult	[159]
ENG	Heritable and idiopathic PAH Hereditary haemorrhagic telangiectasia	Unknown	Autosomal dominant	Telangiectasia	Iron-deficiency anaemia	Adult and paediatric	[160]
ACVRL1	Heritable and idiopathic PAH Hereditary haemorrhagic telangiectasia	Haploinsufficiency	Autosomal dominant	Abnormal blood vessel formation	Presence on imaging of pulmonary, hepatic, cerebral, or spinal arteriovenous malformations	Adult and paediatric	[160]
GDF2	Heritable and idiopathic PAH Hereditary haemorrhagic telangiectasia	Haploinsufficiency	Autosomal dominant	Visceral arteriovenous malformations Bleeding diathesis	Invasive endoscopic assessment of gastrointestinal telangiectasia	Adult and paediatric	[149]

CT, computed tomography; DLCO, lung diffusion capacity for carbon monoxide; PAH, pulmonary arterial hypertension.

Humbert M et al. Eur Respir J 2023

Déficit en GATA2 : déficit de la phagocytose

- Déficit de phagocytose responsable

  - d'infections sévères par des Mycobactéries tuberculeuse et non tuberculeuses

  - de cytopénies sévères

  - de protéïnose alvéolaire (non auto-immune)

  - de leucémie myélomonocytaire et de leucémie aigüe myéloïde

.En rapport avec une mutation autosomique dominante ou sporadique du gêne codant pour GATA2, facteur de transcription pour la différentiation des cellules hématopoïétiques immatures et des cellules endothéliales

Déficit en GATA2 et Hypertension Pulmonaire

Série du NIH: N=95 malades avec déficit en GATA2

hypertension pulmonaire (HP)=9 (10%)

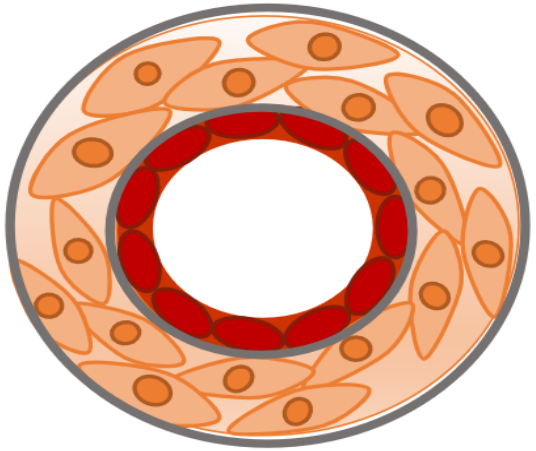
6 avec un syndrôme myélodysplasique

5 allogreffés de cellules souches hématopoïétiques (3 avec PAP, 2 sans PAP) ⇨guérisson de HP dans 5/5 cas

↦Rôle d'une altération de l'expression de la NO synthase au niveau de l'épithélium aérien , qui est dépendant de l'interaction de GATA2 avec le promoteur de la NO synthase endothéliale

