ANCA-associated ILD

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Antineutrophil cytoplasmic antibody-associated vasculitis (AAV)

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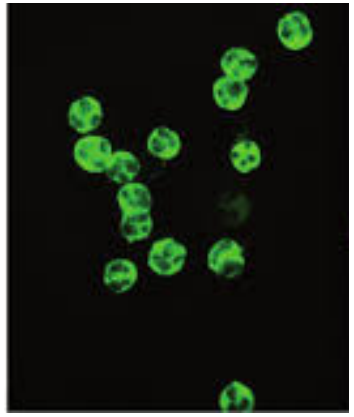
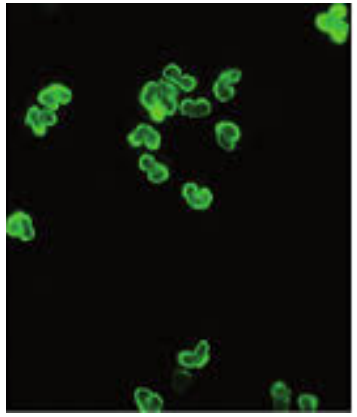
Pauci-immune necrotizing vasculitides that affect small to medium sized blood vessels

Granulomatosis with polyangiitis (GPA)

c-ANCA



p-ANCA



Microscopic polyangiitis (MPA)

Eosinophilic granulomatosis with polyangiitis (EGPA)

Pulmonary complications of AAV are exceedingly common and in 157 AAV patients who had a HRCT at the time of diagnosis, 66.2% had pulmonary involvement (16% asymptomatic)[2]

1. Sinico R.A. et al. (2014). *Clin Exp Rheumatol;* 32 (Suppl. 82): S112-S117 2. Villeneuve et al. (2023). *Semin Arthritis Rheum*; 63:152307

AAV-associated pulmonary disease

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	Microscopic polyangiitis (%)	Granulomatosis with polyangiitis (%)	Eosinophilic granulomatosis with polyangiitis (%)
Upper airway manifestations			
Sinusitis	Rare	61	14–73
Nasal mucosa ulcers/bleeding	Rare	Up to 70	Rare
Saddle nose	Rare	20–50	Rare
Lower airway manifestations			
Asthma	5	8	★ 95–100
Tracheal stricture and stenosis	Rare	15	Rare
Bronchiectasis	16–32	13–20	15–20
Pulmonary manifestations			
Lung nodules	7–30	★ 30–89	11–89
Diffuse alveolar hemorrhage	★ 10–55	5–30	3–8
Lung fibrosis/interstitial lung disease	32–45	23	Rare
Pleural manifestations			
Pleural effusion	22–27	12–20	12–22

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Kim JK et al. (2021). *Tuberc Respir Dis;* 84:255-262

Prevalence of ILD in AAV is increasingly recognized

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First described in 1990[1], but we now know that ILD is somewhat common in AAV:

Lung fibrosis/interstitial lung disease	32–45	23	Rare

The 2022 ACR/EULAR classification for MPA includes ILD as a key item:

CLINICAL CRITERIA	
Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage or septal defect / perforation	-3
LABORATORY, IMAGING, AND BIOPSY CRITERIA	
Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies ANCA positive	+6
Fibrosis or interstitial lung disease on chest imaging	+3
Pauci-immune glomerulonephritis on biopsy	+3
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-1
Blood eosinophil count ≥ 1 x10^9/liter	-4

Sum the scores for 6 items, if present. A score of ≥ 5 is needed for classification of MICROSCOPIC POLYANGIITIS.

Accordingly, a 2020 international consensus on ANCA testing beyond vasculitis recommended testing in all patients with IIP[4]

1. Nada AK etal. (1990). *Mayo Clin* Proc; 65(6):847-56 2. Kim JK et al. (2021). *Tuberc Respir Dis;* 84:255-262 3. Suppiah R. et al. (2022). *Arthritis & Rheumatol; 74* (3): 373-548 4. Moiseev S et al. (2020). *Autoimmunity Reviews*; 19(9): 102618

3 Categories of ILD with ANCA positivity

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AAV-ILD	à la IPAF	IIP
Patients meet diagnostic criteria for MPA or GPA	Doesn't meet criteria for AAV, but believe ANCA is clinically significant	Non-pathogenic ANCA in setting of idiopathic disease

Presence of antibody alone (without other features of vasculitis) does not seem to be clinically significant or affect survival

