2. DACH ANCA VASKULITIS FORUM 2024
22. & 23. NOVEMBER 2024 | MÜNCHEN

CSL Vifor

Infektionsprophylaxe und PLEX - evidenzbasiertes Handeln

Dr. Balazs Odler PhD.
Graz

KLINISCHE ABTEILUNG FÜR NEPHROLOGIE
MEDIZINISCHE UNIVERSITÄT GRAZ LKH UNIV KLINIKUM GRAZ

Plasmapherese und Infektionsprophylaxe bei AAV – evidenzbasiertes Handeln

Dr. med. Balázs ODLER, PhD

Klinische Abteilung für Nephrologie
Universitätsklinik für Innere Medizin
Medizinische Universität Graz

2. DACH-ANCA Vaskulitis Forum 2024
22-23.11.2024
München, Deutschland

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Interessenkonflikte

Speaking fees:	CSL Vifor, Otsuka
Advisory Board:	AstraZeneca, Delta4, Glaxo Smith Kline, Novartis, Otsuka
Unrestricted research grants:	CSL Vifor, Otsuka
Travel support:	Glaxo Smith Kline, Otsuka
Society:	Board member – Young Nephrologists Platform of ERA

„Es ist das, was wir zu wissen glauben, was uns vom Lernen abhält.“

von Claude Bernard

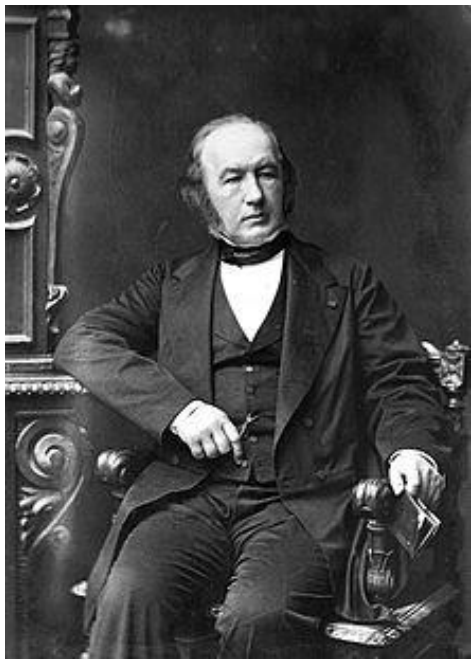
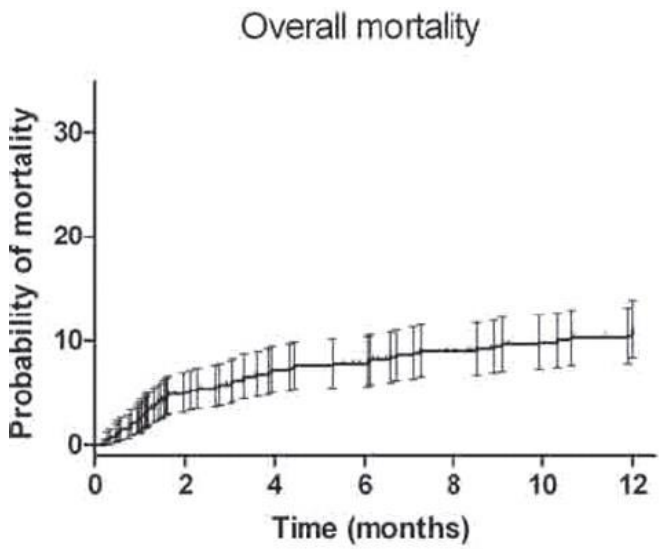
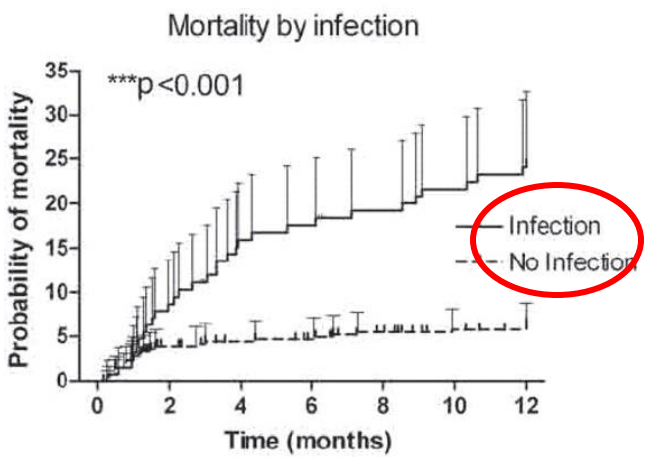


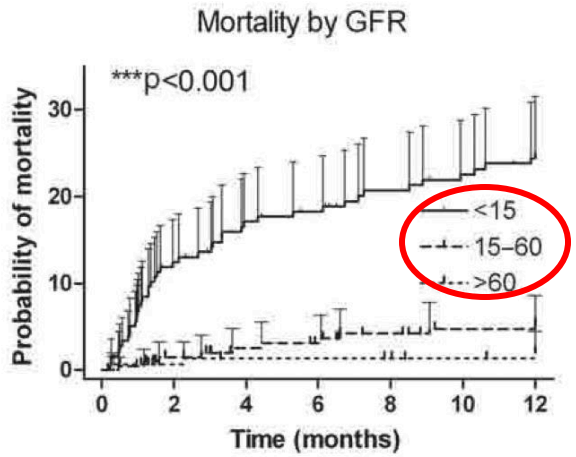
Photo from wikipedia

Mortalität

Unsere größte Herausforderung besteht darin, die Patienten mit dem höchsten Sterberisiko zu erkennen.







Time after diagnosis (up to 12 months)

Infektionen und eine reduzierte GFR sind starke Prädiktoren für erhöhtes Mortalitätsrisiko.

Little M et al. Ann Rheum Dis 2010; 69:1036–43.

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Mortalität

alveoläre Hämorrhagie

N=106 mit DAH

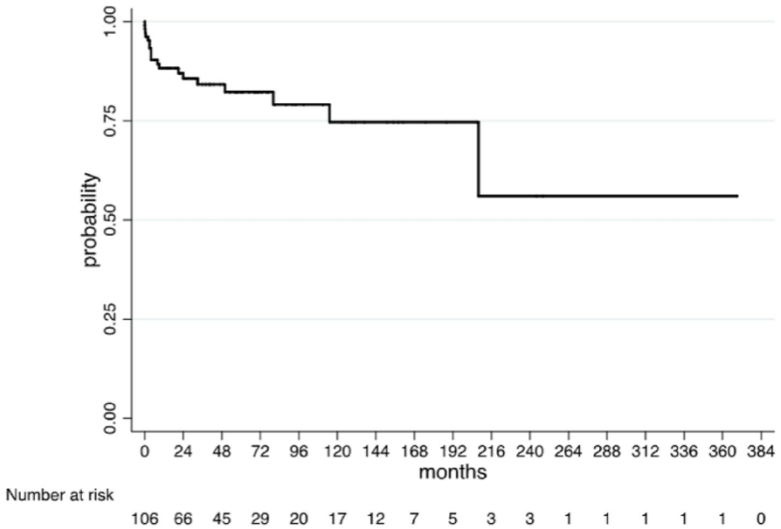
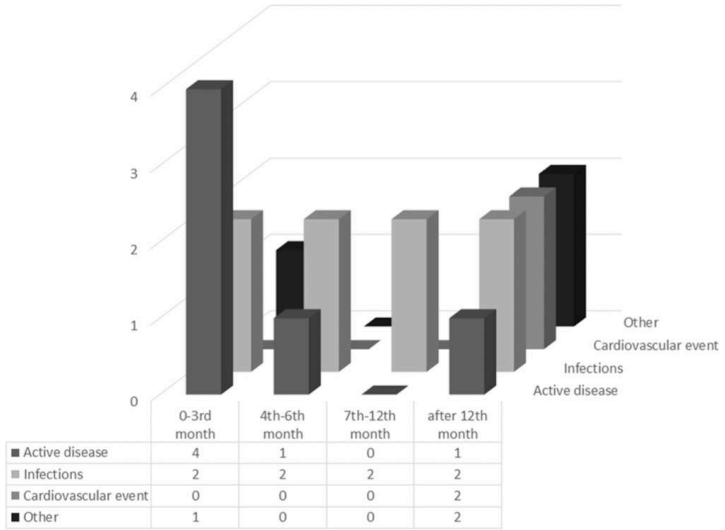


Fig. 2. Overall survival.

Die geschätzte Gesamtüberlebensrate betrug 93 % nach 3 Monaten, 88 % nach 1 Jahr und 82 % nach 5 Jahren.



	0-3rd month	4th-6th month	7th-12th month	after 12th month
Active disease	4	1	0	1
Infections	2	2	2	2
Cardiovascular event	0	0	0	2
Other	1	0	0	2

Sieben (6,6 %) Patienten starben innerhalb von drei Monaten nach Beginn der AH, davon vier an Multiorganversagen aufgrund der aktiven Erkrankung, zwei an **Infektionen** und einer sowohl an AH als auch an einer Infektion. Nach ≥3 Monaten nach Beginn der AH waren Infektionen die Haupttodesursache.

Quartuccio L et al. J Autoimmunity 2020; 108: 102397.

Nierenbeteiligung und alvolare Hämorrhagie

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Diagnosis and management of ANCA-associated vasculitis

Andreas Kronbichler, Ingeborg M Bajema, Annette Bruchfeld, Gianna Mastroianni Kirsztajn, John H Stone

	Kidney involvement	Haemoptysis or diffuse alveolar haemorrhage
MPA	82.2%	19.4%
GPA	58.6%	21.1%
PR3	57.7%	17.8%
MPO	79.2%	22.2%

Kronbichler A et al. Lancet 2024; 403: 683-698.

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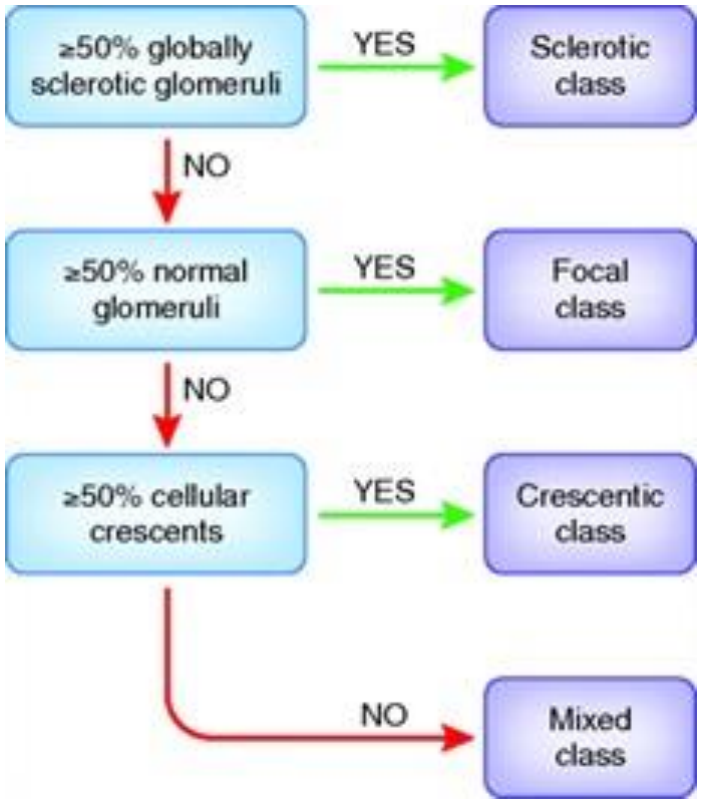
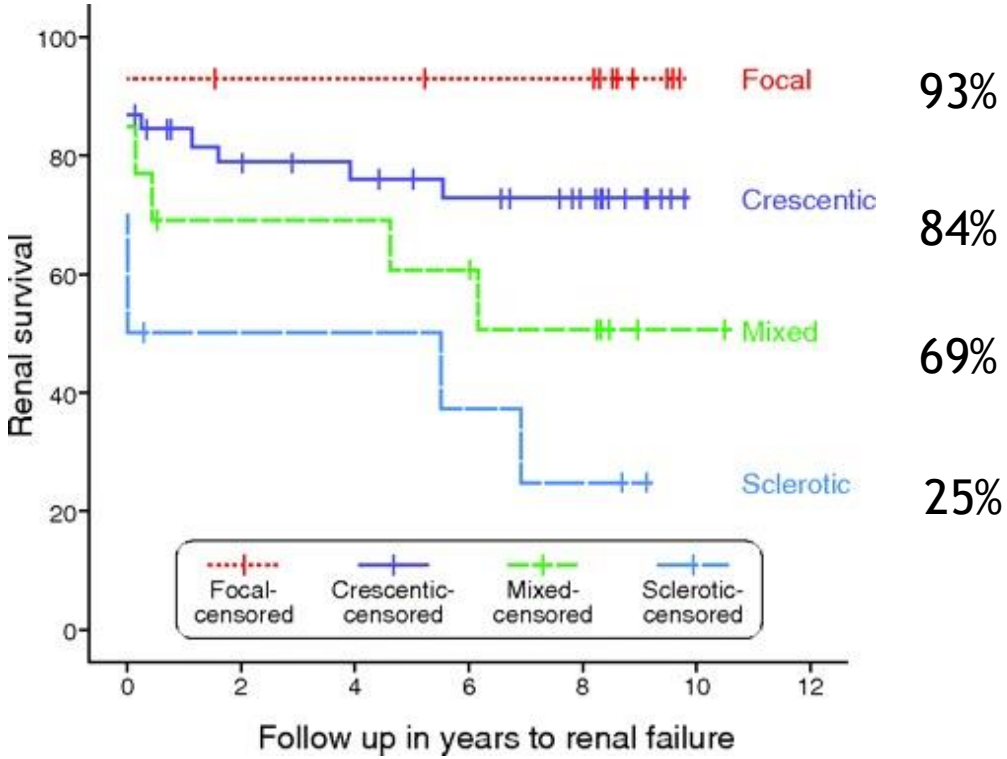
Histopathologie und renales Outcome



