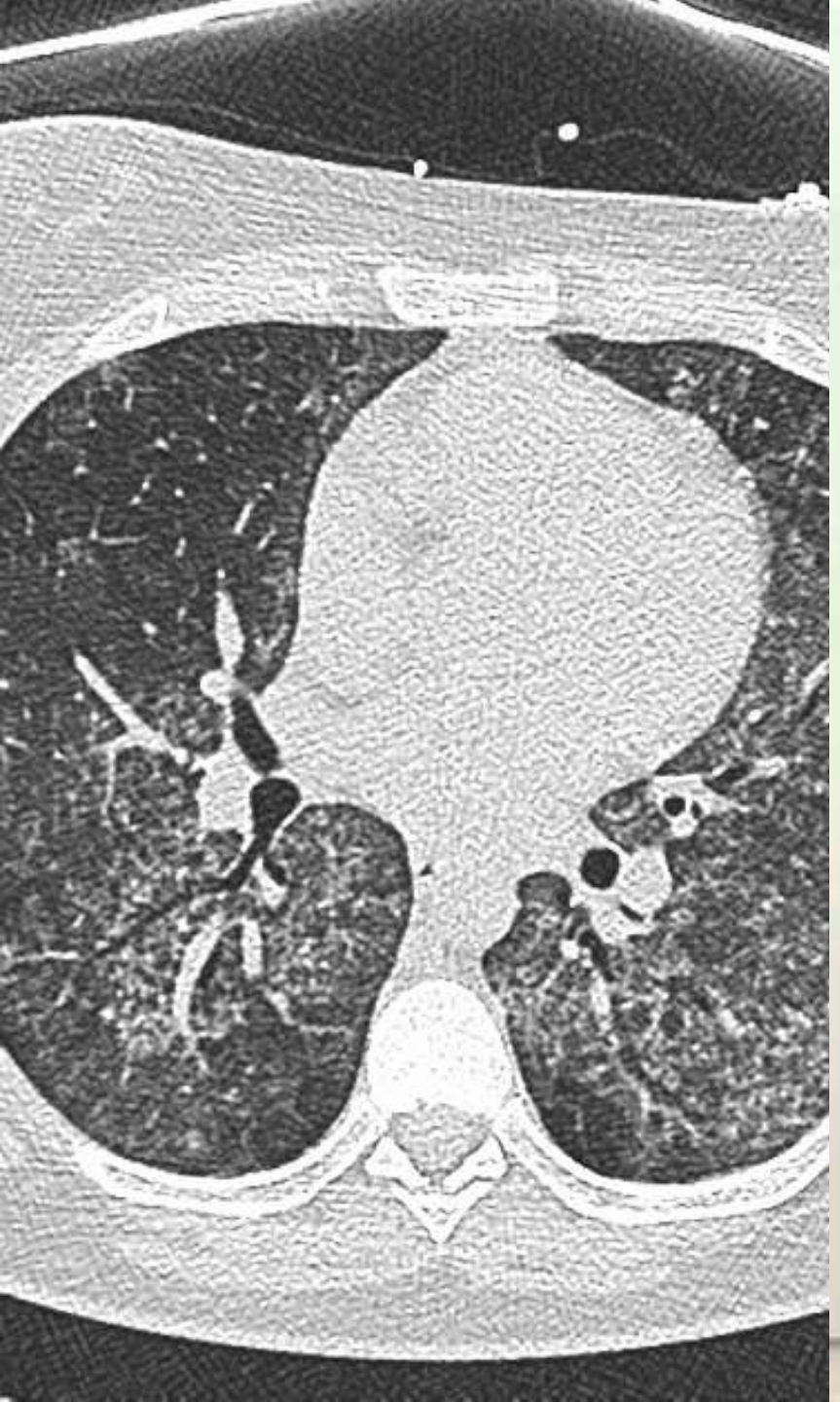
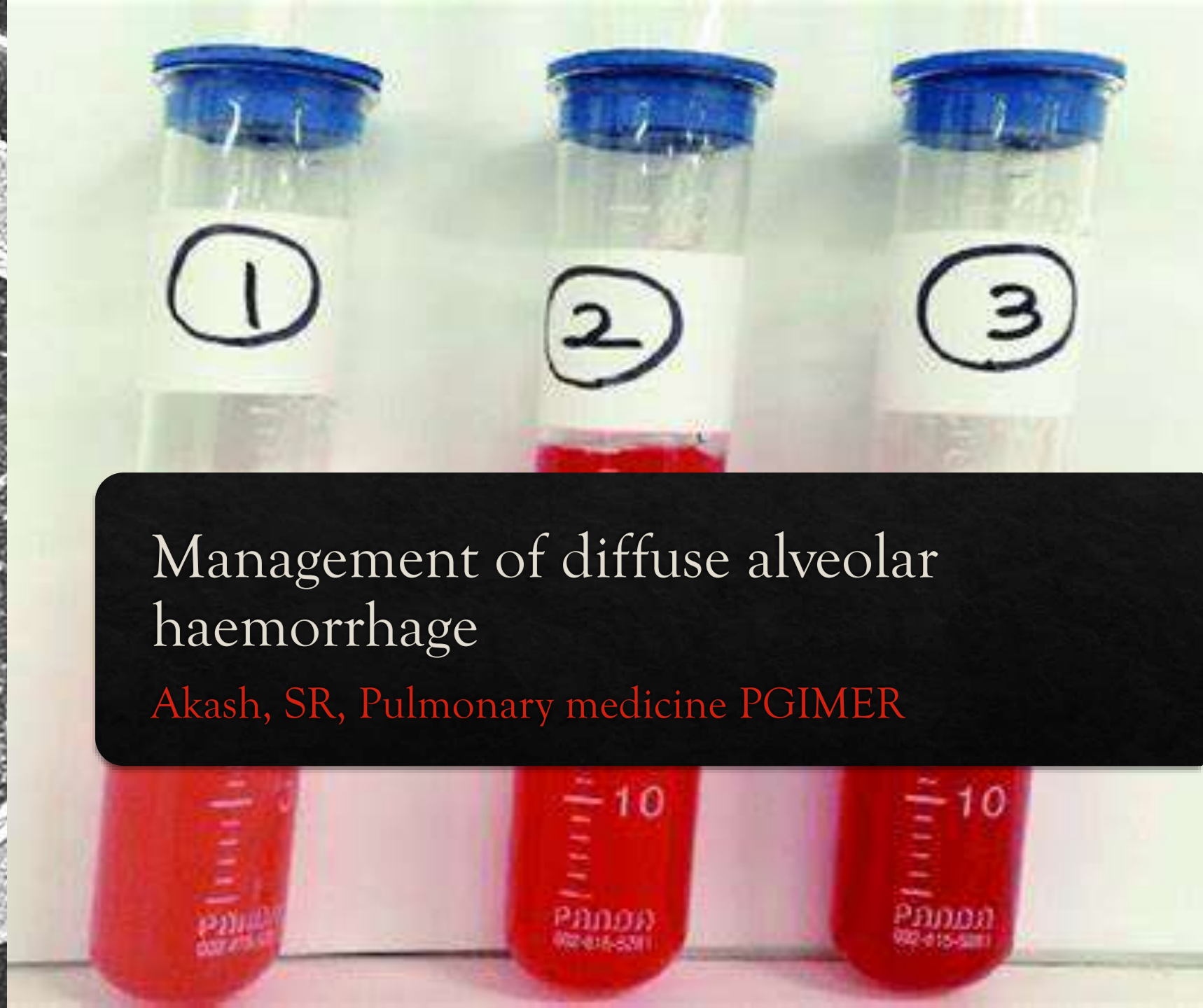




Management of diffuse alveolar haemorrhage

Akash, SR, Pulmonary medicine PGIMER

Questions

DAH: what is it?

Aetiology: what causes it?

Investigations: How to identify the cause?

Treatment: what are the evidences?

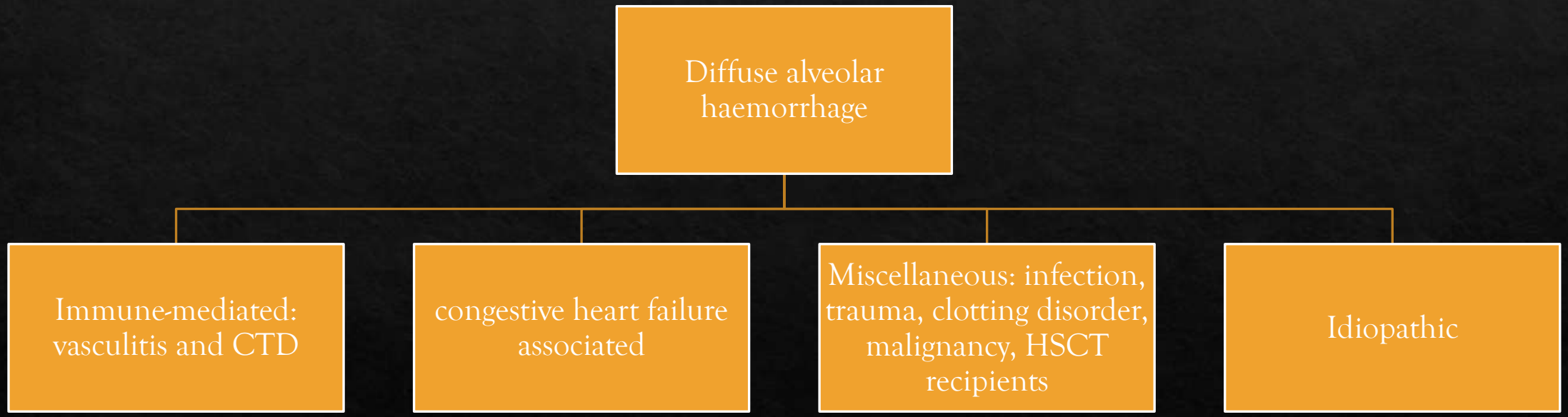
What does the future hold?

Diffuse alveolar haemorrhage

- A distinct form of pulmonary haemorrhage that originates from the pulmonary circulation- arterioles, venules and capillaries
- One of 3 pathological forms can be observed
  - Pulmonary capilleritis
  - Bland pulmonary haemorrhage
  - Diffuse alveolar damage
- A large number of diseases can manifest as DAH

Collard HR, Schwarz MI. Diffuse alveolar hemorrhage. Clinics in Chest Medicine. 2004 Sep;25(3):583–92.

Clinical classification



Pathological classification

Pulmonary capillaritis

- Neutrophilic infiltration of alveolar septae
- Necrosis of septae
- Loss of capillary integrity
- Spillage of RBC in alveoli and interstitium

Bland pulmonary haemorrhage

- Haemorrhage into the alveolar spaces without inflammation/destruction of alveolar structures

Diffuse alveolar damage

- ARDS due to any cause can lead to haemorrhage into the aveolar spaces

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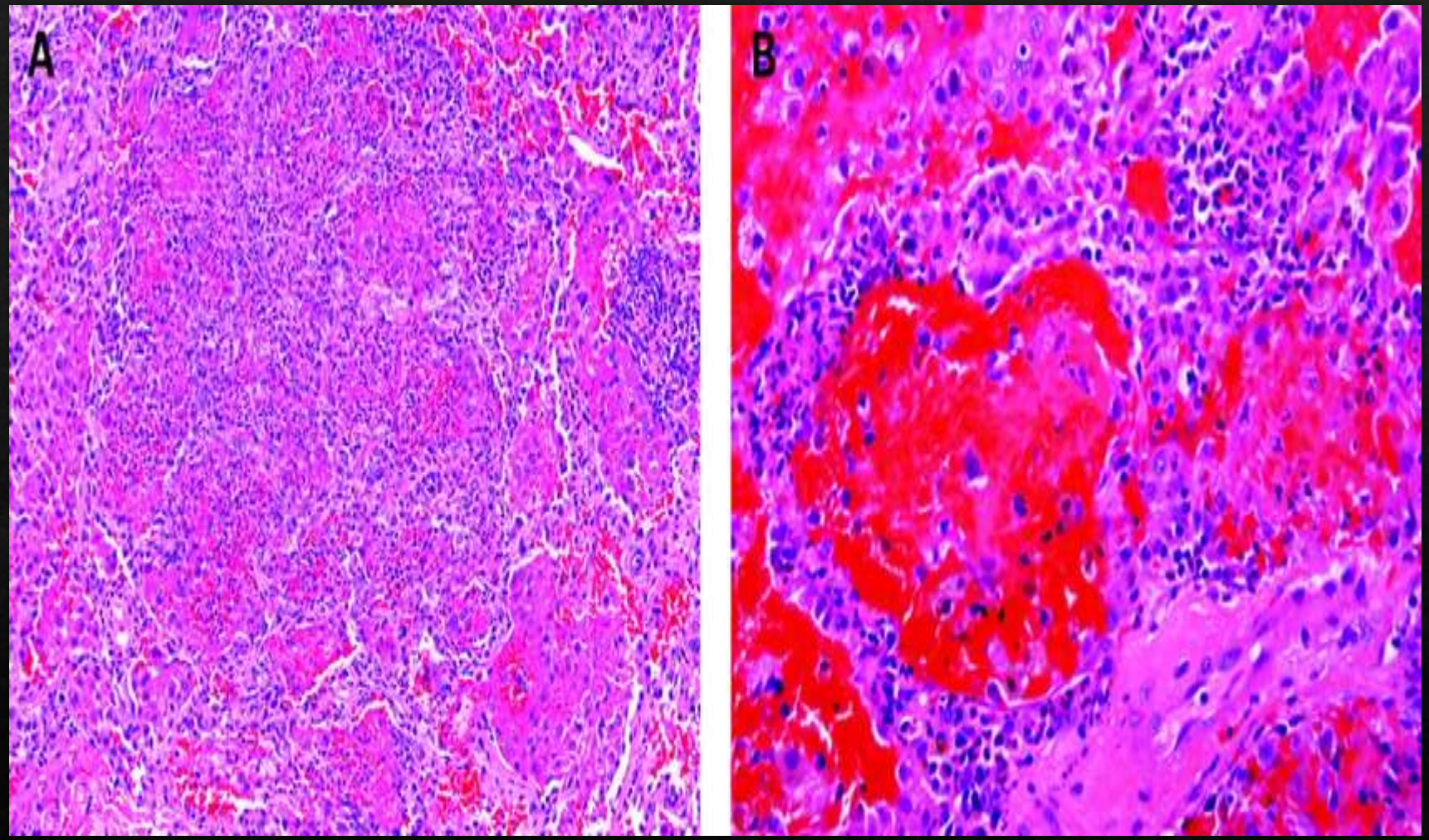


Pulmonary capillaritis

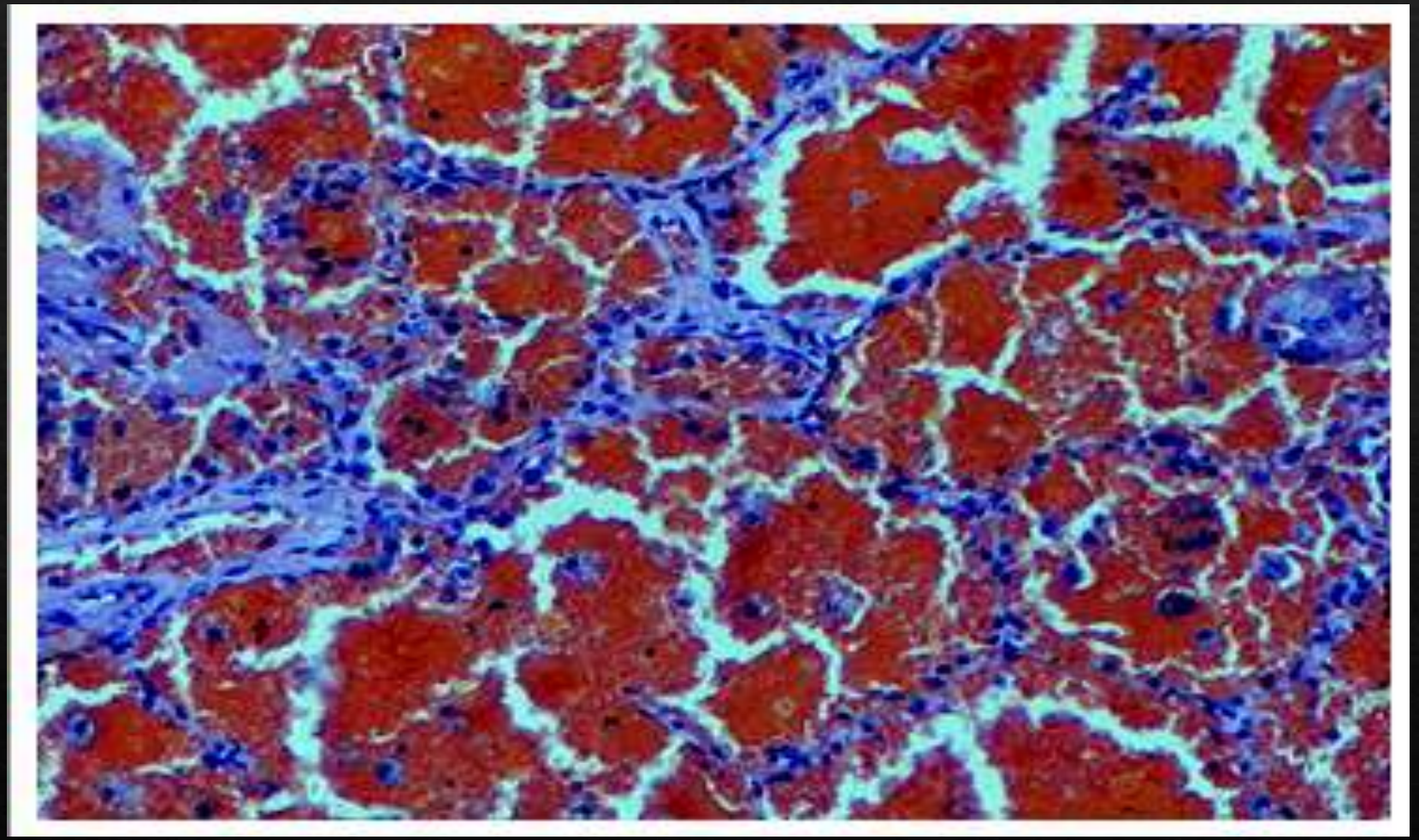
- Neutrophilic infiltration of alveolar septae
- Necrosis of septae
- Loss of capillary integrity
- Spillage of RBC in alveoli and interstitium

Causes:

1. **Systemic vasculitides**: GPA, Henoch-Schonlein purpura, IgA nephropathy, MPA, pauci-immune glomerulonephritis
2. **Rheumatic diseases**: MCTD, anti-GBM disease, isolated pulmonary capillaritis, APLA, polymyositis, RA, SLE, Systemic sclerosis
3. **Drugs:** carbimazole, differentiation syndrome, diphenylhydantoin, hydralazine, PTU, TNF-alpha-I
4. **Other**: HSCT, IE, leptospirosis, UC, lung transplant rejection

Bland pulmonary haemorrhage

- Haemorrhage into the alveolar spaces without inflammation/destruction of alveolar structures



Bland pulmonary haemorrhage

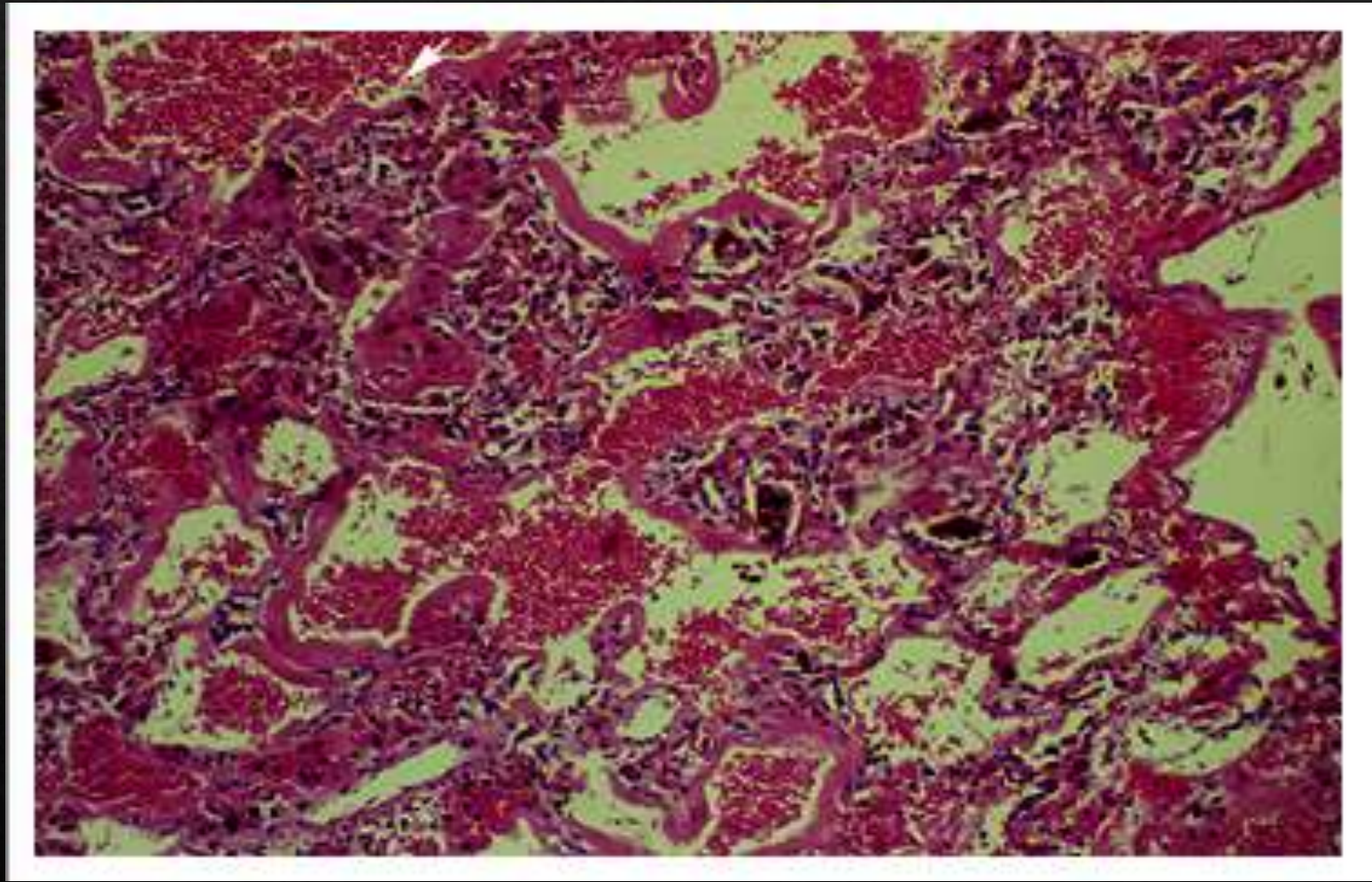
- Haemorrhage into the alveolar spaces without inflammation/destruction of alveolar structures

Causes:

1. CTD- SLE, anti-GBM disease
2. Drugs- anticoagulants, platelet GPIIB-IIIA inhibitors
3. Others- IPH, ITP/TTP/HUS, leptospirosis, MS, promyelocytic lekaemia

Diffuse alveolar damage

- ARDS due to any cause can lead to haemorrhage into the aveolar spaces



Diffuse alveolar damage

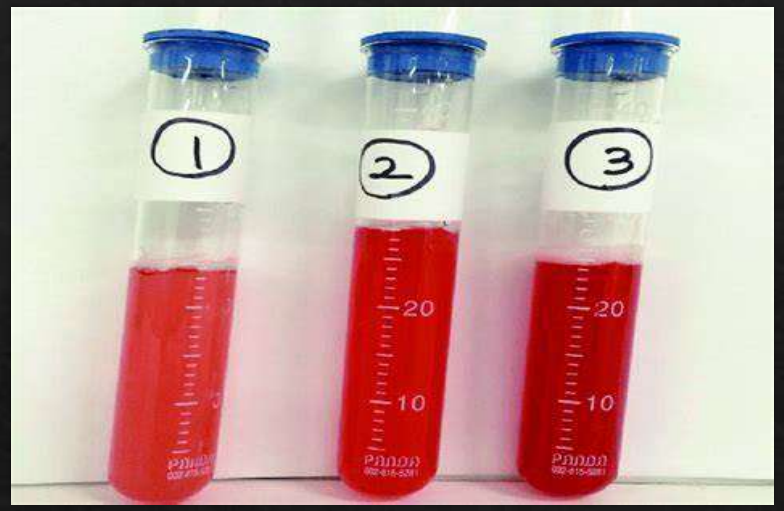
- ARDS due to any cause can lead to haemorrhage into the aveolar spaces

Causes:

1. infections- any infection causing ARDS
2. Rheumatic diseases- SLE, PM
3. Drugs- amiodarone, nitrofurantoin, penicillamine, amphetamine, cytotoxic drugs, crack cocaine
4. Others- AIP, radiation, pulmonary infarction;

Diagnostic evaluation

1. Confirmation of DAH
2. Search for aetiology



Diagnostic evaluation

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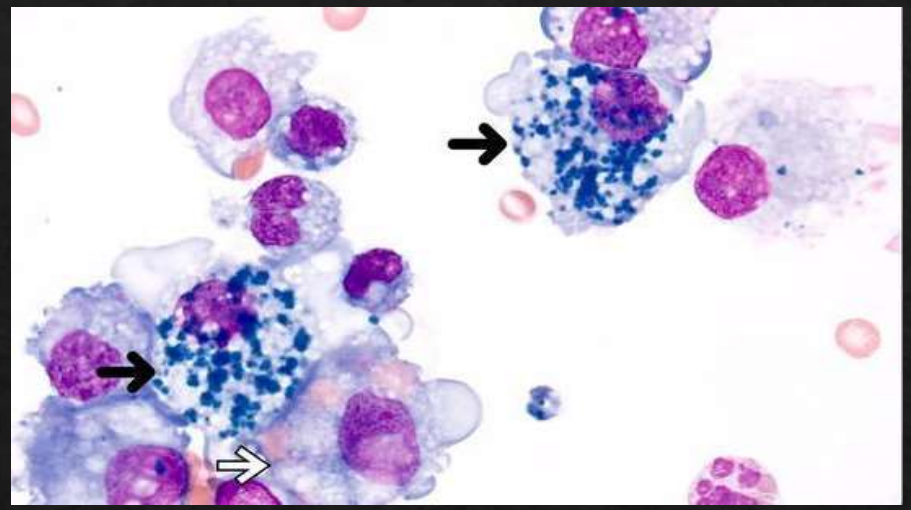

Confirmation of DAH

1. clinical: Hb fall without other cause, haemoptysis, B/L opacity (focal/diffuse) on CXR/CT
2. Sequential BAL demonstrating progressively bloody return
3. Microscopy showing haemosiderin laden macrophages

Search for aetiology

1. History- exposure to drugs/toxins/infections, features of CTD/vasculitides
2. Exclusion of radiographic mimics- pulmonary oedema, viral pneumonia
3. ANCA, anti-dsDNA, anti-cardiolipin ab/Lupus anticoagulant, anti-GBM ab, antitransglutaminase or antiendomysial IgA
4. RFT, urinanalysis
5. Screening for toxins

CLASSIC TETRAD TO SUSPECT DAH

1. CLINICAL: acute onset cough, dyspnea, haemoptysis with or without the background of a consistent disease
2. RADIOLOGICAL: new onset B/L alveolar opacities on radiology
3. LABORATORY: Hb drop without any haemolysis/other explanation
4. BAL/TBLB showing increasingly bloody return on sequential lavage and >20% Haemosiderin laden macrophage

Confirmation of DA

1. clinical: Hb fall
   cause, haemopty
   (focal/diffuse) or
2. Sequential BAL d
   progressively bloody
3. Microscopy showing
   haemosiderin laden
   macrophages

ions, features of

graphic mimics-
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4. BAL/TBLB showing increasingly bloody return on sequential lavage and >20% Haemosiderin laden macrophage

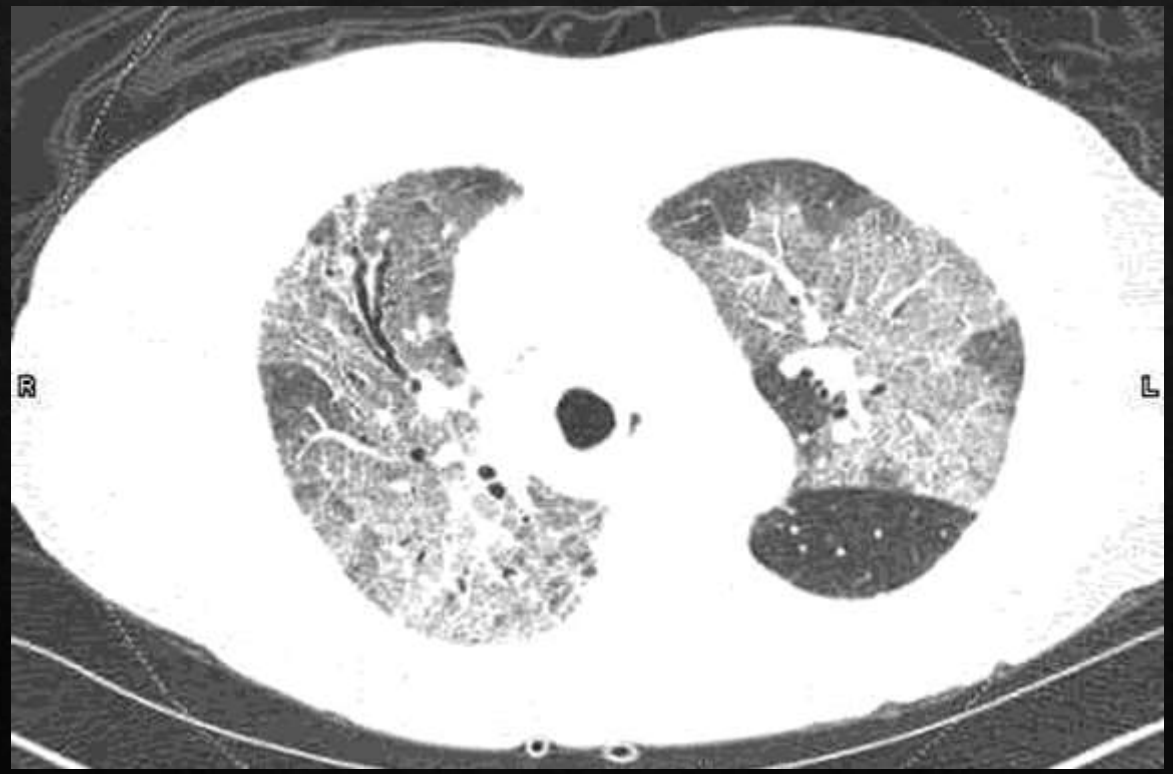
IMMEDIATELY SEND
ANA,ANCA profile
Anti-GBM ab
Urine RME for active sediments

ions, features of

IgA

START treatment urgently without waiting for reports when alternate diagnoses unlikely

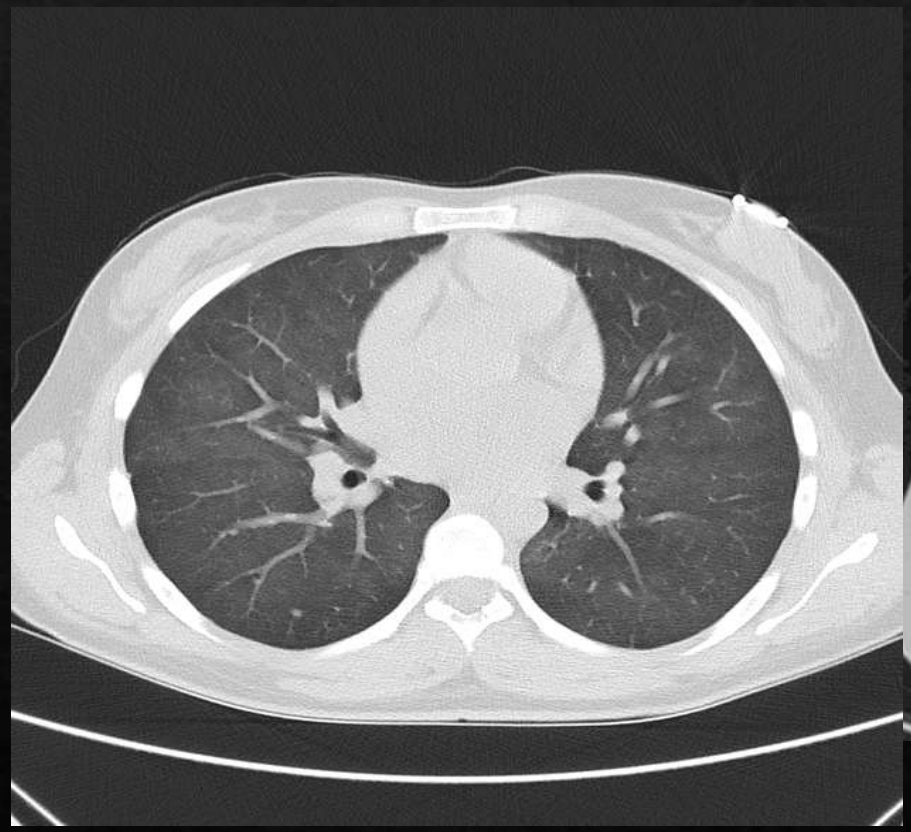
Radiological spectrum



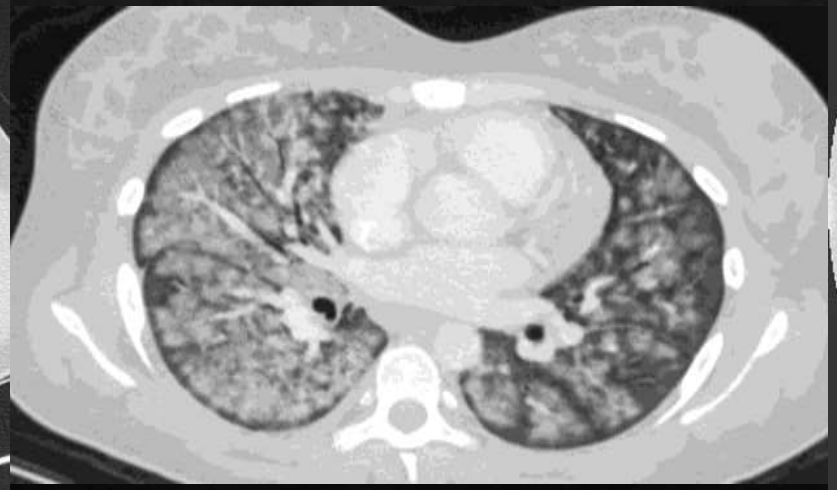
Bilateral ground glass opacity
Inter and intralobular septal thickening
Crazy paving pattern

Cortese G, R. Nicali, Placido R, G. Gariazzo, P. Anrò. Radiological aspects of diffuse alveolar haemorrhage. La radiologia medica. 2008 Feb 1;113(1):16–28.