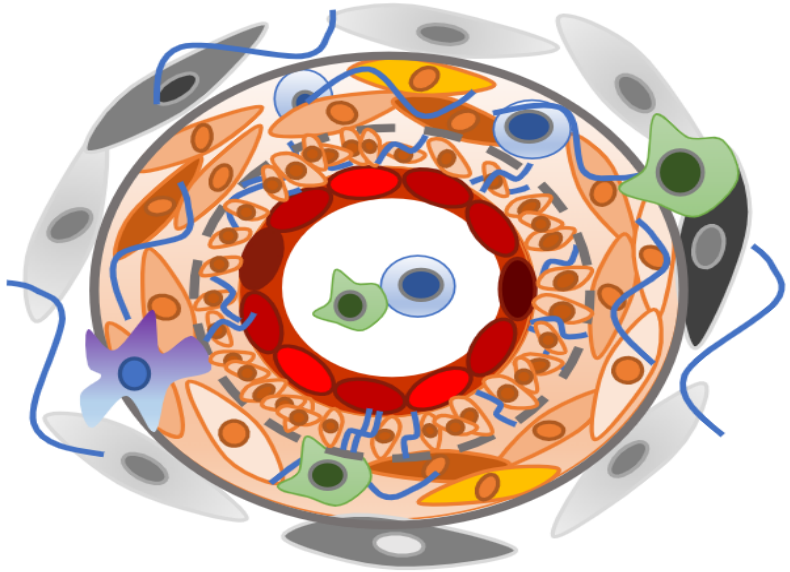
Marciano BE et al. Chest 2021

Vasculopathy



- Vasoconstriction
- BMPR2 mutations

Cellular heterogenity



- Different cellular states/phenotypes
- Altered immune landscape
- Complex – cellular – extracellular matrix cross-talk

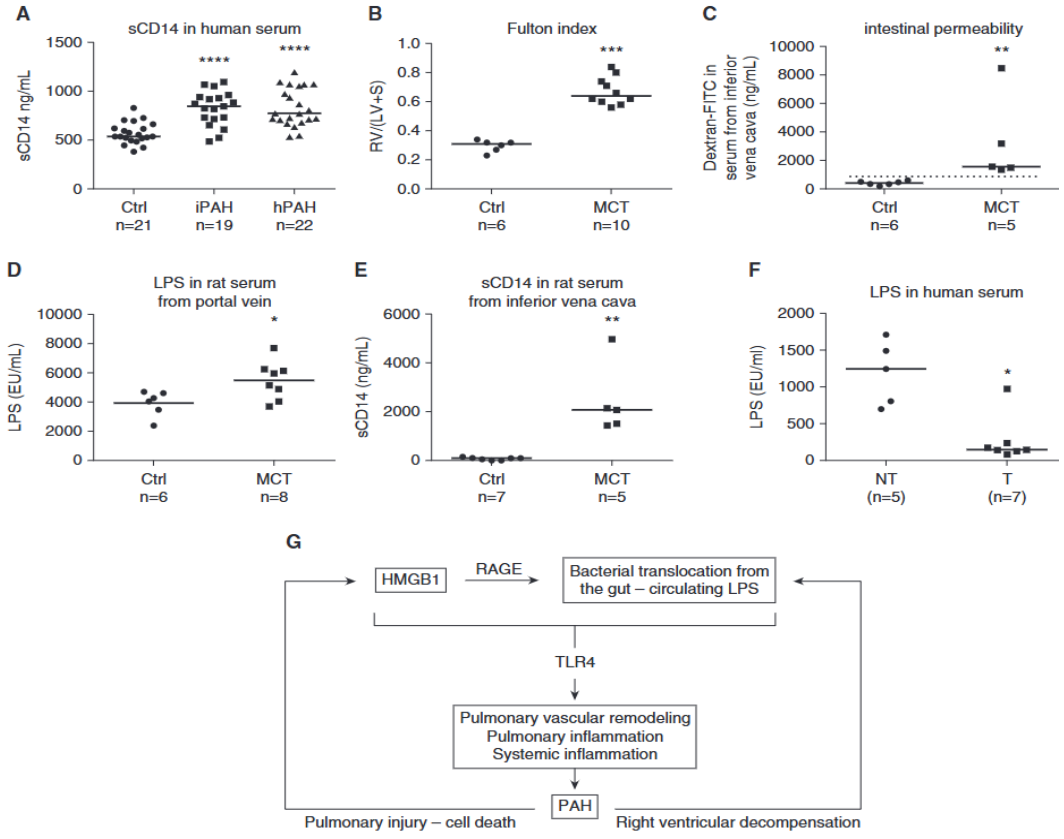
Inter-organ communication

- Altered metabolism
- Hormonal status
- Blood/ surrogates/ biomarkers
- Omics approaches and big data
- Network analysis

Kwapiszewska G. et al Am J Respir Cell Mol Biol 2025

Hypertension Artérielle Pulmonaire : le cercle vicieux de la « Gut-Lung connexion »