Renal survival nach 1 Jahr

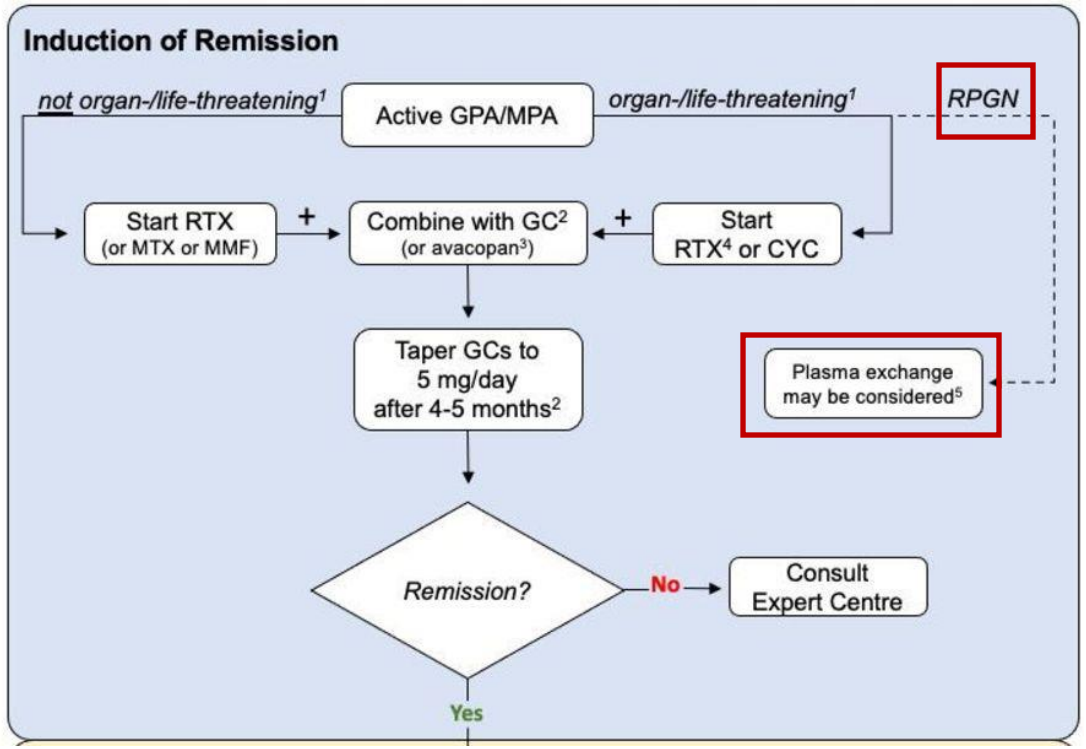


Das nierenbezogene Überleben (keine Entwicklung eines terminalen NV) wird anhand der vier histologischen Kategorien dargestellt. Die sklerotische Kategorie ist mit dem schlechtesten Outcome verbunden.

Berden et al. JASN 2010; 21(10): 1628-1636.

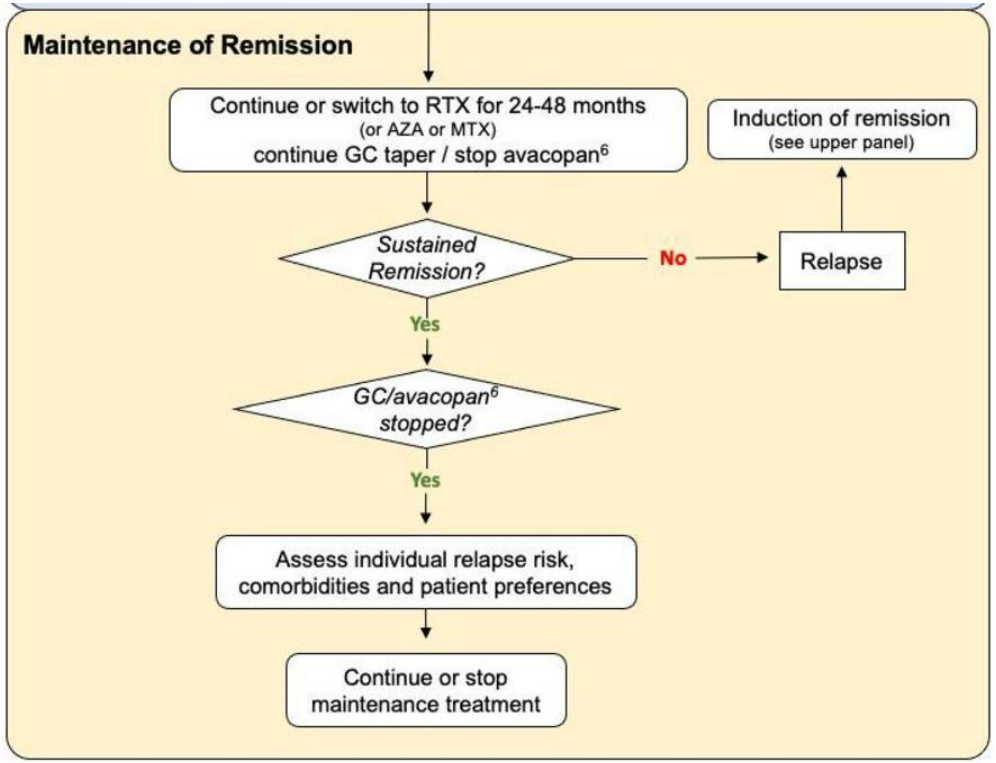
Therapie

Induktionstherapie



Ziel ist es, die Krankheitsaktivität schnell und wirksam zu kontrollieren.

Erhaltungstherapie



Ziel ist es, die Kontrolle der Krankheitsaktivität aufrechtzuerhalten.

Hellmich B et al. Ann Rheum Dis 2023

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EULAR Empfehlung

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

Bernhard Hellmich [1], Beatriz Sanchez-Alamo,[2] Jan H Schirmer,[3] Alvise Berti [4,5] Daniel Blockmans,[6] Maria C Cid [7], Julia U Holle,[8] Nicole Hollinger,[1] Omer Karadag,[9] Andreas Kronbichler,[10,11] Mark A Little,[12] Raashid A Luqmani,[13] Alfred Mahr,[14] Peter A Merkel [15], Aladdin J Mohammad [11,16] Sara Monti [17,18] Chetan B Mukhtyar [19], Jacek Musial,[20] Fiona Price-Kuehne,[11] Mårten Segelmark,[21] Y K Onno Teng [22], Benjamin Terrier [23], Gunnar Tomasson [24,25] Augusto Vaglio [26], Dimitrios Vassilopoulos [27], Peter Verhoeven,[28] David Jayne [11]

	Level of Evidence	Strength of Recommendation	Final Vote (%)	Level of Agreement (0-10)
Plasma exchange may be considered as part of therapy to induce remission in GPA or MPA for those with a serum creatinine > 300 µmol/l due to active glomerulonephritis.	1a	B	95	8.0±1.7
Routine use of plasma exchange to treat alveolar hemorrhage in GPA and MPA is not recommended.	1b	B	90	8.8±1.3

Hellmich et al. Ann Rheum Dis 2024; 83(1): 30-47.

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KDIGO Leitlinie

KLINISCHE ABTEILUNG FÜR NEPHROLOGIE
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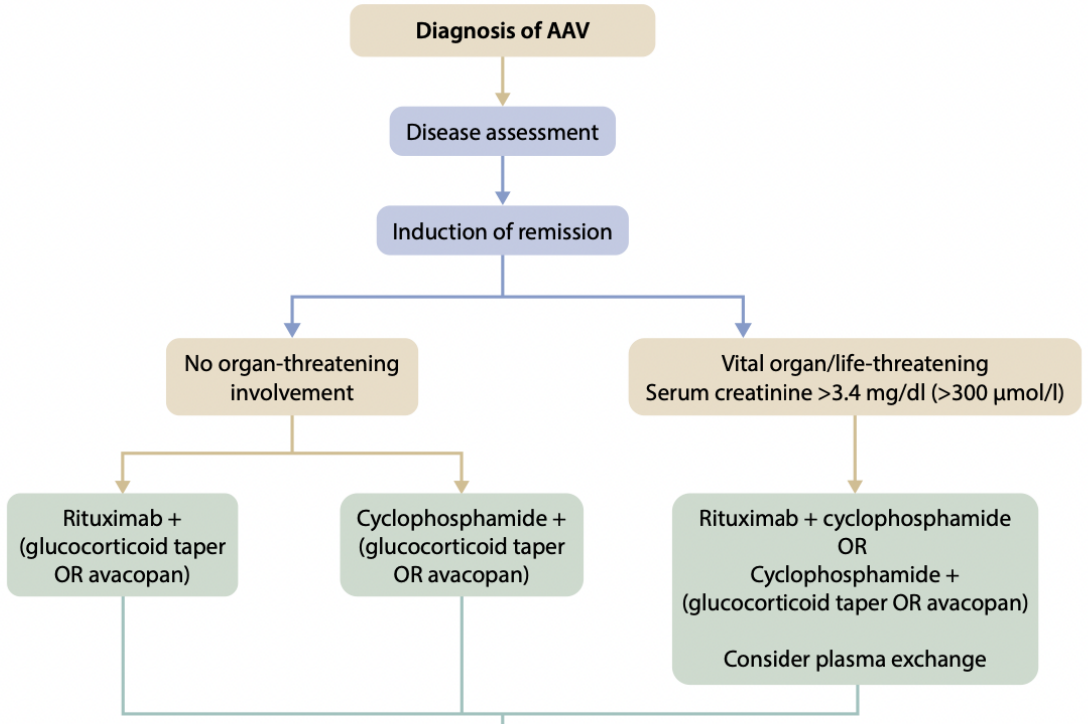
KDIGO 2024 CLINICAL PRACTICE GUIDELINE
FOR THE MANAGEMENT OF ANTINEUTROPHIL CYTOPLASMIC
ANTIBODY (ANCA)–ASSOCIATED VASCULITIS



Practice Point 9.3.1.9: Consider plasma exchange for patients with SCr > 3.4 mg/dL (> 300 µmol/l) requiring dialysis or with rapidly increasing SCr, and in patients with diffuse alveolar hemorrhage who have hypoxemia.