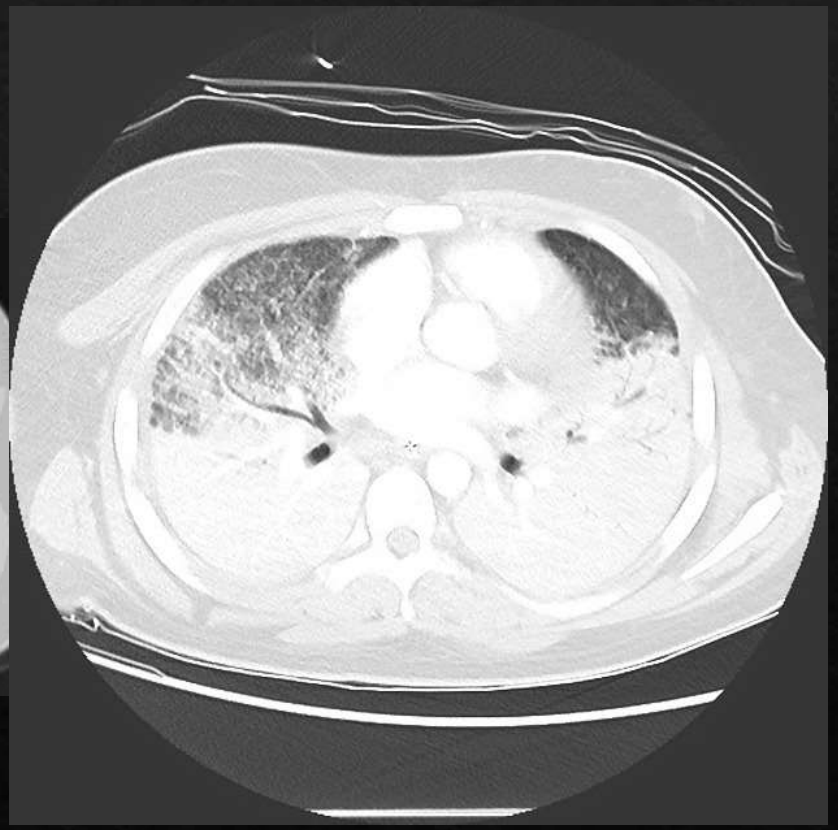
Radiological spectrum



Diffuse ground glass opacity



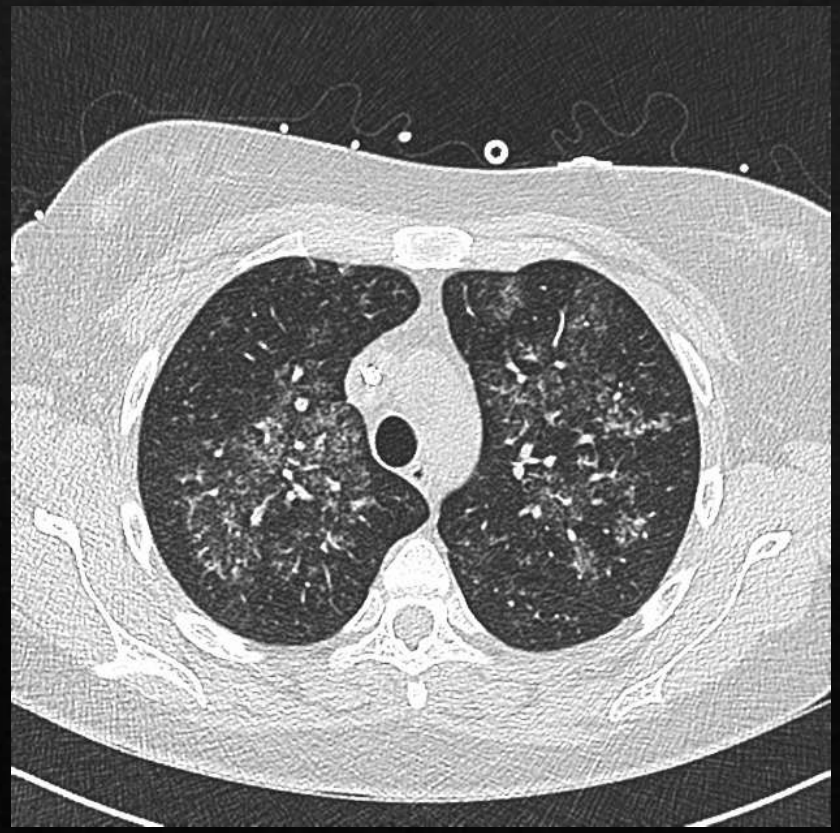
Fluffy alveolar opacity



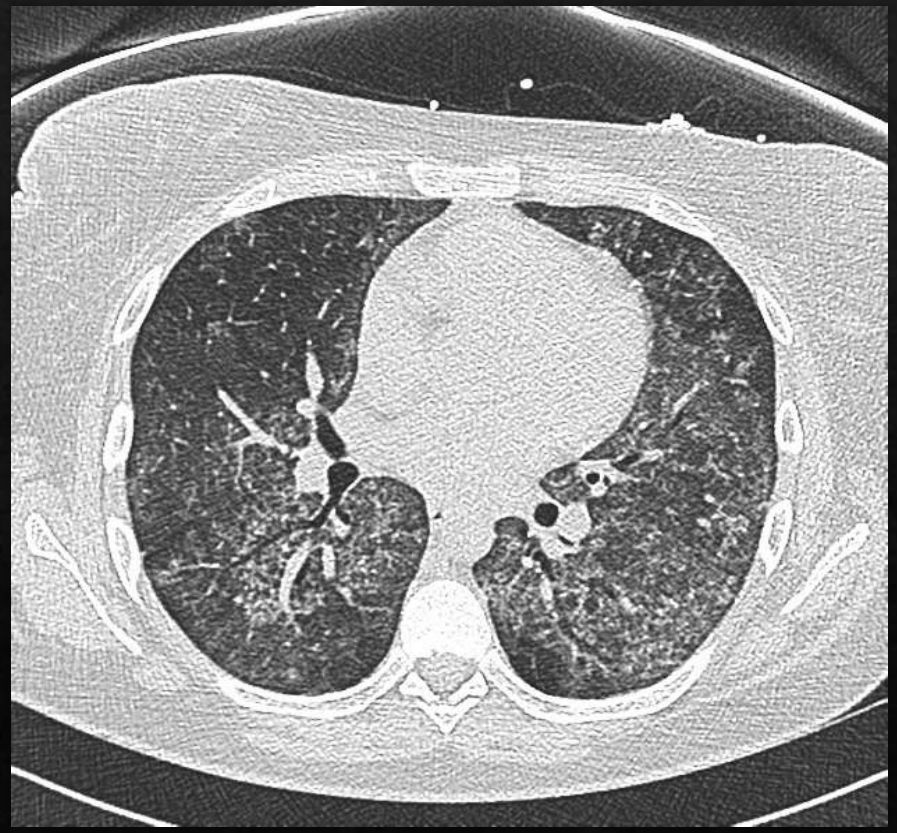
B/L consolidation

Cortese G, R. Nicali, Placido R, G. Gariazzo, P. Anrò. Radiological aspects of diffuse alveolar haemorrhage. La radiologia medica. 2008 Feb 1;113(1):16–28.

Radiological spectrum

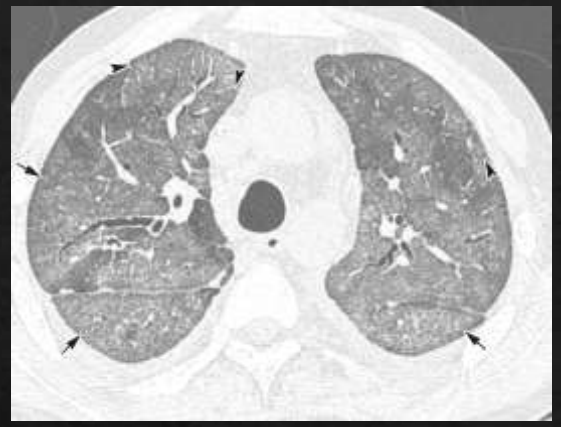


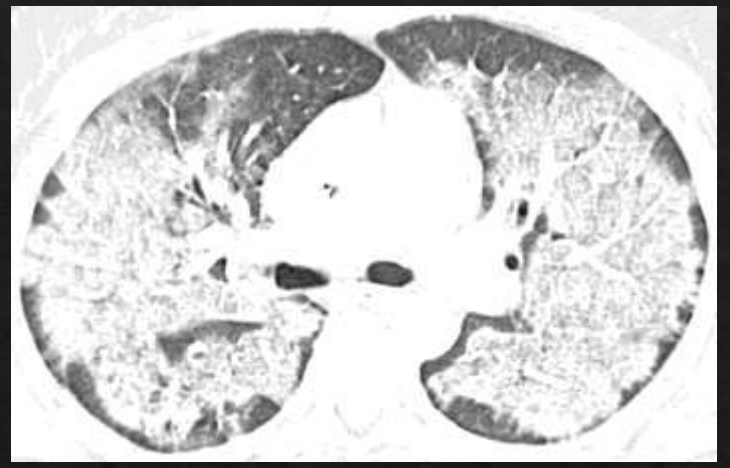
B/L ill-defined nodular opacity
Surrounding GGO

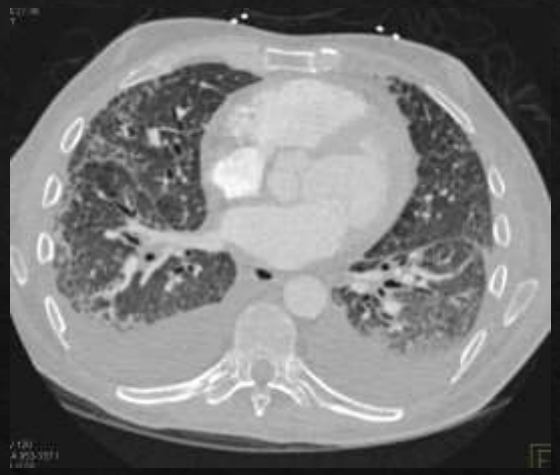


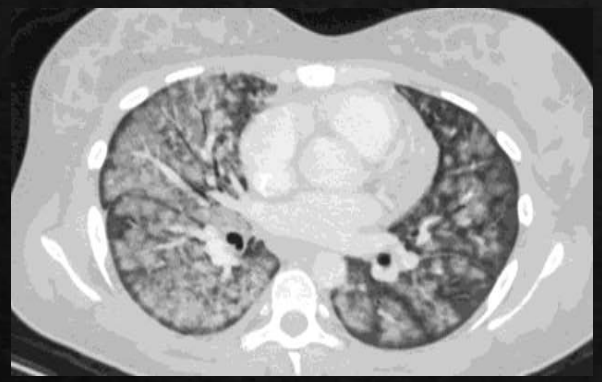
Cortese G, R. Nicali, Placido R, G. Gariazzo, P. Anrò. Radiological aspects of diffuse alveolar haemorrhage. La radiologia medica. 2008 Feb 1;113(1):16–28.

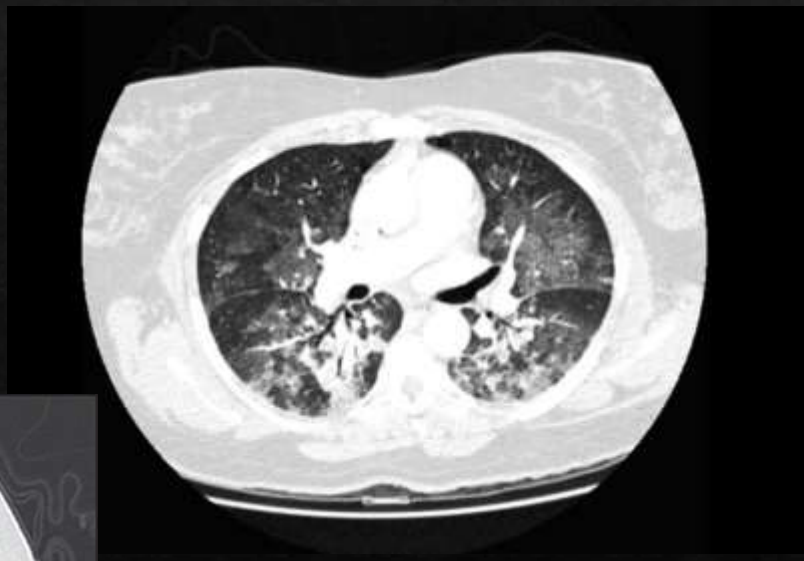
Rule out radiological DAH mimics

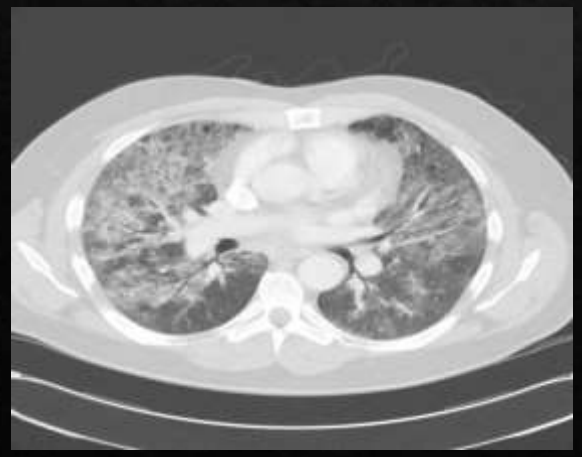


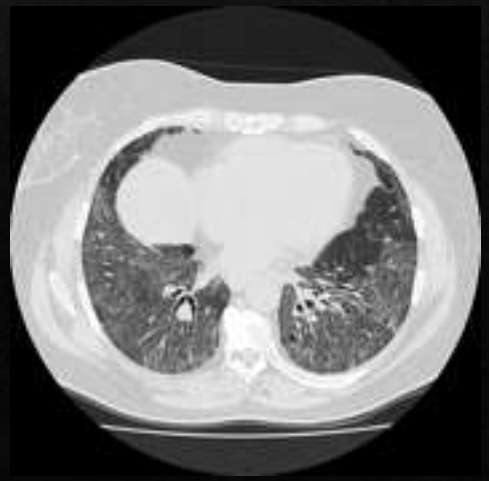


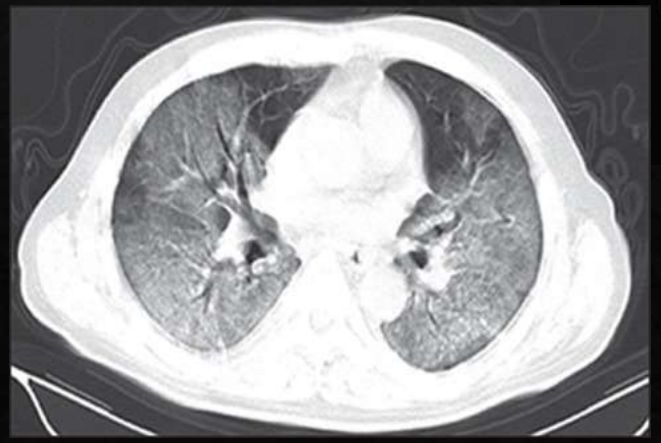




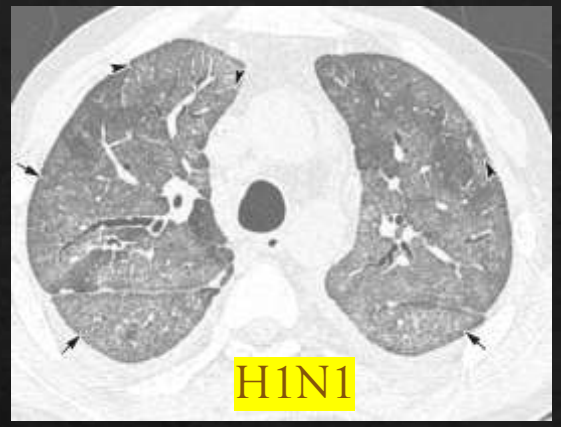


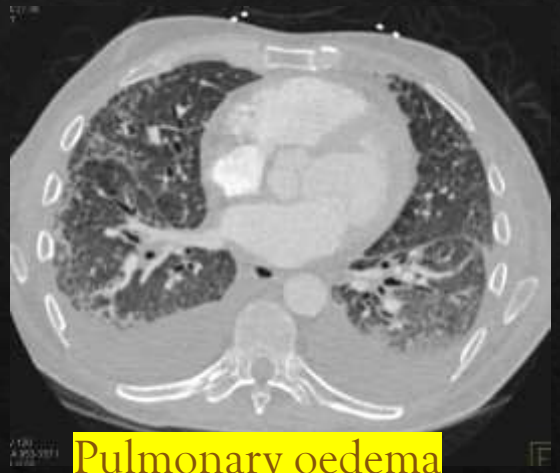


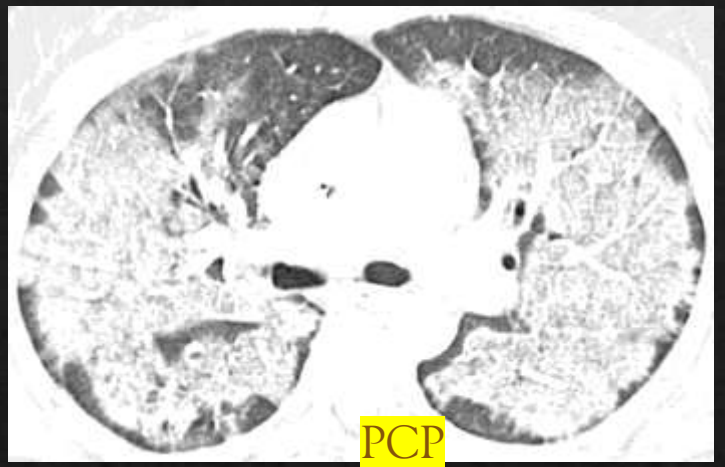


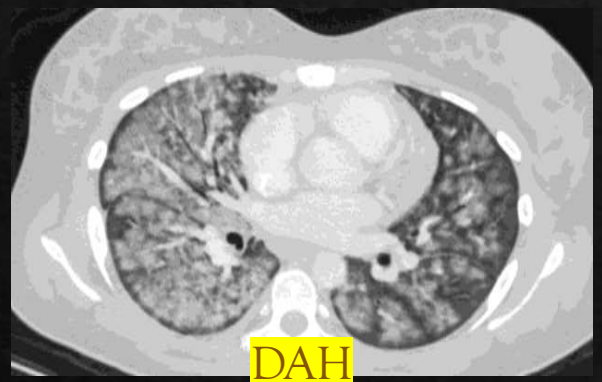


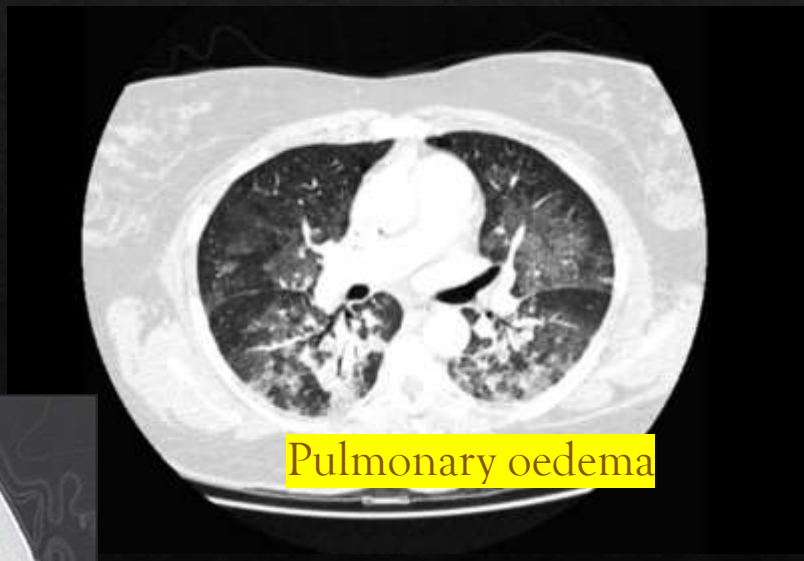
Rule out radiological DAH mimics

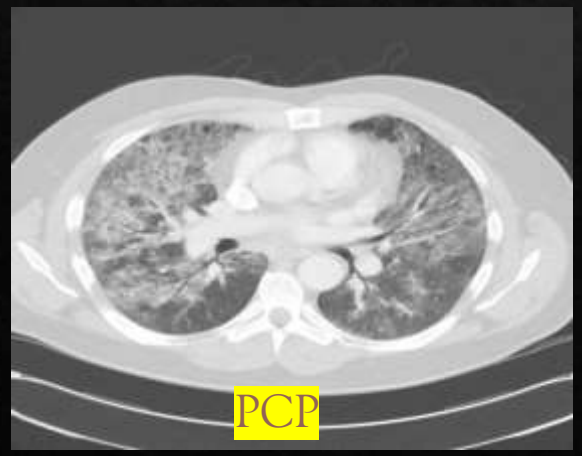

H1N1

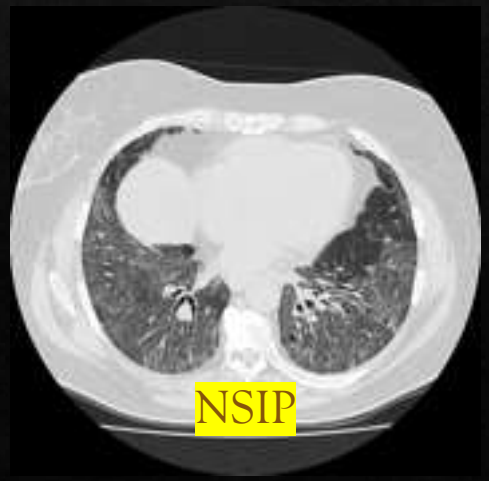

Pulmonary oedema

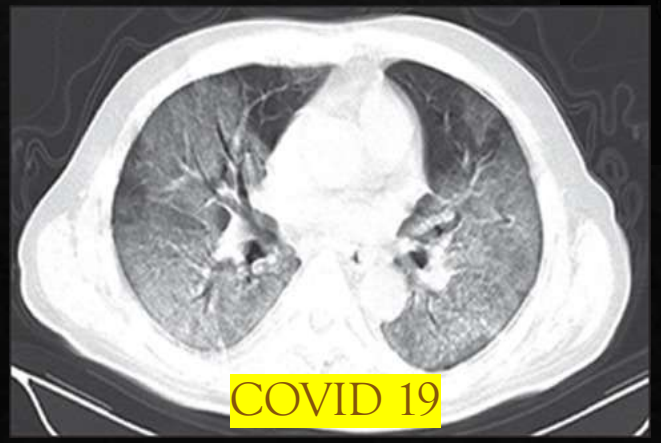

PCP


DAH


Pulmonary oedema


PCP


NSIP


COVID 19

Rule out radiological DAH mimics

- Viral pneumonia/PCP/other infections- nasopharyngeal swab RTPCR+ microbiological evaluation of BAL fluids
- Acute exacerbation of ILD/eosinophilic lung disease- from history, BAL fluid, in addition to ancillary investigations such as DLC, HP panel, Myositis panel, CTD markers
- Pulmonary oedema- BNP, 2D echocardiography
- However, when strong suspicion is present, prompt treatment initiation is mandatory without waiting for reports of investigations

Treatment

- Supportive care
- Specific management

Supportive management

- Supplemental oxygenation
- Invasive mechanical ventilation
- Extra-corporeal membrane oxygenation
- Stoppage of any offending drug/agent

Invasive mechanical ventilation

- In DAH, lungs behave like in ARDS (baby lungs/stiff lungs)
- Lung protective ventilation strategy is undertaken
- Low tidal volume (4-8 mL/Kg of PBW)
- Titration of PEEP in accordance to ARDS-NET protocol
- Avoiding barotrauma by keeping Plateau pressure below 30 cmH20 and RR<35/min
- pH goal- 7.30-7.-40 (permissive hypercapnia up to 7.20)
- Target SpO2- 88-95%/ PO2 55-80 mmHg

What if MV fails

- When despite best efforts invasive mechanical ventilation fails to maintain oxygenation or damage to lung is imminent
- Extracorporeal membrane oxygenation (ECMO) may be used as a rescue method
- No RCT has been conducted to compare efficacy of ECMO with that of IMV
- Case reports, case series, retrospective cohort studies form the basis of use of ECMO in this situation

- A 2021 systematic review examined 32 articles describing 38 patients requiring ECMO for DAH
- about 21% patients had GPA, 21% had SLE, 10% each had anti-GBM ab disease and MPA
- About 23% underwent BAL and a chest imaging for diagnosis of DAH
- 42% of the patients additionally received CYC, 18.4% receive RTX and 90% received steroids in some form

Reddy HG, Maynes EJ, Saxena A, Austin MA, O'Malley TJ, Gadda MN, et al. Utilization of extracorporeal life support for diffuse alveolar damage and diffuse alveolar hemorrhage: A systematic review. Artificial Organs. 2020 Nov 15

Variable	Pre-ECLS	*N*	Post-ECLS	*N*	*P* value
Rate (breaths per min), median [IQR]	12.0 [12.0, 20.0]	5	12.0 [10.0, 13.5]	3	.427
Peep (cm H_2O), median [IQR]	13.0 [11.5, 15.2]	12	8.0 [7.5, 12.0]	9	.014
FiO_2, median [IQR]	1.0 [1.0, 1.0]	13	0.5 [0.5, 0.5]	7	.0025
Partial pressure O_2 mm Hg, median [IQR]	49.0 [45.0, 59.0]	19	80.0 [70.0, 98.8]	16	<.001
Arterial oxygen saturation (%), median [IQR]	82.5 [64.5, 87.8]	4	-		-
Pulse oximetry (%), median [IQR]	75.5 [72.2, 79.5]	8	95.5 [94.3, 96.8]	6	.086
PaO_2:FiO_2, median [IQR]	48.2 [41.4, 54.8]	18	182.0 [149.4, 212.2]	4	<.01

Significant improvement in PaO2 and PF ratio was observed

Variable	Total (*N* = 38)
ECLS type	
VV-ECMO, *n/N* (%)	28/38 (73.7)
VA-ECMO, *n/N* (%)	5/38 (13.2)
RVAD-ECMO, *n/N* (%)	1/38 (2.6)
Unspecified, *n/N* (%)	4/38 (10.5)
Cannulation Sites	
Internal jugular vein cannulation, *n/N* (%)	19/38 (50.0)
Femoral vein cannulation, *n/N* (%)	18/38 (47.3)
Pulmonary artery cannulation, *n/N* (%)	1/38 (2.6)
ECLS data	
VV-ECMO Flow (L/min), median [IQR]	3.8 [3.5, 4.5]

73% patients were put on VV-ECMO

Variable	Total (*N* = 38)
ECLS total time (days), median [IQR]	9.5 [5.2, 14.2]
Length of stay (days), median [IQR]	41 [33, 54]
Survival to decannulation, *n/N* (%)	36/38 (94.7)
In-hospital and 30-day mortality, *n/N* (%)	4/38 (10.5)
VV-ECMO, *n/N* (%)	2/38 (5.3)
VA-ECMO, *n/N* (%)	1/38 (2.6)
Unknown, *n/N* (%)	1/38 (2.6)
Follow-up time (months), median [IQR]	1.9 [0.8, 9.0]
Complications	
Dialysis, *n/N* (%)	17/38 (44.7)
Acute renal failure not requiring dialysis, *n/N* (%)	7/38 (18.4)
Recurrence of hemorrhage during admission, *n/N* (%)	8/38 (21.1)
Diffuse alveolar hemorrhage, *n/N* (%)	5/8 (62.5)
Nonspecific pulmonary hemorrhage, *n/N* (%)	3/8 (37.5)
ECLS circuit thrombus, *n/N* (%)	4/38 (10.5)
Thrombocytopenia, *n/N* (%)	3/38 (7.9)

- Survival to decannulation was >94%
- Survival after 1.9 months was >89%
- 21% patients had recurrence of haemorrhage, 62% of them had DAH again
- Circuit thrombosis was found in 10% patients
- 44% developed renal failure requiring dialysis

Variable	Pre-ECLS	N	Post-ECLS	N	P value
Rate (breaths per min), median [IQR]	12.0 [12.0, 20.0]	5	12.0 [10.0, 13.5]	3	.427
Peep (cm H_2O), median [IQR]	13.0 [11.5, 15.2]	12	8.0 [7.5, 12.0]	9	.014
FiO_2, median [IQR]	1.0 [1.0, 1.0]	13	0.5 [0.5, 0.5]	7	.0025
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PaO_2:FiO_2, median [IQR]	48.2 [41.4, 54.8]	18	182.0 [149.4, 212.2]	4	<.01

Significant improvement in PaO2 and PF ratio was observed

ECMO seems an effective rescue measure in patients of DAH who can not be managed on MV
RCTs comparing MV and ECMO in this matter are required for assessment of relative safety and efficacy
COST of ECMO and the SKILL-SETS and manpower required are major issues in its use

	Total
Unspecified, *n/N* (%)	4/38 (10.5)
Cannulation Sites	
Internal jugular vein cannulation, *n/N* (%)	19/38 (50.0)
Femoral vein cannulation, *n/N* (%)	18/38 (47.3)
Pulmonary artery cannulation, *n/N* (%)	1/38 (2.6)
ECLS data	
VV-ECMO Flow (L/min), median [IQR]	3.8 [3.5, 4.5]

73% patients were put on VV-ECMO

	Total
VA-ECMO, *n/N* (%)	1/38 (2.6)
Unknown, *n/N* (%)	1/38 (2.6)
Follow-up time (months), median [IQR]	1.9 [0.8, 9.0]
Complications	
Dialysis, *n/N* (%)	17/38 (44.7)
Acute renal failure not requiring dialysis, *n/N* (%)	7/38 (18.4)
Recurrence of hemorrhage during admission, *n/N* (%)	8/38 (21.1)
Diffuse alveolar hemorrhage, *n/N* (%)	5/8 (62.5)
Nonspecific pulmonary hemorrhage, *n/N* (%)	3/8 (37.5)
ECLS circuit thrombus, *n/N* (%)	4/38 (10.5)
Thrombocytopenia, *n/N* (%)	3/38 (7.9)

- 21% patients had recurrence of haemorrhage, 62% of them had DAH again
- Circuit thrombosis was found in 10% patients
- 44% developed renal failure requiring dialysis

Specific management

- DAH with pulmonary capillaritis is managed with immunosuppression
- There is no data specific for DAH management from RCTs
- Base of evidence extrapolated from trials on management of AAVs

DAH due to pulmonary capillaritis

- 30-40% of DAH is caused by autoimmune diseases
- 80% is caused by AAV and 20% by SLE and anti-GBM disease
- The first-year mortality ranges from 15-50% in these patients
- Accounts for almost 12% of ICU admission in patients with autoimmune diseases

Haworth SJ, Savage CO, Carr D, Hughes JM, Rees AJ. Pulmonary haemorrhage complicating Wegener's granulomatosis and microscopic polyarteritis. Br Med J (Clin Res Ed) 1985;290:1775–1778.

Predictors of respiratory failure

- A retrospective observational study conducted on 73 adult patients with AAV (GPA and MPA) identified that higher BVAS/WG score, raised BAL neutrophils and elevated CRP levels were associated with severe respiratory failure
- 45% of the patients had active renal involvement, 56% of them required ICU care and 11% died
- This study did not include subjects <18 years of age, those with capillaritis due to anti-GBM disease or SLE, and the subjects were predominantly male and all were of white ethnicity

Cartin-Ceba R, Diaz-Caballero L, Al-Qadi MO, Tryfon S, Fervenza FC, Ytterberg SR, et al. Diffuse Alveolar Hemorrhage Secondary to Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: Predictors of Respiratory Failure and Clinical Outcomes. Arthritis & Rheumatology. 2016 May 26;68(6):1467–76.