1. Liu GY et al. (2019). *CHEST*. 156(4): 715-23 2. Hozumi H et al. (2018): *PLoS One;* 13(6):e019965

Causes of ANCA Positivity

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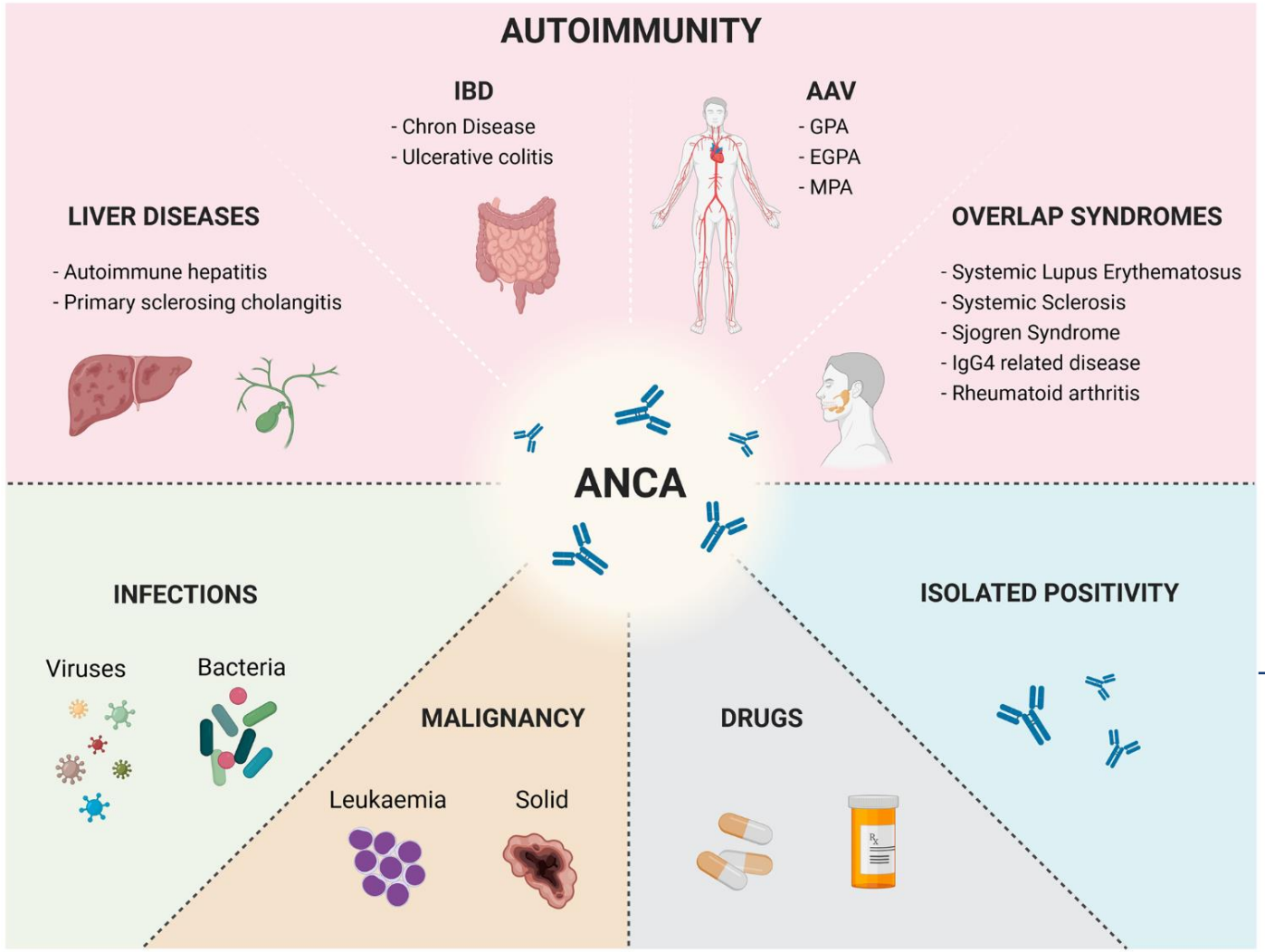

198 Australians with low pre-test clinical suspicion were tested and ANCA was present in 5.1%, but majority low level positives and atypical p-ANCA.

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1. Deshpande P et al. (2016). *Pathology;* 48(5):483-490 2. Folci et al. (2021). *Clin Rev Allergy Immunol.* 63(2):107-23. 3. Moiseev et al. (2020). *Autoimmun Rev.* 19(9):102618

À la IPAF…ANCA + ILD may represent a preclinical phase of vasculitis

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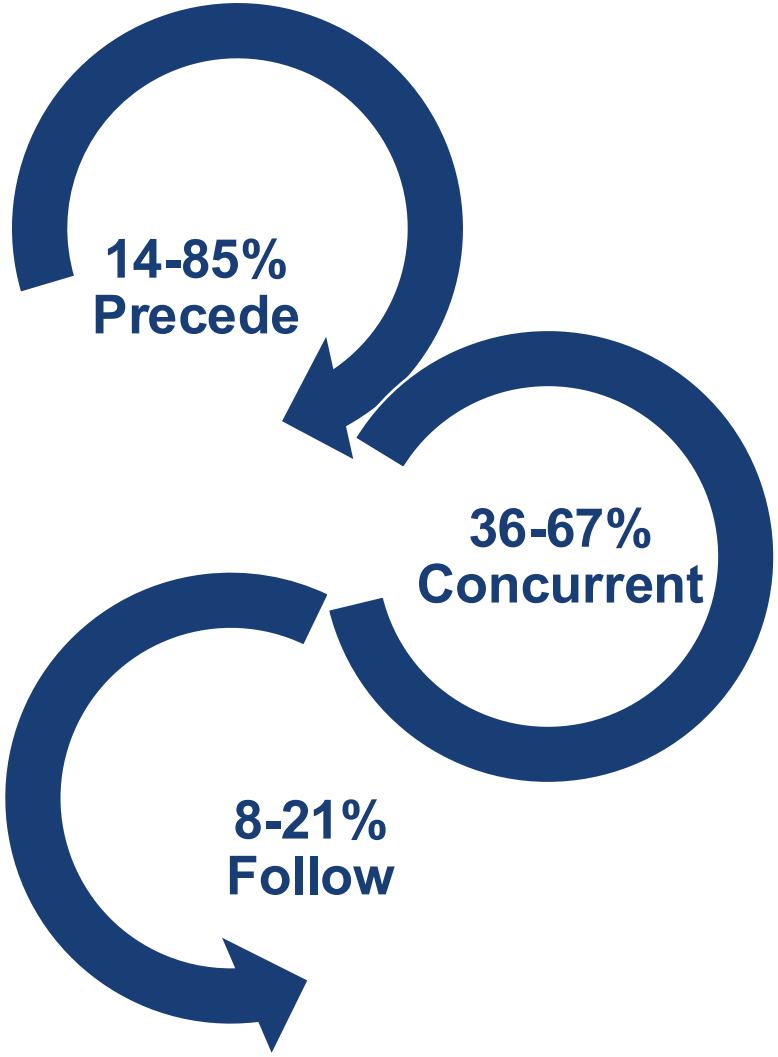
- 5-10% of patients with ILD are ANCA+ when diagnosed
- 10% of patients with IIP will subsequently seroconvert and become ANCA +
- 25% of ANCA+ will progress to overt vasculitis after a median of **2 years**