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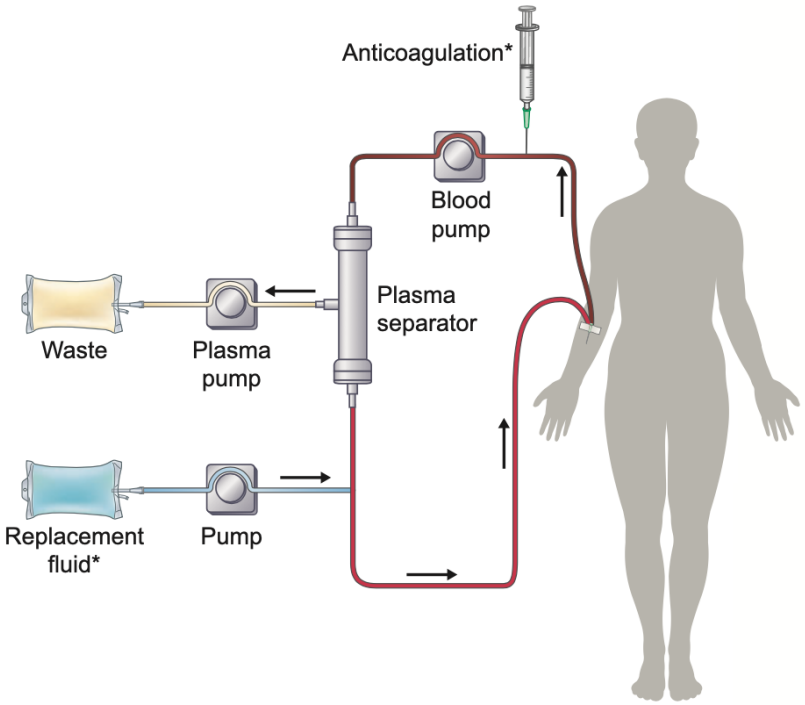
Plasmapherese bei AAV



***Anticoagulation:**
- Heparin or citrate

***Replacement fluid:**
- Human serum albumin (3–5%, depending on local availability); may be combined with crystalloid (e.g. saline)
- Patients with active bleeding may receive supplemental (fresh frozen) plasma to replace clotting factors according to local practice

Seven plasma exchanges of 60 mL/kg are performed within 14 days or randomization

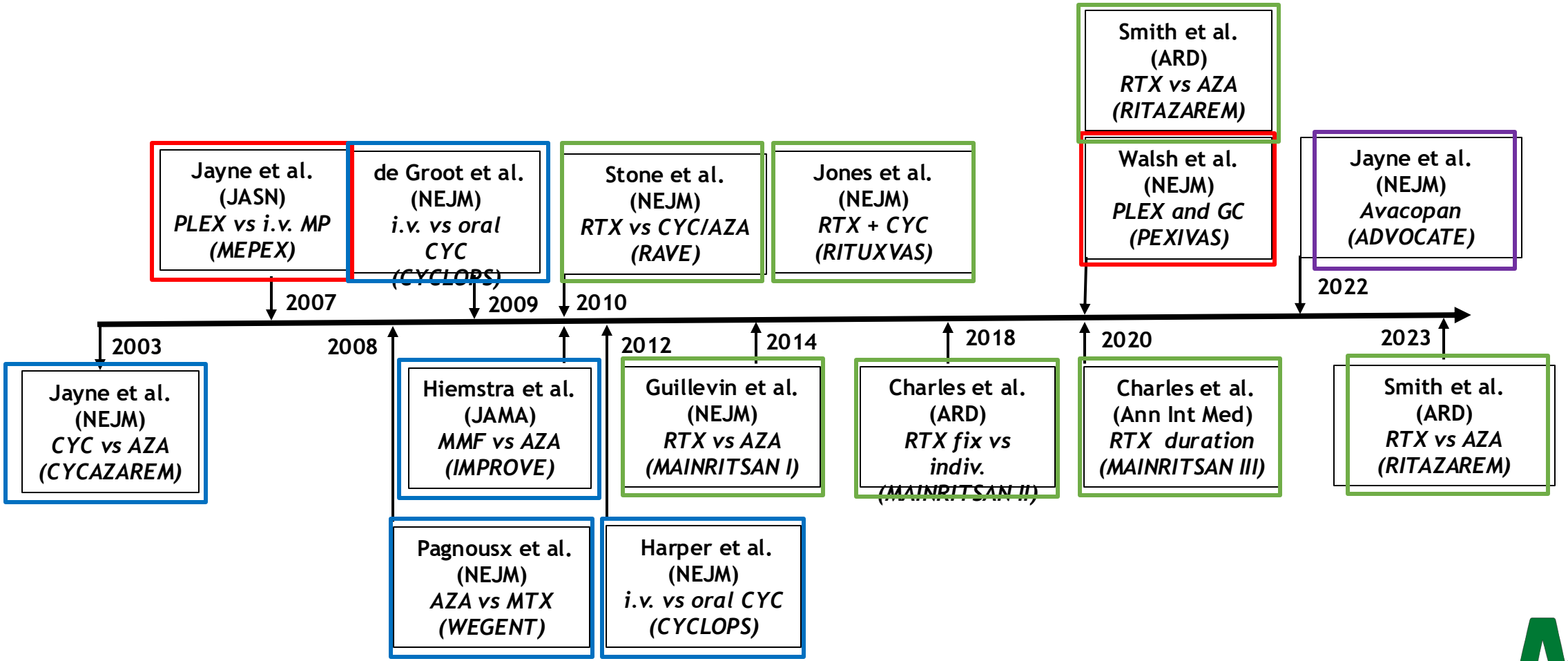
Serologic changes:
- ANCA level reduction > 70% (3–5 PLEX)
- ↓C_3a, C_5a, sC5b9
- C-reactive protein (↓64%, 1 session)
- IL-8 (↓34%), TNF-α (↓52%), VEGF (↓24%) (4–5 sessions)

IL = interleukin
TNF = tumor necrosis factor
VEGF = vascular endothelial growth factor
ANCA = anti-neutrophil cytoplasmic antibody
PLEX = plasma exchange

ANCA sind pathogenetisch und eine rasche Senkung ihrer Spiegel ist aus pathophysiologischer Sicht sinnvoll. PLEX reduziert Antikörper sowie Plasma- und Urinkomplementfaktoren, die eine entscheidende Rolle in der komplexen Pathogenese von AAV spielen.

Kronbichler et al. NDT 2021,36(2): 227-231

AAV Therapie - Landmark Studien



MEPEX Studie

Both groups: CYC 2.5 mg/kg (2 mg/kg age > 60) 3 x 1 g MP 7 sessions
Oral prednisolone: initial 1 mg/kg per day 60 ml/kg

Clinical and Laboratory Features at Entry	Intravenous Methylprednisolone (*n* = 67)	Plasma Exchange (*n* = 70)	Total (*n* = 137)	*P*
Age (yr; median [range])	66 (27 to 81)	67 (28 to 79)	66 (27 to 81)	0.93
Female gender (*n* [%])	24 (36)	29 (41)	53 (38.7)	0.50
Wegener's granulomatosis/microscopic polyangiitis (*n* [%])	24/43 (35.8/64.2 8)	18/52 (25.7/74.3)	42/95 (30.7/69.3)	0.20
Nonoliguric/dialysis requiring (*n* [%])	19/48 (28.4/71.6)	23/47 (32.9/67.1)	42/95 (30.7/69.3)	0.57
PR3-ANCA (*n* [%])	31 (46.3)	26 (37.1)	57 (42.6)	0.35
MPO-ANCA (*n* [%])	31 (46.3)	40 (57.1)	71 (51.9)	
ANCA negative (*n* [%])	3 (4.5)	4 (5.7)	7 (5.3)	
BVAS	21 (12 to 41)	21 (12 to 39)	21 (12 to 41)	0.69
Vasculitis Damage Index (median [range])	0 (0 to 4)	0 (0 to 7)	0 (0 to 7)	0.86
Creatinine (μmol/L; median [range])	718 (498 to 1566)	754 (500 to 1669)	735 (498 to 1669)	0.96
C-reactive protein (mg/L; median [range])	108 (2 to 264)	76 (7 to 281)	93 (2 to 281)	0.23
Erythrocyte sedimentation rate (mm/h; median [range])	84 (2 to 150)	94 (20 to 140)	89 (2 to 150)	0.34

Patients with a serum creatinine of **≥ 500 µmol/l** (equivalent to 5.7 mg/dL)

Jayne et al. J Am Soc Nephrol 2007; 18: 2180-2188.

MEPEX Studie - Nierenbiopsie

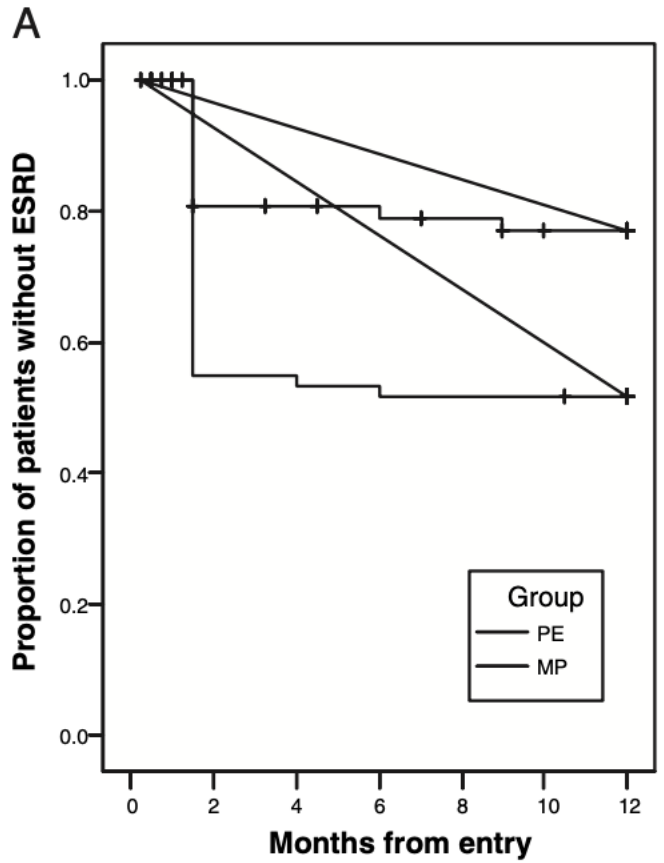
In fast allen Fällen lagen histologische Daten vor.

Histologic Lesion	Intravenous Methylprednisolone (*n* = 49)	Plasma Exchange (*n* = 51)	Total Group (*n* = 100)
Glomerular			
% normal glomeruli	13.6 ± 18.2	12.1 ± 12.1	12.8 ± 15.3
% fibrinoid necrosis	28.9 ± 25.3	22.2 ± 24.9	25.5 ± 25.2
% crescents	59.2 ± 28.6	53.0 ± 28.9	56.0 ± 28.8
segmental	23.1 ± 23.4	28.9 ± 31.3	25.9 ± 27.3
circumferential	76.9 ± 44.3	71.1 ± 54.3	74.1 ± 49.5
cellular	90.4 ± 49.1	90.8 ± 57.2	90.6 ± 53.0
fibrous	9.6 ± 12.6	9.2 ± 18.0	9.4 ± 15.3
% global sclerosis	24.6 ± 26.9	28.2 ± 24.6	26.4 ± 25.7
Tubulointerstitial and vascular			
interstitial edema (0/1)	0.5 ± 0.5	0.5 ± 0.5	0.5 ± 0.5
interstitial infiltrates (0/1/2/3)	1.8 ± 0.7	1.8 ± 0.6	1.8 ± 0.7
neutrophilic (0/1/2)	0.7 ± 0.4	0.7 ± 0.5	0.7 ± 0.5
mononuclear cell (0/1/2)	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4
eosinophilic (0/1/2)	0.4 ± 0.5	0.3 ± 0.5	0.4 ± 0.5
interstitial fibrosis (0/1/2)	1.2 ± 0.6	1.3 ± 0.6	1.2 ± 0.6
tubular casts (0/1)	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3
tubular necrosis (0/1)	0.8 ± 0.4	0.8 ± 0.4	0.8 ± 0.4
tubular atrophy (0/1/2)	1.1 ± 0.5	1.2 ± 0.6	1.1 ± 0.6
intraepithelial infiltrates (0/1)	0.8 ± 0.4	0.8 ± 0.4	0.8 ± 0.4
arteriosclerosis (0/1)	0.8 ± 0.4	0.7 ± 0.4	0.8 ± 0.4

Die Nierenbiopsien zeigten Halbmonde und insbesondere zelluläre Halbmonde als vorherrschenden Befund (>50 %), während eine globale Sklerose in ~25 % der untersuchten Glomeruli festgestellt wurde.