Outline of management of DAH in capillaritis

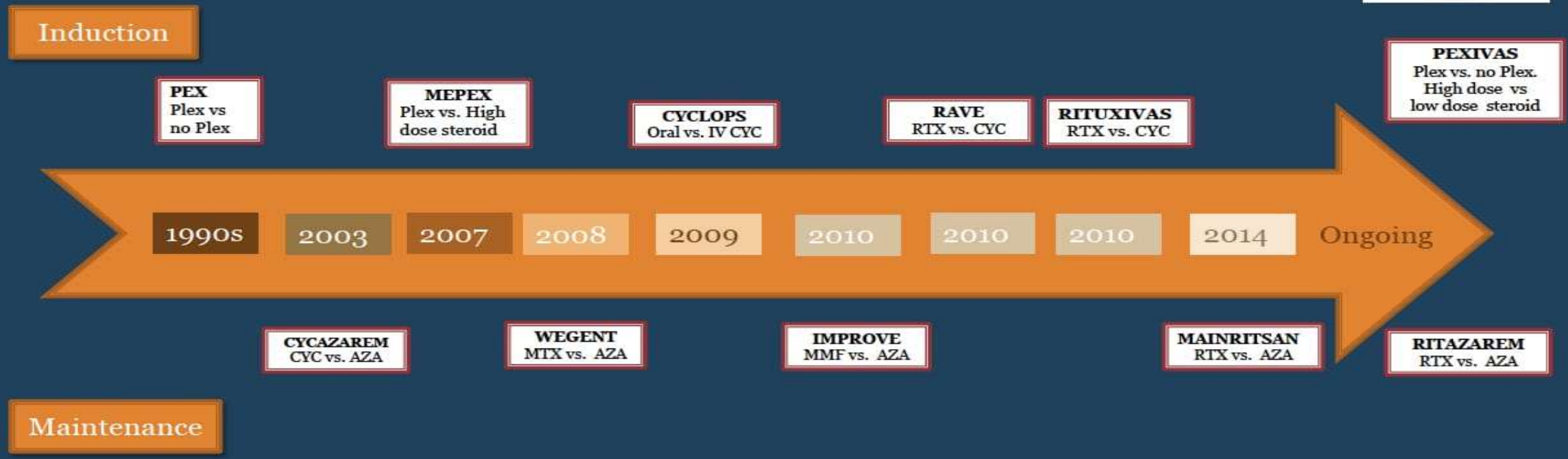
- Methyl prednisolone pulse therapy (500-1000 mg IV for 5 days) followed by oral corticosteroid
- Additional immunosuppression- Cyclophosphamide and Rituximab
- Plasma exchange therapy- in patients with severe organ threatening disease (mostly severe renal involvement)
- Beneficial role of plasma exchange has not been established by RCTs

PULSE STEROID

- Mechanism of action: non-genomic pathway (through binding of cytosolic/membrane-bound glucocorticoid receptors and subsequent utilisation of phoshoinositide-3-kinase, AKT, MAPK to exert various effects and in addition release of proteins to take part in secondary signalling cascade
- Does not require protein synthesis for action and hence the rapid onset of action
- First used in 1969 for treatment of renal allograft rejection
- First clinical trial on lupus nephritis patients with rapidly progressive renal failure(n-7) in 1976 established its efficacy
- Has since been used in various auto-immune disease for control of aggressive disease progression successfully

Cathcart Edgar S, Scheinberg Morton A, Idelson Beldon A, Couser William G. BENEFICIAL EFFECTS OF METHYLPREDNISOLONE "PULSE" THERAPY IN DIFFUSE PROLIFERATIVE LUPUS NEPHRITIS. The Lancet. 1976 Jan;307(7952):163–6.

Landmark Trials in ANCA Nephritis



@yangdanwen @tentenkid @Landmark_Neph

Disease	Severity	New/relapse/refractory	Induction	Alternatives	Maintenance	Alternatives
GPA/MPA	Organ-threatening	New	GC+RTX/CYC	RTX/CYC+AVACOPAN	RTX (24-48 months or longer)	MTX/AZA
		Relapse	GC+RTX>CYC		RTX	MTX/AZA
		Refractory	Revisit comorbidities+use other options			
	Non-organ-threatening	Any	GC+RTX	GC+MTX/MMF	RTX	MTX/AZA

EULAR recommendations for the management of ANCA- associated vasculitis: 2022 update

Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, Blockmans D, Cid MC, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Annals of the Rheumatic Diseases [Internet]. 2023 Mar 16

Table 2 Examples of organ/life-threatening and not organ/life-threatening manifestations in patients with AAV

Examples of potentially organ/life-threatening manifestations*	Examples of manifestations that are not ultimately organ/life-threatening*
Glomerulonephritis	Nasal and paranasal disease without bony involvement (erosion) or cartilage collapse or olfactory dysfunction or deafness
Pulmonary haemorrhage	Skin involvement without ulceration
Meningeal involvement	Myositis (skeletal muscle only)
Central nervous system involvement	Non-cavitating pulmonary nodules
Retro-orbital disease	Episcleritis
Cardiac involvement	
Mesenteric involvement	
Mononeuritis multiplex	

*These are just examples of typical disease manifestations and many other manifestations of AAV exist. Assessment of severity in the individual patient may differ (eg, scleritis can become organ threatening under certain circumstances).
AAV, antineutrophil cytoplasmic antibody-associated vasculitis.

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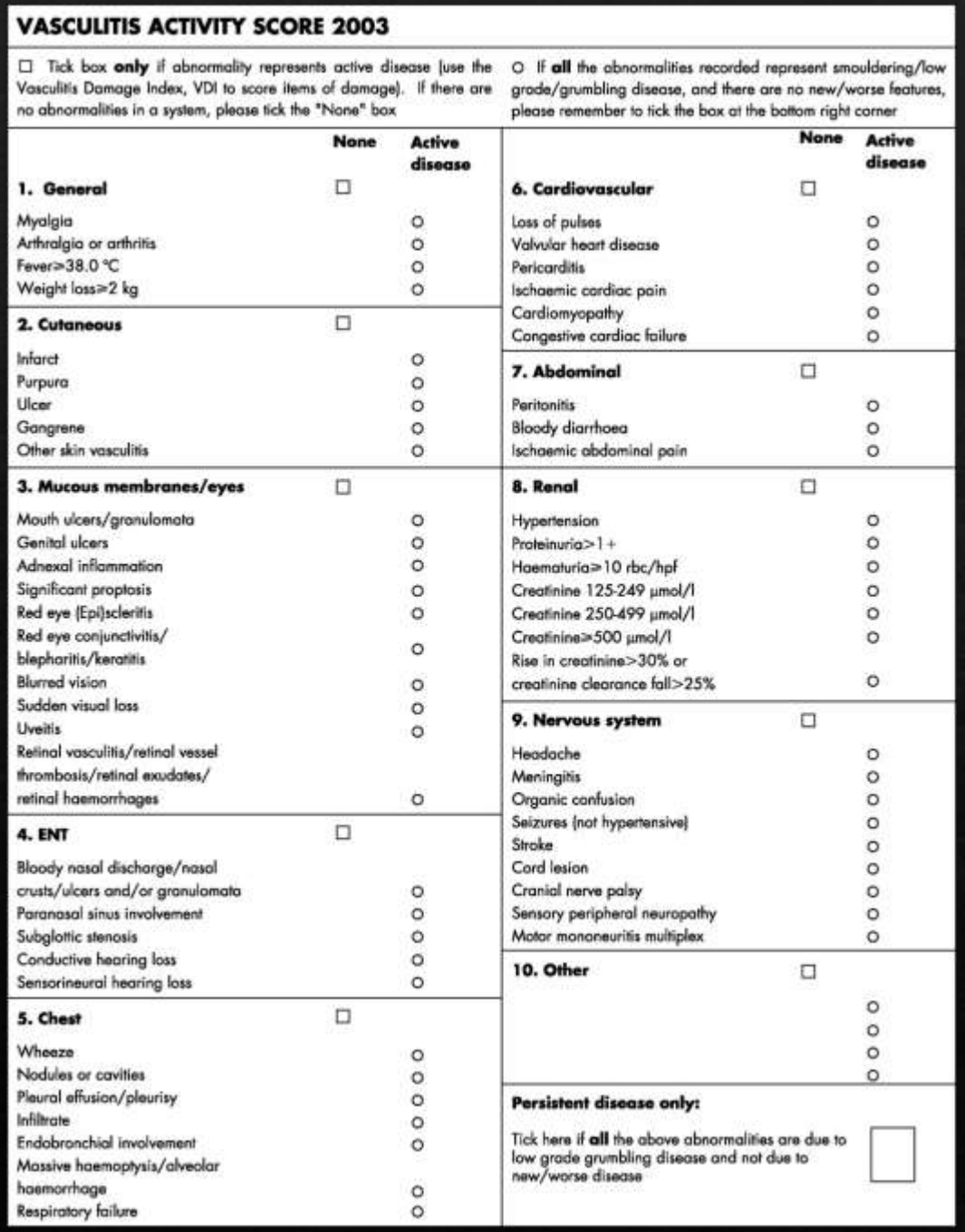

VASCULITIS ACTIVITY SCORE 2003

☐ Tick box **only** if abnormality represents active disease (use the Vasculitis Damage Index, VDI to score items of damage). If there are no abnormalities in a system, please tick the "None" box

○ If **all** the abnormalities recorded represent smouldering/low grade/grumbling disease, and there are no new/worse features, please remember to tick the box at the bottom right corner

	None	Active disease
1. General	☐	
Myalgia		○
Arthralgia or arthritis		○
Fever>38.0 °C		○
Weight loss>2 kg		○
2. Cutaneous	☐	
Infarct		○
Purpura		○
Ulcer		○
Gangrene		○
Other skin vasculitis		○
3. Mucous membranes/eyes	☐	
Mouth ulcers/granulomata		○
Genital ulcers		○
Adnexal inflammation		○
Significant proptosis		○
Red eye (Epi)scleritis		○
Red eye conjunctivitis/ blepharitis/keratitis		○
Blurred vision		○
Sudden visual loss		○
Uveitis		○
Retinal vasculitis/retinal vessel thrombosis/retinal exudates/ retinal haemorrhages		○
4. ENT	☐	
Bloody nasal discharge/nasal crusts/ulcers and/or granulomata		○
Paranasal sinus involvement		○
Subglottic stenosis		○
Conductive hearing loss		○
Sensorineural hearing loss		○
5. Chest	☐	
Wheeze		○
Nodules or cavities		○
Pleural effusion/pleurisy		○
Infiltrate		○
Endobronchial involvement		○
Massive haemoptysis/alveolar haemorrhage		○
Respiratory failure		○

	None	Active disease
6. Cardiovascular	☐	
Loss of pulses		○
Valvular heart disease		○
Pericarditis		○
Ischaemic cardiac pain		○
Cardiomyopathy		○
Congestive cardiac failure		○
7. Abdominal	☐	
Peritonitis		○
Bloody diarrhoea		○
Ischaemic abdominal pain		○
8. Renal	☐	
Hypertension		○
Proteinuria>1+		○
Haematuria>10 rbc/hpf		○
Creatinine 125-249 µmol/l		○
Creatinine 250-499 µmol/l		○
Creatinine>500 µmol/l		○
Rise in creatinine>30% or creatinine clearance fall>25%		○
9. Nervous system	☐	
Headache		○
Meningitis		○
Organic confusion		○
Seizures (not hypertensive)		○
Stroke		○
Cord lesion		○
Cranial nerve palsy		○
Sensory peripheral neuropathy		○
Motor mononeuritis multiplex		○
10. Other	☐	
		○
		○
		○
		○

Persistent disease only:

Tick here if **all** the above abnormalities are due to low grade grumbling disease and not due to new/worse disease ☐

Modification and validation of the Birmingham Vasculitis Activity Score (version 3)

C Mukhtyar,[1] R Lee,[2] D Brown,[1] D Carruthers,[3] B Dasgupta,[4] S Dubey,[5] O Flossmann,[6] C Hall,[2] J Hollywood,[4] D Jayne,[6] R Jones,[6] P Lanyon,[7] A Muir,[7] D Scott,[5] L Young,[8] R A Luqmani[1,2]

- Need for a new score: BVAS 2 had redundant/uncommon parameters
- BVAS 1 disregarded importance of persistent disease (ignored BVAS 2)
- 313 patients of diagnosed vasculitis included in the study
- BVAS 3 showed good correlation with BVAS 2, good reliability (low inter-observer variability), good correlation with disease activity (CRP, physicians' global assessment, five-point Likert scale) and a good sensitivity to response to treatment
- Scores may range from 0-33 for stable disease and 0-63 for new/worsening disease

Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis. 2009;68(12):1827-32.

Study	Aims	Participants	End points	Results	Comments
RITUX vs CYC for remission induction in GPA and MPA (2010) RAVE trial	To compare RTX with CYC for remission induction (both group had GC pulse+continuation)	197 patients with MPA and GPA, both newly diagnosed and relapsing disease	Primary: successful completion of prednisolone taper at 6 months and BVAS/WG score-0 (at 6 months) Secondary: disease flare, BVAS/WG-0 with steroid <10 mg, adverse events, SF-36 scores	RTX was non-inferior to CYC overall (11% difference, <20% non-inferiority margin) RTX was superior to CYC in relapsing disease	28% of patients in each group had DAH and they did not have a clinically significant difference in reaching primary end-point (P-0.48); RTX group patients had more severe renal involvement at baseline, w/o any difference in reaching the primary outcome
RTX vs CYC for remission induction in renal vasculitis (2010) RITUXVAS trial	To compare efficacy and safety of RTX+CYC (2 doses) with CYC f/b Azathioprine maintenance; (both groups initially received GC pulse/PLEX)	44 patients with ANCA vasculitis and renal involvement at presentation	Primary: rate of remission at 12 months, rate of serious adverse events (also death) Secondary: time to achieve remission, BVAS between 0-3 months, change in GFR,SF-36, VDI between 0-12 months	RTX+CYC was non-inferior to CYC in achieving remission at 12 months (93% vs 90%). Serious adverse events were comparable between two groups (1 per P-Y vs 1.10 per P-Y). VDI and SF-36 were not significantly different between two groups. Rate of improvement in GFR was slightly better with RTX (all analysis in ITT population)	Unblinded study with small number of subjects from 8 different institutions. Did not find RTX based regimen superior to conventional CYC regimen. Did not find increased risk of infection among RTX-based group. CYC was also not found to be superior to RTX in vasculitides with renal impairment at presentation. *RTX group did not have any maintenance therapy, CYC group received AZA

In 2013 data from a randomized controlled trial comparing efficacy and safety profile of RTX with CYC f/b AZA maintenance for ANCA associated vasculitis was published

- 197 patients of AAV (GPA or MPA) were randomly assigned to either get RTX or CYC f/b azathioprine
- They were followed up and assessed at 6, 12 and 18 months from treatment onset
- The primary outcome was remission and how long it was sustained (as per BVAS/WG score)

Table 1. Efficacy Outcomes.*

Efficacy Measure	Rituximab (N=99)	Cyclophosphamide–Azathioprine (N=98)	Difference	P Value
	number (percent)		*percentage points (95% CI)*	
Complete remission				
6 mo	63 (64)	52 (53)	11 (−3 to 24)	0.13
12 mo	47 (47)	38 (39)	9 (−5 to 22)	0.22
18 mo	39 (39)	32 (33)	7 (−7 to 20)	0.32
Remission and <10 mg/day of prednisone				
6 mo	70 (71)	60 (61)	10 (−4 to 23)	0.16
12 mo	59 (60)	60 (61)	−2 (−15 to 12)	0.82
18 mo	54 (55)	52 (53)	2 (−12 to 15)	0.84
Complete remission at any time†	76 (77)	70 (71)		0.15
Remission and <10 mg/day of prednisone at any time‡	82 (83)	84 (86)		0.91
Remission at any time‡	89 (90)	89 (91)		0.50
Complete remission in patients with relapsing disease at baseline†				
6 mo	34/51 (67)	21/50 (42)	25 (6 to 44)	0.01
12 mo	25/51 (49)	12/50 (24)	25 (7 to 43)	0.009
18 mo	19/51 (37)	10/50 (20)	17 (0 to 34)	0.06
	milliliters per minute			
Estimated creatinine clearance				
Total cohort				
Baseline	76.83±3.77	91.56±3.75	−14.74	0.01
6 mo	78.59±3.75	93.14±3.73	−14.55	0.01
12 mo	80.36±3.87	94.72±3.86	−14.37	0.01
18 mo§	82.12±4.12	96.30±4.12	−14.18	0.02
Patients with major renal disease¶				
Baseline	53.54±4.63	70.52±4.64	−16.97	0.01
6 mo	57.06±4.59	73.71±4.60	−16.65	0.01
12 mo	60.57±4.80	76.91±4.80	−16.34	0.02
18 mo§	64.08±5.21	80.10±5.10	−16.02	0.03

Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis. New England Journal of Medicine. 2013 Aug;369(5):417–27.

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18 mo	64.08±5.21	80.10±5.10	−16.02	0.03

- In the total patient population (new+relapsed) RTX was non-inferior to CYC for achieving and maintaining remission.
- In patients with relapsing disease at baseline, RTX crossed superiority margin, and patients on RTX treatment achieved more sustained release at 6, 12 but not at18 months.
- In patients with severe renal disease at baseline, CYC did not prove to be superior to RTX
- There was no significant difference between the two groups in terms of grade 3 or 4 AEs (except leukopenia, more commonly in CYC group)

Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis. New England Journal of Medicine. 2013 Aug;369(5):417–27.

- On the basis of the above studies, recommendations were made
- For a newly diagnosed case, CYC and RTX were equally effective along with GC.
- But for a relapsing disease, RTX showed better remission rates (although small difference)
- The long-standing assumption that CYC was better for patients with poorer baseline renal status was not supported by evidence
- The risk of infection due to B-cell depletion by RTX was also not proven

- A single centre retrospective study published in 2015 examined records of patients (n=73) treated for diffuse alveolar haemorrhage (a/w pulmonary capillaritis) with or without plasma exchange, in conjunction with either Rituximab or Cyclophosphamide
- The study found no difference in remission rate and long-term survival between patients treated with and without plasma exchange
- There was no difference in hospital mortality, length of hospital/ICU stay, need of MV and long-time survival among patients treated with Rituximab or Cyclophosphamide.
- However, after adjusting for PE and propensity to undergo PE, the patients treated with Rituximab had higher odds of achieving remission at 6 months (OR 6.45, CI-1.78-29, P=0.003)

Cartin-Ceba R, Diaz-Caballero L, Al-Qadi MO, Tryfon S, Fervenza FC, Ytterberg SR, et al. Diffuse Alveolar Hemorrhage Secondary to Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: Predictors of Respiratory Failure and Clinical Outcomes. Arthritis & Rheumatology. 2016 May 26;68(6):1467–76.

Characteristic	No plasma exchange (n = 41)	Plasma exchange (n = 32)	P
Age, median (IQR) years	63 (48–73)	62 (49–72)	0.70
Sex, no. (%) male	22 (54)	19 (59)	0.62
GPA, no. (%)	27 (66)	17 (53)	0.27
MPA, no. (%)	14 (34)	15 (47)	0.33
BVAS/WG score, median (IQR)	10 (8–12)	12 (10–18)	0.002
Spo_2:Fio_2 at presentation, median (IQR)	292 (158–457)	167 (96–395)	0.03
APACHE III score, median (IQR)†	50 (41–54)	51 (29–61)	0.76
Mechanical ventilation, no. (%)	13 (32)	21 (66)	0.003
Active renal disease, no. (%)	14 (34)	19 (59)	0.03
Requiring new renal replacement therapy, no. (%)	3 (7)	9 (28)	0.01
Hemosiderin-laden macrophages, median (IQR) %	60 (21–93)	55 (28–89)	0.62
Neutrophils in BAL fluid, median (IQR) %	21 (7–66)	32 (15–66)	0.34
Creatinine, median (IQR) mg/dl	1.1 (1–2.6)	1.9 (0.9–4.4)	0.20
GFR, median (IQR) ml/minute	52 (26–75)	26 (11–55)	0.12
Hemoglobin, median (IQR) gm/dl	9.5 (8.4–11)	8.6 (7.6–9.8)	0.08
Decrease in hemoglobin, median (IQR) gm/dl	1.9 (1.3–3.9)	2.6 (1.4–3.7)	0.49
Leukocytes, median (IQR) per mm^3	10.5 (7.2–13)	12 (10.1–15)	0.03
Platelet count, median (IQR) per mm^3	305 (239–396)	253 (175–346)	0.14
PR3-ANCA positive, no. (%)	24 (59)	16 (50)	0.46
MPO-ANCA positive, no. (%)	17 (41)	16 (50)	0.62
ESR, median (IQR) mm/hour	58 (30–80)	68 (32–95)	0.40
CRP, median (IQR) mg/liter	17.2 (3–28)	40 (12–147)	0.005
INR, median (IQR)	1.1 (1–1.3)	1.1 (1–1.2)	0.85
Outcome			
Hospital mortality, no. (%)	3 (7)	5 (16)	0.28
Length of hospital stay, median (IQR) days	7.7 (4–15.3)	10.8 (7–18)	0.06
Length of ICU stay, median (IQR) days	6.1 (2–11)	6 (4.2–9.1)	0.83
Duration of mechanical ventilation, median (IQR) days	2.8 (0.7–5.1)	3.7 (2.4–5.4)	0.48
Complete remission at 6 months, no. (%)	32 (78)	23 (72)	0.54

Characteristic	Cyclophosphamide (n = 31)	Rituximab (n = 37)	P
Age, median (IQR) years	67 (56–74)	58 (42–67)	0.01
Sex, no. (%) male	17 (55)	20 (54)	0.94
GPA, no. (%)	16 (52)	27 (73)	0.06
MPA, no. (%)	15 (48)	10 (27)	0.08
BVAS/WG score, median (IQR)	10 (9–13)	10 (8–12)	0.38
Spo_2:Fio_2 at presentation, median (IQR)	288 (155–442)	205 (115–452)	0.49
APACHE III score, median (IQR)†	50 (33–101)	50 (31–72)	0.59
Mechanical ventilation, no. (%)	13 (42)	18 (49)	0.63
Active renal disease, no. (%)	14 (45)	16 (43)	0.87
Requiring new renal replacement therapy, no. (%)	7 (23)	3 (8)	0.16
Hemosiderin-laden macrophages, median (IQR) %	58 (20–95)	52 (28–85)	0.39
Neutrophils in BAL fluid, median (IQR) %	26 (7–80)	29 (11–66)	0.96
Creatinine, median (IQR) mg/dl	1.4 (1–3.9)	1.1 (0.9–2.4)	0.15
GFR, median (IQR) ml/minute	29 (10–49)	32 (24–60)	0.17
Hemoglobin, median (IQR) gm/dl	8.6 (7.9–9.6)	9.3 (7.8–11.4)	0.16
Decrease in hemoglobin, median (IQR) gm/dl	2.6 (1.5–4.2)	2.3 (1.3–3.3)	0.66
Leukocytes, median (IQR) per mm^3	10.5 (6.9–12.2)	12.1 (7.7–15.4)	0.08
Platelet count, median (IQR) per mm^3	319 (250–418)	274 (192–376)	0.16
PR3-ANCA positive, no. (%)	16 (52)	23 (62)	0.38
MPO-ANCA positive, no. (%)	15 (48)	14 (38)	0.46
ESR, median (IQR) mm/hour	66 (45–93)	47 (24–84)	0.11
CRP, median (IQR) mg/liter	18.4 (3.2–23.6)	28.3 (7.4–138)	0.06
INR, median (IQR)	1.1 (1–1.3)	1.1 (1–1.2)	0.42
Outcome			
Hospital mortality, no. (%)	4 (13)	2 (5.4)	0.40
Length of hospital stay, median (IQR) days	9.8 (6–15)	9.2 (4.9–17)	0.90
Length of ICU stay, median (IQR) days	8 (2–16)	5.2 (3–8.6)	0.56
Duration of mechanical ventilation, median (IQR) days	4.2 (1.2–6.4)	3.6 (0.8–5)	0.77
Complete remission at 6 months, no. (%)	21 (68)	33 (89)	0.02

* Spo_2 = oxygen saturation measured by pulse oximetry; Fio_2 = fraction of inspired oxygen (see Table 1 for other definitions).
† For 41 patients admitted to the ICU.

- Clearly mentioned the number of patients requiring mechanical ventilation
- Confirmed all cases of DAH with bronchoscopy
- This study was a retrospective cohort study from a single centre
- Sample size too small to draw conclusion on long-term survival/mortality
- Involved more patients with GPA than MPA
- There was a bias in choosing plasma exchange for sicker patients
- Collection of data was not uniform

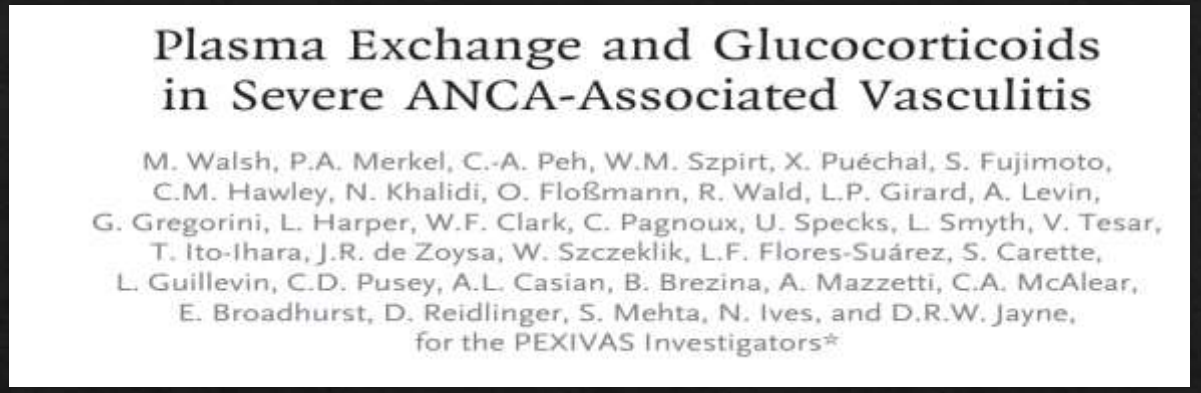
Author, year (ref.)	No. (%) of cases	Age, years†	Hemoptysis, %	GPA, %	MPA, %	BVAS‡	Renal disease, %	Plasma exchange, no. (%)	DAH resolution and hospital survival, no. (%)§	No plasma exchange, no. (%)	DAH resolution and hospital survival, no. (%)¶
Present study	73 (8.3)	61.8 (49.3–72.4)	75	60	40	10 (8–13)#	45	32 (44)	27 (84)	41 (56)	38 (93)
Hruskova et al, 2013 (9)	53 (6.4)	59 (18–81)	86	69.8	30.2	NR	98.1	40 (75)	18 (45)	13 (25)	4 (31)
Kostianovsky et al, 2012 (17)	80**	49 (13–86)	96.3	61.3	26.3	NR	76.3	16 (20)	NR	64 (80)	NR
Ravindran and Watts, 2010 (12)	9**	52	100	66.6	22.2	23.6 ± 6.4	66.6	5 (55)	3 (60)	4 (45)	3 (75)
Chen and Zhao, 2009 (8)	5 (8)	60 (17–78)	NR	–	100	20.8 ± 9.4	100	2 (40)	1 (50)	3 (60)	2 (67)

Others studies conducted thus far suffered from paucity of subjects, inconsistencies in defining DAH or establishing its diagnosis.

PLEX or no PLEX?

The rationale behind PLEX has been that it can readily remove the antibodies causing the capillaritis and prevent adverse outcomes

- PEXIVAS trial was an open-label randomized clinical trial among >700 patients with severe ANCA-associated vasculitis
- Aim was to compare rates of death/ESKD in severe ANCA-associated vasculitis treated with plasma exchange therapy or no plasma exchange therapy in addition to standard immunosuppression.
- They additionally compared a low dose glucocorticoid regimen with the standard glucocorticoid regimen to see whether lower dose GC was non-inferior to standard dose with fewer side effects
- The patients were followed up for 1 year from randomization



Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

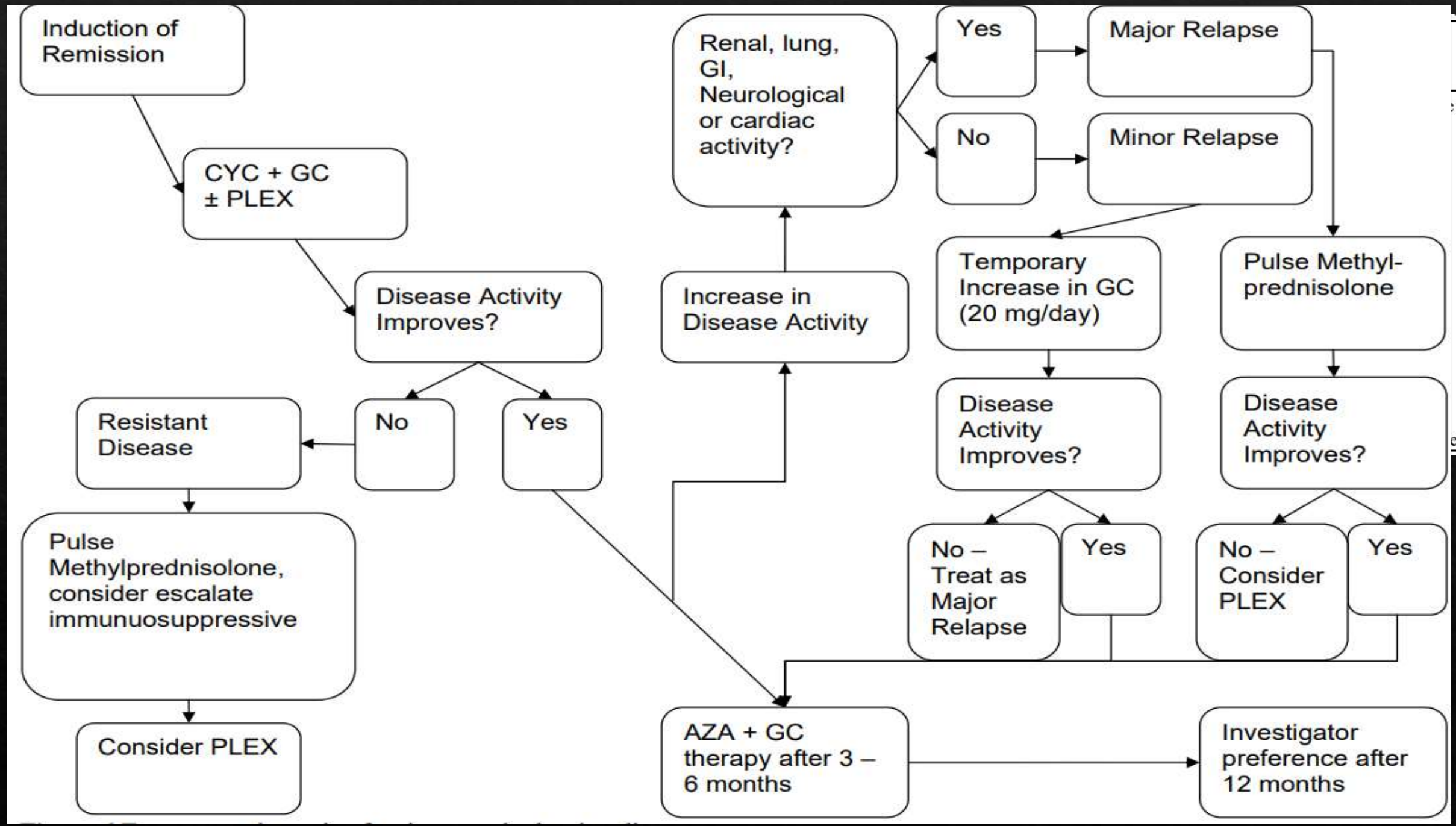
M. Walsh, P.A. Merkel, C.-A. Peh, W.M. Szpirt, X. Puéchal, S. Fujimoto, C.M. Hawley, N. Khalidi, O. Floßmann, R. Wald, L.P. Girard, A. Levin, G. Gregorini, L. Harper, W.F. Clark, C. Pagnoux, U. Specks, L. Smyth, V. Tesar, T. Ito-Ihara, J.R. de Zoysa, W. Szczeklik, L.F. Flores-Suárez, S. Carette, L. Guillevin, C.D. Pusey, A.L. Casian, B. Brezina, A. Mazzetti, C.A. McAlear, E. Broadhurst, D. Reidlinger, S. Mehta, N. Ives, and D.R.W. Jayne, for the PEXIVAS Investigators*

