SUPPLEMENTARY APPENDIX 2: Evidence Report

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of ANCA-Associated Vasculitis

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Diagnostic Testing

- **PICO question 1:** In patients with GPA or MPA, what is the impact of obtaining ANCA levels/titers at fixed intervals vs. not obtaining ANCA levels/titers on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, serious adverse events, toxicity leading to discontinuation

1. In patients with GPA or MPA, what is the impact of obtaining ANCA levels/titers at fixed intervals vs. not obtaining ANCA levels/titers on disease-related outcomes and treatment-related adverse events?
   To analyze the relationship between relapse and ANCA presence, the pool of studies divide the patients into negative conversion and non-negative conversion groups, and they divide them into ANCA reappearance and non-ANCA reappearance groups. Negative conversion was defined when a patient presented with disappearance of MPO- ANCA without relapse by month 6, or had a relapse by month 6 with disappearance of MPO-ANCA before the relapse. Reappearance of MPO-ANCA was defined as conversion from negative to positive after fulfilling the above definition of negative conversion.

   - **Conversion to negative ANCA vs No Conversion to negative ANCA Subgroup analysis:**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Conversion to negative ANCA	No Conversion to negative ANCA	Relative (95% CI)	Absolute (95% CI)		
No of patients with relapse												
7 [a,b,c,d,e,f,g]	observational studies	serious [h]	very serious [i]	not serious	very serious [j]	none	132/479 (27.6%)	75/180 (41.7%)	**OR 0.47** (0.19 to 1.18)	**230 more per 1,000** (from 140 fewer to 590 more)	⨁◯◯◯ VERY LOW	
Mortality												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Conversion to negative ANCA	No Conversion to negative ANCA	Relative (95% CI)	Absolute (95% CI)		
1 [b]	observational studies	serious [h]	not serious	not serious	serious [j]	none	13/195 (6.7%)	3/76 (3.9%)	**OR 1.74** (0.48 to 6.28)	**27 more per 1,000** (from 20 fewer to 166 more)	⨁◯◯◯ VERY LOW	

ESRD-free survival

1 [b]	observational studies	serious [h]	not serious	not serious	serious [j]	none	174/195 (89.2%)	69/76 (90.8%)	**OR 0.84** (0.34 to 2.07)	**16 fewer per 1,000** (from 138 fewer to 45 more)	⨁◯◯◯ VERY LOW	

Relapse Risk

1 [k]	observational studies	not serious	not serious	not serious	serious [j]	none	-/0	-/0	**HR 0.63** (0.42 to 0.95)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	

Time to acheive sustained remission

1 [l]	observational studies	serious [m]	not serious	not serious	serious [j]	none	-/0	-/0	**HR 1.60** (0.97 to 2.64)	**2 fewer per 1,000** (from 3 fewer to 1 fewer)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio; **HR:** Hazard Ratio

Explanations

a. Kyndt, 1999

b. Watanabe, 2018

c. Yamaguchi, 2015

d. Girard, 2001

e. Jayne, 1995

f. Sanders, 2006

g. Terrier, 2008

h. The selection of the intervention group not representative, mostly MPO-ANCA patients.

i. the effect estimate (OR) in Kyndt,1999 does not meet with the confidence interval of the OR in both Watanabe,2018 and Yamaguchi,2015. Heterogeneity I2= 93%

j. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

k. Morgan, 2017

l. Finkelman, 2007

m. The selection of the intervention group not representative, only PR3 patients.

- **Reappearance of ANCA vs No reappearance of ANCA Subgroup analysis:**

- Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reappearance of ANCA	No reappearance of ANCA	Relative (95% CI)	Absolute (95% CI)		
No of patients with Relapse												
8 [a,b,c,d,f,g,h,i]	observational studies	serious [e,j]	not serious	not serious	not serious	strong association	86/188 (45.7%)	21/235 (8.9%)	**OR 8.74** (3.71 to 20.59)	**372 more per 1,000** (from 178 more to 580 more)	⨁⨁◯◯ LOW	

CI: Confidence interval; **OR:** Odds ratio; **HR:** Hazard Ratio

Explanations

a. Watanabe, 2018

b. Yamaguchi, 2015

c. Jayne, 1995

d. Terrier, 2008

e. The selection of the intervention group not representative, mostly MPO-ANCA patients.

f. Han, 2003

g. Boomsa, 2000

h. Gaskin, 1991

i. Cohen Tervaert, 1989

j. High risk of confounding by indication, since treatment was manipulated (and thus risk of relapse) based on even small changes of ANCA titers.

- **References:**

- Randomized controlled trials:

None

- Comparative observational studies:

Author	Year	Title
H. Watanabe	2018	Association between reappearance of myeloperoxidase-antineutrophil cytoplasmic antibody and relapse in antineutrophil cytoplasmic antibody-associated vasculitis: Subgroup analysis of nationwide prospective cohort studies
M. D. Morgan	2017	Negative anti-neutrophil cytoplasm antibody at switch to maintenance therapy is associated with a reduced risk of relapse
M. Yamaguchi	2015	Increase of Antimyeloperoxidase Antineutrophil Cytoplasmic Antibody (ANCA) in Patients with Renal ANCA-associated Vasculitis: Association with Risk to Relapse
J. Finkielman	2007	Antiproteinase 3 antineutrophil cytoplasmic antibodies and disease activity in Wegener granulomatosis
W. K. Han	2003	Serial ANCA titers: useful tool for prevention of relapses in ANCA-associated vasculitis
M. Boomsma	2000	Prediction of relapses in Wegener's granulomatosis by measurement of antineutrophil cytoplasmic antibody levels: a prospective study
X. Kyndt	1999	Serial measurements of antineutrophil cytoplasmic autoantibodies in patients with systemic vasculitis
Jayne DR	1995	ANCA and predicting relapse in systemic vasculitis.
Gaskin G	1991	Anti-neutrophil cytoplasmic antibodies and disease activity during long-term follow-up of 70 patients with systemic vasculitis.
Girard T	2001	Are antineutrophil cytoplasmic antibodies a marker predictive of relapse in Wegener's granulomatosis? A prospective study.
Terrier B	2008	Antimyeloperoxidase antibodies are a useful marker of disease activity in antineutrophil cytoplasmic antibody-associated vasculitides.
Cohen-Tervaert JW	1989	Association between active Wegener's granulomatosis and anticytoplasmic antibodies.

- Studies reviewed and excluded:

Author	Year	Title	Comments
E. Sproson	2007	Lessons learnt in the management of Wegener's Granulomatosis: long-term follow-up of 60 patients	Excluded, single arm
F. Lurati-Ruiz	2005	Predictive value of antineutrophil cytoplasmic antibodies in small-vessel vasculitis	Excluded, Test accuracy study
R. A. Sinico	2005	Value of a new automated fluorescence immunoassay (EliA) for PR3 and MPO-ANCA in monitoring disease activity in ANCA-associated systemic vasculitis	Excluded, Test accuracy study
M. M. Boomsma	2003	Image analysis: a novel approach for the quantification of antineutrophil cytoplasmic antibody levels in patients with Wegener's granulomatosis	Excluded for GPA PICO1 but please include for ANCA Test Accuracy
R. Nowack	2001	ANCA titres, even of IgG subclasses, and soluble CD14 fail to predict relapses in patients with ANCA-associated vasculitis	Excluded for GPA PICO1, please include for ANCA Test Accuracy
A. Davenport	1995	Clinical significance of the serial measurement of autoantibodies to neutrophil cytoplasm using a standard indirect immunofluorescence test	Excluded for GPA PICO 1 (not enough patient level data to abstract), but has ANCA Test Accuracy data
G. S. Kerr	1993	Limited prognostic value of changes in antineutrophil cytoplasmic antibody titers in patients with Wegener's granulomatosis	Excluded for GPA PICO 1 (Case series, not enough data for comparison abstraction), include for ANCA Test accuracy
C. Geffriaud-Ricouard	1993	Clinical significance of ANCA in 98 patients	Excluded for GPA PICO1 (only single arm for reappearance; vague language; not enough data to abstract)
J. W. Tervaert	1990	Prevention of relapses in Wegener's granulomatosis by treatment based on antineutrophil cytoplasmic antibody titre	This study does not address the PICO question
R Pepper	2015	The association of serum calprotectin (S100A8/A9) levels with disease relapse in PR3-ANCA associated vasculitis	This paper did not discuss about ANCA level. It was about different biomarker - calprotectin

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Induction

- **PICO question 2:** In patients with active severe GPA/MPA, what is the impact of using pulse intravenous vs. high-dose oral glucocorticoids for remission induction on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, serious adverse events, toxicity leading to discontinuation (e.g., hyperglycemia, decreased bone mineral density)

2. In patients with active severe GPA/MPA, what is the impact of using pulse intravenous vs. high-dose oral glucocorticoids for remission induction on disease-related outcomes and treatment-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pulse intravenous	high-dose oral glucocorticoids	Relative (95% CI)	Absolute (95% CI)		
Death												
1 [a]	observational studies	not serious	not serious	not serious	serious [b]	strong association	11/57 (19.3%)	20/54 (37.0%)	**OR 0.41** (0.17 to 0.96)	**176 fewer per 1,000** (from 279 fewer to 9 fewer)	⨁⨁◯◯ LOW	
Dialysis Free Survival												
1 [a]	observational studies	not serious	not serious	not serious	serious [b]	strong association	21/57 (36.8%)	4/54 (7.4%)	**OR 7.29** (2.30 to 23.07)	**294 more per 1,000** (from 81 more to 575 more)	⨁⨁◯◯ LOW	
Survival at 12 months												
1 [c]	observational studies	serious [d]	not serious	not serious	serious [b]	none	44/52 (84.6%)	51/62 (82.3%)	**OR 1.19** (0.44 to 3.21)	**24 more per 1,000** (from 152 fewer to 114 more)	⨁◯◯◯ VERY LOW	
Renal Recovery at 12 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pulse intravenous	high-dose oral glucocorticoids	Relative (95% CI)	Absolute (95% CI)		
1 [c]	observational studies	serious [d]	not serious	not serious	serious [b]	none	30/52 (57.7%)	41/62 (66.1%)	**OR 0.70** (0.33 to 1.50)	**84 fewer per 1,000** (from 269 fewer to 84 more)	⨁◯◯◯ VERY LOW	

Relapse at 12 months

1 [c]	observational studies	serious [d]	not serious	not serious	serious [b]	none	6/52 (11.5%)	5/62 (8.1%)	**OR 1.49** (0.43 to 5.18)	**35 more per 1,000** (from 44 fewer to 232 more)	⨁◯◯◯ VERY LOW	

Severe Infection at 3 months

1 [c]	observational studies	serious [d]	not serious	not serious	not serious	strong association	19/52 (36.5%)	12/62 (19.4%)	**OR 2.40** (1.03 to 5.59)	**172 more per 1,000** (from 5 more to 379 more)	⨁⨁◯◯ LOW	

New diagnosis of Diabetes Mellitus at 12 months

1 [c]	observational studies	serious [d]	not serious	not serious	not serious	very strong association	14/52 (26.9%)	4/62 (6.5%)	**OR 5.34** (1.63 to 17.46)	**205 more per 1,000** (from 37 more to 482 more)	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Ma, 2017

b. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

c. Chanouzas, 2019

d. Significantly less Caucasian, more DAH, less other lung diseases, less ENT disease, more PLEX, less CYC, and less oral prednisolone in the IVMP group. Researchers attempted to control for these but it seems clear the two groups were different, raising a risk of confounding by indication. IVMP group seem more likely to have been hospitalized (more DAH, less PO glucocorticoids) but this specifically is not commented on.

3. In patients with active severe GPA/MPA, what is the impact of using pulse intravenous glucocorticoids for remission induction on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Mortality – Early (induction phase or less than one year) mortality ranged from 8% to 17% and long term mortality ranged from 20-41% in protocols with pulse IVMP used. Five studies with 168 patients total with consistent results..	Kamali, 2005	Retrospective cohort, single center	37 months (median)	23 patients with WG per ACR 1990 criteria (11F, mean age @ dx 43.7y, mean dz duration 36m) – Only 1 pt lost to follow up.	"All patients were treated according to the same protocol with minor modifications including pulse and high-dose (1mg/kg body weight) daily prednisolone and pulse CYC for remission induction."	41% mortality at 35 months.
	Andreiana, 2015	Single center, retrospective cohort	3.2 years, median	75 patients with ANCA positive pauci-immune GN by biopsy (52%F, mean age 60, median BVAS 17, 27% required HD, 31% had severe DAH, 76% MPO-ANCA)	All pts received induction with IVMP 0.5-1.0g x 3 days, then prednisone 0.5mgkg per day, tapered after one month, with IV CYC (2 pulses in first month, then monthly for 5 months).	32% mortality by end of observation. - 1 year mortality (12%) - 5 year mortality (33%)
	Geetha, 2016	Multicenter, multinational, retrospective cohort	973 days (median)	37 patients with GPA or MPA with active GN and e GFR <20 (mean age 61, 14F, 22 MPO ANCA, 78% new dx, 30% DAH, 40% HD initially)	All patients treated with IVMP x 3 days and either RTX+CYC or RTX	3/37 (8%) died by 6 months.
	Grcevska, 2011	Single Center, retrospective cohort	2 months to 8 years	18 patients with WG (All had either positive ANCA or	Induction: IVMP 0.5mg-1.0mg/kg/d x 3 days with prednisne 0.5mg/kg/d) and pulse CYC protocol.	3/18 (17%) died in induction period (respiratory failure secondary to vasculitis in 2, GI bleeding in one).

				positive renal biopsy) -6F -mean age 48.6y	Some patients received PLEX.	
	Salvidio, 1991	Single center, restrospective cohort	Up to 4 years	15 patients with renal MPA (positive renal bx, no RA/HSP/Cryo/SLE/Cancer/suspect drug)	All pt received IVMP 15mg/kg x 3 days, then tapered to prednisone 0.8-1.0mg/kg daily and tapered further), CYC PO for one year.	6 months (overall mortality 8%) 12 months (overall mortality 16%) 24 months (overall mortality 20%)
Relapse – Data is sparse on relapse rates in cohorts using IVMP during induction. One study with 23 patients.	Kamali. 2005	Retrospective cohort, single center	37 months (median)	23 patients with WG per ACR 1990 criteria (11F, mean age @ dx 43.7y, mean dz duration 36m) – Only 1 pt lost to follow up.	"All patients were treated according to the same protocol with minor modifications including pulse and high-dose (1mg/kg body weight) daily prednisolone and pulse CYC for remission induction."	2/23 patients relapsed (though 9/23 patients died in induction phase).
Renal Recovery – In general, renal recovery or long term avoidance of HD dependence appear to be achievable goals in most (50%+) of patients when IVMP is used. Five studies with 164 patients total.	Kamali, 2005	Retrospective cohort, single center	37 months (median)	23 patients with WG per 1990 ACR criteria. 10 patients required HD at induction.	"All patients were treated according to the same protocol with minor modifications including pulse and high-dose (1mg/kg body weight) daily prednisolone and pulse CYC for remission induction."	1/10 had renal recovery.
	Andreiana, 2015	Single center, retrospective cohort	3.2 years, median	75 patients with ANCA positive pauci-immune GN by biopsy (52%F, mean age 60, median BVAS 17, 27% required HD, 31% had severe	All pts received induction with IVMP 0.5-1.0g x 3 days, then prednisone 0.5mgkg per day, tapered after one month, with IV CYC (2 pulses in first month, then monthly for 5 months).	Of the 51 patients alive at end of observation period, 38 (51% of whole cohort) were HD-free.

				DAH, 76% MPO-ANCA)		
	Shah, 2015	Single center, retrospective cohort	553 days (median)	14 patients with AAV/ANCA-negative SVV with severe renal disease treated with RTX and GC	All patients treated with IVMP 1g x 3 days, then prednisone 1mg/kg/day with taper. All patients treated with RTX. 11/14 tx with PJP ppx.	Of the 7 patients who required HD, 5 patients recovered renal function and discontinued HD by 6 months.
	Geetha, 2016	Multicenter, multinational, retrospective cohort	973 days (median)	37 patients with GPA or MPA with active GN and e GFR <20 (mean age 61, 14F, 22 MPO ANCA, 78% new dx, 30% DAH, 40% HD initially)	All patients treated with IVMP x 3 days and either RTX+CYC or RTX	Of the 15 patients on HD at presentation, 10 (67%) experienced renal recovery (were able to come off HD).
	Salvidio, 1991	Single center, restrospective cohort	Up to 4 years	15 patients with renal MPA (positive renal bx, no RA/HSP/Cryo/SLE/Cancer/suspect drug)	All pt received IVMP 15mg/kg x 3 days, then tapered to prednisone 0.8-1.0mg/kg daily and tapered further), CYC PO for one year.	6 months (renal survival 75%) 12 months (renal surgical 67%) 2 years (renal survival 60%)
Serious Infection – Infections are common in this population, regardless of if IVMP is used. Serious infections appear to happen in ~30% of patients. Four studies with 300 total patients.	Watanabe, 2017	Prospective, multicenter national registry of newly dx AAV	Induction + six months (scope of the study)	156 pts with AAV -78 with MPA/RLV (mean age 71y, 35F, 97% MPO-ANCA) -33 GPA (mean age 63y, 12F, 54% MPO-ANCA) -14 EGPA -31 “unclassifiable	62/156 (39.7%) received pulse methylprednisolone for induction. All but 2 received prednisolone orally. 68/156 (43.5%) received CYC.	No difference in rate of pulse IVMP use (42.1% v 33.3%, p=0.321) between those without serious infection and those with serious infection. 42/156 (27%) total had serious infection.
	Shah, 2015	Single center, retrospective cohort	553 days (median)	14 patients with AAV/ANCA-negative SVV with severe renal disease treated with RTX and GC	All patients treated with IVMP 1g x 3 days, then prednisone 1mg/kg/day with taper. All patients treated with RTX.	2/14 patients developed infection requiring hospitalization (pneumonia, herpes zoster)

					11/14 tx with PJP ppx.	
	Geetha, 2016	Multicenter, multinational, retrospective cohort	973 days (median)	37 patients with GPA or MPA with active GN and e GFR <20 (mean age 61, 14F, 22 MPO ANCA, 78% new dx, 30% DAH, 40% HD initially)	All patients treated with IVMP x 3 days and either RTX+CYC or RTX	10/37 (27%) developed infections.
	Goupil, 2013	Two centers, retrospective cohort	17 months (median)	93 patients with AAV (either ANCA or positive + per EMA algorithm) that received treatment. - 52%F - 58% PR3	54/93 (58%) had received IVMP as part of induction therapy.	"The use of pulse corticosteroids were not statistically different in patients with (67%) and those without (55%) infectious episodes." 28% of total population had severe infection requiring hospitalization.
ESRD – ESRD occurs in 29-39% of patients. Three studies with 69 patients.	Shah, 2015	Single center, retrospective cohort	553 days (median)	14 patients with AAV/ANCA-negative SVV with severe renal disease treated with RTX and GC	All patients treated with IVMP 1g x 3 days, then prednisone 1mg/kg/day with taper. All patients treated with RTX. 11/14 tx with PJP ppx.	4/14 (29%) ultimately developed ESRD by the end of observation (2 of these had required HD at presentation).
	Geetha, 2016	Multicenter, multinational, retrospective cohort	973 days (median)	37 patients with GPA or MPA with active GN and e GFR <20 (mean age 61, 14F, 22 MPO ANCA, 78% new dx, 30% DAH, 40% HD initially)	All patients treated with IVMP x 3 days and either RTX+CYC or RTX	12/32 (32%) reached ESRD during follow up (5 of these were HD dependent at presentation).
	Grcevska, 2011	Single Center, retrospective cohort	2 months to 8 years	18 patients with WG (All had either positive ANCA or positive renal biopsy) -6F -mean age 48.6y	Induction: IVMP 0.5mg-1.0mg/kg/d x 3 days with prednisne 0.5mg/kg/d) and pulse CYC protocol. Some patients received PLEX.	7/18 (39%) reached ESRD by follow up.

Disease Remission – Most patients appear to achieve remission when IVMP is part of their induction therapy. Total patients 54.	Geetha, 2016	Multicenter, multinational, retrospective cohort	973 days (median)	37 patients with GPA or MPA with active GN and e GFR <20 (mean age 61, 14F, 22 MPO ANCA, 78% new dx, 30% DAH, 40% HD initially)	All patients treated with IVMP x 3 days and either RTX+CYC or RTX	32/33 (97%) achieved remission at 6 months.
	Silva, 2010	Prospective, open-label pilot trial (single center)	72 weeks	17 patients with MPA (CHCC definition). Must have had MPO-pANCA, active GN, Cr<3.	IVMP 1 gram daily for 1-2days followed by PO prednisone 1mg/kg/d on taper. MMF was also used (target dose of 1000mg twice daily, uptitrated to 1500mg twice daily if no response).	13/17 (76%) achieved remission (BVAS = 0 and stable or falling Cr) by 6 months. 12/17 (70%) patients achieved sustained remission at 18 months.

4. In patients with active severe GPA/MPA, what is the impact of using high-dose oral glucocorticoids for remission induction on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention used in relevant population	Results	Comments
Relapse:. Comparing RAVE and SCOUT trails there were higher relapse rates in the lower dose glucocorticoid group.	Walsh M, 2014	Randomized controlled trial (CYCAZAREM)	Median f/u of 8.5 yrs. 144 patients contributed a total of 1016 pt-yrs.	144 patients with either GPA, MPA or RLV. Must be ANCA positive or vasculitis confirmed by biopsy. Severe renal insufficiency or dialysis dependency excluded. All achived remission between 3-6	Oral cyclophosphamide (2mg/kg, reduced by 25mg for age > 60 yrs) and daily oral prednisolone starting at 1mg/kg/d.	Relapses in 63/114 (55.3%) patients.	Only includes patients who achieved remission by 3-6 months with cyclophosphamide were included. 14/144 (9.7%) of patients lost to follow-up.

				months with cyclophosphamide.			
	Kumar A, 2001	Retrospective observational cohort	Median follow-up of 5 yrs (range 4 mo to 11 yrs)	25 GPA patients from India. Based on clinical diagnosis (not classification criteria). 1988-2000.	Prednisolone 1mg/kg/d x 6-8 wks then tapering over next 16 weeks, combined with oral cyclophosphamide (n=22), IV CYC (1), or methotrexate (2)	Relapses in 8/25 (32%) patients.	Classification criteria not used. Mixture of severe and non-severe disease.
	Charlier C, 2009	Retrospective oberservational cohort	Median f/y 6 yrs (range 0-22). 758 pt-yrs	113 GPA patients meeting ACR criteria. French population. Seen between 1984-2006.	Corticoidsteroids (unclear which) at 1mg/kg/d for 4-6 weeks followed by taper (unclear duration of taper) in addition to IV or oral CYC.	Relapses in 52/113 (46%) patients.	The same induction strategy is not utilized for all patients (e.g., some get IV and some oral CYC). The GC taper is also not standardized. Only includes GPA patients. It does not directly state how many have severe disease.
	J. H. Stone, 2010	Randomized, double-blind, double-dummy, noninferiority trial comparing RTX to CYC for induction (RAVE)	6 months	197 patients with GPA or MPA who were ANCA positive, manifestations of severe disease and at least a BVAS/WG of ≥ 3	Rituximab (375mg/m2 x 4) oral cyclophosphamide (2mg/kg/d) plus 1-3 grams of IV methylprednisolone followed by 1mg/kg/d prednisone tapered off by 5 months.	16 patients with severe disease flares by 6 months. 25 patients with non-severe flares by 6 months.	Primary intervention was the comparison between RTX and CYC.
Infections: The best evidence appears to come from 20227 which showed a higher number of	Watanabe K, 2017	Prospective observational cohort	Six months from start of induction therapy	RemIt-JAV prospective cohort. 156 patients (33 GPA, 78 MPA/RLV, 14 EGPA) meeting Eropean Medicines Agency (EMEA) algorithm	This was an observational cohort without any specific interventions.	Comparison of those w/o serious infection (SI) vs those with SI within 6 months of induction therapy: -Prednisolone %: 98.2 vs 100 (p=0.533) -Prednisolone dose at start	-Not a pure population of GPA/MPA patients. -Some comparisons made between high and moderate doses of prednisone at onset of induction.

serious infections in those that got higher initial doses of prednisolone, but no difference based on whether patients got an initial pulse of methylprednisolone.						(mg/d): 40(0-80) vs 50(25-80) (p=0.008) -Pednisolone > 0.8mg/kg/d at start (%): 43.0 vs 64.3, p=0.018. -Received methylprednisolone pulse (%): 42.1 vs 33.3;p=0.321. -IR (/100PY)(95% CI): 110.4 (79.4-149.9) in those on ≥ 0.8mg/kg/d prednisolone. -Crude IRR (95% CI) 1.69 (95% CI 1.02-2.82) comparing ≥ 0.8mg/kg/d prednisolone to < 0.8mg/kg/d prednisolone.	-Unclear if this is only severe disease (probably mixture of severe and nonsevere)
	Charlier C, 2009	Retrospective oberservational cohort	Median f/y 6 yrs (range 0-22). 758 pt-yrs	113 GPA patients meeting ACR criteria. French population. Seen between 1984-2006.	Corticoidsteroids (unclear which) at 1mg/kg/d for 4-6 weeks followed by taper (unclear duration of taper) in addition to IV or oral CYC.	53 major infections in 35/113 (31.0%) patients.	The same induction strategy is not utilized for all patients (e.g., some get IV and some oral CYC). The GC taper is also not standardized. Only includes GPA patients.
	J. H. Stone, 2010	Randomized, double-blind, double-dummy, noninferiority trial comparing RTX to CYC for induction (RAVE)	6 months	197 patients with GPA or MPA who were ANCA positive, manifestations of severe disease and at least a BVAS/WG of ≥ 3	Rituximab (375mg/m2 x 4) oral cyclophosphamide (2mg/kg/d) plus 1-3 grams of IV methylprednisolone followed by 1mg/kg/d prednisone tapered off by 5 months.	Number of infections (events) that were ≥ grade 3: 14 (number of patients with infections not given	Primary intervention was the comparison between RTX and CYC.
Serious adverse events + Deaths:	Walsh M, 2014	Randomized controlled trial (CYCAZAREM)	Median f/u of 8.5 yrs. 144 patients	144 patients with either GPA, MPA or RLV. Must be ANCA positive or	Oral cyclophosphamide (2mg/kg, reduced by 25mg for age > 60 yrs) and daily oral	ESRD in 13/144 (9.0%) Death in 21/144 (14.6%) Malignancies in 17/144 (11.8%)	Only includes patients who achieved remission by 3-6 months with

The best level of evidence appears to come from comparison between RAVE and SCOUT trials which showed fewer total adverse events and deaths in the lower dose glucocorticoid regimen.			contributed a total of 1016 pt-yrs.	vasculitis confirmed by biopsy. Severe renal insufficiency or dialysis dependency excluded. All achived remission between 3-6 months with cyclophosphamide.	prednisolone starting at 1mg/kg/d.		cyclophosphamide were included. 14/144 (9.7%) of patients lost to follow-up.
	J. H. Stone, 2010	Randomized, double-blind, double-dummy, noninferiority trial comparing RTX to CYC for induction (RAVE)	6 months	197 patients with GPA or MPA who were ANCA positive, manifestations of severe disease and at least a BVAS/WG of ≥ 3	Rituximab (375mg/m2 x 4) oral cyclophosphamide (2mg/kg/d) plus 1-3 grams of IV methylprednisolone followed by 1mg/kg/d prednisone tapered off by 5 months.	Number of patients with ≥ 1 grade 3 adverse event: 54/197 (27%) Deaths: 3/197 (2%)	Primary intervention was the comparison between RTX and CYC.
	Seggie, 1990	Multicenter, restrospective cohort	Mean 2y4m	25 patients with MPA by renal biopsy (pre-ANCA testing)	All patients were treated with IV or PO CYC and PO prednisolone (0.5-1.0mg/kg/d initially, then on taper).	5/25 (20%) patients died.	
	Savage, 1985	Single center, retrospective cohort	Long term, Unclear	34 patients with MPA by renal biopsy (pre-ANCA) – 12F, mean age 50y	32/34 patients received prednisolone (29 of which received 60mg/day – the other three received 40, 45, 50 mg/day initially). 27/34 pts received PO CYC 20/34 patients received AZA with their CYC. Some pLEX was used.	Overall mortality rate was 35%. 2-month mortaility was 7/34 (20.6%)	

ESRD – Two studies with 59 pts total showing long term ESRD rates ranging from 22-40%.	Seggie, 1990	Multicenter, restrospective cohort	Mean 2y4m	25 patients with MPA by renal biopsy (pre-ANCA testing)	All patients were treated with IV or PO CYC and PO prednisolone (0.5-1.0mg/kg/d initially, then on taper).	10/25 (40%) progressed to ESRD by end of observation.	
	Savage, 1985	Single center, retrospective cohort	59m, mean	34 patients with MPA by renal biopsy (pre-ANCA) – 12F, mean age 50y	32/34 patients received prednisolone (29 of which received 60mg/day – the other three received 40, 45, 50 mg/day initially). 27/34 pts received PO CYC 20/34 patients received AZA with their CYC. Some pLEX was used.	Of the 22 long term survivors, 5 are HD dependent.	
Disease activity: The best level of evidence appears to come from comparison between RAVE and SCOUT tiral which showed a similar rate of remission by 24 weeks.	Silva F, 2009	Prospective single arm trial	18 months	17 MPA patients meeting CHCC, positive p(MPO)-ANCA, renal involvement and Cr <= 3.0 mg/dl. 2003-2007. Done at Mayo Clinic.	Mycophenolate 1,000mg BID along with methylprednisolone 1-3 g followed by 1mg/kg/d. Glucocorticoids were discontinued by 6 months.	Remission at 6 months in 13/17 (76%) patients. Sustained remission until 18 months in 12/17 (70%) patients	Induction therapy with mycophenolate.
	J. H. Stone, 2010	Randomized, double-blind, double-dummy, noninferiority trial comparing RTX to CYC for induction (RAVE)	6 months	197 patients with GPA or MPA who were ANCA positive, manifestations of severe disease and at least a BVAS/WG of ≥ 3	Rituximab (375mg/m2 x 4) oral cyclophosphamide (2mg/kg/d) plus 1-3 grams of IV methylprednisolone followed by 1mg/kg/d prednisone tapered off by 5 months.	115/197 (58.4%) achieved remission off of glucocorticoids by 6 months.	Primary intervention was the comparison between RTX and CYC.
Disease damage: The best level of evidence appears to	J. H. Stone, 2010	As Above	As Above	As Above	As Above	VDI scores increased by 1.3 in RTX group and 1.5 in CYC group.	As Above

come from the comparison between the RAVE and SCOUT trial which showed a similar change in VDI by 24 weeks.							
Toxicity leading to discontinuation: Only the RAVE trial reports the rate of discontinuation of study drug. There is not similar data in the studies on low dose glucorticoids.	J. H. Stone, 2010	As Above	As Above	As Above	As Above	31/197 (15.7%) had adverse events leading to discontinuation of study drug.	As Above

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

Author	Year	Title
Y. Ma	2017	The impact of intravenous methylprednisolone pulses on renal survival in anti-neutrophil cytoplasmic antibody associated vasculitis with severe renal injury patients: a retrospective study
Chanouzas	2019	Intravenous pulse methylprednisolone for induction of remission in severe ANCA associated Vasculitis: a multi-center retrospective cohort study

- Single arm studies and test accuracy studies:

Author	Year	Title
S. Kamali	2005	Systemic necrotizing vasculitides in Turkey: a comparative analysis of 40 consecutive patients
K. Watanabe-Imai	2017	Clinical characteristics of and risk factors for serious infection in Japanese patients within six months of remission induction therapy for antineutrophil cytoplasmic antibody-associated vasculitis registered in a nationwide, prospective, inception cohort study
I. Andreiana	2015	ANCA positive crescentic glomerulonephritis outcome in a Central East European cohort: a retrospective study
S. Shah	2015	Treatment of severe renal disease in ANCA positive and negative small vessel vasculitis with rituximab
D. Geetha	2016	Rituximab for treatment of severe renal disease in ANCA associated vasculitis
M. Walsh	2014	Long-term follow-up of cyclophosphamide compared with azathioprine for initial maintenance therapy in ANCA-associated vasculitis
R. Goupil	2013	Lymphopenia and treatment-related infectious complications in ANCA-associated vasculitis
L. Grcevska	2011	Renal histopathology and clinical course in patients with Wegener's granulomatosis--single centre experience from the Republic of Macedonia
G. Salvidio	1991	Short- and long-term effects of methylprednisolone pulses and oral cyclophosphamide in renal micropolyarteritis
J. L. Seggie	1990	Microscopic polyarteritis--a treatable cause of rapidly progressive renal failure due to necrotising glomerulonephritis
F. Silva	2010	Mycophenolate mofetil for induction and maintenance of remission in microscopic polyangiitis with mild to moderate renal involvement--a prospective, open-label pilot trial
C. O. Savage	1985	Microscopic polyarteritis: presentation, pathology and prognosis
A. Kumar	2001	Wegener's granulomatosis in India: clinical features, treatment and outcome of twenty-five patients
C. Charlier	2009	Risk factors for major infections in Wegener granulomatosis: analysis of 113 patients
J. H. Stone	2010	Rituximab versus cyclophosphamide for ANCA-associated vasculitis

- Studies reviewed and excluded:

Author	Year	Title	Comments
M. Gordon	1993	Relapses in patients with a systemic vasculitis	Excluded for GPA/MPA PICO 2. Heterogenous treatment regimens and outcomes are not available at the treatment-group level.
J. S. Cameron	1991	Renal vasculitis: microscopic polyarteritis and Wegener's granuloma	Excluded for GPA/MPA PICO 2. Heterogenous treatment regimens and outcomes are not available at the treatment-group level.
L. Guillevin	1988	Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angiitis: a study in 165 patients	Excluded for GPA/MPA PICO 2. No idenitifiable GPA or MPA (or AAV) population.
C. Charlier	2009	Risk factors for major infections in Wegener granulomatosis: analysis of 113 patients	Excluded for GPA/MPA PICO 2. Heterogenous treatment regimens and outcomes are not available at the treatment-group level.
P. K. Wung	2008	Effects of glucocorticoids on weight change during the treatment of Wegener's granulomatosis	Excluded for GPA/MPA PICO 2. Heterogenous treatment regimens and outcomes are not available at the treatment-group level.
D. P. D'Cruz	1989	Ear, nose, and throat symptoms in subacute Wegener's granulomatosis	Excluded for GPA/MPA PICO 2. Heterogenous treatment regimens and outcomes are not available at the treatment-group level.
L. Guillevin	1993	Antineutrophil cytoplasm antibodies in systemic polyarteritis nodosa with and without hepatitis B virus infection and Churg-Strauss syndrome--62 patients	Excluded for GPA/MPA PICO 2. No treatment related outcomes discussed.

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Induction

- **PICO question 3:** In patients with active severe GPA/MPA, what is the impact of using high-dose vs. moderate dose oral glucocorticoids for remission induction on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Disease Activity, Disease Damage, Relapse, Death, Infection, Serious Adverse Events, Toxicity leading to discontinuation (e.g., hyperglycemia, decreased bone mineral density

5. In patients with active severe GPA/MPA, what is the impact of using high-dose vs. moderate dose oral glucocorticoids for remission induction on disease-related outcomes and treatment-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	high-dose glucocorticoids	moderate dose glucocorticoids	Relative (95% CI)	Absolute (95% CI)		
Remission (follow up: median 2.9 years; assessed with: risk through longest follow up)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	-/351	-/353 [b]	**RR 0.96** (0.84 to 1.09)	**-- per 1,000** (from -- to --) [b]	⨁⨁⨁◯ MODERATE	CRITICAL
Relapse (follow up: 2.9 years; assessed with: Risk through longest follow up)												
1	randomised trials	not serious	not serious	not serious	very serious [c]	none	23/351 (6.6%)	32/353 (9.1%)	**RR 0.72** (0.43 to 1.20)	**25 fewer per 1,000** (from 52 fewer to 18 more)	⨁⨁◯◯ LOW	CRITICAL
Mortality (follow up: median 2.9 years; assessed with: Risk over time)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	-/351	-/353 [b]	**HR 1.28** (0.85 to 1.89)	**-- per 1,000** (from -- to --) [b]	⨁⨁◯◯ LOW	CRITICAL
Infection (follow up: 1 years; assessed with: rate ratio of severe infections)												
1	randomised trials	not serious	not serious	not serious	serious [d]	none	-/351	119/353 [b]	**Rate ratio 1.45** (1.08 to 1.92)	**151 more per 1000 patient(s) per years** (from 27 more to 310 more) [e]	⨁⨁⨁◯ MODERATE	CRITICAL
Infection (follow up: 1 years; assessed with: Risk through 1 year- unadjusted)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	131/351 (37.3%)	119/353 (33.7%)	**RR 1.11** (0.91 to 1.35)	**37 more per 1,000** (from 30 fewer to 118 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events (follow up: median 2.9 years; assessed with: Rate ratio through longest follow up)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	high-dose glucocorticoids	moderate dose glucocorticoids	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious [a]	none		446/-	**Rate ratio 1.05** (0.83 to 1.33)	**11 more per 1000 patient(s) per years** (from 36 fewer to 71 more) [f]	⨁⨁⨁◯ MODERATE	CRITICAL
Disease activity - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Disease damage - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Toxicity leading to discontinuation - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanations

a. The confidence interval includes the possibility of important benefit and important harm
b. Baseline risk not provided in the study
c. The confidence interval suggests the possibility of important benefit and large harm
d. The confidence interval includes the possibility of small and large harm
e. Calculated based on incidence rate reported in supplementary material
f. Baseline risk according to number of events across all adverse events in reduced risk group (supplementary material): 446 SAEs in 704 participants over 2.042 patient years

References:

- Randomized Controlled Trials:

Year	Author	Title
2020	M. Walsh	Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

6. In patients with <u>active severe GPA/MPA</u>, what is the impact of using high-dose oral glucocorticoids for remission induction on disease-related outcomes and treatment-related adverse events?
    - **Patient Important Outcomes**

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention used in relevant population	Results	Comments
Relapse: Comparing RAVE and SCOUT trials there were higher relapse rates in the lower dose glucocorticoid group.	Walsh M, 2014	Randomized controlled trial (CYCAZAREM)	Median f/u of 8.5 yrs. 144 patients contributed a total of 1016 pt-yrs.	144 patients with either GPA, MPA or RLV. Must be ANCA positive or vasculitis confirmed by biopsy. Severe renal insufficiency or dialysis dependency excluded. All achived remission between 3-6 months with cyclophosphamide.	Oral cyclophosphamide (2mg/kg, reduced by 25mg for age > 60 yrs) and daily oral prednisolone starting at 1mg/kg/d.	Relapses in 63/114 (55.3%) patients.	Only includes patients who achieved remission by 3-6 months with cyclophosphamide were included. 14/144 (9.7%) of patients lost to follow-up.
	Kumar A, 2001	Retrospective observational cohort	Median follow-up of 5 yrs (range 4 mo to 11 yrs)	25 GPA patients from India. Based on clinical diagnosis (not classification criteria). 1988-2000.	Prednisolone 1mg/kg/d x 6-8 wks then tapering over next 16 weeks, combined with oral cyclophosphamide (n=22), IV CYC (1), or methotrexate (2)	Relapses in 8/25 (32%) patients.	Classification criteria not used. Mixture of severe and non-severe disease.
	Charlier C, 2009	Retrospective oberservational cohort	Median f/y 6 yrs (range 0-22). 758 pt-yrs	113 GPA patients meeting ACR criteria. French population. Seen between 1984-2006.	Corticoidsteroids (unclear which) at 1mg/kg/d for 4-6 weeks followed by taper (unclear duration of taper) in addition to IV or oral CYC.	Relapses in 52/113 (46%) patients.	The same induction strategy is not utilized for all patients (e.g., some get IV and some oral CYC). The GC taper is also not standardized. Only includes GPA patients. It does not directly state how many have severe disease.
	J. H. Stone, 2010	Randomized, double-blind, double-dummy, noninferiorit	6 months	197 patients with GPA or MPA who were ANCA positive, manifestations of severe disease and at	Rituximab (375mg/m2 x 4) oral cyclophosphamide (2mg/kg/d) plus 1-3 grams of IV methylprednisolone	16 patients with severe disease flares by 6 months. 25 patients with non-	Primary intervention was the comparison between RTX and CYC.

		y trial comparing RTX to CYC for induction (RAVE)		least a BVAS/WG of ≥ 3	followed by 1mg/kg/d prednisone tapered off by 5 months.	severe flares by 6 months.	
Infections: The best evidence appears to come from K. Watanabe-Imai et al (2017), which showed a higher number of serious infections in those that got higher initial doses of prednisolone, but no difference based on whether patients got an initial pulse of methylprednisolone.	Watanabe K, 2017	Prospective observational cohort	Six months from start of induction therapy	RemIt-JAV prospective cohort. 156 patients (33 GPA, 78 MPA/RLV, 14 EGPA) meeting Eropean Medicines Agency (EMEA) algorithm	This was an observational cohort without any specific interventions.	Comparison of those w/o serious infection (SI) vs those with SI within 6 months of induction therapy: -Prednisolone %: 98.2 vs 100 (p=0.533) -Prednisolone dose at start (mg/d): 40(0-80) vs 50(25-80) (p=0.008) -Pednisolone > 0.8mg/kg/d at start (%): 43.0 vs 64.3, p=0.018. -Received methylprednisolone pulse (%): 42.1 vs 33.3;p=0.321. -IR (/100PY)(95% CI): 110.4 (79.4-149.9) in those on ≥ 0.8mg/kg/d prednisolone.	-Not a pure population of GPA/MPA patients. -Some comparisons made between high and moderate doses of prednisone at onset of induction. -Unclear if this is only severe disease (probably mixture of severe and nonsevere)

						-Crude IRR (95% CI) 1.69 (95% CI 1.02-2.82) comparing ≥ 0.8mg/kg/d prednisolone to < 0.8mg/kg/d prednisolone.	
	Charlier C, 2009	Retrospective oberservational cohort	Median f/u 6 yrs (range 0-22). 758 pt-yrs	113 GPA patients meeting ACR criteria. French population. Seen between 1984-2006.	Corticoidsteroids (unclear which) at 1mg/kg/d for 4-6 weeks followed by taper (unclear duration of taper) in addition to IV or oral CYC.	53 major infections in 35/113 (31.0%) patients.	The same induction strategy is not utilized for all patients (e.g., some get IV and some oral CYC). The GC taper is also not standardized. Only includes GPA patients.
	J. H. Stone, 2010	Randomized, double-blind, double-dummy, noninferiority trial comparing RTX to CYC for induction (RAVE)	6 months	197 patients with GPA or MPA who were ANCA positive, manifestations of severe disease and at least a BVAS/WG of ≥ 3	Rituximab (375mg/m2 x 4) oral cyclophosphamide (2mg/kg/d) plus 1-3 grams of IV methylprednisolone followed by 1mg/kg/d prednisone tapered off by 5 months.	Number of infections (events) that were ≥ grade 3: 14 (number of patients with infections not given	Primary intervention was the comparison between RTX and CYC.
Serious adverse events + Deaths: The best level of evidence appears to come from comparison between RAVE and SCOUT trials which	Walsh M, 2014	Randomized controlled trial (CYCAZAREM)	Median f/u of 8.5 yrs. 144 patients contributed a total of 1016 pt-yrs.	144 patients with either GPA, MPA or RLV. Must be ANCA positive or vasculitis confirmed by biopsy. Severe renal insufficiency or dialysis dependency excluded. All achived	Oral cyclophosphamide (2mg/kg, reduced by 25mg for age > 60 yrs) and daily oral prednisolone starting at 1mg/kg/d.	ESRD in 13/144 (9.0%) Death in 21/144 (14.6%) Malignancies in 17/144 (11.8%)	Only includes patients who achieved remission by 3-6 months with cyclophosphamide were included. 14/144 (9.7%) of patients lost to follow-up.

showed fewer total adverse events and deaths in the lower dose glucocorticoid regimen.				remission between 3-6 months with cyclophosphamide.			
	J. H. Stone, 2010	Randomized, double-blind, double-dummy, noninferiority trial comparing RTX to CYC for induction (RAVE)	6 months	197 patients with GPA or MPA who were ANCA positive, manifestations of severe disease and at least a BVAS/WG of ≥ 3	Rituximab (375mg/m2 x 4) oral cyclophosphamide (2mg/kg/d) plus 1-3 grams of IV methylprednisolone followed by 1mg/kg/d prednisone tapered off by 5 months.	Number of patients with ≥ 1 grade 3 adverse event: 54/197 (27%) Deaths: 3/197 (2%)	Primary intervention was the comparison between RTX and CYC.
	Seggie, 1990	Multicenter, restrospective cohort	Mean 2y4m	25 patients with MPA by renal biopsy (pre-ANCA testing)	All patients were treated with IV or PO CYC and PO prednisolone (0.5-1.0mg/kg/d initially, then on taper).	5/25 (20%) patients died.	
	Savage, 1985	Single center, retrospective cohort	Long term, Unclear	34 patients with MPA by renal biopsy (pre-ANCA) – 12F, mean age 50y	32/34 patients received prednisolone (29 of which received 60mg/day – the other three received 40, 45, 50 mg/day initially). 27/34 pts received PO CYC 20/34 patients received AZA with their CYC. Some pLEX was used.	Overall mortality rate was 35%. 2-month mortaility was 7/34 (20.6%)	
ESRD – Two studies with 59 pts total showing long term	Seggie, 1990	Multicenter, restrospective cohort	Mean 2y4m	25 patients with MPA by renal biopsy (pre-ANCA testing)	All patients were treated with IV or PO CYC and PO prednisolone (0.5-	10/25 (40%) progressed to ESRD by end of observation.	

ESRD rates ranging from 22-40%.					1.0mg/kg/d initially, then on taper).		
	Savage, 1985	Single center, retrospective cohort	59m, mean	34 patients with MPA by renal biopsy (pre-ANCA) – 12F, mean age 50y	32/34 patients received prednisolone (29 of which received 60mg/day – the other three received 40, 45, 50 mg/day initially). 27/34 pts received PO CYC 20/34 patients received AZA with their CYC. Some pLEX was used.	Of the 22 long term survivors, 5 are HD dependent.	
Disease activity: The best level of evidence appears to come from comparison between RAVE and SCOUT tiral which showed a similar rate of remission by 24 weeks.	Silva F, 2009	Prospective single arm trial	18 months	17 MPA patients meeting CHCC, positive p(MPO)-ANCA, renal involvement and Cr <= 3.0 mg/dl. 2003-2007. Done at Mayo Clinic.	Mycophenolate 1,000mg BID along with methylprednisolone 1-3 g followed by 1mg/kg/d. Glucocorticoids were discontinued by 6 months.	Remission at 6 months in 13/17 (76%) patients. Sustained remission until 18 months in 12/17 (70%) patients	Induction therapy with mycophenolate.
	J. H. Stone, 2010	Randomized, double-blind, double-dummy, noninferiority trial comparing RTX to CYC for induction (RAVE)	6 months	197 patients with GPA or MPA who were ANCA positive, manifestations of severe disease and at least a BVAS/WG of ≥ 3	Rituximab (375mg/m2 x 4) oral cyclophosphamide (2mg/kg/d) plus 1-3 grams of IV methylprednisolone followed by 1mg/kg/d prednisone tapered off by 5 months.	115/197 (58.4%) achieved remission off of glucocorticoids by 6 months.	Primary intervention was the comparison between RTX and CYC.

Disease damage: The best level of evidence appears to come from the comparison between the RAVE and SCOUT trial which showed a similar change in VDI by 24 weeks.	J. H. Stone, 2010	As Above	As Above	As Above	As Above	VDI scores increased by 1.3 in RTX group and 1.5 in CYC group.	As Above
Toxicity leading to discontinuation: Only the RAVE trial reports the rate of discontinuation of study drug. There is not similar data in the studies on low dose glucorticoids.	J. H. Stone, 2010	As Above	As Above	As Above	As Above	31/197 (15.7%) had adverse events leading to discontinuation of study drug.	As Above

7. In patients with <u>active severe GPA/MPA</u>, what is the impact of using moderate dose oral glucocorticoids for remission induction on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention used in relevant population	Results	Comments
Disease Activity: The best level of evidence appears to come from comparison between RAVE and SCOUT trials, which showed a similar rate of remission by 24 weeks.	Miloslacsky E, 2018	Sigle arm prospective pilot study (SCOUT trial)	52 weeks, but protocol only lasted 24 weeks	New or relapsing GPA/MPA (according to CHCC) with BVAS/WG of ≥ 3, excluding 1)PR3 positive with GN, 2)MPO + with advanced renal dysfunction (GFR < 30) and 3) DAH	RTX (375mg/m2 x 4) and prednisone 60mg/d x 2 wks, 40mg/d x 2 wks, 30mg/d x 1wk, 20mg/d x 1wk, 10mg/d x 1wk, 5mg/d x 1wk (8 wk taper). After 24 weeks patient treated by best medical judgement. Bactrim used for PJP. IV solumedrol allowed	Complete remission off prednisone (w/o interceding flares): - 24 weeks: 14/20 (70%). - 52 weeks: 11/20 (55%, but not clear if off prednisone)	Cohort was compared to the RAVE cohort (excluding the same patients as excluded in this cohort) which showed complete remission at 24 weeks (off prednisone) of 14/20 (70%) in current study vs 18/29 (69%) in RAVE; OR 1.58 [0.44-5.62;p=0.6.

				requiring ventilation. N=20	prior to predisone (max 3g).		
Relapse: Comparing RAVE and SCOUT trials there were higher relapse rates in the lower dose glucocorticoid group.	Miloslavsky E, 2018	As Above	As Above	As Above	As Above	Relapses (%): 24 weeks: 6/20 (30%, 5 severe) 52 weeks: 5 additional relapses (4 nonsevere, 1 severe), with 3 occuring in 14 patients in remission at 24 weeks	Cohort was compared to the RAVE cohort (excluding the same patients as excluded in this cohort) which showed 6/20 (30%) in current cohort vs 2/29 (7%) in RAVE (p=0.03).
	Hasegawa M, 2016	Observational cohort	Mean follow-up 54 months (SD 51) from the initiation of dialysis	Japanese cohort. MPO-ANCA positive patients requiring dialysis (1/1991-12/2012). Diagnosis based on EMEA algorithm. N=89 (1 GPA, 70 MPA, 18 RLV)	Mean initial prednisolone dose of 32±12mg/d (0.7±0.2mg/kg/d) in 81 patients (91%) given glucocorticoids. Cyclophosphamide given to 15 patients (17%). Azathioprine to 5 pts, cyclosporine to 3, mizoribine to 3, PLEX in 13, cytapheresis in 11. Dialysis in all.	Relapses: 21 relapses in 13 patients (14.6% of patients relapsed) with IR of 0.05 episodes/person-yr (95% CI, 0.03-0.08). Subgroups: -Those who discontinued GCs: 3/18 (16.7%) -Those who did not receive GCs at onset of vasculitis: 3/11 (27.3%) -Those who continued GCs after starting dialysis: 7/60 (11.7%)	Cohort is primarily MPA patients, all of which go on to dialysis. Cohort may include same patients as the RemIt-JAV cohort. No mention of duration of GC taper.
	Yamagata K, 2012	Observational Cohort	Median f/u 19.1 months (range 0-211.8 months)	Japanese cohort. Patients with RPGN who were ANCA positive and had testing for PR3-ANCA, MPO-ANCA and anti-GBM (n=824)	General recommendation to use < 0.8mg/kg/d initial methylprisolone dose with or w/o cyclophosphamide. Average initial prednisolone dose was 0.71 mg/kg/d (Group C)	Recurrent rate of 0.13/pt-yr in Group C which is statistically higher then those getting higher doses (>0.8mg/kg/d, group A) with recurrence rate of 0.05/pt-yr.	Unclear what is the cumulative dose of GCs or duration.

	Savage C 1985	Single center retrospective observational trial	Mean f/u 47 months (range 3 mon-10 yrs)	MPA patients with glomerulonephritis (no specific criteria). N=34. Done at single center in London.	Treated with oral cyclophosphamide (starting at 3mg/kg/d) and prednisolone 60mg/d tapered to 20mg/d by 4 weeks, then continued on 5-10mg/d for 1 yr or longer.	Relapses occurred in 12/34 patients (35.3%)	Included just patients with kidney involvement. Patients only got cyclophosphamide for induction, none getting Rituximab.
Serious adverse events + Deaths: The best level of evidence appears to come from comparison between RAVE and SCOUT trials which showed fewer total adverse events and deaths in the lower dose glucocorticoid regimen	Miloslavsky E, 2018	Sigle arm prospective pilot study (SCOUT trial)	52 weeks, but protocol only lasted 24 weeks	New or relapsing GPA/MPA (according to CHCC) with BVAS/WG of ≥ 3, excluding 1)PR3 positive with GN, 2)MPO + with advanced renal dysfunction (GFR < 30) and 3) DAH requiring ventilation. N=20	RTX (375mg/m2 x 4) and prednisone 60mg/d x 2 wks, 40mg/d x 2 wks, 30mg/d x 1wk, 20mg/d x 1wk, 10mg/d x 1wk, 5mg/d x 1wk (8 wk taper). After 24 weeks patient treated by best medical judgement. Bactrim used for PJP. IV solumedrol allowed prior to predisone (max 3g).	SAE 11 at 24 weeks (does not specify number of patients with adverse events) including 5 severe relapses, 1 MI, 1 afib, 1 syncopy, 3 malignancies. Death: No deaths at either 24 or 52 weeks.	Cohort was compared to the RAVE cohort (excluding the same patients as excluded in this cohort) which showed less frequent total adverse events (median 2 per patient [IQR 1-3] vs 8 per patient [IQR 3-15], p < 0.001)
	Hasegawa M, 2016	Observational cohort	Mean follow-up 54 months (SD 51) from the initiation of dialysis	Japanese cohort. MPO-ANCA positive patients requiring dialysis (1/1991-12/2012). Diagnosis based on EMEA algorithm. N=89 (1 GPA, 70 MPA, 18 RLV)	Mean initial prednisolone dose of 32±12mg/d (0.7±0.2mg/kg/d) in 81 patients (91%) given glucocorticoids. Cyclophosphamide given to 15 patients (17%). Azathioprine to 5 pts, cyclosporine to 3, mizoribine to 3, PLEX in 13, cytapheresis in 11. Dialysis in all.	K-M survival analysis: 1-year: 83% 3-year: 76% 5-year: 65.6% 10-year: 43.5% Causes of death: Infection: 21 pts (56.8%) CV disease: 11 pts (29.7%) Malignancy: 2 pts (5.4%) Intertitial pneumonia: 1 (2.7%) GI bleeding/perforation: 2 (5.4%)	Cohort is primarily MPA patients, all of which go on to dialysis. Cohort may include same patients as the RemIt-JAV cohort. No mention of duration of GC taper.