Jayne et al. J Am Soc Nephrol 2007; 18: 2180-2188.

MEPEX Studie - Outcome



3 months: Kidney function recovery in 33 (49%) of 67 of the MP group and 48 (69%) of 70 of the PLEX group (p=0.02)

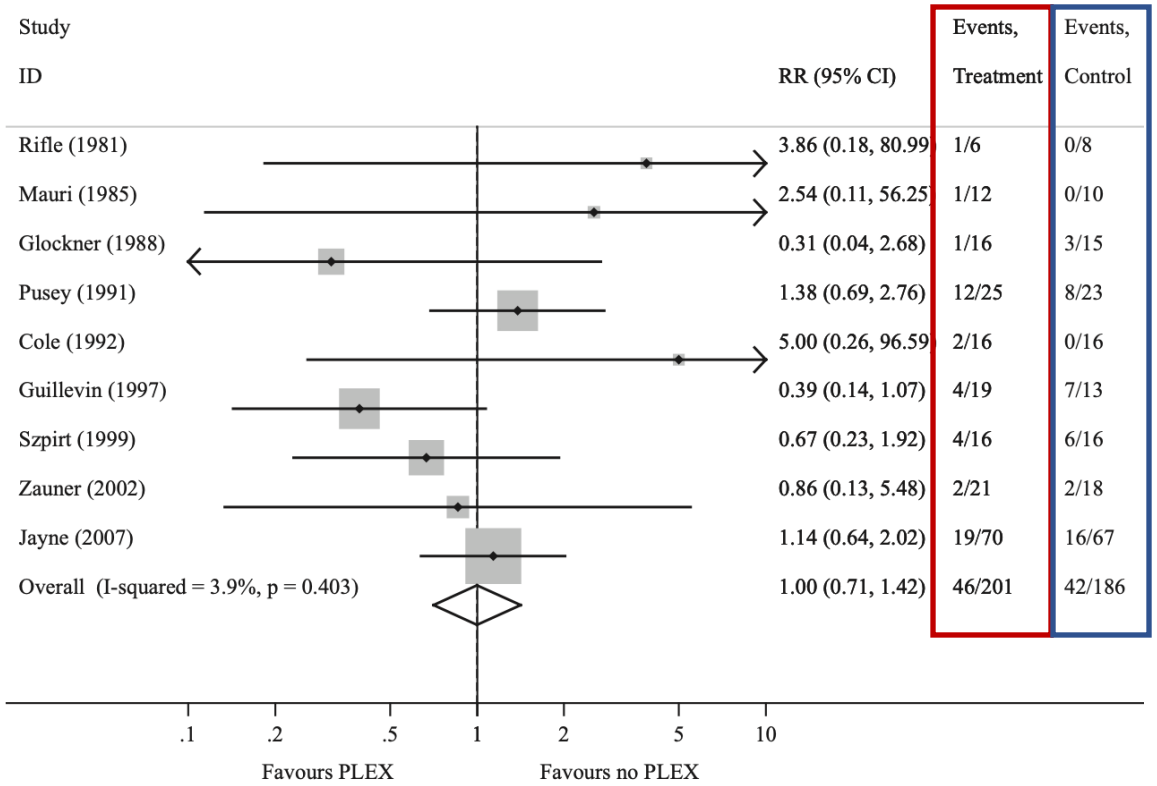
12 months: 29 (57%) of 51 survivors in the MP group and 41 (80%) of 51 survivors in the PLEX group remained dialysis independent (p=0.008)

Survival: 51/67 (76%) in the MP group, and 51 (73%) of 70 in the PLEX group; major cause of death was infection (n=19)

Jayne et al. J Am Soc Nephrol 2007; 18: 2180-2188.

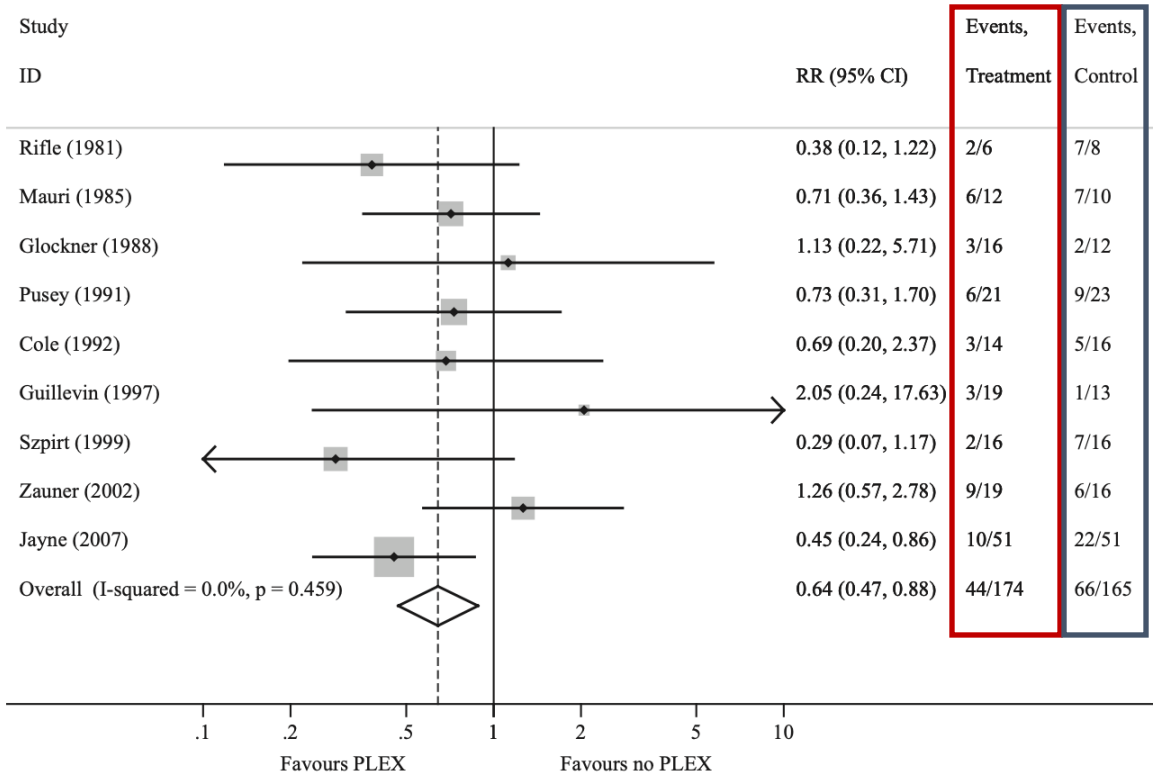
Evidenz nach MEPEX

Mortalität



Keine Differenz

ESKD



Niedrigeres ESKD-Risiko

(follow-up zwischen 12 und 127 Monaten)

Walsh et al. Am J Kidney Dis 2011; 57:566-574.

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PEXIVAS – Studienübersicht

Study population:

- *N=704 patients with AAV*
- *Severe disease: eGFR < 50 ml/min/1.73m² or lung haemorrhage*

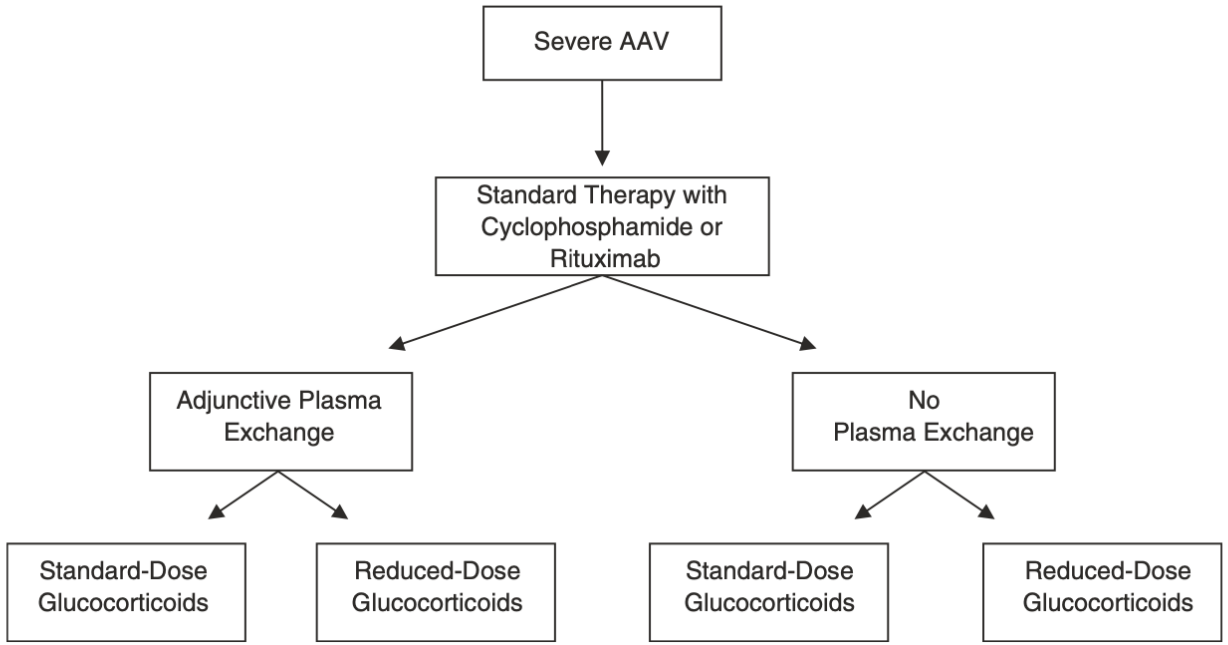
Design:

- *Two-by-two factorial randomized trial*
- *Composite endpoint: end-stage kidney disease (ESKD) or all-cause mortality*

Definition of kidney involvement:

- *kidney biopsy demonstrating focal necrotising glomerulonephritis (GN)* ***or***
- *active urine sediment characterised by glomerular haematuria and proteinuria* ***and***
- *eGFR <50 ml/min per 1.73 m²*

Interventions



to investigate the efficacy of adjunctive PLEX in addition to standard of care immunosuppressive therapy and the efficacy of two different glucocorticoid (GC) regimens (standard versus reduced dose)

Walsh et al. N Eng J Med 2020, 382: 622-631.

PEXIVAS - Patientenkarakteristik

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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
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)
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)

Walsh et al. N Eng J Med 2020, 382: 622-631.