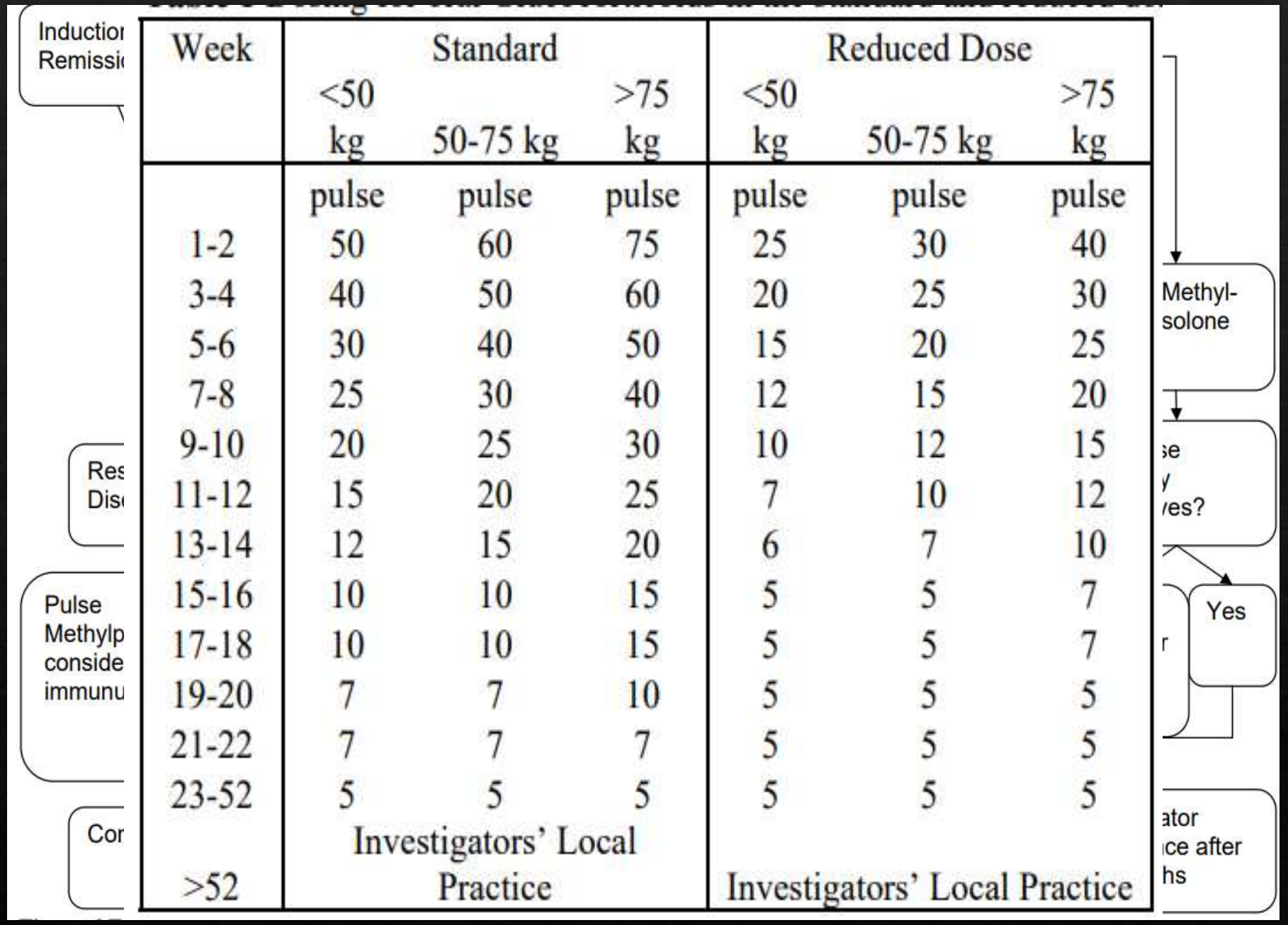
2X2 factorial design

Patients received one of the following regimen

1. Pulse GC f/b RTX or CYC with Plasma exchange f/b systemic GC at 1mg/Kg
2. Pulse GC f/b RTX or CYC without Plasma exchange f/b Systemic GC at 1 mg/Kg
3. Pulse GC f/b RTX or CYC with Plasma exchange f/b systemic GC at 50% of standard dose
4. Pulse GC f/b RTX or CYC without Plasma exchange f/b systemic GC at 50% of standard dose

Patients followed up for the next 12 months with BVAS, SF-36, evidence of development of ESKD/death and severe adverse events


Induction of Remission
CYC + GC ± PLEX
Disease Activity Improves?
No
Yes
Resistant Disease
Pulse Methylprednisolone, consider escalate immunuosuppressive
Consider PLEX
Renal, lung, GI, Neurological or cardiac activity?
Yes
No
Major Relapse
Minor Relapse
Increase in Disease Activity
Temporary Increase in GC (20 mg/day)
Pulse Methyl-prednisolone
Disease Activity Improves?
Disease Activity Improves?
No – Treat as Major Relapse
Yes
No – Consider PLEX
Yes
AZA + GC therapy after 3 – 6 months
Investigator preference after 12 months



Week	Standard			Reduced Dose		
	<50 kg	50-75 kg	>75 kg	<50 kg	50-75 kg	>75 kg
	pulse	pulse	pulse	pulse	pulse	pulse
1-2	50	60	75	25	30	40
3-4	40	50	60	20	25	30
5-6	30	40	50	15	20	25
7-8	25	30	40	12	15	20
9-10	20	25	30	10	12	15
11-12	15	20	25	7	10	12
13-14	12	15	20	6	7	10
15-16	10	10	15	5	5	7
17-18	10	10	15	5	5	7
19-20	7	7	10	5	5	5
21-22	7	7	7	5	5	5
23-52	5	5	5	5	5	5
>52	Investigators' Local Practice			Investigators' Local Practice		

Primary outcome-
Composite death-ESKD

Secondary outcomes-
- Any-cause mortality
- Sustained remission
- Serious AE, infection
- Health related QOL

Crossovers were allowed in the study but was infrequent

INCLUSION CRITERIA

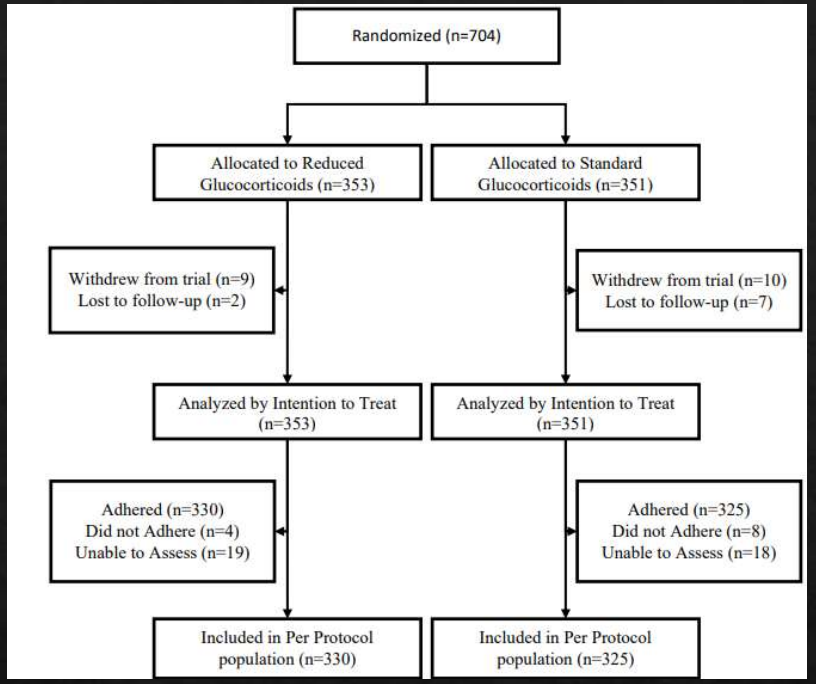
1. Clinically diagnosed new or relapsing GPA/MPA cases AND
2. Positive ANCA report (MPO or PR3) AND
3. Severe vasculitis- Renal involvement (renal biopsy showing FNGN/RME + eGFR<50) OR **alveolar haemorrhage**
4. Consenting adults

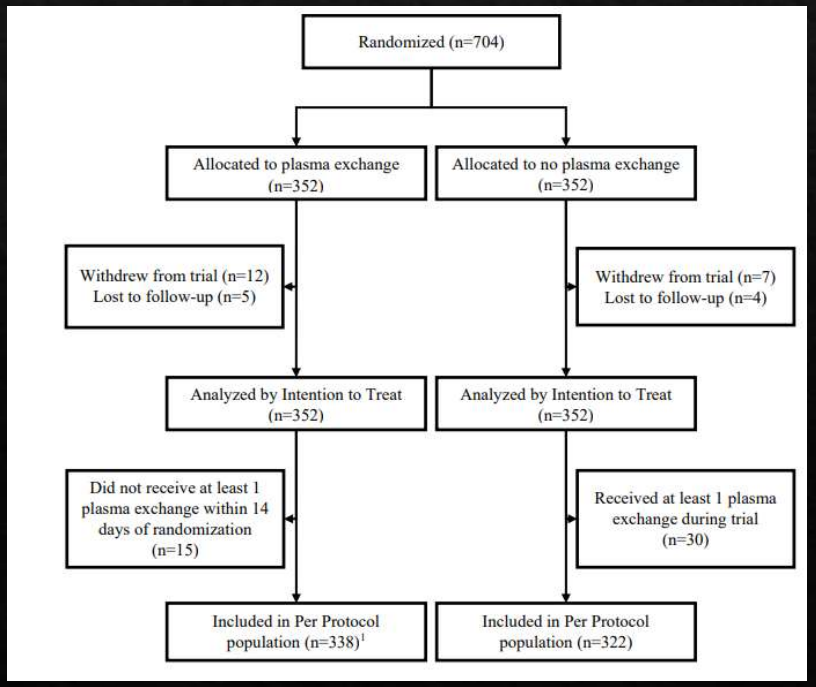
EXCLUSION CRITERIA

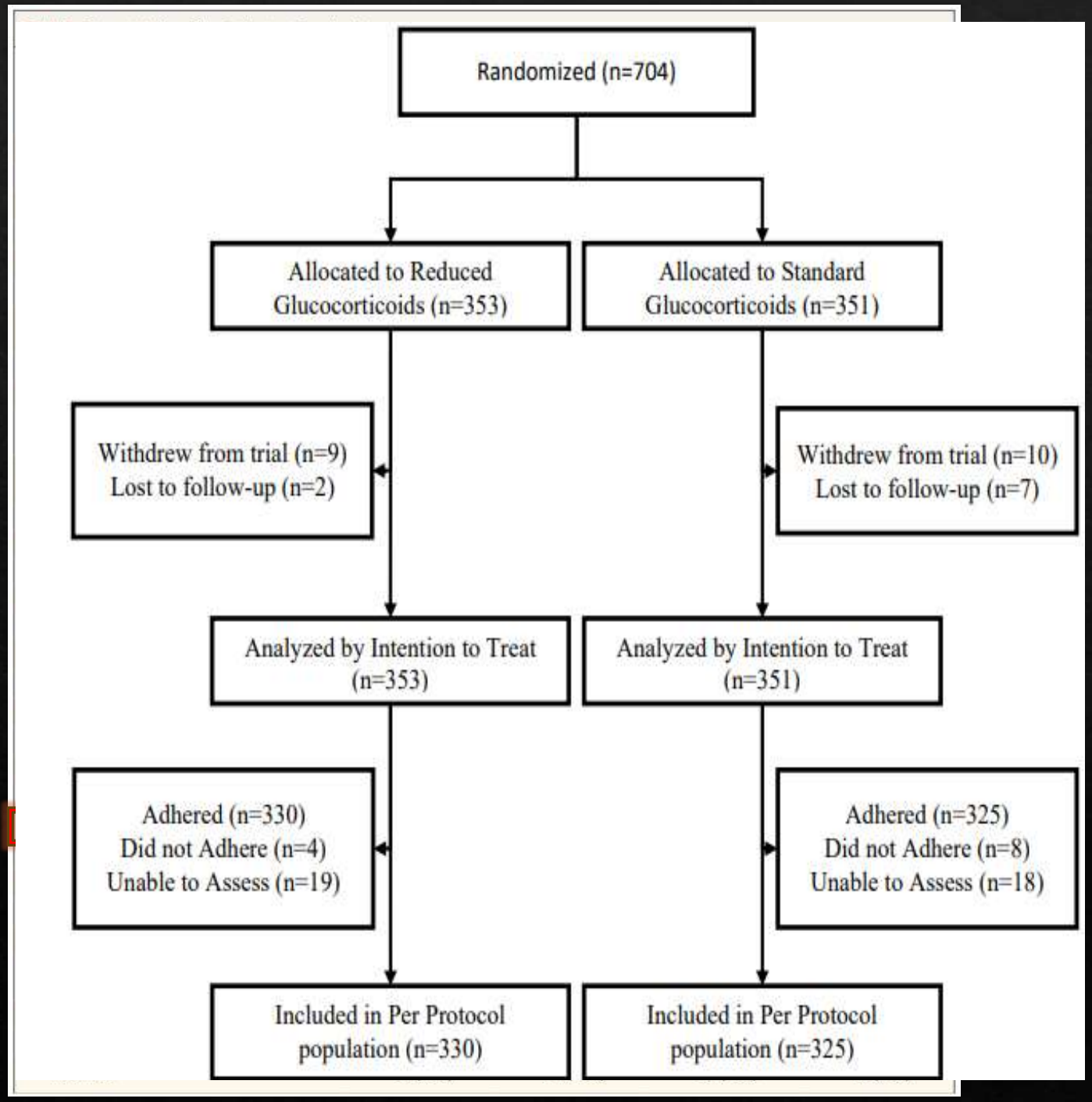
1. Age <15 years (at some centres <18)
2. Vasculitis other than GPA/MPA and anti-GBM disease
3. Undergone RRT >21 days / renal transplant
4. Pregnant
5. In past 28 days received GC/RTX/CYC
6. Received PLEX in past 3 months
7. Any comorbidity that is C/I for PLEX/CYC/RTX

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Plasma Exchange (N=352)	No Plasma Exchange (N=352)	Reduced-Dose Glucocorticoid Regimen (N=353)	Standard-Dose Glucocorticoid Regimen (N=351)
Age — yr	62.8±14.4	63.5±13.7	63.3±14.2	63.1±13.9
Female sex — no. (%)	149 (42.3)	158 (44.9)	156 (44.2)	151 (43.0)
History of vasculitis — no. (%)	35 (9.9)	28 (8.0)	34 (9.6)	29 (8.3)
ANCA subtype — no. (%)				
Proteinase 3	143 (40.6)	143 (40.6)	143 (40.5)	143 (40.7)
Myeloperoxidase	209 (59.4)	209 (59.4)	210 (59.5)	208 (59.3)
Median C-reactive protein level (IQR) — mg/liter	50.9 (13.8–122.8)	42.1 (14.0–97.2)	44.6 (13.0–117.0)	45.5 (14.0–98.0)
Median hemoglobin level (IQR) — g/liter	94 (83–105)	95 (85–105)	95 (84–105)	95 (84.5–105)
Kidney function				
Median serum creatinine level (IQR) — μmol/liter	327 (206–491)	336 (209–495)	320 (190–480)	335 (219–502)
Serum creatinine level ≥500 μmol/liter or undergoing dialysis — no. (%)	101 (28.7)	104 (29.5)	102 (28.9)	103 (29.3)
Undergoing dialysis — no. (%)	66 (18.8)	74 (21)	67 (19.0)	73 (20.8)
Severity of pulmonary hemorrhage — no. (%)				
No hemorrhage	257 (73.0)	256 (72.7)	257 (72.8)	256 (72.9)
Not severe	64 (18.2)	66 (18.8)	65 (18.4)	65 (18.5)
Severe†	31 (8.8)	30 (8.5)	31 (8.8)	30 (8.5)
Organ involvement — no. (%)				
Cutaneous	37 (10.5)	39 (11.1)	34 (9.6)	42 (12.0)
Mucous membranes or eyes	30 (8.5)	36 (10.2)	30 (8.5)	36 (10.3)
Ear, nose, and throat	95 (27.0)	103 (29.3)	98 (27.8)	100 (28.5)
Cardiovascular	6 (1.7)	4 (1.1)	5 (1.4)	5 (1.4)
Gastrointestinal	2 (0.6)	2 (0.6)	1 (0.3)	3 (0.9)
Pulmonary	145 (41.2)	149 (42.3)	147 (41.6)	147 (41.9)
Kidney	342 (97.2)	349 (99.1)	346 (98.0)	345 (98.3)
Nervous system	37 (10.5)	25 (7.1)	33 (9.3)	29 (8.3)
Other	61 (17.3)	59 (16.8)	59 (16.7)	61 (17.4)
Median BVAS/GPA (IQR)‡	9 (7–11)	9 (7–11)	9 (7–11)	9 (7–11)
Planned immunosuppressive treatment — no. (%)				
Intravenous cyclophosphamide	177 (50.3)	177 (50.3)	179 (50.7)	175 (49.9)
Oral cyclophosphamide	120 (34.1)	121 (34.4)	120 (34.0)	121 (34.5)
Rituximab	55 (15.6)	54 (15.3)	54 (15.3)	55 (15.7)






Randomized (n=704)
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Allocated to Standard Glucocorticoids (n=351)
Withdrew from trial (n=9)
Lost to follow-up (n=2)
Withdrew from trial (n=10)
Lost to follow-up (n=7)
Analyzed by Intention to Treat (n=353)
Analyzed by Intention to Treat (n=351)
Adhered (n=330)
Did not Adhere (n=4)
Unable to Assess (n=19)
Adhered (n=325)
Did not Adhere (n=8)
Unable to Assess (n=18)
Included in Per Protocol population (n=330)
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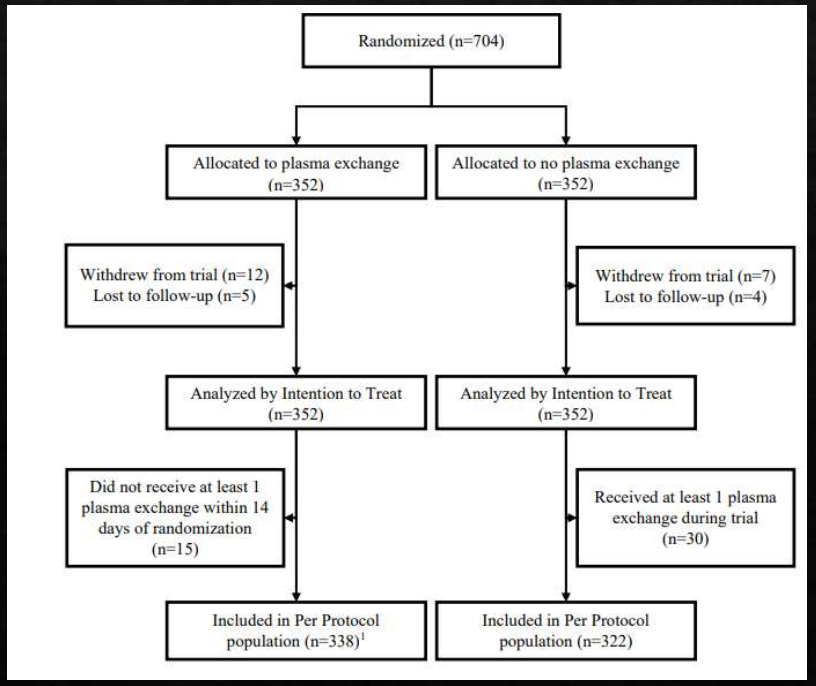
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Received at least 1 plasma exchange during trial (n=30)
Included in Per Protocol population (n=338)[1]
Included in Per Protocol population (n=322)

Table 1. Characteristics of the Patients at Baseline.*

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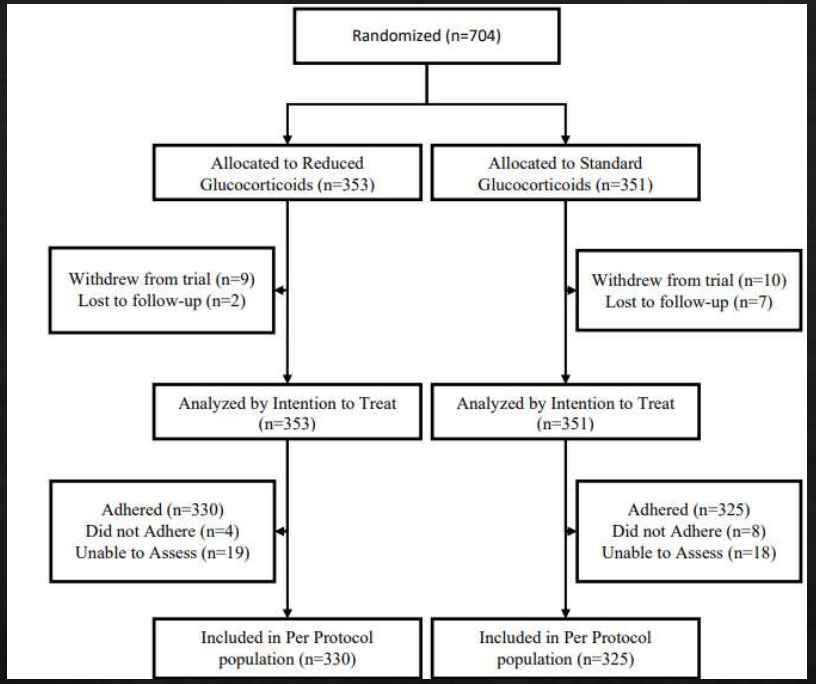

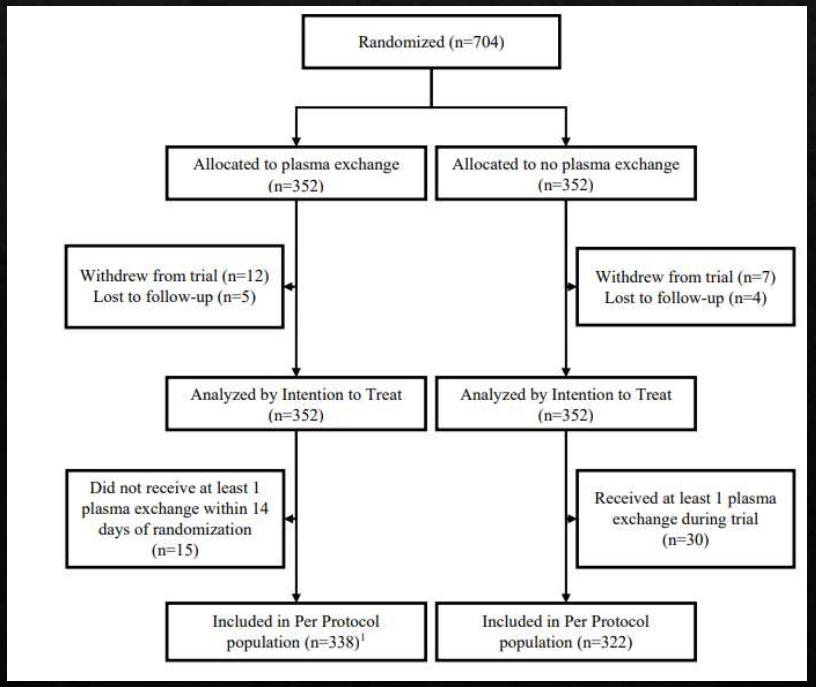

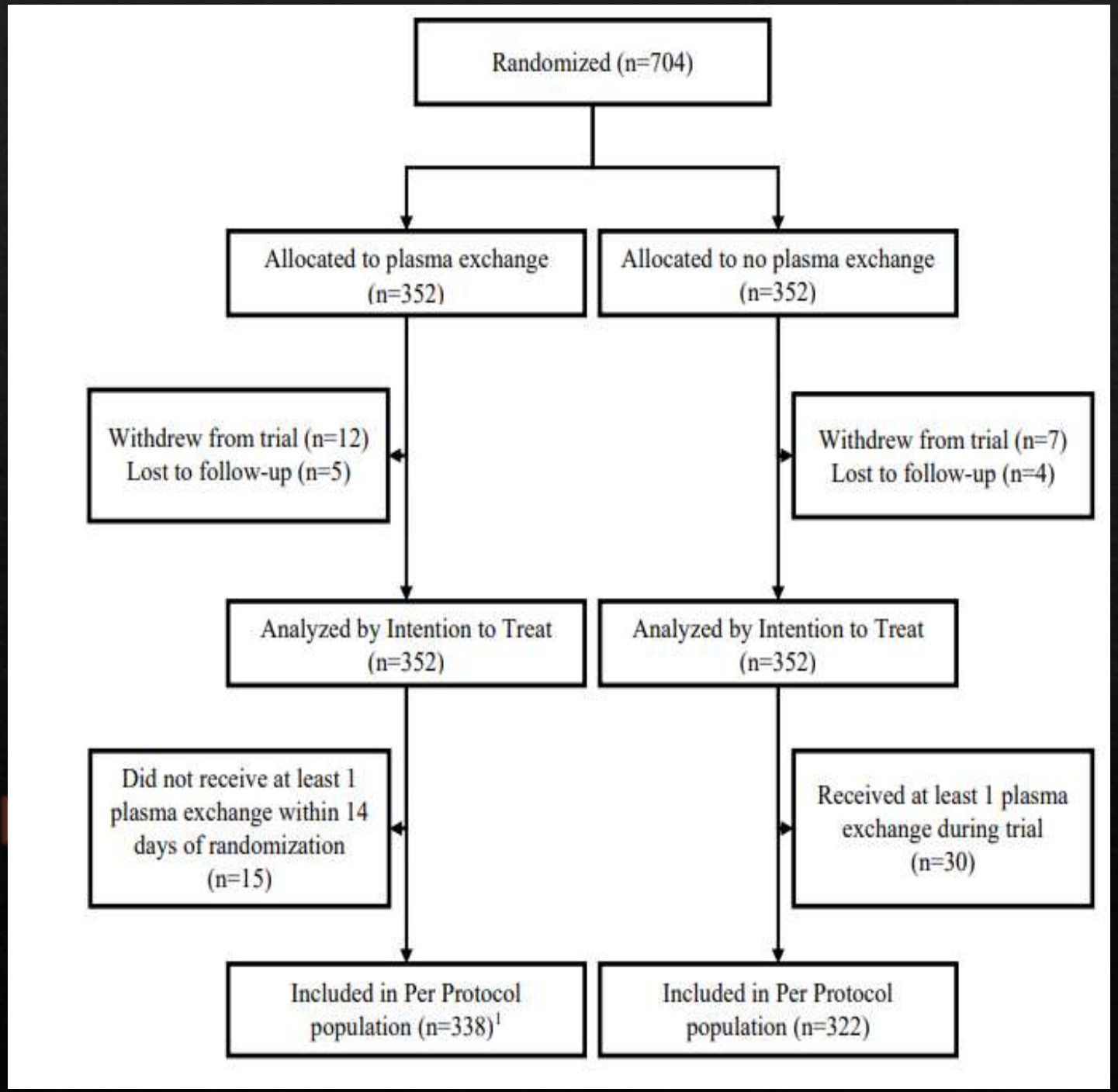
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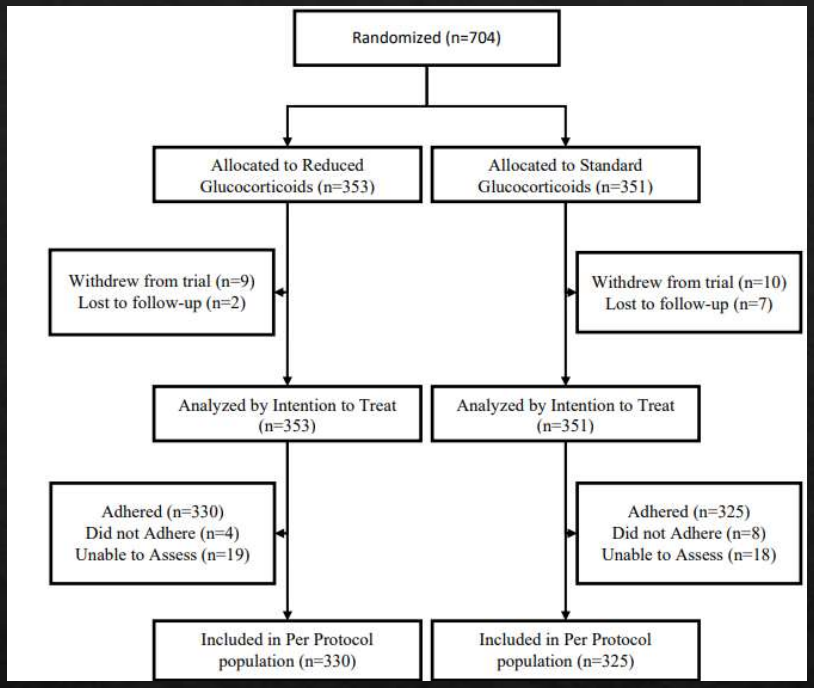
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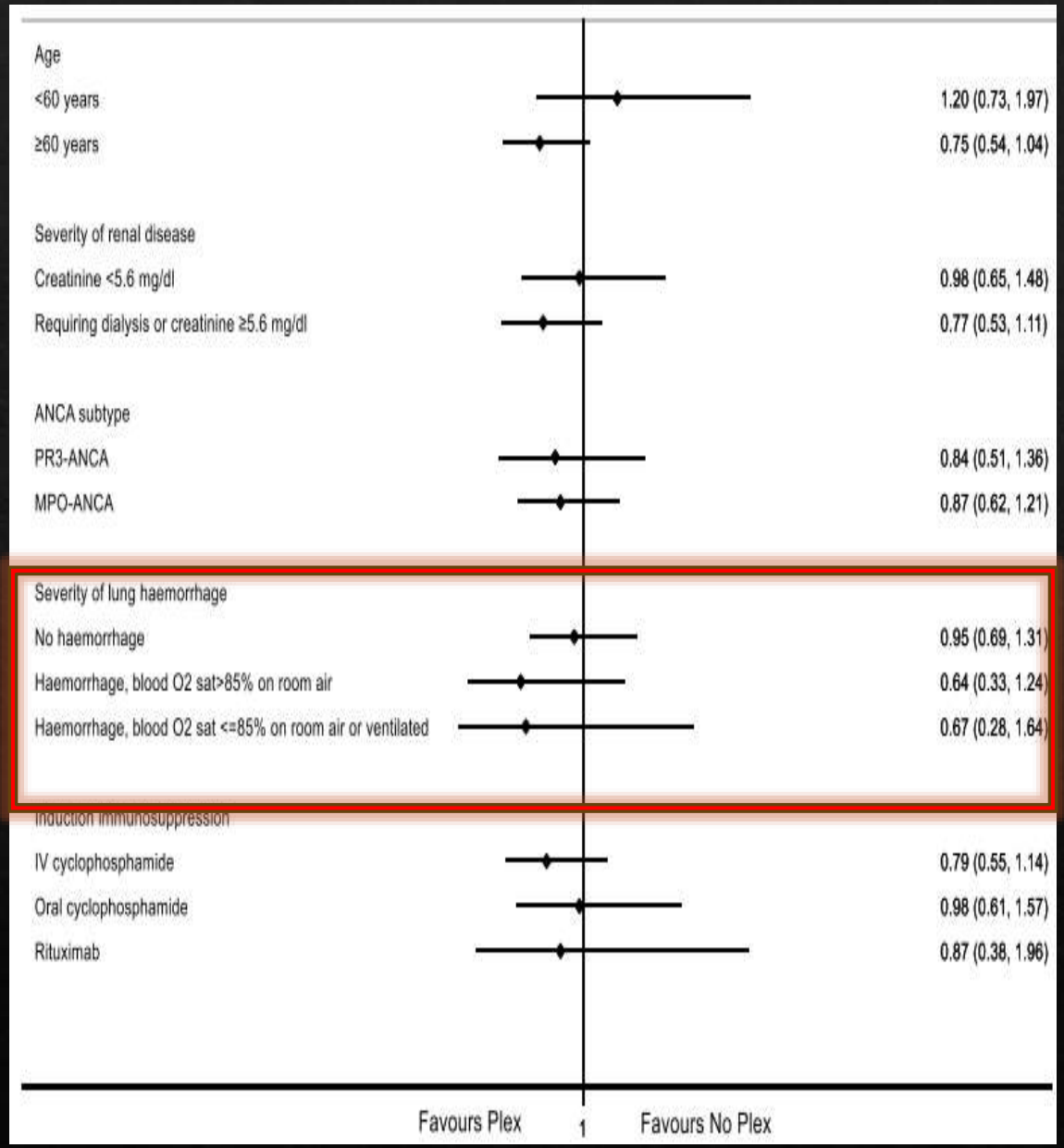
Table 2. Primary Composite Outcome with Plasma Exchange as Compared with No Plasma Exchange.*

Analysis	Plasma Exchange	No Plasma Exchange	Hazard Ratio (95% CI)
	no. with outcome/total no. (%)		
Primary analysis†	100/352 (28.4)	109/352 (31.0)	0.86 (0.65–1.13)
Partially adjusted analysis‡	100/352 (28.4)	109/352 (31.0)	0.89 (0.68–1.17)
Per-protocol analysis	95/338 (28.1)	99/322 (30.7)	0.85 (0.64–1.13)
Analysis at 1-year follow-up	70/352 (19.9)	85/352 (24.1)	0.77 (0.56–1.06)

Secondary Outcome	Plasma Exchange vs. No Plasma Exchange
	effect si
Death from any cause	0.87 (0.58–1.29)
End-stage kidney disease	0.81 (0.57–1.13)
Sustained remission	1.01 (0.89–1.15)
Serious adverse events	1.21 (0.96–1.52)
Serious infections at 1 year	1.16 (0.87–1.56)



Walsh M, Merkel PA, Peh CA, Szpirt WM, Puéchal X, Fujimoto S, et al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. New England Journal of Medicine. 2020 Feb 13;382(7):622–31.