	Yamagata K, 2012	Observational Cohort	Median f/u 19.1 months (range 0-211.8 months)	Japanese cohort. Patients with RPGN who were ANCA positive and had testing for PR3-ANCA, MPO-ANCA and anti-GBM (n=824)	General recommendation to use < 0.8mg/kg/d initial methylprednisolone dose with or w/o cyclophosphamide. Average initial prednisolone dose was 0.71 mg/kg/d (Group C)	1 year survival rates of 81% (compared to 75% survival in those using >0.8mg/kg/d, Group A) 1 yr renal survival rate of 83% (compared to 72% in Group A)	Unclear what is the cumulative dose of GCs or duration.
	Savage C 1985	Single center retrospective observational trial	Mean f/u 47 months (range 3 mon-10 yrs)	MPA patients with glomerulonephritis (no specific criteria). N=34. Done at single center in London.	Treated with oral cyclophosphamide (starting at 3mg/kg/d) and prednisolone 60mg/d tapered to 20mg/d by 4 weeks, then continued on 5-10mg/d for 1 yr or longer.	Patient survival of 65% at end of follow-up	Included just patients with kidney involvement. Patients only got cyclophosphamide for induction, none getting Rituximab.
Disease damage (VDI): The best level of evidence appears to come from the comparison between the RAVE and SCOUT trials, which showed a similar change in VDI by 24 weeks	Miloslacsky E, 2018	Sigle arm prospective pilot study (SCOUT trial)	52 weeks, but protocol only lasted 24 weeks	New or relapsing GPA/MPA (according to CHCC) with BVAS/WG of ≥ 3, excluding 1) PR3 positive with GN, 2) MPO + with advanced renal dysfunction (GFR < 30) and 3) DAH requiring ventilation. N=20	RTX (375mg/m2 x 4) and prednisone 60mg/d x 2 wks, 40mg/d x 2 wks, 30mg/d x 1wk, 20mg/d x 1wk, 10mg/d x 1wk, 5mg/d x 1wk (8 wk taper). After 24 weeks patient treated by best medical judgement. Bactrim used for PJP. IV solumedrol allowed prior to predisone (max 3g).	VDI change at 24 weeks + 0.35 (SD 0.8).	Cohort was compared to the RAVE cohort (excluding the same patients as excluded in this cohort) which was similar (+ 0.31 [±0.66] in current cohort vs. +0.35 [±0.80] in RAVE,p=0.9)
	Savage C 1985	Single center retrospective observational trial	Mean f/u 47 months (range 3 mon-10 yrs)	MPA patients with glomerulonephritis (no specific criteria). N=34. Done at single center in London.	Treated with oral cyclophosphamide (starting at 3mg/kg/d) and prednisolone 60mg/d tapered to 20mg/d by 4 weeks, then continued on 5-10mg/d for 1 yr or longer.	Renal survival in 65% of patients by 1 year and 55% at 5 years.	Included just patients with kidney involvement. Patients only got cyclophosphamide for induction, none getting Rituximab.

Infection: Comparing the SCOUT trial to RAVE suggests higher infection rate in the lower dose glucocoritcoid group, however, not direct comparison was made. The best evidence appears to come from K Watanabe-Imai et al (2017), which showed a higher number of serious infections in those that got higher initial doses of prednisolone, but no difference based on whether patients got an initial pulse of methylprednisolone.	Miloslavsky E, 2018	Sigle arm prospective pilot study (SCOUT trial)	52 weeks, but protocol only lasted 24 weeks	New or relapsing GPA/MPA (according to CHCC) with BVAS/WG of ≥ 3, excluding 1)PR3 positive with GN, 2)MPO + with advanced renal dysfunction (GFR < 30) and 3) DAH requiring ventilation. N=20	RTX (375mg/m2 x 4) and prednisone 60mg/d x 2 wks, 40mg/d x 2 wks, 30mg/d x 1wk, 20mg/d x 1wk, 10mg/d x 1wk, 5mg/d x 1wk (8 wk taper). After 24 weeks patient treated by best medical judgement. Bactrim used for PJP. IV solumedrol allowed prior to predisone (max 3g).	7 infections at 24 weeks (1 gastroenteritis, 1 otitis media, 1 shingles, 3 URI, 1 UTI). Unclear how many patients developed infections.	No comparison made between SCOUT trial and RAVE regarding infections.
	Hasegawa M, 2016	Observational cohort	Mean follow-up 54 months (SD 51) from the initiation of dialysis	Japanese cohort. MPO-ANCA positive patients requiring dialysis (1/1991-12/2012). Diagnosis based on EMEA algorithm. N=89 (1 GPA, 70 MPA, 18 RLV)	Mean initial prednisolone dose of 32±12mg/d (0.7±0.2mg/kg/d) in 81 patients (91%) given glucocorticoids. Cyclophosphamide given to 15 patients (17%). Azathioprine to 5 pts, cyclosporine to 3, mizoribine to 3, PLEX in 13, cytapheresis in 11. Dialysis in all.	Grade 3 or higher infections occurred 110 times in 53 patients (59.6% of patients).	Mean prednisolone dose at time of infection: 16±11 (range, 2.5-45). Cohort is primarily MPA patients, all of which go on to dialysis. Cohort may include same patients as the RemIt-JAV cohort. No mention of duration of GC taper.

- **References:**

- Randomized controlled trials:
  None
- Comparactive observational studies:
  None
- Included Single Arm Studies: 10

Author	Year	Title
E. M. Miloslavsky	2018	Reducing glucocorticoid duration in ANCA-associated vasculitis: A pilot trial
K. Watanabe-Imai	2017	Clinical characteristics of and risk factors for serious infection in Japanese patients within six months of remission induction therapy for antineutrophil cytoplasmic antibody-associated vasculitis registered in a nationwide, prospective, inception cohort study
M. Hasegawa	2016	A retrospective study on the outcomes of MPO-ANCA-associated vasculitis in dialysis-dependent patients
M. Walsh	2014	Long-term follow-up of cyclophosphamide compared with azathioprine for initial maintenance therapy in ANCA-associated vasculitis
K. Yamagata	2012	ANCA-associated systemic vasculitis in Japan: clinical features and prognostic changes
J. H. Stone	2010	Rituximab versus cyclophosphamide for ANCA-associated vasculitis
F. Silva	2010	Mycophenolate mofetil for induction and maintenance of remission in microscopic polyangiitis with mild to moderate renal involvement--a prospective, open-label pilot trial
A. Kumar	2001	Wegener's granulomatosis in India: clinical features, treatment and outcome of twenty-five patients
C. Charlier	2009	Risk factors for major infections in Wegener granulomatosis: analysis of 113 patients
C. O. Savage	1985	Microscopic polyarteritis: presentation, pathology and prognosis
J. L. Seggie	1990	Microscopic polyarteritis--a treatable cause of rapidly progressive renal failure due to necrotising glomerulonephritis

- Studies reviewed and excluded:

Author	Year	Title	Comments
L. Guillevin	1990	Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angiitis: a study in 165 patients	Exclude: This is an older study that only includes patients with PAN and EGPA. This is prior to 1994 CHCC, before MPA was separated from PAN as a diagnosis, however subgroup analysis is not performed.
A. Hara	2018	Risk Factors for Relapse of Antineutrophil Cytoplasmic Antibody-associated Vasculitis in Japan: A Nationwide, Prospective Cohort Study	Exclude: The dosing and duration of glucococticoids was not outlined.
Y. Matsumoto	2012	Evaluation of weekly-reduction regimen of glucocorticoids in combination with cyclophosphamide for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis in Japanese patients	Unclear what group this goes fits?
L. Grcevska	2011	Renal histopathology and clinical course in patients with Wegener's granulomatosis--single centre experience from the Republic of Macedonia	Exclude: There is a lot of missing data in the tables for follow-up period and outcomes.

Z. Hruskova	2009	Intracellular cytokine production in ANCA-associated vasculitis: low levels of interleukin-10 in remission are associated with a higher relapse rate in the long-term follow-up	Exclude: Doses/duration of glucocorticoids are not well defined. Outcomes of interest are missing.
P. K. Wung	2008	Effects of glucocorticoids on weight change during the treatment of Wegener's granulomatosis	Exclude: Outcomes of interest are not directly addressed.
D. P. D'Cruz	1989	Ear, nose, and throat symptoms in subacute Wegener's granulomatosis	Exclude: The majority of the cohort had non-severe disease.
J. L. Seggie	1990	Microscopic polyarteritis--a treatable cause of rapidly progressive renal failure due to necrotising glomerulonephritis	Exclude: There is a wide range of glucocorticoid doses used (0.5-1mg/kg/d) and it is not clear which patients got what dose.
C. Charlier	2009	Risk factors for major infections in Wegener granulomatosis: analysis of 113 patients	Does not report outcomes

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Induction

- **PICO question 4:** In patients with active severe GPA/MPA, what is the impact of using rituximab vs. cyclophosphamide for remission induction on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypogammaglobulinemia)

8. In patients with active severe GPA/MPA, what is the impact of using rituximab vs. cyclophosphamide for remission induction on disease-related outcomes and treatment-related adverse events?

9. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rituximab	cyclophosphamide	Relative (95% CI)	Absolute (95% CI)		
Sustained remission for 6 months												

9. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rituximab	cyclophosphamide	Relative (95% CI)	Absolute (95% CI)		
3 [a,b,c]	randomised trials	not serious	not serious	not serious	serious [d]	none	157/249 (63.1%)	136/247 (55.1%)	**OR 1.39** (0.97 to 1.99)	**79 more per 1,000** (from 8 fewer to 159 more)	⊕⊕⊕◯ MODERATE	

Sustained remission for 12 months

2 [b,c]	randomised trials	not serious	not serious	not serious	very serious [d]	none	70/150 (46.7%)	62/149 (41.6%)	**OR 1.23** (0.78 to 1.94)	**51 more per 1,000** (from 59 fewer to 164 more)	⊕⊕◯◯ LOW	

Sustained remission for 18 months

2 [b,c]	randomised trials	not serious	not serious	not serious	very serious [d]	none	60/150 (40.0%)	54/149 (36.2%)	**OR 1.17** (0.74 to 1.87)	**37 more per 1,000** (from 66 fewer to 153 more)	⊕⊕◯◯ LOW	

Death

9. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rituximab	cyclophosphamide	Relative (95% CI)	Absolute (95% CI)		
2 [b,c]	randomised trials	not serious	not serious	not serious	very serious [d]	none	4/150 (2.7%)	4/149 (2.7%)	**OR 0.99** (0.24 to 4.06)	**0 fewer per 1,000** (from 20 fewer to 74 more)	⨁⨁◯◯ LOW	

number of patients with severe adverse events

2 [b,c]	randomised trials	not serious	not serious	not serious	very serious [d]	none	63/150 (42.0%)	61/149 (40.9%)	**OR 1.05** (0.66 to 1.66)	**12 more per 1,000** (from 96 fewer to 126 more)	⨁⨁◯◯ LOW	

Severe leukopenia

1 [c]	randomised trials	not serious	not serious	not serious	serious [d]	none	5/99 (5.1%)	23/98 (23.5%)	**OR 0.17** (0.06 to 0.48)	**185 fewer per 1,000** (from 217 fewer to 106 fewer)	⨁⨁⨁◯ MODERATE	

Severe infections

9. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rituximab	cyclophosphamide	Relative (95% CI)	Absolute (95% CI)		
1 [c]	randomised trials	not serious	not serious	not serious	very serious [d]	none	12/99 (12.1%)	11/98 (11.2%)	**OR 1.09** (0.46 to 2.61)	**9 more per 1,000** (from 57 fewer to 136 more)	⨁⨁◯◯ LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. S.Unizony, 2016

b. D.Geetha, 2015

c. U.Specks, 2013

d. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

- **References:**

- Randomized controlled trials:

Author	Year	Title
S.Unizony	2016	Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type
D.Geetha	2015	Rituximab versus cyclophosphamide for ANCA-associated vasculitis with renal involvement
U.Specks	2013	Efficacy of remission-induction regimens for ANCA-associated vasculitis

- Studies reviewed and excluded:

Author	Year	Title	Comment
M. Iwabuchi	2016	Effects of cyclophosphamide on the prognosis of Japanese patients with renal vasculitis associated with anti-neutrophil cytoplasmic antibody-positive microscopic polyangiitis	Does not address PICO

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Induction

- **PICO 5 Question :** In patients with active severe GPA/MPA, what is the impact of using IV CYC vs. po CYC for remission induction on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Critical: disease activity, disease damage, relapse, death, malignancy, infection, serious adverse events, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

10. **PICO 5 Question :** In patients with active severe GPA/MPA, what is the impact of using IV CYC vs. po CYC for remission induction on disease-related outcomes and treatment-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulse IV cyclophosphamide	Continuous oral cyclophosphamide	Relative (95% CI)	Absolute (95% CI)	
Relapse											
4 [1,2,3,4]	randomised trials	not serious	not serious	not serious	very serious [a]	none	40/143 (28.0%)	23/141 (16.3%)	**OR 2.04** (1.11 to 3.75)	**121 more per 1,000** (from 15 more to 259 more)	⊕⊕◯◯ LOW
Leukopenia											
3 [1,2,3]	randomised trials	not serious	not serious	not serious	very serious [a]	none	31/122 (25.4%)	61/128 (47.7%)	**OR 0.37** (0.20 to 0.69)	**225 fewer per 1,000** (from 323 fewer to 91 fewer)	⊕⊕◯◯ LOW

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulse IV cyclophosphamide	Continuous oral cyclophosphamide	Relative (95% CI)	Absolute (95% CI)	
Adverse event- severe infection											
2 [2,3]	randomised trials	not serious	not serious	not serious	very serious [a]	none	10/98 (10.2%)	20/98 (20.4%)	**OR 0.45** (0.18 to 1.14)	**101 fewer per 1,000** (from 160 fewer to 22 more)	⨁⨁◯◯ LOW
Death											
4 [1,2,3,4]	randomised trials	not serious	not serious	not serious	very serious [a]	none	23/152 (15.1%)	32/144 (22.2%)	**OR 0.56** (0.29 to 1.07)	**84 fewer per 1,000** (from 146 fewer to 12 more)	⨁⨁◯◯ LOW
Complete remission at 3-5 years											
1 [4]	randomised trials	not serious	not serious	not serious	very serious [a]	none	12/27 (44.4%)	12/23 (52.2%)	**OR 0.73** (0.24 to 2.24)	**78 fewer per 1,000** (from 314 fewer to 188 more)	⨁⨁◯◯ LOW
Any adverse event											
2 [3,4]	randomised trials	serious [3,b]	not serious	not serious	very serious [a]	none	76/103 (73.8%)	72/96 (75.0%)	**OR 0.95** (0.50 to 1.80)	**10 fewer per 1,000** (from 150 fewer to 94 more)	⨁◯◯◯ VERY LOW
Infections											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulse IV cyclophosphamide	Continuous oral cyclophosphamide	Relative (95% CI)	Absolute (95% CI)	
2 [1,3,4]	randomised trials	not serious	not serious	not serious	very serious [a]	none	31/103 (30.1%)	37/96 (38.5%)	**OR 0.57** (0.20 to 1.61)	**122 fewer per 1,000** (from 274 fewer to 117 more)	⨁⨁◯◯ LOW

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Treatment would differ if the upper versus the lower boundary of the CI represented the truth

b. No masking for RCT; since only 2 studies included may bias the results as the weight increased vs. the other outcomes that may be less effected.

References

1. Adu, 1997.

2. Haubitz, 1998.

3. deGroot, 2009.

4. Guillevin, 1997.

- **References:**

- Included Randomized Controlled Trials:

Author	Year	Title
D. Adu	1997	Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis
K. de Groot	2009	Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial
M. Haubitz	1998	Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study
L. Guillevin	1997	A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis

- Studies reviewed and excluded:

Author	Year	Title	Comment
T. Girard	2001	Are antineutrophil cytoplasmic antibodies a marker predictive of relapse in Wegener's granulomatosis? A prospective study	Excluded, serves as Single arm

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Induction

- **PICO question 6:** In patients with active severe GPA/MPA, what is the impact of initiating treatment with rituximab 1000 mg IV days 1 and 15 vs. rituximab 375 mg/m2 qweek x 4 weeks on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Disease Activity, Disease Damage, Relapse, Death, Infection, Serious Adverse Events, Toxicity Leading to Discontinuation (e.g., hypogammaglobulinemia)

11. In patients with active severe GPA/MPA, what is the impact of initiating treatment with rituximab 1000 mg IV days 1 and 15 vs. rituximab 375 mg/m2 qweek x 4 weeks on disease-related outcomes and treatment-related adverse events?
    - No Comparative Data Available

12. In patients with active severe GPA/MPA, what is the impact of initiating treatment with rituximab 1000 mg IV days 1 and 15 on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention used in relevant population	Results	Comments
Remission – One study of 58 relavent patients demonstrated both RTX regimens to induce remission at similar rates.	Jones, 2009	Retrospective, standardize data collection, multicenter, single nation	20 months (median)	65 sequential patients that received RTX for refractory AAV (10 MPA, 46 GPA, 5 CSS, 4 unclassified)	26 patients received four infusions of 375 mg/m2 each given 1 week apart 32 patients received two infusions of 1 gram RTX each given 2 weeks apart	No statistically different rate of remission in the 'lymphoma' protocol vs the 'RA' protocol (81% and 75%, respectively	More of the patients who received the 2 1-gm infusions of rituximab were treated with a course of CYC just prior to the rituximab course.
Time to first relapse - One study of 58 relavent patients demonstrated both RTX regimens to have similar rates of relapse.	Jones, 2009	Retrospective, standardize data collection, multicenter, single nation	20 months (median)	65 sequential patients that received RTX for refractory AAV (10 MPA, 46 GPA, 5 CSS, 4 unclassified)	26 patients received four infusions of 375 mg/m2 each given 1 week apart 32 patients received two infusions of 1 gram RTX each given 2 weeks apart	No statistically different time to first relapse ("duration of reission") in the 'lymphoma' protocol vs the 'RA' protocol (Figure 4B in the paper).	More of the patients who received the 2 1-gm infusions of rituximab were treated with a course of CYC just prior to the rituximab course.

13. In patients with <u>active severe GPA/MPA</u>, what is the impact of initiating treatment with rituximab 375 mg/m2 qweek x 4 weeks on disease-related outcomes and treatment-related adverse events?
    - **Patient Important Outcomes**

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention used in relevant population	Results	Comments
Treatment related adverse effect (BMI change) – One study of ~200 patients demonstrated tendency for higher BMI in patients that received RTX 375mg/m2 protocol.	Wallace, 2017	Subanalysis of RCT (RAVE trial)	18 months	147 GPA patients 48 MPA patients Baseline mean BMI was 28.8+/- 6.3 kg/m2.	Patients with [BVAS/WG[1]] of 3, or 1 major item) were assigned to either CYC (2 mg/kg, adjusted for renal insufficiency) for 3–6 months, followed by azathioprine (AZA; 2 mg/kg) for a total of 18 months; or RTX (4 weekly infusions of 375 mg/m2) followed by placebo	Randomization to rituximab emerged as a predictor of BMI change with month 6 increase in BMI of 0.9 +/- 0.3 kg/m2 compared to CYC group. Disease activity improvement, glucocorticoid exposure, and randomization to Rituximab were each independently associated with increase in BMI ($p < 0.001$ for all analyses)	Patients in both groups received the same glucocorticoid protocol, which included 1–3 days of intravenous methylprednisolone followed by 1 mg/kg/day of prednisone.

- **References:**

- Randomized Controlled Trials:

  None

- Comparactive Observational Studies:

  None

- Single Arm Studies:

[1] Birmingham Vasculitis Activity Score for Wegener's Granulomatosis

Author	Year	Title
Z. S. Wallace	2017	Effect of Disease Activity, Glucocorticoid Exposure, and Rituximab on Body Composition During Induction Treatment of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis
Jones, R. B.	2009 (A&R)	A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody–associated vasculitis.

- Studies reviewed and excluded:

Author	Year	Title	Comments
P. Charles	2014	Rituximab for induction and maintenance treatment of ANCA-associated vasculitides: a multicentre retrospective study on 80 patients	Exclude. There were four different Rituxan regimens, but results were analyzed together. (did not separate results based on regimen)
X. Puechal	2018	Rituximab for induction and maintenance therapy of granulomatosis with polyangiitis: a single-centre cohort study on 114 patients	Exclude. There were two different Rituxan regimens, but results were analyzed together. (did not separate results based on regimen)
F. B. Cortazar	2017	Effect of Continuous B Cell Depletion With Rituximab on Pathogenic Autoantibodies and Total IgG Levels in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis	Exclude: used combination Rituxan and Cytoxan for induction tx
E. Besada	2016	CD4 cell count and CD4/CD8 ratio increase during rituximab maintenance in granulomatosis with polyangiitis patients	Exclude. Study patients received Cytoxan before rituximab. Also rituxan was continued as maintenance therapy for 24 months. This study analyzed treatment adverse event of rituxan as maintenance therapy
A. Knight	2016	Late-onset neutropenia after rituximab in ANCA-associated vasculitis	Exclude. There were different Rituxan regimens, but results were analyzed together. (did not separate results based on regimen)
D. Geetha	2016	Rituximab for treatment of severe renal disease in ANCA associated vasculitis	Exclude. There were two different Rituxan regimens, but results were analyzed together. (did not separate results based on regimen)

E. Besada	2014	Serum immunoglobulin levels and risk factors for hypogammaglobulinaemia during long-term maintenance therapy with rituximab in patients with granulomatosis with polyangiitis	Exclude. This study analyzed treatment effect of rituxan as long term maintenance therapy (PICO 6 queries rituxan as induction treatment)
T. Turner-Stokes	2014	Induction treatment of ANCA-associated vasculitis with a single dose of rituximab	Exclude. Only used one dose of rituxan 375 mg/m2
K. Wawrzycka-Adamczyk	2014	Lower doses of rituximab in remission induction for refractory granulomatosis with polyangiitis	Exclude. Patients were only given lower rituxan dose (median 1.0 gram)
E. Besada	2013	Long-term efficacy and safety of pre-emptive maintenance therapy with rituximab in granulomatosis with polyangiitis: results from a single centre	Exclude. This study analyzed rituxan as maintenance therapy (PICO 6 queries rituxan as induction treatment)
R. B. Jones	2009	A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis	Exclude. This study was on refractory GPA. Might be more appropriate for PICO 30. All patients who received rituximab as first-line therapy were excluded.
L. Guillevin	2003	Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients	Exclude. Rituxan was not used in this study.

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Induction

- **PICO question 7:** In patients with active severe GPA/MPA, what is the impact of using avacopan + cyclophosphamide/rituximab vs. cyclophosphamide/rituximab + steroids alone on disease-related outcomes and treatment-related adverse events.

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, serious adverse events, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypogammaglobulinemia, hyperglycemia, decreased bone mineral density)

14. In patients with active severe GPA/MPA, what is the impact of using avacopan + cyclophosphamide/rituximab vs. cyclophosphamide/rituximab + steroids alone on disease-related outcomes and treatment-related adverse events.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Avacopan+Cytoxan Rituxan	Cytoxan Rituxan +GC for active severe GPA/MPA	Relative (95% CI)	Absolute (95% CI)	
Complete remission (BVAS=0) at week 12											
1	randomised trials	not serious	not serious	not serious	serious [a]	none	7/21 (33.3%)	8/20 (40.0%)	**OR 0.75** (0.21 to 2.68)	**67 fewer per 1,000** (from 277 fewer to 241 more)	⊕⊕⊕◯ MODERATE
Sustained remission week 4 through week 12-secondary end point											
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	6/21 (28.6%)	1/20 (5.0%)	**OR 7.60** (0.82 to 70.16)	**236 more per 1,000** (from 9 fewer to 737 more)	⊕⊕◯◯ LOW
Renal response at week 12-secondary response											
1	randomised trials	not serious	not serious	not serious	serious [a]	none	6/18 (33.3%)	8/20 (40.0%)	**OR 0.75** (0.20 to 2.83)	**67 fewer per 1,000** (from 282 fewer to 254 more)	⊕⊕⊕◯ MODERATE
Serious adverse events (vasculitis, infection, bone fracture, liver enzyme elevation, renal impairment)											
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	8/22 (36.4%)	4/23 (17.4%)	**OR 2.71** (0.68 to 10.84)	**189 more per 1,000** (from 49 fewer to 521 more)	⊕⊕◯◯ LOW
grade 3 or greater adverse events (DVT, febrile infection, pancreatic/liver enzyme elevation, renal impairment, renal vasculitis)											
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	2/22 (9.1%)	2/23 (8.7%)	**OR 1.05** (0.13 to 8.18)	**4 more per 1,000** (from 75 fewer to 351 more)	⊕⊕◯◯ LOW
Infections											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Avacopan+Cytoxan Rituxan	Cytoxan Rituxan +GC for active severe GPA/MPA	Relative (95% CI)	Absolute (95% CI)	
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	1/22 (4.5%)	1/23 (4.3%)	**OR 1.05** (0.06 to 17.85)	**2 more per 1,000** (from 41 fewer to 404 more)	⨁⨁◯◯ LOW

Grade 3 lymphopenia

1	randomised trials	not serious	not serious	not serious	very serious [a]	none	3/22 (13.6%)	0/23 (0.0%)	**OR 8.44** (0.41 to 173.45)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Wide CI; Clinical action would differ if the upper versus the lower boundary of the CI represented the truth.

- **References:**

Included Randomized Controlled Trial:

Author	Year	Title
D. R. W. Jayne	2017	Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Induction

- **PICO question 8:** In patients with active[2] non-severe GPA[3], what is the impact of initiating treatment with azathioprine + glucocorticoids vs. methotrexate + glucocorticoids on disease-related outcomes and treatment-related adverse events?

[2] Active disease: new, persistent, or worsening clinical signs and/or symptoms attributed to GPA/MPA and not related to prior damage

[3] Non-severe GPA: vasculitis without life/organ-threatening manifestations (e.g., sinusitis)

- Critical Outcomes: Disease Activity, Disease Damage, Relapse, Death, Malignancy, Infection, Toxicity Leading to Discontinuation (e.g., leukopenia, hepatotoxicity, hyperglycemia, decreased bone mineral density)

15. In patients with active non-severe GPA, what is the impact of initiating treatment with azathioprine + glucocorticoids vs. methotrexate + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - No Comparative Data Available

16. In patients with active non-severe GPA, what is the impact of initiating treatment with azathioprine + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - **Patient Important Outcomes**

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results
Remission - one study with 11 patients who received AZA and had a rate of 9% only.	Fauci, 1983	Case-series	4-6 weeks to several months	11 patients with active GPA who started taking AZA because of potential concern of toxicity by CYC	Azathioprine	1/11 (9%)
Failure – one study with 11 patients who received AZA and had a rate of 91%.	Fauci, 1983	Case-series	4-6 weeks to several months	11 patients with active GPA who started taking AZA because of potential concern of toxicity by CYC	Azathioprine	10/11 (91%)

17. In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - **Patient Important Outcomes**

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results	Comments
Remission- 117 patients total. Overall, patients were able to achieve remission with MTX, consistent across studies	Kumar, 2001	retrospective	unknown	25 GPA in series, but only 2 limited GPA with flare involving eye treated with MTX	25 patients with GPA (2 limited disease) induced with prednisone and oral Cytoxan. Only 2 patients tx'd with oral pred and MTX 10-12.5mg weekly)	2/2 ocular flares treated with MTX achieved remission	Very small numbers (n=2) for those tx'd with MTX/pred
	Villaforte, 2007	Retrospective review, direct evidence	Median 4.5 years	82 patients with new onset GPA. 57 with severe disease induced with cyc. 25	New onset GPA patients treated with CYC 2mg/kg and pred. mild/mod disease induced with MTX (n=25) and	22/25 (88%) patients tx'd with MTX achieved remission	88% of nonsevere GPA patients achieved remssion with MTX

				with mild-mod disease induced with MTX and steroid (creat<2)	steroid (creat <2) weekly 15mg/wk increased over 4-8 wk to 25mg/week (if needed) and GCS 1mg/kg/d (decreased by 5mg/week after 1 month of therapy). Tx with MTX recommended for at least 2 years. BVAS and labs measured monthly		
	Stone, 1999	retrospective		19 patients with non-life threatening GPA. No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hospitalized at presentation. 94.7% met ACR criteria for GPA.	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	17/19 (89%) improved with treatment and 14 (74%) achieved remission. Only 2 patients (11%) achieved complete remission Remission defined as absence of any active disease in any organ system for at least one month while the patient continued treatment (either MTX or pred), and complete remission as no activity for 1 month off all medications. Relapse defined as recurrence of active GPA in patient who previously achieved remission	74% (14/19) GPA patients induced with MTX achieved remission. Only 2 patients (11%) achieved complete remission. Combination tx is effective but chronic disease courses are the rule with high likelihood of relapse.
	Sneller, 1995	Open label, prospective	19 months	42 patients with active, non severe disease. All pts met ACR criteria for GPA.	All patients rec'd oral pred at 1mg/kg/day. Oral MTX started at 0.3mg/kg (not to exceed 15mg) was given weekly and	Remission achieved in 30/42 (71%) of patients. Time to	In patients with non severe GPA, MTX is able to achieve remission in 71%.

				Excluded those with life threatening disease, Creat>2.5, pulm hemorrhage, chronic liver disease, pregnancy, immunosuppression	increased by 2.5mg weekly up to dose of 20-25mg/week if tolerated (maintained at that level).	remission was 4.2 months	36% relapsed after a median of 29 months
	Hoffman, 1992	Open label pilot study	14.5 month	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	Remission achieved in 69% of patients. 7% improved but had smoldering disease that precluded total withdrawl of GC	Remisson achieved in 69% of patients (20/29)
	deGroot, 2005	RCT	18 months	51 patients with antineutrophilcytoplasmic antibody–associated systemic vasculitis (AASV)	2mg/kg/day, 20–25 mg/week of oral MTX + prednisolone 1 mg/kg/day, tapered to 15mg/day at 12 weeks and 7.5mg/day by 6 months.	Remission rate at 6 months was 89.8%	Data from one arm of RCT
Duration of remission- 86 patients included but length of remission variable across studies (median 10 months, 20.5 and 29 months)	Villaforte, 2007	Retrospective review, direct evidence	Median 4.5 years	82 patients with new onset GPA. 57 with severe disease induced with cyc. 25 with mild-mod disease induced with MTX and steroid (creat<2)	New onset GPA patients treated with CYC 2mg/kg and pred. mild/mod disease induced with MTX (n=25) and steroid (creat <2) weekly 15mg/wk increased over 4-8 wk to 25mg/week (if needed) and GCS 1mg/kg/d (decreased by 5mg/week after 1 month of therapy). Tx with MTX recommended for at least 2 years. BVAS and labs measured monthly	Among patients with 1 or more remissions lasting at least 6 months, mean duration of remission before relapse was 20.5 months (SD +/- 21.2 mo)	Non-severe GPA patients induced with MTX had mean duration of remission for 20.5 months
	Stone, 1999	retrospective		19 patients with non-life threatening GPA. No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2).	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by	Among the 14 patients who achieved remission, 8 relapsed and median time to	Of the 14 who achieved remission, 8 relapsed at ~10 months

				37% hospitalized at presentation. 94.7% met ACR criteria for GPA.	end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	relapse was 10 months (range 4-31)	
	Sneller, 1995	Open label, prospective	19 months	42 patients with active, non severe disease. All pts met ACR criteria for GPA. Excluded those with life threatening disease, Creat>2.5, pulm hemorrhage, chronic liver disease, pregnancy, immunosuppression	All patients rec'd oral pred at 1mg/kg/day. Oral MTX started at 0.3mg/kg (not to exceed 15mg) was given weekly and increased by 2.5mg weekly up to dose of 20-25mg/week if tolerated (maintained at that level).	Median time to relapse in patients achieving remission was 29 months	In patients with non severe GPA, MTX is able to achieve remission in 71%. 36% relapsed after a median of 29 months
Serious infection/requring hospitalization- 25 patients included in 1 study. Relatively low # of hospitalizations, so favors using MTX	Villaforte, 2007	Retrospective review, direct evidence	Median 4.5 years	82 patients with new onset GPA. 57 with severe disease induced with cyc. 25 with mild-mod disease induced with MTX and steroid (creat<2)	New onset GPA patients treated with CYC 2mg/kg and pred. mild/mod disease induced with MTX (n=25) and steroid (creat <2) weekly 15mg/wk increased over 4-8 wk to 25mg/week (if needed) and GCS 1mg/kg/d (decreased by 5mg/week after 1 month of therapy). Tx with MTX recommended for at least 2 years. BVAS and labs measured monthly	2/25 (8%) of MTX/CS patients were hospitalized	8% of patients with non severe GPA induced with MTX required hospitalization for infection
Relapse- 115 patients included. 10-69.5% relapsed across studies. Overall shows MTX can achieve remission, but	Villaforte, 2007	Retrospective review, direct evidence	Median 4.5 years	82 patients with new onset GPA. 57 with severe disease induced with cyc. 25 with mild-mod disease induced with MTX and steroid (creat<2)	New onset GPA patients treated with CYC 2mg/kg and pred. mild/mod disease induced with MTX (n=25) and steroid (creat <2) weekly 15mg/wk increased over 4-8 wk to 25mg/week (if needed) and GCS 1mg/kg/d (decreased	15/25 patients on MTX/CS induction relapsed	15/25 GPA patients induced with MTX had a relapse

significant proportion of patients relapse.					by 5mg/week after 1 month of therapy). Tx with MTX recommended for at least 2 years. BVAS and labs measured monthly		
	Stone, 1999	retrospective	?	19 patients with non-life threatening GPA. No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hospitalized at presentation. 94.7% met ACR criteria for GPA.	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	17/19 achieved remission, but half (8/17, 57%) of those suffered relapses and no patient achieved a durable, complete remission (disease free status free of all meds). Relapse defined as recurrence of active GPA in patient who previously achieved remission	~half of patients who achieved remission relapsed
	Sneller, 1995	Open label, prospective	19 months	42 patients with active, non severe disease. All pts met ACR criteria for GPA. Excluded those with life threatening disease, Creat>2.5, pulm hemorrhage, chronic liver disease, pregnancy, immunosuppression	All patients rec'd oral pred at 1mg/kg/day. Oral MTX started at 0.3mg/kg (not to exceed 15mg) was given weekly and increased by 2.5mg weekly up to dose of 20-25mg/week if tolerated (maintained at that level).	11/30 relapsed after achieving remission (36%). Time to relapse in those who achieved remission was 29 months	In patients with non severe GPA, MTX is able to achieve remission in 71%. 36% relapsed after a median of 29 months
	Hoffman, 1992	Open label pilot study	14.5 month	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	20/29 achieved remission and 2 of them had a relapse (when pred dc'd) requiring retreatment with MTX/GC in one case and CYC in the other	2 patients in remission (out of 20) had a relapse

	deGroot, 2005	RCT	18 months	51 patients with antineutrophilcytoplasmic antibody–associated systemic vasculitis (AASV)	2mg/kg/day, 20–25 mg/week of oral MTX + prednisolone 1 mg/kg/day, tapered to 15mg/day at 12 weeks and 7.5mg/day by 6 months.	Relapse rates at 18 months were 69.5%.	Data from one arm of RCT
Renal disease- 33 patients with renal disease. MTX in near normal creat was not associated with long term decline in renal function. In study with more active renal disease, 4/12 improved. MTX can be effective in renal disease	Langford, 2000	Open label, prospective	76 months (20-108)	42 patients with GPA, 21 with active GN. Mean serum creat in GN patients was 1.4mg/dl. All had active disease. Excluded those with life threatening disease, Creat>2.5, pulm hemorrhage, chronic liver disease, pregnancy, immunosuppression	All patients rec'd oral pred at 1mg/kg/day. Oral MTX started at 0.3mg/kg (not to exceed 15mg) was given weekly and increased by 2.5mg weekly up to dose of 20-25mg/week if tolerated (maintained at that level).	20/21 patients with GN treated with MTX +CS achieved renal remission. At 1 month and 6 onths following tudy entry, serum creat in all patients either remained stable or improved. Only 2 had a rise of >0.2 in creat from time of enrollment to end of follow up. Of the remaining 18, 12 had stable renal function and 6 had improvement in creat by more than 0.2	Use of MTX and pred as initial therapy for pts with GPA related GN and a normal or near-normal level of serum creatinine was not associated with a long-term decline in renal function
	Hoffman, 1992	Open label pilot study	14.5 month	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	4 of 12 patients with active renal disease were treated effectively	
Side Effects- 48 patients in 2 studies. Transaminitis most common SE, some episodes of PJP	Stone, 1999	retrospective	?	19 patients with non-life threatening GPA. No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hospitalized at	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by	2 (11%) of patients on MTX stopped treatment because of side effects (major LFT abnormalities in both cases). 6/19	Transaminitis was most common side effect and led to discontinuation in 2/19 patients

and pneumonitis. Overall aceptible safety profile				presentation. 94.7% met ACR criteria for GPA.	2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	(32%) had some form of hepatotoxicity (in 4 it was transaminitis between 1-2x ULN).	
	Hoffman, 1992	Open label pilot study	14.5 month	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	2 patients (7%) developed fever, dry cough and dyspnea within 2-3 months of starting MTX/GC leading to discontinuation of MTX. 34% had some sort of MTX toxicity. 3 (10%) had transaminitis. 3 (10%) had PCP pneumonia	
	deGroot, 2005	RCT	18 months	51 patients with antineutrophilcytoplasmic antibody–associated systemic vasculitis (AASV)	2mg/kg/day, 20–25 mg/week of oral MTX + prednisolone 1 mg/kg/day, tapered to 15mg/day at 12 weeks and 7.5mg/day by 6 months.	34%	Data from one arm of RCT
Death- 2 deaths in 48 patients	Stone, 1999	Retrospective		19 patients with non-life threatening GPA. No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hospitalized at presentation. 94.7% met ACR criteria for GPA.	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	0 patients died	No deaths

	Hoffman, 1992	Open label pilot study	14.5 month	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	2 patients died	2 patients of 29 developed fatal infections leading to respiratory failure/sepsis
	deGroot, 2005	RCT	18 months	51 patients with antineutrophilcytoplasmic antibody–associated systemic vasculitis (AASV)	2mg/kg/day, 20–25 mg/week of oral MTX + prednisolone 1 mg/kg/day, tapered to 15mg/day at 12 weeks and 7.5mg/day by 6 months.	2/51 (4%)	Data from one arm of RCT
Prednisone dose- 2 studies with 48 patients. Favors using MTX as majority were able to wean pred dose or stop it	Stone, 1999	retrospective		19 patients with non-life threatening GPA. No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hopsitalized at presentation. 94.7% met ACR criteria for GPA.	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	15 patients (79%) were able to taper pred to <10mg/day	A majority of patients were able to wean prednisone
	Hoffman, 1992	Open label pilot study	14.5 month	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	13/20 (65%) of patients in whom remission was achieved were able to discontinue GC therapy with no flare during the following 2-17 months	13/20 (65%) of patients in whom remission was achieved were able to discontinue GC therapy with no flare during the following 2-17 months
	deGroot, 2005	RCT	18 months	51 patients with antineutrophilcytoplasmic antibody–	2mg/kg/day, 20–25 mg/week of oral MTX + prednisolone 1 mg/kg/day.	Prednisolone was tapered to 15mg/day at 12	Data from one arm of RCT

				associated systemic vasculitis (AASV)		weeks and 7.5mg/day by 6 months, and discontinued by 12 months.	

- **References:**

- Randomized Controlled Trials:
  None
- Comparative Observational Studies:
  None
- Included Single Arm Studies: (8)

Author	Year	Title
A. Kumar	2001	Wegener's granulomatosis in India: clinical features, treatment and outcome of twenty-five patients
A. Villa-Forte	2007	Substitution of methotrexate for cyclophosphamide in Wegener granulomatosis: a 12-year single-practice experience
C. A. Langford	2000	Use of methotrexate and glucocorticoids in the treatment of Wegener's granulomatosis. Long-term renal outcome in patients with glomerulonephritis
J. H. Stone	1999	Treatment of non-life threatening Wegener's granulomatosis with methotrexate and daily prednisone as the initial therapy of choice
M. C. Sneller	1995	An analysis of forty-two Wegener's granulomatosis patients treated with methotrexate and prednisone
G. S. Hoffman	1992	The treatment of Wegener's granulomatosis with glucocorticoids and methotrexate
Fauci A.S.	1983	Wegener's Granulomatosis: Prospective Clinical and Therapeutic Experience With 85 Patients for 21 Years.
De Groot, K.	2005	Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody–associated vasculitis.

- Studies reviewed and excluded:

Author	Year	Title	Comments

C. Pagnoux	2015	Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy	Exclude: 35 patients were treated with mainenentce aza but the induction/initial treatment was with Cytoxan, so does not answer PICO 8
A. Kumar	2001	Wegener's granulomatosis in India: clinical features, treatment and outcome of twenty-five patients	Exclude:Very small numbers 2/2 tx'd with MTX achieved remission
J. H. Stone	2001	Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety	Exclude: Does not answer PICO 8
K. Devarasetti	2018	Anti-neutrophil cytoplasmic autoantibodies associated vasculitis - Clinical profile and outcomes	Exclude: Does not answer PICO 8

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Induction

- **PICO Question 9:** In patients with active[4] non-severe GPA[5], what is the impact of initiating treatment with azathioprine+ glucocorticoids vs. MMF+ glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Disease Activity, Disease Damage, Relapse, Death, Malignancy, Infection, Toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hyperglycemia, decreased bone mineral density)

18. In patients with active non-severe GPA, what is the impact of initiating treatment with azathioprine+ glucocorticoids vs. MMF+ glucocorticoids on disease-related outcomes and treatment-related adverse events?
    No Comparative Data Available

19. In patients with active non-severe GPA, what is the impact of initiating treatment with azathioprine+ glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - Patient Important Outcomes

[4] Active disease: new, persistent, or worsening clinical signs and/or symptoms attributed to GPA/MPA and not related to prior damage
[5] Non-severe disease: vasculitis without life/organ-threatening manifestations (e.g., sinusitis)

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results
Remission - one study with 11 patients who receiver AZA and had a rate of 9% only.	Fauci, 1983	Case-series	4-6 weeks to several months	11 patients with active GPA who started taking AZA because of potential concern of toxicity by CYC	Azathioprine	1/11 (9%)
Failure – one study with 11 patients who receiver AZA and had a rate of 91%.	Fauci, 1983	Case-series	4-6 weeks to several months	11 patients with active GPA who started taking AZA because of potential concern of toxicity by CYC	Azathioprine	10/11 (91%)

20. In patients with active non-severe GPA, what is the impact of initiating treatment with MMF+ glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - Patient Important Outcomes

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results
Disease Activity/Remission: In 87 patients with GPA/MPA treated with MMF 67-77% of patients achieved remission by 6 months. Limitations are that some patients had severe disease (Silva et al.).	Jones RB, 2019	RCT, but for PICO single arm	18 months	70 pts with new diagnosis of GPA or MPA with either positive ANCA or biopsy proven. Exclusion of life threatening manifestations, rapid renal decline or eGFR less then 15.	MMF 2g/d (dose increases to 3g/d for uncontrolled disease at 4 weeks) + Prednisolone 1mg/kg/d initially, reducing by 5mg/d at 6 months. Changed to AZA after remission achieved at 3-6 months. Prednisolone 5mg/d continued throughout f/u.	-Remission at 6 months: 47/70 (67%) -Time to remission (Median 91 d, IQR 44-95)
	Silva F, 2010	Prospective, open label	72 weeks	17 patients with MPA (by CHCC), positive p(MPO)-ANCA, renal involvement and Cr ≤ 3 mg/dl	MMF titrated to 1,000mg BID (1500mg BID in those failing to respond) (MMF was continued for 18 months) + Methylprednisolone 1-3g followed by 1mg/kg/d prednisone x 2 weeks then tapered off by 6 months.	Remission at 6 months: 13/17 (76.5%) Sustained remission up to 18 months: 12/17 (70.6%)

Relaspes: In 87 patients with GPA/MPA treated with MMF 8-37% relapsed at 18 months. Relapses were more frequent in PR3-ANCA positive. Limitations are that patients with severe disease were included (Silva et al.)	Jones RB, 2019	RCT, but for PICO single arm	18 months	70 pts with new diagnosis of GPA or MPA with either positive ANCA or biopsy proven. Exclusion of life threatening manifestations, rapid renal decline or eGFR less then 15.	MMF 2g/d (dose increases to 3g/d for uncontrolled disease at 4 weeks) + Prednisolone 1mg/kg/d initially, reducing by 5mg/d at 6 months. Changed to AZA after remission achieved at 3-6 months. Prednisolone 5mg/d continued throughout f/u.	-Relapses (18 mon) 23/63 (36.5%) -Major relapses (18 mon) 4/63 (6.3%) -Ralpse in PR3 positive (18 mon) 19/37 (51.4%) - Relapse in MPO positive (18 mon) 4/25 (16%)
	Silva F, 2010	Prospective, open label	72 weeks	17 patients with MPA (by CHCC), positive p(MPO)-ANCA, renal involvement and Cr ≤ 3 mg/dl	MMF titrated to 1,000mg BID (1500mg BID in those failing to respond) (MMF was continued for 18 months) + Methylprednisolone 1-3g followed by 1mg/kg/d prednisone x 2 weeks then tapered off by 6 months.	Relapses (18 mon): 1/13 (7.7%) (relapse occurred at 9 months)
Response to therapy as measured by BVAS change Total of 12 patients. Overall effect estimate was high. No comparison to other studies.	Joy M, 2005	Single arm. Open lable pilot efficacy and safety study. Dose-escalating approach.	6 months (10/12 pts completed the 6 month treatment phase and were evaluated for an additional 6 months. 2 were withdrawn early.	Patient swere either: Resistant to cyclophosphamide Or Had relapsing disease. 12 adults: 6 with relapsing disease and 6 with disease resistant to cyclophosphamide. GPA=7 pts MPA = 2 pts Renal limited vasculitis = 2 EGPA=1	MMF started at 500 mg twice daily and increased to 1000-1500 mg twice daily by increments of 250 mg twice daily every 2 weeks. Pts could receive prednisone up to 80 mg/d for 30 days, then tapered, and discontinued by the end of the 3rd month. Pts with rapid loss of renal function could receive pulse solumedrol for 3 days.	1 pt was withdrawn within 6 weeks because of febrile illness. 1 pt was withdrawn within 2 weeks because of rapid deterioration of pulmonary disease. 9/10 pts received 1000-1500 mg twice daily and 1/10 received 750 mg twice daily because of neutropenia. BVAS decreased from average 9.1+/- 3.5 (range 3-17) to 2.8 +/- 1.9 (range 1-6), representing a mean change of 7.8 +/- 5.4 at the 24th week (p=0.0013) and to 2.8 +/- 4.3 (range 0-13), representing a mean change of 7.1+/-5.4 at week 52 (p=0.0044).
ANCA titers In 29 patients mixed population of GPA/MPA/EGPA there was no difference in ANCA	Joy M, 2005	As Above	As Above	As Above	As Above	ANCA at baseline was compared to ANCA at weeks 24 and 52. ANCA changes between baseline and week 24 and between baseline and week 54 did not reach statistical significance. (p=0.3736 and p=0.8392)

titers in one study with a significant decline in MPO-ANCA in another study.	Silva F, 2010	Prospecti ve, open label	72 weeks	17 patients with MPA (by CHCC), positive p(MPO)-ANCA, renal involvement and Cr ≤ 3 mg/dl	MMF titrated to 1,000mg BID (1500mg BID in those failing to respond) (MMF was continued for 18 months) + Methylprednisolone 1-3g followed by 1mg/kg/d prednisone x 2 weeks then tapered off by 6 months.	Median MPO titer: 54EU/ml (16-133) at baseline; 5EU/ml (4-10) at 24 wks ($p<0.01$), and 5EU/ml (3-10) at 72 weeks ($p<0.01$).
Persistent use of steroids Total of 12 patients. Overall estimate effect was high. No comparison to other studies.	Joy M, 2005	As Above	As Above	As Above	As Above	Steroids were successfully stopped in 2/5 pts who were on prednisone at study entry. Only one pt was on prednisone at week 52 Baseline (mean and range) pred dose (42 mg, 20-60 mg) was 4-fold higher than dose at week 24 (12.5 mg, 10-20 mg)
Adverse events: From Joy et al. it is unclear how many patients developed AE. In 87 patients with GPA/MPA treated with MMF SAE were reported in 0-50%. In 70 patients serious infections were 26%, death 7% and malingnacy 1%. Limitations include some patients included with severe disease.	Joy M, 2005	As Above	As Above	As Above	As Above	Upper resp infection – 5 UTI – 1 Zoster – 1 Diarrhea – 4 Abd cramping, nausea/vomiting – 2 Constipation – 1 Leukopenia – 2 Insomnia – 2 Epigastric pain- 1 Increased serum amylase – 1 . Adverse events were transient and resolved spontaneously or with dose reduction. None required removal from the study.
	Jones RB, 2019	RCT, but for PICO single arm	18 months	70 pts with new diagnosis of GPA or MPA with either positive ANCA or biopsy proven. Exclusion of life threatening manifestations, rapid renal decline or eGFR less then 15.	MMF 2g/d (dose increases to 3g/d for uncontrolled disease at 4 weeks) + Prednisolone 1mg/kg/d initially, reducing by 5mg/d at 6 months. Changed to AZA after remission achieved at 3-6 months.	SAE: 35/70 patients (50%) Serious infection: 18/70 (26%) Death: 5/70 (7%) Malignancy: 1/70 (1%)

					Prednisolone 5mg/d continued throughout f/u.	
	Silva F, 2010	Prospective, open label	72 weeks	17 patients with MPA (by CHCC), positive p(MPO)-ANCA, renal involvement and Cr ≤ 3 mg/dl	MMF titrated to 1,000mg BID (1500mg BID in those failing to respond) (MMF was continued for 18 months) + Methylprednisolone 1-3g followed by 1mg/kg/d prednisone x 2 weeks then tapered off by 6 months.	No SAE reported Minor AE: 10/17 (58%)
Renal outcomes: In 17 patients with MPA only renal outcomes including eGRF and proteinuria improved by 72 weeks. All patients had renal involvement (i.e., severe disease).	Silva F, 2010	Prospective, open label	72 weeks	17 patients with MPA (by CHCC), positive p(MPO)-ANCA, renal involvement and Cr ≤ 3 mg/dl	MMF titrated to 1,000mg BID (1500mg BID in those failing to respond) (MMF was continued for 18 months) + Methylprednisolone 1-3g followed by 1mg/kg/d prednisone x 2 weeks then tapered off by 6 months.	eGFR: -baseline: 46ml/min (34-63) -wk 24: 47ml/min (33-72) (P=NS) -wk 72: 52 ml/min/m2 (35-67) (p<0.05) Proteinuria: -baseline: 889mg/24h (400-2208) -wk 24: 384mg/24h (151-1071) (p<0.01) -wk 72: 149mg/24h (36-561) (p<0.001)

Summary:
The outcome is favorable and authors suggest the use of MMF as an alternative agent for patients with mild to moderate persistently active disease.
Total number of patients was 12.
Consistency among studies cannot be verified as this is the only study using MMF on this specific population of resistant or relapsing disease.
The effect size cannot be calculated between 2 groups as the study only has one group but if calculated for the difference between BVAS at baseline and after treatment, it can be estimated to be high.

- **References:**

- Randomized Controlled Trials:

None

- Comparative Observational Studies:
  None

- Single Arm Studies:

Author	Year	Title
M. S. Joy	2005	A pilot study using mycophenolate mofetil in relapsing or resistant ANCA small vessel vasculitis
Fauci A.S.	1983	Wegener's Granulomatosis: Prospective Clinical and Therapeutic Experience With 85 Patients for 21 Years.
Jones RB	2019	Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial
Silva F	2010	Mycophenolate mofetil for induction and maintenance of remission in microscopic polyangiitis with mild to moderate renal involvement--a prospective, open-label pilot trial.

- Studies reviewed and excluded:

Author	Year	Title	Comments
J. H. Stone	2001	Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety	Exclude. Does not address the PICO question.
K. Devarasetti	2018	Anti-neutrophil cytoplasmic autoantibodies associated vasculitis - Clinical profile and outcomes	Exclude. 9 pts on AZA and 3 pts on MMF but no reported outcomes for these pts (Descriptive study).
L. Guillevin	2003	Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients	Exclude. Does not address the PICO question.