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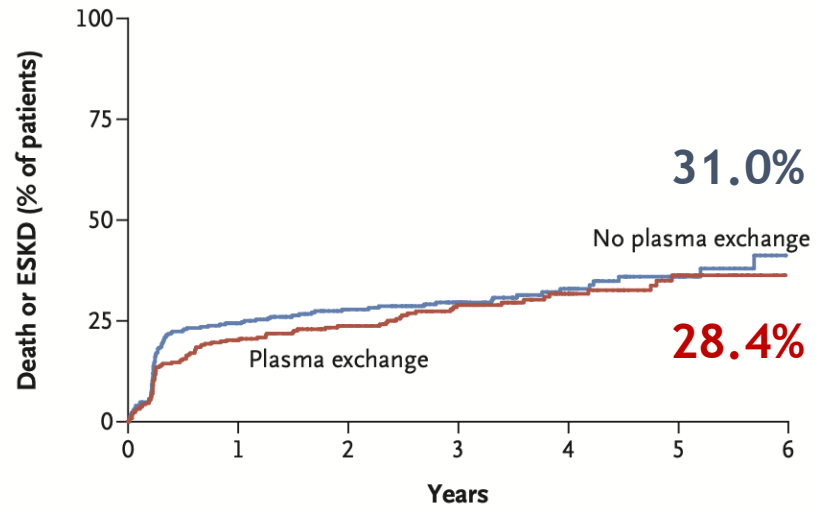
PEXIVAS

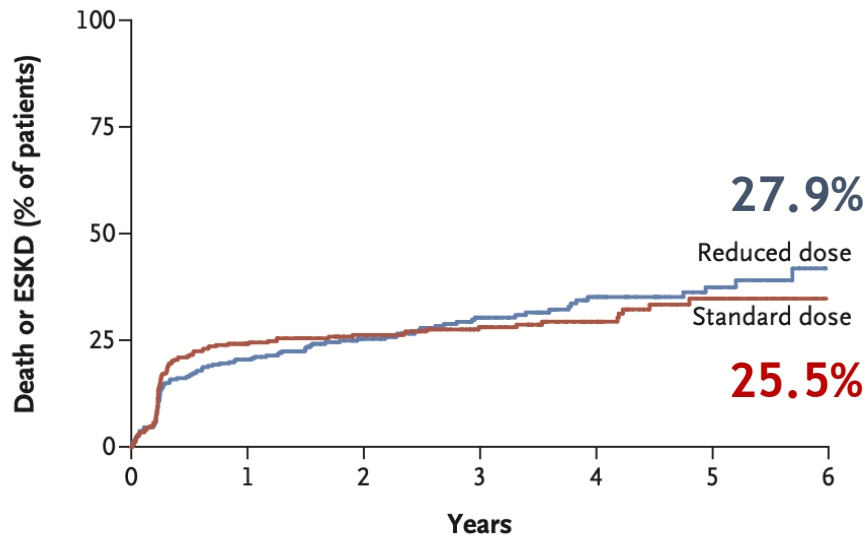
Mediane follow-up Zeit: *2.9 Jahre*
… aber die Wirkung von PLEX setzt sich unmittelbar ein

PLEX



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

Glucocorticoid regimen



No. at Risk							
Reduced dose	353	256	185	133	80	48	9
Standard dose	351	240	184	138	84	39	11

Walsh et al. N Eng J Med 2020, 382: 622-631.

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PEXIVAS - ESKD

Secondary Outcome	*PLEX* Plasma Exchange vs. No Plasma Exchange	*Glucocorticoid regimen* Reduced-Dose vs. Standard-Dose Glucocorticoid Regimen
	effect size (95% CI)	
Death from any cause	0.87 (0.58–1.29)	0.78 (0.53–1.17)
End-stage kidney disease	0.81 (0.57–1.13)	0.96 (0.68–1.34)
Sustained remission	1.01 (0.89–1.15)	1.04 (0.92–1.19)
Serious adverse events	1.21 (0.96–1.52)	0.95 (0.75–1.20)
Serious infections at 1 year	1.16 (0.87–1.56)	0.69 (0.52–0.93)

ESKD nach 1 Jahr: Es wurden keine Unterschiede zwischen den Interventionen festgestellt

Walsh et al. N Eng J Med 2020, 382: 622-631.

MEPEX vs PEXIVAS

Demographics and outcomes of interest	MEPEX IV MeP[a]/PLEX[b]	PEXIVAS PLEX[c]/control[d]
Participants	137 (Europe)	704 (worldwide)
Age (years)	66/67	62.8/63.5
GPA and MPA (%)	35.8 and 64.2/32.9 and 67.1	–
PR3 and MPO (%)	46.3 and 46.3/37.1 and 57.1	40.6 and 59.4/40.6 and 59.4
Serum creatinine, µmol/L	718/754	327/336
Serum creatinine ≥500 µmol/L	[e]	28.7/29.5
Dialysis at baseline (%)	71.6/67.1	18.8/21
Alveolar haemorrhage	[f]	27.0/27.3
Primary endpoint	3 months	Not defined (2.9 years)
Secondary endpoint	12 months	12 months
HR for ESKD	0.47 (95% CI 0.24–0.91) (12 months)	0.81 (95% CI 0.57–1.13)

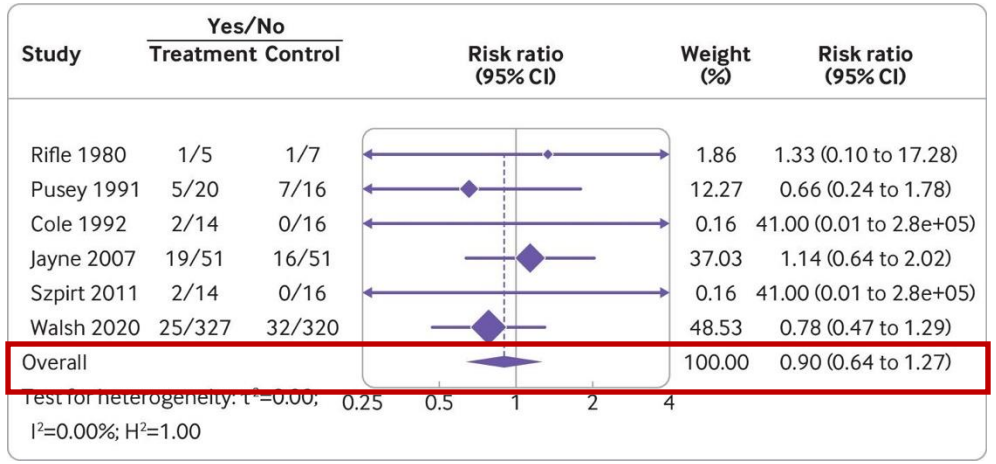
Kronbichler et al. NDT 2021,36(2): 227-231

Evidenz nach PEXIVAS

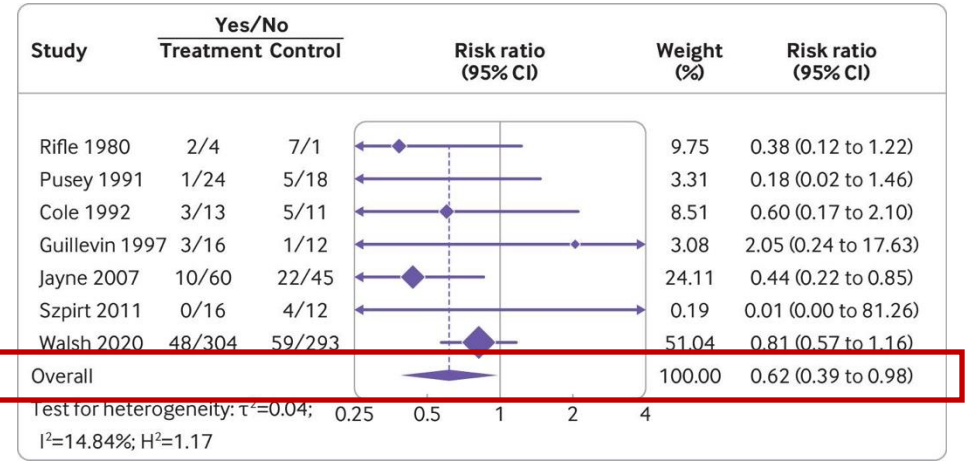
PLEX hatte keine signifikante Auswirkung auf die Mortalität, jedoch verringert das 12-Monats-Risiko einer ESKD und erhöht das Risiko schwerer Infektionen.

- Metaanalyse von 9 PLEX RCTs
- n=1060 PatientInnen mit AAV
- 12 Monaten follow-up Zeit

All-cause mortality



ESKD



Walsh et al. BMJ 2022; 376:e064604

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Nierenfunktion in der Metaanalyse

Certainty assessment						No of patients		Summary effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	PLEX	Ctrl	RR (95% CI)	Absolute difference or MD (95% CI)	Certainty	
End stage kidney disease at 1 year											
7	RCT	NS	NS	NS	NS*	67/504 (13.3%)	0.2%	RR 0.62 (0.39 to 0.98)	1 fewer per 1000 (1 fewer to 0 fewer)	-	
							5.0%		19 fewer per 1000 (31 fewer to 1 fewer)	Moderate (serious imprecision)	
Serum creatinine:						**≥ 300 µmol/l**	11.0%		42 fewer per 1000 (67 fewer to 2 fewer)	Moderate (serious imprecision)	**NNT 23.8**
						≥ 500 µmol/l	38.0%		144 fewer per 1000 (232 fewer to 8 fewer)		**NNT 6.9**
End stage kidney disease at longer term follow-up (median 3 years)											
7	RCT	NS	NS	NS	Serious*	115/501 (23.0%)	139/495 (28.1%)	RR 0.79 (0.58 to 1.08)	59 fewer per 1000 (118 fewer to 22 more)	Low (serious imprecision)	

NNT: number needed to treat; NNH: number needed to harm

Keine Daten bzgl. Nierenfunktionsveränderungen innerhalb von einem Jahr nach Therapieeinleitung.

Walsh et al. BMJ 2022; 376:e064604

Nierenfunktion innerhalb von 1 Jahr: PLEX vs no-PLEX

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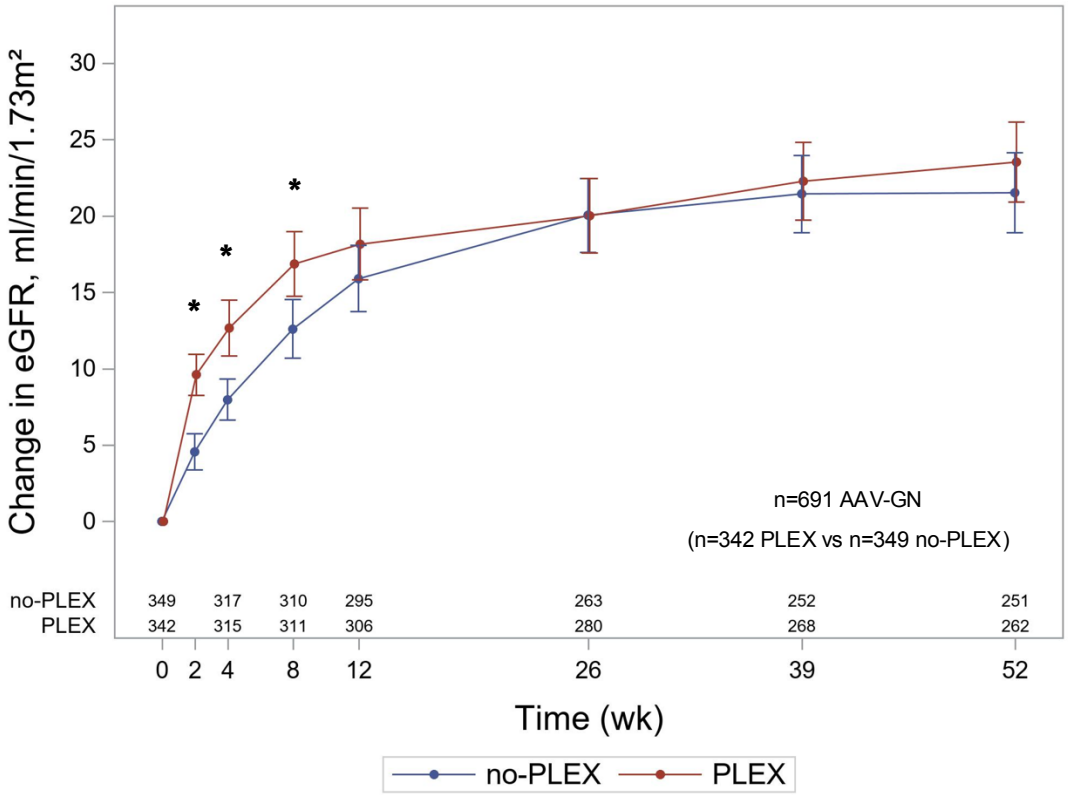
eGFR Veränderung



Weitere primäre (rot) und sekundäre Endpunkte (blau)

Outcome	Week 4	p-value	Week 26	p-value	Week 52	p-value
Recovery of kidney function	1.41 (1.09-1.82)	0.008	1.09 (0.94-1.26)	0.268	1.16 (1.02-1.33)	0.028
Sustained low kidney function	0.76 (0.57-1.01)	0.058	-	-	-	-
Decline in eGFR	0.53 (0.26-1.08)	0.081	-	-	-	-