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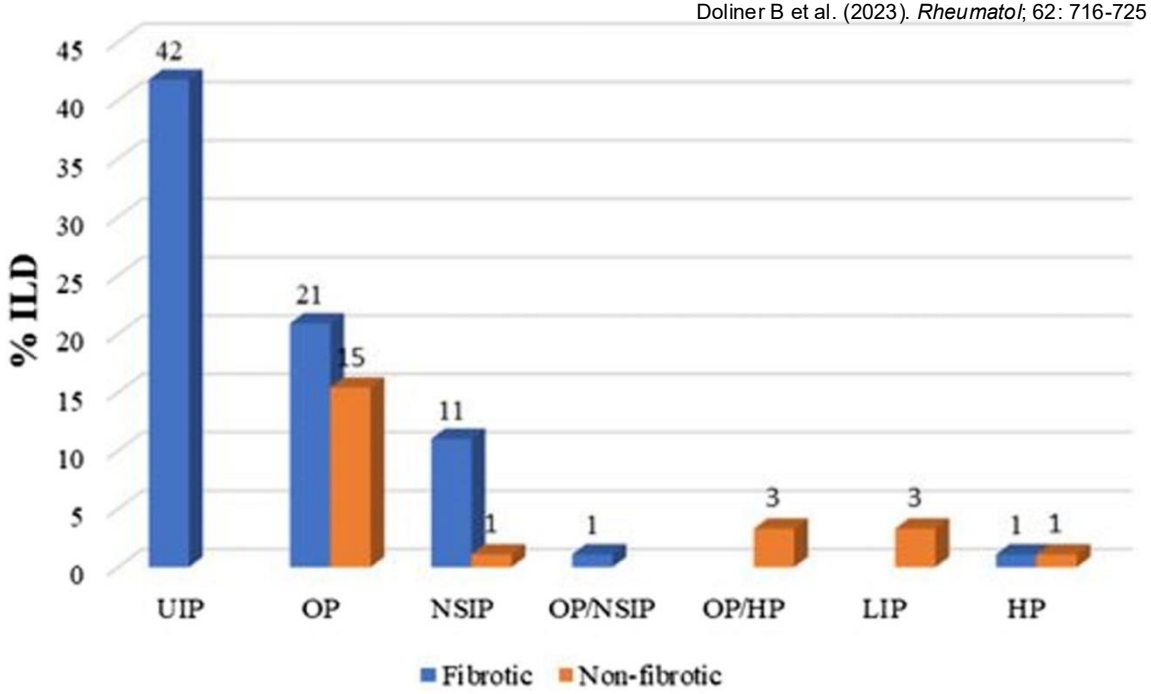
1. Specks U et al. (2025). *Rheumatol;* 64:i42-i47 2. Liu GY et al. (2019). *CHEST*. 156(4): 715-23 3. Kagiyama N et al. (2015): *BMJ Open Respir Res;* 2:e000058 4. Ando M et al. (2013). *Respir Med*;107:608-615 5. Hozumi H et al. (2016). *Lung*; 194: 235-242 6. Doliner B et al. (2023). *Rheumatol*; 62: 716-725 7. Katsumata et al. (2015). *Clin Med Insights*; 9(S1):51-56 8. Shen HC et al. (2024). *ACR Open Rhematol*; 6(8):463-469 9. Hu H et al. (2021). *Int J Rheum Dis;* 24:1460-1466 10. Kadura S et al. (2021). *Eur Respir Rev*; 30:210123

AAV-ILD

- Median age at diagnosis mid-60s to mid-70s vs. median age of MPA w/o ILD is closer to 55
- 76% symptomatic at time of diagnosis
- ILD can be progressive despite clinically quiescent systemic vasculitis
- Like in other SARD-ILD, surgical lung biopsies are rarely required for diagnosis
  - ➢ When performed, biopsies most commonly show histologic diagnosis of UIP followed by NSIP and are without capillaritis

Doliner B et al. (2023). *Rheumatol*; 62: 716-725



1. Kadura S et al. (2021). *Eur Respir Rev*; 30:210123 2. Sun K et al. (2022). *Curr Rheumatol Rep*;24:259-267 3. Moura MC et al. (2025). *Semin Arthritis and Rheum*; 73:152726 4. Maillet T et al. (2020). *Journal of Autoimmunity*; 106:102338 5. Arulkumaran N et al. (2011). *Rheumatol*; 50:2035-2043 6. Foulon G et al. (2008). *Respir Med*:102:1392-1398 7. Baqir M et al. (2019). *Sarcoidosis Vasc Diffuse Lung Dis*: 36:195-201