Table 2. Primary C

Analysis

Primary analysis†

Partially adjusted a

Per-protocol analys

Analysis at 1-year f

Secondary

Death fror

End-stage

Sustained

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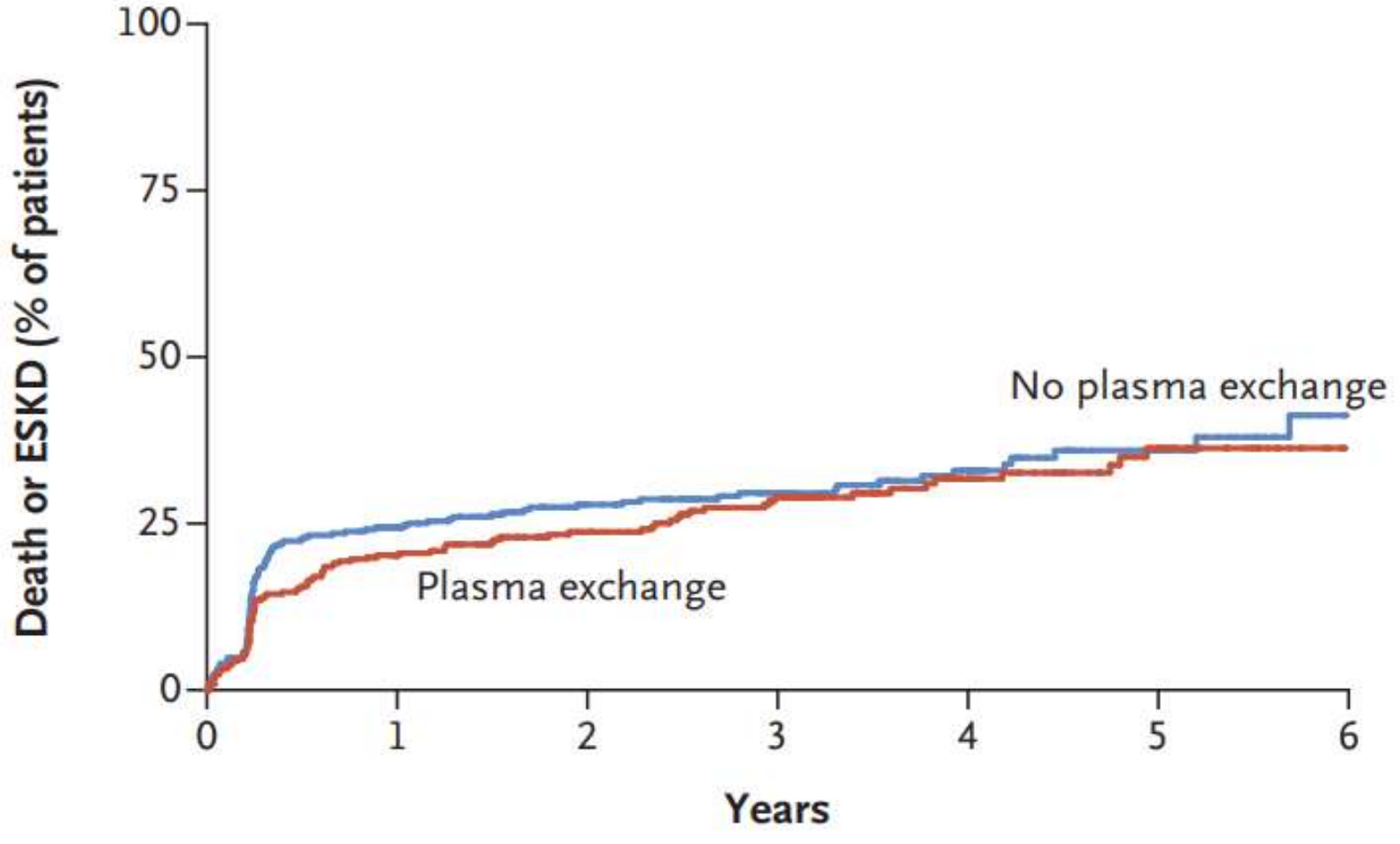

No. at Risk							
No plasma exchange	352	244	183	136	82	44	10
Plasma exchange	352	252	186	135	82	43	10

1.20 (0.73, 1.97)

0.75 (0.54, 1.04)

0.98 (0.65, 1.48)

0.77 (0.53, 1.11)

0.84 (0.51, 1.36)

0.87 (0.62, 1.21)

0.95 (0.69, 1.31)

0.64 (0.33, 1.24)

0.67 (0.28, 1.64)

0.79 (0.55, 1.14)

0.98 (0.61, 1.57)

0.87 (0.38, 1.96)

Favours No Plex

Walsh M, Merkel PA, Peh CA, Szpirt WM, Puéchal X, Fujimoto S, et al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. New England Journal of Medicine. 2020 Feb 13;382(7):622–31.

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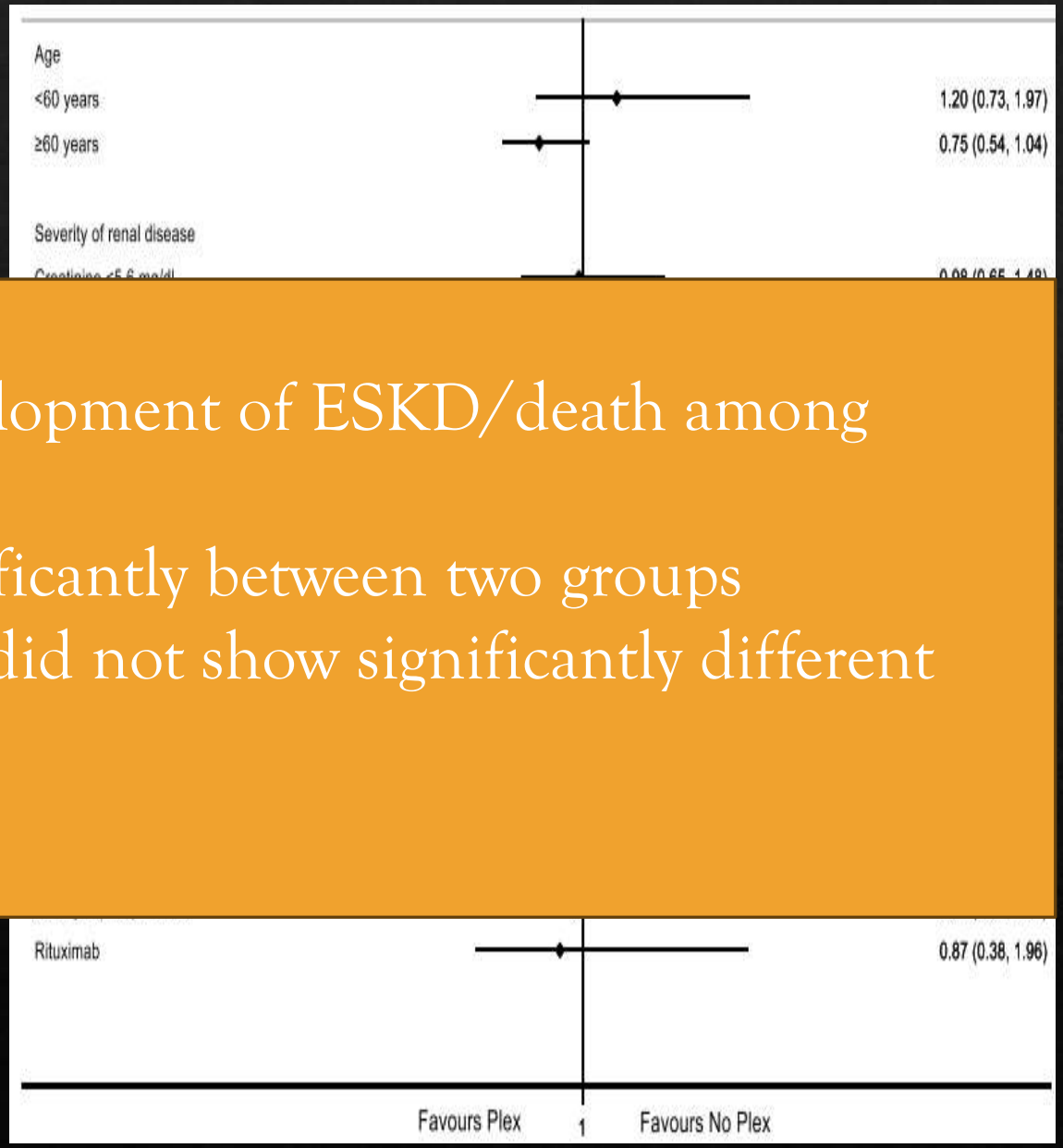
Primary analysis†	100/352 (28.4)	109/352 (31.0)	0.86 (0.65–1.13)
Sustained remission			1.01 (0.89–1.15)
Serious adverse events			1.21 (0.96–1.52)
Serious infections at 1 year			1.16 (0.87–1.56)

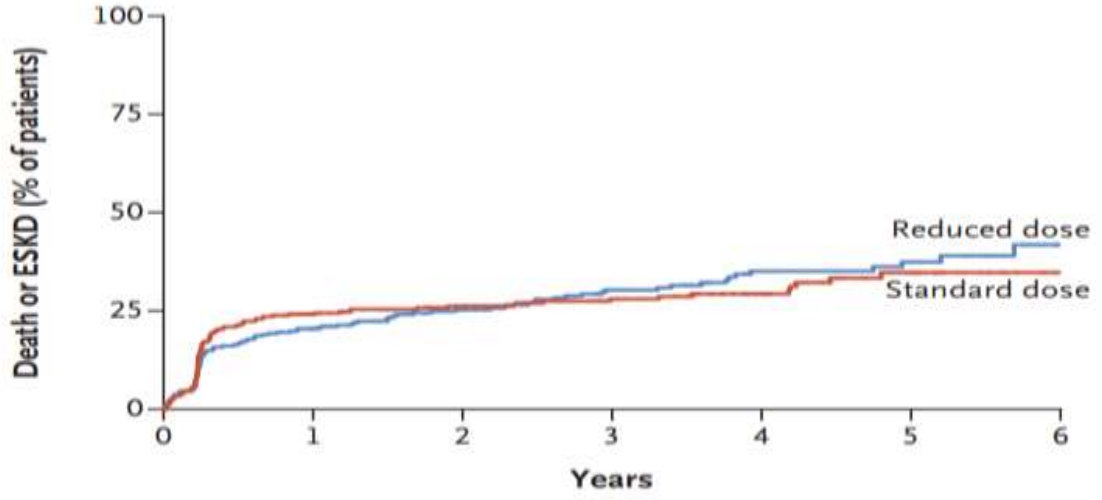


- There was no significant difference in development of ESKD/death among patients treated with or without PLEX
- Serious side effects also did not differ significantly between two groups
- Patients with DAH who underwent PLEX did not show significantly different outcome

Walsh M, Merkel PA, Peh CA, Szpirt WM, Puéchal X, Fujimoto S, et al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. New England Journal of Medicine. 2020 Feb 13;382(7):622–31.

Table 3. Secondary Outcomes.*

Secondary Outcome	Reduced-Dose vs. Standard-Dose Glucocorticoid Regimen (95% CI)
Death from any cause	0.78 (0.53–1.17)
End-stage kidney disease	0.96 (0.68–1.34)
Sustained remission	1.04 (0.92–1.19)
Serious adverse events	0.95 (0.75–1.20)
Serious infections at 1 year	0.69 (0.52–0.93)



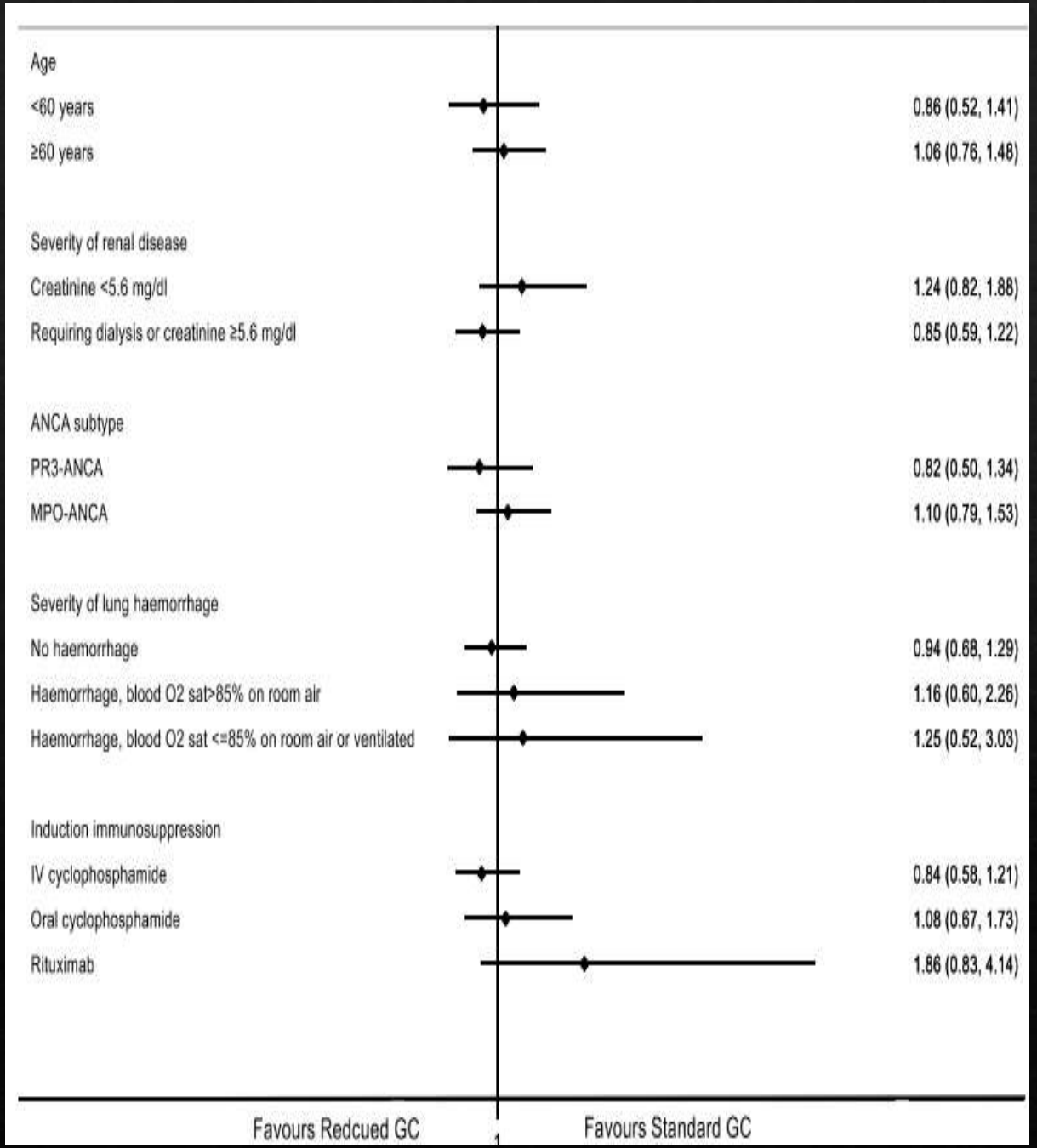
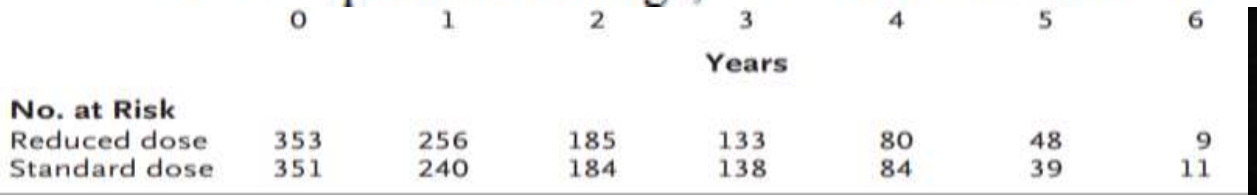


Table 3. Secondary Outcomes.*

Secondary Outcome	Reduced-Dose vs. Standard-Dose Glucocorticoid Regimen					
Serious Adverse Event Type	**PLEX (N=352)**	**No PLEX (n=352)**	**Relative Risk (95% CI)**	**Reduced-Dose Glucocorticoids (N=353)**	**Standard-Dose Glucocorticoids (n=351)**	**Unadjusted Relative Risk (95% CI)**
Cardiovascular	69 (20%)	55 (16%)	1.25 (0.91 to 1.73)	68 (19%)	56 (16%)	1.21 (0.88 to 1.66)
Endocrine	9 (3%)	3 (1%)	3.00 (0.82 to 11.0)	4 (1%)	8 (2%)	0.50 (0.15 to 1.64)
Gastrointestinal	34 (10%)	39 (11%)	0.87 (0.56 to 1.35)	43 (12%)	30 (9%)	1.43 (0.92 to 2.22)
Hematologic	25 (7%)	16 (5%)	1.56 (0.85 to 2.88)	22 (6%)	19 (5%)	1.15 (0.63 to 2.09)
Infection	136 (39%)	114 (32%)	1.19 (0.98 to 1.46)	119 (34%)	131 (37%)	0.90 (0.74 to 1.10)
Kidney/Urinary	41 (12%)	36 (10%)	1.14 (0.75 to 1.74)	50 (14%)	27 (8%)	1.84 (1.18 to 2.87)
Surgery	16 (5%)	13 (4%)	1.23 (0.60 to 2.52)	14 (4%)	15 (4%)	0.93 (0.45 to 1.89)
Vasculitis relapse	23 (7%)	32 (9%)	0.72 (0.43 to 1.20)	32 (9%)	23 (7%)	1.38 (0.83 to 2.32)
Other	89 (25%)	79 (22%)	1.13 (0.86 to 1.47)	91 (26%)	77 (22%)	1.18 (0.90 to 1.53)

PLEX = plasma exchange; CI = confidence interval



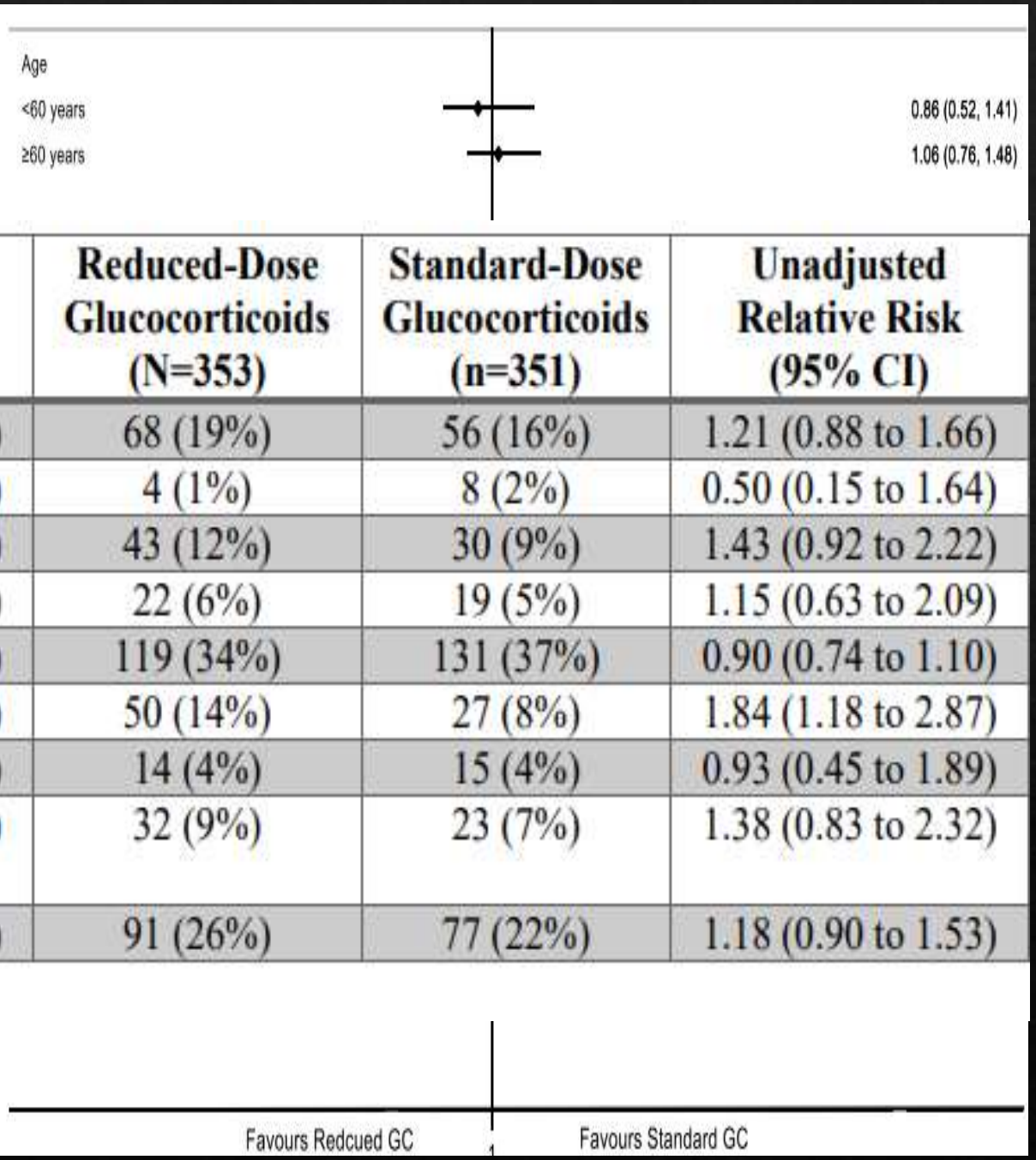
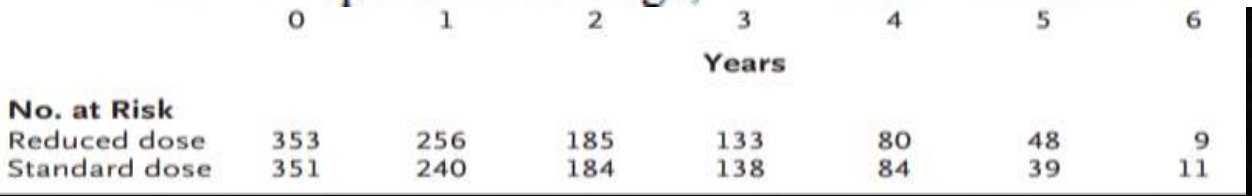


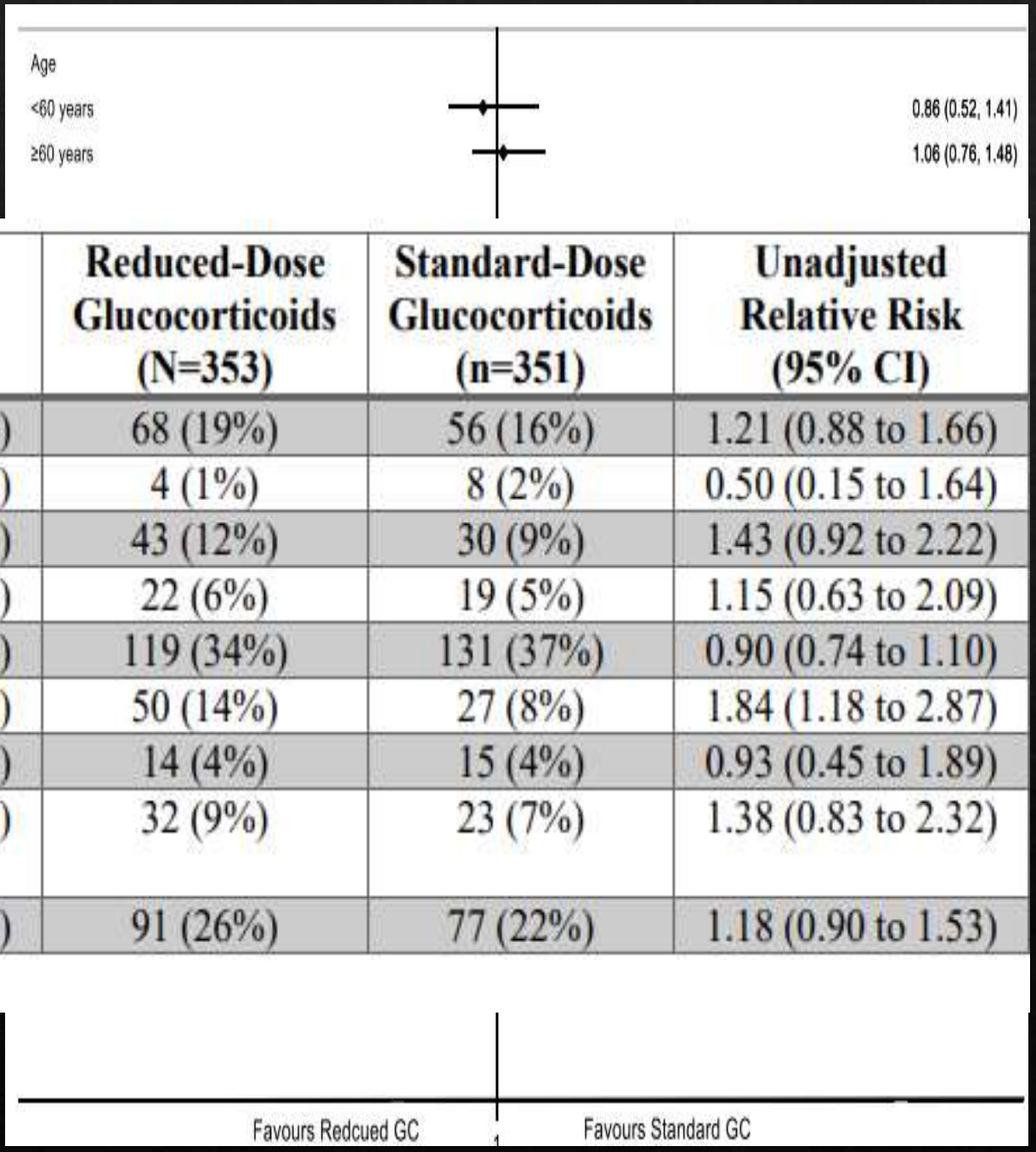
Table 3. Secondary G… Dose vs. Standard-Dose …rticoid Regimen

Lower dose GC was non-inferior to standard dose GC in achieving and maintaining remission

Sec…			Relative Risk (95% CI)	Reduced-Dose Glucocorticoids (N=353)	Standard-Dose Glucocorticoids (n=351)	Unadjusted Relative Risk (95% CI)
C…			…25 (0.91 to 1.73)	68 (19%)	56 (16%)	1.21 (0.88 to 1.66)
I…			…00 (0.82 to 11.0)	4 (1%)	8 (2%)	0.50 (0.15 to 1.64)
G…			…0.87 (0.56 to 1.35)	43 (12%)	30 (9%)	1.43 (0.92 to 2.22)
Hei…			1.56 (0.85 to 2.88)	22 (6%)	19 (5%)	1.15 (0.63 to 2.09)
Infecti…			1.19 (0.98 to 1.46)	119 (34%)	131 (37%)	0.90 (0.74 to 1.10)
Kidney/U…		…0%)	1.14 (0.75 to 1.74)	50 (14%)	27 (8%)	1.84 (1.18 to 2.87)
Surgery		13 (4%)	1.23 (0.60 to 2.52)	14 (4%)	15 (4%)	0.93 (0.45 to 1.89)
Vasculitis relapse	23 (7%)	32 (9%)	0.72 (0.43 to 1.20)	32 (9%)	23 (7%)	1.38 (0.83 to 2.32)
Other	89 (25%)	79 (22%)	1.13 (0.86 to 1.47)	91 (26%)	77 (22%)	1.18 (0.90 to 1.53)

PLEX = plasma exchange; CI = confidence interval





Lower dose GC was non-inferior to standard dose GC in achieving and maintaining remission

Serious adverse events were not significantly different among groups

Table 3. Secondary

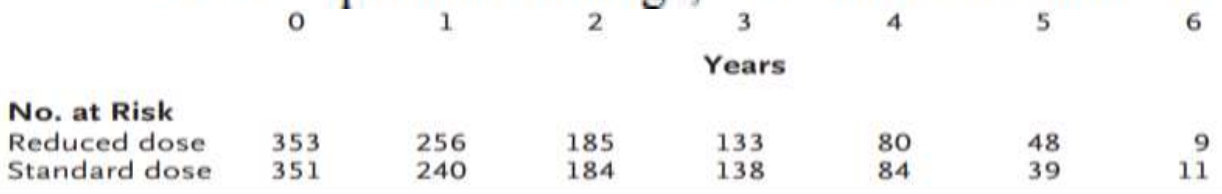
Second

Dose vs. Standard-Dose

rticoid Regimen

S			Relative Ri (95%	se	Standard-Dose Glucocorticoids (n=351)	Unadjusted Relative Risk (95% CI)
			25		56 (16%)	1.21 (0.88 to 1.66)
I			.0		8 (2%)	0.50 (0.15 to 1.64)
G			0.8		30 (9%)	1.43 (0.92 to 2.22)
He			1.5		19 (5%)	1.15 (0.63 to 2.09)
Infect			1.19		131 (37%)	0.90 (0.74 to 1.10)
Kidney/U		%)	1.14		27 (8%)	1.84 (1.18 to 2.87)
Surgery		13 (4%)	1.23 (0.		15 (4%)	0.93 (0.45 to 1.89)
Vasculitis relapse	23 (7%)	32 (9%)	0.72 (0.43		23 (7%)	1.38 (0.83 to 2.32)
Other	89 (25%)	79 (22%)	1.13 (0.86 to 1.47)	91 (26%)	77 (22%)	1.18 (0.90 to 1.53)

PLEX = plasma exchange; CI = confidence interval



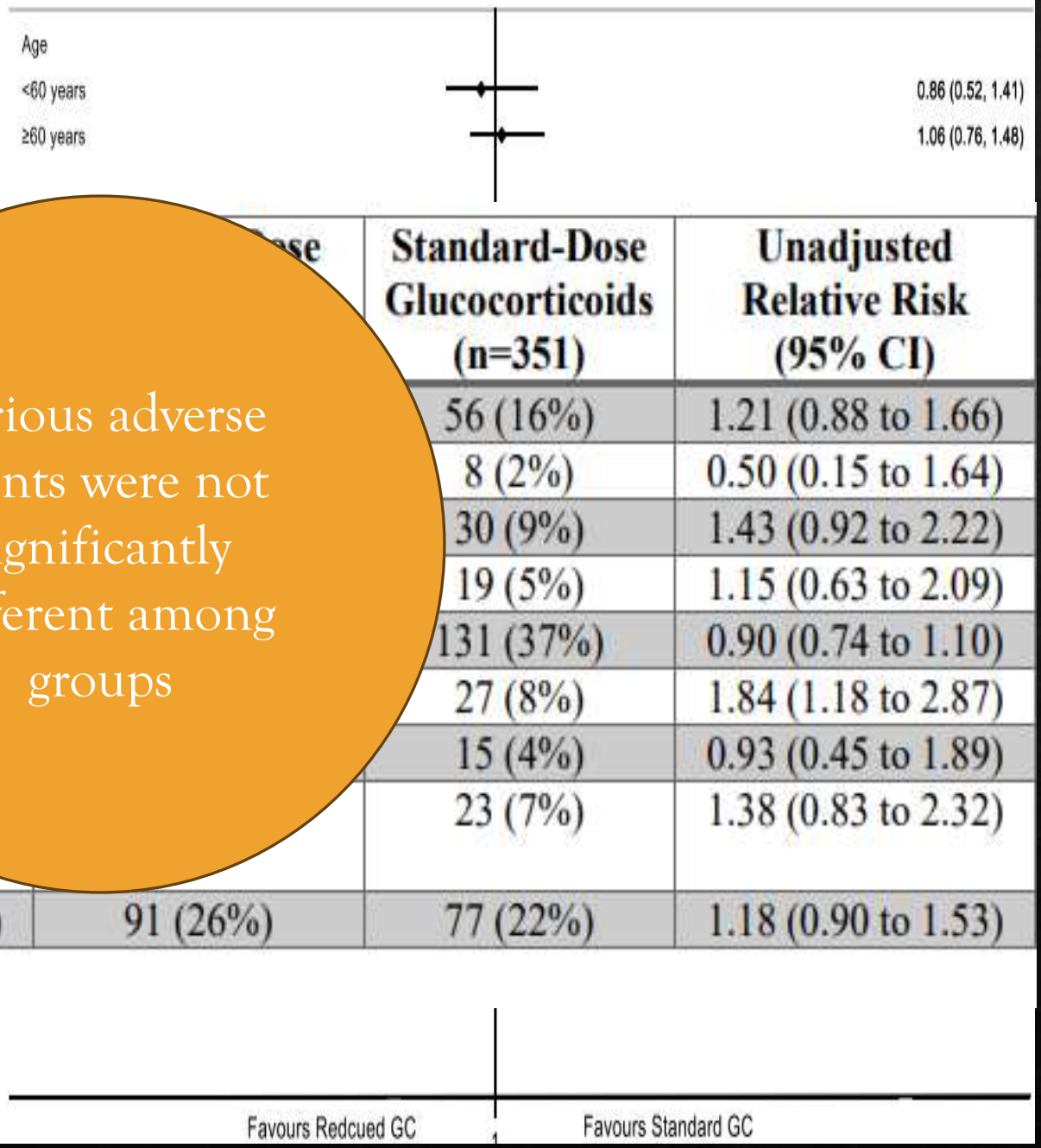


Table 3. Secondary

Second

Dose vs. Standard-Dose

rticoid Regimen

Sc			Relative Ri (95%	se	Standard-Dose Glucocorticoids (n=351)	Unadjusted Relative Risk (95% CI)
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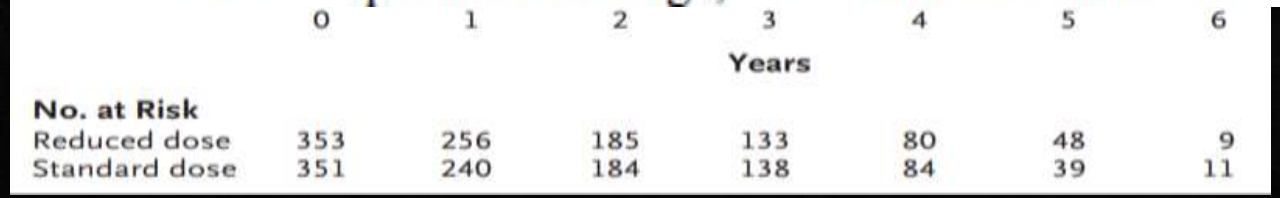
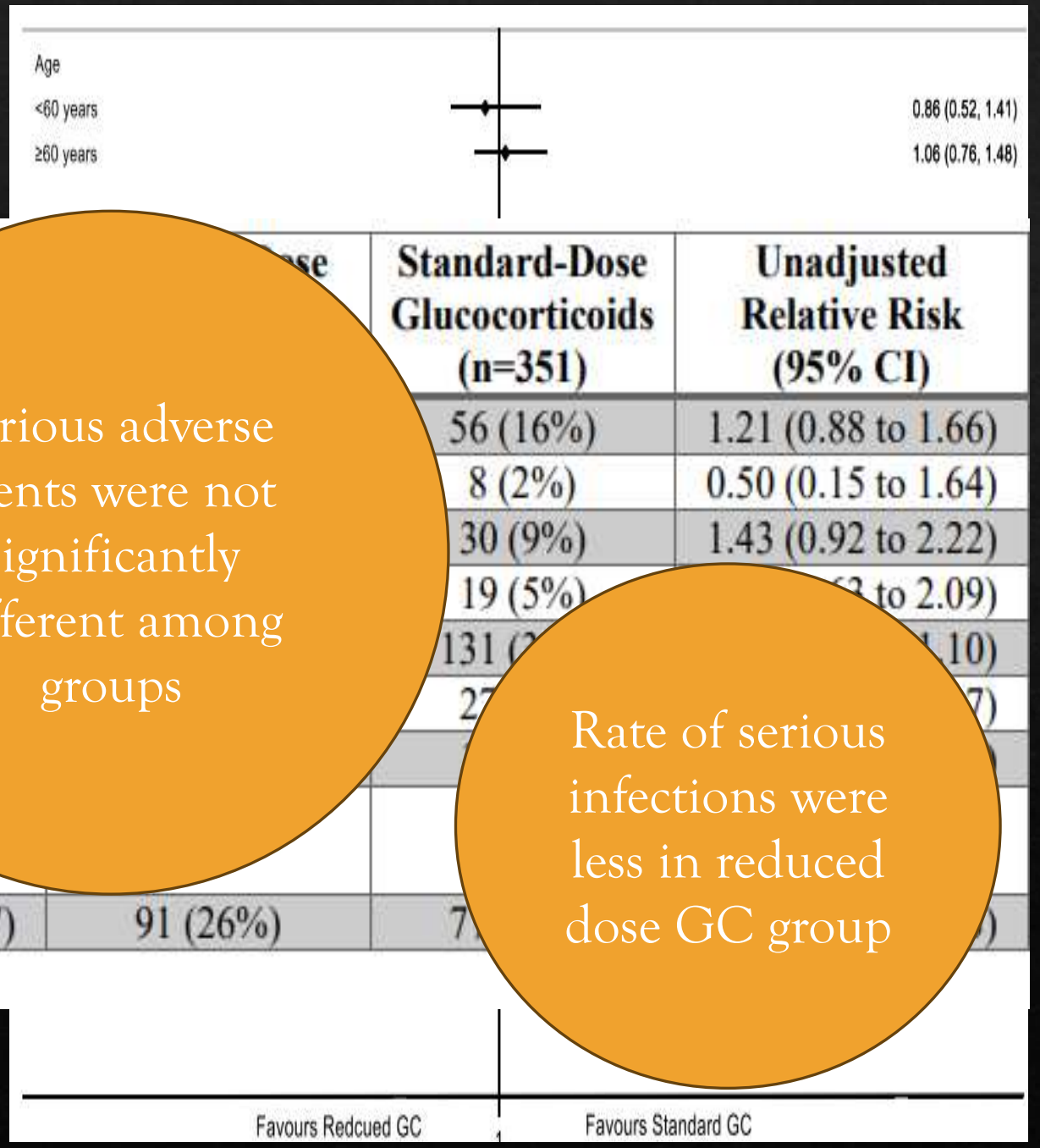
I			.0(		8 (2%)	0.50 (0.15 to 1.64)
G			0.8		30 (9%)	1.43 (0.92 to 2.22)
Hei			1.5		19 (5%)	to 2.09)
Infecti		)	1.19		131 (	.10)
Kidney/U		0%)	1.14 (		27	7)
Surgery		13 (4%)	1.23 (0.			)
Vasculitis relapse	23 (7%)	32 (9%)	0.72 (0.43			
Other	89 (25%)	79 (22%)	1.13 (0.86 to 1.47)	91 (26%)	7	)