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*p<0.05; ; red frame: primary endpoints; blue frame: secondary endpoints

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Nierenfunktion innerhalb von 1 Jahr: ESKD

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PLEX vs no-PLEX

	Relative Risk of ESKD	95% Confidence Interval	P-value
Change in eGFR	0.96	0.95 – 0.97	<0.001
Kidney function recovery (yes vs no)	0.29	0.16 – 0.52	<0.001
Sustained low eGFR (yes vs no)	5.11	3.72 – 7.04	<0.001
Decline in eGFR (yes vs no)	1.26	0.64 – 2.49	0.501

Odler B et al. Accepted for publication in Kidney International

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Nierenfunktion innerhalb von 1 Jahr: MPO-ANCA vs PR3-ANCA

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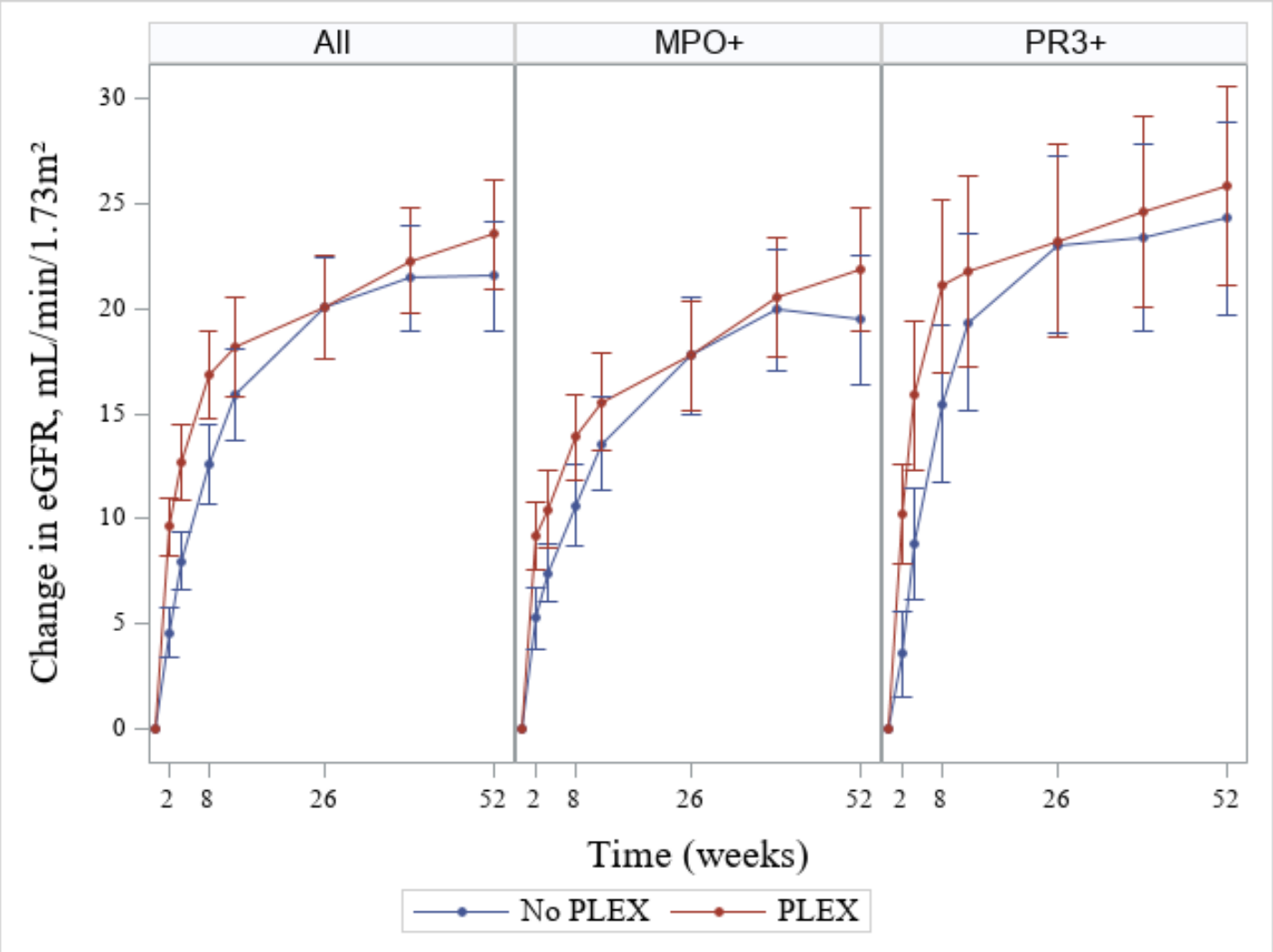
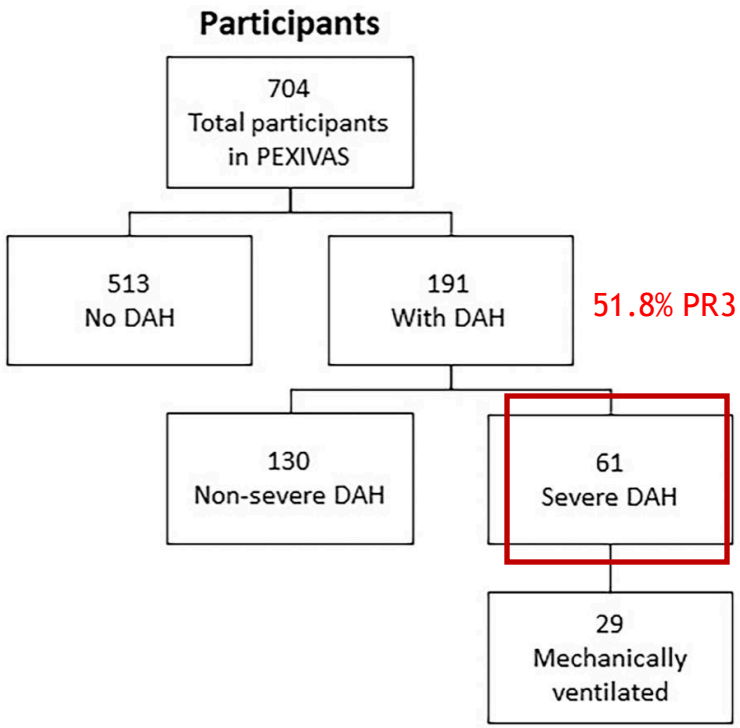


Keine signifikanten Unterschiede ergaben sich bei Subgruppenanalysen für ANCA-Subtypen.

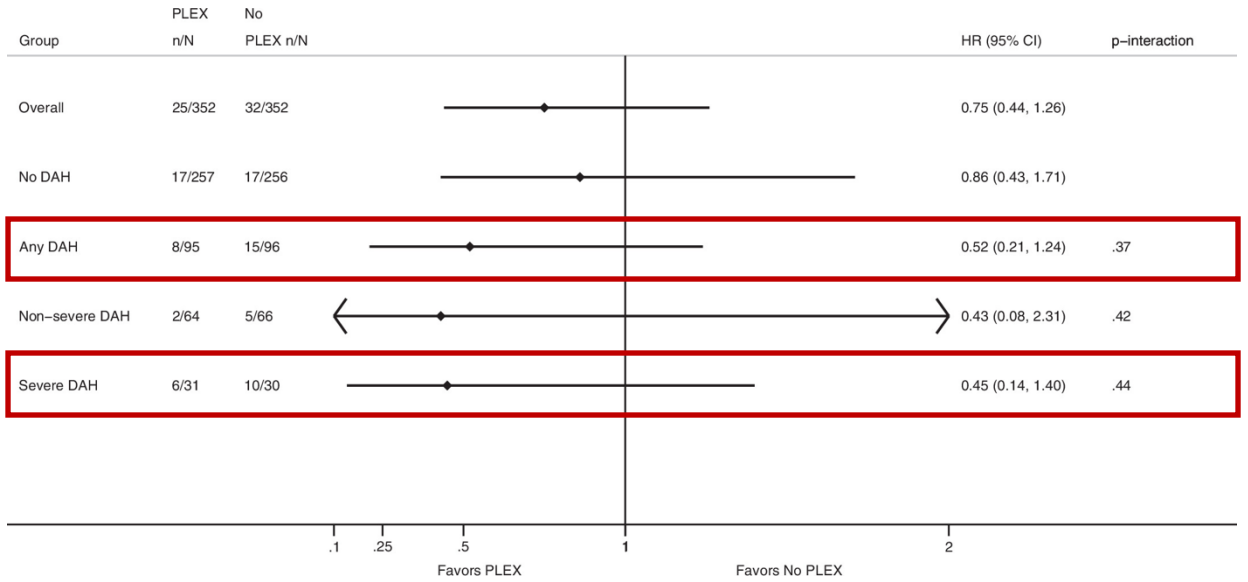
Odler B et al. Accepted for publication in Kidney International

Post-hoc Analyse: alveoläre Hämorrhagie

Die Definition einer schweren DAH war eine Sauerstoffsättigung von ⩽85 % bei Raumluft oder eine mechanische Beatmung.



10 (33.3 %) Patienten in der Kontrollgruppe und 6 (19.4 %) in der PLEX-Gruppe starben innerhalb des ersten Jahres.



Wenn eine **RCT** mit Fokus auf **schwere AH** durchgeführt werden soll, müssten **312 Teilnehmer** auf der Basis der PEXIVAS-Kriterien rekrutiert werden, um zu zeigen, ob die Zugabe von PLEX in einem solchen Szenario einen Nutzen hat oder nicht. Mit anderen Worten: Nahezu **3.600 Patienten** mit schwerer AAV müssten einem **Screening** unterzogen werden, um eine genaue Anzahl von Patienten für eine solche Studie randomisieren zu können.

Fussner et al. Am J Resp Crit Care Med 2023; 209(9): 1141-1151.

Post-hoc Analyse: Krankheitsschübe

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204 Krankheitsschübe bei 147 (22.7%) StudienteilnehmerInnen

Table 2. Results of competing risk regression models in which death competes with the risk of relapse for participants in the PEXIVAS trial*

	Model 1, sHR (95% CI)	Model 2, sHR (95% CI)	Model 3, sHR (95% CI)
Participant characteristics			
Age ≥60 y	0.87 (0.61–1.23)	0.97 (0.68–1.38)	1.04 (0.72–1.50)
PR3-ANCA vs MPO-ANCA	**2.12 (1.52–2.96)**	**1.91 (1.32–2.75)**	**1.77 (1.22–2.59)**
Female vs male	NA	0.73 (0.52–1.02)	0.75 (0.53–1.06)
Relapsing disease	NA	0.99 (0.58–1.69)	0.93 (0.53–1.62)
Treatment			
Reduced-dose glucocorticoids	0.93 (0.67–1.29)	0.94 (0.68–1.30)	0.94 (0.68–1.30)
Use of plasma exchange	0.91 (0.66–1.26)	0.94 (0.67–1.30)	0.94 (0.68–1.31)
Intravenous cyclophosphamide	Referent	Referent	Referent
Rituximab	0.72 (0.44–1.18)	0.70 (0.40–1.22)	0.72 (0.41–1.28)
Oral cyclophosphamide	**0.63 (0.43–0.93)**	**0.57 (0.39–0.85)**	**0.52 (0.34–0.78)**
BVAS/WG score	NA	1.20 (1.06–1.36)	NA
Disease manifestations			
Need for dialysis or serum creatinine >500 μ*M*	**0.57 (0.38–0.86)**	NA	NA
Serum creatinine, μ*M*	NA	0.9995 (0.999–1.0004)	0.9996 (0.999–1.0004)
On dialysis	NA	**0.49 (0.28–0.86)**	**0.48 (0.27–0.86)**
No pulmonary hemorrhage	Referent	Referent	Referent
Pulmonary hemorrhage	0.92 (0.59–1.42)	0.75 (0.47–1.19)	0.83 (0.52–1.31)
Severe pulmonary hemorrhage	0.93 (0.49–1.75)	0.76 (0.38–1.50)	0.70 (0.35–1.37)
Nonhemorrhagic respiratory	NA	NA	**1.44 (1.003–2.07)**
Constitutional	NA	NA	1.32 (0.91–1.91)
Cutaneous	NA	NA	1.55 (0.997–2.44)
Mucous membrane and eye	NA	NA	1.40 (0.90–2.18)
Ears, nose, and throat	NA	NA	0.99 (0.67–1.45)
Cardiac	NA	NA	2.96 (0.75–11.7)
Gastrointestinal	NA	NA	1.21 (0.10–15.10)
Neurologic	NA	NA	0.60 (0.30–1.23)

Junek ML et al. Arthritis Rheum 2024; 76(9): 1431-1438.