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Induction

- **PICO question 10:** In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate + glucocorticoids vs. MMF + glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hyperglycemia, decreased bone mineral density)

21. In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate + glucocorticoids vs. MMF + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - No comparative data available

22. In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate + glucocorticoids on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results	Comments
Remission- 117 patient total. Overall patient were able to achieve remission with MTX, consistent across studies	Kumar, 2001	Retrospective	unknown	25 GPA in series, but only 2 limited GPA with flare involving eye treated with MTX	25 patients with GPA (2 limited disease) induced with prednisone and oral Cytoxan. Only 2 patients tx'd with oral pred and MTX 10-12.5mg weekly)	2/2 ocular flares treated with MTX achieved remission	Very small numbers (n=2) for those tx'd with MTX/pred
	Villaforte, 2007	Retrospective review, direct evidence	Median 4.5 years	82 patients with new onset GPA. 57 with severe disease induced with cyc. 25 with mild-mod disease induced with MTX and steroid (creat<2)	New onset GPA patients treated with CYC 2mg/kg and pred. mild/mod disease induced with MTX (n=25) and steroid (creat <2) weekly 15mg/wk increased over 4-8 wk to 25mg/week (if needed) and GCS 1mg/kg/d (decreased by 5mg/week after 1 month of therapy). Tx with MTX recommended for at least 2 years. BVAS and labs measured monthly	22/25 (88%) patients tx'd with MTX achieved remission	88% of nonsevere GPA patients achieved remssion with MTX

	Stone, 1999	retrospective		19 patients with non-life threatening GPA. No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hospitalized at presentation. 94.7% met ACR criteria for GPA.	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	17/19 (89%) improved with treatment and 14 (74%) achieved remission. Only 2 patients (11%) achieved complete remission Remission defined as absence of any active disease in any organ system for at least one month while the patient continued treatment (either MTX or pred), and complete remission as no activity for 1 month off all medications. Relapse defined as recurrence of active GPA in patient who previously achieved remission	74% (14/19) GPA patients induced with MTX achieved remission. Only 2 patients (11%) achieved complete remission. Combination tx is effective but chronic disease courses are the rule with high likelihood of relapse.
	Sneller, 1995	Open label, prospective	19 months	42 patients with active, non severe disease. All pts met ACR criteria for GPA. Excluded those with life threatening disease, Creat>2.5, pulm hemorrhage, chronic liver disease, pregnancy, immunosuppression	All patients rec'd oral pred at 1mg/kg/day. Oral MTX started at 0.3mg/kg (not to exceed 15mg) was given weekly and increased by 2.5mg weekly up to dose of 20-25mg/week if tolerated (maintained at that level).	Remission achieved in 30/42 (71%) of patients. Time to remission was 4.2 months	In patients with non severe GPA, MTX is able to achieve remission in 71%. 36% relapsed after a median of 29 months

	Hoffman, 1992	Open label pilot study	14.5 month	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	Remission achieved in 69% of patients. 7% improved but had smoldering disease that precluded total withdrawl of GC	Remisson achieved in 69% of patients (20/29)
	deGroot, 2005	RCT	18 months	51 patients with antineutrophilcytoplasmic antibody–associated systemic vasculitis (AASV)	2mg/kg/day, 20–25 mg/week of oral MTX + prednisolone 1 mg/kg/day, tapered to 15mg/day at 12 weeks and 7.5mg/day by 6 months.	Remission rate at 6 months was 89.8%	Data from one arm of RCT
Duration of remission- 86 patients included but length of remission variable across studies (median 10 months, 20.5 and 29 months)	Villaforte, 2007	Retrospective review, direct evidence	Median 4.5 years	82 patients with new onset GPA. 57 with severe disease induced with cyc. 25 with mild-mod disease induced with MTX and steroid (creat<2)	New onset GPA patients treated with CYC 2mg/kg and pred. mild/mod disease induced with MTX (n=25) and steroid (creat <2) weekly 15mg/wk increased over 4-8 wk to 25mg/week (if needed) and GCS 1mg/kg/d (decreased by 5mg/week after 1 month of therapy). Tx with MTX recommended for at least 2 years. BVAS and labs measured monthly	Among patients with 1 or more remissions lasting at least 6 months, mean duration of remission before relapse was 20.5 months (SD +/- 21.2 mo)	Non-severe GPA patients induced with MTX had mean duration of remission for 20.5 months
	Stone, 1999	Retrospective		19 patients with non-life threatening GPA. No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hospitalized at presentation. 94.7% met ACR criteria for GPA.	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	Among the 14 patients who achieved remission, 8 relapsed and median time to relapse was 10 months (range 4-31)	Of the 14 who achieved remission, 8 relapsed at ~10 months

	Sneller, 1995	Open label, prospective	19 months	42 patients with active, non severe disease. All pts met ACR criteria for GPA. Excluded those with life threatening disease, Creat>2.5, pulm hemorrhage, chronic liver disease, pregnancy, immunosuppression	All patients rec'd oral pred at 1mg/kg/day. Oral MTX started at 0.3mg/kg (not to exceed 15mg) was given weekly and increased by 2.5mg weekly up to dose of 20-25mg/week if tolerated (maintained at that level).	Median time to relapse in patients achieving remission was 29 months	In patients with non severe GPA, MTX is able to achieve remission in 71%. 36% relapsed after a median of 29 months
Serious infection/requring hospitalization- 25 patients included in 1 study. Relatively low # of hospitalizations, so favors using MTX	Villaforte, 2007	Retrospective review, direct evidence	Median 4.5 years	82 patients with new onset GPA. 57 with severe disease induced with cyc. 25 with mild-mod disease induced with MTX and steroid (creat<2)	New onset GPA patients treated with CYC 2mg/kg and pred. mild/mod disease induced with MTX (n=25) and steroid (creat <2) weekly 15mg/wk increased over 4-8 wk to 25mg/week (if needed) and GCS 1mg/kg/d (decreased by 5mg/week after 1 month of therapy). Tx with MTX recommended for at least 2 years. BVAS and labs measured monthly	2/25 (8%) of MTX/CS patients were hospitalized	8% of patients with non severe GPA induced with MTX required hospitalization for infection
Relapse- 115 patients included. 10-69.5% relapsed across studies. Overall shows MTX can achieve remission, but significant proportion of patients relapse.	Villaforte, 2007	Retrospective review, direct evidence	Median 4.5 years	82 patients with new onset GPA. 57 with severe disease induced with cyc. 25 with mild-mod disease induced with MTX and steroid (creat<2)	New onset GPA patients treated with CYC 2mg/kg and pred. mild/mod disease induced with MTX (n=25) and steroid (creat <2) weekly 15mg/wk increased over 4-8 wk to 25mg/week (if needed) and GCS 1mg/kg/d (decreased by 5mg/week after 1 month of therapy). Tx with MTX recommended for at least 2 years. BVAS and labs measured monthly	15/25 patients on MTX/CS induction relapsed	15/25 GPA patients induced with MTX had a relapse
	Stone, 1999	retrospective	?	19 patients with non-life threatening GPA. No patient had	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred	17/19 achieved remission, but half (8/17, 57%) of those	~half of patients who achieved remission relapsed

				received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hospitalized at presentation. 94.7% met ACR criteria for GPA.	(median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	suffered relapses and no patient achieved a durable, complete remission (disease free status free of all meds). Relapse defined as recurrence of active GPA in patient who previously achieved remission	
	Sneller, 1995	Open label, prospective	19 months	42 patients with active, non severe disease. All pts met ACR criteria for GPA. Excluded those with life threatening disease, Creat>2.5, pulm hemorrhage, chronic liver disease, pregnancy, immunosuppression	All patients rec'd oral pred at 1mg/kg/day. Oral MTX started at 0.3mg/kg (not to exceed 15mg) was given weekly and increased by 2.5mg weekly up to dose of 20-25mg/week if tolerated (maintained at that level).	11/30 relapsed after achieving remission (36%). Time to relapse in those who achieved remission was 29 months	In patients with non severe GPA, MTX is able to achieve remission in 71%. 36% relapsed after a median of 29 months
	Hoffman, 1992	Open label pilot study	14.5 months	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	20/29 achieved remission and 2 of them had a relapse (when pred dc'd) requiring retreatment with MTX/GC in one case and CYC in the other	2 patients in remission (out of 20) had a relapse
	deGroot, 2005	RCT	18 months	51 patients with antineutrophilcytoplasmic antibody–associated systemic vasculitis (AASV)	2mg/kg/day, 20–25 mg/week of oral MTX + prednisolone 1 mg/kg/day, tapered to 15mg/day at 12 weeks and 7.5mg/day by 6 months.	Relapse rates at 18 months were 69.5%.	Data from one arm of RCT
Renal disease- 33 patients with renal disease. MTX in near	Langford, 2000	Open label, prospective	76 months (20-108)	42 patients with GPA, 21 with active GN. Mean serum creat in GN patients was	All patients rec'd oral pred at 1mg/kg/day. Oral MTX started at 0.3mg/kg (not to exceed 15mg) was given weekly and	20/21 patients with GN treated with MTX +CS achieved renal remission. At 1	Use of MTX and pred as initial therapy for pts with GPA related GN and

normal creat was not associated with long term decline in renal function. In study with more active renal disease, 4/12 improved. MTX can be effective in renal disease				1.4mg/dl. All had active disease. Excluded those with life threatening disease, Creat>2.5, pulm hemorrhage, chronic liver disease, pregnancy, immunosuppression	increased by 2.5mg weekly up to dose of 20-25mg/week if tolerated (maintained at that level).	month and 6 onths following tudy entry, serum creat in all patients either remained stable or improved. Only 2 had a rise of >0.2 in creat from time of enrollment to end of follow up. Of the remaining 18, 12 had stable renal function and 6 had improvement in creat by more than 0.2	a normal or near-normal level of serum creatinine was not associated with a long-term decline in renal function
	Hoffman, 1992	Open label pilot study	14.5 months	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	4 of 12 patients with active renal disease were treated effectively	
Side Effects- 48 patients in 2 studies. Transaminitis most common SE, some episodes of PJP and pneumonitis. Overall aceptible safety profile	Stone, 1999	retrospective	?	19 patients with non-life threatening GPA. No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hospitalized at presentation. 94.7% met ACR criteria for GPA.	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	2 (11%) of patients on MTX stopped treatment because of side effects (major LFT abnormalities in both cases). 6/19 (32%) had some form of hepatotoxicity (in 4 it was transaminitis between 1-2x ULN).	Transaminitis was most common side effect and led to discontinuation in 2/19 patients
	Hoffman, 1992	Open label pilot study	14.5 months	29 patients with non life threatening GPA.	Weekly administration of MTX (mean stable dose of 20mg)	2 patients (7%) developed fever, dry	

				All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	cough and dyspnea within 2-3 months of starting MTX/GC leading to discontinuation of MTX. 34% had some sort of MTX toxicity. 3 (10%) had transaminitis. 3 (10%) had PCP pneumonia	
	deGroot, 2005	RCT	18 months	51 patients with antineutrophilcytoplasmic antibody–associated systemic vasculitis (AASV)	2mg/kg/day, 20–25 mg/week of oral MTX + prednisolone 1 mg/kg/day, tapered to 15mg/day at 12 weeks and 7.5mg/day by 6 months.	34%	Data from one arm of RCT
Death- 2 deaths in 48 patients	Stone, 1999	retrospective		19 patients with non-life threatening GPA. No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hospitalized at presentation. 94.7% met ACR criteria for GPA.	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	0 patients died	No deaths
	Hoffman, 1992	Open label pilot study	14.5 months	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	2 patients died	2 patients of 29 developed fatal infections leading to respiratory failure/sepsis

	deGroot, 2005	RCT	18 months	51 patients with antineutrophilcytoplasmic antibody–associated systemic vasculitis (AASV)	2mg/kg/day, 20–25 mg/week of oral MTX + prednisolone 1 mg/kg/day, tapered to 15mg/day at 12 weeks and 7.5mg/day by 6 months.	2/51 (4%)	Data from one arm of RCT
Prednisone dose-2 studies with 48 patients. Favors using MTX as majority were able to wean pred dose or stop it	Stone, 1999	Retrospective		19 patients with non-life threatening GPA. No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hospitalized at presentation. 94.7% met ACR criteria for GPA.	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	15 patients (79%) were able to taper pred to <10mg/day	A majority of patients were able to wean prednisone
	Hoffman, 1992	Open label pilot study	14.5 month	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	13/20 (65%) of patients in whom remission was achieved were able to discontinue GC therapy with no flare during the following 2-17 months	13/20 (65%) of patients in whom remission was achieved were able to discontinue GC therapy with no flare during the following 2-17 months
	deGroot, 2005	RCT	18 months	51 patients with antineutrophilcytoplasmic antibody–associated systemic vasculitis (AASV)	2mg/kg/day, 20–25 mg/week of oral MTX + prednisolone 1 mg/kg/day.	Prednisolone was tapered to 15mg/day at 12 weeks and 7.5mg/day by 6 months, and discontinued by 12 months.	Data from one arm of RCT

23. In patients with active non-severe GPA, what is the impact of initiating treatment with MMF + glucocorticoids on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Remission	Jones RB, 2019	RCT, but for PICO single arm	18 months	70 pts with new diagnosis of GPA or MPA with either positive ANCA or biopsy proven. Exclusion of life threatening manifestations, rapid renal decline or eGFR less then 15.	MMF 2g/d (dose increases to 3g/d for uncontrolled disease at 4 weeks) + Prednisolone 1mg/kg/d initially, reducing by 5mg/d at 6 months. Changed to AZA after remission achieved at 3-6 months. Prednisolone 5mg/d continued throughout f/u.	-Remission at 6 months: 47/70 (67%) -Time to remission (Median 91 d, IQR 44-95)
	Silva F, 2010	Prospective, open label	72 weeks	17 patients with MPA (by CHCC), positive p(MPO)-ANCA, renal involvement and Cr ≤ 3 mg/dl	MMF titrated to 1,000mg BID (1500mg BID in those failing to respond) (MMF was continued for 18 months) + Methylprednisolone 1-3g followed by 1mg/kg/d prednisone x 2 weeks then tapered off by 6 months.	Remission at 6 months: 13/17 (76.5%) Sustained remission up to 18 months: 12/17 (70.6%)
Relapse	Jones RB, 2019	RCT, but for PICO single arm	18 months	70 pts with new diagnosis of GPA or MPA with either positive ANCA or biopsy proven. Exclusion of life threatening manifestations, rapid renal decline or eGFR less than 15.	MMF 2g/d (dose increases to 3g/d for uncontrolled disease at 4 weeks) + Prednisolone 1mg/kg/d initially, reducing by 5mg/d at 6 months. Changed to AZA after remission achieved at 3-6 months. Prednisolone 5mg/d continued throughout f/u.	-Relapses (18 mon) 23/63 (36.5%) -Major relapses (18 mon) 4/63 (6.3%) -Ralpse in PR3 positive (18 mon) 19/37 (51.4%) - Relapse in MPO positive (18 mon) 4/25 (16%)
	Silva F, 2010	Prospective, open label	72 weeks	17 patients with MPA (by CHCC), positive p(MPO)-ANCA, renal involvement and Cr ≤ 3 mg/dl	MMF titrated to 1,000mg BID (1500mg BID in those failing to respond) (MMF was continued for 18 months) +	Relapses (18 mon): 1/13 (7.7%) (relapse occurred at 9 months)

					Methylprednisolone 1-3g followed by 1mg/kg/d prednisone x 2 weeks then tapered off by 6 months.	
Death	Jones RB, 2019	RCT, but for PICO single arm	18 months	70 pts with new diagnosis of GPA or MPA with either positive ANCA or biopsy proven. Exclusion of life threatening manifestations, rapid renal decline or eGFR less then 15.	MMF 2g/d (dose increases to 3g/d for uncontrolled disease at 4 weeks) + Prednisolone 1mg/kg/d initially, reducing by 5mg/d at 6 months. Changed to AZA after remission achieved at 3-6 months. Prednisolone 5mg/d continued throughout f/u.	Death: 5/70 (7%)
	Silva F, 2010	Prospective, open label	72 weeks	17 patients with MPA (by CHCC), positive p(MPO)-ANCA, renal involvement and Cr ≤ 3 mg/dl	MMF titrated to 1,000mg BID (1500mg BID in those failing to respond) (MMF was continued for 18 months) + Methylprednisolone 1-3g followed by 1mg/kg/d prednisone x 2 weeks then tapered off by 6 months.	Deaths: 0/17 at 72 weeks
Infections	Jones RB, 2019	RCT, but for PICO single arm	18 months	70 pts with new diagnosis of GPA or MPA with either positive ANCA or biopsy proven. Exclusion of life threatening manifestations, rapid renal decline or eGFR less then 15.	MMF 2g/d (dose increases to 3g/d for uncontrolled disease at 4 weeks) + Prednisolone 1mg/kg/d initially, reducing by 5mg/d at 6 months. Changed to AZA after remission achieved at 3-6 months. Prednisolone 5mg/d continued throughout f/u.	Serious infection: 18/70 (26%)
Malignancy	Jones RB, 2019	RCT, but for PICO single arm	18 months	70 pts with new diagnosis of GPA or MPA with either positive ANCA or biopsy proven. Exclusion of life	MMF 2g/d (dose increases to 3g/d for uncontrolled disease at 4 weeks) + Prednisolone 1mg/kg/d initially, reducing by 5mg/d at 6 months. Changed to	Malignancy: 1/70 (1%)

				threatening manifestations, rapid renal decline or eGFR less then 15.	AZA after remission achieved at 3-6 months. Prednisolone 5mg/d continued throughout f/u.	
Adverse events	Jones RB, 2019	RCT, but for PICO single arm	18 months	70 pts with new diagnosis of GPA or MPA with either positive ANCA or biopsy proven. Exclusion of life threatening manifestations, rapid renal decline or eGFR less then 15.	MMF 2g/d (dose increases to 3g/d for uncontrolled disease at 4 weeks) + Prednisolone 1mg/kg/d initially, reducing by 5mg/d at 6 months. Changed to AZA after remission achieved at 3-6 months. Prednisolone 5mg/d continued throughout f/u.	SAE: 35/70 patients (50%)
	Silva F, 2010	Prospective, open label	72 weeks	17 patients with MPA (by CHCC), positive p(MPO)-ANCA, renal involvement and Cr ≤ 3 mg/dl	MMF titrated to 1,000mg BID (1500mg BID in those failing to respond) (MMF was continued for 18 months) + Methylprednisolone 1-3g followed by 1mg/kg/d prednisone x 2 weeks then tapered off by 6 months.	No SAE reported Minor AE: 10/17 (58%)
Renal outcomes	Silva F, 2010	Prospective, open label	72 weeks	17 patients with MPA (by CHCC), positive p(MPO)-ANCA, renal involvement and Cr ≤ 3 mg/dl	MMF titrated to 1,000mg BID (1500mg BID in those failing to respond) (MMF was continued for 18 months) + Methylprednisolone 1-3g followed by 1mg/kg/d prednisone x 2 weeks then tapered off by 6 months.	eGFR: -baseline: 46ml/min (34-63) -wk 24: 47ml/min (33-72) (P=NS) -wk 72: 52 ml/min/m2 (35-67) (p<0.05) Proteinuria: -baseline: 889mg/24h (400-2208) -wk 24: 384mg/24h (151-1071) (p<0.01) -wk 72: 149mg/24h (36-561) (p<0.001)

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies:

Author	Year	Title
Jones RB	2019	Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial
Silva F	2010	Mycophenolate mofetil for induction and maintenance of remission in microscopic polyangiitis with mild to moderate renal involvement--a prospective, open-label pilot trial.
A. Kumar	2001	Wegener's granulomatosis in India: clinical features, treatment and outcome of twenty-five patients
A. Villa-Forte	2007	Substitution of methotrexate for cyclophosphamide in Wegener granulomatosis: a 12-year single-practice experience
C. A. Langford	2000	Use of methotrexate and glucocorticoids in the treatment of Wegener's granulomatosis. Long-term renal outcome in patients with glomerulonephritis
J. H. Stone	1999	Treatment of non-life threatening Wegener's granulomatosis with methotrexate and daily prednisone as the initial therapy of choice
M. C. Sneller	1995	An analysis of forty-two Wegener's granulomatosis patients treated with methotrexate and prednisone
G. S. Hoffman	1992	The treatment of Wegener's granulomatosis with glucocorticoids and methotrexate
De Groot	2005	Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody–associated vasculitis.

- Studies reviewed and excluded:

Author	Year	Title	Comments
J. H. Stone	2001	Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety	ETN used as main treatment. MTX was used just in 45% of patients with no separate data for them. Exclude
K. Devarasetti	2018	Anti-neutrophil cytoplasmic autoantibodies associated vasculitis - Clinical profile and outcomes	Mixed treatments with other medications. Exclude

L. Guillevin	2003	Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients	Irrelevant treatments. Exclude

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Induction

- **PICO question 11:** In patients with active non-severe GPA, what is the impact of initiating treatment with glucocorticoids plus either SMZ/TMP vs. methotrexate or azathioprine on disease related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Disease Activity, Disease Damage, Relapse, Death, Malignancy, Infection, Toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hyperglycemia, decreased bone mineral density)

24. In patients with active non-severe GPA, what is the impact of initiating treatment with glucocorticoids plus either SMZ/TMP vs. methotrexate or azathioprine on disease related outcomes and treatment-related adverse events?
    - No Comparative Data Available

25. In patients with active non-severe GPA, what is the impact of initiating treatment with glucocorticoids plus either SMZ/TMP on disease related outcomes and treatment-related adverse events?
    - **Patient Important Outcomes**

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Relapse Risk- 65 patients with high relapse rate overall (~50%). Not in favor of SMZ/TMP for tx	Samela, 2017	Retrospective review	Not specified	Review of 200 AAV patients. 55 of 200 (27.5%) received prophylactic trimethoprim/sulfa against PJP. Patients came from NORAM and CYCAZAREM studies	Evaluation for all AAV patients to determine chronic, intermittent and non-carriers of staph. 65 patients were relapsing patients and staph carrier status identified. Chronic carrier defines as >75% of at least 4 nasal cultures are positive. T/S given 960mg three times/week	For all aAV patients, chronic nasal SA carriage (CNSAC) was not associated with increased relapse risk (OR 1.57, p=0.3). prophylactic T/S was not associated with a reduced relapse risk (OR=0.71, CI 0.36-1.41, p=0.33). Significant association between CNSAC and relapse in	Frequency of CNSAC in newly dx'd GPA parallels general population. This subset of GPA patients (23/151), has a high relapse rate despite immunosuppression and prophylactic T/S.

						generalized AAV (OR 4.64, p=0.02) but not early systemic AAV (OR 0.52, p=0.31). Relapse occurred in 15/55 (27.3%) of patients treated with T/S. In patients not on T/S relapse occurred in 50/145 (34.5%)	
	Israel, 1988	Retrospective case series	Not specified	Series of 10 patient with GPA aged 18-68, Caucasian.	All patients initially rec'd doses of 1600mg sulfamethoxazole and 320mg of trimethoprim. One patient was continued on CYC due to renal involvement for 8 months and then maintained on SMX/TMZ	Relapses occurred in 4 patients (of 10) after 4-30 months, but responded to increased doses of trimethoprim in 2 patients. 2 required additional cytotoxic agents.	SMZ/TMP was effective in treating non severe GPA, but relapses occurred and half the time responded to increased doses of SMX//TMP
Chronic Nasal Staph carriage- 1 study of 55 patients on TMP/SMZ with decrease in cnsac. Favors using medication	Samela, 2017	Retrospective review	Not specified	Review of 200 AAV patients. 55 of 200 (27.5%) received prophylactic trimethoprim/sulfa against PJP. Patients came from NORAM and CYCAZAREM studies	Evaluation for all AAV patients to determine chronic, intermittent and non-carriers of staph. 65 patients were relapsing patients and staph carrier status identified. Chronic carrier defines as >75% of at least 4 nasal cultures are positive. T/S given 960mg three times/week	Prophylactic T/S reduced CNSAC (OR =0.19, CI 0.04,0.91, p=0.04). Relapse rates were higher in generalized GPA patients (n=73, HR 4.10) and early systemic GPA patients (n=78,HR 2.73) in those who were chronic SA carriers	Prophylactic T/S reduced CNSAC
Remission- 22 patients. Bactrim was able to induce remission in 20. Favors using bactrim	Israel, 1988	Retrospective case series	Not specified	Series of 10 patient with GPA aged 18-68, Caucasian.	All patients initially rec'd doses of 1600mg sulfamethoxazole and 320mg of trimethoprim. One patient was continued on CYC due to renal involvement for 8 months and then maintained on SMX/TMZ	9/10 patients achieved remission	SMZ/TMP was able to put most patients into remission. (of note, some were on other concomitant immunosuppressive meds)

	DeRemee, 1985	Retrospective case series	unclear	12 patients with GPA whose clinical courses were indolent or not improving on standard regimens of cyclophosphamide with or without glucocorticoid.	Trimethoprim-sulfamethoxazole 1 DS tab daily	11/12 patients improved with Bactrim. One patient had resolution and flare with withdrawal, repeat resolutino with bactrim. 3 treated primarily with TMP/SMZ also responded. In 5 patients, addition of TMP/SMZ to previously established regimens resulted in clear improvement in clinical course. One pt had no improvement after 8 weeks of tx and cyc eventually controlled disease	Bactrim was able to induce remission in 11/12 patients
Side Effects- 10 patients, 2 with SE. Favors using med	Israel, 1988	Retrospective case series	Not specified	Series of 10 patient with GPA aged 18-68, Caucasian.	All patients initially rec'd doses of 1600mg sulfamethoxazole and 320mg of trimethoprim.	2/10 developed thrombocytopenia while on SMZ/TMP, but subsequently tolerated TMP without issue. 1 patient had exacerbation of hepatitis	SMZ/TMP was able to put most patients into remission. (of note, some were on other concomitant immunosuppressive meds)

26. In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate or azathioprine on disease related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results	Comments
Remission- 117 patient total. Overall patient were able to achieve remission with	Kumar, 2001	retrospective	unknown	25 GPA in series, but only 2 limited GPA with flare involving eye treated with MTX	25 patients with GPA (2 limited disease) induced with prednisone and oral Cytoxan. Only 2 patients tx'd with oral pred and MTX 10-12.5mg weekly)	2/2 ocular flares treated with MTX achieved remission	Very small numbers (n=2) for those tx'd with MTX/pred

MTX, consistent across studies	Villaforte, 2007	Retrospective review, direct evidence	Median 4.5 years	82 patients with new onset GPA. 57 with severe disease induced with cyc. 25 with mild-mod disease induced with MTX and steroid (creat<2)	New onset GPA patients treated with CYC 2mg/kg and pred. mild/mod disease induced with MTX (n=25) and steroid (creat <2) weekly 15mg/wk increased over 4-8 wk to 25mg/week (if needed) and GCS 1mg/kg/d (decreased by 5mg/week after 1 month of therapy). Tx with MTX recommended for at least 2 years. BVAS and labs measured monthly	22/25 (88%) patients tx'd with MTX achieved remission	88% of nonsevere GPA patients achieved remssion with MTX
	Stone, 1999	retrospective		19 patients with non-life threatening GPA. No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hospitalized at presentation. 94.7% met ACR criteria for GPA.	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	17/19 (89%) improved with treatment and 14 (74%) achieved remission. Only 2 patients (11%) achieved complete remission Remission defined as absence of any active disease in any organ system for at least one month while the patient continued treatment (either MTX or pred), and complete remission as no activity for 1 month off all medications. Relapse defined as recurrence of active GPA in patient who previously achieved remission	74% (14/19) GPA patients induced with MTX achieved remission. Only 2 patients (11%) achieved complete remission. Combination tx is effective but chronic disease courses are the rule with high likelihood of relapse.

	Sneller, 1995	Open label, prospective	19 months	42 patients with active, non severe disease. All pts met ACR criteria for GPA. Excluded those with life threatening disease, Creat>2.5, pulm hemorrhage, chronic liver disease, pregnancy, immunosuppression	All patients rec'd oral pred at 1mg/kg/day. Oral MTX started at 0.3mg/kg (not to exceed 15mg) was given weekly and increased by 2.5mg weekly up to dose of 20-25mg/week if tolerated (maintained at that level).	Remission achieved in 30/42 (71%) of patients. Time to remission was 4.2 months	In patients with non severe GPA, MTX is able to achieve remission in 71%. 36% relapsed after a median of 29 months
	Hoffman, 1992	Open label pilot study	14.5 month	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	Remission achieved in 69% of patients. 7% improved but had smoldering disease that precluded total withdrawl of GC	Remisson achieved in 69% of patients (20/29)
	deGroot, 2005	RCT	18 months	51 patients with antineutrophilcytoplasmic antibody–associated systemic vasculitis (AASV)	2mg/kg/day, 20–25 mg/week of oral MTX + prednisolone 1 mg/kg/day, tapered to 15mg/day at 12 weeks and 7.5mg/day by 6 months.	Remission rate at 6 months was 89.8%	Data from one arm of RCT
Duration of remission- 86 patients included but length of remission variable across studies (median 10 months, 20.5 and 29 months)	Villaforte, 2007	Retrospective review, direct evidence	Median 4.5 years	82 patients with new onset GPA. 57 with severe disease induced with cyc. 25 with mild-mod disease induced with MTX and steroid (creat<2)	New onset GPA patients treated with CYC 2mg/kg and pred. mild/mod disease induced with MTX (n=25) and steroid (creat <2) weekly 15mg/wk increased over 4-8 wk to 25mg/week (if needed) and GCS 1mg/kg/d (decreased by 5mg/week after 1 month of therapy). Tx with MTX recommended for at least 2 years. BVAS and labs measured monthly	Among patients with 1 or more remissions lasting at least 6 months, mean duration of remission before relapse was 20.5 months (SD +/- 21.2 mo)	Non-severe GPA patients induced with MTX had mean duration of remission for 20.5 months
	Stone, 1999	retrospective		19 patients with non-life threatening GPA.	Patients given oral weekly MTX (starting at 7.5-	Among the 14 patients who	Of the 14 who achieved remission,

				No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hospitalized at presentation. 94.7% met ACR criteria for GPA.	10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	achieved remission, 8 relapsed and median time to relapse was 10 months (range 4-31)	8 relapsed at ~10 months
	Sneller, 1995	Open label, prospective	19 months	42 patients with active, non severe disease. All pts met ACR criteria for GPA. Excluded those with life threatening disease, Creat>2.5, pulm hemorrhage, chronic liver disease, pregnancy, immunosuppression	All patients rec'd oral pred at 1mg/kg/day. Oral MTX started at 0.3mg/kg (not to exceed 15mg) was given weekly and increased by 2.5mg weekly up to dose of 20-25mg/week if tolerated (maintained at that level).	Median time to relapse in patients achieving remission was 29 months	In patients with non severe GPA, MTX is able to achieve remission in 71%. 36% relapsed after a median of 29 months
Serious infection/requring hospitalization- 25 patients included in 1 study. Relatively low # of hospitalizations, so favors using MTX	Villaforte, 2007	Retrospective review, direct evidence	Median 4.5 years	82 patients with new onset GPA. 57 with severe disease induced with cyc. 25 with mild-mod disease induced with MTX and steroid (creat<2)	New onset GPA patients treated with CYC 2mg/kg and pred. mild/mod disease induced with MTX (n=25) and steroid (creat <2) weekly 15mg/wk increased over 4-8 wk to 25mg/week (if needed) and GCS 1mg/kg/d (decreased by 5mg/week after 1 month of therapy). Tx with MTX recommended for at least 2 years. BVAS and labs measured monthly	2/25 (8%) of MTX/CS patients were hospitalized	8% of patients with non severe GPA induced with MTX required hospitalization for infection
Relapse- 115 patients included. 10-69.5% relapsed	Villaforte, 2007	Retrospective review, direct evidence	Median 4.5 years	82 patients with new onset GPA. 57 with severe disease induced with cyc. 25	New onset GPA patients treated with CYC 2mg/kg and pred. mild/mod disease induced with MTX (n=25) and	15/25 patients on MTX/CS induction relapsed	15/25 GPA patients induced with MTX had a relapse

across studies. Overall shows MTX can achieve remission, but significant proportion of patients relapse.				with mild-mod disease induced with MTX and steroid (creat<2)	steroid (creat <2) weekly 15mg/wk increased over 4-8 wk to 25mg/week (if needed) and GCS 1mg/kg/d (decreased by 5mg/week after 1 month of therapy). Tx with MTX recommended for at least 2 years. BVAS and labs measured monthly		
	Stone, 1999	retrospective	?	19 patients with non-life threatening GPA. No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hospitalized at presentation. 94.7% met ACR criteria for GPA.	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	17/19 achieved remission, but half (8/17, 57%) of those suffered relapses and no patient achieved a durable, complete remission (disease free status free of all meds). Relapse defined as recurrence of active GPA in patient who previously achieved remission	~half of patients who achieved remission relapsed
	Sneller, 1995	Open label, prospective	19 months	42 patients with active, non severe disease. All pts met ACR criteria for GPA. Excluded those with life threatening disease, Creat>2.5, pulm hemorrhage, chronic liver disease, pregnancy, immunosuppression	All patients rec'd oral pred at 1mg/kg/day. Oral MTX started at 0.3mg/kg (not to exceed 15mg) was given weekly and increased by 2.5mg weekly up to dose of 20-25mg/week if tolerated (maintained at that level).	11/30 relapsed after achieving remission (36%). Time to relapse in those who achieved remission was 29 months	In patients with non severe GPA, MTX is able to achieve remission in 71%. 36% relapsed after a median of 29 months
	Hoffman, 1992	Open label pilot study	14.5 month	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	20/29 achieved remission and 2 of them had a relapse (when pred dc'd) requiring retreatment with	2 patients in remission (out of 20) had a relapse

				duration prior to MTX was 6.4 years		MTX/GC in one case and CYC in the other	
	deGroot, 2005	RCT	18 months	51 patients with antineutrophilcytoplasmic antibody–associated systemic vasculitis (AASV)	2mg/kg/day, 20–25 mg/week of oral MTX + prednisolone 1 mg/kg/day, tapered to 15mg/day at 12 weeks and 7.5mg/day by 6 months.	Relapse rates at 18 months were 69.5%.	Data from one arm of RCT
Renal disease- 33 patients with renal disease. MTX in near normal creat was not associated with long term decline in renal function. In study with more active renal disease, 4/12 improved. MTX can be effective in renal disease	Langford, 2000	Open label, prospective	76 months (20-108)	42 patients with GPA, 21 with active GN. Mean serum creat in GN patients was 1.4mg/dl. All had active disease. Excluded those with life threatening disease, Creat>2.5, pulm hemorrhage, chronic liver disease, pregnancy, immunosuppression	All patients rec'd oral pred at 1mg/kg/day. Oral MTX started at 0.3mg/kg (not to exceed 15mg) was given weekly and increased by 2.5mg weekly up to dose of 20-25mg/week if tolerated (maintained at that level).	20/21 patients with GN treated with MTX +CS achieved renal remission. At 1 month and 6 onths following tudy entry, serum creat in all patients either remained stable or improved. Only 2 had a rise of >0.2 in creat from time of enrollment to end of follow up. Of the remaining 18, 12 had stable renal function and 6 had improvement in creat by more than 0.2	Use of MTX and pred as initial therapy for pts with GPA related GN and a normal or near-normal level of serum creatinine was not associated with a long-term decline in renal function
	Hoffman, 1992	Open label pilot study	14.5 month	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	4 of 12 patients with active renal disease were treated effectively	
Side Effects- 48 patients in 2 studies. Transaminitis	Stone, 1999	retrospective	?	19 patients with non-life threatening GPA. No patient had received previous tx	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose	2 (11%) of patients on MTX stopped treatment because of side effects	Transaminitis was most common side effect and led to

most common SE, some episodes of PJP and pneumonitis. Overall aceptible safety profile				for GPA. 9/19 had GN (no serum creat >1.2). 37% hospitalized at presentation. 94.7% met ACR criteria for GPA.	40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	(major LFT abnormalities in both cases). 6/19 (32%) had some form of hepatotoxicity (in 4 it was transaminitis between 1-2x ULN).	discontinuation in 2/19 patients
	Hoffman, 1992	Open label pilot study	14.5 month	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	2 patients (7%) developed fever, dry cough and dyspnea within 2-3 months of starting MTX/GC leading to discontinuation of MTX. 34% had some sort of MTX toxicity. 3 (10%) had transaminitis. 3 (10%) had PCP pneumonia	
	deGroot, 2005	RCT	18 months	51 patients with antineutrophilcytoplasmic antibody–associated systemic vasculitis (AASV)	2mg/kg/day, 20–25 mg/week of oral MTX + prednisolone 1 mg/kg/day, tapered to 15mg/day at 12 weeks and 7.5mg/day by 6 months.	34%	Data from one arm of RCT
Death- 2 deaths in 48 patients	Stone, 1999	Retrospective		19 patients with non-life threatening GPA. No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hospitalized at presentation. 94.7% met ACR criteria for GPA.	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and	0 patients died	No deaths

					mean duration of treatment was 95 weeks		
	Hoffman, 1992	Open label pilot study	14.5 month	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	2 patients died	2 patients of 29 developed fatal infections leading to respiratory failure/sepsis
	deGroot, 2005	RCT	18 months	51 patients with antineutrophilcytoplasmic antibody–associated systemic vasculitis (AASV)	2mg/kg/day, 20–25 mg/week of oral MTX + prednisolone 1 mg/kg/day, tapered to 15mg/day at 12 weeks and 7.5mg/day by 6 months.	2/51 (4%)	Data from one arm of RCT
Prednisone dose- 2 studies with 48 patients. Favors using MTX as majority were able to wean pred dose or stop it	Stone, 1999	Retrospective		19 patients with non-life threatening GPA. No patient had received previous tx for GPA. 9/19 had GN (no serum creat >1.2). 37% hopsitalized at presentation. 94.7% met ACR criteria for GPA.	Patients given oral weekly MTX (starting at 7.5-10mg/week) and pred (median starting dose 40mg/d, range 20-60). MTX increased to 15mg/week by end of first month and then by 2.5mg/week until disease was controlled. Pred tapered to 20mg/day by end of 2nd months. Mean max dose of MTX was 18.7mg/week and mean duration of treatment was 95 weeks	15 patients (79%) were able to taper pred to <10mg/day	A majority of patients were able to wean prednisone
	Hoffman, 1992	Open label pilot study	14.5 months	29 patients with non life threatening GPA. All had been on prior other immunosuppressive tx. Mean disease duration prior to MTX was 6.4 years	Weekly administration of MTX (mean stable dose of 20mg) started at 0.3mg/kg and GC 1mg/kg/d (in 24/29). Others were on variable doses (mean daily dose 51mg/d)	13/20 (65%) of patients in whom remission was achieved were able to discontinue GC therapy with no flare during the following 2-17 months	13/20 (65%) of patients in whom remission was achieved were able to discontinue GC therapy with no flare during the following 2-17 months

	deGroot, 2005	RCT	18 months	51 patients with antineutrophilcytoplasmic antibody–associated systemic vasculitis (AASV)	2mg/kg/day, 20–25 mg/week of oral MTX + prednisolone 1 mg/kg/day.	Prednisolone was tapered to 15mg/day at 12 weeks and 7.5mg/day by 6 months, and discontinued by 12 months.	Data from one arm of RCT

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single Arm Studies:

Author	Year	Title
A. Salmela	2017	Chronic nasal Staphylococcus aureus carriage identifies a subset of newly diagnosed granulomatosis with polyangiitis patients with high relapse rate
H. L. Israel	1988	Sulfamethoxazole-trimethoprim therapy for Wegener's granulomatosis
R. A. DeRemee	1985	Wegener's granulomatosis: observations on treatment with antimicrobial agents
A. Kumar	2001	Wegener's granulomatosis in India: clinical features, treatment and outcome of twenty-five patients
A. Villa-Forte	2007	Substitution of methotrexate for cyclophosphamide in Wegener granulomatosis: a 12-year single-practice experience
C. A. Langford	2000	Use of methotrexate and glucocorticoids in the treatment of Wegener's granulomatosis. Long-term renal outcome in patients with glomerulonephritis
J. H. Stone	1999	Treatment of non-life threatening Wegener's granulomatosis with methotrexate and daily prednisone as the initial therapy of choice
M. C. Sneller	1995	An analysis of forty-two Wegener's granulomatosis patients treated with methotrexate and prednisone
G. S. Hoffman	1992	The treatment of Wegener's granulomatosis with glucocorticoids and methotrexate
De Groot	2005	Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody–associated vasculitis.

- Studies reviewed and excluded:

Author	Year	Title	Comments
J. H. Stone	2001	Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety	Exclude: Does not answer PICO 11
K. Devarasetti	2018	Anti-neutrophil cytoplasmic autoantibodies associated vasculitis - Clinical profile and outcomes	Exclude: Numbers too small (i.e., n=2 treated with MTX)
C. A. Stegeman	1996	Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group.	Exclude: SMX/TMP was to prevent relapse, not for remission induction

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Induction

- **PICO 12 Question :** In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate or azathioprine vs. rituximab on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypogammaglobulinemia)

27. In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate or azathioprine vs. rituximab on disease-related outcomes and treatment-related adverse events?
    - Methotrexate vs. Rituximab

Certainty assessment							Effect	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	
1	observational studies	serious [a]	not serious	not serious	serious	none	**OR 11.50** (6.40 to 20.66)	⊕◯◯◯ VERY LOW
1	observational studies	serious [a]	not serious	not serious	serious	none	**12.00** (5.90 to 24.41)	⊕◯◯◯ VERY LOW

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. subjects receiving RTX were routinely given methylprednisolone 100 mg intravenously as premedication prior to each infusion; **only OR reported per intervention**

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

Author	Year	Title
L. Lally	2014	Effectiveness of rituximab for the otolaryngologic manifestations of granulomatosis with polyangiitis (Wegener's)

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Induction

- **PICO Question 13 :** In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate or azathioprine vs. cyclophosphamide on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

28. **PICO Question 13 :** In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate or azathioprine vs. cyclophosphamide on disease-related outcomes and treatment-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate	Cyclophosphamide	Relative (95% CI)	Absolute (95% CI)	
Remission at 6 months											
1	randomized trials	not serious	not serious	not serious	very serious [a]	none	44/49 (89.8%)	43/46 (93.5%)	**OR 0.61** (0.14 to 2.73)	**37 fewer per 1,000** (from 267 fewer to 40 more)	⊕⊕◯◯ LOW
Time to remission											
1	randomized trials	not serious	not serious	not serious	serious [a]	none	-/0	-/0	**HR 0.80** (0.52 to 1.23)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE
Total relapses at 18 months											
1	randomized trials	not serious	not serious	not serious	very serious [a]	none	32/49 (65.3%)	20/46 (43.5%)	**OR 2.45** (1.07 to 5.60)	**219 more per 1,000** (from 17 more to 377 more)	⊕⊕◯◯ LOW
Major relapses											
1	randomized trials	not serious	not serious	not serious	very serious [a]	none	14/49 (28.6%)	9/46 (19.6%)	**OR 1.64** (0.63 to 4.28)	**90 more per 1,000** (from 63 fewer to 314 more)	⊕⊕◯◯ LOW
Time to relapse											

Certainty assessment							№ of patients		Effect		Certainty Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate	Cyclophosphamide	Relative (95% CI)	Absolute (95% CI)	
1	randomized trials	not serious	not serious	not serious	serious [a]	none	-/0	-/0	**HR 1.85** (1.06 to 3.23)	**2 fewer per 1,000** (from 3 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE
Relapses after remission at 18 months											
1	randomized trials	not serious	not serious	not serious	very serious [a]	none	32/46 (69.6%)	20/43 (46.5%)	**OR 2.63** (1.10 to 6.26)	**231 more per 1,000** (from 24 more to 380 more)	⊕⊕◯◯ LOW
Deaths											
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	2/49 (4.1%)	2/46 (4.3%)	**OR 0.94** (0.13 to 6.94)	**3 fewer per 1,000** (from 38 fewer to 196 more)	⊕⊕◯◯ LOW
Severe infections											
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	4/49 (8.2%)	3/46 (6.5%)	**OR 1.27** (0.27 to 6.03)	**16 more per 1,000** (from 47 fewer to 231 more)	⊕⊕◯◯ LOW
Number of SAE											
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	9/49 (18.4%)	6/46 (13.0%)	**OR 1.50** (0.49 to 4.61)	**53 more per 1,000** (from 62 fewer to 278 more)	⊕⊕◯◯ LOW
Cumulative glucocorticoid use											
1	randomised trials	not serious	not serious	not serious	serious [a]	none	49	46	-	MD **2.23 higher** (1.06 higher to 3.4 higher)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Wide CI; Treatment would differ if the upper versus the lower boundary of the CI represented the truth.

- **References:**

- Randomized controlled trials:

Author	Year	Title
K. De Groot	2005	Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Induction

- **PICO question 14:** In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate or azathioprine vs. glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hyperglycemia, decreased bone mineral density)

29. In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate or azathioprine vs. glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - No data available

30. In patients with active non-severe GPA, what is the impact of initiating treatment with methotrexate or azathioprine on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Remission- 14/20 patients given aza achieved remission and	Ribi, 2010	Prospective multicenter therapeutic trial	62+/-33 months	124 patients with newly diagnosed PAN (n=58) or MPA (n=66) (FFS of 0). No alveolar	Treatment with steroids alone. At time of treatment failure or relapse (or unable to wean pred below 20mg/d), patients were randomized to oral azathioprine 2mg/kg or	14 of the 20 patients randomized to receive oral aza achieved disease remission (70%). 6 had sustained remission (43%)

43% had sustained remission. Favors using aza				hemorrhage or severe renal impairment	cyclophosphamide 6 IV pulses (600mg/m2). One IV methyl pred pulse of 15mg/kg was allowed followed by dose of 1mg/kg/day for 3 weeks. Tapered by 5mg every 10 days to dose of 0.5mg/kg/day, then by 2.5mg every 10 days until a dose of 15mg/day, and finally by 1mg every 10 days to the minimal effective dose or when possible, until withdrawal	
Relapse- 8 of 14 MPA/PAN patents experience a relapse. High number of relapses in combo group with aza. Does not support aza	Ribi, 2010	Prospective multicenter therapeutic trial	62+/-33 months	124 patients with newly diagnosed PAN (n=58) or MPA (n=66) (FFS of 0). No alveolar hemorrhage or severe renal impairment	Treatment with steroids alone. At time of treatment failure or relapse (or unable to wean pred below 20mg/d), patients were randomized to oral azathioprine 2mg/kg or cyclophosphamide 6 IV pulses (600mg/m2). One IV methyl pred pulse of 15mg/kg was allowed followed by dose of 1mg/kg/day for 3 weeks. Tapered by 5mg every 10 days to dose of 0.5mg/kg/day, then by 2.5mg every 10 days until a dose of 15mg/day, and finally by 1mg every 10 days to the minimal effective dose or when possible, until withdrawal	8 of the 14 experienced a relapse within 25 +/-18 months (range 7-59 months) after randomization
Adverse events: 12 patients on aza (of 20 total) had an adverse event. Not split up by MPA or PAN.	Ribi, 2010	Prospective multicenter therapeutic trial	62+/-33 months	124 patients with newly diagnosed PAN (n=58) or MPA (n=66) (FFS of 0). No alveolar hemorrhage or severe renal impairment	Treatment with steroids alone. At time of treatment failure or relapse (or unable to wean pred below 20mg/d), patients were randomized to oral azathioprine 2mg/kg or cyclophosphamide 6 IV pulses (600mg/m2). One IV methyl pred pulse of 15mg/kg was allowed followed by dose of 1mg/kg/day for 3 weeks. Tapered by 5mg every 10 days to dose of 0.5mg/kg/day, then by 2.5mg every 10 days until a dose of 15mg/day, and finally by 1mg every 10 days to the minimal effective dose or when possible, until withdrawal	12 patients on aza had an adverse event (5 infections, 3 osteoporotic fractures, 2 deaths in aza group)

31. In patients with active non-severe GPA, what is the impact of initiating treatment with glucocorticoids on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Remission- 66 patients with MPA but results reported for both MPA and PAN (124 patients). 79%achieved remission and 40% had sustained remission. Supports use of steroids first line in non severe MPA	Ribi, 2010	Prospective multicenter therapeutic trial	62+/-33 months	124 patients with newly diagnosed PAN (n=58) or MPA (n=66) (FFS of 0). No alveolar hemorrhage or severe renal impairment	Treatment with steroids alone. At time of treatment failure or relapse (or unable to wean pred below 20mg/d), patients were randomized to oral azathioprine 2mg/kg or cyclophosphamide 6 IV pulses (600mg/m2). One IV methyl pred pulse of 15mg/kg was allowed followed by dose of 1mg/kg/day for 3 weeks. Tapered by 5mg every 10 days to dose of 0.5mg/kg/day, then by 2.5mg every 10 days until a dose of 15mg/day, and finally by 1mg every 10 days to the minimal effective dose or when possible, until withdrawal	Treatment with steroids alone induced remission in 98 patients. 26 patients failed steroids alone (21%). 50 patients (40%) achieved sustained disease remission
Relapse-same cohort of 124 patients with PAN/MPA. Almost half relapsed. High number of relapses with CS alone. Favoring alternate therapy	Ribi, 2010	Prospective multicenter therapeutic trial	62+/-33 months	124 patients with newly diagnosed PAN (n=58) or MPA (n=66) (FFS of 0). No alveolar hemorrhage or severe renal impairment	Treatment with steroids alone. At time of treatment failure or relapse (or unable to wean pred below 20mg/d), patients were randomized to oral azathioprine 2mg/kg or cyclophosphamide 6 IV pulses (600mg/m2). One IV methyl pred pulse of 15mg/kg was allowed followed by dose of 1mg/kg/day for 3 weeks. Tapered by 5mg every 10 days to dose of 0.5mg/kg/day, then by 2.5mg every 10 days until a dose of 15mg/day, and finally by 1mg every 10 days to the minimal effective dose or when possible, until withdrawal	Of the 98 who achieved remission, 2 became steroid dependent and the other 46 experienced a relapse.
Malignancy	Ribi, 2010	Prospective multicenter therapeutic trial	62+/-33 months	124 patients with newly diagnosed PAN (n=58) or MPA (n=66) (FFS of 0). No alveolar	Treatment with steroids alone. At time of treatment failure or relapse (or unable to wean pred below 20mg/d), patients were randomized to oral azathioprine 2mg/kg or cyclophosphamide 6 IV pulses	1 patient with MPA treated with steroids alone developed a malignancy

				hemorrhage or severe renal impairment	(600mg/m2). One IV methyl pred pulse of 15mg/kg was allowed followed by dose of 1mg/kg/day for 3 weeks. Tapered by 5mg every 10 days to dose of 0.5mg/kg/day, then by 2.5mg every 10 days until a dose of 15mg/day, and finally by 1mg every 10 days to the minimal effective dose or when possible, until withdrawal	

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies:

Author	Year	Title
Ribi	2010	Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: A prospective randomized study of one hundred twenty-four patients

- Studies reviewed and excluded:

Author	Year	Title	Comments
C. Pagnoux	2015	Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy	Exclude: does not answer pico 14. Variable steroid regimen, variable cyc regimen
J. S. Cameron	1991	Renal vasculitis: microscopic polyarteritis and Wegener's granuloma	Exclude: Report on renal vasculitis which by definition is severe disease. Does not answer PICO 14
A. Hara	2018	Risk Factors for Relapse of Antineutrophil Cytoplasmic Antibody-associated Vasculitis in Japan: A Nationwide, Prospective Cohort Study	Exclude: prospective patient cohort was in remission, so not “active, non-severe GPA”

J. H. Stone	2001	Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety	Exclude: does not answer PICO 14
C. A. Langford	2000	Use of methotrexate and glucocorticoids in the treatment of Wegener's granulomatosis. Long-term renal outcome in patients with glomerulonephritis	Exclude: MTX+Pred: Use of MTX and pred as initial therapy for pts with GPA related GN and a normal or near-normal level of serum creatinine was not associated with a long-term decline in renal function
J. H. Stone	1999	Treatment of non-life threatening Wegener's granulomatosis with methotrexate and daily prednisone as the initial therapy of choice	Exclude: MTX+Pred: 74% (14/19) GPA patients induced with MTX achieved remission. Only 2 patients (11%) achieved complete remission. Combination tx is effective but chronic disease courses are the rule with high likelihood of relapse (~half of those who achieved remission).
M. C. Sneller	1995	An analysis of forty-two Wegener's granulomatosis patients treated with methotrexate and prednisone	Exclude: MTX+Pred: In patients with non severe GPA, MTX is able to achieve remission in 71%. 36% relapsed after a median of 29 months
G. S. Hoffman	1992	The treatment of Wegener's granulomatosis with glucocorticoids and methotrexate	Exclude: MTX+Pred
K. Devarasetti	2018	Anti-neutrophil cytoplasmic autoantibodies associated vasculitis - Clinical profile and outcomes	Exclude: Does not answer PICO 14

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Maintanance

- **PICO Question 15:** In patients with severe GPA or MPA who have entered remission, what is the impact of using methotrexate vs. azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

32. In patients with severe GPA or MPA who have entered remission, what is the impact of using methotrexate vs. azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate	Azathioprine	Relative (95% CI)	Absolute (95% CI)	
Risk of relapse											
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	-/0	-/0	**HR 0.92** (0.52 to 1.63)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⊕⊕◯◯ LOW
Severe adverse events											
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	11/63 (17.5%)	5/63 (7.9%)	**OR 2.45** (0.80 to 7.53)	**95 more per 1,000** (from 15 fewer to 314 more)	⊕◯◯◯ VERY LOW
Severe infections											
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	5/63 (7.9%)	1/63 (1.6%)	**OR 5.34** (0.61 to 47.13)	**63 more per 1,000** (from 6 fewer to 416 more)	⊕◯◯◯ VERY LOW
Cancer											
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	1/63 (1.6%)	2/63 (3.2%)	**OR 0.49** (0.04 to 5.57)	**16 fewer per 1,000** (from 30 fewer to 123 more)	⊕◯◯◯ VERY LOW
Deaths											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate	Azathioprine	Relative (95% CI)	Absolute (95% CI)	
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	1/63 (1.6%)	0/63 (0.0%)	**OR 3.05** (0.12 to 76.26)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW

CI: Confidence interval; **HR:** Hazard Ratio; **OR:** Odds ratio

Explanations

a. No clear blinding of participants or investigators.

b. Treatment would differ if the upper versus the lower boundary of the CI represented the truth.

c. Wide CI; Treatment would differ if the upper versus the lower boundary of the CI represented the truth.