PLEX = plasma exchange; CI = confidence interval





Lower dose GC was non-inferior to standard dose GC in achieving and maintaining remission

Serious adverse events were not significantly different among groups

Rate of serious infections were less in reduced dose GC group

- It was the first large RCT to include DAH patient requiring Mechanical ventilation
- Showed that PLEX did not provide an added benefit in patients with DAH
- Reduced dose GC would be as effective as standard dose with lower risk of serious infection
- Open label study, allowed cross-over (very insignificant number)
- CI was broad for some of the parameters

- It was the first large RCT to include DAH patient requiring Mechanical ventilation

Offered results contradicting few preceding studies that showed benefit with PLEX

- Open label study, allowed cross-over (very insignificant number)
- CI was broad for some of the parameters

ORIGINAL ARTICLE

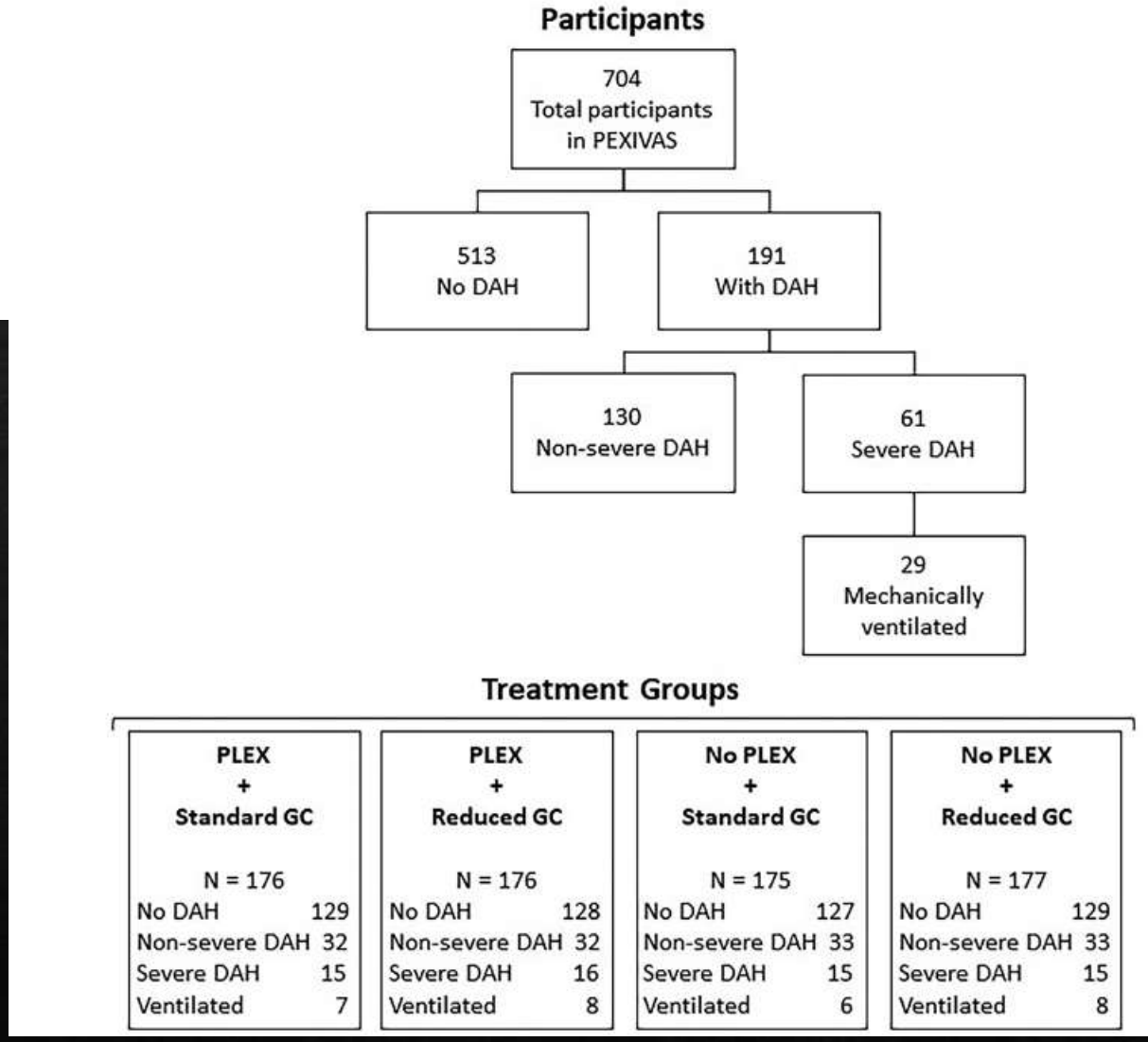
Alveolar Hemorrhage in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Results of an International Randomized Controlled Trial (PEXIVAS)

Lynn A. Fussner[1], Luis Felipe Flores-Suárez[2], Rodrigo Cartin-Ceba[3], Ulrich Specks[4], P. Gerard Cox[5], David R. W. Jayne[9], Peter A. Merkel[10,11], and Michael Walsh[6,7,8]; for the PEXIVAS Investigators

	Any DAH ($n=191$)	No DAH ($n=513$)	*P* Value
Age, yr, mean (SD)	61.1 (15.4)	63.9 (13.4)	0.018
Female	78 (40.8)	229 (44.6)	0.37
ANCA			<0.001
Anti-PR3	99 (51.8)	187 (36.5)	
Anti-MPO	92 (48.2)	326 (63.6)	
New diagnosis of AAV	164 (85.8)	477 (93.0)	0.004
BVAS/WG	11 (9–13)	7 (6–9)	<0.001
Creatinine, μmol/L	184 (115–320)	304 (212–442)	<0.001
Dialysis at baseline	48 (25.3)	92 (18.0)	0.033
Randomized to PLEX	95 (49.7)	257 (50.1)	0.93
Randomized to reduced GC	96 (50.3)	257 (50.1)	0.97
Immunosuppression			<0.001
Oral cyclophosphamide	44 (23.0)	197 (38.4)	
Intravenous cyclophosphamide	107 (56.0)	247 (48.2)	
Rituximab	40 (20.9)	69 (13.4)	

A cohort analysis of PEXIVAS trial showed similar results in DAH patients treated with or without PLEX



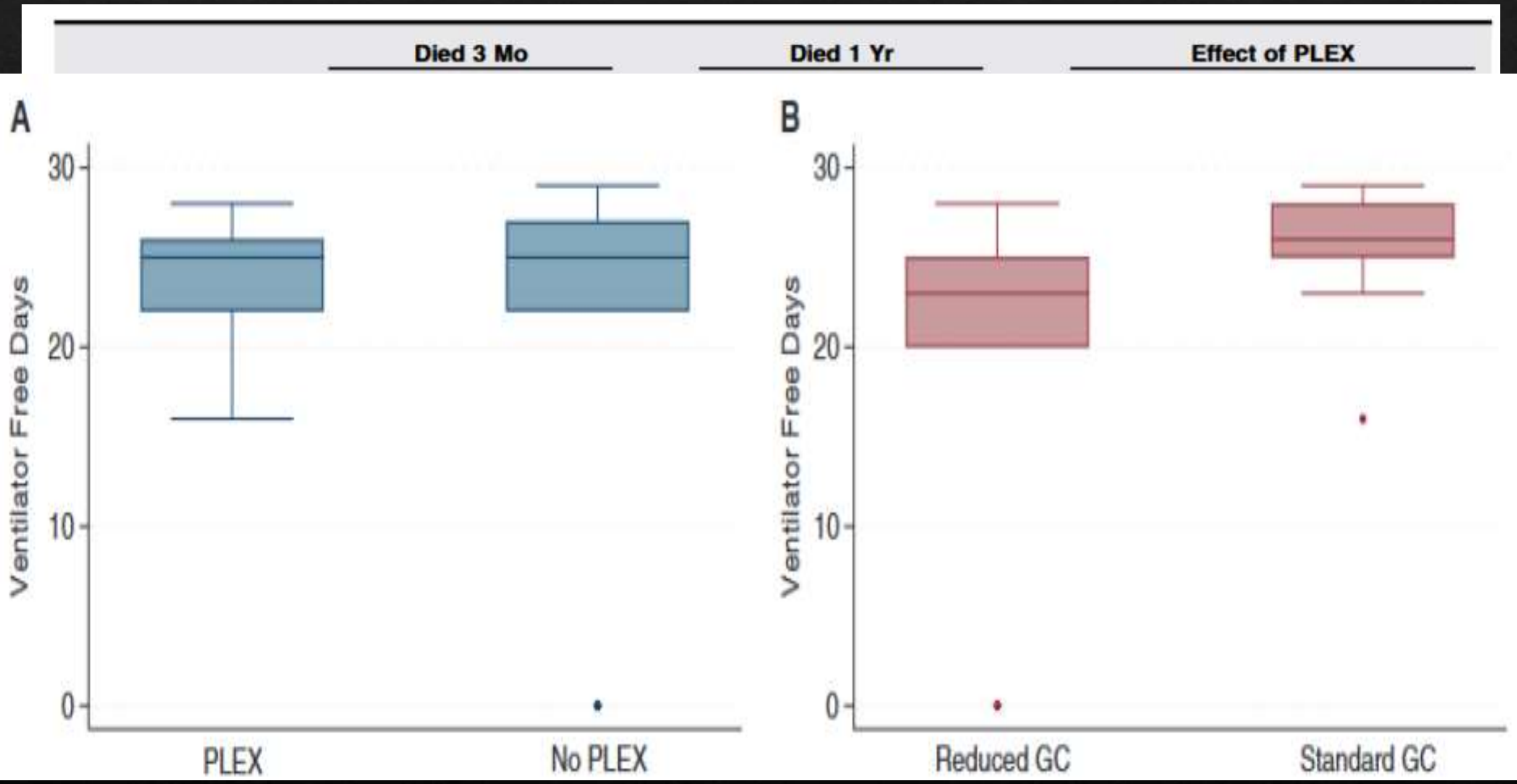
Fussner LA, Luis Felipe Flores-Suárez, Cartin-Ceba R, Specks U, P. Gerard Cox, David, et al. Alveolar Hemorrhage in ANCA-associated Vasculitis: Results of an International, Randomized, Controlled Trial (PEXIVAS). American journal of respiratory and critical care medicine. 2024 Feb 12

	Died 3 Mo		Died 1 Yr		Effect of PLEX	
	PLEX	No PLEX	PLEX	No PLEX	HR (95% CI)	*P*-interaction
Overall	18 (5.1)	21 (6.0)	25 (7.1)	32 (9.1)	0.74 (0.44–1.26)	
No DAH	12 (4.7)	9 (3.5)	17 (6.6)	17 (6.6)	0.86 (0.43–1.71)	
Any DAH	6 (6.3)	12 (12.5)	8 (8.4)	15 (15.6)	0.52 (0.21–1.24)	0.37
Nonsevere DAH	1 (1.6)	3 (4.6)	2 (3.1)	5 (7.6)	0.43 (0.08–2.31)	0.42
Severe DAH	5 (16.1)	9 (30.0)	6 (19.4)	10 (33.3)	0.45 (0.14–1.40)	0.44

Definition of abbreviations: CI = confidence interval; DAH = diffuse alveolar hemorrhage; HR = hazard ratio; PLEX = plasma exchange.
Effects of PLEX are expressed as HR over the first year and are adjusted for age, sex, antineutrophil cytoplasmic antibody subtype, baseline kidney function, and initial treatments.

	Died 3 Mo		Died 1 Yr		Effect of Reduced GC	
	Reduced GC	Standard GC	Reduced GC	Standard GC	HR (95% CI)	*P*-interaction
Overall	16 (4.5)	23 (6.6)	24 (6.8)	33 (9.4)	0.69 (0.41–1.17)	
No DAH	7 (2.7)	14 (5.5)	11 (4.3)	23 (9.0)	0.46 (0.22–0.94)	
Any DAH	9 (9.4)	9 (9.5)	13 (13.5)	10 (10.5)	1.33 (0.57–3.13)	0.10
Nonsevere DAH	1 (1.5)	3 (4.6)	3 (4.6)	4 (6.2)	0.62 (0.12–3.21)	0.65
Severe DAH	8 (25.8)	6 (20.0)	10 (32.3)	6 (20.0)	2.02 (0.64–6.39)	0.08

Definition of abbreviations: CI = confidence interval; DAH = diffuse alveolar hemorrhage; GC = glucocorticoid; HR = hazard ratio.
Effects of GC are expressed as HR over the first year and are adjusted for age, sex, antineutrophil cytoplasmic antibody subtype, baseline kidney function, and initial treatments.


Died 3 Mo
Died 1 Yr
Effect of PLEX
A
B
Ventilator Free Days
30
20
10
0
PLEX
No PLEX
Reduced GC
Standard GC

No difference in ESKD/death, infection risk or QOL between PLEX and no-PLEX

Some numerical differences in deaths at 3 months and 1 year between PLEX and no-PLEX group: significance unknown

Some increase in death at 1 year among the reduced GC dose

Fewer ventilator free days in patients treated with standard GC

kidney function, and initial treatments.

For maintenance of remission: AZA or RTX?

- CYCAZAREM study in 2003 randomized patients with ANCA associated vasculitis to receive CYC (oral, 1.5 mg/Kg/D) (N-73) or AZA (oral, 2 mg/Kg/D) (N-71) after they achieved remission with CYC pulse and GC
- All patients received GC maintenance and was followed up over 18 months
- Relapse occurred in 15.5% patients in AZA group and 13.7% in CYC group (P-0.65)
- Rate of serious adverse events were similar between the two groups
- This RCT established that AZA is a safe and effective alternative to CYC in maintaining remission among patients with AAV

Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JWC, Dadoniené J, et al. A Randomized Trial of Maintenance Therapy for Vasculitis Associated with Antineutrophil Cytoplasmic Autoantibodies. New England Journal of Medicine. 2003 Jul 3;349(1):36–44.

For maintenance of remission: AZA or RTX?

CLINICAL SCIENCE

Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial

Rona M Smith ,[1] Rachel B Jones,[2] Ulrich Specks,[3] Simon Bond,[4] Marianna Nodale ,[4] Reem Al-jayyousi,[5] Jacqueline Andrews,[6] Annette Bruchfeld,[7] Brian Camilleri,[8] Simon Carette,[9] Chee Kay Cheung,[10] Vimal Derebail,[11] Tim Doulton,[12] Alastair Ferraro,[13] Lindsy Forbess,[14] Shouichi Fujimoto ,[15] Shunsuke Furuta ,[16] Ora Gewurz-Singer,[17] Lorraine Harper ,[18] Toshiko Ito-Ihara,[19] Nader Khalidi ,[20] Rainer Klocke,[21] Curry Koening,[22] Yoshinori Komagata,[23] Carol Langford,[24] Peter Lanyon,[25] Raashid Luqmani,[26] Carol McAlear,[27] Larry W Moreland,[28] Kim Mynard,[29] Patrick Nachman,[30] Christian Pagnoux,[31] Chen Au Peh,[32] Charles Pusey,[33] Dwarakanathan Ranganathan,[34] Rennie L Rhee ,[35] Robert Spiera ,[36] Antoine G Sreih,[27] Vladamir Tesar,[37] Giles Walters ,[38] Caroline Wroe,[39] David Jayne ,[40] Peter A Merkel,[41] RITAZAREM co-investigators

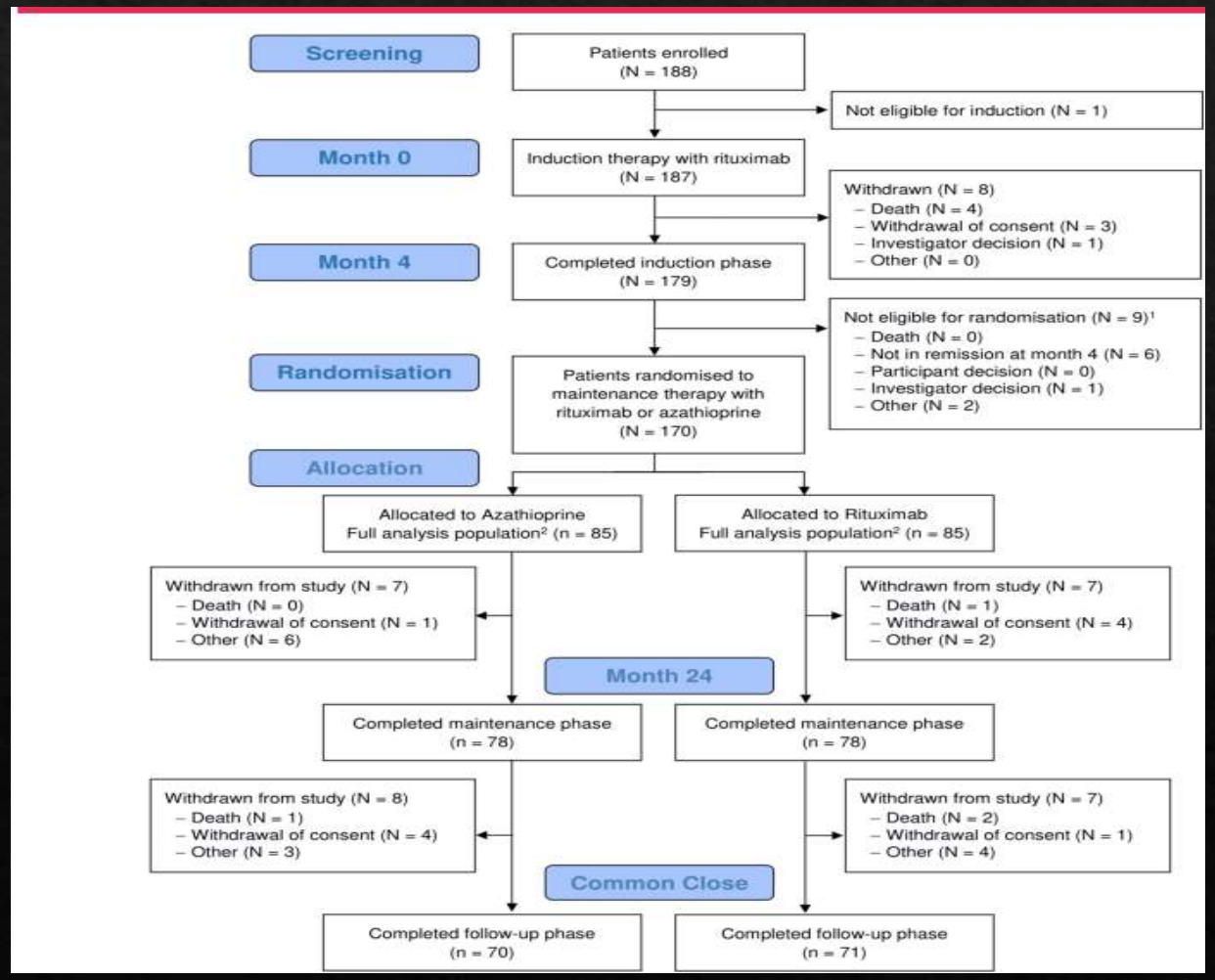
Smith RM, Jones RB, Specks U, Bond S, Nodale M, Reem Al-jayyousi, et al. Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial. Annals of the Rheumatic Diseases. 2023 Mar 23;ard-223559.

e	Participants	Arms	End-points	Results	Comments
WEGENT: an RCT to compare MTX to AZA for maintenance of remission in AAV (2008)	>18 years of age with GPA/MPA who has gone into remission after GC (pulse+maintenance)+CYC (pulse) (N-126, DAH in 20.6% patients, more in AZA)	1. AZA 2 mg/Kg/D 2. MTX 0.3 mg/Kg/Wk increased 2.5 mg/Wk to 25 mg/Wk Both for 12 months	Primary: severe AE (death/discontinuation) Secondary: any AE, relapse-free survival, event-free survival	11% in AZA group and 19% in MTX group met primary end-point (P-0.21) 36% in AZA and 33% in MTX grp had relapse (P-0.71) RFS and EFS were not significantly different	MTX and AZA were similarly effective for maintenance and MTX was not a/w better safety profile.
MAINRITSAN : An RCT to compare RTX vs AZA for maintenance of remission in AAV patients (2014) (unblinded)	18-75 years old patients diagnosed with GPA/MPA/renal limited vasculitis who have achieved remission (BVAS-0) with CYC+GC (N-115) (alveolar haemorrhage in 19% of AZA and 16% of RTX group, pulmonary involvement in 66% and 58% of AZA and RTX respectively)	1. IV RTX 500 mg on D0 and D14 f/b at months 6,12,18. 2. Oral AZA 2mg/Kg/D for 12 months, then 1.5 mg/Kg/D for 6 months and 1 mg/Kg/D g for 4 months Both received tapering doses of GC at least for 18 months	Primary: major relapse within at 28 months follow up (BVAS>0 and organ threatening disease) Secondary: minor relapse, AE, mortality	Major relapses happened more frequently in AZA group in comparison to RTX group (29% vs 5%, HR 6.61, CI-95%, 1.56-27.96, P<0.002) Minor relapse more in AZA group (16% vs 11%, P=0.43) Severe infections were more frequent in RTX group (19% vs 14%)	Establishes RTX as an effective and safe agent for remission maintenance. Unblinded study; Majority of patients had GPA, very small MPA/renal-limited vasculitis; Early cross-over of patients from AZA to RTX group due to major relapses;

- Open-label unblinded RCT to compare rates of relapse in patients of AAV treated with RTX or AZA as maintenance therapy
- Initial induction phase (0-4 months) saw patients treated with RTX as the induction agent in addition to GC
- Over next 4-24 months patients received either RTX or CYC along with GC for maintenance of remission once it was achieved
- Patients were followed up till 48 months from initiation of induction

CLINICAL SCIENCE

Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial



- Open-label unblinded RCT to compare rates of relapse in patients of AAV treated with RTX or AZA as maintenan[illegible]py
- Initi[illegible]4 month[illegible] pa[illegible]s the[illegible] in[illegible]to
- C[illegible]ents eiti[illegible]with C[illegible] maint[illegible]n once it w[illegible] achieved
- Patients were followed up till 48 months from initiation of induction

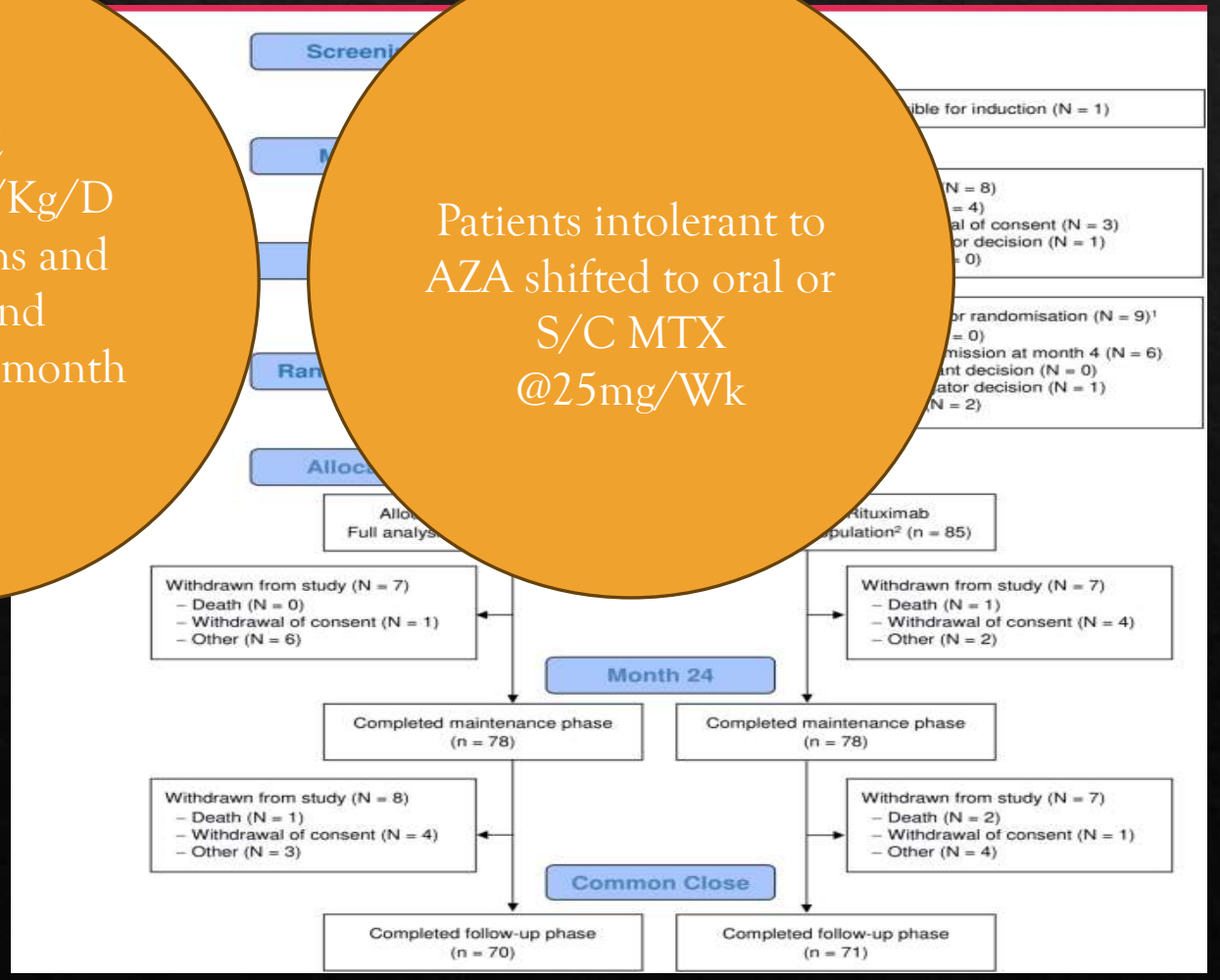
ARM 1
RTX @1000 mg/dose at months 4,8,12,16,20 (from enrolment)

ARM 2
AZA @2 mg/Kg/D for 24 months and tapered and withdrawn at month 27

Patients intolerant to AZA shifted to oral or S/C MTX @25mg/Wk

CLINICAL SCIENCE

Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial



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- Initi[illegible]4 month[illegible] pa[illegible]s the[illegible] ir[illegible]to
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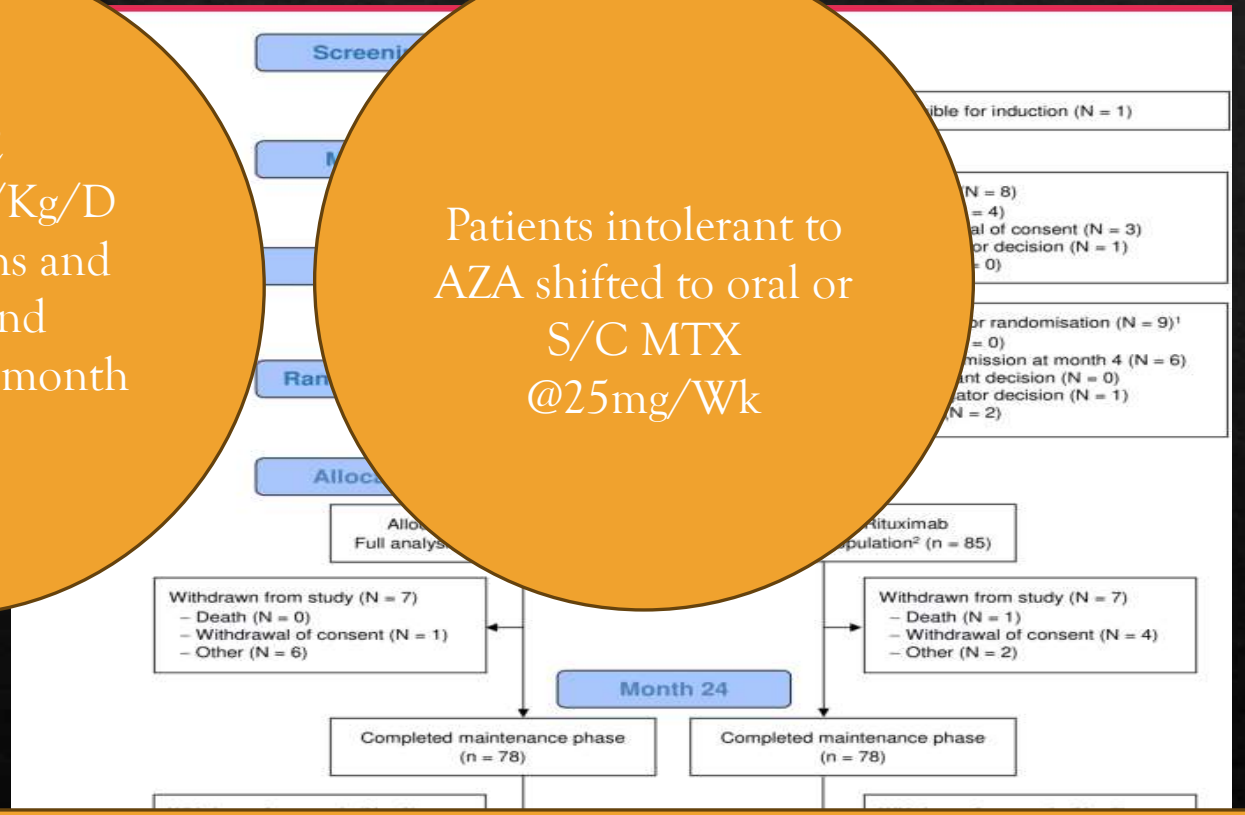
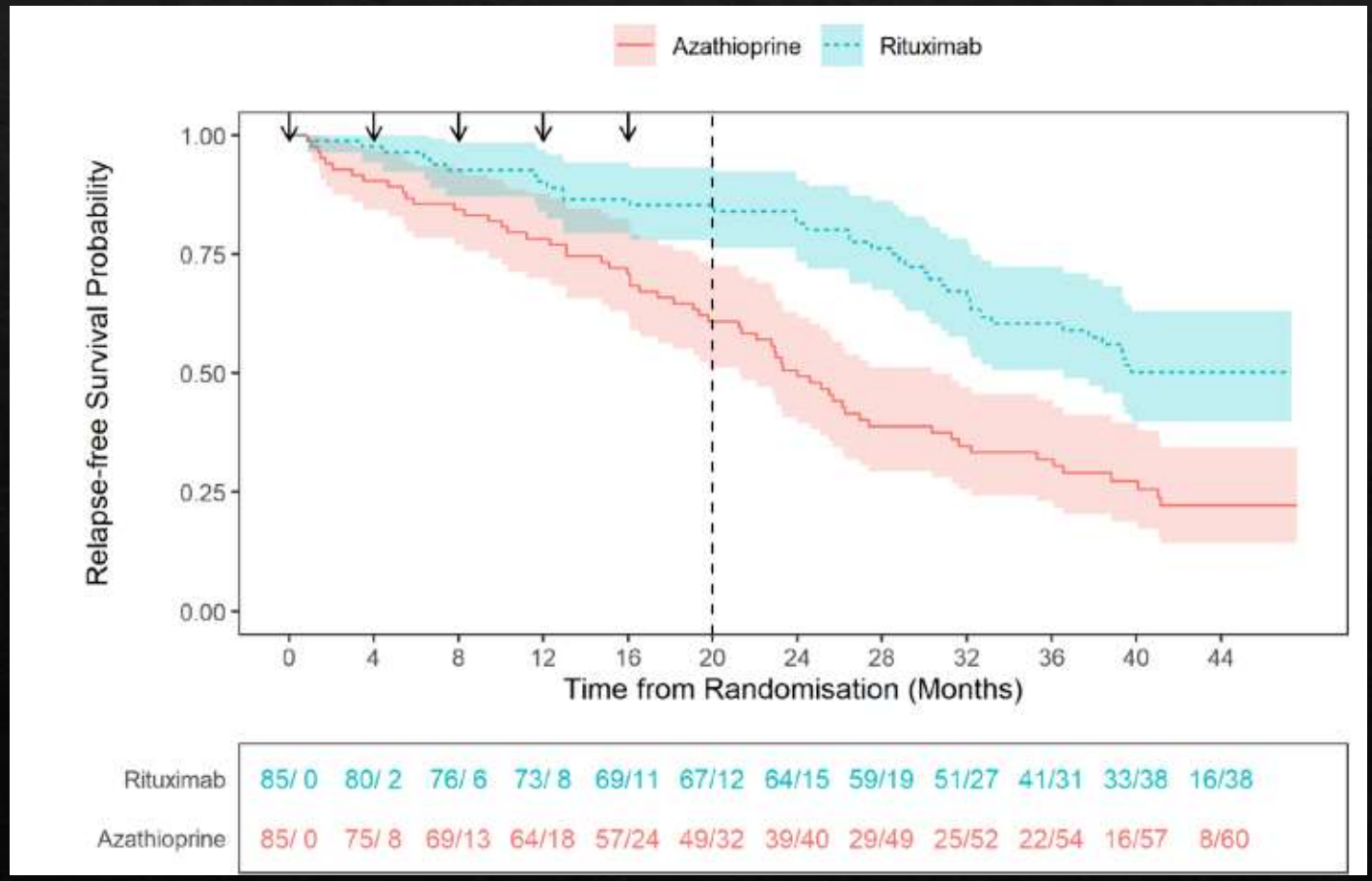