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PEXIVAS - Infektionen

Secondary Outcome	*PLEX* Plasma Exchange vs. No Plasma Exchange	*Glucocorticoid regimen* Reduced-Dose vs. Standard-Dose Glucocorticoid Regimen
	effect size (95% CI)	
Death from any cause	0.87 (0.58–1.29)	0.78 (0.53–1.17)
End-stage kidney disease	0.81 (0.57–1.13)	0.96 (0.68–1.34)
Sustained remission	1.01 (0.89–1.15)	1.04 (0.92–1.19)
Serious adverse events	1.21 (0.96–1.52)	0.95 (0.75–1.20)
Serious infections at 1 year	1.16 (0.87–1.56)	0.69 (0.52–0.93)

Schwere Infektionen nach 1 Jahr: Kein signifikanter Trend, dass PLEX das Risiko schwerer Infektionen erhöht; reduziertes GC-Schema war mit einer 31%igen Reduktion schwerer Infektionen assoziiert.

Walsh et al. N Eng J Med 2020, 382: 622-631.

PEXIVAS - Infektionen

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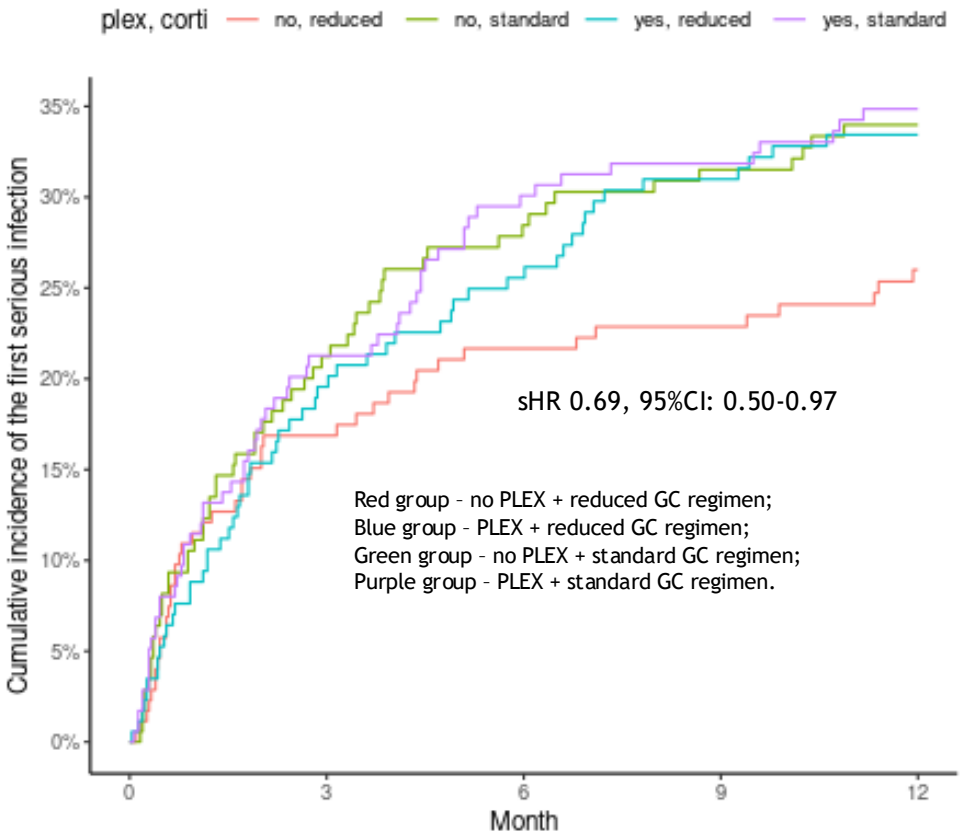
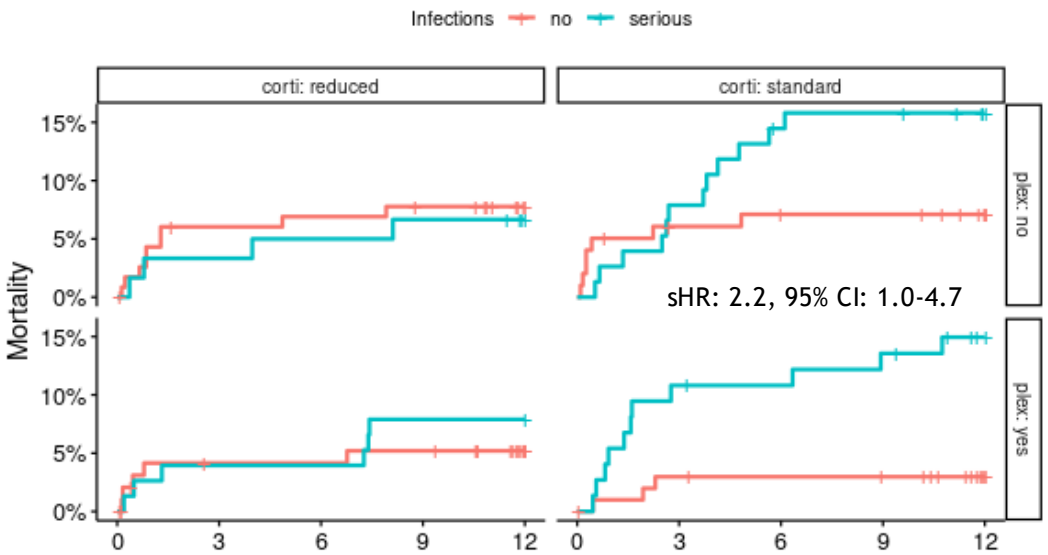
Kumulative Inzidenz der ersten schweren Infektionen



1-Jahres Überleben



Matyjek A et al. Manuscript in preparation. With permission.

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Schwere Infektionen

RAVE Trial, niedrige Frequenz

Variable	Rituximab (N=99)	Cyclophosphamide–Azathioprine (N=98)	Total (N=197)	P Value
Total no. of participant-months	1371.5	1331.9	2703.4	
Deaths — no. (%)†	2 (2)	2 (2)	4 (2)	
Participants with ≥1 episode of leukopenia of grade 2 or higher — no. (%)	5 (5)	23 (23)	28 (14)	<0.001
Participants with ≥1 episode of infection of grade 3 or higher — no. (%)	12 (12)	11 (11)	23 (12)	>0.99
Pneumonia-related adverse events				
Total no. of events	4	11	15	
Participants with ≥1 episode of pneumonia — no. (%)	3 (3)	11 (11)	14 (7)	0.03
Pneumonia-related adverse events/participant-mo	0.0029	0.0083	0.0055	0.08

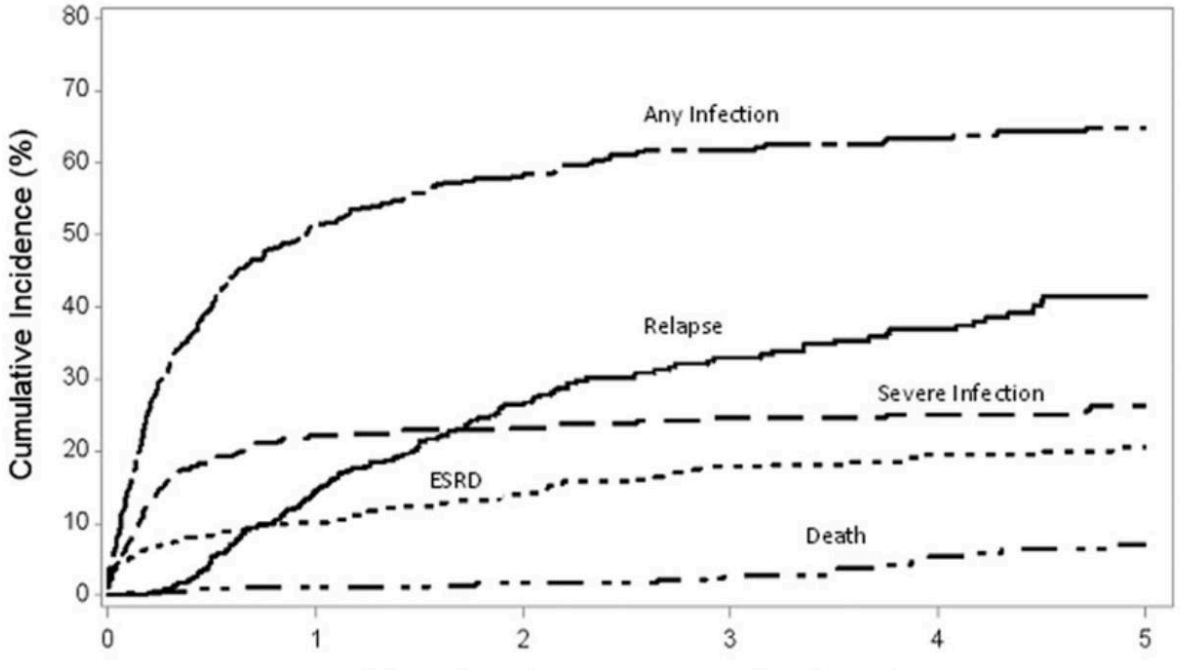
Specks U et al. N Engl J Med 2013; 369:417-27.

Schwere Infektionen

Infektionen treten früh im Krankheitsverlauf auf.

Einfluss demographischer und krankheitsbezogener Faktoren

Wichtiger Mortalitätsprediktor



	0 infections (n=123)	Non-severe infections (n=155)	Severe infection (n=96)
Age	52 ± 19	56 ± 18	59 ± 18
Female sex	39%	50%	59%
Steroid-induced DM	20%	23%	45%
eGFR (BL) ml/min/1.73 m^2	24	25	17
Death from any cause	7%	6%	25%

McGregor JAG et al. Nephrol Dial Transplant 2015; 30:i171-i181.