- **References:**

- Included Randomized Controlled Trial:

Author	Year	Title
C. Pagnoux	2008	Azathioprine or methotrexate maintenance for ANCA-associated vasculitis

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Maintanance

- **PICO question 16:** In patients with severe GPA or MPA who have entered remission with cyclophosphamide therapy, what is the impact of using rituximab vs. methotrexate or azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypogammaglobulinemia)

33. In patients with severe GPA or MPA who have entered remission with cyclophosphamide therapy, what is the impact of using rituximab vs. methotrexate or azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

34. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rituximab	methotrexate or azathioprine	Relative (95% CI)	Absolute (95% CI)		
All relapses at 28 months												
2 [a,b]	randomised trials	serious [c]	not serious	not serious	not serious	none	17/114 (14.9%)	52/116 (44.8%)	**OR 0.22** (0.11 to 0.41)	**297 fewer per 1,000** (from 366 fewer to 198 fewer)	⊕⊕⊕◯ MODERATE	
All relapses at 60 months												
1 [a]	randomised trials	serious [c]	not serious	not serious	serious [d]	none	23/57 (40.4%)	31/58 (53.4%)	**OR 0.59** (0.28 to 1.23)	**131 fewer per 1,000** (from 291 fewer to 51 more)	⊕⊕◯◯ LOW	
Severe adverse events at 60 months												

34. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rituximab	methotrexate or azathioprine	Relative (95% CI)	Absolute (95% CI)		
1 [a]	randomised trials	serious [c]	not serious	not serious	serious [d]	none	23/57 (40.4%)	27/58 (46.6%)	**OR 0.78** (0.37 to 1.63)	**61 fewer per 1,000** (from 222 fewer to 121 more)	⊕⊕◯◯ LOW	

Death at 60 months

1 [a]	randomised trials	serious [c]	not serious	not serious	very serious [d]	strong association	0/57 (0.0%)	4/58 (6.9%)	**OR 0.11** (0.01 to 2.00)	**61 fewer per 1,000** (from 68 fewer to 60 more)	⊕⊕◯◯ LOW	

Severe infections at 28 months

1 [e]	randomised trials	serious [c]	not serious	not serious	serious [d]	none	11/57 (19.3%)	8/58 (13.8%)	**OR 1.49** (0.55 to 4.04)	**55 more per 1,000** (from 57 fewer to 255 more)	⊕⊕◯◯ LOW	

SF-36 Physical component change at 24 months (score over 100)

34. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rituximab	methotrexate or azathioprine	Relative (95% CI)	Absolute (95% CI)		
1 [e]	randomised trials	serious [c]	not serious	not serious	very serious [d]	none			MD **3.95 higher** (0.28 lower to 8.18 higher)		⊕◯◯◯ VERY LOW	

SF-36 Mental component change at 24 months (score over 100)

1 [e]	randomised trials	serious [c]	not serious	not serious	serious [d]	none			MD **4.23 higher** (0.17 higher to 8.29 higher)		⊕⊕◯◯ LOW	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. B. Terrier, 2018

b. L. Guillevin, 2014

c. Performance and detection bias: Blinding of participants and personnel, and blinding of outcome assessment not mentioned

d. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

e. G. Pugnet, 2016

- **References:**

- Randomized controlled trials:

Author	Year	Title
B. Terrier	2018	Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides
G. Pugnet	2016	Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: impact on global disability and health-related quality of life
L. Guillevin	2014	Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Maintanance

- **PICO question 17:** In patients with severe GPA or MPA who have entered remission with rituximab therapy, what is the impact of using rituximab vs. methotrexate or azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypogammaglobulinemia)

35. In patients with severe GPA or MPA who have entered remission with rituximab therapy, what is the impact of using rituximab vs. methotrexate or azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?
    - No comparative data available

36. In patients with severe GPA or MPA who have entered remission with rituximab therapy, what is the impact of using rituximab for remission maintenance on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease activity: In 102 GPA/MPA patients, the	Calich AL, 2014	Retrospective Single-arm cohort	34.2±26.2 months	66 GPA patients (fulfilling ACR criteria) and CHCC.	All got induction with RTX (375mg/m2 x 4 or 1,000mg x 2). 60 patients (92.3%) received RTX	12 months: 49/57 (86.0%) patients were either in remission or showed improvement	Indirect: A minority (n=16, 24%) got additional

majority of patients are able to achieve a treatment response with Rituximab induction therapy followed by maintenance Rituxiamb (86-96% at 12-44 months). Cartin-Ceba data excluded (see comments).				2002-2013. Single center in France.	maintenance with 375mg/m2 or 500mg every 6 months for 18 months.	(not refractory). Multivariable analysis shows SGS as an independent risk factor for treatment failure (OR 31.3,95% CI 2.2-435.1,p=0.0104).	immunosuppressives (AZA, MTX, CYC, MMF).
	Smith RM, 2012	Retrospective single center observational cohort	Median follow-up 44 months (range 4-61)	Diagnosis of GPA or MPA (no criteria mentioned). 2002-2006. Done in UK.	Rituximab 1,000mg x 2 for induction therapy followed by 1,000mg every 6 months for maintenance.	43/45 (96%) achieved a complete or partial remission.	Direct evidence: Study has 3 arms. Data only abstracted from Group B which does has relevant population. However, may not all be severe disease at induction.
	Cartin-Ceba R, 2012	Single center retrospective observational cohort	Median f/u of 4.4 years (IQR 2.7-6.2)	53 refractory GPA/MPA patients who either had biopsy proven disease or met ACR or CHCC criteria. All patients received at least 2 courses of RTX for refractory disease. 2000-2010.	RTX (375mg/m2 x 4 or 1,000mg x 2) + glucocorticoids (IV MP for up to 3g when needed, then prednisone 1mg/kg/d with taper d/c by 5 months) for induction. RTX repeated for remission maintenance at same dosing.	Remission: 53/53 (100%)	Indirect evidence: There is bias in this design. The patients had to have received multiple courses of RTX, thus implying that they had to have responded to the first course. Excluded this from the final summary.
Relapse: In 259 patients with GPA/MPA the relapse rate ranged from 8-13% 1-2 years which is consistent with MAINRITSAN trial where CYC used as induction followed by Rituximab. Longer term	Alberici, 2015	Retrospective, observational single-arm cohort	Median f/u of 59.3 months (IQR 44.5-73.3). Median f/u post-treatment (24 weeks of RTX maintenance)	69 patients with relapsing/refractory GPA or MPA (no criteria mentioned). United Kingdom population. 2006-2013.	Rituximab induction with either 1g x 2, 2 weeks apart, or 375mg/m2 weekly for 4 wks. Maintenance therapy with Rituxiamb 1,000mg every 6 months for 24 months.	During RTX maintenance: 9/69 (13%) relapsed a median of 11 months after the first RTX infusion. 2/69 (2.9%) were severe relapses. After completion of 24 weeks RTX maintenance: 28/69 (40.6%) experienced flares after a median time of 15.5 mon (IQR 12-22.9). 12/69 (17.4%) had severe flares.	Direct evidence: Homogeneous population which fits our criteria. However, not clear that all patients had severe disease. Patients would receive increased doses of glucocoritcoids or other immunosuppressives for flares.

follow-up in 175 GPA/MPA patients showed a relapse rate of 40-60% at 4-5 years. Relapses were common after discontinuing Rituximab.			was 34.5 (IQR 19.2-47.2)				
	Calich AL, 2014	Single-arm cohort	34.2±26.2 months	66 GPA patients (fulfilling ACR criteria) and CHCC. 2002-2013. Single center in France.	All got induction with RTX (375mg/m2 x 4 or 1,000mg x 2). 60 patients (92.3%) received RTX maintenance with 375mg/m2 or 500mg every 6 months for 18 months.	Relapse rate of 11.2/100 pt-yrs. 5/60 (8.3%) relapsed within 2 years. Mean relapse free survival was 48.4% at 5 yrs.	Indirect: A minority (n=16, 24%) got additional immunosuppressives (AZA, MTX, CYC, MMF).
	Smith RM, 2012	Retrospective single center observational cohort	Median follow-up 44 months (range 4-61)	Diagnosis of GPA or MPA (no criteria mentioned). 2002-2006. Done in UK.	Rituximab 1,000mg x 2 for induction therapy followed by 1,000mg every 6 months for maintenance.	2 years: Relapses in 5/43 (12%) Last follow-up: Relapses in 11/43 (26%)	Direct evidence: Study has 3 arms. Data only abstracted from Group B which does has relevant population. However, may not all be severe disease at induction.
	Charles, 2018	RCT (used one arm only)	28 months	162 patients, 117 (72.2%) had GPA, and 45 (27.8%) had MPA. Data extracted from one arm (81 patients).	A fixed 500mg rituximab infusion on days 0 and 14 postrandomisation, then 6, 12 and 18 months after the first infusion.	Relapses in 8/81 (9.9%). Relapse-free survival rate was 86.4% (95% CI 79.2 to 94.2).	RCT (used one arm only). Data extracted from one arm (81 patients).
	Cartin-Ceba R, 2012	Single center retrospective observational cohort	Median f/u of 4.4 years (IQR 2.7-6.2)	53 refractory GPA/MPA patients who either had biopsy proven disease or met ACR or CHCC criteria. All patients received at least 2 courses of RTX for refractory disease. 2000-2010.	RTX (375mg/m2 x 4 or 1,000mg x 2) + glucocorticoids (IV MP for up to 3g when needed, then prednisone 1mg/kg/d with taper d/c by 5 months) for induction. RTX repeated for remission maintenance at same dosing.	Relapse: 32/53 (60.4%)	Indirect evidence: Maintenance Rituximab was not given to all paticiants. Sometimes the second course of RTX was because of flare. Maintenance RTX was given if ANCA titers rose following B-cell reconstitution, B-cells repopulated in patients who never had positive ANCA or B-cell

							reconstitution only in those with a prior history of relapse with B-cell reconstitution.
	Puechal, 2019	Single center cohort study	Median follow-up was 3.6 years	One hundred and fourteen adults with relapsing (65%), refractory/grumbling (22%) or new-onset (13%) GPA received RTX for induction	At remission, protocolized maintenance RTX infusions were given every 6 months for 18 months.	Overall, 40/91 (44%) patients relapsed, with 26 (29%) minor relapses and/or 18 (20%) major relapses, during the observation period, with median (IQR) time to flare 3.2 (1.5□4.5) years.	
	McClare, 2019	Single Center Observational cohort	Median f/u of 59 months (IQR 44-72)	53 GPA/MPA patients with positive PR3-ANCA (?) treated with induction Rituximab (1,000mg x2). 2011-2016	Rituximab 2g in first 2 weeks, then 1,000mg once every 6 months for 2 years and concommittant corticosteroids (0.5-1mg/kg)	Relapse in 24/53 (45.3%) Median time to relapse 1107 days (36 months)	Direct: It is unusual that the patient only included PR3-ANCA positive patients which is fairly specific for GPA, yet there are a significant number of MPA patients.
Death: In 248 GPA/MPA patients Mortality rate was in 3-7% at 44-60 months follow-up. The causes of death were not easily abstracted so it is difficult to say how much this is related to the disease/treatment.	Alberici, 2015	Retrospective, observational single-arm cohort	Median f/u of 59.3 months (IQR 44.5-73.3). Median f/u post-treatment (24 weeks of RTX maintenance) was 34.5 (IQR	69 patients with relapsing/refractory GPA or MPA (no criteria mentioned). United Kingdom population. 2006-2013.	Rituximab induction with either 1g x 2, 2 weeks apart, or 375mg/m2 weekly for 4 wks. Maintenance therapy with Rituxiamb 1,000mg every 6 months for 24 months.	2/69 patients (2.9%) died from perintoneal cardinoma and one from unknown cause.	Direct evidence: Homogeneous population which fits our criteria. However, not clear that all patients had severe disease. Patients would receive increased doses of glucocoritcoids or other immunosuppressives for flares.

			19.2-47.2)				
	Smith RM, 2012	Retrospective single center observational cohort	Median follow-up 44 months (range 4-61)	Diagnosis of GPA or MPA (no criteria mentioned). 2002-2006. Done in UK.	Rituximab 1,000mg x 2 for induction therapy followed by 1,000mg every 6 months for maintenance.	3 deaths (3/45= 6.7%).	Direct evidence: Study has 3 arms. Data only abstracted from Group B which does has relevant population. However, may not all be severe disease at induction.
	Charles, 2018	RCT (used one arm only)	28 months	162 patients, 117 (72.2%) had GPA, and 45 (27.8%) had MPA. Data extracted from one arm (81 patients).	A fixed 500mg rituximab infusion on days 0 and 14 postrandomisation, then 6, 12 and 18 months after the first infusion.	3/81 (3.7%)	RCT (used one arm only). Data extracted from one arm (81 patients).
	Cartin-Ceba R, 2012	Single center retrospective observational cohort	Median f/u of 4.4 years (IQR 2.7-6.2)	53 refractory GPA/MPA patients who either had biopsy proven disease or met ACR or CHCC criteria. All patients received at least 2 courses of RTX for refractory disease. 2000-2010.	RTX (375mg/m2 x 4 or 1,000mg x 2) + glucocorticoids (IV MP for up to 3g when needed, then prednisone 1mg/kg/d with taper d/c by 5 months) for induction. RTX repeated for remission maintenance at same dosing.	Mortality: 2/53 (3.8%)	Indirect evidence: Maintenance Rituximab was not given to all paticiants.
Malignancy: In 261 GPA/MPA patients 2-6% of patients developed malignancies with a median follow-up ranging from 34-60 months. Some patients were exposed or had been	Alberici, 2015	Retrospective, observational single-arm cohort	Median f/u of 59.3 months (IQR 44.5-73.3). Median f/u post-treatment (24 weeks of RTX	69 patients with relapsing/refractory GPA or MPA (no criteria mentioned). United Kingdom population. 2006-2013.	Rituximab induction with either 1g x 2, 2 weeks apart, or 375mg/m2 weekly for 4 wks. Maintenance therapy with Rituxiamb 1,000mg every 6 months for 24 months.	4/69 patients (5.8%) developed malignancies (lung, bladder, peritoneal and breast).	Direct evidence: Homogeneous population which fits our criteria. However, not clear that all patients had severe disease. Patients would receive increased doses of glucocoritcoids or other immunosuppressives for flares.

exposed by other immunosuppressives known to increase the risk of malignancy.			maintenance) was 34.5 (IQR 19.2-47.2)				
	Calich AL, 2014	Single-arm cohort	34.2±26.2 months (? Mean)	66 GPA patients (fulfilling ACR criteria) and CHCC. 2002-2013. Single center in France.	All got induction with RTX (375mg/m2 x 4 or 1,000mg x 2). 60 patients (92.3%) received RTX maintenance with 375mg/m2 or 500mg every 6 months for 18 months.	2/66 patients developed malignancy (1 bladder cancer and 1 cervical cancer). Patient with bladder cancer had previously been on high cumulative CYC.	Indirect: A minority (n=16, 24%) got additional immunosuppressives (AZA, MTX, CYC, MMF).
	Smith, RM 2012	Retrospective single center observational cohort	Median follow-up 44 months (range 4-61)	Diagnosis of GPA or MPA (no criteria mentioned). 2002-2006. Done in UK.	Rituximab 1,000mg x 2 for induction therapy followed by 1,000mg every 6 months for maintenance.	1/45 (2.2%) developed cancer during follow-up.	Direct evidence: Study has 3 arms. Data only abstracted from Group B which does has relevant population. However, may not all be severe disease at induction.
	Charles, 2018	RCT (used one arm only)	28 months	162 patients, 117 (72.2%) had GPA, and 45 (27.8%) had MPA. Data extracted from one arm (81 patients).	A fixed 500mg rituximab infusion on days 0 and 14 postrandomisation, then 6, 12 and 18 months after the first infusion.	2/81 (2.5%)	RCT (used one arm only). Data extracted from one arm (81 patients).
Infection: In 296 patients with GPA/MPA the rate of severe infections ranged from 6-29% with median follow-up of 24-59 months.	Besada, 2016	Observational prospective registry	24 months	35 patients from Northern Norway with an established diagnosis of GPA (no criteria mentioned).	All patients got Rituximab induction (1g twice in a fortnight) combined with oral prednisolone (median 20mg/d) and an immunosuppressive drug. 49% received Rituximab maintenance with 2g annual regimen (1g twice in a fortnight per year), 40% received maintenance with 1g	2 severe infections (5.7%) occurring 3 and 4 months after induction rituximab. Severe infections defined as requiring IV antibiotics and/or hospitalization.	Indirect evidence: The majority of patients were receiving Rituximab induction for relapsing disease (80%) and had prior exposure to cyclophosphamide.

					biannually (1 g every 6 months) and 11% did not receive maintenance therapy.		
	Alberici, 2015	Retrospective, observational single-arm cohort	Median f/u of 59.3 months (IQR 44.5-73.3). Median f/u post-treatment (24 weeks of RTX maintenance) was 34.5 (IQR 19.2-47.2)	69 patients with relapsing/refractory GPA or MPA (no criteria mentioned). United Kingdom population. 2006-2013.	Rituximab induction with either 1g x 2, 2 weeks apart, or 375mg/m2 weekly for 4 wks. Maintenance therapy with Rituxiamb 1,000mg every 6 months for 24 months.	Severe infections in 20/69 patients (29.0%), 57% of which affecting the lower respiratory tract.	Direct evidence: Homogeneous population which fits our criteria. However, not clear that all patients had severe disease. Patients would receive increased doses of glucocoritcoids or other immunosuppressives for flares.
	Calich AL, 2014	Single-arm cohort	34.2±26.2 months (? Mean)	66 GPA patients (fulfilling ACR criteria) and CHCC. 2002-2013. Single center in France.	All got induction with RTX (375mg/m2 x 4 or 1,000mg x 2). 60 patients (92.3%) received RTX maintenance with 375mg/m2 or 500mg every 6 months for 18 months.	Severe infections in 9/66 patients (13.6%, 13 events).	Indirect: A minority (n=16, 24%) got additional immunosuppressives (AZA, MTX, CYC, MMF).
	Smith RM, 2012	Retrospective single center observational cohort	Median follow-up 44 months (range 4-61)	Diagnosis of GPA or MPA (no criteria mentioned). 2002-2006. Done in UK.	Rituximab 1,000mg x 2 for induction therapy followed by 1,000mg every 6 months for maintenance.	Severe infections in 12/45 (27%) of patients (30 events)	Direct evidence: Study has 3 arms. Data only abstracted from Group B which does has relevant population. However, may not all be severe disease at induction.

	Charles, 2018	RCT (used one arm only)	28 months	162 patients, 117 (72.2%) had GPA, and 45 (27.8%) had MPA. Data extracted from one arm (81 patients).	A fixed 500mg rituximab infusion on days 0 and 14 postrandomisation, then 6, 12 and 18 months after the first infusion.	18/81 (22%)	Direct: RCT (used one arm only). Data extracted from one arm (81 patients).
	Cartin-Ceba R, 2012	Single center retrospective observational cohort	Median f/u of 4.4 years (IQR 2.7-6.2)	53 refractory GPA/MPA patients who either had biopsy proven disease or met ACR or CHCC criteria. All patients received at least 2 courses of RTX for refractory disease. 2000-2010.	RTX (375mg/m2 x 4 or 1,000mg x 2) + glucocorticoids (IV MP for up to 3g when needed, then prednisone 1mg/kg/d with taper d/c by 5 months) for induction. RTX repeated for remission maintenance at same dosing.	30 infection events. Study does not report number of patients who got infections.	Indirect evidence: Maintenance Rituximab was not given to all paticiants. Since study does not report number of patients with infections, it was not included in the summary statement.
Severe adverse events + Toxicity leading to discontinuation: In 195 patients with GPA/MPA the rate of SAE was 38-52% with a median follow-up of 28-59 months. Hypogammaglobulinemia seems to be frequent (40% in one study) but rarely severe or requiring discontinuation.	Alberici, 2015	Retrospective, observational single-arm cohort	Median f/u of 59.3 months (IQR 44.5-73.3). Median f/u post-treatment (24 weeks of RTX maintenance) was 34.5 (IQR 19.2-47.2)	69 patients with relapsing/refractory GPA or MPA (no criteria mentioned). United Kingdom population. 2006-2013.	Rituximab induction with either 1g x 2, 2 weeks apart, or 375mg/m2 weekly for 4 wks. Maintenance therapy with Rituxiamb 1,000mg every 6 months for 24 months.	SAE: 93 SAE in 36/69 patients (52.2%). Hypogammaglobulinemia: 28/69 patients (40.6%) developed IgG hypogammaglobulinemia. 2/69 patients (2.9%) with severe hypogammaglobulinemia	Direct evidence: Homogeneous population which fits our criteria. However, not clear that all patients had severe disease. Patients would receive increased doses of glucocoritcoids or other immunosuppressives for flares.
	Calich AL, 2014	Single-arm cohort	34.2±26.2 months (? Mean)	66 GPA patients (fulfilling ACR criteria) and CHCC.	All got induction with RTX (375mg/m2 x 4 or 1,000mg x 2). 60 patients (92.3%) received RTX	Rituximab discontinued before end of 18 months in 14/60 (23%). Reasons include increase in BVAS	Indirect: A minority (n=16, 24%) got additional

				2002-2013. Single center in France.	maintenance with 375mg/m2 or 500mg every 6 months for 18 months.	(5), pregnancy (2), patient decision (3), severe infection (1), hypogammaglobulinemia (1), severe infusion reaction (1), severe late onset neutropenia (1)	immunosuppressives (AZA, MTX, CYC, MMF).
	Smith RM, 2012	Retrospective single center observational cohort	Median follow-up 44 months (range 4-61)	Diagnosis of GPA or MPA (no criteria mentioned). 2002-2006. Done in UK.	Rituximab 1,000mg x 2 for induction therapy followed by 1,000mg every 6 months for maintenance.	SAE: 21/45 (47%) patients (45 events)	Direct evidence: Study has 3 arms. Data only abstracted from Group B which does has relevant population. However, may not all be severe disease at induction.
	Charles, 2018	RCT (used one arm only)	28 months	162 patients, 117 (72.2%) had GPA, and 45 (27.8%) had MPA. Data extracted from one arm (81 patients).	A fixed 500mg rituximab infusion on days 0 and 14 postrandomisation, then 6, 12 and 18 months after the first infusion.	SAE: 31/81 (38%)	RCT (used one arm only). Data extracted from one arm (81 patients).
	Cartin-Ceba R, 2012	Single center retrospective observational cohort	Median f/u of 4.4 years (IQR 2.7-6.2)	53 refractory GPA/MPA patients who either had biopsy proven disease or met ACR or CHCC criteria. All patients received at least 2 courses of RTX for refractory disease. 2000-2010.	RTX (375mg/m2 x 4 or 1,000mg x 2) + glucocorticoids (IV MP for up to 3g when needed, then prednisone 1mg/kg/d with taper d/c by 5 months) for induction. RTX repeated for remission maintenance at same dosing.	SAE unclear (1 sentence reports no SAE and later death due to PJP reported?) Infusion related events: 16 (unclear number of patients with events)	Indirect evidence: Maintenance Rituximab was not given to all paticiants. Not included in final summary statement since number of patients not reported (reported as events only).
VDI was reported by one study with 81 patients hwo had standard treatment with RTX. The mean score changed	Charles, 2018	RCT (used one arm only)	28 months	162 patients, 117 (72.2%) had GPA, and 45 (27.8%) had MPA. Data extracted from one arm (81 patients).	A fixed 500mg rituximab infusion on days 0 and 14 postrandomisation, then 6, 12 and 18 months after the first infusion.	VDI (SD) was 1.86 (1.70) at inclusion and 2.09 (1.97) at 28 months.	RCT (used one arm only). Data extracted from one arm (81 patients).

from1.86 to 2.09 in 28 months.							

37. In patients with severe GPA or MPA who have entered remission with rituximab therapy, what is the impact of using methotrexate or azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Relapse: Based on only one study that provides direct evidence. The relapse rate was 35% at 18 months which is higher then that seen with Rituximab maintenance as above. Results are consistent with MAINRITSAN where CYC was used as induction instead.	Azar, 2014	Retrospective, observational cohort	Median f/u after first RTX tx was 23 months (IQR 10-55 months)	89 patients with GPA meeting both ACR and CHCC criteria who received Rituximab induction therapy (before 11/2011), achieved remission, and did not receive preemptive Rituximab therapy for maintenance. Done at Cleveland Clinic.	Induction therapy with Rituximab 375mg/m2 x 4 weeksly infusions (27%) or 2 fixed doses of 1,000mg IV 2 weeks apart (73%). 47 patients received either methotrexate (n=11, median dose 25mg/wk), azathioprine (n=29, median dose 150mg/d) or mycophenolate (n=7, median dose 2gm/d) for maintenance therapy.	Relapse in 35% of patients by 18 months. 19 relapses total. 5 of which were severe relapses (26%)	Direct evidence: All patients received induction Rituximab. Data abstracted only for those started on additional maintenance immunosuppressive (MTX, AZA, MMF). A very small number (n=7) got MMF for maintenance. The cohort receiving additional immunosuppressive therapy was compared to patients not receiving additional immunosuppressive therapy after Rituximab and there was a dramatic decrease in the relapse rate.
Infection: Based on one study. Infection rate is low (4.3%) and compariable to those receiving Rituximab	Azar, 2014	Retrospective, observational cohort	Median f/u after first RTX tx was 23 months (IQR 10-55 months)	89 patients with GPA meeting both ACR and CHCC criteria who received Rituximab induction therapy (before 11/2011), achieved remission,	Induction therapy with Rituximab 375mg/m2 x 4 weeksly infusions (27%) or 2 fixed doses of 1,000mg IV 2 weeks apart (73%). 47 patients received either methotrexate (n=11,	4 serious infections in 2 patients (2/47 = 4.3%).	Direct evidence: All patients received induction Rituximab. Data abstracted only for those started on additional maintenance immunosuppressive (MTX, AZA, MMF). A very small

without maintenance therapy. It appears that this infectious risk is lower then those getting Rituximab maintenance as above.				and did not receive preemptive Rituximab therapy for maintenance. Done at Cleveland Clinic.	median dose 25mg/wk), azathioprine (n=29, median dose 150mg/d) or mycophenolate (n=7, median dose 2gm/d) for maintenance therapy.		number (n=7) got MMF for maintenance. Cohort was compared to patients not receiving additional immunosuppression after RTX (3 serious infections in 2 patients) and no clear increase in infections were seen.

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies:

Author	Year	Title
Besada	2016	CD4 cell count and CD4/CD8 ratio increase during rituximab maintenance in granulomatosis with polyangiitis patients
Alberici	2015	Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis
Azar	2014	Rituximab with or without a conventional maintenance agent in the treatment of relapsing granulomatosis with polyangiitis (Wegener's): a retrospective single-center study
Calish	2014	Rituximab for induction and maintenance therapy in granulomatosis with polyangiitis (Wegener's). Results of a single-center cohort study on 66 patients
Smith	2012	Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis
Charles	2018	Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2).

Cartin-Ceba	2012	Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center
McClure	2019	Evaluation of PR3-ANCA Status After Rituximab for ANCA-Associated Vasculitis
Pucheal	2019	Rituximab for induction and maintenance therapy of granulomatosis with polyangiitis: a single-centre cohort study on 114 patients

- Studies reviewed and excluded:

Author	Year	Title	Comments
E. J. Gapud	2018	Long-term Clinical Course of Antineutrophil Cytoplasmic Antibody-associated Vasculitis Patients off Maintenance Therapy	Exclude: Only 8 patients received Rituximab induction therapy, but these patients did not get maintenance therapy. Study also only includes patients able to sustain remission for > 36 weeks of maintenance therapy.
S. P. McAdoo	2018	Long-term follow-up of a combined rituximab and cyclophosphamide regimen in renal anti-neutrophil cytoplasm antibody-associated vasculitis	Exclude: Patients got a combination of Cyclophosphamide and Rituximab for induction therapy.
A. A. E. de Joode	2017	Long term azathioprine maintenance therapy in ANCA-associated vasculitis: combined results of long-term follow-up data	Exclude: All patients got induction with Cyclophosphamide.
F. B. Cortazar	2017	Effect of Continuous B Cell Depletion With Rituximab on Pathogenic Autoantibodies and Total IgG Levels in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis	Exclude: All patients got induction with a combination of Rituximab and cyclosphamide.
E. Besada	2014	Serum immunoglobulin levels and risk factors for hypogammaglobulinaemia during long-term maintenance therapy with rituximab in patients with granulomatosis with polyangiitis	Exclude: The article does not separate data out for patients who got Rituximab or other immunosuppressive therapies after induction. Also, it appears that some patients also got cyclophosphamide for induction.
J. Narvaez	2007	Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis	Excluded: Patients received Cyclophosphamide for induction therapy whereas the PICO addresses maintenance after Rituximab induction therapy.

C. Roubaud-Baudron	2012	Rituximab maintenance therapy for granulomatosis with polyangiitis and microscopic polyangiitis	Exclude: The majority of patients got induction therapy with something other then Rituximab or a RTX + other immunosuppressives.
N. Mansfield	2011	Prolonged disease-free remission following rituximab and low-dose cyclophosphamide therapy for renal ANCA-associated vasculitis	Exclude: Patients received induction therapy with a combination of Rituximab and cyclophosphamide.
H. A. Hauer	2002	Determinants of outcome in ANCA-associated glomerulonephritis: a prospective clinico-histopathological analysis of 96 patients	Exclude: Irrelevant outcomes.
B Terrier	2013	Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis.	Exclude: Patients received Cyclophosphamide for induction therapy whereas the PICO addresses maintenance after Rituximab induction therapy.

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Maintanance

- **PICO question 18:** In patients with severe GPA or MPA who have entered remission with cyclophosphamide or rituximab therapy, what is the impact of using rituximab 1000 mg IV q4 months vs. rituximab 1000 mg IV q6 months vs. rituximab 500 mg IV q6 months for remission maintenance on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, serious adverse events, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypogammaglobulinemia)

38. In patients with severe GPA or MPA who have entered remission with cyclophosphamide or rituximab therapy, what is the impact of using rituximab 1000 mg IV q4 months vs. rituximab 1000 mg IV q6 months vs. rituximab 500 mg IV q6 months for remission maintenance on disease-related outcomes and treatment-related adverse events?
    - No comparative data available

39. In patients with severe GPA or MPA who have entered remission with cyclophosphamide or rituximab therapy, what is the impact of using rituximab 1000 mg IV q4 months for remission maintenance on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Relapse: Two studies used either 1g every 4 months or 500mg every 6 months of Rituximab. Relapses occurred in 7% and 10% over 1-2 year follow-up. This seems similar to other RTX regimens.	Rhee EP, 2010	Retrospective, single center review	All 39 had follow-up for at least 1 year, 20 had f/u for at least 2 yrs after RTX initiation. 708 pt months f/u.	GPA and MPA that were ANCA positive (no criteria mentioned). Done at Mass General hospital with RTX initiation between 2006-2008.	RTX 375mg/m2 x 4 or 1g x 2 for induction therapy. Patients were then scheduled to get 1g every 4 months. 33/39 patients (84.6%) followed this maintenance regimen w/o interruption.	3/39 patients (7.7%) had flares (defined as BVAS/WG of at least 2).
	Charles, 2018	RCT (used one arm only)	28 months	162 patients, 117 (72.2%) had GPA, and 45 (27.8%) had MPA. Data extracted from one arm (81 patients).	A fixed 500mg rituximab infusion on days 0 and 14 postrandomisation, then 6, 12 and 18 months after the first infusion.	Relapses in 8/81 (9.9%). Relapse-free survival rate was 86.4% (95% CI 79.2 to 94.2).
Infection: Only based on 2 studies. Low infection rate of 2.6% in one study but 22% in another study. It is also difficult to say how accurate this is based on concurrent cytotoxic therapy and unclear standardization for reporting adverse events.	Rhee EP, 2010	Retrospective, single center review	All 39 had follow-up for at least 1 year, 20 had f/u for at least 2 yrs after RTX initiation. 708 pt months f/u.	GPA and MPA that were ANCA positive (no criteria mentioned). Done at Mass General hospital with RTX initiation between 2006-2008.	RTX 375mg/m2 x 4 or 1g x 2 for induction therapy. Patients were then scheduled to get 1g every 4 months. 33/39 patients (84.6%) followed this maintenance regimen w/o interruption.	Infections requiring hospitalization: 1/39 patients (2.6%).
	Charles, 2018	RCT (used one arm only)	28 months	162 patients, 117 (72.2%) had GPA, and 45 (27.8%) had MPA. Data extracted from one arm (81 patients).	A fixed 500mg rituximab infusion on days 0 and 14 postrandomisation, then 6, 12 and 18 months after the first infusion.	18/81 (22%)
Serious adverse events + toxicity leading to discontinuation: Only based on 2 studies. Late onset neutropenia seems high (5%). No data on hypogammaglobulinemia.	Rhee EP, 2010	Retrospective, single center review	All 39 had follow-up for at least 1 year, 20 had f/u for at least 2 yrs after RTX initiation. 708 pt months f/u.	GPA and MPA that were ANCA positive (no criteria mentioned). Done at Mass General hospital with RTX initiation between 2006-2008.	RTX 375mg/m2 x 4 or 1g x 2 for induction therapy. Patients were then scheduled to get 1g every 4 months. 33/39 patients (84.6%) followed this maintenance regimen w/o interruption.	Severe adverse events in 4/39 (10.3%) including infusion reaction (requiring hospitalization, 1), infection (1), late onset neutropenia (2). Study did not monitor for Hypogammaglobulinemia.
	Charles, 2018	RCT (used	28 months	162 patients, 117 (72.2%) had GPA,	A fixed 500mg rituximab infusion on days 0 and 14	SAE: 31/81 (38%)

		one arm only)		and 45 (27.8%) had MPA. Data extracted from one arm (81 patients).	postrandomisation, then 6, 12 and 18 months after the first infusion.	
Malignancy was reported by one study with 81 patients and rate of 2.5%.	Charles, 2018	RCT (used one arm only)	28 months	162 patients, 117 (72.2%) had GPA, and 45 (27.8%) had MPA. Data extracted from one arm (81 patients).	A fixed 500mg rituximab infusion on days 0 and 14 postrandomisation, then 6, 12 and 18 months after the first infusion.	2/81 (2.5%)
VDI was reported by one study with 81 patients hwo had standard treatment with RTX. The mean score changed from1.86 to 2.09 in 28 months.	Charles, 2018	RCT (used one arm only)	28 months	162 patients, 117 (72.2%) had GPA, and 45 (27.8%) had MPA. Data extracted from one arm (81 patients).	A fixed 500mg rituximab infusion on days 0 and 14 postrandomisation, then 6, 12 and 18 months after the first infusion.	VDI (SD) was 1.86 (1.70) at inclusion and 2.09 (1.97) at 28 months.
Death was reported by one study with 81 patients and rate of 3.7% over 28 months.	Charles, 2018	RCT (used one arm only)	28 months	162 patients, 117 (72.2%) had GPA, and 45 (27.8%) had MPA. Data extracted from one arm (81 patients).	A fixed 500mg rituximab infusion on days 0 and 14 postrandomisation, then 6, 12 and 18 months after the first infusion.	3/81 (3.7%)

40. In patients with severe GPA or MPA who have entered remission with cyclophosphamide or rituximab therapy, what is the impact of using rituximab 1000 mg IV q6 months for remission maintenance on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Disease activity: 83-96% of patients achieved remission with induction dose of Rituximab. However, this is not indicative of effect of maintenance RTX. Not clear evidence regarding change in BVAS score with maintenance RTX.	Smith RM, 2012	Retrospective single center observational cohort	Median follow-up 44 months (range 4-61)	Diagnosis of GPA or MPA (no criteria mentioned). 2002-2006. Done in UK.	Rituximab 1,000mg x 2 for induction therapy followed by 1,000mg every 6 months for maintenance.	43/45 (96%) achieved a complete or partial remission.
	Besada E, 2013	Retrospective	Median f/u 47 (2-88)	35 GPA patients meeting ACR and/or CHCC	Rituximab 1,000mg x 2 for inducation. Then RTX given for	6 months after RTX initiation: 29/35 (82.9%) achieved

		single center observational cohort		treated with RTX between 2004-2011. Done in Norway.	maintenance as either 1g every 6 months or 1g x 2 every 12 months.	remission and 33/35 had remission or partial response (94.3%)	
Relapse: While on Rituximab 1,000mg every 6 months the relapse rate appears to be around 12-13% over 44-60 months of follow-up. This is slightly higher then 500mg q 6 months and similar to MAINRITSAN trial.	Alberici, 2015	Retrospective, observational single-arm cohort	Median f/u of 59.3 months (IQR 44.5-73.3). Median f/u post-treatment (24 weeks of RTX maintenance) was 34.5 (IQR 19.2-47.2)	69 patients with relapsing/refractory GPA or MPA (no criteria mentioned). United Kingdom population. 2006-2013.	Rituximab induction with either 1g x 2, 2 weeks apart, or 375mg/m2 weekly for 4 wks. Maintenance therapy with Rituxiamb 1,000mg every 6 months for 24 months.	During RTX maintenance: 9/69 (13%) relapsed a median of 11 months after the first RTX infusion. 2/69 (2.9%) were severe relapses. After completion of 24 weeks RTX maintenance: 28/69 (40.6%) experienced flares after a median time of 15.5 mon (IQR 12-22.9). 12/69 (17.4%) had severe flares.	
	Smith RM, 2012	Retrospective single center observational cohort	Median follow-up 44 months (range 4-61)	Diagnosis of GPA or MPA (no criteria mentioned). 2002-2006. Done in UK.	Rituximab 1,000mg x 2 for induction therapy followed by 1,000mg every 6 months for maintenance.	2 years: Relapses in 5/43 (12%) Last follow-up: Relapses in 11/43 (26%)	
	Besada E, 2013	Retrospective single center observational cohort	Median f/u 47 (2-88)	35 GPA patients meeting ACR and/or CHCC treated with RTX between 2004-2011. Done in Norway.	Rituximab 1,000mg x 2 for inducation. Then RTX given for maintenance as either 1g every 6 months or 1g x 2 every 12 months.	9 relapses over 1636 months of f/u, 6.6/100 pt-yrs.	
	McClare, 2019	Single Center Observational cohort	Median f/u of 59 months (IQR 44-72)	53 GPA/MPA patients with positive PR3-ANCA (?) treated with induction Rituximab (1,000mg x2). 2011-2016	Rituximab 2g in first 2 weeks, then 1,000mg once every 6 months for 2 years and concommittant corticosteroids (0.5-1mg/kg)	Relapse in 24/53 (45.3%) Median time to relapse 1107 days (36 months)	Direct: I patient ANCA p which is GPA, ye significa patients
Death: Deaths ranged from 3-7% over follow-up of 44-60 months. This is slightly higher then that seen with 500mg every 6 months and	Alberici, 2015	Retrospective, observational single-	Median f/u of 59.3 months (IQR 44.5-73.3). Median f/u post-treatment (24 weeks of RTX	69 patients with relapsing/refractory GPA or MPA (no criteria mentioned). United	Rituximab induction with either 1g x 2, 2 weeks apart, or 375mg/m2 weekly for 4 wks. Maintenance therapy with	2/69 patients (2.9%) died from perintoneal cardinoma and one from unknown cause.	

connot compare to 1,000mg every 4 months.		arm cohort	maintenance) was 34.5 (IQR 19.2-47.2)	Kingdom population. 2006-2013.	Rituxiamb 1,000mg every 6 months for 24 months.	
	Smith RM, 2012	Retrospective single center observational cohort	Median follow-up 44 months (range 4-61)	Diagnosis of GPA or MPA (no criteria mentioned). 2002-2006. Done in UK.	Rituximab 1,000mg x 2 for induction therapy followed by 1,000mg every 6 months for maintenance.	3 deaths (3/45= 6.7%).
	Besada E, 2013	Retrospective single center observational cohort	Median f/u 47 (2-88)	35 GPA patients meeting ACR and/or CHCC treated with RTX between 2004-2011. Done in Norway.	Rituximab 1,000mg x 2 for inducation. Then RTX given for maintenance as either 1g every 6 months or 1g x 2 every 12 months.	2 deaths (5.7%) from bowel obstrauction + E coli sepsis 2/2 to colon cancer and other from sepsis complicating a myeloproliferative malignancy.
Infection: Among the studies with direct evidence the severe infection rate is 27-29% over 44-60 monhts f/u. This is higher compared to 500mg every 6 months (13-17%) and difficult to compare to 1,000mg every 4 months.	Besada, 2016	Observational prospective registry	24 months	35 patients from Northern Norway with an established diagnosis of GPA (no criteria mentioned).	All patients got Rituximab induction (1g twice in a fortnight) combined with oral prednisolone (median 20mg/d) and an immunosuppressive drug. 49% received Rituximab maintenance with 2g annual regimen (1g twice in a fortnight per year), 40% received maintenance with 1g biannually (1 g every 6 months) and 11% did not receive maintenance therapy.	2 severe infections (5.7%) occurring 3 and 4 months after induction rituximab. Severe infections defined as requiring IV antibiotics and/or hospitalization.
	Alberici, 2015	Retrospective, observational single-arm cohort	Median f/u of 59.3 months (IQR 44.5-73.3). Median f/u post-treatment (24 weeks of RTX maintenance) was 34.5 (IQR 19.2-47.2)	69 patients with relapsing/refractory GPA or MPA (no criteria mentioned). United Kingdom population. 2006-2013.	Rituximab induction with either 1g x 2, 2 weeks apart, or 375mg/m2 weekly for 4 wks. Maintenance therapy with Rituxiamb 1,000mg every 6 months for 24 months.	Severe infections in 20/69 patients (29.0%), 57% of which affecting the lower respiratory tract.
	Smith RM, 2012	Retrospective single center observati	Median follow-up 44 months (range 4-61)	Diagnosis of GPA or MPA (no criteria mentioned). 2002-2006. Done in UK.	Rituximab 1,000mg x 2 for induction therapy followed by 1,000mg every 6 months for maintenance.	Severe infections in 12/45 (27%) of patients (30 events)

		onal cohort				
	Besada E, 2013	Retrospective single center observational cohort	Median f/u 47 (2-88)	35 GPA patients meeting ACR and/or CHCC treated with RTX between 2004-2011. Done in Norway.	Rituximab 1,000mg x 2 for inducation. Then RTX given for maintenance as either 1g every 6 months or 1g x 2 every 12 months.	Severe infections in 9/35 (25.7%). Rate of severe infections was 6.6/100 pt-yrs. Chronic/relapsing infections in 10/35 (29%)
Serious adverse events + toxicity leading to discontinuation: Among direct evidence 47-52% developed SAE which is lower then with 500mg every 6 months. Hypogammaglobulinemia appears to be a significant problem with up to 33% of patients discontinueing RTX due to hypogammaglobulinemia. Late onset neutropenia is similar to 1,000mg every 4 months (around 5%).	Alberici, 2015	Retrospective, observational single-arm cohort	Median f/u of 59.3 months (IQR 44.5-73.3). Median f/u post-treatment (24 weeks of RTX maintenance) was 34.5 (IQR 19.2-47.2)	69 patients with relapsing/refractory GPA or MPA (no criteria mentioned). United Kingdom population. 2006-2013.	Rituximab induction with either 1g x 2, 2 weeks apart, or 375mg/m2 weekly for 4 wks. Maintenance therapy with Rituxiamb 1,000mg every 6 months for 24 months.	SAE: 93 SAE in 36/69 patients (52.2%). Hypogammaglobulinemia: 28/69 patients (40.6%) developed IgG hypogammaglobulinemia. 2/69 patients (2.9%) with severe hypogammaglobulinemia
	Smith RM, 2012	Retrospective single center observational cohort	Median follow-up 44 months (range 4-61)	Diagnosis of GPA or MPA (no criteria mentioned). 2002-2006. Done in UK.	Rituximab 1,000mg x 2 for induction therapy followed by 1,000mg every 6 months for maintenance.	SAE: 21/45 (47%) patients (45 events)
	Besada E, 2014	Restrospective single center observational cohort	Median f/u 4 years	29 GPA patients (only 12 of which got RTX 1,000mg every 6 months) meeting ACR and/or CHCC criteria. Single center. Done in Norway between 2004-2011.	Rituximab 1,000mg x 2 for induction therapy followed by Rituximab maintenance as either 1,000mg x 2 annually (6) or 1,000mg every 6 months (12) or a combination of the two (11).	Patients discontinuing RTX due to hypogammaglobulinemia: 4/12 (33.3%)
	Besada E, 2013	Retrospective single center observational cohort	Median f/u 47 (2-88)	35 GPA patients meeting ACR and/or CHCC treated with RTX between 2004-2011. Done in Norway.	Rituximab 1,000mg x 2 for inducation. Then RTX given for maintenance as either 1g every 6 months or 1g x 2 every 12 months.	RTX discontinued in 13/35 patients (37.1%) Discontinued reason: Hypogam: 8/35 (22.9%) Late onset neutropenia 2/35 (5.7%) Severe infection 3/35 (8.6%)

						Renal transplant (4), malignancy (2), colitis (1), pregnancy (1)

41. In patients with severe GPA or MPA who have entered remission with cyclophosphamide or rituximab therapy, what is the impact of using rituximab 500 mg IV q6 months for remission maintenance on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease activity : 86% of patients achieved either remission or improvement (not refractory) by 12 months. It is difficult to make comparisons with other groups.	Calich AL, 2014	Retrospective Single-arm cohort	34.2±26.2 months (? Mean)	66 GPA patients (fulfilling ACR criteria) and CHCC. 2002-2013. Single center in France.	All got induction with RTX (375mg/m2 x 4 or 1,000mg x 2). 60 patients (92.3%) received RTX maintenance with 375mg/m2 or 500mg every 6 months for 18 months.	12 months: 49/57 (86.0%) patients were either in remission or showed improvement (not refractory). Multivariable analysis shows SGS as an independent risk factor for treatment failure (OR 31.3,95% CI 2.2-435.1,p=0.0104).	Indirect: A minority (n=16, 24%) got additional immunosuppressives (AZA, MTX, CYC, MMF). Also, some of patients got 375mg/m2 x 1 every 6 months instead of 500mg (but for most will be close to same dose).
Relapse: There are no studies with direct evidence. The relapse rate appears to be 5-15% at 18-24 months which is comparable to the other groups.	Calich AL, 2014	Single-arm cohort	34.2±26.2 months (? Mean)	66 GPA patients (fulfilling ACR criteria) and CHCC. 2002-2013. Single center in France.	All got induction with RTX (375mg/m2 x 4 or 1,000mg x 2). 60 patients (92.3%) received RTX maintenance with 375mg/m2 or 500mg every 6 months for 18 months.	Relapse rate of 11.2/100 pt-yrs. 5/60 (8.3%) relapsed within 2 years. Mean relapse free survival was 48.4% at 5 yrs.	Indirect: A minority (n=16, 24%) got additional immunosuppressives (AZA, MTX, CYC, MMF). Also, some of patients got 375mg/m2 x 1 every 6 months instead of 500mg (but for most will be close to same dose).
	Puechal X, 2018	Retrospective, single center, observational	Medial f/u after first RTX infusion was 3.6 yrs (IQR 1.6-5.8)	100 GPA patients fulfilling ACR and/or CHCC. 2005-2016. Single center in France.	All got induction with RTX (375mg/m2 x 4 or 1,000mg x 2). 100 of the entire cohort (114) received RTX maintenance therapy. 90 received 500mg RTX every 6 months and 10 got other RTX regimens.	Of patients that reached remission at 6 months (n=91) 40 patients (44%) relapsed. 18 major relapses (20%). 1, 2 and 3 year relapse free survival were 93% (95% CI 88.0,98.0), 85% (95% CI 78.0, 92.0) and 82% (95% CI 75.0, 90.0)	Indirect: There is a small number of patients (n=10) that got "other" Rituximab regimens, however, the majority (n=90) got 500mg every 6 months. Also, some of the cohort did not get maintenance Rituximab (14).
	Guivellin, 2014	RCT, Maintenance of	22 months	Patients with newly diagnosed or	Patients were randomly as-signed to receive either 500	At month 28, major relapse had occurred in 3 patients	

		Remission using Rituximab in Systemic ANCA-associated Vascu- litis (MAINRITSAN)		relapsing granulomatosis with polyangiitis, mi-croscopic polyangiitis, or renal-limited ANCA-associated vasculitis in complete remission after a cyclophosphamide–glucocorticoid regimen.	mg of rituximab on days 0 and 14 and at months 6, 12, and 18 after study entry or daily azathioprine until month 22.	in the rituximab group (5%) and 17 patients (29%) on patients taking azathioprine	
Death: Only 2 deaths (1.8%) which is lower compared to 1,000mg every 6 months. Cannot compare with 1,000mg every 4 months.	Puechal X, 2018	Retrospective, single center, observational	Medial f/u after first RTX infusion was 3.6 yrs (IQR 1.6-5.8)	100 GPA patients fulfilling ACR and/or CHCC. 2005-2016. Single center in France.	All got induction with RTX (375mg/m2 x 4 or 1,000mg x 2). 100 of the entire cohort (114) received RTX maintenance therapy. 90 received 500mg RTX every 6 months and 10 got other RTX regimens.	2 deaths (1.8%) from sepsis and GPA flare respectively.	Indirect: There is a small number of patients (n=10) that got "other" Rituximab regimens, however, the majority (n=90) got 500mg every 6 months. Also, some of the cohort did not get maintenance Rituximab (14).
Infection: Indirected evidence only. Severe infections in 14-18% of patients which seems significantly lower then 1,000mg every 6 months. It is difficult to compare with the 1,000mg every 4 months.	Calich AL, 2014	Single-arm cohort	34.2±26.2 months (? Mean)	66 GPA patients (fulfilling ACR criteria) and CHCC. 2002-2013. Single center in France.	All got induction with RTX (375mg/m2 x 4 or 1,000mg x 2). 60 patients (92.3%) received RTX maintenance with 375mg/m2 or 500mg every 6 months for 18 months.	Severe infections in 9/66 patients (13.6%, 13 events).	Indirect: A minority (n=16, 24%) got additional immunosuppressives (AZA, MTX, CYC, MMF). Also, some of patients got 375mg/m2 x 1 every 6 months instead of 500mg (but for most will be close to same dose).
	Puechal X, 2018	Retrospective, single center, observational	Medial f/u after first RTX infusion was 3.6 yrs (IQR 1.6-5.8)	100 GPA patients fulfilling ACR and/or CHCC. 2005-2016. Single center in France.	All got induction with RTX (375mg/m2 x 4 or 1,000mg x 2). 100 of the entire cohort (114) received RTX maintenance therapy. 90 received 500mg RTX every 6 months and 10 got other RTX regimens.	20 patients (17.5%) had serious infections (22 events). Most frequent were respirator infections (n=11) and sepsis (n=5)	Indirect: There is a small number of patients (n=10) that got "other" Rituximab regimens, however, the majority (n=90) got 500mg every 6 months. Also, some of the cohort did not get maintenance Rituximab (14).
Serious adverse events + toxicity leading to discontinuation:	Calich AL, 2014	Single-arm cohort	34.2±26.2 months (? Mean)	66 GPA patients (fulfilling ACR criteria) and CHCC. 2002-	All got induction with RTX (375mg/m2 x 4 or 1,000mg x 2). 60 patients (92.3%) received RTX maintenance	Rituximab discontinued before end of 18 months in 14/60 (23%). Reasons include increase in BVAS	Indirect: A minority (n=16, 24%) got additional immunosuppressives (AZA, MTX, CYC, MMF). Also,

Indirect evidence only. SAE in 27% based on one study which is lower compared to 1,000mg every 6 months. Hypogammaglobulinemia continues to be a problem, but it is difficult to make comparison with the other groups.				2013. Single center in France.	with 375mg/m2 or 500mg every 6 months for 18 months.	(5), pregnancy (2), patient decision (3), severe infection (1), hypogammaglobulinemia (1), severe infusion reaction (1), severe late onset neutropenia (1)	some of patients got 375mg/m2 x 1 every 6 months instead of 500mg (but for most will be close to same dose).
	Puechal X, 2018	Retrospective, single center, observational	Medial f/u after first RTX infusion was 3.6 yrs (IQR 1.6-5.8)	100 GPA patients fulfilling ACR and/or CHCC. 2005-2016. Single center in France.	All got induction with RTX (375mg/m2 x 4 or 1,000mg x 2). 100 of the entire cohort (114) received RTX maintenance therapy. 90 received 500mg RTX every 6 months and 10 got other RTX regimens.	31 patients (31/114 = 27.2%) (36 events) had SAE Hypogammaglobulin: 6 months: 36/75 (48%) 12 mon: 30/65 (46%) 24 mon: 26/45 (58%) Severe hypogam: 6 months: 3/75 (4%) 12 mon: 3/65 (5%) 24 mon: 3/45 (7%)	Indirect: There is a small number of patients (n=10) that got "other" Rituximab regimens, however, the majority (n=90) got 500mg every 6 months. Also, some of the cohort did not get maintenance Rituximab (14).

- **References:**

- Randomized controlled trials:
  None

- Comparactive observational studies:
  None

- Single arm studies and test accuracy studies:

Author	Year	Title
Puechal	2018	Rituximab for induction and maintenance therapy of granulomatosis with polyangiitis: a single-centre cohort study on 114 patients
Besada	2016	CD4 cell count and CD4/CD8 ratio increase during rituximab maintenance in granulomatosis with polyangiitis patients
Alberici	2015	Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis
Besada	2014	Serum immunoglobulin levels and risk factors for hypogammaglobulinaemia during long-term maintenance therapy with rituximab in patients with granulomatosis with polyangiitis

Calish	2014	Rituximab for induction and maintenance therapy in granulomatosis with polyangiitis (Wegener's). Results of a single-center cohort study on 66 patients
Besada	2013	Long-term efficacy and safety of pre-emptive maintenance therapy with rituximab in granulomatosis with polyangiitis: results from a single centre
Smith	2012	Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis
Rhee	2010	Rituximab as maintenance therapy for anti-neutrophil cytoplasmic antibody-associated vasculitis
Charles	2018	Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2).
Guillevin	2014	Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis
McClare	2019	Evaluation of PR3-ANCA Status After Rituximab for ANCA-Associated Vasculitis

- Studies reviewed and excluded:

Author	Year	Title	Comments
F. B. Cortazar	2017	Effect of Continuous B Cell Depletion With Rituximab on Pathogenic Autoantibodies and Total IgG Levels in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis	Exclude: Patients got a combination of rituximab and cyclophosphamide for induction. The maintenance dosing of Rituximab varied with time (i.e., every 4 months for 2 years then every 6 months).
A. Knight	2016	Late-onset neutropenia after rituximab in ANCA-associated vasculitis	Exclude: Mixed population of Rituximab maintenance regiments and article does not include subgroup analysis based on the Rituximab regimen.
Z. Chocova	2015	Rituximab use in patients with ANCA-associated vasculitis: clinical efficacy and impact on immunological parameters	Exclude: The manuscript contains seemingly contradictory information regarding the patients receiving Rituximab maintenance therapy.
A. Knight	2014	Efficacy and safety of rituximab as maintenance therapy for relapsing granulomatosis with polyangiitis-a case series	Exclude: Patients were treated with Rituximab 1,000mg x 2 every 6 months for maintenance.
R. Cartin-Ceba	2012	Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center	Exclude: Not all patients got a regular Rituximab maintenance and the maintenance strategy was different then this PICO (1g x 2 or based on B-cells/ANCA).