Patients followed up for major or minor relapses over 48 months in total with periodic visits and assessment of BVAS/WG

Table 1 Baseline demographics of randomised study population in the RITAZAREM trial

	Total (N=170)	Rituximab (N=85)	Azathioprine (N=85)
Age, years: mean (SD)	57.8 (14.5)	57.1 (15.1)	58.6 (13.9)
Male, number (%)	84 (49%)	43 (51%)	41 (48%)
Race, number (%)			
White	155 (91%)	78 (92%)	77 (91%)
Asian	10 (6%)	5 (6%)	5 (6%)
Hispanic	3 (2%)	2 (2%)	1 (1%)
Black	0	0	0
Other	2 (1%)	0	2 (2%)
Disease duration, years: mean (SD)	7.16 (6.52)	7.38 (6.94)	6.93 (6.10)
Prior treatment with cyclophosphamide			
Number of patients (%)	133 (78%)	67 (79%)	66 (78%)
Cumulative dose, grams (g): mean (SD)	25.7 (43.3)	24.4 (50.4)	26.9 (35.5)
Prior rituximab therapy			
Number of patients (%)	60 (35%)	33 (39%)	27 (32%)
Cumulative dose, grams (g): mean (SD)	4.88 (3.24)	4.47 (2.95)	5.40 (3.57)
Glucocorticoid induction regimen			
1 mg/kg/day starting dose (1A)	48 (28%)	24 (28%)	24 (28%)
0.5 mg/kg/day starting dose (1B)	122 (72%)	61 (72%)	61 (72%)
ANCA type			
Anti-proteinase 3	123 (72%)	61 (72%)	62 (73%)
Anti-myeloperoxidase	47 (28%)	24 (28%)	23 (27%)
Relapse type on entry into trial			
Severe	106 (62%)	52 (61%)	54 (64%)
Non-severe	64 (38%)	33 (39%)	31 (36%)

- Rituximab was superior to azathioprine for the prevention of major or minor disease relapse: HR 0.41, 95% CI 0.27 to 0.61, p<0.001
- The HR during the maintenance phase was 0.35, 95%CI 0.18 to 0.66, p=0.001, and during the follow-up phase was 0.45, 95%CI 0.26 to 0.78, p=0.004



Events	RTX	AZA	HR	P-value
Total relapses	52 38/85 patients (45%)	89 60/85 (71%)		
Major relapses	11	28	0.36	0.004
Minor relapse	41	61		
Relapse during Maintenance	13/85 (15%)	32/85 (38%)		
Relapse during Follow-up	33	49		
Sustained remission rate at 48 months	0.50	0.22		

- Rituximab was superior to azathioprine for the prevention of major or minor disease relapse: HR 0.41, 95% CI 0.27 to 0.61, p<0.001
- The HR during the maintenance phase was 0.35, 95%CI 0.18 to 0.66, p=0.001, and during the follow-up phase was 0.45, 95%CI 0.26 to 0.78, p=0.004

Table 2 Adverse events according to treatment regimen in the RITAZAREM trial

	Total (N=188)	Rituximab (N=85)	Azathioprine (N=85)	Not randomised (N=18)
Number (%) of patients with a serious adverse event	92 (49%)	37 (44%)	48 (56%)	7 (39%)
Number (%) of patients with a serious infection	39 (21%)	15 (18%)	19 (22%)	5 (28%)
Number (%) of patients with a non-serious infection	119 (63%)	54 (64%)	62 (73%)	3 (17%)
Number (%) of patients with plasma IgG<5 g/L	66 (35%)	36 (42%)	26 (31%)	4 (22%)
Number (%) of patients with plasma IgG<3 g/L	17 (9%)	8 (9%)	6 (7%)	3 (17%)

- Severe infections occurred in 15 (18%) patients in the rituximab and 27 in 19 (22%) patients in the azathioprine groups
- 197 and 207 non-severe infections occurred in 54 (64%) and 62 (73%) patients in the rituximab and azathioprine groups, respectively

- Rituximab was superior to azathioprine for the prevention of major or minor disease relapse: HR 0.41, 95% CI 0.27 to 0.61, p<0.001
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Table 2 Adverse events according to treatment regimen in the RITAZAREM trial

				domised
Number (%) of p				
Number (%) of p				
Number (%) of p				
Number (%) of patients with plasma IgG<3 g/L				
Number (%) of patients with plasma IgG<3 g/L	17 (9%)	8 (9%)	6 (7%)	3 (17%)

- RTX was superior in efficacy to AZA as a maintenance agent in AAV
- Risk of severe adverevets were not significantly more in the RTX group

- Severe infections occurred in 15 (18%) patients in the rituximab and 27 in 19 (22%) patients in the azathioprine groups
- 197 and 207 non-severe infections occurred in 54 (64%) and 62 (73%) patients in the rituximab and azathioprine groups, respectively

Comparison of dose and duration of medications used in different studies

Study	Induction Agent And Dosage	Duration	Maintenance agent and Dosage	Duration
RAVE Remission: BVAS<1 for >2 months	RTX 375 mg/BSA once weekly for 4 weeks + MPS 1 g for 1-3 day followed by prednisolone 1mg/Kg/D tapered to <5 mg by 6 months and stopped by 18-24 months (taper to 40 mg/d by 1 month and decrease every 2 weekly)		GC	18-24 months
	CYC 2 mg/Kg orally (renal function and age-adjusted dose) daily for 3 months + MPS 1 g for 1 day followed by prednisolone 1mg/Kg/D tapered to <5 mg by 6 months and stopped by 18-24 months (taper to 40 mg/d by 1 month and decrease every 2 weekly)	3 months	AZA 2 mg/Kg/D from 4th month if remission was achieved	Up to 18 months
RITUXVAS Remission- BVAS=0 for >2 months	RTX 375 mg/BSA once weekly for 4 weeks + CYC 15 mg/Kg with 1st and 3rd dose of RTX + IV MPS 1 g 1 day f/b prednisolone 1 mg/Kg tapered over 6 months to <5 mg/day and then stop by 18-24 months		GC	18-24 months
	CYC 15 mg/Kg every 2 weeks for first 3 doses and then 3 weekly until remission (minimum 3 months and maximum 6 months) + IV MPS 1 g 1 day f/b prednisolone 1 mg/Kg tapered over 6 months to <5 mg/day and then stop by 18-24 months	3-6 months	AZA 2 mg/Kg/D from the time of remission	Until trial ends
PEXIVAS	CYC Oral 2 mg/Kg/day (max 200 mg) dose adjusted to age, renal function, Cytopenias (monitor CBC every weekly for 4 wks/weekly for 4 weeks after each dose change and monthly thereafter) Or IV 15 mg/Kg/dose 2 weekly for first 3 doses and then 3 weekly (monitor CBC every 14 days and 1 day before each pulse) + Plasma exchange	Minimum 13 weeks and maximum 26 weeks 7 sessions in 14 days	(started after remission or after 26 weeks) AZA 2 mg/Kg/D (modify acc to age, renal function and cytopenia) Monitor CBC every 2 weeks for the first month and then monthly	

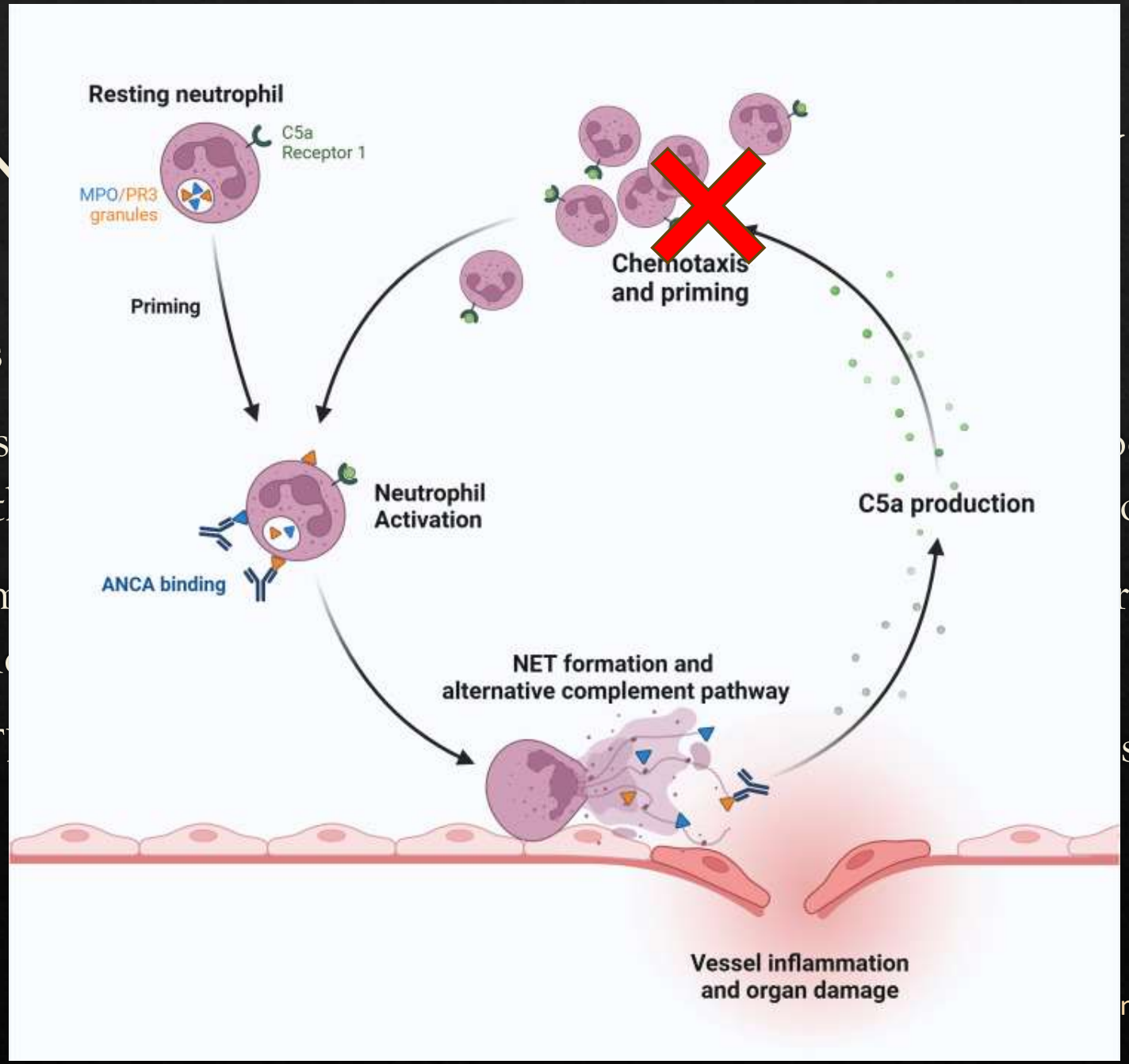
Newer therapies- AVACOPAN?

- Avacopan is an orally administered selective C5a receptor antagonist
- In Vasculitis, activation of the alternative pathway, and subsequent production of C5a drives the inflammation (neutrophil chemoattraction and activation)
- In Murine models, Avacopan has shown to block C5a receptors and prevent ANCA-driven glomerulonephritis
- ADVOCATE trial examined its efficacy in maintaining sustained remission in AAV patients

Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the Treatment of ANCA-Associated Vasculitis. New England Journal of Medicine. 2021 Feb 18;384(7):599–609.

N ?

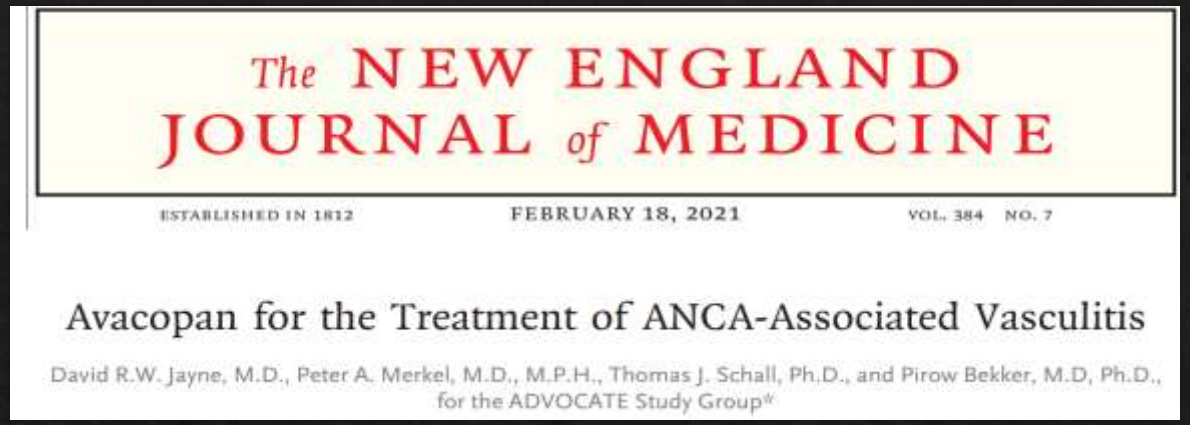
- Avacopan is
- In Vasculitis oduction of C5a drives t on)
- In Murine m revent ANCA-driven glom
- ADVOCAT ssion in AAV patients



Jayne DRW, Merkel nd Journal of Medicine. 2021 Feb 18;384(7):599–609.

Phase 3 randomized controlled trial
Participants: patients with ANCA associated vasculitis

IMPORTANTLY: Patients with alveolar haemorrhage requiring mechanical ventilation anticipated to continue beyond the study period were excluded (Chest involvement was present in ~42% of patients)


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 18, 2021 VOL. 384 NO. 7

Avacopan for the Treatment of ANCA-Associated Vasculitis

David R.W. Jayne, M.D., Peter A. Merkel, M.D., M.P.H., Thomas J. Schall, Ph.D., and Pirow Bekker, M.D, Ph.D., for the ADVOCATE Study Group*

Arm 1
AVACOPAN
Placebo+ GC
(20 wks)

Arm 2
AVACOPAN
(30 mg
BD)+GC
placebo
(52 wks)

Primary: remission at 26 weeks
Secondary: sustained remission at 52 weeks
Follow up period: 60 weeks

Phase 3 randomized controlled trial
Participants: patients with ANCA associated vasculitis

IMPORTANTLY: Patients with alveolar haemorrhage requiring mechanical ventilation anticipated to continue beyond the study period were excluded (Chest involvement was present in ~42% of patients)

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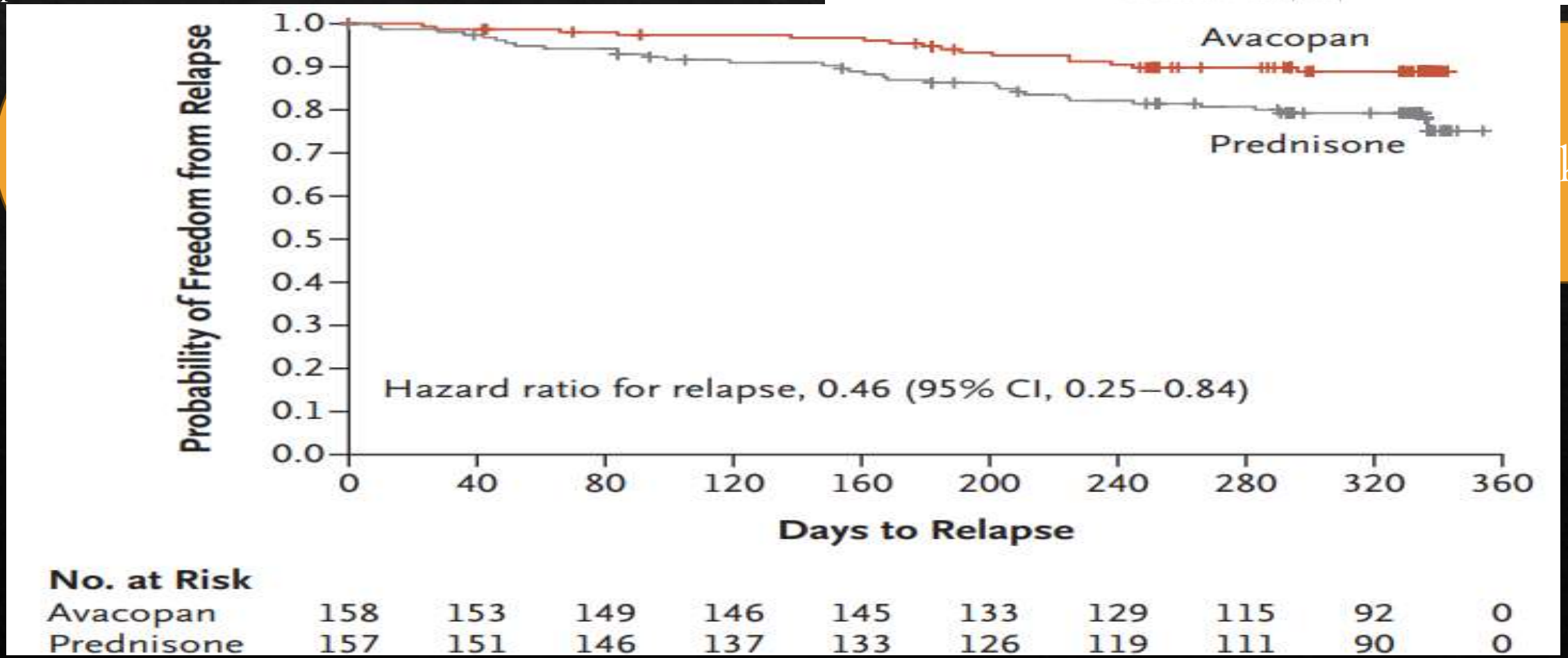

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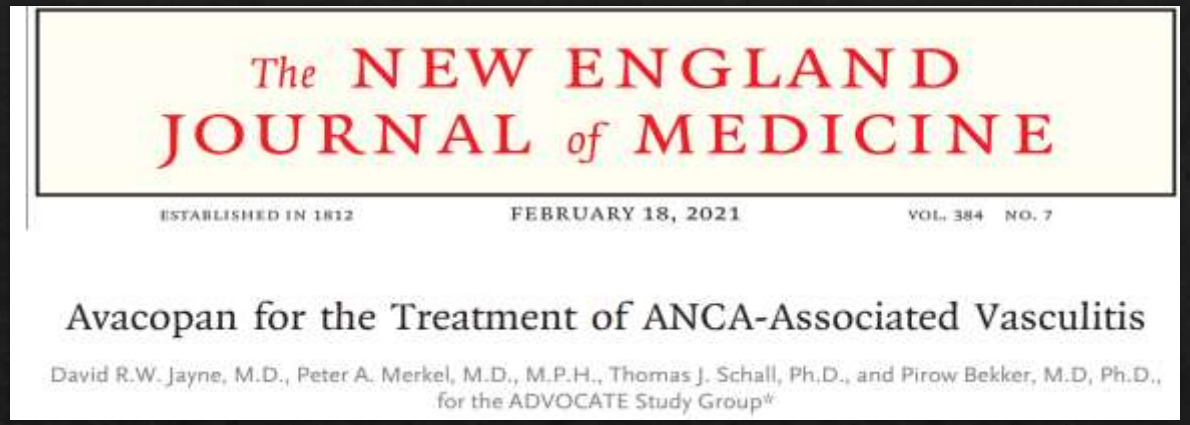
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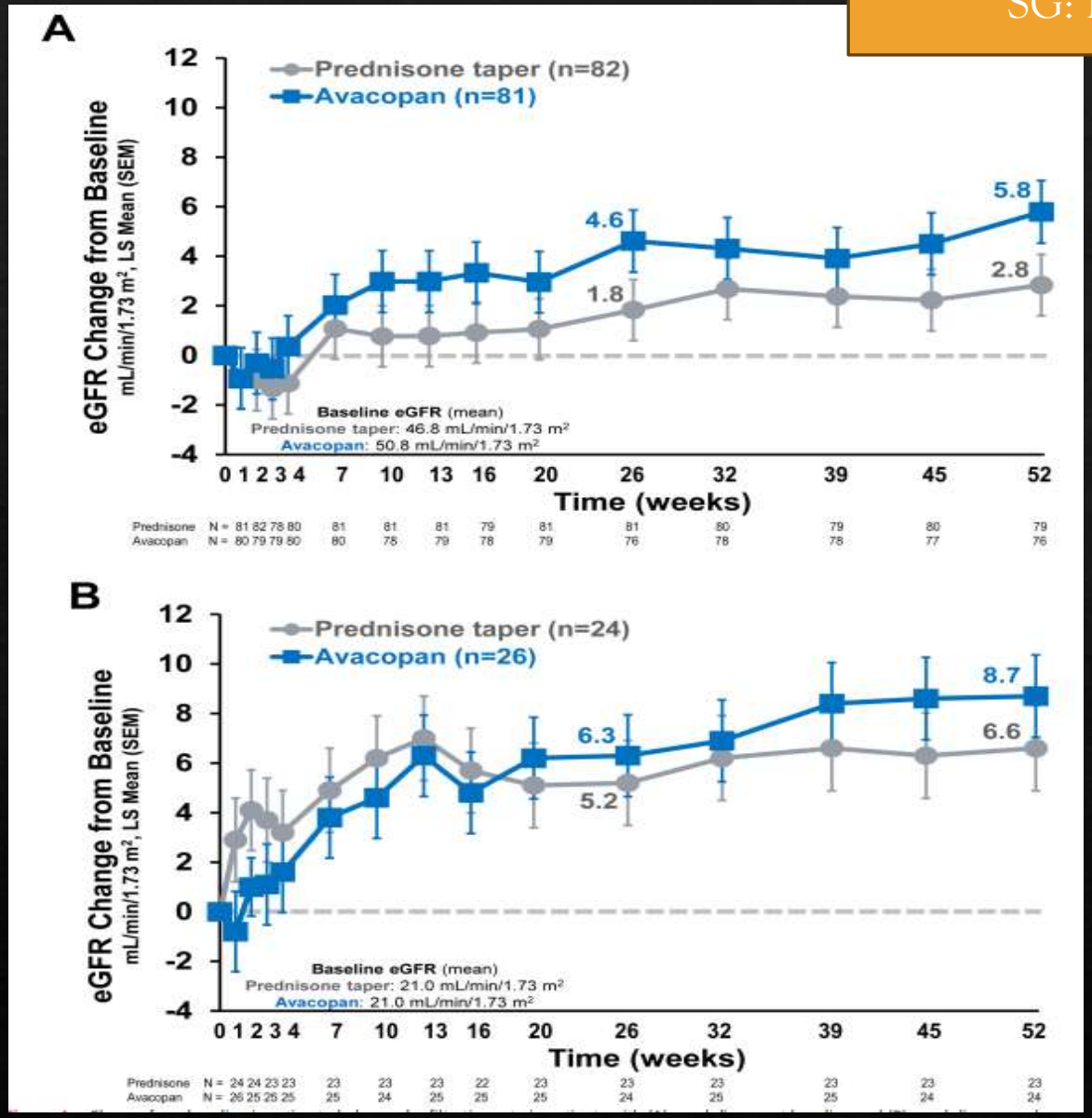
Arm 1
AVACOPAN
Placebo+ GC
(20 wks)

Arm 2
AVACOPAN
(30 mg
BD)+GC
placebo
(52 wks)

Primary: remission at 26 weeks
Secondary: sustained remission at 52 weeks
Follow up period: 60 weeks

- Remission at week 26 was observed in 120 of 166 patients (72.3%) in the avacopan group and in 115 of 164 patients (70.1%) in the prednisone group (P<0.001 for non-inferiority but P=0.24 for superiority)
- Sustained remission at week 52 was observed in 109 of 166 patients (65.7%) in the avacopan group and in 90 of 164 patients (54.9%) in the prednisone group (estimated common difference, 12.5 percentage points) (P <0.001 for non-inferiority and P=0.007 for superiority)

SG: RTX treated



AVACOPAN showed a greater improvement in renal function from baseline in comparison to the tapering prednisolone group

Geetha D, Dua A, Yue H, Springer J, Salvarani C, Jayne D, et al. Efficacy and safety of avacopan in patients with ANCA-associated vasculitis receiving rituximab in a randomised trial. Annals of the Rheumatic Diseases [Internet]. 2024 Jan 11;83(2):223–32.

SG: RTX treated

Long term safety in the AVACOPAN group was comparable to the prednisolone group;
Risks of any serious adverse events were slightly higher in the prednisolone group.

	Prednisone taper+rituximab group (N=107)	Avacopan+ rituximab group (N=107)
Any adverse event, n (%)	105 (98.1)	105 (98.1)
No. of events	1239	1074
Any infection, n (%)	77 (72.0)	68 (63.6)
No. of events	188	136
Any serious adverse event, n (%)	42 (39.3)	37 (34.6)
No. of events	91	62
Any serious infection, n (%)	15 (14.0)	11 (10.3)
No. of events	19	12
Discontinuation of trial medication due to adverse event, n (%)	16 (15.0)	13 (12.1)
Serious adverse event of abnormality on liver-function testing, n (%)	4 (3.7)	3 (2.8)
Fatal, n (%)	3 (2.8)	0 (0.0)

Geetha D, Dua A, Yue H, Springer J, Salvarani C, Jayne D, et al. Efficacy and safety of avacopan in patients with ANCA-associated vasculitis receiving rituximab in a randomised trial. Annals of the Rheumatic Diseases [Internet]. 2024 Jan 11;83(2):223–32.

Guideline	EULAR	KDIGO	CAN-VASC
Treatment recommendation	Avacopan in combination with rituximab or cyclophosphamide may be considered for induction of remission in GPA or MPA, as part of a strategy to substantially reduce exposure to glucocorticoids.	We recommend that glucocorticoids in combination with rituximab or cyclophosphamide be used as initial treatment of new-onset AAV. Avacopan may be used as an alternative to glucocorticoids	The addition of oral avacopan can be considered for induction of remission in patients with newly diagnosed or relapsing GPA or MPA treated with cyclophosphamide or rituximab. After starting avacopan, a faster glucocorticoid tapering protocol aiming for discontinuation by the end of week 4 should be considered.
Patients most likely to benefit	• Patients at risk of development or worsening of GC-related adverse effects and complications. • Patients with active glomerulonephritis and rapidly deteriorating kidney function	• Patients at increased risk of GC toxicity, including those with high infection risk, preexisting diabetes mellitus, psychiatric disorders, and osteoporosis. • Patients with lower kidney function (eGFR <20 mL/min per 1.73 m2).	• Patients at increased risk of GC toxicity • Patients with renal involvement • Patients refractory to conventional treatments
Treatment duration	Stop avacopan after duration of treatment of 6–12 months; there are no data on use of avacopan beyond 1 year, so longer-term use cannot be recommended.	There is a lack of long-term data on avacopan usage.	When initiated as part of induction therapy, avacopan can be continued for one year.

Abbreviations: EGFR, estimated glomerular filtration rate; GPA, granulomatosis with polyangiitis; GC, glucocorticoids; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase-3.

van Leeuwen J, Quartuccio L, Draibe J, Gunnarson I, Sprangers B, Teng YKO. Evaluating Avacopan in the Treatment of ANCA-Associated Vasculitis: Design, Development and Positioning of Therapy. Drug Design, Development and Therapy [Internet]. 2025 Jan;Volume 19:23–37.