Antibiotische Prophylaxe

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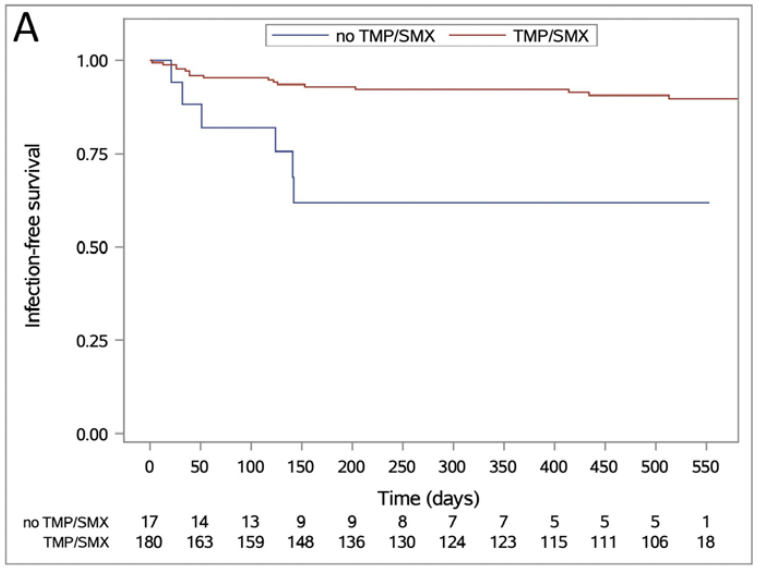
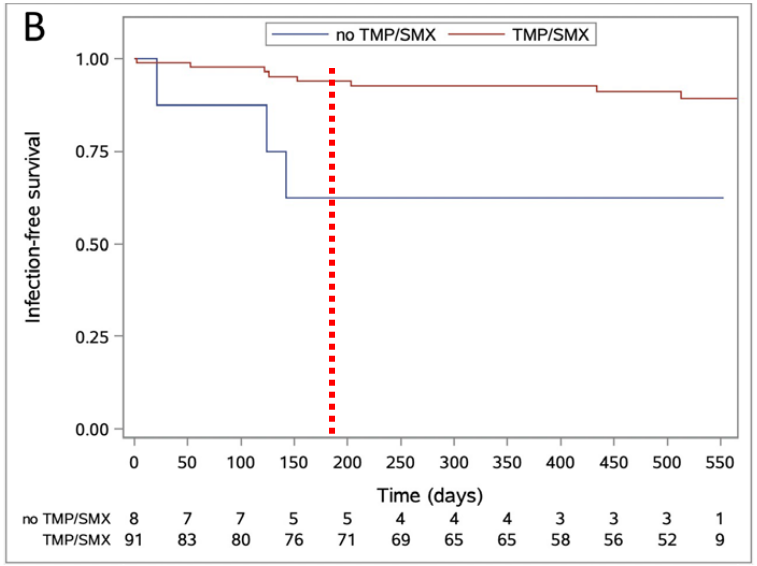
RAVE Trial, n=22 schwere Infektionen binnen18-monatigen Follow-up

Gesamte Studienpopulation

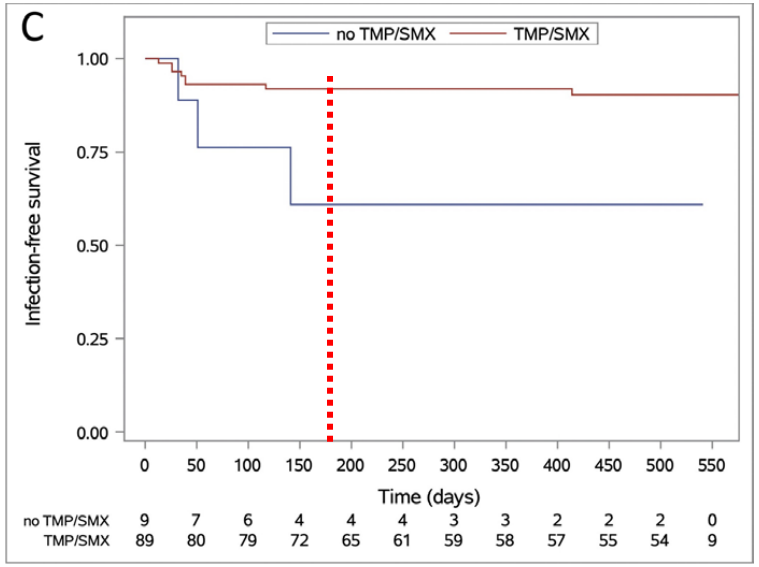


Rituximab



HR: 0.204; 95% CI: 0.054-0.772; p=0.019

CYC/AZA



HR: 0.232; 95% CI: 0.061-0.884; p=0.032

Niedrig dosierte PJP-Prophylaxe mit Trimethoprim/Sulfamethaxazol war mit einem geringeren Risiko für schwere Infektionen jeglicher Art verbunden.

Odler B et al. Ann Rheum Dis 2023, 82(5):681-687.

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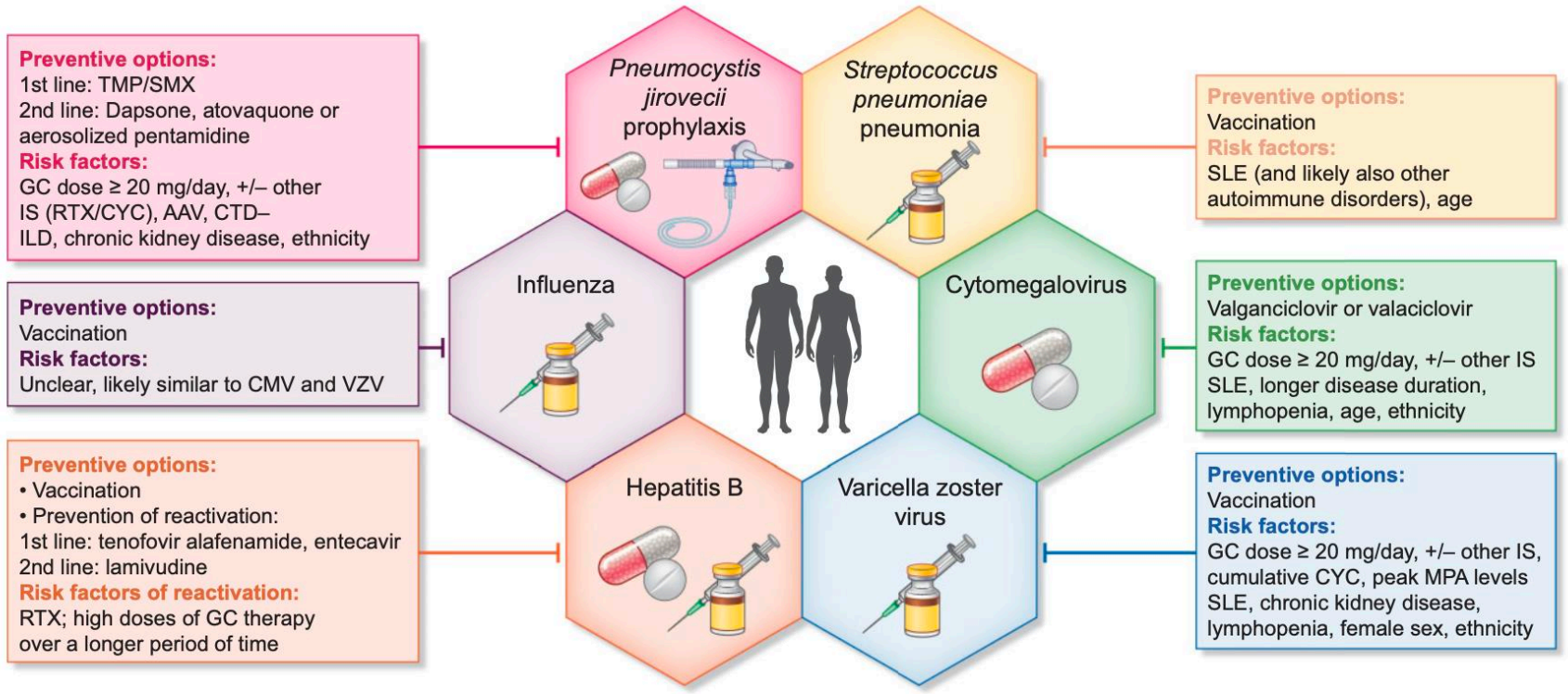
Prophylaktische Maßnahmen



Windpessl M et al. Nephrol Dial Transplant 2023, 38(Supplement_2):ii40-ii49.

Zusammenfassung

- Hohe Mortalitätsraten – Infektionen und eingeschränkte Nierenfunktion als wichtige Prädiktoren
- PLEX ist eine zusätzliche Behandlungsoption:
  - bessere Erholung der Nierenfunktion nach Therapieeinleitung und ESKD-Outcome nach 1 Jahr
  - kein statistisch signifikanter Effekt auf die DAH, aber die Einschränkungen der bisherigen Studien sollten berücksichtigt werden;
  - reduziert nicht das Rezidivrisiko
  - Erhöhtes Infektrisiko
  - PLEX sollte nach individueller Entscheidung in Erwägung gezogen werden
- Schwere Infektionen können zum Teil durch Prophylaxe gemildert werden; vergessen Sie nicht die Präventivmaßnahmen (Impfungen!)

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Vielen Dank für Ihre Aufmerksamkeit!

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Gekürzte Verschreibungsinformationen

Schweiz:

Tavneos®. Z: Avacopan. **I:** Tavneos, als ergänzende Therapie zu einer immunsuppressiven Standardbehandlung auf Basis von Rituximab oder Cyclophosphamid mit Glukokortikoiden, ist für die Behandlung erwachsener Patienten mit schwerer aktiver ANCA Vaskulitis (GPA/MPA) indiziert. **D:** Orale Einnahme morgens und abends 2x täglich 30 mg (3 Kapseln zu je 10 mg) mit Nahrung. **KI:** Überempfindlichkeit gegen den Wirkstoff oder einen der Hilfsstoffe. **VM:** Hepatotoxizität; Angioödem; Überwachung des Blutbildes (weisse Blutkörperchen); Schwere Infektionen; Reaktivierung des Hepatitis-B-Virus; Herzbeschwerden; Bösartige Tumore; Macroglycerinhydroxystearat. **S/S:** Eine Anwendung während der Schwangerschaft und bei Frauen im gebärfähigen Alter, die keine Verhütungsmethode anwenden, ist nicht empfohlen. Es ist nicht bekannt, ob Avacopan in die Muttermilch ausgeschieden wird. Der Nutzen des Stillens für das Kind sollte gegen den Nutzen der Behandlung für die Patientin abgewogen werden. **UW:** Sehr häufig: Infektion der oberen Atemwege, Nasopharyngitis; Kopfschmerzen; Erbrechen, Durchfall, Übelkeit; erhöhter Lebertest; verminderte Anzahl weisser Blutkörperchen. Häufig: Lungenentzündung, Infektion der unteren Atemwege, Influenza, Bronchitis, Zellulitis, Infektion der Harnwege, Herpes zoster, Sinusitis, orale Candidose, Herpes im Mundbereich, Otitis media, Rhinitis, Gastroenteritis; Neutropenie; Oberbauchschmerzen; Anstieg der Kreatinphosphokinase im Blut. Gelegentlich: Angioödeme. **IA:** Avacopan ist ein Substrat von CYP3A4. Die gleichzeitige Verabreichung von Induktoren oder Inhibitoren dieses Enzyms kann die Pharmakokinetik von Avacopan beeinflussen. Siehe Fachinformation. **P:** Tavneos 10 mg: 30 und 180 Hartkapseln. **Liste B**. Detaillierte Informationen**:** www.swissmedicinfo.ch. Stand der Information**:** Januar 2024. **Zulassungsinhaberin:** Vifor Fresenius Medical Care Renal Pharma Ltd., St. Gallen. **Vertrieb:** Vifor Pharma Switzerland AG, CH-1752 Villars-sur-Glâne |

▼Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Für weitere Informationen, siehe Fachinformation TAVNEOS® auf www.swissmedicinfo.ch.

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Tavneos® Fachkurzinformation
Tavneos®10mg Hartkapsel

Zusammensetzung: Jede Hartkapsel enthält 10 mg Avacopan. Sonstige Bestandteile mit bekannter Wirkung:245 mg Macrogolglycerolhydroxystearat(Ph.Eur). **Anwendungsgebiete:** Tavneos® ist in Kombination mit einem Rituximab- oder Cyclophopamid-Dosierungsschema indiziert zur Behandlung erwachsener Patienten mit schwerer aktiver Granulomatose mit Polyangiitis (GPA) oder mikroskopischer Polyangiitis (MPA). **Gegenanzeigen:** Überempfindlichkeit gegen den Wirkstoff oder einen der sonstigen Bestandteile. **Pharmakotherapeutische Gruppe:** Komplement-Inhibitoren **ATC- Code:** L04AJ05 **Inhaber der Zulassung:** Vifor France, 100-101 Terrasse Boieldieu Tour Franklin La Defense 8 92042 Paris La Defense Cedex, Frankreich. Rezept- und apothekenpflichtig. Weitere Angaben zu Warnhinweisen und Vorsichtsmaßnahmen für die Anwendung, Wechselwirkungen mit anderen Arzneimitteln oder sonstigen Wechselwirkungen, Schwangerschaft und Stillzeit und Nebenwirkungen sowie Gewöhnungseffekten sind der veröffentlichten Fachinformation zu entnehmen. Stand der Information: Mai 2023

▼Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Dies ermöglicht eine schnelle Identifizierung neuer Sicherheitsdaten. Angehörige der Gesundheitsberufe werden gebeten, alle Verdachtsfälle von unerwünschten Wirkungen zu melden.