C. Roubaud-Baudron	2012	Rituximab maintenance therapy for granulomatosis with polyangiitis and microscopic polyangiitis	Exclude: Mixture of patients getting different Rituximab regiments (cannot separate out groups). In addition, half of patients were receiving other non-glucocorticoid immunosuppressives as well.
R. B. Jones	2009	A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis	Exclude: Maintenance Rituximab was only given in 6 patients and subgroup analysis was not done.

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Maintanance

- **PICO Question 19:** In patients with severe GPA or MPA who have entered remission with cyclophosphamide or rituximab therapy, what is the impact of using MMF for remission maintenance vs. methotrexate or azathioprine on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

1. In patients with severe GPA or MPA who have entered remission with cyclophosphamide or rituximab therapy, what is the impact of using MMF for remission maintenance vs. methotrexate or azathioprine on disease-related outcomes and treatment-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate	Azathioprine	Relative (95% CI)	Absolute (95% CI)	
Relapses during study											
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	42/76 (55.3%)	30/80 (37.5%)	**OR 2.06** (1.09 to 3.90)	**178 more per 1,000** (from 20 more to 326 more)	⊕◯◯◯ VERY LOW
Major Relapses											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate	Azathioprine	Relative (95% CI)	Absolute (95% CI)	
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	18/76 (23.7%)	10/80 (12.5%)	**OR 2.17** (0.93 to 5.07)	**112 more per 1,000** (from 8 fewer to 295 more)	⊕◯◯◯ VERY LOW
Serious Adverse Events (Absolute)											
1	randomised trials	serious [a]	not serious	not serious	not serious	none	8/76 (10.5%)	22/80 (27.5%)	**OR 0.31** (0.13 to 0.75)	**170 fewer per 1,000** (from 228 fewer to 54 fewer)	⊕⊕⊕◯ MODERATE
Mortality											
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/76 (1.3%)	1/80 (1.3%)	**OR 1.05** (0.06 to 17.15)	**1 more per 1,000** (from 12 fewer to 166 more)	⊕◯◯◯ VERY LOW
Participants with 1 or more Serious Adverse Event											
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	8/76 (10.5%)	13/80 (16.3%)	**OR 0.61** (0.24 to 1.56)	**57 fewer per 1,000** (from 118 fewer to 70 more)	⊕⊕◯◯ LOW
Malignancy											
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	1/76 (1.3%)	5/80 (6.3%)	**OR 0.20** (0.02 to 1.75)	**49 fewer per 1,000** (from 61 fewer to 42 more)	⊕⊕◯◯ LOW
Drug withdrawal due to intolerance											
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	2/76 (2.6%)	6/80 (7.5%)	**OR 0.33** (0.07 to 1.71)	**49 fewer per 1,000** (from 69 fewer to 47 more)	⊕⊕◯◯ LOW

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Performance bias; Detection bias- Open Label

b. Wide CI; Treatment would differ if the upper versus the lower boundary of the CI represented the truth.

c. Treatment would differ if the upper versus the lower boundary of the CI represented the truth.

- **References:**

- Included Randomized Controlled Trial:

Author	Year	Title
T. F. Hiemstra	2010	Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Maintanance

- **PICO Question 20 :** In patients with severe GPA or MPA who have entered remission with cyclophosphamide or rituximab therapy, what is the impact of using LEF for remission maintenance vs. methotrexate or azathioprine on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

42. In patients with severe GPA or MPA who have entered remission with cyclophosphamide or rituximab therapy, what is the impact of using LEF for remission maintenance vs. methotrexate or azathioprine on disease-related outcomes and treatment-related adverse events?

43. Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LEF	MTX	Relative (95% CI)	Absolute (95% CI)	
Relapses											

43. Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LEF	MTX	Relative (95% CI)	Absolute (95% CI)	
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	6/26 (23.1%)	13/28 (46.4%)	**OR 0.35** (0.11 to 1.12)	**232 fewer per 1,000** (from 377 fewer to 28 more)	⊕◯◯◯ VERY LOW

Drug withdrawal due to intolerance

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	5/26 (19.2%)	1/28 (3.6%)	**OR 6.43** (0.70 to 59.28)	**157 more per 1,000** (from 10 fewer to 651 more)	⊕◯◯◯ VERY LOW

Major Relapse

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/26 (3.8%)	7/28 (25.0%)	**OR 0.12** (0.01 to 1.06)	**212 fewer per 1,000** (from 247 fewer to 11 more)	⊕◯◯◯ VERY LOW

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Not blinded

b. Wide CI; Treatment would differ if the upper versus the lower boundary of the CI represented the truth.

2. In patients with severe GPA or MPA who have entered remission with cyclophosphamide or rituximab therapy, what is the impact of using methotrexate or azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease Activity/Relapse: In 52 GPA/MPA patients relapse	Jayne, 2019	RCT, single arm for PICO	3 years	52 patients GPA or MPA meeting CHCC. Multicenter, multinational	RTX or CYC induction followed by AZA 2mg/kg/d target and low	Vasculitis relapse (defined as BVAS >= 6 major item or use of	Direct evidence: Relapse is defined differently from other studies (generally is any BVAS or

rate was 15% at 3 years.					dose glucocorticoids below 10mg/d	habitedted medication) : 8/52 (15%)	BVAS of at least 3). Patients are also allowed to stay on up to 10mg/d GC's.
Disease damate (VDI): In 52 GPA/MPA patients there was no change in VDI at 3 years.	Jayne, 2019	RCT, single arm for PICO	3 years	52 patients GPA or MPA meeting CHCC. Multicenter, multinational	RTX or CYC induction followed by AZA 2mg/kg/d target and low dose glucocorticoids below 10mg/d	No absolute change in VDI by the end of the study in 52 patients	Direct evidence: Patients allowed to stay on up to 10mg/d GC's.
Infections: In 52 patients there were 4 major infections at 3 years.	Jayne, 2019	RCT, single arm for PICO	3 years	52 patients GPA or MPA meeting CHCC. Multicenter, multinational	RTX or CYC induction followed by AZA 2mg/kg/d target and low dose glucocorticoids below 10mg/d	Any infection: 30/52 (57%) patients Serious infections in 4/52 (7%) patients	Direct evidence: Patients allowed to stay on up to 10mg/d GC's.
SAE: In 52 GPA/MPA patients there were 16 SAE in 3 years.	Jayne, 2019	RCT, single arm for PICO	3 years	52 patients GPA or MPA meeting CHCC. Multicenter, multinational	RTX or CYC induction followed by AZA 2mg/kg/d target and low dose glucocorticoids below 10mg/d	SAE in 16/52 (31%) patients	Direct evidence: Patients allowed to stay on up to 10mg/d GC's.
Toxicity leading to discontinuation: In GPA/MPA patients treated with AZA14% d/c'd drug due to adverse events.	Jayne, 2019	RCT, single arm for PICO	3 years	52 patients GPA or MPA meeting CHCC. Multicenter, multinational	RTX or CYC induction followed by AZA 2mg/kg/d target and low dose glucocorticoids below 10mg/d	Adversent event leading to drug discontinuation in 7/52 (14%)	Direct evidence: Patients allowed to stay on up to 10mg/d GC's.
Malignancy: There were no malignancies in 52 patients with GPA/MPA treated with AZA.	Jayne, 2019	RCT, single arm for PICO	3 years	52 patients GPA or MPA meeting CHCC. Multicenter, multinational	RTX or CYC induction followed by AZA 2mg/kg/d target and low dose glucocorticoids below 10mg/d	No malignancies in 52 patients	Direct evidence: Patients allowed to stay on up to 10mg/d GC's.
Death: At 3 years there were no deaths in 52 patients with GPA/MPA treated with AZA.	Jayne, 2019	RCT, single arm for PICO	3 years	52 patients GPA or MPA meeting CHCC. Multicenter, multinational	RTX or CYC induction followed by AZA 2mg/kg/d target and low dose glucocorticoids below 10mg/d	No deaths	Direct evidence: Patients allowed to stay on up to 10mg/d GC's.

- **References:**

- Randomized Controlled Trials:

Author	Year	Title
C. Metzler	2007	Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis

- Single arm studies:

Author	Year	Title
Jayne D	2019	Efficacy and Safety of Belimumab and Azathioprine for Maintenance of Remission in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis: A Randomized Controlled Study

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Maintanance

- **PICO Question 21 :** In patients with non-severe GPA who have entered remission, what is the impact of using SMZ/TMP vs. methotrexate or azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, serious adverse events, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity**)**

1. In patients with non-severe GPA who have entered remission, what is the impact of using SMZ/TMP vs. methotrexate or azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	T/S	Relative (95% CI)	Absolute (95% CI)	
Complete remission											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	T/S	Relative (95% CI)	Absolute (95% CI)	
1	observational studies	not serious	not serious	not serious	very serious [a]	none	19/22 (86.4%)	14/24 (58.3%)	**OR 4.52** (1.05 to 19.54)	**280 more per 1,000** (from 12 more to 381 more)	⨁◯◯◯ VERY LOW
Relapses											
1	observational studies	not serious	not serious	not serious	serious [a]	none	3/22 (13.6%)	10/24 (41.7%)	**OR 0.22** (0.05 to 0.95)	**281 fewer per 1,000** (from 382 fewer to 12 fewer)	⨁◯◯◯ VERY LOW
Adverse events											
1	observational studies	not serious	not serious	not serious	very serious [a]	none	12/33 (36.4%)	6/32 (18.8%)	**OR 2.48** (0.79 to 7.71)	**176 more per 1,000** (from 33 fewer to 453 more)	⨁◯◯◯ VERY LOW

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Wide CI; Treatment would differ if the upper versus the lower boundary of the CI represented the truth.

- **References:**

- Included Randomized Controlled Trials:

Author	Year	Title
K. de Groot	1996	Therapy for the maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis. Methotrexate versus trimethoprim/sulfamethoxazole

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Maintanance

- **PICO question 22 :** In patients with severe GPA who have entered remission, what is the impact of using SMZ/TMP vs. methotrexate or azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, serious adverse events, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

44. In patients with severe GPA who have entered remission, what is the impact of using SMZ/TMP vs. methotrexate or azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?
    - No Comparative Data Available

45. In patients with severe GPA who have entered remission, what is the impact of using SMZ/TMP for remission maintenance on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Relapse: In 38 GPA patients with both severe and nonsevere disease treated with SMZ/TMP for maintenance 18% relapsed by 24 months. Differences in population and severity make comparison with MTX/AZA difficult.	Stegeman CA, 1996	Blinded RCT, however for PICO functions as prosective cohort	24 months	38 GPA patients who were either a) biopsy proven renal with upper/lower airway dz, b) "limited" disease with positive biopsy, or c) fulfilles ACR criteria and positive ANCA. All these patients had 24 months follow-up (down from 41). Study conducted in Netherlands from 1990-1994.	After achieving remission treated with SMZ/TMP 800mg/160mg BID for 24 months.	Relapse (24 mon): 7/38 (18.4%)	Indirect: Includes patients who had both severe and nonsevere disease who entered remission.
Death: In 41 GPA patients treated with SMZ/TMP	Stegeman CA, 1996	Blinded RCT, however for PICO functions	24 months	41 GPA patients who were either a) biopsy proven renal with upper/lower	After achieving remission treated with SMZ/TMP 800mg/160mg BID for 24 months.	Mortality rate (24 mon): 0/41	Indirect: Includes patients who had both severe and nonsevere

for maintenance there were no deaths at 24 months.		as prosective cohort		airway dz, b) "limited" disease with positive biopsy, or c) fulfilles ACR criteria and positive ANCA. Study conducted in Netherlands from 1990-1994.			disease who entered remission.
Infection: In 41 patients with GPA treated with SMZ/TMP there were significantly fewer annual infections compared to placebo.	Stegeman CA, 1996	Blinded RCT, however for PICO functions as prosective cohort	24 months	41 GPA patients who were either a) biopsy proven renal with upper/lower airway dz, b) "limited" disease with positive biopsy, or c) fulfilles ACR criteria and positive ANCA. Study conducted in Netherlands from 1990-1994.	After achieving remission treated with SMZ/TMP 800mg/160mg BID for 24 months.	Annual infection episodes per patient: median 0 (range 0-3) which was significantly lower then placebo ($p<0.001$)	Indirect: Includes patients who had both severe and nonsevere disease who entered remission.
Toxicity leading to discontinuation: In 41 GPA patients treated with SMZ/TMP for maintenance 20% developed AE leading to drug discontinuation by 24 months.	Stegeman CA, 1996	Blinded RCT, however for PICO functions as prosective cohort	24 months	41 GPA patients who were either a) biopsy proven renal with upper/lower airway dz, b) "limited" disease with positive biopsy, or c) fulfilles ACR criteria and positive ANCA. Study conducted in Netherlands from 1990-1994.	After achieving remission treated with SMZ/TMP 800mg/160mg BID for 24 months.	D/C due to side effects: 8/41 (19.5%) Side effects included: anorexia/nausea (4), rash (2), interstitial nephritis w/ fever + eosinophilia (1), and asymptomatic heptotoxic effects (1). All resolved with stopping medication.	Indirect: Includes patients who had both severe and nonsevere disease who entered remission.

46. In patients with severe GPA who have entered remission, what is the impact of using methotrexate or azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Relapse: In 126 GPA/MPA patients with mostly severe disease treated with either MTX or AZA 35% relapsed by a median of 29 months.	Pagnoux, 2008	RCT, but for PICO functions as prospective cohort	29±13mon	126 GPA/MPA patients meeting ACR or CHCC criteria achieving remission with CYC and subsequently treated with **MTX or AZA for maintenance** (one arm of study). 1998-2005.	MTX (n=63) was started at 0.3mg/kg/wk and titrated to 25mg/wk. AZA (n=63) was started at 2 mg/kg/d.	Overall relapse rate: 44/126 (34.9%) Relapse rate per group: -MTX: 21/63 (33.3%) -AZA: 23/63 (36.5%)	Indirect evidence: Includes both GPA and MPA. Also, it is not clear if all patients had severe disease at baseline, but based on criteria I would suspect the majority had severe disease.
Death: The overall death rate is no clear. In 126 GPA/MPA patients treated with MTX or AZA only 1 death due to medication was reported at median of 29 months.	Pagnoux, 2008	RCT, but for PICO functions as prospective cohort	29±13mon	126 GPA/MPA patients meeting ACR or CHCC criteria achieving remission with CYC and subsequently treated with **MTX or AZA for maintenance** (one arm of study). 1998-2005.	MTX (n=63) was started at 0.3mg/kg/wk and titrated to 25mg/wk. AZA (n=63) was started at 2 mg/kg/d.	Death due to study drug: 1/126 (0.8%) (in MTX group)	Indirect evidence: Includes both GPA and MPA. Also, it is not clear if all patients had severe disease at baseline, but based on criteria I would suspect the majority had severe disease.
Infection: In 126 GPA/MPA patients the number of patients with severe infections was 5% and any infection 21%. This is higher then that	Pagnoux, 2008	RCT, but for PICO functions as prospective cohort	29±13mon	126 GPA/MPA patients meeting ACR or CHCC criteria achieving remission with CYC and subsequently treated with **MTX or AZA for maintenance** (one arm of study). 1998-2005.	MTX (n=63) was started at 0.3mg/kg/wk and titrated to 25mg/wk. AZA (n=63) was started at 2 mg/kg/d.	# of patients with any infections: -Overall: 27/126 (21%) -MTX: 15/63(24%) -AZA: 12/63(19%) Severe infections: -Overall: 6/126 (5%) -MTX 5/63 (8%) -AZA 1/63 (2%)	Indirect evidence: Includes both GPA and MPA. Also, it is not clear if all patients had severe disease at baseline, but based on criteria I would suspect the majority had severe disease.

reported with SMZ/TMP.							
SAE: In 126 GPA/MPA patients treated with MTX or AZA the number of patients with SAE was 13%.	Pagnoux, 2008	RCT, but for PICO functions as prospective cohort	29±13mon	126 GPA/MPA patients meeting ACR or CHCC criteria achieving remission with CYC and subsequently treated with **MTX or AZA for maintenance** (one arm of study). 1998-2005.	MTX (n=63) was started at 0.3mg/kg/wk and titrated to 25mg/wk. AZA (n=63) was started at 2 mg/kg/d.	Overall SAE: 16/126 (13%) MTX group: 11/63 (18%) AZA group: 5/63 (8%)	Indirect evidence: Includes both GPA and MPA. Also, it is not clear if all patients had severe disease at baseline, but based on criteria I would suspect the majority had severe disease.
Toxicity leading to discontinuation: In 126 patients with GPA/MPA receiving AZA or MTX the number of patients with AE leading to discontinuation of drug was 15% which is similar to that reported for SMZ/TMP.	Pagnoux, 2008	RCT, but for PICO functions as prospective cohort	29±13mon	126 GPA/MPA patients meeting ACR or CHCC criteria achieving remission with CYC and subsequently treated with **MTX or AZA for maintenance** (one arm of study). 1998-2005.	MTX (n=63) was started at 0.3mg/kg/wk and titrated to 25mg/wk. AZA (n=63) was started at 2 mg/kg/d.	AE leading to d/c of study drug or death: 19/126 (15.1%) -MTX 12/63 (19.0%) -AZA 7/63 (11.1%)	Indirect evidence: Includes both GPA and MPA. Also, it is not clear if all patients had severe disease at baseline, but based on criteria I would suspect the majority had severe disease.

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies:

Author	Year	Title
Stegeman CA	1996	Trimethoprim–Sulfamethoxazole (Co-Trimoxazole) for the Prevention of Relapses of Wegener's Granulomatosis.
Pagnoux C	2008	Azathioprine or methotrexate maintenance for ANCA-associated vasculitis.

- Studies reviewed and excluded:

Author	Year	Title	Comments
A. Salmela	2017	Chronic nasal Staphylococcus aureus carriage identifies a subset of newly diagnosed granulomatosis with polyangiitis patients with high relapse rate	Exclude. This study was a sub-study of NORAM and CYCAZAREM, which included active GPA. The analysis did not differentiate the use of Bactrim in active or inactive (remission) GPA

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Maintanance

- **PICO question 23:** In patients with GPA who have entered remission, what is the impact of adding SMZ/TMP for remission maintenance (e.g., 1 DS tab twice a day) to other remission maintenance therapy agents (i.e., azathioprine, methotrexate, rituximab, mycophenolate mofetil, leflunomide) vs. not adding SMZ/TMP on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, serious adverse events, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

47. In patients with GPA who have entered remission, what is the impact of adding SMZ/TMP for remission maintenance (e.g., 1 DS tab twice a day) to other remission maintenance therapy agents (i.e., azathioprine, methotrexate, rituximab, mycophenolate mofetil, leflunomide) vs. not adding SMZ/TMP on disease-related outcomes and treatment-related adverse events?

48. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	add SMZ/TMP for remission maintenance	not add SMZ/TMP	Relative (95% CI)	Absolute (95% CI)		
Remission												
2	randomised trials	not serious	not serious	not serious	very serious [a]	none	43/57 (75.4%)	31/52 (59.6%)	**OR 2.06** (0.91 to 4.69)	**156 more per 1,000** (from 23 fewer to 278 more)	⊕⊕◯◯ LOW	
Annual number of infectious episodes												
1 [b]	randomised trials	not serious	not serious	not serious	serious [a]	none	41	40	- MD **0.69 lower** (1.03 lower to 0.35 lower)		⊕⊕⊕◯ MODERATE	
Relapse proportional-hazards re- gression model												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	-/0		**HR 0.38** (0.24 to 0.60)	**0 fewer per 1,000** (from 1 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference; **HR:** Hazard Ratio

Explanations

a. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

b. C. A. Stegeman, 1996

- **References:**

- Randomized controlled trials:

Author	Year	Title
K. Zycinska	2009	Co-trimoxazole and prevention of relapses of PR3-ANCA positive vasculitis with pulmonary involvement
C. A. Stegeman	1996	Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Maintanance

- **PICO question 24:** In patients with GPA/MPA on rituximab for remission maintenance therapy, what is the impact of using CD19 counts to guide re-dosing of rituximab vs. scheduled re-dosing of rituximab on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, infection, serious adverse events, toxicity leading to discontinuation (e.g., hypogammaglobulinemia)

49. In patients with GPA/MPA on rituximab for remission maintenance therapy, what is the impact of using CD19 counts to guide re-dosing of rituximab vs. scheduled re-dosing of rituximab on disease-related outcomes and treatment-related adverse events?

50. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	use CD19 counts to guide re-dosing of rituximab	scheduled re-dosing of rituximab	Relative (95% CI)	Absolute (95% CI)		
Relapses at Month 28												

50. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	use CD19 counts to guide re-dosing of rituximab	scheduled re-dosing of rituximab	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	14/81 (17.3%)	8/81 (9.9%)	**OR 1.91** (0.75 to 4.83)	**74 more per 1,000** (from 23 fewer to 247 more)	⊕◯◯◯ VERY LOW	

Vasculitis Damage Index at Month 28

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	81	81	MD **0.1 lower** (0.65 lower to 0.45 higher)		⊕◯◯◯ VERY LOW	

Patients with 1 or more Serious Adverse Events

1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	26/81 (32.1%)	31/81 (38.3%)	**OR 0.76** (0.40 to 1.46)	**62 fewer per 1,000** (from 184 fewer to 92 more)	⊕⊕◯◯ LOW	

Mortality

50. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	use CD19 counts to guide re-dosing of rituximab	scheduled re-dosing of rituximab	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/81 (1.2%)	3/81 (3.7%)	**OR 0.33** (0.03 to 3.19)	**25 fewer per 1,000** (from 36 fewer to 72 more)	⊕◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Allocation concealment (selection bias) and Blinding of participants and personnel (performance bias) not available

b. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

- **References:**

- Randomized controlled trials:

Author	Year	Title
P. Charles	2018	Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2)

- Comparative observational studies:

None

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Maintanance

- **PICO question 25:** In patients with GPA/MPA on rituximab for remission maintenance therapy, what is the impact of using ANCA titers to guide re-dosing of rituximab vs. scheduled re-dosing of rituximab on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, infection, serious adverse events, toxicity leading to discontinuation (e.g., hypogammaglobulinemia)

51. In patients with GPA/MPA on rituximab for remission maintenance therapy, what is the impact of using ANCA titers to guide re-dosing of rituximab vs. scheduled re-dosing of rituximab on disease-related outcomes and treatment-related adverse events?

52. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	use ANCA titers	scheduled re-dosing of rituximab	Relative (95% CI)	Absolute (95% CI)		
Relapses at Month 28												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	14/81 (17.3%)	8/81 (9.9%)	**OR 1.91** (0.75 to 4.83)	**74 more per 1,000** (from 23 fewer to 247 more)	⊕◯◯◯ VERY LOW	
Vasculitis Damage Index at Month 28												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	81	81	MD **0.1 lower** (0.65 lower to 0.45 higher)		⊕◯◯◯ VERY LOW	

52. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	use ANCA titers	scheduled re-dosing of rituximab	Relative (95% CI)	Absolute (95% CI)		
Patients with 1 or more Serious Adverse Events												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	26/81 (32.1%)	31/81 (38.3%)	**OR 0.76** (0.40 to 1.46)	**62 fewer per 1,000** (from 184 fewer to 92 more)	⊕⊕◯◯ LOW	
Mortality												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/81 (1.2%)	3/81 (3.7%)	**OR 0.33** (0.03 to 3.19)	**25 fewer per 1,000** (from 36 fewer to 72 more)	⊕◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Allocation concealment (selection bias) and Blinding of participants and personnel (performance bias) not available

b. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

Author	Year	Title
P. Charles	2018	Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2)

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Maintanance

- **PICO question 26:** In a patient with severe GPA/MPA using remission maintenance therapy, what is the impact of continuing remission maintenance therapy for > 18 months vs. stopping remission maintenance therapy at or prior to 18 months on disease related outcomes and treatment related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, serious adverse events, toxicity leading to discontinuation

53. In a patient with severe GPA/MPA using remission maintenance therapy, what is the impact of continuing remission maintenance therapy for > 18 months vs. stopping remission maintenance therapy at or prior to 18 months on disease related outcomes and treatment related adverse events?

54. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	stopping remission maintenance therapy at or prior to 18 months	continuing remission maintenance therapy for > 18 months	Relative (95% CI)	Absolute (95% CI)		
Adverse event												

54. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	stopping remission maintenance therapy at or prior to 18 months	continuing remission maintenance therapy for > 18 months	Relative (95% CI)	Absolute (95% CI)		
1 [a]	randomised trials	not serious	not serious	not serious	very serious [b]	none	20/51 (39.2%)	26/59 (44.1%)	**OR 0.82** (0.38 to 1.75)	**48 fewer per 1,000** (from 210 fewer to 139 more)	⨁⨁◯◯ LOW	

Relapse

2 [a,c]	randomised trials	not serious	not serious	not serious	very serious [b]	strong association	43/75 (57.3%)	18/80 (22.5%)	**OR 4.70** (2.31 to 9.55)	**352 more per 1,000** (from 176 more to 510 more)	⨁⨁⨁◯ MODERATE	

ESRD

1 [a]	randomised trials	not serious	not serious	not serious	very serious [b]	strong association	4/51 (7.8%)	0/59 (0.0%)	**OR 11.27** (0.59 to 214.65)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE	

54. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	stopping remission maintenance therapy at or prior to 18 months	continuing remission maintenance therapy for > 18 months	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1 [a]	randomised trials	not serious	not serious	not serious	very serious [b]	strong association	2/51 (3.9%)	5/59 (8.5%)	**OR 0.44** (0.08 to 2.38)	**46 fewer per 1,000** (from 77 fewer to 96 more)	⊕⊕⊕◯ MODERATE	
VDI (vasculitis damage index)												
1 [a]	randomised trials	not serious	not serious	not serious	serious [b]	none	51	59	MD **0** (0.07 lower to 0.07 higher)		⊕⊕⊕◯ MODERATE	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Karras, 2017

b. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

c. Sanders, 2016

- **References:**

- Randomized controlled trials:

None

- Comparative observational studies:
  None

Author	Year	Title
A. Karras	2017	Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis
J-Sf Sanders	2016	Extended versus standard azathioprine maintenance therapy in newly diagnosed proteinase-3 anti-neutrophil cytoplasmic antibody-associated vasculitis patients who remain cytoplasmic anti-neutrophil cytoplasmic antibody-positive after induction of remission: a randomized clinical trial

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Remission Maintanance

- **PICO question 27:** In patients with severe GPA/MPA starting remission maintenance therapy that includes prednisone, what is the impact of treatment with prednisone for 6 months or less vs.6-18 months vs. longer than 18 months during remission maintenance on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, serious adverse events, toxicity leading to discontinuation

55. In patients with severe GPA/MPA starting remission maintenance therapy that includes prednisone, what is the impact of treatment with prednisone for 6 months or less vs.6-18 months vs. longer than 18 months during remission maintenance on disease-related outcomes and treatment-related adverse events?

56. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	stopping Prednisone at 4 months	continuing Prednisone for > 18 months	Relative (95% CI)	Absolute (95% CI)		
Adverse event												

56. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	stopping Prednisone at 4 months	continuing Prednisone for > 18 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	20/51 (39.2%)	26/59 (44.1%)	**OR 0.82** (0.38 to 1.75)	**48 fewer per 1,000** (from 210 fewer to 139 more)	⊕⊕◯◯ LOW	

Relapse

1	randomised trials	not serious	not serious	not serious	very serious [b]	strong association	32/51 (62.7%)	13/59 (22.0%)	**OR 5.96** (2.58 to 13.77)	**407 more per 1,000** (from 201 more to 575 more)	⊕⊕⊕◯ MODERATE	

ESRD

1	randomised trials	not serious	not serious	not serious	very serious [b]	strong association	4/51 (7.8%)	0/59 (0.0%)	**OR 11.27** (0.59 to 214.65)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	

Mortality

56. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	stopping Prednisone at 4 months	continuing Prednisone for > 18 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [b]	strong association	2/51 (3.9%)	5/59 (8.5%)	**OR 0.44** (0.08 to 2.38)	**46 fewer per 1,000** (from 77 fewer to 96 more)	⊕⊕⊕◯ MODERATE	

VDI (vasculitis damage index)

1	randomised trials	not serious	not serious	not serious	serious [b]	none	51	59	MD **0** (0.07 lower to 0.07 higher)		⊕⊕⊕◯ MODERATE	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

Author	Year	Title
A. Karras	2017	Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Relapse

- **PICO question 28:** In patients with GPA/MPA who have relapsed with severe disease manifestations after prior remission induction with cyclophosphamide or rituximab **and** on either non-rituximab maintenance therapy or no maintenance therapy, what is the impact of using the same agent vs. switching to the other agent for remission induction on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Disease Activity, Disease Damage, Relapse, Death, Malignancy, Infection, Toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypogammaglobulinemia)

57. In patients with GPA/MPA who have relapsed with severe disease manifestations after prior remission induction with cyclophosphamide or rituximab and on either non-rituximab maintenance therapy or no maintenance therapy, what is the impact of using the same agent vs. switching to the other agent for remission induction on disease-related outcomes and treatment-related adverse events?
    - No Comparative Data Available

58. In patients with GPA/MPA who have relapsed with severe disease manifestations after prior remission induction with cyclophosphamide or rituximab and on either non-rituximab maintenance therapy or no maintenance therapy, what is the impact of using the same agent for remission induction on disease-related outcomes and treatment-related adverse events?
    - **Patient Important Outcomes**

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention used in relevant population	Results	Comments
Disease Activity	Miloslavsky, 2014	Prospective. Open-label extension study of RAVE trial (included patients who had severe relapse	Average of 311 days (range 29-427 days)	15 patients initially treated with rituxan were retreated with rituxan 11 patients initially treated with Cytoxan were treated with ritiuxan on relapse	Rituxan 375 mg/m2 x 4 weekly doses	-On those who were retreated with rituxan: Remission=87% Complete response= 67% Complete remission= 40% VDI 12 mos after rituxan= 4.6 Adverse event= 85 events in 14 patients -On those who got Cytoxan for induction then treated with rituxan for relapse:	Direct evidence Remission=BVAS/WG=0 Complete response= BVAS/WG =0/prednisone dose <10 mg per day Complete remission= BVAS/WG=0/predni

		between 6-18 months)				Remission: 91% Complete response= 82% Complete remission= 64% VDI 12 mos after rituxan = 3.7 Adverse events= 71 events in 9 patients	sone dose 0 mg per day
	Yusof, 2015	Retrospective analysis	Data of patients from January 2006 to September 2013. 162 patient-years follow up	35 GPA patients	Rituximab 1000 mg IV at 0,2 weeks were given during each relapse	Ovedrall response rates (BVAS=0) were >83%. Response rates (BVAS=0) for Cycle 1–5 were 33/35 (94%), 28/28 (100%),17/20 (85%), 11/13 (85%) and 5/6 (83%) respectively. 1.) The mean BVAS on clinical relapse for each cycle was significantly lower than the mean BVAS at original baseline (p<0.001)	Indirect evidence. Relapse was not categorized if it was severe or limited.

59. In patients with GPA/MPA who have relapsed with severe disease manifestations after prior remission induction with cyclophosphamide or rituximab and on either non-rituximab maintenance therapy or no maintenance therapy, what is the impact of switching to the other agent for remission induction on disease-related outcomes and treatment-related adverse events?
- Patient Important Outcomes

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results	Comments
Disease activity and adverse event	Knight, 2014	Retrospective case series	Median 32 months	12 relapsing GPA patients who initially received Cytoxan, then received pre-emptive treatment with rituximab for induction therapy	Rituximab 375 mg /m2 x 4 weekly doses, Rituximab 1000 mg IV at 0,2 weeks. Rituximab were repeated pre-emptively every 6	After first rituximab course: Remission rate= 30% Response rate=58% Last follow up: Remission rate= 92% Response rate= 8% 7 infections recorded that needed antibiotics/anti viral.	Direct evidence Remission: BVAS=0, prednisolone of 7.5 mg or less Response: BVAS 0, prednisolone more than 7.5 mg a day

					months (with varying doses)		
	Lovric, 2009	Retropectiv e cohort	Median 15 months	13 GPA, MPA, 1, EGPA. All had previously received Cytoxan, had relapsing disease.	Rituximab 375 mg /m2 x 4 weekly doses	-Complete remission achieved in 6 patients, partial remission achieved in 8 patients. -Median time to remission 4 months. -Complete renal remission was achieved in all patients who were not on dialysis -3 patients relapsed -Leukpenia occurred in 2 patients -2 patients died	Indirect evidence. Did not clearly categorized relapsing vs refractory disease. Complete remission: BVAS 0 Partial remission: reduction of BVAS at least 50%

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Included Single Arm Studies :

Author	Year	Title
M. Y. Md Yusof	2015	Repeat cycles of rituximab on clinical relapse in ANCA-associated vasculitis: identifying B cell biomarkers for relapse to guide retreatment decisions
R. B. Jones	2015	Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial
A. Knight	2014	Efficacy and safety of rituximab as maintenance therapy for relapsing granulomatosis with polyangiitis-a case series
S. Lovric	2009	Rituximab as rescue therapy in anti-neutrophil cytoplasmic antibody-associated vasculitis: a single-centre experience with 15 patients

- Studies reviewed and excluded:

Author	Year	Title	Comments
F. Rees	2011	Long-term follow-up of different refractory systemic vasculitides treated with rituximab	Exclude. Included Refractory and relapsing GPA

S. Lionaki	2017	Cyclophosphamide followed by rituximab for aggressive multiple-relapsing antineutrophil cytoplasmic antibody-associated vasculitis	Exclude. Patient was given combination Cytoxan and Rituxan on relapse.
L. Azar	2014	Rituximab with or without a conventional maintenance agent in the treatment of relapsing granulomatosis with polyangiitis (Wegener's): a retrospective single-center study	Exclude. Does not address PICO question
T. Turner-Stokes	2014	Induction treatment of ANCA-associated vasculitis with a single dose of rituximab	Exclude. Does not address PICO question
R. Pullerits	2012	Off-trial evaluation of the B cell-targeting treatment in the refractory cases of antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: long-term follow-up from a single centre	Exlcude. Refractory GPA. Does not address PICO question
R. Cartin-Ceba	2012	Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center	Exclude. Does not address PICO question
N. Venhoff	2012	Impact of rituximab on immunoglobulin concentrations and B cell numbers after cyclophosphamide treatment in patients with ANCA-associated vasculitides	Exclude. Does not address PICO question
M. Wendt	2012	Rituximab in relapsing or refractory ANCA-associated vasculitis: a case series of 16 patients	Exclude. Did not separate Refractory GPA vs relapsing GPA. Patients who received rituximab were also taking other DMARDs concurrently.
L. Joshi	2011	Rituximab in refractory ophthalmic Wegener's granulomatosis: PR3 titers may predict relapse, but repeat treatment can be effective	Exclude. Refractory GPA
V. Martinez	2008	Intravenous immunoglobulins for relapses of systemic vasculitides associated with antineutrophil cytoplasmic autoantibodies: results of a multicenter, prospective, open-label study of twenty-two patients	Exclude. Used IVIG
C. A. Langford	2000	Use of methotrexate and glucocorticoids in the treatment of Wegener's granulomatosis. Long-term renal outcome in patients with glomerulonephritis	Exclude. Used MTX
A. S. Fauci	1983	Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years	Exclude. Does not address PICO question
A. Dembla	NA	Clinical profile and long-term outcome of granulomatosis with polyangiitis (GPA): A corporate hospital-based study from northern India	Exclude. Does not address PICO question

A Goceroglu	2016	The Dutch transplantation in vasculitis (DUTRAVAS) study: outcome of renal transplantation in antineutrophil cytoplasmic antibody-associated glomerulonephritis	Exclude. Does not address PICO question

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Relapse

- **PICO question 29:** In patients with GPA/MPA who have relapsed with severe disease manifestations while on rituximab for remission maintenance, what is the impact of continuing rituximab at a higher dose vs. switching to cyclophosphamide for remission induction on disease-related outcomes and treatment-related adverse effects?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypogammaglobulinemia)

60. In patients with GPA/MPA who have relapsed with severe disease manifestations while on rituximab for remission maintenance, what is the impact of continuing rituximab at a higher dose vs. switching to cyclophosphamide for remission induction on disease-related outcomes and treatment-related adverse effects?
    - No data available

61. In patients with GPA/MPA who have relapsed with severe disease manifestations while on rituximab for remission maintenance, what is the impact of continuing rituximab at a higher dose for remission induction on disease-related outcomes and treatment-related adverse effects?

62. In patients with GPA/MPA who have relapsed with severe disease manifestations while on rituximab for remission maintenance, what is the impact of switching to cyclophosphamide for remission induction on disease-related outcomes and treatment-related adverse effects?

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies:
  None

- Studies reviewed and excluded:

Author	Year	Title	Comments
F. Rees	2011	Long-term follow-up of different refractory systemic vasculitides treated with rituximab	Exclude. Does not address PICO question
S. Lionaki	2017	Cyclophosphamide followed by rituximab for aggressive multiple-relapsing antineutrophil cytoplasmic antibody-associated vasculitis	Exclude. Does not address PICO question
A. Dembla	NA	Clinical profile and long-term outcome of granulomatosis with polyangiitis (GPA): A corporate hospital-based study from northern India	Exclude. Does not address PICO question

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Refractory Disease

- **PICO question 30:** In patients with refractory severe GPA/MPA after using rituximab or cyclophosphamide for remission induction, what is the impact of using rituximab with cyclophosphamide vs. switching to the other therapy on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypogammaglobulinemia)

63. In patients with refractory severe GPA/MPA after using rituximab or cyclophosphamide for remission induction, what is the impact of using rituximab with cyclophosphamide vs. switching to the other therapy on disease-related outcomes and treatment-related adverse events?

64. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	using rituximab with cyclophosphamide	switching to the other therapy	Relative (95% CI)	Absolute (95% CI)		
Remission												

64. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	using rituximab with cyclophosphamide	switching to the other therapy	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	very serious [b]	none	11/12 (91.7%)	21/25 (84.0%)	**OR 2.10** (0.21 to 21.10)	**77 more per 1,000** (from 316 fewer to 151 more)	⨁◯◯◯ VERY LOW	

Infections

1	observational studies	serious [a]	not serious	not serious	very serious [b]	none	2/12 (16.7%)	8/25 (32.0%)	**OR 0.42** (0.07 to 2.41)	**155 fewer per 1,000** (from 288 fewer to 211 more)	⨁◯◯◯ VERY LOW	

ESRD

1	observational studies	serious [a]	not serious	not serious	very serious [b]	none	4/12 (33.3%)	8/25 (32.0%)	**OR 1.06** (0.25 to 4.60)	**13 more per 1,000** (from 215 fewer to 364 more)	⨁◯◯◯ VERY LOW	

64. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	using rituximab with cyclophosphamide	switching to the other therapy	Relative (95% CI)	Absolute (95% CI)		
Leukopenia												
1	observational studies	serious [a]	not serious	not serious	very serious [b]	none	2/12 (16.7%)	2/25 (8.0%)	**OR 2.30** (0.28 to 18.70)	**87 more per 1,000** (from 56 fewer to 539 more)	⨁◯◯◯ VERY LOW	
Death at 6 months												
1	observational studies	serious [a]	not serious	not serious	very serious [b]	none	0/12 (0.0%)	3/25 (12.0%)	**OR 0.26** (0.01 to 5.39)	**86 fewer per 1,000** (from 119 fewer to 304 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Limited to patients with severe renal involvement, Rituximab group also recieved cyclophosphamide

b. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:

Author	Year	Title
D. Geetha	2016	Rituximab for treatment of severe renal disease in ANCA associated vasculitis

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Treatment: Refractory Disease

- **PICO question 31:** In patients with refractory GPA/MPA, what is the impacting of adding IVIg to current therapy vs. not adding IVIg on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, serious adverse events, toxicity leading to discontinuation

65. In patients with refractory GPA/MPA, what is the impacting of adding IVIg to current therapy vs. not adding IVIg on disease-related outcomes and treatment-related adverse events?

66. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	adding IVIg to current therapy	not adding IVIg	Relative (95% CI)	Absolute (95% CI)		
Relapse												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	5/16 (31.3%)	4/15 (26.7%)	**OR 1.25** (0.26 to 5.94)	**46 more per 1,000** (from 180 fewer to 417 more)	⊕⊕◯◯ LOW	

66. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	adding IVIg to current therapy	not adding IVIg	Relative (95% CI)	Absolute (95% CI)		
Therapeutic response												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	14/17 (82.4%)	6/17 (35.3%)	**OR 8.56** (1.74 to 42.17)	**471 more per 1,000** (from 134 more to 605 more)	⨁⨁◯◯ LOW	
1 month Change in disease activity using BVAS												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	17	17	-	MD **2.33 higher** (1.15 higher to 3.51 higher)	⨁⨁⨁◯ MODERATE	
3 months Change in disease activity using BVAS												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	17	17	-	MD **1.8 higher** (0.35 higher to 3.25 higher)	⨁⨁⨁◯ MODERATE	
Number of Adverse events												

66. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	adding IVIg to current therapy	not adding IVIg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious [a]	none	12/17 (70.6%)	4/17 (23.5%)	**OR 7.80** (1.69 to 36.06)	**471 more per 1,000** (from 107 more to 682 more)	⨁⨁⨁◯ MODERATE	

Active lesions 3 months

1	randomised trials	not serious	not serious	not serious	very serious [a]	none	3/12 (25.0%)	7/12 (58.3%)	**OR 0.24** (0.04 to 1.36)	**332 fewer per 1,000** (from 530 fewer to 72 more)	⨁⨁◯◯ LOW	

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

- **References:**

- Randomized controlled trials:

Author	Year	Title

D. R. Jayne	2000	Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO question 32:** In patients with active GPA/MPA unable to receive immunosuppressive therapy, what is the impact of administering IVIg vs. not administering IVIg on disease related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, serious adverse events, toxicity leading to discontinuation

67. In patients with active GPA/MPA unable to receive immunosuppressive therapy, what is the impact of administering IVIg vs. not administering IVIg on disease related outcomes and treatment-related adverse events?
    - No comparative data available

68. In patients with active GPA/MPA unable to receive immunosuppressive therapy, what is the impact of administering IVIg on disease related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease Activity - 1 study with 25 relavent patients. Evidence is sparse that this approach works in this population.	Jayne, 1993	Single center cohort	8 weeks	26 patients (13 female, mean age 52y, 14 with WG, 11 with MPA, one with RA vasculitis) 16 had disease resistant to conventional therapy, 9 were untreated	IVIg: patients were admitted to hospital and recenved 400mg/kg/d x 5 days (total dose 2g/kg).	13 patients demonstrated a full response 13 patients demonstrated a partial response	Indirect – Disease activity score 2=active disease, 1 = partial remission, 0=full remission, not blinded
Relapse - 1 study with 25 relavent patients. Short term	Jayne, 1993	Single center cohort	8 weeks	26 patients (13 female, mean age 52y, 14 with WG, 11 with MPA, one with RA vasculitis)	IVIg: patients were admitted to hospital and recenved 400mg/kg/d x 5 days (total dose 2g/kg).	Six relapses occurred that required increase or start of another therapy	Indirect

relapses were common with this approach.				16 had disease resistant to conventional therapy, 9 were untreated		Six relapses occurred that did not require change of therapy	

69. In patients with active GPA/MPA unable to receive immunosuppressive therapy, what is the impact of not administering IVIg on disease related outcomes and treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparactive observational studies:
  None

- Single arm studies and test accuracy studies:

Author	Year	Title
Jayne	1993	Pooled intravenous immunoglobulin in the management of systemic vasculitis

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO question 33:** In patients with GPA/MPA in remission and currently only on prednisone, what is the impact of continuing with low dose prednisone long-term (e.g., > 18 months) vs. stopping low dose prednisone on disease-related outcomes and treatment related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, toxicity leading to discontinuation (e.g., hyperglycemia, decreased bone mineral density)

70. In patients with GPA/MPA in remission and currently only on prednisone, what is the impact of continuing with low dose prednisone long-term (e.g., > 18 months) vs. stopping low dose prednisone on disease-related outcomes and treatment related adverse events?
    - No comparative data available

71. In patients with GPA/MPA in remission and currently only on prednisone, what is the impact of continuing with low dose prednisone long-term (e.g., > 18 months) on disease-related outcomes and treatment related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Relapse – Per these 2 studies with 134 patients and heterogenous study design, continuing steroid use seems to lower risk of relapse.	Pagnoux, 2015	Multicenter, open-label RCT (only conventional arm considered here)	3 years	51 patients (75 years*, 32 males, 29%GPA, 45% MPA, 12% EGPA, 14% PAN) 0 80% ANCA+ 41 patients achieved remission and are considered.	FFS >0: CYC (for induction) +GC (continued for ~26 months) FFS=0, only GC (continued for ~26 months)	12 (29%) of patients that achieved remission had a relapse.
	Hara, 2018	Multicenter, single nation, observational cohort	24 months	83 patients (35 male, 23 GPA, 40 MPA, 9 EGPA, 11 unclassifiable)	Observational study, so no defined GC dose. *GC dose at month 24 was idenitified in univariate analysis as risk factor for relapse. ROC analysis done to evaluate threshold (2.5mg prednisone daily) of GC dose that could discriminate risk of relapse.	HR for relapse was 3.1 (95% CI 1.1 -8.5, p<0.05) for GC dose =<2.5mg prednisone daily.
Serious adverse events – From 1 study with 51 patients, many patients continued on glucocorticoids have a serious adverse event.	Pagnoux, 2015	Multicenter, open-label RCT (only conventional arm considered here)	3 years	51 patients (75 years*, 32 males, 29%GPA, 45% MPA, 12% EGPA, 14% PAN) 0 80% ANCA+	FFS >0: CYC (for induction) +GC (continued for ~26 months) FFS=0, only GC (continued for ~26 months)	40 (78%) patients had 1 or more SAE
Severe infections – Per one study with 83 patients, more serious infections happen in patients on	Hara, 2018	Multicenter, single nation, observational cohort	24 months	83 patients (35 male, 23 GPA, 40 MPA, 9 EGPA, 11 unclassifiable)	Observational study, so no defined GC dose. *GC dose at month 24 was idenitified in univariate analysis as risk factor for relapse. ROC analysis done to evaluate threshold (2.5mg prednisone daily) of GC dose that could discriminate risk of relapse.	Numerically more (18% vs 10%, p=1.0) serious infections in patients treated with GC>=pred 2.5mg/day.

higher steroid dose.						
Osteoporosis – Per one study with 83 patients, rates of osteoporosis were not higher whether patient was on higher or lower than pred 2.5mg daily.	Hara, 2018	Multicenter, single nation, observational cohort	24 months	83 patients (35 male, 23 GPA, 40 MPA, 9 EGPA, 11 unclassifiable)	Observational study, so no defined GC dose. *GC dose at month 24 was idenitified in univariate analysis as risk factor for relapse. ROC analysis done to evaluate threshold (2.5mg prednisone daily) of GC dose that could discriminate risk of relapse.	Patients receiving GC >2.5mg pred daily had lower rate of osteoporosis and bone fracture than patients receiving less GC (no typo). 5.5% vs 10% "osteoporosis" 4.1% vs 10% bone fracture/femur head necrosis No formal statistical comparison performed due to small numbers.

72. In patients with GPA/MPA in remission and currently only on prednisone, what is the impact of stopping low dose prednisone on disease-related outcomes and treatment related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
    None

- Comparactive observational studies:
    None

- Single arm studies and test accuracy studies:

Author	Year	Title
Pagnou	2015	Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy

Hara	2018	Risk Factors for Relapse of Antineutrophil Cytoplasmic Antibody-associated Vasculitis in Japan: A Nationwide, Prospective Cohort Study

- Studies reviewed and excluded:

1. De Groot K, Reinhold-Keller E, Tatsis E,Paulsen J, Heller M, Nolle B, et al. Therapy for the maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis: methotrexate versus trimethoprim/sulfarnethoxazole. *Arthritis Rheum* 1996; **39**: 2052–61. **(Excluded, inappropriate population – not on only prednisone).**
2. Jayne D, Rasmussen N, Andrassy K,Bacon P, Tervaert JW, Dadoniene J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med*2003; **349**: 36–44 **(inappropriate population for PICO, not on only prednisone).**
3. De Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al.Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009; **150**:670–80 **(population not appropriate for PICO, induction trial, maintenance therapy is not prednisone monotherapy).**
4. Sneller MC, Hoffman GS, Talar-Williams C, Kerr GS, Hallahan CW, Fauci AS. An analysis of forty-two Wegener's granulomatosis patients treated with methotrexate and prednisone. *Arthritis Rheum* 1995; **38**: 608–13 **(inappropriate population for PICO33, not on prednisone monotherapy)**
5. Reinhold-Keller E, Fink CO, Herlyn K,Gross WL, De Groot K. High rate of renal relapse in 71 patients with Wegener's granulomatosis under maintenance of remission with low-dose methotrexate.*Arthritis Rheum* 2002; **47**: 326–32 **(inappropriate population for PICO33, not on prednisone monotherapy).**
6. Guillevin L, Cohen P, Mahr A, Arene JP,Mouthon L, Puechal X, et al, and the French Vasculitis Study Group. Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients. *Arthritis Rheum* 2003;**49**: 93–**100 (induction trial, not appropriate population for PICO).**
7. Langford CA, Talar-Williams C, Barron KS, Sneller MC. Use of a cyclophosphamide-induction methotrexate-maintenance regimen for the treatment of Wegener's granulomatosis: extended follow-up and rate of relapse. *Am J Med* 2003; **114**: 463–9. **(inappropriate population for PICO33, not on prednisone monotherapy).**
8. De Groot K, Jayne D, Tesar V, Savage C.Randomised controlled trial of daily oral versus pulse cyclophosphamide for induction of remission in ANCA-associated systemic vasculitis [abstract]. *Kidney Blood Pres Res* 2005; **28**: 195 **(inappropriate population for PICO33, most patients not on on prednisone monotherapy; 5 patients on prednisone monotherapy – no outcomes available on those specific patients).**
9. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* 2005; **352**:351–61. **(inappropriate population for PICO33, not on prednisone monotherapy).**
10. Stassen PM, Cohen Tervaert JW,Stegeman CA. Induction of remission in active anti-neutrophil cytoplasmic antibody-associated vasculitis with mycophenolate mofetil in patients who cannot be treated with cyclophosphamide. *Ann Rheum Dis* 2007; **66**: 798–802. **(induction trial, no period of prednisone monotherapy, not appropriate population for PICO).**
11. Metzler C, Miehle N, Manger K, Iking-Konert C, De Groot K, Hellmich B, et al.Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis. *Rheumatology (Oxford)* 2007; **46**: 1087–91. **(inappropriate population for PICO33, not on prednisone monotherapy).**

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO Question 34:** In patients with GPA/MPA with active glomerulonephritis, what is the impact of adding plasma exchange to cyclophosphamide or rituximab vs. not adding plasma exchange on disease-related outcomes and treatment-related adverse events?