Diseases other than AAV

- Treatment of DAH secondary to anti-GBM disease
- Treatment of alveolar haemorrhage associated with drugs
- Treatment of idiopathic pulmonary haemosiderosis

Anti-GBM disease

- <1% of all causes of end-stage renal diseases
- 90% have renal involvement
- 40% may have isolated renal involvement at beginning
- 10% may have isolated lung disease
- When both affected→ pulmonary renal syndrome (Goodpasture disease)

CLINICAL PRESENTATION

- Rapidly progressive glomerulonephritis (55-85%) – often HD dependent at presentation
- Macroscopic haematuria <25%, microscopic haematuria in almost all patients
- Cough, shortness of breath, haemoptysis (25-30%)
- Anaemia

DIAGNOSIS

- IgG antibody against GBM (alpha3 IV ag) (ELISA)
- Biosensor assay, Chemiluminiscence assay
- Kidney biopsy with classical histology and direct IF showing linear IgG deposition

(exclude other possibilities)

- Lung histopathology and direct IF

PATHOGENESIS

- Auto-antibodies (IgG) form against the otherwise hidden antigens in GBM in susceptible individuals
- Laminin-521, Peroxidasin have been identified to activate CD4+T cells
- Auto-antibodies bind to these antigens, on collagen type-IV structures (alpha3 NC1 domain) and disrupt glomerular basement membrane integrity
- Laminin521 has been associated with higher risk of Pulmonary involvement due to binding with alveolar epithelium

Treatment regimen

- PLASMAPHERESIS: centrifugal bowl or plasma filter method with high plasma volume (50-60 mL/kg/session to a maximum of 4 L) exchanged daily until anti-GBM antibodies are undetectable or at least for 14 days
- Corticosteroids: pulse methylprednisolone followed by oral maintenance therapy tapered over 6-9 months as per clinical status of disease
- CYC oral or IV pulse/ Alternatively RTX
- Kidney transplant in ESRD if no circulating auto-antibody for 6 weeks

- Randomized clinical trial involving 17 patients conducted in 1985
- All patients had met 2 of 3 criteria: circulating anti-GBM ab, histological evidence of liner deposition of IgG in kidney/lung or anti-GBM ab eluted from lung or kidney
- Randomized to either undergo only immunosuppression with CYC and GC or Plasma exchange in addition to CYC and GC

Johnson JP, Moore JJ, Austin H a. I, Balow JE, Antonovych TT, Wilson CB. Therapy of Anti-Glomerular Basement Membrane Antibody Disease: Analysis of Prognostic Significance of Clinical, Pathologic and Treatment Factors. Medicine [Internet]. 1985 Jul 1 [cited 2024 Apr 13];64(4):219

ARM 1

1. GC- 2 mg/Kg/D for 1 Wk f/b 1 mg/Kg/D for 2 weeks f/b alternate day dosage for 3 months
2. CYC 2 mg/Kg/D for 3 months f/b 1 mg/kg/D for remainder of therapy

ARM 2

1. GC- 2 mg/Kg/D for 1 Wk f/b 1 mg/Kg/D for 2 weeks f/b alternate day dosage for 3 months
2. CYC 2 mg/Kg/D for 3 months f/b 1 mg/kg/D for remainder of therapy
3. PLASMA exchange- 4 L every 3 days until anti-GBM ab<5% binding OR 30 days stable on MHD

Those who had breakthrough alveolar haemorrhage with Pa02<60 mmHg were allowed to be treated with pulses of methylprednisolone

Johnson JP, Moore JJ, Austin H a. I, Balow JE, Antonovych TT, Wilson CB. Therapy of Anti-Glomerular Basement Membrane Antibody Disease: Analysis of Prognostic Significance of Clinical, Pathologic and Treatment Factors. Medicine [Internet]. 1985 Jul 1 [cited 2024 Apr 13];64(4):219

TABLE 1. Demographic and clinical characteristics of the two groups at entry into the study

Patient No.	Age	Sex	Race	Duration of Symptoms Prior to Entry (days)	Hematocrit (vol %)	Serum Creatinine at Presentation (mg/dl)	Serum Creatinine at Institution of Treatment (mg/dl)	Creatinine Clearance (ml/min)	Serum Albumin (mg/dl)	Proteinuria (g/24 hours)	Pulmonary Symptoms	Abnormal CXR	Abnormal PFTs	Anti-GBM Antibody Titer (% binding)	Lung Biopsy Positive
Group I															
1	29	M	C	150	27	5.3	9.5	13	3.3	4.8	+	+	ND	30.7	−
2	25	M	C	30	28	7.2	7.7	10	2.5	3.5	−	+	ND	48.1	−
3	23	M	C	120	31	1.0	1.1	124	4.2	0.1	+	+	ND	16.6	−
4	22	M	C	60	24	2.7	5.2	50	2.3	5.0	+	+	ND	25.4	+
5	18	M	C	20	26	0.9	1.0	116	3.6	0	+	+	ND	36.9	ND
6	23	M	C	90	45	1.4	2.5	50	4.1	3.9	−	−	−	4.6	−
7	21	F	C	30	16	20.0	15.6	2.5	3.8	1.2	+	−	+	42.5	ND
8	23	M	C	40	27	1.6	1.8	79	3.3	1.2	+	+	+	29.5	+
9	22	F	C	30	17	1.7	3.7	15	3.2	3.0	+	+	+	24.6	ND
Mean ± S.E.M.	22.9 ± 3.0			63 ± 16	27 ± 3	4.6 ± 2.1	5.3 ± 1.6	51 ± 15	3.4 ± 0.2	2.5 ± 0.6				28.7 ± 4.5	
Group II															
10	22	M	B	150	27	5.0	5.0	15	1.8	5.2	+	+	ND	21.7	ND
11	19	M	C	60	30	1.2	1.3	113	4.5	3.0	+	+	ND	36.5	+
12	20	M	AI	7	17	25.0	15.0	1.0	2.9	0.4	+	+	+	55.9	−
13	22	M	C	180	25	0.9	1.2	110	3.7	10.6	+	−	−	22.6	−
14	28	M	C	120	26	2.9	4.4	48	3.1	22.0	+	−	+	17.6	−
15	21	M	C	30	18	1.5	1.5	100	4.0	2.5	+	−	−	37.4	+
16	27	M	C	30	22	1.5	2.6	51	3.7	1.7	+	+	+	23.4	ND
17	39	M	C	160	23	3.0	3.0	27	3.8	5.0	+	+	+	19.9	−
Mean ± S.E.M.	24.8 ± 2.3			92 ± 24	24 ± 2	5.1 ± 2.3	4.3 ± 1.6	58 ± 15	3.4 ± 0.3	6.3 ± 2.5				29.4 ± 4.6	

Group I = Immunosuppression; Group II = Immunosuppression and Plasma Exchange.
C = Caucasian; B = Black; AI = American Indian; ND = Not Done; CXR = Chest x-ray; PFTs = Pulmonary function tests.
No significant differences in demographic or clinical characteristics between the two groups were detected by Group *t*-test.

TABLE 1. Demographic and clinical characteristics of the two groups at entry into the study

Patient No.	Age	Sex	Race	Duration of Symptoms Prior to Entry (days)	Hematocrit (vol %)	Serum Creatinine at	Serum Creatinine at Institution	Creatinine Clearance	Serum Albumin	Proteinuria (g/24 hours)	Pulmonary Symptoms	Abnormal CXR	Abnormal PFTs	Anti-GBM Antibody Titer (% binding)	Lung Biopsy Positive
Group I															
1	29	M	C	150								+	ND	30.7	–
2	25	M	C	30								+	ND	48.1	–
3	23	M	C	120								+	ND	16.6	–
4	22	M	C	60								+	ND	25.4	+
5	18	M	C	20								+	ND	36.9	ND
6	23	M	C	90								–	–	4.6	–
7	21	F	C	30								–	+	42.5	ND
8	23	M	C	40								+	+	29.5	+
9	22	F	C	30								+	+	24.6	ND
Mean ± S.E.M.	22.9 ± 3.0			63 ± 16										28.7 ± 4.5	
Group II															
10	22	M	B	150								+	ND	21.7	ND
11	19	M	C	60								+	ND	36.5	+
12	20	M	AI	7								+	+	55.9	–
13	22	M	C	180								–	–	22.6	–
14	28	M	C	120								–	+	17.6	–
15	21	M	C	30								–	–	37.4	+
16	27	M	C	30								+	+	23.4	ND
17	39	M	C	160								+	+	19.9	–
Mean ± S.E.M.	24.8 ± 2.3			92 ± 24										29.4 ± 4.6	

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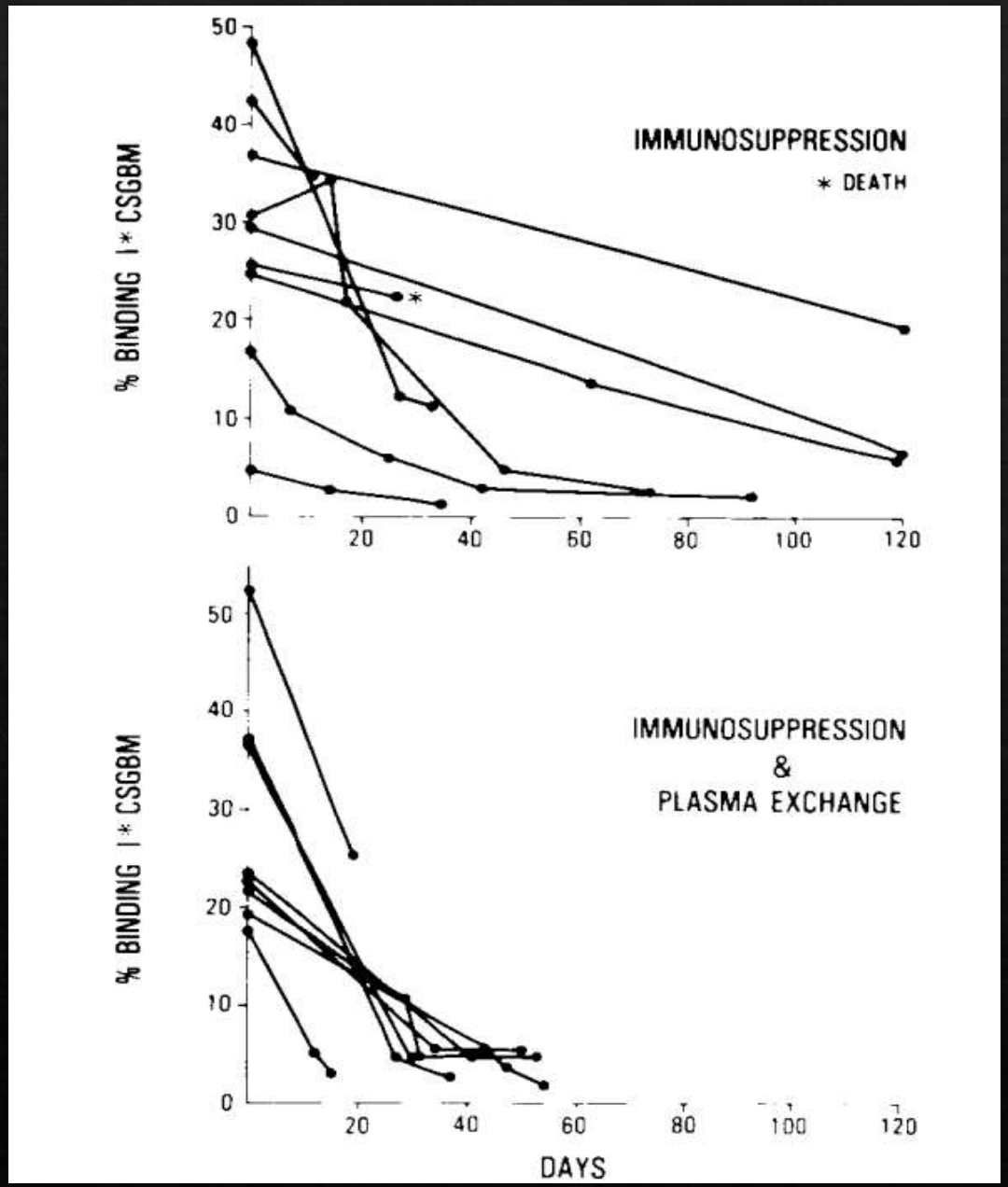
C = Caucasian; B = Black; AI = American Indian; ND = Not Done; CXR = Chest x-ray; PFTs = Pulmonary function tests.
No significant differences in demographic or clinical characteristics between the two groups were detected by Group *t*-test.

Most of the patients were young males

Diagnosis had variable latency, but it did not have any impact on outcome

15 of 17 patients had pulmonary symptoms

TBLB done in 10 patients, renal biopsy in 15 patients



- Rate of disappearance of auto-antibodies were significantly more rapid among patients treated with PLEX ($P<0.05$)

- The effect of therapy on alveolar haemorrhage was similar among the two groups (no advantage)
- Renal function improvement was substantially more in the group treated with PLEX (Creatinine at the end of therapy was significantly lower)

Patient No.	Duration of Therapy (weeks)	Serum Creatinine at End of Therapy	Serum Creatinine at Discharge	Chronic Dialysis	Change in Renal Function During Therapy	Bolus Steroid (Reason)	Leukopenia (WBC < 3K)	Infections
Group I								
1	10	15.0	11.5	+*	↓	P	–	–
2	6	15.0	10.5	+*	↓	–	+	+
3	12	1.1	1.1	–	→	–	–	–
4	4	15.0	13.0	+**	↓	P	–	+
5	20	1.1	1.2	–	→	–	–	–
6	24	0.8	0.8	–	↑	–	–	–
7	2	13.0	12.0	+	→	P	+	+
8	36	12.4	17.0	+	↓	P	+	–
9	18	10.9	16.0	+	↓	R	+	–
Mean ± S.E.M.	14.7 ± 3.7	9.5 ± 0.7	9.2 ± 0.7					
Group II								
10	20	10.4	8.9	+	↓	P	+	+
11	24	1.3	1.3	–	→	–	–	–
12	5	12.4	12.0	+	→	P	+	+
13	20	1.3	1.3	–	↓	–	–	–
14	8	2.3	2.3	–	↑	–	–	–*
15	24	1.2	1.2	–	↑	–	–	–
16	32	1.5	1.5	–	↑	P	–	+
17	18	4.9	4.2	–***	↑***	P + R	+	+*
Mean ± S.E.M.	18.9 ± 3.1	4.4 ± 0.6	4.1 ± 0.5					

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Patient No.	Duration of Therapy (weeks)	Serum Creatinine at End of Therapy	Serum Creatinine at Discharge	Chronic Dialysis	Change in Renal Function During Therapy	Bolus Steroid (Reason)	Leukopenia (WBC < 3K)	Infections
Group II								
10	20	10.4	8.9	+	↓	P	+	+
11	24	1.3	1.3	−	→	−	−	−
12	5	12.4	12.0	+	→	P	+	+
13	20	1.3	1.3	−	↓	−	−	−
14	8	2.3	2.3	−	↑	−	−	−*
15	24	1.2	1.2	−	↑	−	−	−
16	32	1.5	1.5	−	↑	P	−	+
17	18	4.9	4.2	−***	↑***	P + R	+	+*
Mean ± S.E.M.	18.9 ± 3.1	4.4 ± 0.6	4.1 ± 0.5					

Very small number of patients were included in the study
PLEX was instituted at a lower frequency than usual
Larger RCT with more aggressive PLEX may establish a more significant role of PLEX in DAH

Newer option

- Imlifidase is an enzyme derived from Streptococcus pyogenes
- Cleaves IgG within hours into F(ab) and F(c) fragments rendering it non-functional
- Does not improve renal status
- Phase II trials have shown its ability to clear anti-GBM antibodies readily and effectively
- Currently a phase III trial is in enrolment stage to assess efficacy and safety of Imlifidase in randomized control trial setting

DAH in other settings

- DAH secondary to SLE/APLA/other auto-immune diseases
- DAH secondary to cryoglobulineamia
- Drug-induced DAH
- Idiopathic pulmonary haemosiderosis
- DAH due to excess anti-coagulation
- DAH in allogenic HSCT recipients
- DAH due to infection

- No data from large RCT
- Data on treatment extrapolated from treatment of DAH in AAV or from case series/observational cohort studies
- Management of the underlying condition is often the mainstay of treatment

- A 2021 systematic review and metaanalysis examined 8 studies with 251 SLE patients who had 262 episodes of diffuse alveolar haemorrhage
- All the patients had SLE according to ACR classification and DAH on the basis of cough/dyspnea/haemoptysis, acute onset b/l lung infiltrates on imaging, drop of Hb>1.5g/dL without bleeding elsewhere and haemosiderin-laden macrophages on BAL/TBLB
- The article evaluated risk factors for poor outcome and responses to treatment in the studies which were conducted in USA, S. Korea, China, USA, Columbia and Sigapore.

Jiang M, Chen R, Li Z, Zhang X. Risk factors for mortality of diffuse alveolar hemorrhage in systemic lupus erythematosus: a systematic review and meta-analysis. 2021 Feb 16;23(1).

Variables	No. of studies	Number of enrolled episodes	Effects model	I^2 (%)	OR/SMD (95%CI)	*P* values	Relationship	Publication bias (*P* value of Begg's test)
Demographic and clinical characteristics								
Age	7	243	Fixed	0.0%	0.35 (0.08, 0.61)	0.010	Increased risks	None (1.000)
Female	4	189	Fixed	42.6%	0.69 (0.31, 1.54)	0.369	No association	None (0.734)
Disease duration	6	226	Fixed	0.0%	0.28 (0.01, 0.55)	0.042	Increased risks	None (0.260)
Lupus nephritis	3	140	Random	58.4%	5.45 (0.52, 56.95)	0.160	No association	None (0.296)
NPSLE	3	124	Fixed	42.2%	0.96 (0.43, 2.15)	0.920	No association	None (1.000)
Laboratory data and disease activity								
Platelet	6	219	Random	69.1%	− 0.29 (− 0.86, 0.29)	0.328	No association	None (0.260)
Drop of hemoglobin	5	202	Random	57.5%	0.34 (− 0.17, 0.85)	0.190	No association	None (0.806)
C3	3	132	Random	77.0%	0.48 (− 0.51, 1.46)	0.340	No association	None (1.000)
SLEDAI	6	186	Random	76.9%	0.24 (− 0.52, 0.99)	0.540	No association	None (1.000)
Comorbidity and treatment								
Infection	6	223	Fixed	37.5%	2.77 (1.55, 4.95)	0.001	Increased risks	None (0.260)
CTX treatment	6	224	Random	75.5%	0.74 (0.16, 3.41)	0.700	No association	None (1.000)
IVIG treatment	3	175	Random	61.2%	1.28 (0.24, 6.87)	0.780	No association	None (0.296)
Plasmapheresis	5	167	Fixed	14.6%	1.96 (1.04, 3.70)	0.038	Increased risks	None (0.806)
Mechanical ventilation	8	262	Fixed	23.3%	6.11 (3.27, 11.39)	< 0.0001	Increased risks	None (1.000)

- They identified an increased risk of mortality associated with advanced age at presentation, long duration of disease, association of infection and need for mechanical ventilation and plasmapheresis.
- There was no association between treatment with or without cyclophosphamide.
- The ones requiring plasmapheresis may be sicker at the onset and this may explain higher mortality in this group

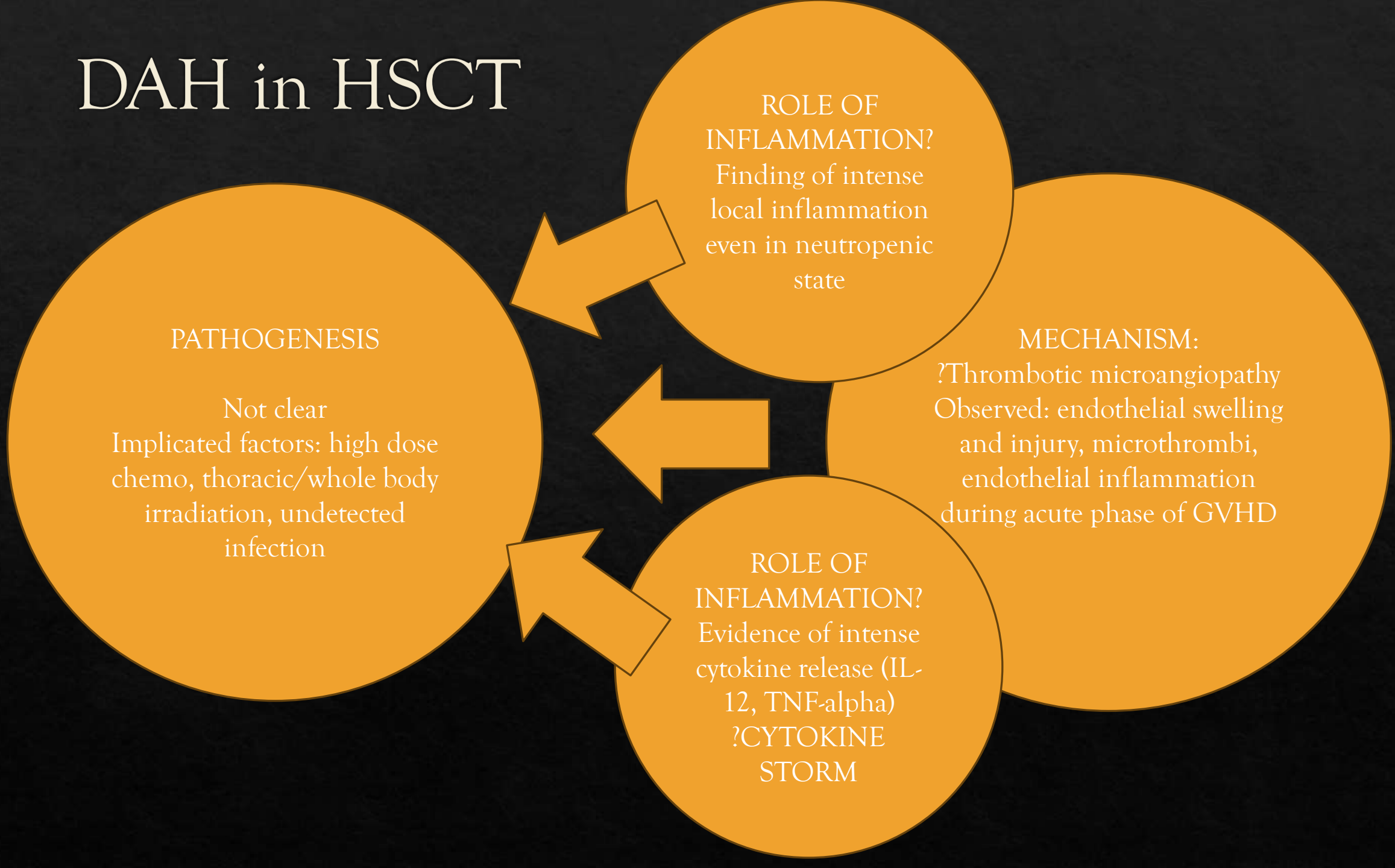
DAH in HSCT

PATHOGENESIS

Not clear
Implicated factors: high dose chemo, thoracic/whole body irradiation, undetected infection

MECHANISM:
?Thrombotic microangiopathy
Observed: endothelial swelling and injury, microthrombi, endothelial inflammation during acute phase of GVHD

DAH in HSCT


ROLE OF INFLAMMATION?
Finding of intense local inflammation even in neutropenic state
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ROLE OF INFLAMMATION?
Evidence of intense cytokine release (IL-12, TNF-alpha)
?CYTOKINE STORM

DAH in HSCT

ROLE OF INFLAMMATION? Finding of intense local inflammation even in neutropenic state

These form the basis of managing DAH with immunosuppressive therapy (no RCT)
IV corticosteroids (methylprednisolone) 250 mg-2g/day for 5 days, followed by 1mg/Kg prednisolone tapered over 2-4 weeks (basis: retrospective observational studies and anecdotal reports)
No role of other immunosuppressive therapies and PLEX has been demonstrated

INFLAMMATION? Evidence of intense cytokine release (IL-12, TNF-alpha) ?CYTOKINE STORM

Bekele Afessa, Ayalew Tefferi, Litzow MR, Krowka MJ, Wylam ME, Peters SG. Diffuse Alveolar Hemorrhage in Hematopoietic Stem Cell Transplant Recipients. 2002 Sep 1;166(5):641–5.

Loecher AM, West K, Quinn TD, Defayette AA. Management of diffuse alveolar hemorrhage in the hematopoietic stem cell transplantation population: A systematic review. Pharmacotherapy [Internet]. 2021 Nov;41(11):943–52

Idiopathic pulmonary haemosiderosis

- A 2022 systematic review examined cases of IPH and Lane-Hamilton syndrome (IPH+celiac disease) between 1971 and 2022
- They found that although majority of patients were diagnosed at a young age, delay in diagnosis of IPH was substantial
- The patients with only IPH has been treated with glucocorticoids in >90% of cases and about 10% of them required additional immunosuppression (CYC)
- Only 40% of cases of Lane-Hamilton syndrome were treated with GC and few of them were treated with gluten free diet.
- They found a rate of recurrence of around 56% in IPH patients and 28% in LHS
- In a follow up period of about 3 years, 21% of IPH patients died despite treatment (0% among LHS group)

Saha BK, Datar P, Aiman A, Bonnier A, Saha S, Milman NT. Comparative Analysis of Adult Patients With Idiopathic Pulmonary Hemosiderosis and Lane-Hamilton Syndrome: A Systematic Review of the Literature in the Period 1971-2022. Cureus [Internet]. 2022;14(3):e23482.

- DAH secondary to SLE/APLA/other auto-immune diseases

PULSE METHYPPREDNISOLONE + CYC (alternative-RTX/AZA/MMF)

- DAH secondary to cryoglobulineamia

PULSE METHYPPREDNISOLONE + CYC (alternative-RTX/AZA/MMF)
+
Treatment of underlying cause of cryoglubilinaemia
+
PLEX (warm the exchange fluid) (unproven benefit)

- Drug-induced DAH

- Idiopathic pulmonary haemosiderosis

STOP offending drug (s)
+
Systemic glucocorticoids (in severe cases)

Systemic glucocorticoids (pulse+maintenance)

- DAH due to excess anti-coagulation

STOP anticoagulation
TREAT IPT/TTP-TMA if present
TREAT with Platelet transfusion/VitK/4 factor PCC
USE of FACTOR VIIa (?)

- DAH in allogenic HSCT recipients

PULSE GC+ maintenance GC
AMINOCAPROIC ACID (doubtful benefit)

- DAH due to infection

MANAGEMENT of underlying infection with ANTI-VIRALS/ANTI_BACTERIALS

- DAH due to MS/CCF

Diuretics
Optimisation of medical management of heart failure
Consideration of surgical correction

rFACTOR VIIa for DAH

- rFVIIa is a haemostatic agent and approved for treatment of hameophilia A and B (who acquired Ab to factor VII and IX)
- A retrospective study reported characteristics and outcomes in patients between 2003 and 2013 who received rFVIIa for diffuse alveolar haemorrhage (n-23)
- All patients received rFVIIa at a dose of 35-120 mcg/Kg every 2 hours for total 4 times/day (standard dose was 75 mcg/Kg)
- All received standard of care immunosuppression additionally
- Treatment was deemed successful if Haematocrit was stabilized along with resolution/stabilization of Pulmonary infiltrates and ventilatory parameters

Pathak V, Kuhn J, Gabriel D, Barrow J, Jennette JC, Henke DC. Use of Activated Factor VII in Patients with Diffuse Alveolar Hemorrhage: A 10 Years Institutional Experience. Lung. 2015 Mar 23;193(3):375–9.

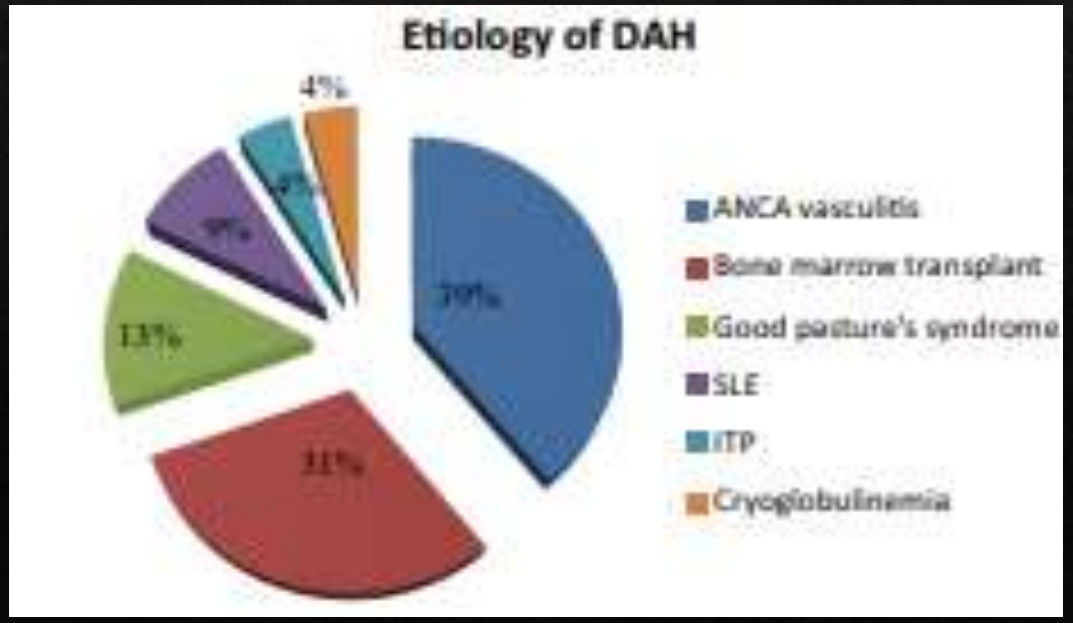
Diagnosis	No. of patients	Mean age (years)	Alveolar hemorrhage	ICU admission	Intubation	RFVIIa dose (mean) (mg)	Other treatments	Mortality
ANCA vasculitis	09	48	Resolved	Yes	6/9	09	Plasmapheresis, corticosteroids, and cytotoxic drugs	1/9
Bone marrow transplant	07	44	Resolved	Yes	6/7	11	Platelet transfusions and corticosteroids	6/7
Good pasture's syndrome	03	42	Resolved[1]	Yes	3/3	3.5	Plasmapheresis, corticosteroids, and cytotoxic drugs	1/3
SLE	02	24	Resolved	Yes	2/2	5.5	Plasmapheresis, platelet transfusion, and corticosteroids	0
ITP	01	57	Resolved	No	No	02	Platelet transfusion, IVIG, and corticosteroids	0
Cryoglobulinemia	01	60	Resolved	Yes	1/1	15	Plasmapheresis, corticosteroids, and cytotoxic drugs	0
Total	23				18/23			8/23

ANCA anti-neutrophil cytoplasmic antibody, *SLE* systemic lupus erythematosus, *ITP* idiopathic thrombocytopenic purpura, *IVIG* intravenous immunoglobulin

Resolved In one patient with Good pasture's syndrome, bleeding did not stop and the patient died

Other treatments The corticosteroids used was methylprednisone; cytotoxic drugs used were either cyclophosphamide or rituximab based on the severity of illness

- 22 of the 23 patients required ICU admission and 18 required mechanical ventilation
- DAH resolved in 22 of 23 patients
- However, 8 patients died (6 bone marrow transplant recipient, 2 ANCA vasculitis)
- Deaths were due to multiorgan failure and progression of underlying disease
- No thrombotic adverse events was observed due to rFVIIa



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SLE	02						transfusion, and corticosteroids	0
ITP	01						and corticosteroids	0
Cryoglobulinemia	01						roids, and cytotoxic drugs	0
Total	23							8/23

ANCA anti-neutrophil cytoplasmic … unoglobulin

Resolved In one patient with Good …

Other treatments The corticosteroid … everity of illness

The treatment stopped alveolar haemorrhage without any impact on underlying disease progression

Actual benefit of treatment could be confounded by other treatments offered

Randomized clinical trials are required to establish the drug as a effective management of DAH

- 22 of the 23 patient… required mechanica…
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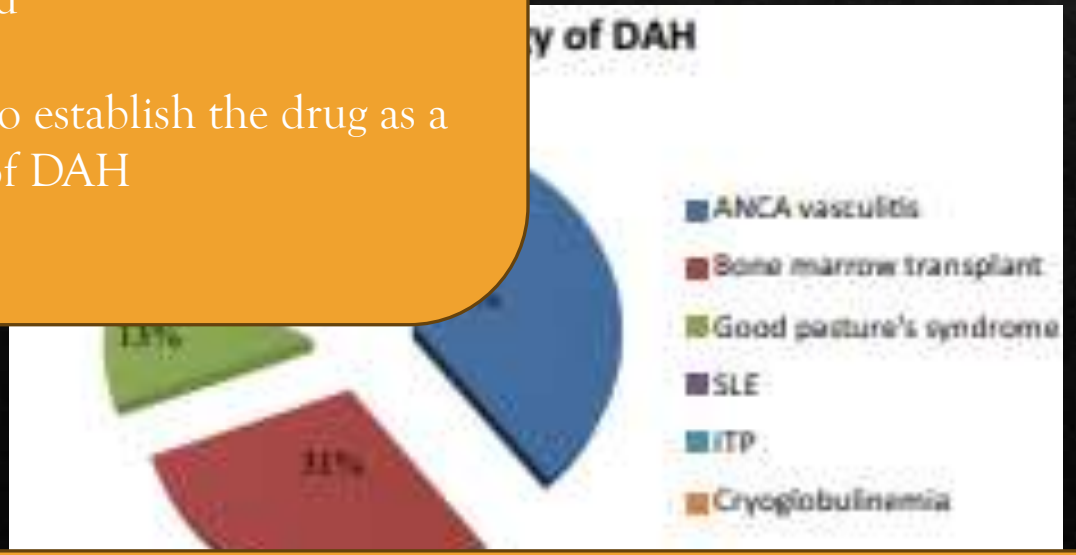

rVIIa has been associated with life-threatening venous and arterial thromboembolic events which requires farther safety assessment

CONCLUSION

- DAH is a life-threatening manifestation of multiple disease processes
- It requires prompt identification and management as delay in diagnosis is a/w higher rate of adverse outcome
- Management of DAH depends largely on treatment of the underlying inflammation
- Current mainstay of treatment: immunosuppression:

A. Induction with CYC/RTX (with or without AVACOPAN)+ IV pulse corticosteroid

(consider RTX better in relapsing disease)

A. Maintenance with RTX/AZA + tapering glucocorticoids for adequate duration
B. PLASMA EXCHANGE has doubtful role
C. Newer adjunctive therapies

CONCLUSION

- Research lacunae: many large RCTs exclude patients with severe DAH, do not report results of DAH subgroup separately and do not mention nature of pulmonary involvement
- Larger RCTs are required to examine roles of newer therapies such as AVACOPAN, rFVIIa and IMLIFIDASE considering the high risk of side effects of cytotoxic agents and long-term systemic glucocorticoids
- Role of IVIg can be reviewed (anecdotal reports of benefit)
- RCTs are required to evaluate treatment options in DAH associated with diseases other than AAV/drugs/infections

Proposed management of DAH

- Induction of remission:
- IV methyl prednisolone 1 gram for 3 days
- IV Rituximab 375 mg/BSA once weekly for 4 weeks
- Continue oral prednisolone 1 mg/Kg/day for 1 week followed by 0.5 mg/Kg/day to be tapered to <5mg/day 6 months and stop if possible
- Maintenance:
- Rituximab 375 mg/BSA 6 monthly until 18-24 months

- Major relapse: re-introduction with Rituximab (same dose as induction)
- With or without additional pulse dose of steroids
- Alternative: Cyclophosphamide pulse doses (if renal involvement predominates)
- Minor relapse: increased dose of oral glucocorticoids (0.5 mg/Kg/day) and tapered back to baseline dose by 4 weeks

- In refractory disease (remission not achieved by proposed regimen)
- Options include-

A. Re-induction with CYC 15 mg/Kg/d 2 weekly for 3 doses and then 2 weekly until remission (3-6 months)

B. Alternatively, plasma exchange therapy (more chance of benefit in anti-GBM disease and in patients with poor baseline/new onset renal impairment)

C. Additional pulse doses of methylprednisolone

- Experimental options-

A. Recombinant factor VIIa: 75 mcg/Kg/dose 2 hourly for 4 doses a day until DAH resolves

B. IMLIFIDASE

THANK YOU