AAV-ILD is associated with a higher risk of death vs. AAV alone

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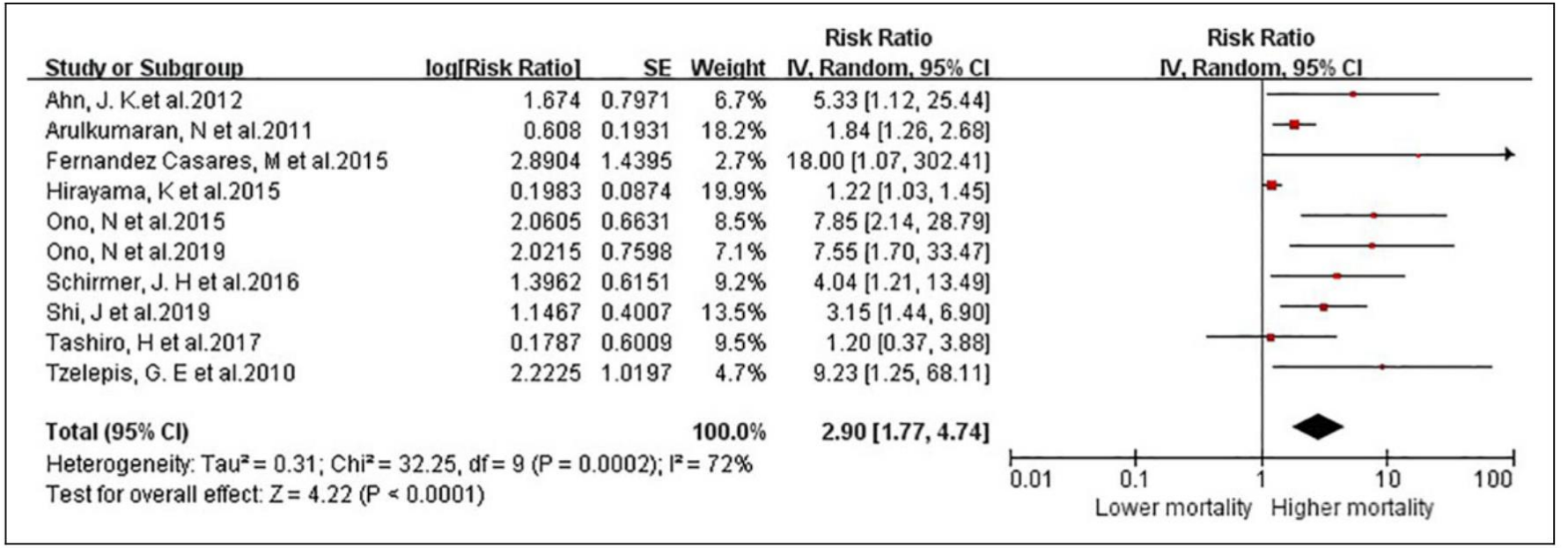
Zhou P et al. (2021). *Chron Resp Dis*; 18:1-11



Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Ahn, J. K et al.2012	1.674	0.7971	6.7%	5.33 [1.12, 25.44]
Arulkumaran, N et al.2011	0.608	0.1931	18.2%	1.84 [1.26, 2.68]
Fernandez Casares, M et al.2015	2.8904	1.4395	2.7%	18.00 [1.07, 302.41]
Hirayama, K et al.2015	0.1983	0.0874	19.9%	1.22 [1.03, 1.45]
Ono, N et al.2015	2.0605	0.6631	8.5%	7.85 [2.14, 28.79]
Ono, N et al.2019	2.0215	0.7598	7.1%	7.55 [1.70, 33.47]
Schirmer, J. H et al.2016	1.3962	0.6151	9.2%	4.04 [1.21, 13.49]
Shi, J et al.2019	1.1467	0.4007	13.5%	3.15 [1.44, 6.90]
Tashiro, H et al.2017	0.1787	0.6009	9.5%	1.20 [0.37, 3.88]
Tzelepis, G. E et al.2010	2.2225	1.0197	4.7%	9.23 [1.25, 68.11]
Total (95% CI)			**100.0%**	**2.90 [1.77, 4.74]**

Heterogeneity: Tau² = 0.31; Chi² = 32.25, df = 9 (P = 0.0002); I² = 72%

Test for overall effect: Z = 4.22 (P < 0.0001)

In a meta-analysis performed by He et al. 50% of MPA-ILD patients died within 6 years of follow-up

Increased mortality

- UIP pattern
- Honeycombing
- Age
- Ever smoker
- FVC decline
- MPA
- AE

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1. Moura MC et al. (2025). *Semin Arthritis and Rheum*; 73:152726 2. He X et al. (2025). *Clinical Rheumatol;*44:1675-1689