- Critical outcomes: progression to end-stage renal disease, disease activity, disease damage, relapse, death, serious adverse events, toxicity leading to discontinuation

73. In patients with GPA/MPA with active glomerulonephritis, what is the impact of adding plasma exchange to cyclophosphamide or rituximab vs. not adding plasma exchange on disease-related outcomes and treatment-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PLEX	no PLEX	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 1 years to 10 years; assessed with: Risk through longest follow-up)												
6	randomised trials	not serious [a]	not serious	not serious	very serious [b]	none	39/147 (26.5%)	32/139 (23.0%)	**RR 1.15** (0.77 to 1.70)	**35 more per 1,000** (from 53 fewer to 161 more)	⨁⨁◯◯ LOW	CRITICAL
Mortality (follow up: median 2.9 years; assessed with: Risk over time)												
1	randomised trials	not serious	not serious	not serious	serious [c]	none	-/0	32/139 (23.0%) [d]	**HR 0.87** (0.58 to 1.31)	**27 fewer per 1,000** (from 89 fewer to 60 more)	⨁⨁⨁◯ MODERATE	CRITICAL
End-stage kidney disease (follow up: range 1 years to 12 years; assessed with: Risk through longest follow-up)												
6	randomised trials	serious [e]	not serious	not serious	serious [f]	none	35/128 (27.3%)	58/123 (47.2%)	**RR 0.61** (0.42 to 0.90)	**184 fewer per 1,000** (from 273 fewer to 47 fewer)	⨁⨁◯◯ LOW	CRITICAL
								10.0%		**39 fewer per 1,000** (from 58 fewer to 10 fewer)		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PLEX	no PLEX	Relative (95% CI)	Absolute (95% CI)		
								61.1%		**238 fewer per 1,000** (from 354 fewer to 61 fewer)		

End-stage kidney disease (follow up: range 1 years to 2.9 years; assessed with: Risk over time)

2	randomised trials	not serious	not serious	not serious	serious [g]	none	-/0	58/123 (47.2%) [h]	**HR 0.72** (0.53 to 0.98) [i]	**103 fewer per 1,000** (from 185 fewer to 7 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								10.0%		**27 fewer per 1,000** (from 46 fewer to 2 fewer)		
								61.1%		**118 fewer per 1,000** (from 217 fewer to 7 fewer)		

Remission (follow up: range 1 years to 2.9 years; assessed with: Risk through longest follow-up)

2	randomised trials	not serious	not serious	not serious	very serious [c]	none	-/0	5/16 (31.3%) [j]	**RR 1.34** (0.64 to 2.80)	**106 more per 1,000** (from 112 fewer to 563 more)	⨁⨁◯◯ LOW	CRITICAL

Serious adverse events (follow up: range 1 years to 5 years; assessed with: Risk through longest follow up)

3	randomised trials	not serious	not serious	not serious	not serious	none	36/92 (39.1%)	34/91 (37.4%)	**RR 1.04** (0.74 to 1.46)	**15 more per 1,000** (from 97 fewer to 172 more)	⨁⨁⨁⨁ HIGH	CRITICAL

Serious adverse events (follow up: median 2.9 years; assessed with: Rate ratio through longest follow-up)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PLEX	no PLEX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious [k]	none	0/0	0/0 [l]	**Rate ratio 1.21** (0.96 to 1.53)	**40 more per 1000 patient(s) per years** (from 7 fewer to 100 more) [m]	⨁⨁⨁◯ MODERATE	CRITICAL

Severe infection (follow up: range 1 years to 5 years; assessed with: Risk through longest follow-up)

4	randomised trials	not serious	not serious	not serious	serious [n]	none	159/444 (35.8%)	133/443 (30.0%)	**RR 1.19** (0.99 to 1.42)	**57 more per 1,000** (from 3 fewer to 126 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Severe infection (follow up: median 2.9 years; assessed with: Rate ratio)

1	randomised trials	not serious	not serious	not serious	very serious [n]	none	136/352	114/352	**Rate ratio 1.16** (0.87 to 1.55)	**52 more per 1000 patient(s) per years** (from 42 fewer to 178 more) [o]	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanations

a. The trials judged at low risk of bias have approximately 60% of the weight of the pooled estimate, and their results are not inconsistent with the other trials
b. The CI of the pooled estimate includes the possibility of important benefit and important harm. The optimal information size is not met.
c. The CI suggests the possibility of important benefit and important harm.
d. Based on the control arms of trials included in meta-analysis of risk of mortality
e. The 2 trials judged at low risk of bias provide only 30% of the evidence.
f. Although the CI suggests only benefit, the optimal information size is not met.
g. The CI suggests the possibility of important benefit as well as harm
h. Based on the control arms of trials included in the meta-analysis of risk of ESKD
i. Using a fixed effect model. Pooled HR using a random effect model (0.67 [95% CI 0.40-1.11])
j. Based on the trial from this meta-analysis that reported the risk per group (Jayne, 2007)
k. The CI suggests the possibility of benefit as well as important harm
l. Total of 273/352 patients experienced SAEs (not including infections). However, some patients may be counted twice as they could have experienced more than 1 SAE
m. Based on 387 SAEs in 752 patients over 2,042 patient years (median follow up per patient 2.9 years)
n. The CI crosses the threshold of an important effect
o. Calculated based on 352 patients who provided information for 1021 patients/years (median follow-up 2.9 years, in which 114 patients experienced severe infection). Rate in control group is 112 per 1000 patient/years

- **References:**

- Randomized Controlled Trials:

-

Author	Year	Title
Szpirt	2011	Plasma exchange for induction and cyclosporine A for maintenance of remission in Wegener's granulomatosis--a clinical randomized controlled trial
Jayne	2007	Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis
Walsh	2013	Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear
J.M. Mauri	1985	Therapeutic plasma exchange in the treatment of rapidly progressive glomerulonephritis.
C. Pusey	1991	Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies
G. Rifle	1981	Treatment of idiopathic acute crescentic glomerulonephritis by immunodepression and plasma-exchanges. A prospective randomised study.
I Za¨uner	2002	Predictive Value of Initial Histology and Effect of Plasmapheresis on Long-Term Prognosis of Rapidly Progressive Glomerulonephritis
M. Walsh	2020	Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

- Studies reviewed and excluded:

Author	Year	Title	Comments
Nishida	2019	Plasma Exchange Is Highly Effective for Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis Patients With Rapidly Progressive Glomerulonephritis Who Have Advanced to Dialysis Dependence: A Single-Center Case Series	Exclude as single arm study since comparative data is not available

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO Question 35 :** In patients with GPA/MPA with active alveolar hemorrhage, what is the impact of adding plasma exchange to cyclophosphamide or rituximab vs. not adding plasma exchange on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** decreased pulmonary function, disease activity, disease damage, relapse, death, serious adverse events, toxicity leading to discontinuation

1. In patients with GPA/MPA with active alveolar hemorrhage, what is the impact of adding plasma exchange to cyclophosphamide or rituximab vs. not adding plasma exchange on disease-related outcomes and treatment-related adverse events?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PLEX	no PLEX	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 4 years to 5 years; assessed with: Risk through longest follow up)												
2	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	39/85 (45.9%)	41/84 (48.8%)	**RR 0.95** (0.70 to 1.30)	**24 fewer per 1,000** (from 146 fewer to 146 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality- HR (follow up: range 2.9 years to 4 years; assessed with: Risk over time)												
2	randomised trials	not serious	not serious	not serious	very serious [b]	none	-/0	41/84 (48.8%) [c]	**HR 0.95** (0.70 to 1.30)	**17 fewer per 1,000** (from 114 fewer to 93 more)	⨁⨁◯◯ LOW	CRITICAL
End-stage kidney disease (follow up: range 4 years to 5 years; assessed with: Risk through longest follow up)												
2	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	25/85 (29.4%)	40/84 (47.6%)	**RR 0.58** (0.29 to 1.16)	**200 fewer per 1,000** (from 338 fewer to 76 more)	⨁◯◯◯ VERY LOW	CRITICAL
End-stage kidney disease (follow up: range 2.9 years to 4 years; assessed with: Risk over time)												
2	randomised trials	not serious	not serious	not serious	serious [d]	none	-/0	40/84 (47.6%) [c]	**HR 0.74** (0.56 to 0.99)	**96 fewer per 1,000** (from 172 fewer to 3 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PLEX	no PLEX	Relative (95% CI)	Absolute (95% CI)		
Remission (follow up: range 2.9 years to 5 years; assessed with: Risk through longest follow up)												
3	randomised trials	not serious	not serious	not serious	very serious [b]	none	-/0	57/84 (67.9%) [c]	**RR 1.09** (0.92 to 1.31)	**61 more per 1,000** (from 54 fewer to 210 more)	⨁⨁◯◯ LOW	CRITICAL
Remission (follow up: 4 years; assessed with: Risk over time)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	-/0	57/84 (67.9%) [c]	**HR 0.88** (0.32 to 2.42)	**47 fewer per 1,000** (from 374 fewer to 257 more)	⨁◯◯◯ VERY LOW	
Serious adverse events (follow up: 2.9 years; assessed with: Rate ratio)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	-/0	-/0	**Rate ratio 1.21** (0.96 to 1.53)	**40 more per 1000 patient(s) per years** (from 7 fewer to 100 more) [e]	⨁⨁◯◯ LOW	
Serious adverse events (follow up: range 1 years to 5 years; assessed with: Risk through time)												
2	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	35/86 (40.7%)	34/83 (41.0%)	**RR 0.88** (0.32 to 2.42)	**49 fewer per 1,000** (from 279 fewer to 582 more)	⨁◯◯◯ VERY LOW	
Disease activity (follow up: 1 years; assessed with: Birmingham Vasculitis Activity Score)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	One study reported this outcome at the one-year follow up. By the third month, both groups reached scores close to 0, which was mantained until the longest follow up of 1 year. There were no statistical differences in the scores between the groups.				⨁⨁⨁◯ MODERATE	
Decreased pulmonary function - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PLEX	no PLEX	Relative (95% CI)	Absolute (95% CI)		
Disease damage - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Suboptimal description of methods for randomization, some imbalances in baseline characteristics, and lack of description about how losses to follow up were handled increase the risk of bias of the trial that has most of the weight and from which raw numbers were taken for this meta-analysis

b. The confidence interval suggests the possibility of important benefit and important harm

c. Based on control arms of trials that reported the raw numbers

d. The confidence interval suggests the possibility of trivial and large benefit

e. Calculated based on 352 patients who provided information for 1021 patients/years (median follow-up 2.9 years, in which 114 patients experienced severe infection). Rate in control group is 112 per 1000 patient/years

References:

- Randomized Controlled Trials:

Author	Year	Title
M. Walsh	2013	Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear
W. M. Szpirt	2011	Plasma exchange for induction and cyclosporine A for maintenance of remission in Wegener's granulomatosis--a clinical randomized controlled trial
M. Walsh	2020	Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO question 36:** In patients with sino-nasal involvement in GPA, what is the impact of using nasal rinses vs. not using nasal rinses on disease related outcomes and treatment-related adverse events?

- **Critical Outcomes:** sinonasal symptoms, disease activity, disease damage, relapse, infection, toxicity leading to discontinuation, patient reported outcomes

2. In patients with sino-nasal involvement in GPA, what is the impact of using nasal rinses vs. not using nasal rinses on disease related outcomes and treatment-related adverse events?
   - No data available

3. In patients with sino-nasal involvement in GPA, what is the impact of using nasal rinses on disease related outcomes and treatment-related adverse events?

4. In patients with sino-nasal involvement in GPA, what is the impact of not using nasal rinses on disease related outcomes and treatment-related adverse events?
   No data available

- **References:**

- Randomized controlled trials:
  None

- Comparactive observational studies:
  None

- **Single arm studies and test accuracy studies :**
- No data available

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO question 37:** In patients with sino-nasal involvement in GPA, what is the impact of using nasal antibiotics vs. not using nasal antibiotics on disease related outcomes and treatment-related adverse events?

- **Critical Outcomes:** sinonasal symptoms, disease activity, disease damage, relapse, infection, toxicity leading to discontinuation, patient reported outcomes

5. In patients with sino-nasal involvement in GPA, what is the impact of using nasal antibiotics vs. not using nasal antibiotics on disease related outcomes and treatment-related adverse events?
   - No comparative data available

6. In patients with sino-nasal involvement in GPA, what is the impact of using nasal antibiotics on disease related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease activity – one study of 43 patients using a radiographic disease activity measure shows higher disease activity in patients using topical mupirocin.	Zycinska, 2016	Single center, cohort	Only first CT scan was reviewed	43 patients with GPA per ACR crtieria (12 M, mean age 47.7y)	Mupirocin (no details known)	"Higher L-M scores were related to mupirocin treatment." $p<0.05$. No other data shown.	Indirect, Disease activity measured by radiographic Lund-Mackay Score.
Olfactory dysfunction – One study with 76 patients shows more olfactory dysfunction in patients using topical mupirocin.	Laudien, 2009	Single, center cohort	Cross sectional	76 consecutive patients with WG (32M, median age 55)	Topical mupirocin	More patients who had local mupirocin treatment had olfactory dysfunction (13/38 vs 1/38).	Indirect, Outcome is a psychophysical test (questionnaire plus exam).

7. In patients with sino-nasal involvement in GPA, what is the impact of not using nasal antibiotics on disease related outcomes and treatment-related adverse events?
   No single arm data available

- **References:**

- Randomized controlled trials:

  None

- Comparactive observational studies:

  None

- Single arm studies and test accuracy studies:

Author	Year	Title
Zycinska	2016	Lund-Mackay System for Computed Tomography Evaluation of Paranasal Sinuses in Patients with Granulomatosis and Polyangiitis
Laudien	2009	Olfactory dysfunction in Wegener's granulomatosis

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO question 38:** In patients with chronic sino-nasal disease and mucosal damage, what is the impact of topical nasal lubricants (e.g., oils, ointments, and hyaluronic acid spray) on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** sinonasal symptoms, disease activity, disease damage, relapse, infection, toxicity leading to discontinuation, patient reported outcomes

8. In patients with chronic sino-nasal disease and mucosal damage, what is the impact of topical nasal lubricants (e.g., oils, ointments, and hyaluronic acid spray) on disease-related outcomes and treatment-related adverse events?
   - No data available

- **References:** None

- **Single arm studies and test accuracy studies:** None

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO question 39:** In patients with chronic sino-nasal disease and mucosal inflammation, what is the impact of topical corticosteroid therapies on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** sinonasal symptoms, disease activity, disease damage, relapse, infection, toxicity leading to discontinuation, patient reported outcomes

9. In patients with chronic sino-nasal disease and mucosal inflammation, what is the impact of topical corticosteroid therapies on disease-related outcomes and treatment-related adverse events?
    - No data available

- **References:** None

- **Single arm studies and test accuracy studies:** None

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO question 40:** In patients with GPA and subglottic and/or endobronchial stenosis, what is the impact of treatment with immunosuppression vs. surgical dilation with intralesional glucocorticoid injection on disease-related outcomes and treatment related adverse events?

- **Critical Outcomes:** Maintenance of patent airway, need for repeat dilation procedures, disease activity, disease damage, infection, complication of surgical procedure, patient reported outcomes

10. In patients with GPA and subglottic and/or endobronchial stenosis, what is the impact of treatment with immunosuppression vs. surgical dilation with intralesional glucocorticoid injection on disease-related outcomes and treatment related adverse events?
    - No Comparative Data Available

11. In patients with GPA and subglottic and/or endobronchial stenosis, what is the impact of treatment with immunosuppression on disease-related outcomes and treatment related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results	Comments
Remission – One study with 26 patients with GPA related tracheobronchial disease show remission rate 46% (13/28) with only medical therapy.	Girard, 2015	Two centers, single nation, cohort	70 months	26 patients with GPA per ACR criteria and Chapel Hill nom (9 M, median age 32). Only patients with tracheobronchial disease are included in this study	RTX or CYC	*Overall, remission rate 46% (13/28) with only medical therapy.* In SGS patients, CYC allowed to achieve remission in 17% cases when used without associated local treatment, 20% when part of combined therapy. In BS patients, remission was achieved after CYC treatment in 50% cases when associated with local procedure, 67% when not.	Indirect BS: bronchial stenosis
Treatment Failure – One study with 47 patients with GPA related tracheobronchail disease showed higher doses of glucocorticoids to be associated with less treatment failure.	Terrier, 2015	Nationwide, restrospective cohort	112 months	47 patients with GPA and tracheobronchial disease	*Notably, most patients were also receiving systemic therapy (90% GCs, 38% AZA, 19% MTX, 17.5% CYC, 7.5% MMF)* 187 Endoscopic procedures: tracheal dilatation (n= 101), local steroid injection (n= 38), conservative laser surgery(n= 23) and stenting (n= 9), whereas bronchial stenosis were mainly treated by endoscopic dilatation (n= 48), and less frequently by silicone or metal stenting (n= 10) or conservative laser surgery (n= 9)	Prednisone dose > 30 mg/day was associated with a lower cumulative incidence of treatment failure (HR 0.53 95%CI 0.35-0.89, adjusted p=0.007).	Indirect
Disease Activity – One study that included 54 patients with GPA related subglottic involvement showed that RTX based approach can help ENT manifestations in	Lally, 2014	Single Center, retrospective study	975 office visits in 99 subjects	99 patients with GPA – either ANCA positive or biopsy positive or both (83 were ANCA positive, mean age 50y, 68F)	RTX (ever) vs RTX (never) Those who received RTX were more likely to have had severe GPA (48% versus 26%; P=0.027) and were also more likely to have had ENT damage (94% versus 73%; P=0.004)	Subjects receiving RTX had no active ENT disease for 92.4% of the observational period compared with subjects not receiving RTX who had no active ENT disease for 53.7% of the observational period (odds ratio [OR] 11.0[95% confidence interval (95% CI) 5.5–22.0],P=0.0001)	Indirect Only ENT activity was considered While subjects with subglottic involvement in this cohort

general. Quite indirect. Half of patients had also received endoscopic therapy.				*54/99 had subglottic inflammation*			demonstrated response to RTX, nearly half (46%) underwent concurrent endoscopic intervention
Tracheostomy/otomy – Two older studies with 60 patients showed fairly high rates (53-56%) of tracheotomy/ostomy were required with CYC or MTX based IS regimens.	Langford, 1996	Single center (NIH), retrospective	6m-22y	43 patients with WG related SGS, 20 of which were treated with dilation/injection (14 W, median age 31.5y)	Intratracheal dilation and injection (methylprednisolone acetate) 13/20 patients were on immunsuppressives	Of the 18 patients requiring a tracheostomy,10 (56%) had received systemic immunosuppressive therapy for >2 months prior to undergoing tracheostomy (2 taking cyclophosphamide plus glucoeorticoid, 2 taking cyclophosphamide, 5 taking glucocorticoid, and 1 taking azathioprine)	Indirect
	Neel, 1982	Single Center case series	81m, mean	17 patients with WG related tracheobronchial disease	Patients were treated with CYC and corticosteroids	9/17 (53%) required tracheotomy	Indirect

12. In patients with GPA and subglottic and/or endobronchial stenosis, what is the impact of treatment with surgical dilation with intralesional glucocorticoid injection on disease-related outcomes and treatment related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results	Comments
Remission – One study with 26 patients showed fairly low remission rates (23%) with endoscopic approach. Traditional remission measures were not common in the included studies.	Girard, 2015	Two centers, single nation, cohort	70 months	26 patients with GPA per ACR criteria and Chapel Hill nom (9 M, median age 32) – Only patients with tracheobronchial disease are included in this study	Dilation procedure, IL GC, granulation tissue removal, mitoC, open procedure, or laser (with or without medical therapy)	SGS-remission rates were 23% after any kind of endoscopic procedure (alone or combined with medical treatment), 37% after laser therapy, and 40% following surgical	Indirect

						intervention, with respective means of 17 and 19 months before the next relapse for the latter 2 procedures.	
Maintenance of Airway Patency – Seven studies with 196 patients with varying measures of maintaining airway patency and varying endoscopic methods showed that many patients can ultimately achieve airway patency for a period of 6-12 months.	Terrier, 2015	Nationwide, restrospective cohort	112 months, median	47 patients with GPA and tracheobronchial disease	187 Endoscopic procedures: tracheal dilatation (n= 101), local steroid injection (n= 38), conservative laser surgery (n= 23) and stenting (n= 9), whereas bronchial stenosis were mainly treated by endoscopic dilatation (n= 48), and less frequently by silicone or metal stenting (n= 10) or conservative laser surgery (n= 9) Notably, most patients were also receiving systemic therapy (90% GCs, 38% AZA, 19% MTX, 17.5% CYC, 7.5% MMF)	Cumulative incidence of endoscopic treatment failure was 49% at 1 year, 70% at 2 years and 80% at 5 years	Indirect
	Martinez Del Pero, 2014	Retrospective single-center study	62.5 months	44 patients with GPA and airway disease (34F, median age 37.6y, 61% PR3 ANCA positivity, 25% ANCA neg)	213 interventions in 39 patients Balloon dilation (60.8%) Bougie dilation (15.9%) Laser dissection (11.2%) Diathermy dissection (2.3%) Argon-plasma (2.3%) Cryotherapy (4.2% IL GC (9.3%) MitoC (14.7%) IL alemtuzumab (3.5%)	12-month period of airway stability was ultimately achieved in 34 of 36 cases (97%) after some number of interventions.	Indirect
	Hseu, 2014	Single center, retrospective study	2.4 years, median	39 (45% of cohort) with GPA diagnosis. Part of a series of 92 patients with SGS of all types	Steroid injection, incision, dilation (bougie and balloon), MitoC all included in study	In patients who required more than one procedure, GPA and idiopathic patients were more likely to need their second surgery after 1 year, compared to trauma related etiologies.	Indirect

	Nouraei, 2007	Single center, retrospective study	Unclear, long term	18 patients with GPA (mean age 40y, 9F) and airway compromise due to active disease	31 procedures, with a median number of one procedure per patient (range 1–4). MitoC was used in 7 procedures.	The overall mean intervention-free interval following endoscopic treatment was 26.1 (SEM 2.8) months (95% CI 19.4 to 30.7 months)	Indirect
	Gluth, 2003	Single center, retrospective study	6.4y mean	27 patients with WG (all ANCA +, 16F, mean age 40.3y)	12/27 CO2 laser resection and dilation 27/27 treated with systemic steroids 11/27 IL steroids 5/27 mitoC	13/27 (48.1%) required multiple procedures. Among all patients who underwent CO2laser dilation, 4 of 12 (33.3%) required subsequent repeatsurgical management	Indirect
	Hoffman, 2002	Single center, retrospective study	40.6m, mean	21 patients with WG	64 procedures (IL methylpred plus dilation) MitoC was used in some	Patients who did not have scarring from prior procedures required a mean of 2.4 procedures at mean intervals of 11.6 months to maintain subglottic patency. Patients with established laryngotracheal scarring required a mean of 4.1 procedures at mean intervals of 6.8 months to maintain patency	Indirect
	Langford, 1996	Single center (NIH) retrospective	6m-22y	43 patients with WG related SGS, 20 of which were treated with dilation/injection (14 W, median age 31.5y)	Intratracheal dilation and injection (methylprednisolone acetate) 13/20 patients were on immunsuppressives	Following the institution of intratracheal therapy, no other surgical procedures were required on any of the 20 patients in the treated population.	Indirect
Adverse events – Five studies with 143 patients with heterogenous	Terrier, 2015	Nationwide, restrospective cohort	112 months, median	47 patients with GPA and tracheobronchial disease	187 Endoscopic procedures: tracheal dilatation (n= 101), local steroid injection (n= 38), conservative laser surgery(n= 23)	Per-endoscopic events were noted in only 5/173 cases (2.9%) and included haemorrhage (n= 4),	Indirect

reporting showed that restenosis was common and bleeding and infection are possible but uncommon.					and stenting (n= 9), whereas bronchial stenosis were mainly treated by endoscopic dilatation (n= 48), and less frequently by silicone or metal stenting (n= 10) or conservative laser surgery (n= 9). Notably, most patients were also receiving systemic therapy (90% GCs, 38% AZA, 19% MTX, 17.5% CYC, 7.5% MMF)	alveolar hypo-ventilation (n= 1) and airway obstruction (n=1). Adverse events occurring after the procedure were noted in 132/173 cases (76%) and included restenosis (n= 125), periprosthetic stenosis (n= 12), prosthesis migration(n= 4; 2 for subglottic stenosis and 2 for bronchial stenoses) and prosthesis expulsion (n= 1)	
	Martinez Del Pero, 2014	Retrospective single-center study	62.5 months	44 patients with GPA and airway disease (34F, median age 37.6y, 61% PR3 ANCA positivity, 25% ANCA neg)	213 interventions in 39 patients Balloon dilation (60.8%) Bougie dilation (15.9%) Laser dissection (11.2%) Diathermy dissection (2.3%) Argon-plasma (2.3%) Cryotherapy (4.2% IL GC (9.3%) MitoC (14.7%) IL alemtuzumab (3.5%)	Fourteen adverse events were recorded (6.6%) - Two hemorrhage - Two perforation - Five infections - One developed Polyps - One allergy - Two stent complications - One death	Indirect
	Arebo, 2012	Single center case series	Retrospective Single center case series	13 patients with WG (mean age 37.5y, 10 were ANCA positive)	"New endoscopic procedure:" endoscopically, the proceduralist removed the stenotic part submucosally, sealing back the raised mucosal flap, and the bare areas were soaked with mitomycin-C.	1 with post op bleeding	Indirect
	Nouraei, 2007	Single center, retrospective study	Unclear, long term	18 patients with GPA (mean age 40y, 9F) and airway compromise due to active disease	31 procedures, with a median number of one procedure per patient (range 1–4). MitoC was used in 7 procedures.	0/18 patients had bleeding or infection	Indirect

	Hoffman, 2002	Single center, retrospective study	40.6m, mean	21 patients with WG	64 procedures (IL methylpred plus dilation)	2 pneumothoraces	Indirect
Tracheotomy/ostomy- 4 studies with 97 patients showed that rates of tracheostomy/otomy after endoscopic procedure is fairly low (0-40%).	Taylor, 2013	Single center case series	8.2 (mean) and 9.9 (median) years	15 patients with GPA (ANCA or bx positive) 14/15 required endoscopic dilation	48 procedures in 14 patients Dilations, IL GC, MitoC, laser *All patients were also receiving immunosuppression [corticosteroids (n = 13), methotrexate sodium (n = 11),and cyclophosphamide (n = 9)]*	6/15 (40%) patients with GPA-SGS underwent tracheotomy as a result of disease-related complications and 2/15 (13%) remained tracheotomy dependent at the date of last followup	Indirect
	Nouraei, 2007	Single center, retrospective study	Unclear, long term	18 patients with GPA (mean age 40y, 9F) and airway compromise due to active disease	31 procedures, with a median number of one procedure per patient (range 1–4). MitoC was used in 7 procedures.	0/18 patients required tracheotomy/ostomy	Indirect
	Hoffman, 2002	Single center, retrospective study	40.6m, mean	21 patients with WG	64 procedures (IL methylpred plus dilation)	0/21 patients required new tracheostomy/otomy	Indirect
	Langford, 1996	Single center (NIH), retrospective	6m-22y	43 patients with WG related SGS	Intratracheal dilation and injection (methylprednisolone acetate) 13/20 patients were on immunsuppressives	In 20 patients treated with intratracheal therapy, none required tracheostomy and 6 with previous tracheostomies were decannulated	Indirect
Quality of life – 1 study with 13 patients showed improved QOL in patients underoing endoscopic procedure for GPA related SGS.	Arebo, 2012	Single center case series	Single center case series	13 patients with WG (mean age 37.5y, 10 were ANCA positive)	"New endoscopic procedure:" endoscopically, the proceduralist removedthe stenotic part submucosally, sealing back the raised mucosal flap, and the bare areas were soaked with mitomycin-C.	Ten of 13 patients reported a much improved QOL and 1 reported an improved QOL. Two reported unchanged QOL. Nobody reported a poorer QOL.	Interview Telephone interview

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:
  None

- Single Arm Studies:

Author	Year	Title
C. Girard	2015	Tracheobronchial Stenoses in Granulomatosis With Polyangiitis (Wegener's): A Report on 26 Cases
B. Terrier	2015	Granulomatosis with polyangiitis: endoscopic management of tracheobronchial stenosis: results from a multicentre experience
M. Martinez Del Pero	2014	Long-term outcome of airway stenosis in granulomatosis with polyangiitis (Wegener granulomatosis): an observational study
L. Lally	2014	Effectiveness of rituximab for the otolaryngologic manifestations of granulomatosis with polyangiitis (Wegener's)
A. F. Hseu	2014	Subglottic stenosis: a ten-year review of treatment outcomes
S. C. Taylor	2013	Clinical manifestations and treatment of idiopathic and Wegener granulomatosis-associated subglottic stenosis
J. Arebro	2012	New treatment of subglottic stenosis due to Wegener's granulomatosis
S. A. Nouraei	2008	Results of endoscopic surgery and intralesional steroid therapy for airway compromise due to tracheobronchial Wegener's granulomatosis
M. B. Gluth	2003	Subglottic stenosis associated with Wegener's granulomatosis
G. S. Hoffman	2003	Treatment of subglottic stenosis, due to Wegener's granulomatosis, with intralesional corticosteroids and dilation
C. A. Langford	1996	Clinical features and therapeutic management of subglottic stenosis in patients with Wegener's granulomatosis

- Studies reviewed and excluded:

Author	Year	Title	Comments
F. Y. Bhora	2016	Treatment of Benign Tracheal Stenosis Using Endoluminal Spray Cryotherapy	Excluded for GPA PICO 40 single arm, not an intervention of interest
M. Wierzbicka	2016	The efficacy of submucosal corticosteroid injection and dilatation in subglottic stenosis of different aetiology	Excluded for GPA PICO 40 single arm, less than 10 GPA patients
I. J. Malm	2014	Otolaryngological progression of granulomatosis with polyangiitis after systemic treatment with rituximab	Excluded for GPA PICO 40 single arm, no outcomes of interest in patients with tracheobronchial disease.
K. Zycinska	2013	Subglottic and tracheal stenosis due to Wegener's granulomatosis	Excluded for GPA PICO 40 single arm, epidemiologic/descriptive series

N. E. Wolter	2010	Intralesional corticosteroid injection and dilatation provides effective management of subglottic stenosis in Wegener's granulomatosis	Excluded for GPA PICO 40 single arm, less than 10 GPA patients.
M. Martinez Del Pero	2009	B-cell depletion with rituximab for refractory head and neck Wegener's granulomatosis: a cohort study	Excluded for GPA PICO 40 single arm, no outcomes of interest in patients with tracheobronchial disease.

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO question 41: I**n patients with GPA and orbital pseudotumor, what is the impact of treatment with immunosuppression vs. surgical removal of pseudotumor tissue on disease-related outcomes, ocular symptoms (e.g., ocular/orbital pain, diplopia, and vision loss) and treatment-related adverse events?

- **Critical Outcomes:** Ocular Symptoms, Disease Activity, Disease Damage, Infection, Serious Adverse Events, Complication of surgical procedure, Patient reported outcomes

13. **I**n patients with GPA and orbital pseudotumor, what is the impact of treatment with immunosuppression vs. surgical removal of pseudotumor tissue on disease-related outcomes, ocular symptoms (e.g., ocular/orbital pain, diplopia, and vision loss) and treatment-related adverse events?
    - No Comparative Data Available

14. **I**n patients with GPA and orbital pseudotumor, what is the impact of treatment with immunosuppression on disease-related outcomes, ocular symptoms (e.g., ocular/orbital pain, diplopia, and vision loss) and treatment-related adverse events?
    - Patient Important Outcomes

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results	Comments
Remission	Lavnish, Joshi 2015	Retrospective Single arm	36.5 months (range 6-56 months)	Pts with GPA and ocular disease Total n of patients – 37 Total n of orbital disease 17/37	All patients with GPa and ocular disease who received rituximab between 2004 and 2013 were reviewed. Main outcome measure: % in remisison at 6 months, time to remission, % relapsing, side effects	14/17 (82%) pts with orbital disease achieved remission. (Remission was defined as inactive disease with prednisolone ≤7.5 mg/day) Time to remission 88 (median days) Relapses 7/17 (41%)	The study aim was to compare generalized vs ocular disease and not all data is available for just the orbital group. The group is not well defined in terms of diagnosis, imaging studies, extension of disease and pseudotumor is not mentioned.

						Time to relapse 33 (median months)	The conclusion of the study states that rituximab is effective for inducing remission in localized and generalized ocular disease.
	Holle, Julia 2013	Retrospective Single arm Retrospective analysis of outcome of patients with GPA related orbital mass	1988-2011	40 patients with orbital masses were included 18 females 22 males	32/44 (80%) received immunosuppressive therapy at diagnosis of orbital disease. - (75.7%) received steroids plus Cytoxan - (8.1%) received a combination of steroids, Cytoxan and an additional anti-TNF or Rituximab. - (13.5%) received steroids and rituximab. - (13.5 %)– other therapies (one surgical decompression)	3 pts (8.1%) achieved remission. 10 pts (27.0%) had partial response (included the 1 pt who had surgery) 9 pts (24.3%) disease was unchanged 14 (40.5%) had disease progression.	The majority of pts received steroids + Cytoxan Overall treatment effect size was very small. Only 2 patients received rituximab – no conclusion can be drawn.
Improvement (The term remission was not used)	Baslund, B 2012	Case series retrospective	1 year	10 pts with refractory orbital disease treated with rituximab 7 females/3 males	Rituximab – 2 infusions of 1 g each, 2 weeks apart In addition to rituximab: -Cellcept + prednisolone were given to 2 pts -prednisolone to 1 pt	9/10 pts – subjective improvement of symptoms -4 pts – improvement of vision -Progression was stopped in all cases -Mass size reduction in 2 pts	The use of rituximab was overall beneficial but mass size reduction was only seen in 2/10 pts. No pts had mass progression.
Disease activity: Rituximab appears to have an advantage over CYC in response and worsening of disease	Durel, 2018	Observational	Median follow-up 68 months (range 6-301)	59 GPA patients with AAV meeting ACR or CHCC cirteria and orbital disease. French study.	Various immunosuppressives including RTX, CYC, AZA, MMF, MTX, TNFa, etc.	Remission: 15/59 (27%) Response: 27/59 (48%) Stable disease: 10/59 (18%) Worsening 4/59 (7%) By treatment (RTX vs CYC) Remission: 27 vs 26% Response: 64 vs 26%	Direct evidence: Various immunosuppressives used, however, authors specifically stratify outcomes in those treated with RTX and CYC.

						Stable: 9 vs 30% Worsening: 0 vs 17%	
Occular symptoms	Durel, 2018	Observational	Median follow-up 68 months (range 6-301)	59 GPA patients with AAV meeting ACR or CHCC cirteria and orbital disease. French study.	Various immunosuppressives including RTX, CYC, AZA, MMF, MTX, TNFa, etc.	Visual impairment: 16 (28%) Blindness 10 (17%) Diplopia 11 (19%)	Direct evidence: Various immunosuppressives used. Unable to stratify by treatment.
Disease Damage	Durel, 2018	Observational	Median follow-up 68 months (range 6-301)	59 GPA patients with AAV meeting ACR or CHCC cirteria and orbital disease. French study.	Various immunosuppressives including RTX, CYC, AZA, MMF, MTX, TNFa, etc.	Median VDI at f/u was 2 (range 0-5)	Direct evidence: Various immunosuppressives used. Unable to stratify by treatment.

15. **I**n patients with GPA and orbital pseudotumor, what is the impact of treatment with surgical removal of pseudotumor tissue on disease-related outcomes, ocular symptoms (e.g. ocular/orbital pain, diplopia, and vision loss) and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results	Comments
Improvement (The term remission was not used)	Del Pero Martinez, 2009	Retrospective Single arm Outcome Evaluate efficacy of rituximab	2002-2008	Refractory GPA treated with rituximab	5/34 refractory GPA patients had orbital disease	4/5 pts with orbital disease improved with rituximab 1 /4 responders relapsed	Small number of pts Adverse events were not specified if affecting pts with orbital disease. Not exactly clear how improvement was defined other than the ability to reduce steroids and a reduction in BVCAS, which was not specified for this group

Remission	Lavnish Joshi, 2011	Retrospective Case-Series	Median f/u 24 months Range 12-60 months	20 consecutive pts with refractory ophthalmologic manifestation who received rituximab.	2 infusions of rituximab of 1 g each, 2 weeks apart + prednisolone al pts received induction therapy followed by no maintenance	All 20 pts achieved remission within 6 months	
	Taylor Simon, 2009	Open-label study of 10 pts with refractory ophthalmic manifestations	Median of 12 months Range 6-36 months	Refractory ophthalmologic cases 7/10 with orbital disease 5 males/5 females	Ritusximab 2 infusions of 1 g each, 2 weeks apart	All 10 pts achieved remission within 7 months Remission was sustained for a median of 6.5 months in 6/10 pts and for at least 12 months in 4/10 Visual acuity improvement: 5/7 pts had improvement of visual acuity 2 pts were considered in remission but visual lost despite rituximab – thought to be from fibrosis	Definition of remission allowed for prednisolone use up to 7.5 mg/day
Relapse	Lavnish Joshi, 2011	Retrospective Case-Series	Median f/u 24 months Range 12-60 months	20 consecutive pts with refractory ophthalmologic manifestation who received rituximab	2 infusions of rituximab of 1 g each, 2 weeks apart + prednisolone all pts received induction therapy followed by no maintenance	7 pts (35%) relapse at a median of 13 months of those, 3 had a relapse of orbital disease	Repeat infusions of rituximab were given to 5 pts and they all achieved remission again

- **References:**

- Randomized controlled trials:

None

- Comparative observational studies:

None

- Single Arm Studies:

Author	Year	Title
L. Joshi	2015	Long-term Outcomes of Rituximab Therapy in Ocular Granulomatosis with Polyangiitis: Impact on Localized and Nonlocalized Disease
J. U. Holle	2013	Orbital masses in granulomatosis with polyangiitis are associated with a refractory course and a high burden of local damage
B. Baslund	2012	Treatment of orbital inflammation with rituximab in Wegener's granulomatosis
L. Joshi	2011	Rituximab in refractory ophthalmic Wegener's granulomatosis: PR3 titers may predict relapse, but repeat treatment can be effective
M. Martinez Del Pero	2009	B-cell depletion with rituximab for refractory head and neck Wegener's granulomatosis: a cohort study
S. R. Taylor	2009	Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis
Durel	2018	Orbital mass in ANCA-associated vasculitides: data on clinical, biological, radiological and histological presentation, therapeutic management, and outcome from 59 patients

- Studies reviewed and excluded:

Author	Year	Title	Comments
S. B. Cannady	2009	Sinonasal Wegener granulomatosis: a single-institution experience with 120 cases	Exclude. Only 3 patients with orbital disease.
F. P. Fechner	2002	Wegener's granulomatosis of the orbit: a clinicopathological study of 15 patients	Exclude. Should not be used.
S. R. Perry	1997	The clinical and pathologic constellation of Wegener granulomatosis of the orbit	Exclude. Does not address PICO.
C. L. Bullen	1983	Ocular complications of Wegener's granulomatosis	Exclude. Does not address PICO.
S. A. Jennings	2000	Wegener's granulomatosis: The ocular manifestations revisited	Exclude. Does not address PICO.

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO question 42:** In patients with GPA and mass lesions aside from orbital pseudotumor (e.g., lung, brain, parotid gland, kidney, prostate gland), what is the impact of treatment with immunosuppression vs. surgical removal of the mass lesion on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** clinical symptoms arising from mass lesion, disease activity, disease damage, infection, serious adverse events, complication of surgical procedure, patient reported outcomes

16. In patients with GPA and mass lesions aside from orbital pseudotumor (e.g., lung, brain, parotid gland, kidney, prostate gland), what is the impact of treatment with immunosuppression vs. surgical removal of the mass lesion on disease-related outcomes and treatment-related adverse events?
    - No comparative data available

17. In patients with GPA and mass lesions aside from orbital pseudotumor (e.g., lung, brain, parotid gland, kidney, prostate gland), what is the impact of treatment with immunosuppression on disease-related outcomes and treatment-related adverse events?
    - No single arm data available

18. In patients with GPA and mass lesions aside from orbital pseudotumor (e.g., lung, brain, parotid gland, kidney, prostate gland), what is the impact of treatment with surgical removal of the mass lesion on disease-related outcomes and treatment-related adverse events?
    - No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies:
  None

- Studies reviewed and excluded:

Author	Year	Title	Comments
M. Martinez Del Pero	2009	B-cell depletion with rituximab for refractory head and neck Wegener's granulomatosis: a cohort study	Exclude. Does not address PICO

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO question 43:** In patients with GPA/MPA on cyclophosphamide or rituximab, what is the impact of using Pneumocystis prophylaxis vs. not using Pneumocystis prophylaxis on the development of Pneumocystis pneumonia and treatment-related adverse events?

- **Critical Outcomes:** Pneumocystis infection, death, other infection, serious adverse events, toxicity leading to discontinuation (e.g., adverse reaction to prophylaxis)

19. In patients with GPA/MPA on cyclophosphamide or rituximab, what is the impact of using Pneumocystis prophylaxis vs. not using Pneumocystis prophylaxis on the development of Pneumocystis pneumonia and treatment-related adverse events?
    - No data available

20. In patients with GPA/MPA on cyclophosphamide or rituximab, what is the impact of using Pneumocystis prophylaxis on the development of Pneumocystis pneumonia and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Pneumocystis infection – Two modern studies (one for CYC and one for RTX) of 51 patients with	Samson, 2017	Prospective cohort (CHUSPAN RCT)	10 years	64 patients with MPA (n=40) or non-HBV PAN (n=24)	Patients were randomized to 12 vs 6 CYC pulses with glucocroticoids. All patients received co-trimoxazole.	No PJP infections were reported.	Indirect

MPA demonstrate no rate of Pneumocystis infection when treated with prophylaxis.	Basu, 2015	Retrospective cohort	20.9 months (median)	11 pediatric patients with MPA	Patients received IVMP, PLEX, oral prednisolone and at least two RTX infusions. All patients received co-trimoxazole.	No PJP infections were reported.	Indirect

21. In patients with GPA/MPA on cyclophosphamide or rituximab, what is the impact of using. not using Pneumocystis prophylaxis on the development of Pneumocystis pneumonia and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Death – Two studies of 18 patients who contracted pneumocystis pneumonia demonstrated high rates of mortality (~50%).	Godeau, 1994	Retrospective case series	N/A	34 patients with CTD and PJP diagnosis, of which 12 patient had WG It does not appear these patients were on primary prophylaxis for PJP.	All patients had been on CYC and corticosteroids Most (11/12) had leukopenia (<1.0 x10^9/L) at time of PJP diagnosis. All patients were treated with TMP-SMX acutely.	5/12 died	Indirect
	Jarrousse, 1993	Prospective cohort (RCT)	10 months	6 patients with PJP and WG with renal involvement	All patients had received CYC (IV or PO) and prednisone. All patients were treated with TMP-SMX acutely.	3/6 died	Indirect
Pneumocystis infection – An early RCT demonstrated high rates of Pneumocystis in patients getting CYC, prompting	Jarrousse, 1993	Prospective cohort (RCT)	10 months	23 patients with biopsy proven WG with renal involvement	Patients were randomized to prednisone + IV pulse CYC OR prednisone + daily low dose continuous CYC	6/23 had PJP infection	Indirect This rate of infection prompted protocol adjustment to tailor CYC dose to renal function (had not previously). 5/6 infections were in the first 13 patients and 1/6

a protocol change.							were after protocol modification.

- **References:**

- Randomized controlled trials:
  None

- Comparactive observational studies:
  None

- Single arm studies:

Author	Year	Title
Godeau	1994	Pneumocystis carinii pneumonia in the course of connective tissue disease: report of 34 cases
Jarrouss	1993	Increased risk of Pneumocystis carinii pneumonia in patients with Wegener's granulomatosis
Samson	2017	Microscopic polyangiitis and non-HBV polyarteritis nodosa with poor-prognosis factors: 10-year results of the prospective CHUSPAN trial
Basu	2015	Favourable renal survival in paediatric microscopic polyangiitis: efficacy of a novel treatment algorithm

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO question 44:** In patients with GPA/MPA on remission maintenance therapy with rituximab who have hypogammaglobulinemia (IgG< 3 g/L), what is the impact of IVIG supplementation vs. no IVIG supplementation on the development of infections and treatment-related adverse events?

- **Critical Outcomes:** Incidence of infection, serious adverse events, toxicity leading to discontinuation

22. In patients with GPA/MPA on remission maintenance therapy with rituximab who have hypogammaglobulinemia (IgG< 3 g/L), what is the impact of IVIG supplementation vs. no IVIG supplementation on the development of infections and treatment-related adverse events?

- No data available

23. In patients with GPA/MPA on remission maintenance therapy with rituximab who have hypogammaglobulinemia (IgG< 3 g/L), what is the impact of IVIG supplementation on the development of infections and treatment-related adverse events?

24. In patients with GPA/MPA on remission maintenance therapy with rituximab who have hypogammaglobulinemia (IgG< 3 g/L), what is the impact of no IVIG supplementation on the development of infections and treatment-related adverse events?

- **References:**

- Randomized controlled trials:
  None

- Comparactive observational studies:
  None

- **Single arm studies and test accuracy studies:** None

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO question 45:** In patients with GPA/MPA in remission and nasal bridge collapse/nasal fistulas, what is the impact of reconstructive surgery vs. no surgery on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** patient reported outcomes, complications of surgical procedure, disease activity (sino-nasal activity), disease relapse, infection

25. In patients with GPA/MPA in remission and nasal bridge collapse/nasal fistulas, what is the impact of reconstructive surgery vs. no surgery on disease-related outcomes and treatment-related adverse events?
    - No comparative data available

26. In patients with GPA/MPA in remission and nasal bridge collapse/nasal fistulas, what is the impact of reconstructive surgery on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Successful primary surgery: 143 patients in 3 studies. Ranged between 76% and 83%	Sepehr, 2011	Retrospective case-series	Average follow-up of 20.8 months	10 patients with GPA and saddle nose deformity	Costal cartilage autograft reconstruction	8/10 (80%)
	Cannady, 2009	Retrospective case-series	Mean follow-up was 33.8 months (range, 1–121 months)	120 patients with GPA and referred for otolaryngology consultation	Primary functional endoscopic sinus surgery (FESS) or dacryocystorhinotomy (DCR) prior to referral.	At 1, 6, and 12 months was 83%, 76%, and 76%
	Congdon, 2002	Retrospective case-series	Mean follow-up 59 months (range, 10–177 mo)	13 patients with GPA who had external nasal reconstruction.	Reconstructive surgery	10 of 13 patients (77%)
Postoperative complications: 23 patients in 2 studies. Ranged between 6% and 40%	Sepehr, 2011	Retrospective case-series	Average follow-up of 20.8 months	10 patients with GPA and saddle nose deformity	Costal cartilage autograft reconstruction	4/10 (40%)
	Congdon, 2002	Retrospective case-series	Mean follow-up 59 months (range, 10–177 mo)	13 patients with GPA who had external nasal reconstruction.	16 reconstructive operations	Early complications in 1 of 16 (6%); Late complications: 3 of 16 operations (19%).
Wound infections: 23 patients in 2 studies. Wound infections ranged between 7.7% and 20%	Sepehr, 2011	Retrospective case-series	Average follow-up of 20.8 months	10 patients with GPA and saddle nose deformity	Costal cartilage autograft reconstruction	2/10 (20%)
	Congdon, 2002	Retrospective case-series	Mean follow-up 59 months (range, 10–177 mo)	13 patients with GPA who had external nasal reconstruction.	Reconstructive surgery	1/13 (7.7%)

27. In patients with GPA/MPA in remission and nasal bridge collapse/nasal fistulas, what is the impact of no surgery on disease-related outcomes and treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
    None

- Comparactive observational studies:
  None

- Single arm studies:

Author	Year	Title
Sepehr	2011	Detailed analysis of graft techniques for nasal reconstruction following Wegener granulomatosis
Cannady	2009	Sinonasal Wegener granulomatosis: a single-institution experience with 120 cases
Congdom	2002	Long-term follow-up of repair of external nasal deformities in patients with Wegener's granulomatosis

- Studies reviewed and excluded:

Author	Year	Title	Comments
A. S. Fauci	1983	Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years	Patients did not have nasal bridge collapse/nasal fistulas. Exclude

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO question 46:** In patients with GPA/MPA in remission and chronic kidney disease stage V, what is the impact of renal transplantation vs. no renal transplantation on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** patient reported outcomes, death, complications of transplant (immunosuppression/surgery), disease activity, relapse

28. In patients with GPA/MPA in remission and chronic kidney disease stage V, what is the impact of renal transplantation vs. no renal transplantation on disease-related outcomes and treatment-related adverse events?
    - No comparative data available

29. In patients with GPA/MPA in remission and chronic kidney disease stage V, what is the impact of renal transplantation on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Reduction of the risk of mortality was reported by one study with 946 patients with renal transplantation.	Wallace, 2018	Retrospective case-control	Not reported	946 GPA patients with renal transplantations, 579 controls	Renal transplantation	70% reduction in the risk of all-cause mortality (RR=0.30, 95%CI 0.25 to 0.37) 90% reduction in the risk of death due to CVD (RR=0.10, 95% 0.06–0.16). Reduction of risk of death due to infection (RR=0.55, 95%CI 0.31 to 0.97)
Patient survival was reported by 6 studies with 1750 patients in total and ranged from 100% at first year, 92% at 5 years, to 67.4%-74.8% at 10 years	Buttigieg, 2017	Retrospective case-control	Median follow-up 60 months (range, 0.5-226 mo)	24 patients s (17 GPA and 7 MPA) with end-stage renal disease	31 kidney allografts	Patient survival at 1 and 5 years was 92% and 88%
	Hruskova, 2015	Case-control	10 years	618 patients with AAV	Renal transplantation	10-year patient survival was 74.8% [95% CI, 69.9%-79.0%]
	Romeu, 2015	Case-control	The median follow-up of 13 (IQR 1.5–50) months	58 AAV patients	Renal transplantation	51/58 (88%)
	Tang, 2013	Case-control	3.0-3.3 (1.0–5.8) years	46 MPA and 47 GPA patients	Renal allografts	HR, 0.58; 95% CI, 0.23-2.27; P=0.58
	Geetha, 2011	Retrospective case-series	Median follow-up 64 (range, 3–165) months	85 patients with GPA (n=42) and MPA (n=43)	Renal transplantations	100% at 1 year, 93.4% at 5 years, 67.4% at 10 years
	Shen, 2010	Case-control	9 years	919 GPA patients	Renal transplantations	79.2%
Relapse was reported by 5 studies with 273 patients and ranged from 8.2% to 12% in	Buttigieg, 2017	Retrospective case-control	Median follow-up 60 months (range, 0.5-226 mo)	24 patients with end-stage renal disease	31 kidney allografts	Patient and allograft relapse rates were 0.022 and 0.016 relapse/patient-years
	Geetha, 2015	Retrospective case-control	The median follow up was 3.9 years (range 1–11 years)	16 AAV ANCA+ patients	Renal transplantations	6/16 (37.5%)

three studies, and 37.5% in one study. One study reported as 0.022 relapse per patient-years.	Geetha, 2011	Retrospective case-series	Median follow-up 64 (range, 3–165) months	85 patients with GPA (n=42) and MPA (n=43)	Renal transplantations	7/85 (8.2%)
	Gera, 2007	Case-series	Mean follow-up 4.4 years	35 patients with MPA and GPA	Renal transplantations	3/35 (8.6%)
	Göçeroğlu, 2016	Case-series	5 years	113 AAV patients GPA (68%) and MPA (32%)	Renal transplantations	13/113 (12%)
Death was reported by 9 studies with 1911 patients and ranged from 3.5% to 21% with median/mean follow-ups from 13 months to 10 years	Buttigieg, 2017	Retrospective case-control	Median follow-up 60 months (range, 0.5-226 mo)	24 patients with end-stage renal disease	31 kidney allografts	5/24 (21%)
	Hruskova, 2015	Case-control	10 years	618 patients with AAV	Renal transplantation	127/618 (21%)
	Romeu, 2015	Case-control	The median follow-up of 13 (IQR 1.5–50) months	58 AAV patients	Renal transplantation	2/58 (3.5%)
	Tang, 2013	Case-control	3.0-3.3 (1.0–5.8) years	46 MPA and 47 GPA patients	Renal allografts	13/93 (14%)
	Geetha, 2011	Retrospective case-series	Median follow-up 64 (range, 3–165) months	85 patients with GPA (n=42) and MPA (n=43)	Renal transplantations	11/85 (13%)
	Shen, 2010	Case-control	9 years	919 GPA patients	Renal transplantations	HR = 0.63
	Gera, 2007	Case-series	Mean follow-up 4.4 years	35 patients with MPA and GPA	Renal transplantations	4/35 (11.4%)
	Wrenger, 1997	Case-series	Mean follow-up 49.9 (4-107) months	13 patients with GPA	Renal transplantations	2/13 (15%)
	Göçeroğlu, 2016	Case-series	5 years	113 AAV patients GPA (68%) and MPA (32%)	Renal transplantations	6/113 (5%)
Allograft rejection was reported by 8 studies with 1286 patients and ranged from 8.6% to 38%.	Geetha, 2015	Retrospective case-control	The median follow up was 3.9 years (range 1–11 years)	16 AAV ANCA+ patients	Renal transplantations	5/16 (31%)
	Romeu, 2015	Case-control	The median follow-up of 13 (IQR 1.5–50) months	58 AAV patients	Renal transplantation	5/58 (8.6%)
	Geetha, 2011	Retrospective case-series	Median follow-up 64 (range, 3–165) months	85 patients with GPA (n=42) and MPA (n=43)	Renal transplantations	13/85 (15%)
	Geetha, 2010	Retrospective case-series	Median follow-up 37 months	17 patients with GPA and MPA	Renal transplantations	3/17 (18%)

	Shen, 2010	Case-control	9 years	919 GPA patients	Renal transplantations	38.1%
	Gera, 2007	Case-series	Mean follow-up 4.4 years	35 patients with MPA and GPA	Renal transplantations	6/35 (23%)
	Wrenger, 1997	Case-series	Mean follow-up 49.9 (4-107) months	13 patients with GPA	Renal transplantations	2/13 (15%)
	Göçeroğlu, 2016	Case-series	5 years	113 AAV patients GPA (68%) and MPA (32%)	Renal transplantations	19/113 (17%)
Remission was reported by one study with 16 patients and had 94% rate	Geetha, 2015	Retrospective case-control	The median follow up was 3.9 years (range 1–11 years)	16 AAV ANCA+ patients	Renal transplantations	15/16 (94%)
Flare was reported by one study with 17 patients and had 12% rate	Geetha, 2010	Retrospective case-series	Median follow-up 37 months	17 patients with GPA and MPA	Renal transplantations	2/17 (12%)

30. In patients with GPA/MPA in remission and chronic kidney disease stage V, what is the impact of no renal transplantation on disease-related outcomes and treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
    None

- Comparative observational studies:
    None

- Single arm studies:

Author	Year	Title
Wallace	2018	Improved survival with renal transplantation for end-stage renal disease due to granulomatosis with polyangiitis: data from the United States Renal Data System
Buttigieg	2017	Outcome of Kidney Transplant in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

Geetha	2015	Relevance of ANCA positivity at the time of renal transplantation in ANCA associated vasculitis
Hruskova	2015	Characteristics and Outcomes of Granulomatosis With Polyangiitis (Wegener) and Microscopic Polyangiitis Requiring Renal Replacement Therapy: Results From the European Renal Association-European Dialysis and Transplant Association Registry
Romeu	2015	Survival of patients with ANCA-associated vasculitis on chronic dialysis: data from the French REIN registry from 2002 to 2011
Tang	2013	The outcomes of patients with ESRD and ANCA-associated vasculitis in Australia and New Zealand
Geetha	2010	Renal transplantation in antineutrophil cytoplasmic antibody-associated vasculitis: a multicenter experience
Geetha	2010	Renal transplant in Wegener's granulomatosis compared to microscopic polyangiitis
Shen	2010	Outcomes of renal transplantation in recipients with Wegener's granulomatosis
Gera	2007	Recurrence of ANCA-associated vasculitis following renal transplantation in the modern era of immunosupression
Wrenger	1997	Single-center experience with renal transplantation in patients with Wegener's granulomatosis
Göçeroğlu	2016	The Dutch transplantation in vasculitis (DUTRAVAS) study: outcome of renal transplantation in antineutrophil cytoplasmic antibody-associated glomerulonephritis

- Studies reviewed and excluded:

Author	Year	Title	Comments
A. M. Kouri	2017	Clinical presentation and outcome of pediatric ANCA-associated glomerulonephritis	Less than 10 patients with end-stage renal disease. Exclude
J. L. Merino	2011	A retrospective study on outcome of microscopic polyangiitis in chronic renal replacement therapy	Less than 10 had renal transplantation. Exclude

Granulomatosis with polyangiitis (GPA)/Microscopic polyangiitis (MPA)

Other

- **PICO question 47:** In patients with GPA/MPA and venous thromboembolism what is the impact of anticoagulation for 6 months vs. anticoagulation for 6-18 months vs. anticoagulation > 18 months on the development of recurrent venous thromboembolic events and treatment-related side effects?