Ranchoux B et al. Am J Respir Cell Mol Biol 2017



Immunological linkage mechanisms between the gut and the lungs

Zhu J et al. Front Immunol 2025

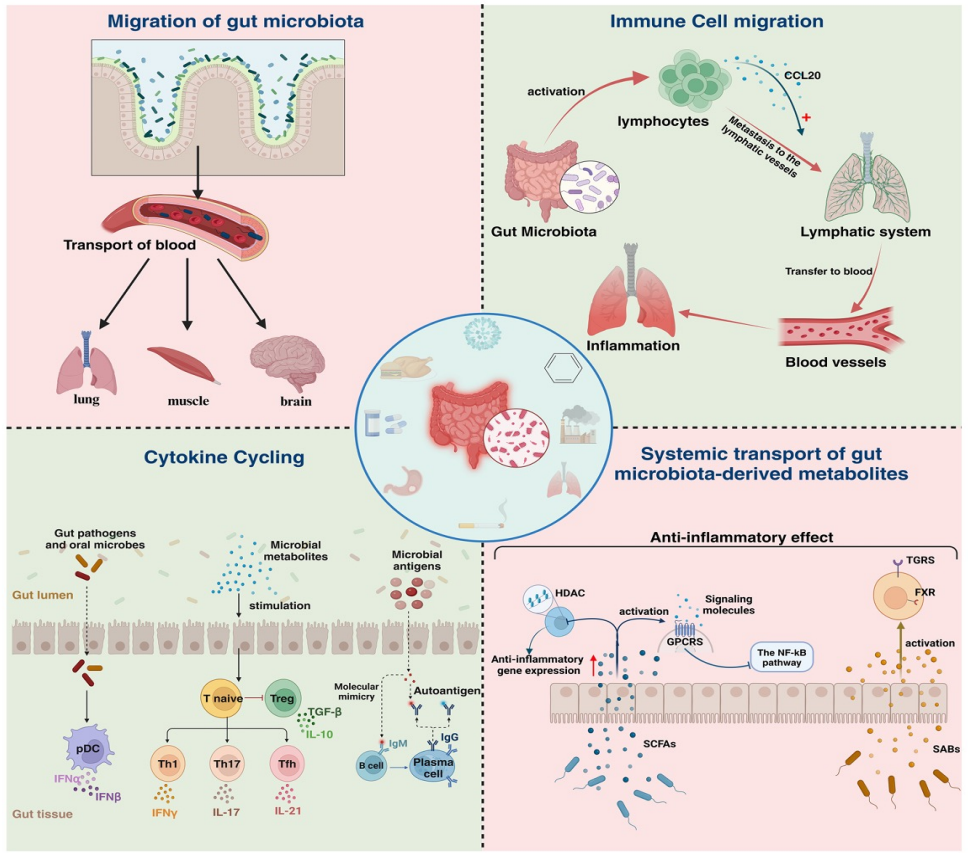


FIGURE 2
Specific manifestations of lung and intestinal immune correlations. Lung and intestinal immune relevance is manifested in four main areas: Migration of gut bacteria, immune cell migration,cytokine recycling and systemic transport of gut microbiota-derived metabolites. HDAC, histone deacetylases; GPCRS, G protein-coupled receptors;SCFAS, short-chain fatty acids; TGRS, traditional gender roles; FXR, Farnesoid X receptor ;SABs, Secondary bile acids.

Hypertension Pulmonaire et DIP /IEI

2ème (et dernière…) série de messages et quelques suggestions

*Rechercher sur les TDM des signes suggérant une HP: diamètre des artères pulmonaires ; taille du VD

*Surveillance échocardiographique chez malades avec DICV, surtout les femmes, avec GILD et/ou hépatopathie

⇨ faire étude échocardiographique des DICV (travaux disponibles insuffisants)

⇨Registre des malades avec HP au sein du CEREDIH

*Prise en charge multidisciplinaire +++

Johnston SL et al. Postgrad Med 2004 Ali Akbar Z et al. J Cardiov Med 2010 Cambray-Gutierrez JC et al Rev Alerg Mex 2015

Hypertension pulmonaire et DIP/IEI

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