Acute Exacerbations 2/2 AAV-ILD

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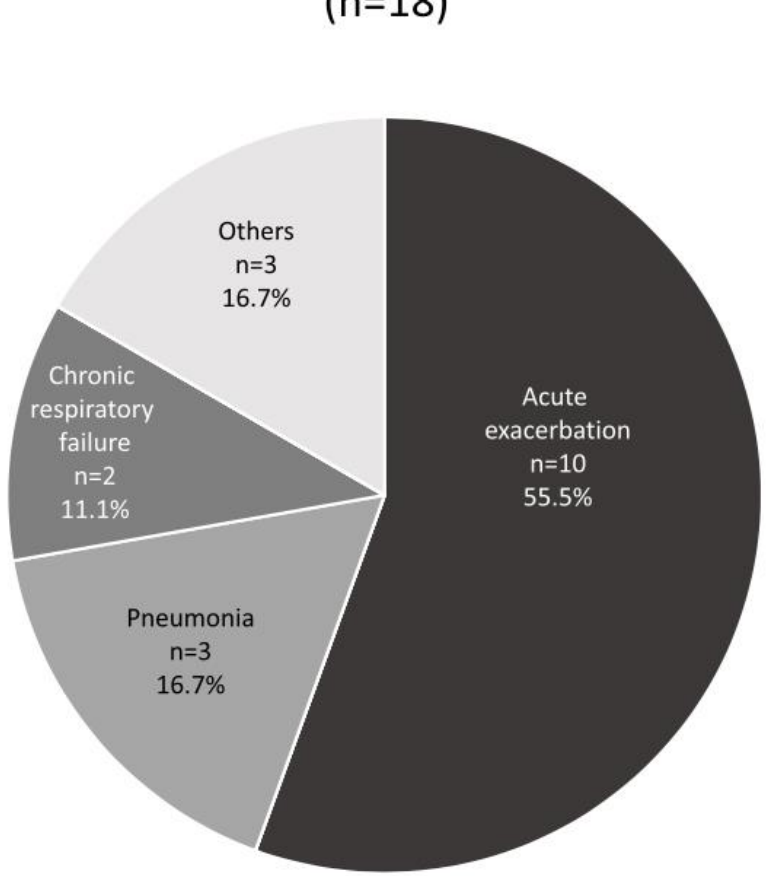
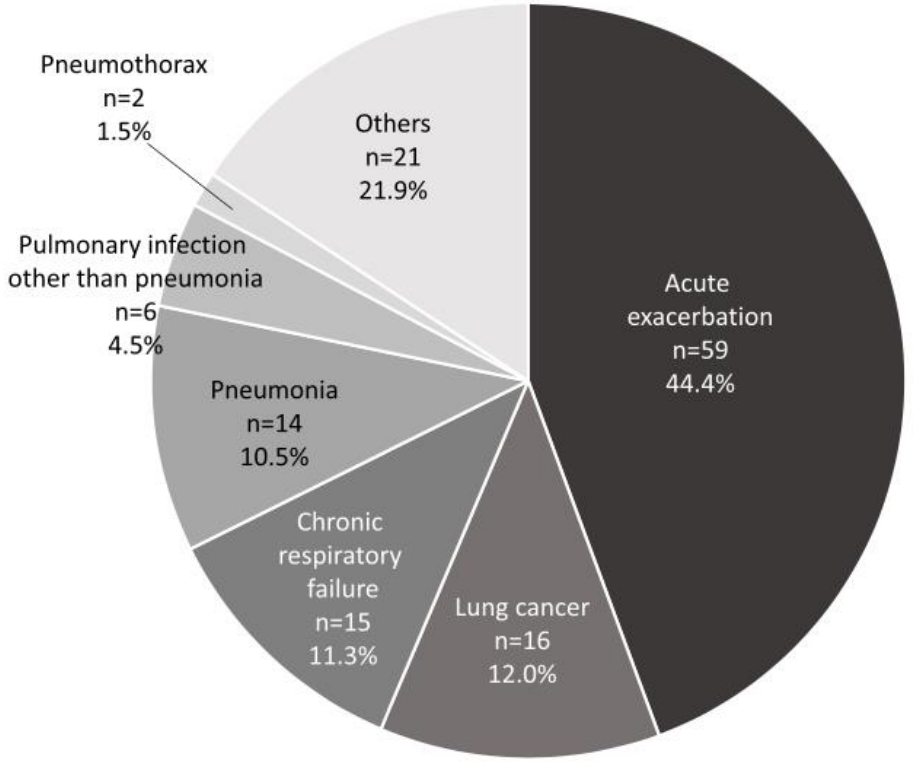
(A) (A) ANCA-ILD (n=18)



(B) IPF (n=133)



In mul uniforml

d they survival

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1. Otsuka J et al. (2022). *Respiratory Med*; 106992 2. We T et al. (2022). *Ther Adv Respir Dis*;16:1-12 3. Hozumi H et al. (2021).*CHEST*;159:2334-2345

Treatment of AAV-ILD

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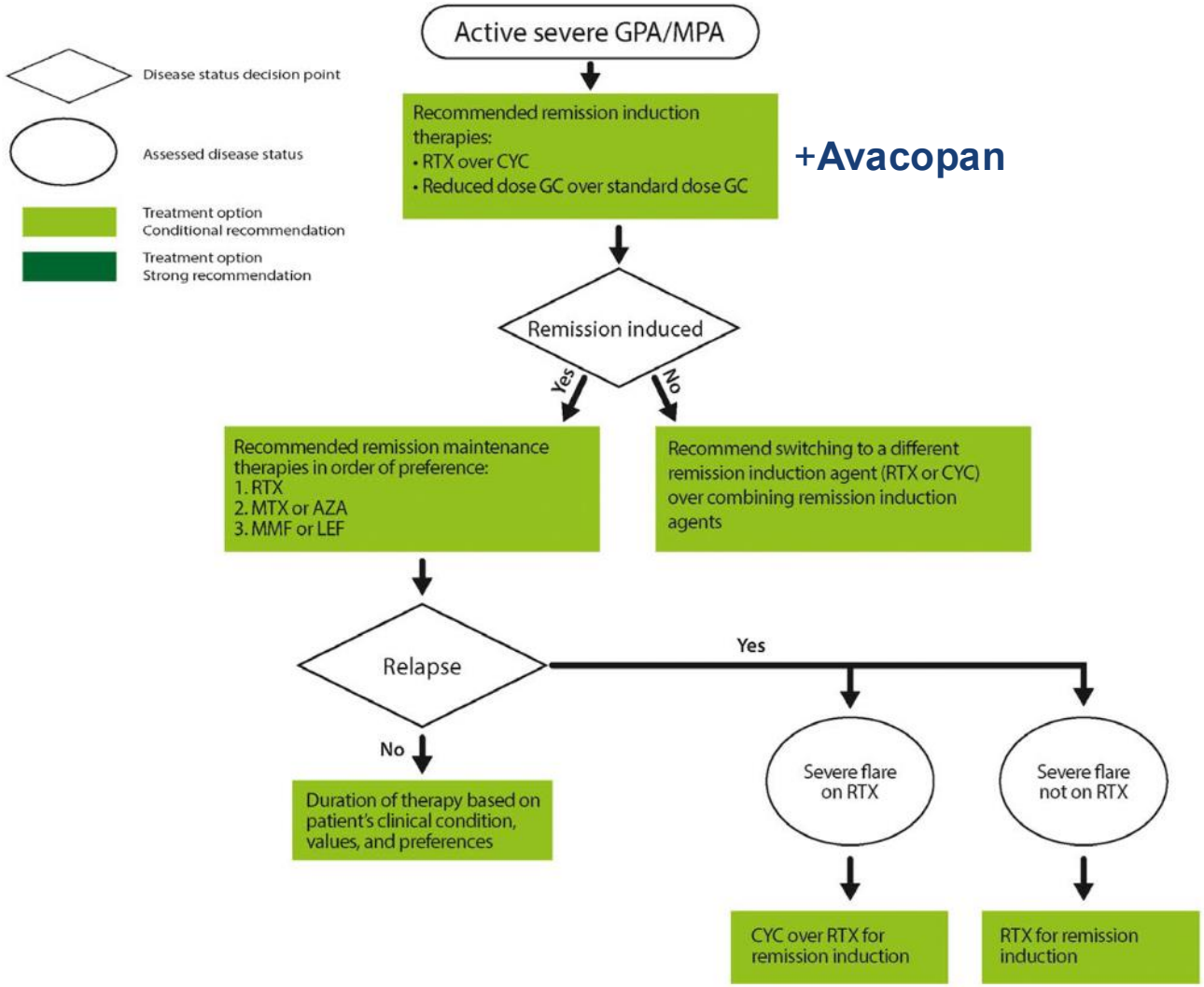
Severe Disease
Vasculitis with life- or organ-threatening manifestations