- **Critical Outcomes:** incidence of venous thromboembolic events, death, serious adverse events, toxicity leading to discontinuation (e.g., hemorrhage)

31. In patients with GPA/MPA and venous thromboembolism what is the impact of anticoagulation for 6 months vs. anticoagulation for 6-18 months vs. anticoagulation > 18 months on the development of recurrent venous thromboembolic events and treatment-related side effects?
    No comparative data available

32. In patients with GPA/MPA and venous thromboembolism what is the impact of anticoagulation > 18 months on the development of recurrent venous thromboembolic events and treatment-related side effects?
    No single arm data available

33. In patients with GPA/MPA and venous thromboembolism what is the impact of anticoagulation for 6-18 months on the development of recurrent venous thromboembolic events and treatment-related side effects?
    No single arm data available

34. In patients with GPA/MPA and venous thromboembolism what is the impact of anticoagulation > 18 months on the development of recurrent venous thromboembolic events and treatment-related side effects?
    No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies:
  None

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Role of FFS

- **PICO question 1:** In patients with EGPA, what is the impact of using the Five Factor Score vs. intuitive assessment of patient's status to guide therapy on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, serious adverse events, toxicity leading to discontinuation

35. In patients with EGPA, what is the impact of using the Five Factor Score vs. intuitive assessment of patient's status to guide therapy on disease-related outcomes and treatment-related adverse events?
    No comparative data available

36. In patients with EGPA, what is the impact of using the Five Factor Score to guide therapy on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Mortality: was reported by 7 studies with 1062 EGPA patients who had FFS evaluaiton, and ranged from 6.8% to 31.3%	Guillevin, 2011	Retrospective case-series	Various but more than 5 years	230 patients with EGPA	FFS evaluation	32/230 (13.9%)
	Bourgarit, 2005	Case-control	Mean follow-up of 6.4 years	133 patients with EGPA	FFS evaluation	9/133 (6.8%). Among those who died: Progressive worsening 5/9 (56%); Initial improvement 4/9 (44%); New event, n = 4 Time to new events (days), mean ± SD 74 ± 51
	Guillevin, 1996	Case-series	Mean follow-up 40 months	336 patients with EGPA	FFS evaluation	64/336 (19%)
	Samson, 2013	Case-series	Mean follow-up 81.3 months	118 patients with EGPA	FFS evaluation	12 (10%)
	Moosig, 2012	Case-series	Follow-up 92±5 Months	150 patients with EGPA	FFS evaluation	12/150 (8%)
	Vinit, 2011	Case-series	Mean follow-up 7.7 years	31 patients with EGPA	FFS evaluation	6/31 (19%)
	Gayraud, 2001	Case-series	Mean follow-up 88.3±51.9 months	64 patients with EGPA	FFS evaluation	Overall: 20/64 (31.3%) Deaths due to vasculitis: 4/64 (6.3%)

Survival rates were reported by 4 studies with 635 EGPA patients who had FFS evaluation, and ranged from 79% to 97% at 5 year	Guillevin, 1996	Case-series	Mean follow-up 40 months	336 patients with EGPA	FFS evaluation	5-year survival rate 78.9%
	Samson, 2013	Case-series	Mean follow-up 81.3 months	118 patients with EGPA	FFS evaluation	Survival 1-, 3-, 5- and 7-year rates were: 98%, 94%, 92% and 90%, respectively
	Moosig, 2013	Case-series	Follow-up 92±5 months	150 patients with EGPA	FFS evaluation	5-year survival rate was 97%; 10-year survival rate was 89%
	Vinit, 2011	Case-series	Mean follow-up 7.7 years	31 patients with EGPA	FFS evaluation	5 year survival rate was 93%
Relapse was reported by 4 studies with 362 EGPA patients who had FFS evaluation, and ranged from 14% regardless of FFS score to 68% with FFS ≥ 1	Kim, 2017	Case-series	Follow-up duration 2 years	30 patients with EGPA	FFS evaluation	Relapse in patients with FFS ≥ 1: 68.8%, with FFS <1: 7.1%, (p = 0.001; relative risk 28.6).
	Samson, 2013	Case-series	Mean follow-up 81.3 months	118 patients with EGPA	FFS evaluation	47/118 (41%)
	Moosig, 2013	Case-series	Follow-up 92±5 months	150 patients with EGPA	FFS evaluation	21 (14%)
	Gayraud, 2001	Case-series	Mean follow-up 88.3±51.9 months	64 patients with EGPA	FFS evaluation	13/64 (20.3%)
Remission was reported by 2 studies with 268 EGPA patients who had FFS evaluation, and ranged from 29% as a long-term, and 92% as initial remission	Samson, 2013	Case-series	Mean follow-up 81.3 months	118 patients with EGPA	FFS evaluation	Initial remission: 108 (92%); Long-term remission: 34 (29%)
	Moosig, 2013	Case-series	Follow-up 92±5 months	150 patients with EGPA	FFS evaluation	70/104 (67.3%)
Serious Adverse Events was reported in 1 study with 64 EGPA patients who had FFS evaluation and was 37.5%	Gayraud, 2001	Case-series	Mean follow-up 88.3±51.9 months	64 patients with EGPA	FFS evaluation	37.5%

37. In patients with EGPA, what is the impact of using the intuitive assessment of patient's status to guide therapy on disease-related outcomes and treatment-related adverse events?
    - No single arm studies available
    - **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies:

Author	Year	Title
Guillevin	2015	The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort
Bourgarit	2005	Deaths occurring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: a retrospective analysis of causes and factors predictive of mortality based on 595 patients
Guillevin	1996	Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients
Kim	2017	Five factor score of more than 1 is associated with relapse during the first 2 year-follow up in patients with eosinophilic granulomatosis with polyangiitis
Samson	2013	Long-term outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) enrolled in two prospective trials
Moosig	2013	A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): monocentric experiences in 150 patients
Vinit	2011	Churg-Strauss syndrome: retrospective study in Burgundian population in France in past 10 years
Gayraud	2001	Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients

- Studies reviewed and excluded:

Author	Year	Title	Comments
C. Pagnoux	2005	Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis,	Mixed pool of patients. Exclude

		Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis	

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Cardiac imaging

- **PICO question 2:** In patients with EGPA, what is the impact of performing cardiac imaging at time of diagnosis and yearly vs. not performing cardiac imaging on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** Cardiac outcomes (e.g., heart failure, myocardial infarction, conduction abnormalities), disease damage, death

38. In patients with EGPA, what is the impact of performing cardiac imaging at time of diagnosis and yearly vs. not performing cardiac imaging on disease-related outcomes and treatment-related adverse events?
    No comparative data available

39. In patients with EGPA, what is the impact of performing cardiac imaging at time of diagnosis and yearly on disease-related outcomes and treatment-related adverse events?
    - Patient important outcomes (Indirect Evidence below)

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention	Results	Comments
Cardiac Outcomes; Cardiac MRI performed in 9 studies, echocardiography in 5 studies, and electrocardiography in 4 studies. CMRI findings include Gadolinium enhancement, LVEF, presence of myocardial edema,	Cereda, 2017	Retrospective, case-control	0	11 patients with EGPA in remission. Compared to 11 heatlhy subjects, matched for age and gender	Cardiac magnetic resonance protocol including functional analysis, and pre and post-contrast tissue characterization was performed	EGPA patients had lower LVEF compared to healthy control (p value 0.02). Late gadolinuim enhancement was positive in 9/11 (82%), 3/11 (27%) myocardial edema was detected, 3/11 (27%) patients had LV thrombus	Indirect. Imagings were done in EPGA patients during remission
	Fijolek, 2016	Retrospective-Prospective	12 months	Total of 33 EGPA patients:	Cardiac MRI scans were performed with the clinical 1.5-T scanner	100% of patients had heart injury in CMR imaging. 87.5% had	Indirect.

cardiomyopathy. All indirect evidence. Please read comments for each study.				21 EGPA had cardiac MRI done during moment of diagnosis, 12 EGPA patients had cardiac MRI done after treatment		myocardial edema, 54.5% had perfusion defects, 100% had late gadolinium enhancement were detected. Of patient who had CMR after treatment (32 patients), Improvement was observed in 81%. Evolution to global fibrosis was found in 35%. 7% of patients had achieved stabilization.	Study included cardiac MR scan on EGPA during diagnosis and also patient who were already treated.
	Yune, 2016	Retrospecti ve chart review	Mean 40.5+/- 12.8 months	16 EGPA patients with active disease	Cardiac MRI were done once during active phase of disease, echocardiography, Electrocardiography	50% of patients had late gadolinium enhancement (LGE) with 87.5% in subendocardial layer. Extent of LGE had significant negative correlation with left ventricular ejection fraction (LVEF,q=-0.723,p=0.043). Presence of LGE was associated with larger end-systolic left ventricle internal dimension (34 vs. 28 mm,p=0.027) and presence of diastolic dysfunction (75 vs. 0%, p=0.008) on echocardiography. One patient developed heart failure 4 years later	Indirect. Cardiac MR were only done once during diagnosis. Cardiac MR not repeated yearly.

						during remission. 14 patients remained free from cardiac problem.	
	Hazebroek, 2015	Prospective, prevalence study	Mean 52 +/- 25 months	50 EGPA patients (study also included 41 GPA patients) in sustained remission	Electrocardiogram, 24-hour holter registration, echocardiography, cardiac MRI	66% of EGPA patients had cardiac involvement even when in remission. Cardiovascular death in 12% EGPA patients	Indirect. Cardiac imagings were done during remission phase, and were only performed once.
	Szczeklik, 2011	Case control	0	20 consecutive EGPA patients in remission, with 20 sex-age matched controls	Electrocardiography, 24-hour holter monitoring, cardiac MRI, echocardiography	90% of EGPA had cardiac involvement. LVEF was lower in EGPA compared to control (p= <0.05). 89% had LGE in all layers of myocardium. Sign of ongoing inflammation and edema were present in 6/19 EGPA patients.	Indirect. Cardiac imagings were done in remission. And were done once only
	Dunogue, 2015	Monocentric retrospective	4.55 years	42 EGPA patients	Cardiac MRI was performed using 1.5T scanner	82.4% had late gadolinium enhancement (LGE) with cardiomyopathy vs 44% without cardiomyopathy (p= 0.024). On follow up, among the 11 patients without cardiomyopathy but with myocardial LGE on the first CMRI, 18.2% developed cardiac complications. Among the 14 patients without cardiomyopathy and without myocardial LGE, only 7.1% developed cardiac complication. No significant differences, in terms of cardiac or general outcome, were	Indirect Some of the patients had already been treated during CMRI

						seen among patients without cardiomyopathy, whetherthey had myocardial LGE lesions or not. Among the 15 patients with cardiomyopathy, 7 patients had improved or normal LGE during follow-up CMRI. improvement of myocardial LGE on follow-up CMRI was significantly associated with the absence of new cardiac complications during follow-up, while the worsening or long-term stabilization of CMRI was significantly associated with the advent of new cardiac events (P = 0.026, using Fischer's test).	
	Dennert , 2010	Case control	0	32 consecutive EGPA patients in stable disease condition. 32 age-sex matched controls	EKG, echocardiography, cardiac MRI	62% prevalence of cardiac involvement in EGPA patients. EKG abnormality in 66% of EGPA patients. Echocardiographic defects in 50% of EGPA pts, Cardiac MRI defects in 62% of EGPA patients. 38% of asymptomatic patients with normal EKG had echocardiographic or cardiac MRI abnormalities.	Indirect. Cardiac imagings were done once only during in remission

						In presence of abnormal cardiac MRI, echocardiography could detect cardiac involvement with 83% sensitivity and 80% specificity	
	Marmursztejn, 2009	Prospective	2.2 years	20 consecutive EGPA patients diagnosed using ACR criteria	Cardiac MRI using 1.5 t Imager Avanto	Cardiac MRI abnormalities with delayed enhancements were detected in 13/20 patients (all 9 symptomatic, 4/11 asymptomatic patients). On follow up, images remained unchanged for 5 of the 6 with CMRI abnormalities and for 1 of the 2 patients with normal CMRI. CMRI lesion progression was seen in 1 patient with a history of cardiac insufficiency but asymptomatic at the time of CMRI. 4 patients whose cardiac involvement was limited to CMRI abnormalities had no EGPA relapse or appearance of cardiac symptoms during follow-up.	Indirect
	Neumann, 2009	Retrospective cross-sectional	Mean 3.9 +/- 4.6 years	49 EGPA patients fulfilled 1990 ACR criteria and/or	Echocardiography, cardiac MRI	59% had endomyocarditis as detected by cardiac MRI, 50% had impaired LV	Indirect. Cardiac imaging was only obtained once. No follow

				Chapel Hill definition		function, 41% had pericardial effusion. Diagnosis of Loffler endocarditis was associated with an even more pronounced reduced left ventricular function (mean LVEF, 43.6% +/-15.4%) compared to patients with cardiac involvement other than endomyocarditis (mean, 57.1% +/-7.6%; p = 0.047)	up imagings were reported. Not all patients had cardiac MRI done
	Wassmuth, 2008	Retrospective	Median 4 years	11 consecutive EGPA patients filfilled 1990 ACR criteria and 1994 Chapel Hill consensus conference, were referred to clinic for clinical suspicion of cardiac involvement	Cardiac MRI. Scans were performed annually	Cardiac MRI detected abnormalities in all patients and had late enhancement lesions in 9 of 11 patients, even in those with normal left ventricular size and function. There was no clear relationship between systolic function and the presence or the extent of fibrotic lesions. On follow up, relapses did occur with recurrent deterioration in LV function in 4 patients, all of whom had late enhancement lesions. Acute episodes of clinical deterioration were paralleled by myocardial edema and	

						increased early contrast enhancement on T1-weighted images. These findings were transient and resolved after escalation of therapy.	
Cardiac outcome	Mavrogeni, 2013	Retropective	2 years	28 EGPA patients, all were diagnosed for more than 3 yrs	Cardiac MRI	Cardiac MRI revealed acute cardiac lesions in 100% ANCA negative EGPA pts with active disease and acute cardiac symptoms, only 1 in asymptomatic ANCA positive EGPA pt. In 2 yrs CMR follow up, 1/3 of CSS with DSF presented LV function deterioration and one died	Indirect. Almost all patients were in remission, and were diagnosed of EGPA for more than 3 years.

- Test Accuracy results:

Author, year	Patient Selection	Risk of bias	Index Test	Risk of bias	Reference Standard	Risk of bias	Flow and timing Rsk of bias	Sens	Low CI	Up CI	Spec	Prevalence
Dunogue, 2015	42 EGPA patients who had consecutively undergone cardiac MRI at diagnosis or during follow up in a referral center were included retrepectively.	Unclear	Index test included myocardial late gadolinium enhacement in cardiac MRI	Low	Reference standard included clinical data, ECG results, troponin, BNP or NT-pro BNP, echocardiography	Low	Low	82.4%	0.59	0.93	56% (0.37-0.73)	

	Some were part of a prospective study											

40. In patients with EGPA, what is the impact of not performing cardiac imaging on disease-related outcomes and treatment-related adverse events?
    - No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single Arm Studies and Test Accuracy Studies:

	Author	Year	Title
Patient Important Outcomes	A. F. Cereda	2017	Comprehensive evaluation of cardiac involvement in eosinophilic granulomatosis with polyangiitis (EGPA) with cardiac magnetic resonance
	J. Fijolek	2017	The significance of cardiac magnetic resonance imaging in detection and monitoring of the treatment efficacy of heart involvement in eosinophilic granulomatosis with polyangiitis patients
	S. Yune	2017	Detecting cardiac involvement with magnetic resonance in patients with active eosinophilic granulomatosis with polyangiitis
	M. R. Hazebroek	2016	Prevalence and prognostic relevance of cardiac involvement in ANCA-associated vasculitis: eosinophilic granulomatosis with polyangiitis and granulomatosis with polyangiitis
	S. Mavrogeni	2016	Cardiac involvement in ANCA (+) and ANCA (-) Churg-Strauss syndrome evaluated by cardiovascular magnetic resonance
	W. Szczeklik	2016	Multimodality assessment of cardiac involvement in Churg-Strauss syndrome patients in clinical remission
	R. M. Dennert	2016	Cardiac involvement in Churg-Strauss syndrome
	J. Marmursztejn	2016	Impact of cardiac magnetic resonance imaging for assessment of Churg-Strauss syndrome: a cross-sectional study in 20 patients
	T. Neumann	2015	Cardiac involvement in Churg-Strauss syndrome: impact of endomyocarditis
	R. Wassmuth	2015	Cardiovascular magnetic resonance imaging detects cardiac involvement in Churg-Strauss syndrome

	R. Wassmuth	2016	Cardiovascular magnetic resonance imaging detects cardiac involvement in Churg-Strauss syndrome
Test Accuracy Study	B. Dunogue	2017	Impact of cardiac magnetic resonance imaging on eosinophilic granulomatosis with polyangiitis outcomes: A long-term retrospective study on 42 patients

- Studies reviewed and excluded:

Author	Year	Title	Comments
J. Marmursztejn	2013	Churg-Strauss syndrome cardiac involvement evaluated by cardiac magnetic resonance imaging and positron-emission tomography: a prospective study on 20 patients	Excluded. Study compared Cardiac MRI with FDG-PET. Does not address PICO question
T. Miszalski-Jamka	2012	The mechanics of left ventricular dysfunction in patients with Churg-Strauss syndrome	Exclude. Heart echo were only used to study the mechanics of LV dysfunction. Does not address PICO questions
G. Pela	2006	Cardiac involvement in the Churg-Strauss syndrome	Excluded. Study only discussed echocardiographic parameters of EGPA vs control patients. Does not address PICO
S. Greulich	2017	T1 and T2 mapping for evaluation of myocardial involvement in patients with ANCA-associated vasculitides	Exclude. Does not address PICO question

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remisison induction

- **PICO question 3:** In patients with active severe EGPA, what is the impact of using pulse intravenous vs. high-dose oral glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, serious adverse events, toxicity leading to discontinuation (e.g., hyperglycemia, decreased bone mineral density)

41. In patients with active severe EGPA, what is the impact of using pulse intravenous vs. high-dose oral glucocorticoids on disease-related outcomes and treatment-related adverse events?
    No comparative data available

42. In patients with active severe EGPA, what is the impact of using pulse intravenous glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - Patient important outcomes:

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Disease Activity	Cohen P, 2007	Prospective, multicenter, randomized controlled trial in France, Belgium and UK	8 years	48 patients with EGPA. All patients had biopsies showing vasculitis. 79% met ACR criteria. All satisfied CHCC. All patients had ≥ 1 FFS.	All received IV methylprednisolone 15mg/kg/d x 3 days followed by oral prednisone (1mg/kg/d) for 3 weeks followed by taper. Patients were randomized to get either 6 or 12 IV cyclosphamide infusions (0.6gm/m2). IV CYC was given every 2 weeks x 1 month then every 4 weeks.	Complete remission achieved by 42/48 (87.5%) which included 21 (91.3%) in 6 pulse and 21 (84%) in 12 pulse groups. Out of the 6 patients that did not achieve remission, 3 achieved partial remission. Disease free survival and event-free survival were higher in 12 pulse group by KM method.
Relapse	Cohen P, 2007	Prospective, multicenter, randomized controlled trial in France, Belgium and UK	8 years	48 patients with EGPA. All patients had biopsies showing vasculitis. 79% met ACR criteria. All satisfied CHCC. All patients had ≥ 1 FFS.	All received IV methylprednisolone 15mg/kg/d x 3 days followed by oral prednisone (1mg/kg/d) for 3 weeks followed by taper. Patients were randomized to get either 6 or 12 IV cyclosphamide infusions (0.6gm/m2). IV CYC was given every 2 weeks x 1 month then every 4 weeks.	Out of 42 patients who achieved remission: All relapses: 31/41 (73.8%) had at least 1 relapse: 18/21 (85.7%) in 6 pulse and 13/21 (61.9%) in 12 pulse (P=0.07) Major relapses: 18/42 (42.9%) Minor relapses: 20/42 (47.6%). Significantly more minor relapses occurred in 6 pulse regimen (p=0.02).
Death	Cohen P, 2007	Prospective, multicenter, randomized controlled trial in France, Belgium and UK	Mean follow-up 42.5 months	48 patients with EGPA. All patients had biopsies showing vasculitis. 79% met ACR criteria. All satisfied CHCC. All patients had ≥ 1 FFS.	All received IV methylprednisolone 15mg/kg/d x 3 days followed by oral prednisone (1mg/kg/d) for 3 weeks followed by taper. Patients were randomized to get either 6 or 12 IV cyclosphamide infusions (0.6gm/m2). IV CYC was given every 2 weeks x 1 month then every 4 weeks.	4 deaths (8.3%) occurred with no difference between groups.

Infection	Cohen P, 2007	Prospective, multicenter, randomized controlled trial in France, Belgium and UK	Mean follow-up 42.5 months	48 patients with EGPA. All patients had biopsies showing vasculitis. 79% met ACR criteria. All satisfied CHCC. All patients had ≥ 1 FFS.	All received IV methylprednisolone 15mg/kg/d x 3 days followed by oral prednisone (1mg/kg/d) for 3 weeks followed by taper. Patients were randomized to get either 6 or 12 IV cyclosphamide infusions (0.6gm/m2). IV CYC was given every 2 weeks x 1 month then every 4 weeks.	21 infections (unclear how many patients, It is difficult to draw conclusion)
Serious Adverse Events	Cohen P, 2007	Prospective, multicenter, randomized controlled trial in France, Belgium and UK	Mean follow-up 42.5 months	48 patients with EGPA. All patients had biopsies showing vasculitis. 79% met ACR criteria. All satisfied CHCC. All patients had ≥ 1 FFS.	All received IV methylprednisolone 15mg/kg/d x 3 days followed by oral prednisone (1mg/kg/d) for 3 weeks followed by taper. Patients were randomized to get either 6 or 12 IV cyclosphamide infusions (0.6gm/m2). IV CYC was given every 2 weeks x 1 month then every 4 weeks.	SAE: 24/48 (50%) of patients with no significant difference between groups.
Toxicity leading to discontinuat oin	Cohen P, 2007	Prospective, multicenter, randomized controlled trial in France, Belgium and UK	Mean follow-up 42.5 months	48 patients with EGPA. All patients had biopsies showing vasculitis. 79% met ACR criteria. All satisfied CHCC. All patients had ≥ 1 FFS.	All received IV methylprednisolone 15mg/kg/d x 3 days followed by oral prednisone (1mg/kg/d) for 3 weeks followed by taper. Patients were randomized to get either 6 or 12 IV cyclosphamide infusions (0.6gm/m2). IV CYC was given every 2 weeks x 1 month then every 4 weeks.	Treatment related SAE: 24/48 (50%) of patients experienced 52 treatment side effects.

43. In patients with active severe EGPA, what is the impact of using. high-dose oral glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - No single arm data available

- **References:**

- Randomized controlled trials:

None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:

Author	Year	Title
Gullevin	1988	Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angiitis: a study in 165 patients
Cohen	2007	Treatment of Churg Strauss syndrome (css) with poor prognosis factor(s): a prospective, randomized, multicenter trial comparing corticosteroids (cs) and 6 vs 12 cyclophosphamide

- Studies reviewed and excluded:

Author	Year	Title	Comments
L. Guillevin	1999	Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients	Exclude: The regimen of glucocorticoids (i.e., IV versus oral) was not well defined. The outcomes are not subgrouped based on what glucocorticoid regiment was received.
L. Guillevin	1992	Lack of superiority of steroids plus plasma exchange to steroids alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome. A prospective, randomized trial in 78 patients	Exclude, minority of patients with EGPA
L. C. Chumbley	1977	Allergic granulomatosis and angiitis (Churg-Strauss syndrome). Report and analysis of 30 cases	Exclude: Paper does not define the dose or the route (IV vs oral) of glucocorticoids.
N. Tsurikisawa	2017	Longterm Prognosis of 121 Patients with Eosinophilic Granulomatosis with Polyangiitis in Japan	Exclude: Paper includes EGPA patients that did and did not get IV pulse glucocorticoids, however, the data is not stratified based on whether they got IV pulse glucocorticoids.

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission induction

- **PICO question 4:** In patients with active severe EGPA, what is the impact of using rituximab vs. cyclophosphamide for remission induction on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypogammaglobulinemia)

44. In patients with active severe EGPA, what is the impact of using rituximab vs. cyclophosphamide for remission induction on disease-related outcomes and treatment-related adverse events?
    - Patient Important Outcomes

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX	CYC	Relative (95% CI)	Absolute (95% CI)	
Relapse Free Survival After Remission Induction within 30 months											
1	observational studies	not serious	not serious	not serious	serious [a]	none	4/14 (28.6%)	6/14 (42.9%)	**OR 0.53** (0.11 to 2.56)	**144 fewer per 1,000** (from 352 fewer to 229 more)	⊕◯◯◯ VERY LOW
Adverse Events											
1	observational studies	not serious	not serious	not serious	serious [a]	none	3/14 (21.4%)	4/14 (28.6%)	**OR 0.68** (0.12 to 3.83)	**72 fewer per 1,000** (from 240 fewer to 319 more)	⊕◯◯◯ VERY LOW

45. In patients with active severe EGPA, what is the impact of using rituximab for remission induction on disease-related outcomes and treatment-related adverse events?

Outcomes	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Outcome 1: Disease treatment	Moham mad, 2016	Retrospective study	12 months	41 subjects with diagnosis of EGPA who were treated with rituximab between	19 subjects received one course of rituxan. 22 subjects got 2 or 3 courses.	By 6 months, 83% improved with remission in 34% and partial response in 49%.

outcome/ disease activity				2003 and 2013 at four centres 15 refractory disease 21 relapsing disease 5 Initial induction tx EGPA was dx using 1990 ACR classification criteria	Data collection at 0,3,6,9,12 months Outcome was disease remission w BVAS=0. Remission was defined as a BVAS of zero. Partial response was defined as reduction of ≥50% in the BVAS compared with baseline score	By 12 months, 49% were in remission and 39% had a partial response. Prednisolone doses decreased in all patients by 6 and 12 months.
Outcome 2: Treatment adverse events	Moham mad, 2016	Retrospective study	12 months	41 subjects with diagnosis of EGPA who were treated with rituximab between 2003 and 2013 at four centres 15 refractory disease 21 relapsing disease 5 Initial induction tx EGPA was dx using 1990 ACR classification criteria	19 subjects received one course of rituxan. 22 subjects got 2 or 3 courses. Data collection at 0,3,6,9,12 months Outcome was disease remission w BVAS=0. Remission was defined as a BVAS of zero. Partial response was defined as reduction of ≥50% in the BVAS compared with baseline score	At 1 year, there were 31 adverse events. Includes 15 infections (6 were severe). No cases of rituximab-related late-onset leukopenia. No deaths occurred within 1 year.

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

Author	Year	Title
J. Thiel	2017	Rituximab as Induction Therapy in Eosinophilic Granulomatosis with Polyangiitis Refractory to Conventional Immunosuppressive Treatment: A 36-Month Follow-Up Analysis

- Single arm studies:

Author	Year	Title
Mohammad AJ	2016	Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss).

- Comments:

Author	Year	Title	Comment
Novikov P, et al.	2016	Rituximab as induction therapy in relapsing eosinophilic granulomatosis with polyangiitis: A report of 6 cases.	Exclude, less than 10 subjects
Thiel J, et al	2013	Rituximab in the treatment of refractory or relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).	Exclude. Only has 9 subjects

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission Induction

- **PICO question 5:** In patients with active severe EGPA, what is the impact of using mepolizumab plus glucocorticoids vs. glucocorticoids alone on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, serious adverse events, toxicity leading to discontinuation (e.g., hyperglycemia, decreased bone mineral density)

46. In patients with active severe EGPA, what is the impact of using mepolizumab plus glucocorticoids vs. glucocorticoids alone on disease-related outcomes and treatment-related adverse events?

47. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mepolizumab plus glucocorticoids	glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)		
Remission at week 36												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	13/68 (19.1%)	1/68 (1.5%)	**OR 15.84** (2.01 to 124.87)	**177 more per 1,000** (from 14 more to 636 more)	⨁⨁⨁◯ MODERATE	
EGPA relapse												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	38/68 (55.9%)	56/68 (82.4%)	**OR 0.27** (0.12 to 0.60)	**266 fewer per 1,000** (from 465 fewer to 87 fewer)	⨁⨁⨁◯ MODERATE	
Serious adverse events (most commonly exacerbation or worsening of asthma)												

47. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mepolizumab plus glucocorticoids	glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	12/68 (17.6%)	18/68 (26.5%)	**OR 0.60** (0.26 to 1.36)	**87 fewer per 1,000** (from 179 fewer to 64 more)	⨁⨁◯◯ LOW	

Death

1	randomised trials	not serious	not serious	not serious	very serious [a]	none	1/68 (1.5%)	0/68 (0.0%)	**OR 3.04** (0.12 to 76.06)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth

- **References:**

- Randomized controlled trials:

Author	Year	Title
M. E. Wechsler	2017	Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission induction

- **PICO question 6:** In patients with active severe EGPA, what is the impact of using mepolizumab vs. rituximab for remission induction on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, serious adverse events, toxicity leading to discontinuation (e.g., hypogammaglobulinemia)

48. In patients with active severe EGPA, what is the impact of using mepolizumab vs. rituximab for remission induction on disease-related outcomes and treatment-related adverse events?
    No comparative data available

49. In patients with active severe EGPA, what is the impact of using mepolizumab for remission induction on disease-related outcomes and treatment-related adverse events?

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Disease activity: The results can't be compared to the CYC studies both because of the population and asthma was considered as part of disease control.	Wechsler ME, 2017	Randomized, placebo-controlled double-blinded, parallel group, multicenter phase 3 trial	52 weeks	151 Relapsing or refractory EGPA defined as asthma, eosinophilia and 2 or more criteria (features typical of EGPA). Patients with life or organ threatening manifestations (i.e., severe manifestations) were excluded. Participatents recruited from 2014 to 2015. Did not include patients with severe disease	300mg SQ monthly Mepolizumab versus placebo on top of standard of care. A total of 151 patients were recruited with 68 randomly assigned to Mepolizumab group.	Achieved remission (defined as BVAS of 0 and ≤ 4mg/d prednisone or prednisolone): 36/68 (52.9%)
Death	Wechsler ME, 2017	Randomized, placebo-controlled double-blinded, parallel group, multicenter phase 3 trial	52 weeks	151 Relapsing or refractory EGPA defined as asthma, eosinophilia and 2 or more criteria (features typical of EGPA). Patients with life or organ threatening manifestations (i.e., severe manifestations) were excluded. Participatents recruited from 2014 to 2015. Did not include patients with severe disease	300mg SQ monthly Mepolizumab versus placebo on top of standard of care. A total of 151 patients were recruited with 68 randomly assigned to Mepolizumab group.	Death: 1/68 (1.5%) which was due to cardiac arrest deemed not related to the trial regimen.

SAE and Toxicity leading to discontinuation: SAE (4%) were much lower than in the CYC group, however, this may be related to the higher doses of glucocorticoids required for severe disease in the CYC studies. Asthma exacerbation was lower in Mepolizumab compared to placebo.	Wechsler ME, 2017	Randomized, placebo-controlled double-blinded, parallel group, multicenter phase 3 trial	52 weeks	151 Relapsing or refractory EGPA defined as asthma, eosinophilia and 2 or more criteria (features typical of EGPA). Patients with life or organ threatening manifestations (i.e., severe manifestations) were excluded. Participatents recruited from 2014 to 2015. Did not include patients with severe disease.	300mg SQ monthly Mepolizumab versus placebo on top of standard of care. A total of 151 patients were recruited with 68 randomly assigned to Mepolizumab group.	All SAE: 12/68 (18%) SAE related to trial agent: 3/68 (4%) Events leading to trial agent discontinuation or trial withdrawal: 2/68 (3%) Exacerbation or worsening of asthma as SAE: 2/68 (3%) which was less than seen in placebo (6%)

50. In patients with active severe EGPA, what is the impact of using rituximab for remission induction on disease-related outcomes and treatment-related adverse events?

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease activity: Among 99 patients the majority of patients were able to achieve at least a partial reponse. This response seems to	Mohammad AJ, 2014	Retrospective, multicenter study	Median follow-up not included, but results are reported at 6 and 12 months after initial Rituximab.	41 EGPA patients meeting the 1990 ACR criteria. The majority were refractory (37%) or relapsing (51%). All were treated with RTX between 2003-2013.	Initial Rituximab dosing was either 375mg/m2 x 4 (n=10) or 1,000mg x 2 (n=30) or 800mg x 2 (n=1). 19/41 (46.3%) were given a single course of RTX. Retreatment was given to 22/41 (53.7%) at 6 months and 17/41 (41.5%) got an additional dose at 12 months (subsequent dosing regimen variable). Mean prednisone/prednisolone	Remission rates: 6 months: 14/41 (34%) 12 months: 20/41 (49%) Remission or partial response: 6 months: 34/41 (82.9%) 12 months: 36/41 (87.8%) Remission at 12 months statified by ANCA status: ANCA +: 12/15 (80%)	Indirect: This population includes a mixture of severe and nonsevere EGPA and does not stratify by disease severity.

be better in ANCA-positive patients.					dose was 15mg/d (IQR 10-30mg) at baseline.	ANCA -: 8/21 (38%) (p=0.013) (unclear why denominator is not 41)	
	Thiel J, 2017	Retrospective, single center study	Median f/u after RTX 48 months (IQR 15-67.25)	28 EGPA patients (14 treated with RTX) who met 1990 ACR criteria and had at least 12 months follow-up. All but 1/14 had FFS of at least 1 (severe disease).	Initial RTX regiment was 1,000mg x 2, 2 weeks apart. Median prednisone dose at baseline was 22.5mg/d (IQR 14-32.5mg)	Complete remission in 5/14 (35.7%). Complete or partial response: 14/14 (100%)	Indirect: The population includes primarily patients with severe EGPA.
	Teixiera, V	Retrospective, single center study	A standardised dataset was collected at time of initial treatment and every 3 months for 24 months.	EGPA patients from a tertiary centre who received rituximab for mostly refractory EGPA or in whom cyclophosphamide was contraindicated were studied.	Sixty-nine patients (44 female) received rituximab. Response was defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 and partial response as ≥50% reduction in BVAS from baseline. Remission was defined as a BVAS of 0 on prednisolone dose ≤5 mg.	Improvement (response and partial response) was observed in 76.8% of patients at 6 months, 82.8% at 12 months and in 93.2% by 24 months	Indirect: The population includes primarily patients with severe EGPA.
Relapse: Among 55 patients the relapse rate was highly variable (12-80%) making interpretation difficult.	Mohammad AJ, 2014	Retrospective, multicenter study	Median follow-up not included, but results are reported at 6 and 12 months after initial	41 EGPA patients meeting the 1990 ACR criteria. The majority were refractory (37%) or relapsing (51%). All were treated with RTX between 2003-2013.	Initial Rituximab dosing was either 375mg/m2 x 4 (n=10) or 1,000mg x 2 (n=30) or 800mg x 2 (n=1). 19/41 (46.3%) were given a single course of RTX. Retreatment was given to 22/41 (53.7%) at 6 months and 17/41 (41.5%) got an additional dose at 12 months (subsequent dosing	Realpse rate at 12 months among patients who improved at 6 months: 4/34 (12%)	Indirect: This population includes a mixture of severe and nonsevere EGPA and does not stratify by disease severity.

			Rituximab.		regimen variable). Mean prednisone/prednisolone dose was 15mg/d (IQR 10-30mg) at baseline.		
	Thiel J, 2017	Retrospective, single center study	Median f/u after RTX 48 months (IQR 15-67.25)	28 EGPA patients (14 treated with RTX) who met 1990 ACR criteria and had at least 12 months follow-up. All but 1/14 had FFS of at least 1 (severe disease).	Initial RTX regiment was 1,000mg x 2, 2 weeks apart. Median prednisone dose at baseline was 22.5mg/d (IQR 14-32.5mg)	4 relapses (80% of those entering remission) with 3 minor and 1 major	Indirect: The population includes primarily patients with severe EGPA.
Death: Among 41 EGPA patients with relapsing/refractory disease no deaths at 12 months.	Mohammad AJ, 2014	Retrospective, multicenter study	Median follow-up not included, but results are reported at 6 and 12 months after initial Rituximab.	41 EGPA patients meeting the 1990 ACR criteria. The majority were refractory (37%) or relapsing (51%). All were treated with RTX between 2003-2013.	Initial Rituximab dosing was either 375mg/m2 x 4 (n=10) or 1,000mg x 2 (n=30) or 800mg x 2 (n=1). 19/41 (46.3%) were given a single course of RTX. Retreatment was given to 22/41 (53.7%) at 6 months and 17/41 (41.5%) got an additional dose at 12 months (subsequent dosing regimen variable). Mean prednisone/prednisolone dose was 15mg/d (IQR 10-30mg) at baseline.	No deaths at 12 months follow-up	Indirect: This population includes a mixture of severe and nonsevere EGPA and does not stratify by disease severity.
Malignancy: 1 study with 28 EGPA patients treated with RTX showed a malignancy	Thiel J, 2017	Retrospective, single center study	Median f/u after RTX 48 months (IQR 15-67.25)	28 EGPA patients (14 treated with RTX) who met 1990 ACR criteria and had at least 12 months follow-up. All but 1/14 had FFS of at least 1 (severe disease).	Initial RTX regiment was 1,000mg x 2, 2 weeks apart. Median prednisone dose at baseline was 22.5mg/d (IQR 14-32.5mg)	1/14 (7.1%) malignancy (prostate carcinoma) occurred.	Indirect: The population includes primarily patients with severe EGPA.

rate of 7% at 48 months. The malignancy was likely not related to Rituximab.							
Infection: Among 55 patients, there were 14 patients that developed infections (25.5%)	Mohammad AJ, 2014	Retrospective, multicenter study	Median follow-up not included, but results are reported at 6 and 12 months after initial Rituximab.	41 EGPA patients meeting the 1990 ACR criteria. The majority were refractory (37%) or relapsing (51%). All were treated with RTX between 2003-2013.	Initial Rituximab dosing was either 375mg/m2 x 4 (n=10) or 1,000mg x 2 (n=30) or 800mg x 2 (n=1). 19/41 (46.3%) were given a single course of RTX. Retreatment was given to 22/41 (53.7%) at 6 months and 17/41 (41.5%) got an additional dose at 12 months (subsequent dosing regimen variable). Mean prednisone/prednisolone dose was 15mg/d (IQR 10-30mg) at baseline.	15 Infections (both mild and severe) occurred in 14 patients (34.1%). Six serious infections (? # patients) occurred.	Indirect: This population includes a mixture of severe and nonsevere EGPA and does not stratify by disease severity.
	Thiel J, 2017	Retrospective, single center study	Median f/u after RTX 48 months (IQR 15-67.25)	28 EGPA patients (14 treated with RTX) who met 1990 ACR criteria and had at least 12 months follow-up. All but 1/14 had FFS of at least 1 (severe disease).	Initial RTX regiment was 1,000mg x 2, 2 weeks apart. Median prednisone dose at baseline was 22.5mg/d (IQR 14-32.5mg)	No major infections reported.	Indirect: The population includes primarily patients with severe EGPA.
Adverse events + Toxicity leading to	Mohammad AJ, 2014	Retrospective, multicenter study	Median follow-up not included, but	41 EGPA patients meeting the 1990 ACR criteria. The majority were refractory (37%) or	Initial Rituximab dosing was either 375mg/m2 x 4 (n=10) or 1,000mg x 2 (n=30) or 800mg x 2 (n=1). 19/41 (46.3%)	31 adverse events in 21/41 (51%)	Indirect: This population includes a mixture of severe and nonsevere EGPA and does not

discontinuation: Among 55 patients adverse events occurred in 50% of patients or more (both nonsevere and severe). Hypogammaglobulinemia seems to be a frequent side effect.			results are reported at 6 and 12 months after initial Rituximab.	relapsing (51%). All were treated with RTX between 2003-2013.	were given a single course of RTX. Retreatment was given to 22/41 (53.7%) at 6 months and 17/41 (41.5%) got an additional dose at 12 months (subsequent dosing regimen variable). Mean prednisone/prednisolone dose was 15mg/d (IQR 10-30mg) at baseline.		stratify by disease severity.
	Thiel J, 2017	Retrospective, single center study	Median f/u after RTX 48 months (IQR 15-67.25)	28 EGPA patients (14 treated with RTX) who met 1990 ACR criteria and had at least 12 months follow-up. All but 1/14 had FFS of at least 1 (severe disease).	Initial RTX regiment was 1,000mg x 2, 2 weeks apart. Median prednisone dose at baseline was 22.5mg/d (IQR 14-32.5mg)	7/14 (50%) developed hypogammaglobulinemia. 3 of these were both IgG and IgM. 2 patients required replacement immunoglobulin therapy.	Indirect: The population includes primarily patients with severe EGPA.

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:

Author	**Year**	**Title**
Mohammad AJ et al.	2014	Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Thiel J et al.	2017	Rituximab as induction therapy in Eosinophilic Granulomatosis with Polyangiitis refractory to conventional immunosuppressive treatment: a 36-month follow-up analysis.

Teixeira	2019	Efficacy and safety of rituximab in the treatment of eosinophilic granulomatosis with polyangiitis.
Wechsler	2017	Mepolizumab or Placebo for Eosinophilic Granulomatosis with polyangiitis

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission induction

- **PICO question 7:** In patients with active severe EGPA, what is the impact of using mepolizumab vs. cyclophosphamide for remission induction in disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypogammaglobulinemia)

51. In In patients with active severe EGPA, what is the impact of using mepolizumab vs. cyclophosphamide for remission induction in disease-related outcomes and treatment-related adverse events?
    No comparative data available

52. In In patients with active severe EGPA, what is the impact of using mepolizumab for remission induction in disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results
Disease activity: The results can't be compared to the CYC studies both because of the population and asthma was considered as part of disease control.	Wechsler ME, 2017	Randomized, placebo-controlled double-blinded, parallel group, multicenter phase 3 trial	52 weeks	151 Relapsing or refractory EGPA defined as asthma, eosinophilia and 2 or more criteria (features typical of EGPA). Patients with life or organ threatening manifestations (i.e., severe manifestations) were excluded. Participatents recruited from 2014 to 2015. Did not include patients with severe disease	300mg SQ monthly Mepolizumab versus placebo on top of standard of care. A total of 151 patients were recruited with 68 randomly assigned to Mepolizumab group.	Achieved remission (defined as BVAS of 0 and ≤ 4mg/d prednisone or prednisolone): 36/68 (52.9%)

Death	Wechsler ME, 2017	Randomized, placebo-controlled double-blinded, parallel group, multicenter phase 3 trial	52 weeks	151 Relapsing or refractory EGPA defined as asthma, eosinophilia and 2 or more criteria (features typical of EGPA). Patients with life or organ threatening manifestations (i.e., severe manifestations) were excluded. Participatents recruited from 2014 to 2015. Did not include patients with severe disease	300mg SQ monthly Mepolizumab versus placebo on top of standard of care. A total of 151 patients were recruited with 68 randomly assigned to Mepolizumab group.	Death: 1/68 (1.5%) which was due to cardiac arrest deemed not related to the trial regimen.
SAE and Toxicity leading to discontinuation: SAE (4%) were much lower than in the CYC group, however, this may be related to the higher doses of glucocorticoids required for severe disease in the CYC studies. Asthma exacerbation was lower in Mepolizumab compared to placebo.	Wechsler ME, 2017	Randomized, placebo-controlled double-blinded, parallel group, multicenter phase 3 trial	52 weeks	151 Relapsing or refractory EGPA defined as asthma, eosinophilia and 2 or more criteria (features typical of EGPA). Patients with life or organ threatening manifestations (i.e., severe manifestations) were excluded. Participatents recruited from 2014 to 2015. Did not include patients with severe disease.	300mg SQ monthly Mepolizumab versus placebo on top of standard of care. A total of 151 patients were recruited with 68 randomly assigned to Mepolizumab group.	All SAE: 12/68 (18%) SAE related to trial agent: 3/68 (4%) Events leading to trial agent discontinuation or trial withdrawal: 2/68 (3%) Exacerbation or worsening of asthma as SAE: 2/68 (3%) which was less then seen in placebo (6%)

53. In In patients with active severe EGPA, what is the impact of using cyclophosphamide for remission induction in disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results

Disease activity: 3 studies including 72 EGPA patients showed complete or partial response in 50-100%, however, it is not clear that asthma exacebation was considered.	Cohen P, 2007	Prospective, multicenter, randomized controlled trial in France, Belgium and UK	8 years	48 patients with EGPA. All patients had biopsies showing vasculitis. 79% met ACR criteria. All satisfied CHCC. All patients had ≥ 1 FFS.	All received IV methylprednisolone 15mg/kg/d x 3 days followed by oral prednisone (1mg/kg/d) for 3 weeks followed by taper. Patients were randomized to get either 6 or 12 IV cyclosphamide infusions (0.6gm/m2). IV CYC was given every 2 weeks x 1 month then every 4 weeks.	Complete remission achieved by 42/48 (87.5%) which included 21 (91.3%) in 6 pulse and 21 (84%) in 12 pulse groups. Out of the 6 patients that did not achieve remission 3 achieved partial remission. Disease free survival and event-free survival were higher in 12 pulse group by KM method.
	Pagnoux, 2015	RCT; however, for PICO, functions as single arm	3 years	14 EGPA patients with newly diagnosed disease, fulfilling 1990 ACR criteria and/or 1994 CHCC, and at least 65 years old.	Both treatment arms got IV CYC. Experimental arm got corticosteroids for about 9 months and max of six 500mg IV CYC every 2-3 weeks then changed to maintenance. Control arm got approx. 26 mon corticosteroids combined with 500mg/m2 IV CYC every 2-3 weeks until remission, then maintenance therapy for those with FFS≥1.	Complete or partial response in 14/14 (100%)
	Ribi, 2008	Randomized trial, but for PICO, functions as case series	Mean follow-up 56.2mon±31.7	10 patients with newly diagnosed EGPA meeting either ACR criteria or confirmed by biopsy and having a FFS of 0. Done in France and Belgium. All these patients had relapsing or refractory disease to glucocorticoid monotherapy during the trial.	Glucocorticoids and cyclophosphamide IV for 6 pulses (600mg/m2 every 2 weeks for 1 month, then every 4 weeks thereafter)	Remission achieved in 5/5 (50%) of patients
Relapse: 2 studies including 62 patients with EGPA showed a relapse rate of 36-74%.	Cohen P, 2007	Prospective, multicenter, randomize	8 years	48 patients with EGPA. All patients had biopsies showing vasculitis. 79% met ACR criteria. All satisfied CHCC. All patients had ≥ 1 FFS.	All received IV methylprednisolone 15mg/kg/d x 3 days followed by oral prednisone (1mg/kg/d) for 3 weeks followed by taper.	Out of 42 patients who achieved remission: All relapses: 31/41 (73.8%) had at least 1 relapse: 18/21 (85.7%)

		d controlled trial in France, Belgium and UK			Patients were randomized to get either 6 or 12 IV cyclosphamide infusions (0.6gm/m2). IV CYC was given every 2 weeks x 1 month then every 4 weeks.	in 6 pulse and 13/21 (61.9%) in 12 pulse (P=0.07) Major relapses: 18/42 (42.9%) Minor relapses: 20/42 (47.6%). Significantly more minor relapses occurred in 6 pulse regimen (p=0.02).
	Pagnoux, 2015	RCT; however, for PICO, functions as single arm	3 years	14 EGPA patients with newly diagnosed disease, fulfilling 1990 ACR criteria and/or 1994 CHCC, and at least 65 years old.	Both treatment arms got IV CYC. Experimental arm got corticosteroids for about 9 months and max of six 500mg IV CYC every 2-3 weeks then changed to maintenance. Control arm got approx. 26 mon corticosteroids combined with 500mg/m2 IV CYC every 2-3 weeks until remission, then maintenance therapy for those with FFS≥1.	5/14 (35.7%)
Death: 2 studies including 62 patients with EGPA showed a mortality rate from 0-8.3%.	Cohen P, 2007	Prospective, multicenter, randomized controlled trial in France, Belgium and UK	Mean follow-up 42.5 months	48 patients with EGPA. All patients had biopsies showing vasculitis. 79% met ACR criteria. All satisfied CHCC. All patients had ≥ 1 FFS.	All received IV methylprednisolone 15mg/kg/d x 3 days followed by oral prednisone (1mg/kg/d) for 3 weeks followed by taper. Patients were randomized to get either 6 or 12 IV cyclosphamide infusions (0.6gm/m2). IV CYC was given every 2 weeks x 1 month then every 4 weeks.	4 deaths (8.3%) occurred with no difference between groups.
	Pagnoux, 2015	RCT; however, for PICO, functions as single arm	3 years	14 EGPA patients with newly diagnosed disease, fulfilling 1990 ACR criteria and/or 1994 CHCC, and at least 65 years old.	Both treatment arms got IV CYC. Experimental arm got corticosteroids for about 9 months and max of six 500mg IV CYC every 2-3 weeks then changed to maintenance. Control arm got approx. 26	0/14 (none)

					mon corticosteroids combined with 500mg/m2 IV CYC every 2-3 weeks until remission, then maintenance therapy for those with FFS≥1.	
Infection: No clear conclusion can be drawn as the number of patients with infections was not reported.	Cohen P, 2007	Prospective, multicenter, randomized controlled trial in France, Belgium and UK	Mean follow-up 42.5 months	48 patients with EGPA. All patients had biopsies showing vasculitis. 79% met ACR criteria. All satisfied CHCC. All patients had ≥ 1 FFS.	All received IV methylprednisolone 15mg/kg/d x 3 days followed by oral prednisone (1mg/kg/d) for 3 weeks followed by taper. Patients were randomized to get either 6 or 12 IV cyclosphamide infusions (0.6gm/m2). IV CYC was given every 2 weeks x 1 month then every 4 weeks.	21 infections (unclear how many patients)
Toxicity leading to discontinuation: 2 studies including 62 patients with EGPA showed SAE seen in 50-71% of patients.	Cohen P, 2007	Prospective, multicenter, randomized controlled trial in France, Belgium and UK	Mean follow-up 42.5 months	48 patients with EGPA. All patients had biopsies showing vasculitis. 79% met ACR criteria. All satisfied CHCC. All patients had ≥ 1 FFS.	All received IV methylprednisolone 15mg/kg/d x 3 days followed by oral prednisone (1mg/kg/d) for 3 weeks followed by taper. Patients were randomized to get either 6 or 12 IV cyclosphamide infusions (0.6gm/m2). IV CYC was given every 2 weeks x 1 month then every 4 weeks.	SAE: 24/48 (50%) of patients with no significant difference between groups. Treatment related SE: 24/48 (50%) of patients experienced 52 treatment side effects.
	Pagnoux, 2015	RCT; however, for PICO, functions as single arm	3 years	14 EGPA patients with newly diagnosed disease, fulfilling 1990 ACR criteria and/or 1994 CHCC, and at least 65 years old.	Both treatment arms got IV CYC. Experimental arm got corticosteroids for about 9 months and max of six 500mg IV CYC every 2-3 weeks then changed to maintenance. Control arm got approx. 26 mon corticosteroids combined with 500mg/m2 IV CYC every 2-3 weeks until remission, then maintenance therapy for those with FFS≥1.	10/14 (71.4%) with SAE

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies:

Author	Year	Title
Cohen	2007	Treatment of Churg Strauss syndrome (css) with poor prognosis factor(s): a prospective, randomized, multicenter trial comparing corticosteroids (cs) and 6 vs 12 cyclophosphamide
Wechsler	2017	Mepolizumab or Placebo for Eosinophilic Granulomatosis with polyangiitis
Pagnoux	2015	Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy.
Ribi	2008	Treatment of Churg-Strauss syndrome without poor-prognosis factors: a multicenter, prospective, randomized, open-label study of seventy-two patients.

- Studies reviewed and excluded:

Author	Year	Title	Comments
C. Pagnoux	2015	Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy	Excluded: Study includes 108 patients with GPA, MPA, EGPA and PAN. Only 14 patients (13%) were EGPA and outcome data was not stratified by disease.
F. Moosig	2013	A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): monocentric experiences in 150 patients. Ann Rheum Dis. 2013 Jun;72(6):1011-7	Excluded: The study includes a heterogeneous population including both severe and non-severe disease that were treated with different immunosuppressive medications. Almost 30% did not receive cyclophosphamide. The outcomes are not broken down by severity or treatment the patients received.

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission induction

- **PICO question 8:** In patients with active non-severe EGPA, what is the impact of initiating treatment with azathioprine + glucocorticoids vs. methotrexate + glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hyperglycemia, decreased bone mineral density)

54. In patients with active non-severe EGPA, what is the impact of initiating treatment with azathioprine + glucocorticoids vs. methotrexate + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    No comparative data available

55. In patients with active non-severe EGPA, what is the impact of initiating treatment with azathioprine + glucocorticoids on disease-related outcomes and treatment-related adverse events?