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1. Chung SA et al. (2021). *Arthritis & Rheumatol; 73* (8): 1366-1383. 2. Jane DRW et al. (2021). *NEJM*; 384(7):599-609.

However, impact of immunosuppression on fibrosis is uncertain

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- Immunosuppression with cytoxan or rituximab led to improvement in 96% with DAH and 90% with nodules, but 53% of those with ILD had progressive disease despite AAV remission after induction regimen
- Additionally, infection remains a frequent cause of death in AAV-ILD as it is in AAV
- There are reasonable concerns for possible harm due to the many similarities between AAV-ILD and IPF (particularly in patients without extra-pulmonary evidence of active vasculitis)
  - Advanced age
  - Male predominance
  - Risk of smoking
  - UIP predominance
  - Acute exacerbations with high mortality
  - Association with MUC5B promoter

1. Villeneuve et al. (2023). *Semin Arthritis Rheum*; 63:152307 2. Namba N et al. (2019). *Ann Rheum Dis*:78:1144-1146

Multiple, small studies suggest no benefit with immunosuppression

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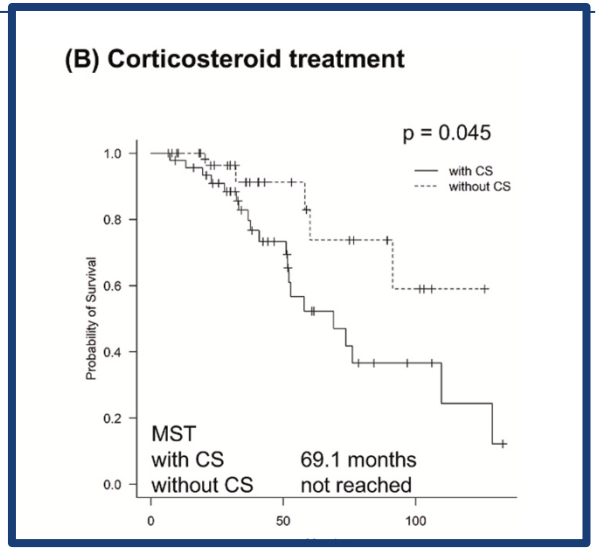
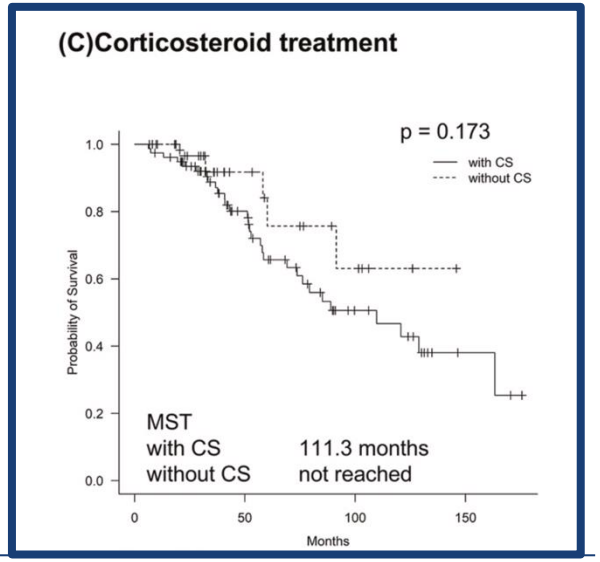
- Shimamura et al. found that patients with pulmonary-limited vasculitis treated with immunosuppression had a shorter survival time than those not treated
- In the prior systematic review (Zhou et al.) that assessed mortality risk of AAV-ILD, there was no beneficial effect in the immunosuppressive treatment subgroup and infection was one of the most frequent causes of death
- In a cohort study of 62 patients with AAV-ILD, neither immunosuppression for induction nor maintenance demonstrated any difference in survival
- In a group of elderly patients with AAV-ILD, steroid pulse therapy was reported as a significant risk factor for severe infection





1. *Shimamura T et al.* (2025). *Resp Investigation.*;63:1-6 2. Zhou P et al. (2021). *Chron Resp Dis*; 18:1-11 3. Maillet T et al. (2020).*J Autoimmun;* 106:102338 4. Yamaguchi K et al. (2021). *Rheumatol Int*;41:1641-1650

BUT, rationale for immunosuppression in other SARD-UIP could support use in AAV-UIP

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- Based on belief that background immune process is fueling fibrotic progression
- scRNA-seq of lung tissue obtained at the time of transplant from patients with IPF and SSc-ILD (7/8 UIP) showed many similarities, but distinct transcriptional signatures despite the shared histologic pattern
- RA-ILD responds well to immunosuppression regardless of ILD pattern
- AAV-ILD patients with UIP on biopsy were found to have significantly more inflammation than patients with IPF
- In a retrospective case series of 49 patients with AAV-ILD the combo of steroids + cytoxan or rituximab for induction appeared to lead to better outcomes with 3 year survival of 94% compared to 64% in patients with steroids alone

1. Valenzi, et al. (2021). *Front. Immunol.;12:595811 2.* Matson *et al.* (2022). *Chest.* 163(4):861-86 3. Comarmond C et al. (2014). *Medicine*. 93(24):340-9 4. Hosoda C et al. (2016). *Respirology;*21:920-6 5. Ando M et al. (2013).*Respir Med;*107:608-15

The role of antifibrotics

- INBUILD included one patient with ANCA-ILD and another with AAV-ILD and did not allow background immunosuppression such as cytoxan, rituximab, or high dose steroids
- There have been more trials on pirfenidone's efficacy in ILD other than IPF, but quality of evidence of lower
- RELIEF included 37 patients with CTD-ILD and a progressive phenotype, trial was terminated due to under recruitment and primary outcome was non-significant, but there were trends towards preserved lung fxn and relative treatment effects were similar to SENSCIS and INBUILD
- PIRFENIVAS, a phase 2 trial for Pirfenidone in ANCA-ILD (with or without systemic features) was unfortunately terminated prematurely because of slow recruitment (7 out of 15 anticipated patients)

Soooo a pretty data free zone, but would be reasonable to follow the PPF guidelines:

We suggest nintedanib for the treatment of PPF in patients who have failed standard management for fibrotic ILD, other than IPF

1. Behr, et al. (2021). *Lancet Respir Med: 9:476-86 2.* Flaherty *et al.* (2022). *Eur Respir J*; 59: 2004538

New kid on the block→ Nerandomilast

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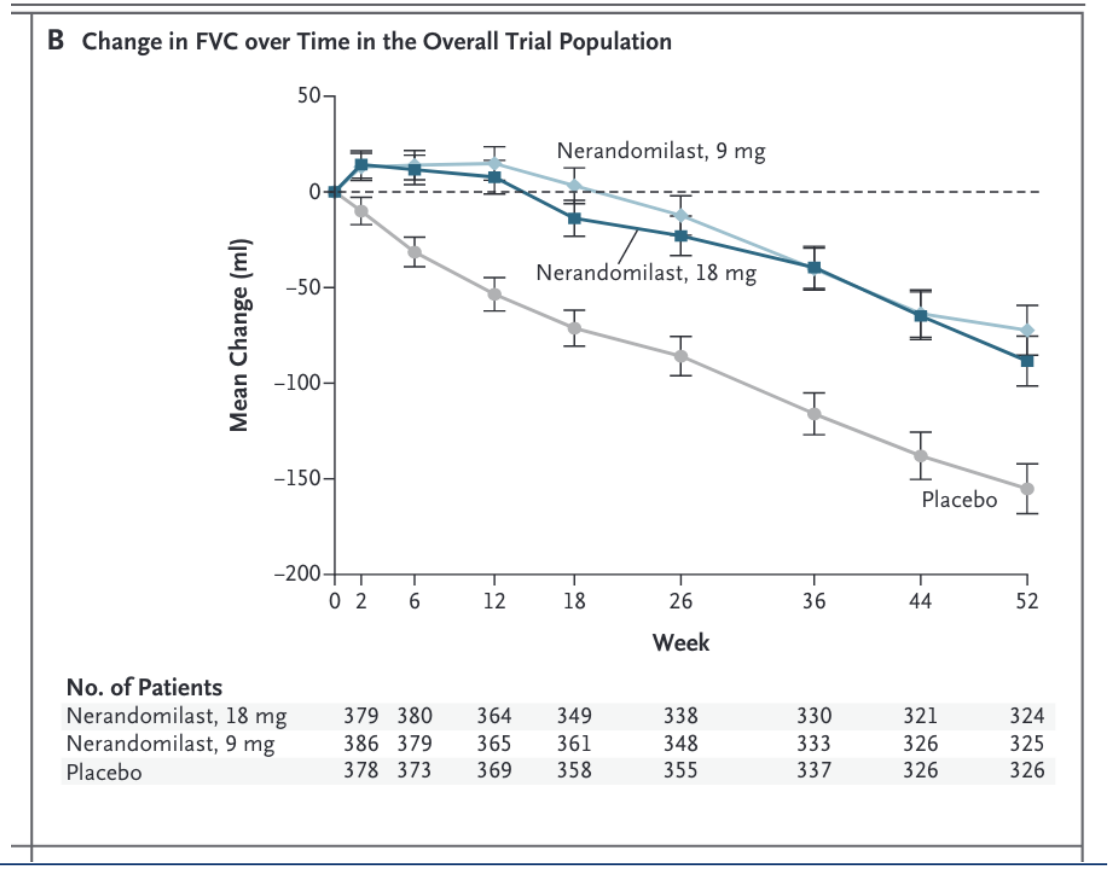
- Preferential phosphodiesterase 4B inhibitor which prevents inactivation of cAMP
- Elevated cAMP produces antifibrotic and immunomodulatory effects

Data comes from recently published phase 3 clinical trial (**FIBRONEER**)

- Progressive pulmonary fibrosis
- Stable immunosuppression allowed, but cytoxan, rituximab, and prednisone > 15 excluded
- Included 225 patients with autoimmune ILD (type not specified)
- Shown to slow progression consistently across ILD subtypes
- There is concern for vasculitis as an AE with PDE4 inhibition, but this was not seen in the trial



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Maher et al. (2025). *NEJM:392(22):2203-14*

ANCA-ILD Management Summary

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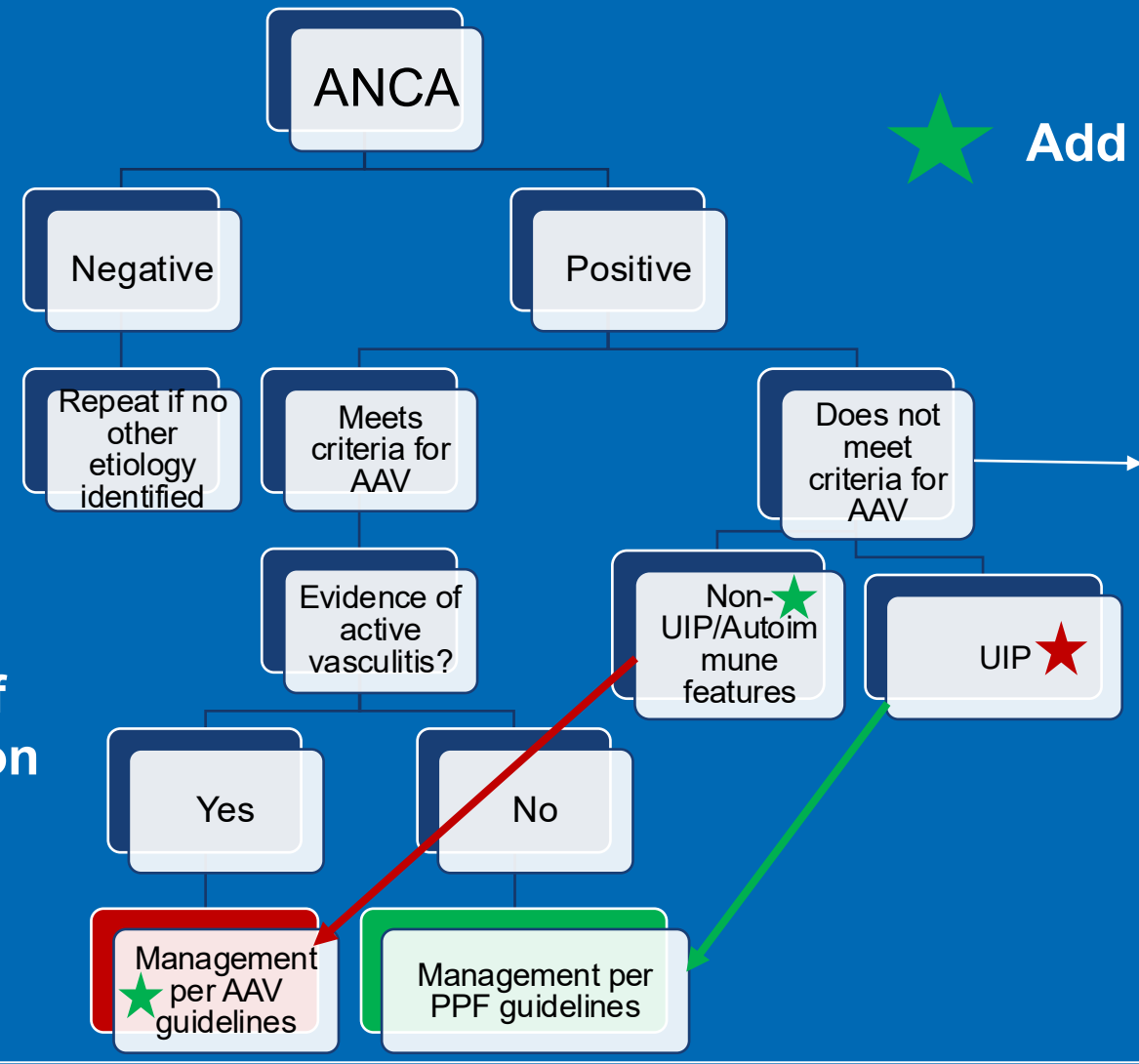

Add anti-fibrotic if progressive disease

Monitor for development of rhinosinusitis, arthralgias, rashes, neurologic dysfxn, hematuria, renal fxn

Consider a trial of immunosuppression

Summary

1. Historically, interest in the pulmonary manifestations of AAV has focused on DAH, but more recently ILD has been increasingly appreciated as a common manifestation

2. A diagnosis of ILD can precede, occur concurrently, or follow a diagnosis of AAV

3. The most common radiologic and histopathologic pattern seen in AAV-ILD is UIP followed by NSIP (without evidence of capillaritis) and diagnosis of AAV-ILD does not require a biopsy

4. Respiratory failure is a significant cause of death in AAV-ILD and may be driven by acute exacerbations

5. Optimal treatment regimen remains uncertain, but current practice follows guidelines for AAV and PPF