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease Activity: One study including 25 EGPA patients with FFS=0 had 100% initial remission, higher than that seen with methotrexate	Puechal, 2017-2019	RCT; however, functions as case series for PICO	24 months	25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma symptoms + AZA 2mg/kg/d (max 200mg/d).	Initial remission: 25/25 (100%)	Direct evidence: small population, but fits PICO and patients followed prospectively as part of RCT.
Relapse: One study including	Puechal, 2017-2019	RCT; however, functions as	24 months	25 EGPA patients meeting CHCC and	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum	Any relapse: 12/25 (48%)	Direct evidence: small population, but fits PICO and patients followed

25 EGPA patients with FFS=0 had 48%, lower than that seen with methotrexate.		case series for PICO		ACR criteria as well as having FFS=0.	dose to control asthma symptoms + AZA 2mg/kg/d (max 200mg/d).	Major relapse: 4/25 (16%) Minor relapse: 7/25 (28%)	prospectively as part of RCT.
Death: One study with 25 EGPA patients with FFS=0 with mortality rate of 0% at 24 months, similar to that seen with methotrexate.	Puechal, 2017-2019	RCT; however, functions as case series for PICO	24 months	25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma symptoms + AZA 2mg/kg/d (max 200mg/d).	Mortality: 0/25	Direct evidence: small population, but fits PICO and patients followed prospectively as part of RCT.
Toxicity leading to discontinuation: One study with 46 EGPA/MPA/PAN with 17% having SAE related to treatment, higher than that seen with	Puechal, 2017-2019	RCT; however, functions as case series for PICO	24 months	46 EGPA/MPA/PAN patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma symptoms + AZA 2mg/kg/d (max 200mg/d).	SAE related to treatment: 8/46 (17.4%) Any treatment AE: 25/46 (54.3%)	Indirect evidence: data includes a mixed population of EGPA, PAN and MPA

methotrexate.							

56. In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease Activity: One study including 11 patients with EGPA with non-severe disease had remission rate of 55%, lower than that seen with azathioprine.	Metzler, C 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ -threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for induction group and 8mg/d (range 0-15).	Complete remission: 6/11 (54.5%) Complete + partial remission: 8/11 (72.7%)	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative.
Relapse: One study with 11 EGPA with nonsevere disease with a relapse rate of 67%, higher than with	Metzler, C 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ -threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range	4 relapses in 6 patients that achived complete remission (66.7%)	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative. Also of note, patients who achieved remission with methotrexate were

azathioprine.				maintenance were ANCA positive.	5-50) for induction group and 8mg/d (range 0-15).		continued on methotrexate for maintenance.
Death: One study with 11 EGPA patients with nonsevere disease with 0% mortality at mean 48 months f/u, similar to that seen with azathioprine.	Metzler, C 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ-threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for induction group and 8mg/d (range 0-15).	No deaths reported among 11 patients getting methotrexate induction.	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative.
Malignancy: One study with 11 EGPA patients with nonsevere disease showing no malignancies at 48 months.	Metzler, C 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ -threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for induction group and 8mg/d (range 0-15).	No malignancies reported in this limited cohort of 11 patients.	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative.
Infection: One study but does not define how many	Metzler, C 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ -threatening	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as	3 mild to moderate infections (2 URI and 1 UTI). The paper does not	Direct evidence: This is a small population but fits the PICO well.

patients with infection (only absolute number of infections).				disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for induction group and 8mg/d (range 0-15).	define how many patients got infections and does not report any severe infections.	Of note, all the patients getting induction Methotrexate were ANCA negative.
Toxicity leading to discontinuation: One study with 11 EGPA patients with nonsevere disease with 9% developing a SAE related to treatment, lower then that seen with azathioprine.	Metzler C 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ-threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for induction group and 8mg/d (range 0-15).	1/11 developed treatment related toxicity (pneumonitis)	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative.

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:

Author	Year	Title
Metzler	2004	Churg Strauss syndrome - Successful induction of remission with methotrexate and unexpected high cardiac and pulmonary relapse ratio during maintenance treatment
Puechal	2017	Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial.
Puechal	2019	Non-severe eosinophilic granulomatosis with polyangiitis: long term outcomes after remission-induction trial.

- Studies reviewed and excluded:

Author	Year	Title	Comments
A. Della Rossa	2002	Churg-Strauss syndrome: clinical and serological features of 19 patients from a single Italian centre	Exclude: Study included a mixture of patients treated with azathioprine or methotrexate. Outcomes were not stratified by the treatment received.

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission induction

- **PICO question 9:** In patients with active non-severe EGPA, what is the impact of initiating treatment with azathioprine+ glucocorticoids vs. MMF+ glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hyperglycemia, decreased bone mineral density)

57. In patients with active non-severe EGPA, what is the impact of initiating treatment with azathioprine+ glucocorticoids vs. MMF+ glucocorticoids on disease-related outcomes and treatment-related adverse events?
    No comparative data available

58. In patients with active non-severe EGPA, what is the impact of initiating treatment with azathioprine+ glucocorticoids on disease-related outcomes and treatment-related adverse events?

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease Activity: One study including 25 EGPA patients with FFS=0 had 100% initial remission, higher than that seen with methotrexate	Puechal, 2017	RCT; however, functions as case series for PICO	24 months	25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma symptoms + AZA 2mg/kg/d (max 200mg/d).	Initial remission: 25/25 (100%)	Direct evidence: small population, but fits PICO and patients followed prospectively as part of RCT.
Relapse: One study including 25 EGPA patients with FFS=0 had 48%, lower than that seen with methotrexate.	Puechal, 2017	RCT; however, functions as case series for PICO	24 months	25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma symptoms + AZA 2mg/kg/d (max 200mg/d).	Any relapse: 12/25 (48%) Major relapse: 4/25 (16%) Minor relapse: 7/25 (28%)	Direct evidence: small population, but fits PICO and patients followed prospectively as part of RCT.
Death: One study with 25 EGPA patients with FFS=0 with mortality rate of 0% at 24	Puechal, 2017	RCT; however, functions as case series for PICO	24 months	25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma symptoms + AZA 2mg/kg/d (max 200mg/d).	Mortality: 0/25	Direct evidence: small population, but fits PICO and patients followed prospectively as part of RCT.

months, similar to that seen with methotrexate.							
Toxicity leading to discontinuation: One study with 46 EGPA/MPA/PAN with 17% having SAE related to treatment, higher than that seen with methotrexate.	Puechal, 2017	RCT; however, functions as case series for PICO	24 months	46 EGPA/MPA/PAN patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma symptoms + AZA 2mg/kg/d (max 200mg/d).	SAE related to treatment: 8/46 (17.4%) Any treatment AE: 25/46 (54.3%)	Indirect evidence: data includes a mixed population of EGPA, PAN and MPA

59. In patients with active non-severe EGPA, what is the impact of initiating treatment with MMF+ glucocorticoids on disease-related outcomes and treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
    None

- Comparative observational studies:
    None

- Single arm studies and test accuracy studies:

Author	Year	Title
Puechal	2017	Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial.

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission induction

- **PICO question 10:** In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate + glucocorticoids vs. MMF + glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hyperglycemia, decreased bone mineral density)

60. In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate + glucocorticoids vs. MMF + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    No comparative data available

61. In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease activity	Metzler, C 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ-threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for	Complete remission: 6/11 (54.5%) Complete + partial remission: 8/11 (72.7%)	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative.

					induction group and 8mg/d (range 0-15).		
Relapse	Metzler, C 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ-threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for induction group and 8mg/d (range 0-15).	4 relapses in 6 patients that achived complete remission (66.7%)	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative. Also of note, patients who achieved remission with methotrexate were continued on methotrexate for maintenance.
Death	Metzler, C 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ-threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for induction group and 8mg/d (range 0-15).	No deaths reported among 11 patients getting methotrexate induction.	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative.
Malignancy	Metzler, C 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ-threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was	No malignancies reported in this limited cohort of 11 patients.	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative.

				maintenance were ANCA positive.	10mg/d (range 5-50) for induction group and 8mg/d (range 0-15).		
Infection	Metzler, C 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ-threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for induction group and 8mg/d (range 0-15).	3 mild to moderate infections (2 URI and 1 UTI). The paper dose not define how many patients got infections and does not report any severe infections.	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative.
Toxicity leading to discontinuation	Metzler, C 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ-threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for induction group and 8mg/d (range 0-15).	1/11 developed treatment related toxicity (pneumonitis)	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative.

62. In patients with active non-severe EGPA, what is the impact of initiating treatment with MMF + glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:
  None

- Single arm studies:

Author	Year	Title
Metzler	2004	Churg Strauss syndrome - Successful induction of remission with methotrexate and unexpected high cardiac and pulmonary relapse ratio during maintenance treatment

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission induction

- **PICO question 11:** In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate/azathioprine/MMF + glucocorticoids vs. rituximab + glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hyperglycemia, decreased bone mineral density, hypogammaglobulinemia)

63. In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate/azathioprine/MMF + glucocorticoids vs. rituximab + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    No comparative data available

64. In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate/azathioprine/MMF + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease activity: 2 studies with 36 EGPA patients with either FFS=0 or nonsevere	Metzler C, 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ-threatening disease. Enrolled	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as	Complete remission: 6/11 (54.5%) Complete + partial remission: 8/11 (72.7%)	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction

disease with 54-100% achieving full remission, similar to that seen with RTX (49%).				between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for induction group and 8mg/d (range 0-15).		Methotrexate were ANCA negative.
	Puechal, 2017	RCT; however, functions as case series for PICO	24 months	25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma symptoms + AZA 2mg/kg/d (max 200mg/d).	Initial remission: 25/25 (100%)	Direct evidence: small population, but fits PICO and patients followed prospectively as part of RCT.
Relapse: 2 studies with 36 patients with EGPA relapse rate of 48-67% at 24-48 months. The longer follow-up in these studies makes it difficult to compare with RTX.	Metzler C, 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ-threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for induction group and 8mg/d (range 0-15).	4 relapses in 6 patients that achieved complete remission (66.7%)	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative. Also of note, patients who achieved remission with methotrexate were continued on methotrexate for maintenance.
	Puechal, 2017	RCT; however, functions as case series for PICO	24 months	25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma symptoms + AZA	Any relapse: 12/25 (48%) Major relapse: 4/25 (16%) Minor relapse: 7/25 (28%)	Direct evidence: small population, but fits PICO and patients followed prospectively as part of RCT.

					2mg/kg/d (max 200mg/d).		
Death: 2 studies including 36 EGPA patients with FFS=0 or nonsevere disease with mortality rate of 0% at 24-48 months, similar to with RTX but these studies had a longer follow-up.	Metzler C, 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ-threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for induction group and 8mg/d (range 0-15).	No deaths reported among 11 patients getting methotrexate induction.	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative.
	Puechal, 2017	RCT; however, functions as case series for PICO	24 months	25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma symptoms + AZA 2mg/kg/d (max 200mg/d).	Mortality: 0/25	Direct evidence: small population, but fits PICO and patients followed prospectively as part of RCT.
Malignancy: 1 study with 11 patients with EGPA with no malignancies reported at a mean of 48 months follow-up, lower then that seen with Rituximab (7%), however, the malignancy that occurred was	Metzler C, 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ-threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for	No malignancies reported in this limited cohort of 11 patients.	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative.

likely not due to RTX.					induction group and 8mg/d (range 0-15).		
Infection: 1 study with 11 patients with EGPA, however, paper does not report number of patients who developed malignancies (only absolute number of malignancies).	Metzler C, 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ-threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for induction group and 8mg/d (range 0-15).	3 mild to moderate infections (2 URI and 1 UTI). The paper dose not define how many patients got infections and does not report any severe infections.	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative.
Toxicity leading to discontinuation: 2 studies including 57 patients (mix of EGPA, MPA and PAN) with 48% developing any SAE and 9-17% developing SAE related to treatment. Total SAE rate was similar to RTX.	Metzler C, 2004	Open-label, prospective, single center	Median 48 mon	EGPA fulfilling both ACR and CHCC criteria without immediate critical organ -threatening disease. Enrolled between 1995-2000. All receiving induction were ANCA negative. 4/19 receiving MTX maintenance were ANCA positive.	11 patients got induction with methotrexate (0.3mg/kg/wk IV + folinic acid) (9 at initial diagnosis, 2 at relapse). 25 patients got MTX as maintenance (initiated at 7.5mg/wk IV and increased by 2.5mg steps to 0.3mg/kg/wk IV) (including 8 who got the methotrexate induction). Mean prednisone was 10mg/d (range 5-50) for induction group and 8mg/d (range 0-15).	1/11 developed treatment related toxicity (pneumonitis)	Direct evidence: This is a small population but fits the PICO well. Of note, all the patients getting induction Methotrexate were ANCA negative.
	Puechal, 2017	RCT; however, functions as case series for PICO	24 months	46 EGPA/MPA/PAN patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma symptoms + AZA	Any SAE: 22/46 (47.8%) SAE related to treatment: 8/46 (17.4%) Any treatment AE: 25/46 (54.3%)	Indirect evidence: data includes a mixed population of EGPA, PAN and MPA

					2mg/kg/d (max 200mg/d).		

65. In patients with active non-severe EGPA, what is the impact of initiating treatment with rituximab + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease activity: Among 99 patients the majority of patients were able to achieve at least a partial reponse. This response seems to be better in ANCA-positive patients.	Mohammad AJ, 2014	Retrospective, multicenter study	Median follow-up not included, but results are reported at 6 and 12 months after initial Rituximab.	41 EGPA patients meeting the 1990 ACR criteria. The majority were refractory (37%) or relapsing (51%). All were treated with RTX between 2003-2013.	Initial Rituximab dosing was either 375mg/m2 x 4 (n=10) or 1,000mg x 2 (n=30) or 800mg x 2 (n=1). 19/41 (46.3%) were given a single course of RTX. Retreatment was given to 22/41 (53.7%) at 6 months and 17/41 (41.5%) got an additional dose at 12 months (subsequent dosing regimen variable). Mean prednisone/prednisolone dose was 15mg/d (IQR 10-30mg) at baseline.	Remission rates: 6 months: 14/41 (34%) 12 months: 20/41 (49%) Remission or partial response: 6 months: 34/41 (82.9%) 12 mon: 36/41 (87.8%) Remission at 12 months statified by ANCA status: ANCA +: 12/15 (80%) ANCA -: 8/21 (38%) (p=0.013) (unclear why denominator is not 41)	Indirect: This population includes a mixture of severe and nonsevere EGPA and does not stratify by disease severity.
	Thiel J, 2017	Retrospective, single center study	Median f/u after RTX 48 months (IQR 15-67.25)	28 EGPA patients (14 treated with RTX) who met 1990 ACR criteria and had at least 12 months follow-up. All but 1/14 had FFS of at least 1 (severe disease).	Initial RTX regimen was 1,000mg x 2, 2 weeks apart. Median prednisone dose at baseline was 22.5mg/d (IQR 14-32.5mg)	Complete remission in 5/14 (35.7%). Complete or partial response: 14/14 (100%)	Indirect: The population includes primarily patients with severe EGPA.

	Teixiera V	Retrospective, single center study	A standard ised dataset was collected at time of initial tre atment a nd every 3 months for 24 months.	EGPA patients from a tertiary centre who received rituximab for mostly refractory EGPA or in whom cyclophosphamide was contraindicated were studied.	Sixty-nine patients (44 female) received rituximab. Response was defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 and partial response as ≥50% reduction in BVAS from baseline. Remission was defined as a BVAS of 0 on prednisolone dose ≤5 mg.	Improvement (response and partial response) was observed in 76.8% of patients at 6 months, 82.8% at 12 months and in 93.2% by 24 months	Indirect: The population includes primarily patients with severe EGPA.
Relapse: Among 55 patients the relapse rate was highly variable (12-80%) making interpretati on difficult.	Moham mad AJ, 2014	Retrospective, multicenter study	Median follow-up not included, but results are reported at 6 and 12 months after initial Rituxima b.	41 EGPA patients meeting the 1990 ACR criteria. The majority were refractory (37%) or relapsing (51%). All were treated with RTX between 2003-2013.	Initial Rituximab dosing was either 375mg/m2 x 4 (n=10) or 1,000mg x 2 (n=30) or 800mg x 2 (n=1). 19/41 (46.3%) were given a single course of RTX. Retreatment was given to 22/41 (53.7%) at 6 months and 17/41 (41.5%) got an additional dose at 12 months (subsequent dosing regimen variable). Mean prednisone/prednisolone dose was 15mg/d (IQR 10-30mg) at baseline.	Realpse rate at 12 months among patients who improved at 6 months: 4/34 (12%)	Indirect: This population includes a mixture of severe and nonsevere EGPA and does not stratify by disease severity.
	Thiel J, 2017	Retrospective, single center study	Median f/u after RTX 48 months (IQR 15-67.25)	28 EGPA patients (14 treated with RTX) who met 1990 ACR criteria and had at least 12 months follow-up. All but 1/14 had	Initial RTX regimen was 1,000mg x 2, 2 weeks apart. Median prednisone dose at baseline was 22.5mg/d (IQR 14-32.5mg)	4 relapses (80% of those entering remission) with 3 minor and 1 major	Indirect: The population includes primarily patients with severe EGPA.

				FFS of at least 1 (severe disease).			
Death: Among 41 EGPA patients with relapsing/refractory disease no deaths at 12 months.	Mohammad AJ, 2014	Retrospective, multicenter study	Median follow-up not included, but results are reported at 6 and 12 months after initial Rituximab.	41 EGPA patients meeting the 1990 ACR criteria. The majority were refractory (37%) or relapsing (51%). All were treated with RTX between 2003-2013.	Initial Rituximab dosing was either 375mg/m2 x 4 (n=10) or 1,000mg x 2 (n=30) or 800mg x 2 (n=1). 19/41 (46.3%) were given a single course of RTX. Retreatment was given to 22/41 (53.7%) at 6 months and 17/41 (41.5%) got an additional dose at 12 months (subsequent dosing regimen variable). Mean prednisone/prednisolone dose was 15mg/d (IQR 10-30mg) at baseline.	No deaths at 12 months follow-up	Indirect: This population includes a mixture of severe and nonsevere EGPA and does not stratify by disease severity.
Malignancy: 1 study with 28 EGPA patients treated with RTX showed a malignancy rate of 7% at 48 months. The malignancy was likely not related to Rituximab.	Thiel J, 2017	Retrospective, single center study	Median f/u after RTX 48 months (IQR 15-67.25)	28 EGPA patients (14 treated with RTX) who met 1990 ACR criteria and had at least 12 months follow-up. All but 1/14 had FFS of at least 1 (severe disease).	Initial RTX regimen was 1,000mg x 2, 2 weeks apart. Median prednisone dose at baseline was 22.5mg/d (IQR 14-32.5mg)	1/14 (7.1%) malignancy (prostate carcinoma) occurred.	Indirect: The population includes primarily patients with severe EGPA.

Infection: Among 55 patients there were 14 patients that developed infections (25.5%)	Mohammad AJ, 2014	Retrospective, multicenter study	Median follow-up not included, but results are reported at 6 and 12 months after initial Rituximab.	41 EGPA patients meeting the 1990 ACR criteria. The majority were refractory (37%) or relapsing (51%). All were treated with RTX between 2003-2013.	Initial Rituximab dosing was either 375mg/m2 x 4 (n=10) or 1,000mg x 2 (n=30) or 800mg x 2 (n=1). 19/41 (46.3%) were given a single course of RTX. Retreatment was given to 22/41 (53.7%) at 6 months and 17/41 (41.5%) got an additional dose at 12 months (subsequent dosing regimen variable). Mean prednisone/prednisolone dose was 15mg/d (IQR 10-30mg) at baseline.	15 Infections (both mild and severe) occurred in 14 patients (34.1%). Six serious infections (? # patients) occurred.	Indirect: This population includes a mixture of severe and nonsevere EGPA and does not stratify by disease severity.
	Thiel J, 2017	Retrospective, single center study	Median f/u after RTX 48 months (IQR 15-67.25)	28 EGPA patients (14 treated with RTX) who met 1990 ACR criteria and had at least 12 months follow-up. All but 1/14 had FFS of at least 1 (severe disease).	Initial RTX regimen was 1,000mg x 2, 2 weeks apart. Median prednisone dose at baseline was 22.5mg/d (IQR 14-32.5mg)	No major infections reported.	Indirect: The population includes primarily patients with severe EGPA.
Adverse events + Toxicity leading to discontinuation: Among 55 patients adverse events occurred in 50% of patients or more (both	Mohammad AJ, 2014	Retrospective, multicenter study	Median follow-up not included, but results are reported at 6 and 12 months after initial	41 EGPA patients meeting the 1990 ACR criteria. The majority were refractory (37%) or relapsing (51%). All were treated with RTX between 2003-2013.	Initial Rituximab dosing was either 375mg/m2 x 4 (n=10) or 1,000mg x 2 (n=30) or 800mg x 2 (n=1). 19/41 (46.3%) were given a single course of RTX. Retreatment was given to 22/41 (53.7%) at 6 months and 17/41 (41.5%) got an additional dose at 12 months (subsequent dosing regimen variable). Mean	31 adverse events in 21/41 (51%)	Indirect: This population includes a mixture of severe and nonsevere EGPA and does not stratify by disease severity.

nonsevere and severe). Hypogammaglobulinemia seems to be a frequent side effect.			Rituximab.		prednisone/prednisolone dose was 15mg/d (IQR 10-30mg) at baseline.		
	Thiel J, 2017	Retrospective, single center study	Median f/u after RTX 48 months (IQR 15-67.25)	28 EGPA patients (14 treated with RTX) who met 1990 ACR criteria and had at least 12 months follow-up. All but 1/14 had FFS of at least 1 (severe disease).	Initial RTX regimen was 1,000mg x 2, 2 weeks apart. Median prednisone dose at baseline was 22.5mg/d (IQR 14-32.5mg)	7/14 (50%) developed hypogammaglobulinemia. 3 of these were both IgG and IgM. 2 patients required replacement immunoglobulin therapy.	Indirect: The population includes primarily patients with severe EGPA.

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies:

Author	Year	Title
Metzler et al.	2004	Churg Strauss syndrome - Successful induction of remission with methotrexate and unexpected high cardiac and pulmonary relapse ratio during maintenance treatment
Mohammad AJ	2014	Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Thiel J et al.	2017	Rituximab as induction therapy in Eosinophilic Granulomatosis with Polyangiitis refractory to conventional immunosuppressive treatment: a 36-month follow-up analysis.
Puechal	2017	Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial.
Teixeira	2019	Efficacy and safety of rituximab in the treatment of eosinophilic granulomatosis with polyangiitis.

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission induction

- **PICO question 12:** In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate/azathioprine/MMF + glucocorticoids vs. cyclophosphamide + glucocorticoids on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hyperglycemia, decreased bone mineral density)

66. In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate/azathioprine/MMF + glucocorticoids vs. cyclophosphamide + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - No comparative data available

67. In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate/azathioprine/MMF + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention used in relevant population (	Results
Remission-9 of 11 with complete or partial remission. Favors use of MTX in non-severe EGPA for remission induction	Metzler C, 2004	Open label	-	11 patients with non-severe EPGA treated with MTX for induction of remission at initial diagnosis (n-9) and relapse (n=2). Excluded chronic liver disease, alcohol abuse renal insuff (creat >1.5), bone marrow insufficiency active infection and inadequate contraception. 0/11 were ANCA positive. FFS at start=0-1, BVAS 6 (3-11)	MTX of 0.3mg/kg IV weekly with folinic acid on day fter MTX. All patients pre-treated with prednisone. If BVAS>10, pred increased to 1mg/kg/d and tapered by 10mg q 3 days until 20mg/d, then by 2.5mg weekly until 5mg/d, then by 1mg/month if possible. Simultaneous use of other IS not allowed. Clinical and serologic assessment done monthly and then q 3 months after remission	6/11 patients achieved complete remission and 2/11 achieved partial remission *Complete remission=absence of pathologic findings in clinical, radiologic and sero-immunologic investigations Partial remission- partial improvement in disease persisting for at least 3 months. Persisting asthma or isolated inc in eos did not influence remission or relapse defn

Time to remission						Median time of 5 (2-12) months
MTX discontinuation/adverse effects-						11 patients, 1 pneumonitis and 2 infections. Favors using MTX for induction in non-severe EGPA
Prednisone dose						11 patients with ability to taper pred from 10→6.25mg/d by end of study. Prednisone range much better after using MTX. Favors using MTX
Disease Activity: One study including 25 EGPA patients with FFS=0 had 100% initial remission, higher then that seen with methotrexate	Puechal, 2017	RCT, however functions as case series for PICO	24 months	25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma symptoms + AZA 2mg/kg/d (max 200mg/d).	Initial remission: 25/25 (100%)
Relapse: One study including 25 EGPA patients with FFS=0 had 48%, lower then that seen with methotrexate.				25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.		Any relapse: 12/25 (48%) Major relapse: 4/25 (16%) Minor relapse: 7/25 (28%)
Death: One study with 25 EGPA patients with FFS=0 with mortality rate of 0% at 24 months, similar to that seen with methotrexate.				25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.		Mortality: 0/25
Toxicity leading to discontinuation: One study with 46 EGPA/MPA/PAN with 17% having SAE related to treatment, higher then that seen with methotrexate.				46 EGPA/MPA/PAN patients meeting CHCC and ACR criteria as well as having FFS=0.		SAE related to treatment: 8/46 (17.4%) Any treatment AE: 25/46 (54.3%)

68. In patients with active non-severe EGPA, what is the impact of initiating treatment with cyclophosphamide + glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - No Data Avaliable

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Included Single Arm Studies:

Author	Year	Title
Metzler, C.	2004	Churg Strauss syndrome - Successful induction of remission with methotrexate and unexpected high cardiac and pulmonary relapse ratio during maintenance treatment
Puechal	2017	Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial.

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission induction

- **PICO question 13:** In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate/azathioprine/MMF + glucocorticoids vs. mepolizumab + glucocorticoids on disease-related outcomes and treatment related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hyperglycemia, decreased bone mineral density)

69. In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate/azathioprine/MMF + glucocorticoids vs. mepolizumab + glucocorticoids on disease-related outcomes and treatment related adverse events?
    - No comparative data available

70. In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate/azathioprine/MMF + glucocorticoids on disease-related outcomes and treatment related adverse events?
    - **Patient important outcomes (same single arm outcomes reported in PICO 12)**

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention used in relevant population (	Results
Remission-9 of 11 with complete or partial remission. Favors use of MTX in non-severe EGPA for remission induction	Metzler C, 2004	Open label	-	11 patients with non-severe EPGA treated with MTX for induction of remission at initial diagnosis (n-9) and relapse (n=2). Excluded chronic liver disease, alcohol abuse renal insuff (creat >1.5), bone marrow insufficiency active infection and inadequate contraception. 0/11 were ANCA positive. FFS at start=0-1, BVAS 6 (3-11)	MTX of 0.3mg/kg IV weekly with folinic acid on day fter MTX. All patients pre-treated with prednisone. If BVAS>10, pred increased to 1mg/kg/d and tapered by 10mg q 3 days until 20mg/d, then by 2.5mg weekly until 5mg/d, then by 1mg/month if possible. Simultaneous use of other IS not allowed. Clinical and serologic assessment done monthly and then q 3 months after remission	6/11 patients achieved complete remission and 2/11 achieved partial remission *Complete remission=absence of pathologic findings in clinical, radiologic and sero-immunologic investigations Partial remission- partial improvement in disease persisting for at least 3 months. Persisting asthma or isolated inc in eos did not influence remission or relapse defn
Time to remission						Median time of 5 (2-12) months
MTX discontinuation/adverse effects-						11 patients, 1 pneumonitis and 2 infections. Favors using MTX for induction in non-severe EGPA
Prednisone dose						11 patients with ability to taper pred from 10→6.25mg/d by end of study. Prednisone range much better after using MTX. Favors using MTX
Disease Activity: One study including 25 EGPA patients with FFS=0 had 100%	Puechal, 2017	RCT; however, functions as case	24 months	25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose	Initial remission: 25/25 (100%)

initial remission, higher then that seen with methotrexate		series for PICO			to control asthma symptoms + AZA 2mg/kg/d (max 200mg/d).	
Relapse: One study including 25 EGPA patients with FFS=0 had 48%, lower then that seen with methotrexate.				25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.		Any relapse: 12/25 (48%) Major relapse: 4/25 (16%) Minor relapse: 7/25 (28%)
Death: One study with 25 EGPA patients with FFS=0 with mortality rate of 0% at 24 months, similar to that seen with methotrexate.				25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.		Mortality: 0/25
Toxicity leading to discontinuation: One study with 46 EGPA/MPA/PAN with 17% having SAE related to treatment, higher then that seen with methotrexate.				46 EGPA/MPA/PAN patients meeting CHCC and ACR criteria as well as having FFS=0.		SAE related to treatment: 8/46 (17.4%) Any treatment AE: 25/46 (54.3%)

71. In patients with active non-severe EGPA, what is the impact of initiating treatment with mepolizumab + glucocorticoids on disease-related outcomes and treatment related adverse events?
    - No Data Avaliable
    - **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Included Single arm Studies:

Author	Year	Title
Metzler, C.	2004	Churg Strauss syndrome - Successful induction of remission with methotrexate and unexpected high cardiac and pulmonary relapse ratio during maintenance treatment

Puechal	2017	Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial.

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission induction

- **PICO question 14:** In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate/azathioprine/MMF + glucocorticoids vs. glucocorticoids alone on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hyperglycemia, decreased bone mineral density)

72. In patients with active non-severe EGPA, what is the impact of initiating treatment with methotrexate/azathioprine/MMF + glucocorticoids vs. glucocorticoids alone on disease-related outcomes and treatment-related adverse events?

73. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azathioprine + glucocorticoids	glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)		
Remission induction failures and relapses at month 24												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	12/25 (48.0%)	12/26 (46.2%)	**OR 1.08** (0.36 to 3.24)	**19 more per 1,000** (from 226 fewer to 274 more)	⊕⊕◯◯ LOW	
Initial remission												

73. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azathioprine + glucocorticoids	glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	25/25 (100.0%)	25/26 (96.2%)	**OR 3.00** (0.12 to 77.17)	**25 more per 1,000** (from 212 fewer to 38 more)	⊕⊕◯◯ LOW	

Major relapses month 24 [1]

1	randomised trials	not serious	not serious	not serious	very serious [a]	none	4/25 (16.0%)	3/24 (12.5%)	**OR 1.33** (0.27 to 6.70)	**35 more per 1,000** (from 88 fewer to 364 more)	⊕⊕◯◯ LOW	

Minor relapses month 24 [2]

1	randomised trials	not serious	not serious	not serious	very serious [a]	none	7/25 (28.0%)	7/24 (29.2%)	**OR 0.94** (0.27 to 3.26)	**13 fewer per 1,000** (from 192 fewer to 281 more)	⊕⊕◯◯ LOW	

Asthma/rhinosinusitis exacerbation

73. Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azathioprine + glucocorticoids	glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	6/25 (24.0%)	5/26 (19.2%)	**OR 1.33** (0.35 to 5.06)	**48 more per 1,000** (from 115 fewer to 354 more)	⨁⨁◯◯ LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth, leading to very serious imprecision

[1.] major relapse was defined as the recurrence or new onset of potentially organ- or life-threatening disease activity that cannot be treated with glucocorticoid intensification alone and requires further therapeutic escalation

[2.] minor relapse was defined as the recurrence or new onset of manifestations that are not potentially organ- or life-threatening.

- **References:**

- Randomized controlled trials:

Author	Year	Title
X. Puechal	2017	Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission maintanance

- **PICO question 15:** In patients with severe EGPA who have entered remission, what is the impact of using methotrexate vs. azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

74. In patients with severe EGPA who have entered remission, what is the impact of using methotrexate vs. azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?
    - No Comparative data available

75. In patients with severe EGPA who have entered remission, what is the impact of using methotrexate for remission maintenance on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention used in relevant population	Results	Comments
Relapse 12/40 patients with EGPA treated with MTX for remission maintenance experience relapse. Moderately favors using MTX for maintenence	Maritati F, 2018	Single center, open label randomized trial	24 months from remission	71 patients: 30 with EGPA (only included those with FFS>or equal to 1 or with peripheral neuropathy), MPA (n=14) and GPA (n=27) who achieved remission induction with CYC randomized to Cyc (n=33) vs MTX (n=38) for maintenance. 13 EGPA patients randomized to maintenance with CYC and 17 randomized to MTX	All enrolled patients rec'd 3 IV pulse doses of 500mg steroids followed by oral pred (1mg/lg/d) with taper and cytoxan 2mk/kg/d for induction of remission (had to be reached by month 9). Randomized to cyc or MTX using computer at 1:1. Maintenance CYC given at 1.5mg/kg/d while MTX given at 15mg/week, increased until dose of 0.3mg/kg/week (max 20mg/week). IF GFR 30-50ml, rec'd half dose MTX. Maintenance continued for 12 months and patients followed for 24 months	1/17 (6%) of EGPA patients maintained on MTX relapsed at 12 months. 1/17 relapsed at 18 months. 3/17 (18%) relapsed by 24 months	

	Metzler C, 2004	Open label, prospective, monocentric	48 months from start of mainten ance regimen	28 consecutive EGPA patients. 11 induced with MTX. 25 treated for maintenance of remission with methotrexate (including the 8 in whom remission was successfully induced with MTX). Excluded chronic liver disease, creat >1.5, alcohol abuse, BM insufficiency, active infection or insufficient contraception. No life threatening disease. 11 induced with oral cyc, 3 with IV cyc, one with AZA and 8 with MTX. 15 were in complete remission and 8 were in partial remission at switch to MTX	In the maintenance group, MTX initiated at 7.5mg IV weekly and increased by 2.5mg to a weekly dose of 0.3mg/kg BW IV. In those already on MTX from induction, current dose maintained after remission until prednisone stopped. If patient was off prednisone and in complete remission after 6 months, MTX treatment was tapered by 2.5mg/month	2/25 lost to follow up and not included in analysis. 11/23 patients (47.8%) experienced a relapse after a median of 9 months (1-80 months). 8 had major relapse (3 new cardiac ischemiae, 5 with pulm activity). 3 relapses were minor (ENT, constitutional sx, arthritis). At time of relapse all patients were on MTX dose of 20mg/week and median pred of 9mg/d (4-20mg) No dif in disease variables or demographics of those who experienced a relapse and those who did not	Pateints on maintenance MTX were not only “severe egpa patients who entered remission”. BVAS at start of induction ranged from 3-29, FFS 0-2

Reduction in Prednisone	Metzler C, 2004	Open label, prospective, monocentric	48 months from start of maintenance regimen	28 consecutive EGPA patients. 11 induced with MTX. 25 treated for maintenance of remission with methotrexate (including the 8 in whom remission was successfully induced with MTX). Excluded chronic liver disease, creat >1.5, alcohol abuse, BM insufficiency, active infection or insufficient contraception. No life threatening disease. 11 induced with oral cyc, 3 with IV cyc, one with AZA and 8 with MTX. 15 were in complete remission and 8 were in partial remission at switch to MTX	In the maintenance group, MTX initiated at 7.5mg IV weekly and increased by 2.5mg to a weekly dose of 0.3mg/kg BW IV. In those already on MTX from induction, current dose maintained after remission until prednisone stopped. If patient was off prednisone and in complete remission after 6 months, MTX treatment was tapered by 2.5mg/month	2/25 lost to follow up and not included in analysis. 11/23 relapsed. In the other 12 who remained in remission, prednisone was decreased from 7.5mg at study start (3-12.5mg/d) to 4mg/d (0-14mg) at study end	Pateints on maintenance MTX were not only "severe egpa patients who entered remission". BVAS at start of induction ranged from 3-29, FFS 0-2
Side Effects	Metzler C, 2004	Open label, prospective, monocentric	48 months from start of maintenance regimen	28 consecutive EGPA patients. 11 induced with MTX. 25 treated for maintenance of remission with methotrexate (including the 8 in whom remission was successfully induced with MTX).	In the maintenance group, MTX initiated at 7.5mg IV weekly and increased by 2.5mg to a weekly dose of 0.3mg/kg BW IV. In those already on MTX from induction, current dose maintained after remission until prednisone stopped. If patient was off	2/23 had to decrease MTX dose 2/2 leucopenia (both after pre-treatment with oral cyc) 7/23 had URI requiring outpatient antibiotic therapy	Pateints on maintenance MTX were not only "severe egpa patients who entered remission". BVAS at start of induction ranged from 3-29, FFS 0-2

				Excluded chronic liver disease, creat >1.5, alcohol abuse, BM insufficiency, active infection or insufficient contraception. No life threatening disease. 11 induced with oral cyc, 3 with IV cyc, one with AZA and 8 with MTX. 15 were in complete remission and 8 were in partial remission at switch to MTX	prednisone and in complete remission after 6 months, MTX treatment was tapered by 2.5mg/month	1 death from cardiac failure (EGPA) after relapse No opportunistic infections, osteoporotic fractures or diabetes during entire follow up period	

76. In patients with severe EGPA who have entered remission, what is the impact of using azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?
    - No Data Avaliable

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies: (2)

Author	Year	Title
F. Maritati	2017	Methotrexate versus cyclophosphamide for remission maintenance in ANCA-associated vasculitis: A randomised trial
Metzler C.	2014	Churg Strauss syndrome - Successful induction of remission with methotrexate and unexpected high cardiac and pulmonary relapse ratio during maintenance treatment

- Studies reviewed and excluded:

Author	Year	Title	Comments
J. Yoo	2018	Cancer development in Korean patients with ANCA-associated vasculitis: a single centre study	31 patients with EGPA, but no data regarding treatment modalities in the 31 EGPA patients or disease severity. Does not answer any of the PICOS for EGPA

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remisison maintanance

- **PICO question 16:** In patients with severe EGPA who have entered remission, what is the impact of using methotrexate vs. MMF for remission maintenance on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

77. In patients with severe EGPA who have entered remission, what is the impact of using methotrexate vs. MMF for remission maintenance on disease-related outcomes and treatment-related adverse events?
    - No Comparative Data Available

78. In patients with severe EGPA who have entered remission, what is the impact of using methotrexate for remission maintenance on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes: (Same Evidence for single arm in PICO 15)**

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention used in relevant population	Results	Comments
Relapse 12/40 patients with EGPA treated with MTX for remission maintenance experience relapse. Moderately favors using MTX for maintenence	Maritati F, 2017	Single center, open label randomized trial	24 months from remissio n	71 patients: 30 with EGPA (only included those with FFS>or equal to 1 or with peripheral neuropathy), MPA (n=14) and GPA (n=27) who achieved remission induction with CYC	All enrolled patients rec'd 3 IV pulse doses of 500mg steroids followed by oral pred (1mg/lg/d) with taper and cytoxan 2mk/kg/d for induction of remission (had to be reached by month 9). Randomized to cyc or MTX using computer at	1/17 (6%) of EGPA patients maintained on MTX relapsed at 12 months. 1/17 relapsed at 18 months. 3/17 (18%) relapsed by 24 months	

				randomized to Cyc (n=33) vs MTX (n=38) for maintenance. 13 EGPA patients randomized to maintenance with CYC and 17 randomized to MTX	1:1. Maintenance CYC given at 1.5mg/kg/d while MTX given at 15mg/week, increased until dose of 0.3mg/kg/week (max 20mg/week). IF GFR 30-50ml, rec'd half dose MTX. Maintenance continued for 12 months and patients followed for 24 months		
	Metzler C, 2004	Open label, prospective, monocentric	48 months from start of maintenance regimen	28 consecutive EGPA patients. 11 induced with MTX. 25 treated for maintenance of remission with methotrexate (including the 8 in whom remission was successfully induced with MTX). Excluded chronic liver disease, creat >1.5, alcohol abuse, BM insufficiency, active infection or insufficient contraception. No life threatening disease. 11 induced with oral cyc, 3 with IV cyc, one with AZA and 8 with MTX. 15 were in complete remission and 8 were in partial	In the maintenance group, MTX initiated at 7.5mg IV weekly and increased by 2.5mg to a weekly dose of 0.3mg/kg BW IV. In those already on MTX from induction, current dose maintained after remission until prednisone stopped. If patient was off prednisone and in complete remission after 6 months, MTX treatment was tapered by 2.5mg/month	2/25 lost to follow up and not included in analysis. 11/23 patients (47.8%) experienced a relapse after a median of 9 months (1-80 months). 8 had major relapse (3 new cardiac ischemiae, 5 with pulm activity). 3 relapses were minor (ENT, constitutional sx, arthritis). At time of relapse all patients were on MTX dose of 20mg/week and median pred of 9mg/d (4-20mg) No dif in disease variables or demographics of those who experienced a relapse and those who did not	Pateints on maintenance MTX were not only "severe egpa patients who entered remission". BVAS at start of induction ranged from 3-29, FFS 0-2

				remission at switch to MTX			
Reduction in Prednisone	Metzler C, 2004	Open label, prospective, monocentric	48 months from start of maintenance regimen	28 consecutive EGPA patients. 11 induced with MTX. 25 treated for maintenance of remission with methotrexate (including the 8 in whom remission was successfully induced with MTX). Excluded chronic liver disease, creat >1.5, alcohol abuse, BM insufficiency, active infection or insufficient contraception. No life threatening disease. 11 induced with oral cyc, 3 with IV cyc, one with AZA and 8 with MTX. 15 were in complete remission and 8 were in partial remission at switch to MTX	In the maintenance group, MTX initiated at 7.5mg IV weekly and increased by 2.5mg to a weekly dose of 0.3mg/kg BW IV. In those already on MTX from induction, current dose maintained after remission until prednisone stopped. If patient was off prednisone and in complete remission after 6 months, MTX treatment was tapered by 2.5mg/month	2/25 lost to follow up and not included in analysis. 11/23 relapsed. In the other 12 who remained in remission prednisone was decreased from 7.5mg at study start (3-12.5mg/d) to 4mg/d (0-14mg) at study end	Pateints on maintenance MTX were not only "severe egpa patients who entered remission". BVAS at start of induction ranged from 3-29, FFS 0-2
Side Effects	Metzler C, 2004	Open label, prospective, monocentric	48 months from start of maintenance regimen	28 consecutive EGPA patients. 11 induced with MTX. 25 treated for maintenance of remission with methotrexate (including the 8 in whom remission	In the maintenance group, MTX initiated at 7.5mg IV weekly and increased by 2.5mg to a weekly dose of 0.3mg/kg BW IV. In those already on MTX from induction, current dose maintained after remission until	2/23 had to decrease MTX dose 2/2 leucopenia (both after pre-treatment with oral cyc) 7/23 had URI requiring outpatient antibiotic therapy	Pateints on maintenance MTX were not only "severe egpa patients who entered remission". BVAS at start of induction ranged from 3-29, FFS 0-2

				was successfully induced with MTX). Excluded chronic liver disease, creat >1.5, alcohol abuse, BM insufficiency, active infection or insufficient contraception. No life threatening disease. 11 induced with oral cyc, 3 with IV cyc, one with AZA and 8 with MTX. 15 were in complete remission and 8 were in partial remission at switch to MTX	prednisone stopped. If patient was off prednisone and in complete remission after 6 months, MTX treatment was tapered by 2.5mg/month	1 death from cardiac failure (EGPA) after relapse No opportunistic infections, osteoporotic fractures or diabetes during entire follow up period	

79. In patients with severe EGPA who have entered remission, what is the impact of using MMF for remission maintenance on disease-related outcomes and treatment-related adverse events?
    - No Data Avaliable

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Included Single Arm Studies and Test Accuracy Studies: (2)

Author	Year	Title
F. Maritati	2017	Methotrexate versus cyclophosphamide for remission maintenance in ANCA-associated vasculitis: A randomised trial

Metzler, C.	2014	Churg Strauss syndrome - Successful induction of remission with methotrexate and unexpected high cardiac and pulmonary relapse ratio during maintenance treatment

- Studies reviewed and excluded:

Author	Year	Title	Comments
C. Iatrou	2009	Mycophenolate mofetil as maintenance therapy in patients with vasculitis and renal involvement	Only includes 1 patient with EGPA in the study. Did not abstract data

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission maintanance

- **PICO question 17:** In patients with severe EGPA who have entered remission, what is the impact of using azathioprine vs. MMF for remission maintenance on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

80. In patients with severe EGPA who have entered remission, what is the impact of using azathioprine vs. MMF for remission maintenance on disease-related outcomes and treatment-related adverse events?
    No comparative data available

81. In patients with severe EGPA who have entered remission, what is the impact of using azathioprine for remission maintenance on disease-related outcomes and treatment-related adverse events?

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease Activity: One study including	Puechal, 2017	RCT, however functions as case series for PICO	24 months	25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma	Initial remission: 25/25 (100%)	Direct evidence: small population, but fits PICO and patients followed

25 EGPA patients with FFS=0 had 100% initial remission.					symptoms + AZA 2mg/kg/d (max 200mg/d).		prospectively as part of RCT.
Relapse: One study including 25 EGPA patients with FFS=0 had 48%.	Puechal, 2017	RCT; however, functions as case series for PICO	24 months	25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma symptoms + AZA 2mg/kg/d (max 200mg/d).	Any relapse: 12/25 (48%) Major relapse: 4/25 (16%) Minor relapse: 7/25 (28%)	Direct evidence: small population, but fits PICO and patients followed prospectively as part of RCT.
Death: One study with 25 EGPA patients with FFS=0 with mortality rate of 0% at 24 months.	Puechal, 2017	RCT; however, functions as case series for PICO	24 months	25 EGPA patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma symptoms + AZA 2mg/kg/d (max 200mg/d).	Mortality: 0/25	Direct evidence: small population, but fits PICO and patients followed prospectively as part of RCT.
Toxicity leading to discontinuation: One study with 46 EGPA/MPA/PAN with 17% having SAE related to treatment.	Puechal, 2017	RCT; however, functions as case series for PICO	24 months	46 EGPA/MPA/PAN patients meeting CHCC and ACR criteria as well as having FFS=0.	Prednisone 1mg/kg/d x 3 weeks (up to 80mg/d) with taper over 12 months to the minimum dose to control asthma symptoms + AZA 2mg/kg/d (max 200mg/d).	SAE related to treatment: 8/46 (17.4%) Any treatment AE: 25/46 (54.3%)	Indirect evidence: data includes a mixed population of EGPA, PAN and MPA

82. In patients with severe EGPA who have entered remission, what is the impact of using MMF for remission maintenance on disease-related outcomes and treatment-related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies:

Author	Year	Title
Puechal	2017	Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial.

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission maintanance

- **PICO question 18:** In patients with severe EGPA who have entered remission with cyclophosphamide therapy, what is the impact of using rituximab vs. methotrexate/azathioprine/MMF for remission maintenance on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypogammaglobulinemia)

83. In patients with severe EGPA who have entered remission with cyclophosphamide therapy, what is the impact of using rituximab vs. methotrexate/azathioprine/MMF for remission maintenance on disease-related outcomes and treatment-related adverse events?
    No comparative data available

84. In patients with severe EGPA who have entered remission with cyclophosphamide therapy, what is the impact of using rituximab for remission maintenance on disease-related outcomes and treatment-related adverse events?
    No single arm data available

85. In patients with severe EGPA who have entered remission with cyclophosphamide therapy, what is the impact of using methotrexate/azathioprine/MMF for remission maintenance on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Relapse: 2 studies including 30 patient with EGPA with relapse rate of 18-46% at 24-48 months.	Metzler, 2004	Open label, prospective, single center	48 months, median	13 patients with CSS were treated with MTX during maintenance phase after having been induced with CYC. Two patients lost to follow up and not considered.	"MTX therapy was initiated at a dose of 7.5 mg i.v. once weekly and increased by 2.5 mg steps to a weekly dose of 0.3 mg/kg BW i.v., provided there were no contraindications to dose escalation, e.g. leucopenia. An equivalent dose of folinic acid was given on the day following MTX." Equivalent dose of folinic acid was given on day after dosing.	6/13 (46%) experienced a relapse.	Direct evidence: Data limited to methotrexate.
	Maritati, 2017	Single-center randomized trial but functions as single arm for this PICO.	24 months	17 EGPA patients meeting ACR criteria and/or CHCC with FFS≥1 in remission within 9 months after CYC induction.	Induction with IV methprednisolone followed by prednisone + CYC (2mg/kg/d). Changed to MTX after remission achieved. Initial dose was 15mg/wk, increased until achieving 0.3mg/kg/wk (max 20mg/wk.	12 mon: 1/17(6%) 18 mon: 1/17 (6%) 24 mon: 3/17 (18%)	Direct evidence: This study is limited to methotrexate after cyclophosphamide induction.
Death: 1 study with 38 GPA, MPA and EGPA with mortality rate of 2.6% at 24 months.	Maritati, 2017	Single-center randomized trial but functions as single arm for this PICO.	24 months	38 GPA, MPA or EGPA patients meeting ACR criteria and/or CHCC in remission within 9 months after CYC induction.	Induction with IV methprednisolone followed by prednisone + CYC (2mg/kg/d). Changed to MTX after remission achieved. Initial dose was 15mg/wk, increased until achieving 0.3mg/kg/wk (max 20mg/wk.	1/38 (2.6%) mortality rate by 24 months. Death was due to B-cell lymphoma	Indirect evidence: This was a mixed population including GPA and MPA in addition to EGPA. It is unclear what disease the patient had that died.
Infection: 1 study with 38 EGPA, GPA and MPA	Maritati, 2017	Single-center randomized trial but functions as	24 months	38 GPA, MPA or EGPA patients meeting ACR criteria and/or CHCC in remission	Induction with IV methprednisolone followed by prednisone + CYC (2mg/kg/d). Changed to MTX after remission achieved. Initial dose	Total infections: 9/38 (23.7%) Severe infections: 2/38 (5.3%)	Indirect evidence: This was a mixed population including GPA and MPA in addition to EGPA. The infections were not

with severe infection rate of 5% at 24 months.		single arm for this PICO.		within 9 months after CYC induction.	was 15mg/wk, increased until achieving 0.3mg/kg/wk (max 20mg/wk.		broken down by disease subtype.
Adverse Events: Only one of the studies reports the results as SAE and includes EGPA, GPA and MPA with SAE rate of 13% at 24 months.	Metzler, 2004	Open label, prospective, single center	48 months, median	25 patients with CSS were treated with MTX. Two patients lost to follow up and not considered.	"MTX therapy was initiated at a dose of 7.5 mg i.v. once weekly and increased by 2.5 mg steps to a weekly dose of 0.3 mg/kg BW i.v., provided there were no contraindications to dose escalation, e.g. leucopenia. An equivalent dose of folinic acid was given on the day following MTX." Equivalent dose of folinic acid was given on day after dosing.	2 patients had to reduce MTX dose due to leukopenia (both had received CYC induction) 7 patients had upper respiratory infections No opportunistic infections or osteoporotic fractures were found during the observation period.	Indirect. The induction of the remission regimen consisted of daily oral CYC in 11 patients, i.v. pulse CYC in 3, AZA in one, PRD in a further 2 (at daily doses of 25 and 40 mg PRD) and MTX in 8.
	Maritati , 2017	Single-center randomized trial but functions as single arm for this PICO.	24 months	38 GPA, MPA or EGPA patients meeting ACR criteria and/or CHCC in remission within 9 months after CYC induction.	Induction with IV methprednisolone followed by prednisone + CYC (2mg/kg/d). Changed to MTX after remission achieved. Initial dose was 15mg/wk, increased until achieving 0.3mg/kg/wk (max 20mg/wk.	SAE: 5/38 (13.1%)	Indirect evidence: This was a mixed population including GPA and MPA in addition to EGPA. The infections were not broken down by disease subtype.
Prednisone dose	Metzler, 2004	Open label, prospective, single center	48 months, median	25 patients with CSS were treated with MTX. Two patients lost to follow up and not considered.	"MTX therapy was initiated at a dose of 7.5 mg i.v. once weekly and increased by 2.5 mg steps to a weekly dose of 0.3 mg/kg BW i.v., provided there were no contraindications to dose escalation, e.g. leucopenia. An equivalent dose of folinic acid was given on the day following MTX." Equivalent dose of folinic acid was given on day after dosing.	"Prednisone could be reduced in the 12 patients who remained in remisssion throughout the study, from 7.5 mg/d at the study start (3 – 12.5 mg/d) to 4 mg/d at the study end (0 – 14 mg/d) (p= 0.056)."	Indirect. The induction of the remission regimen consisted of daily oral CYC in 11 patients, i.v. pulse CYC in 3, AZA in one, PRD in a further 2 (at daily doses of 25 and 40 mg PRD) and MTX in 8.

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies:

Author	Year	Title
Metzler	2004	Churg Strauss syndrome - Successful induction of remission with methotrexate and unexpected high cardiac and pulmonary relapse ratio during maintenance treatment
Maritati	2017	Methotrexate versus cyclophosphamide for remission maintenance in ANCA-associated vasculitis: A randomised trial.

- Studies reviewed and excluded:

Author	Year	Title	Comments
C. Pagnoux	2015	Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy	Excluded, 14 patients with EGPA included but 9 of these had FFS = 0 and thus did not get maintenance therapy (i.e., only 5 patients had maintenance AZA or MTX – and no patient level data available on these patients to inform the PICO).

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission maintanance

- **PICO question 19:** In patients with severe EGPA who have entered remission with mepolizumab therapy, what is the impact of using methotrexate/azathioprine/MMF vs. continuing mepolizumab for remission maintenance on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

86. In patients with severe EGPA who have entered remission with mepolizumab therapy, what is the impact of using methotrexate/azathioprine/MMF vs. continuing mepolizumab for remission maintenance on disease-related outcomes and treatment-related adverse events?
No comparative data available

87. In patients with severe EGPA who have entered remission with mepolizumab therapy, what is the impact of using methotrexate/azathioprine/MMF for remission maintenance on disease-related outcomes and treatment-related adverse events?
No single arm data available

88. In patients with severe EGPA who have entered remission with mepolizumab therapy, what is the impact of using continuing mepolizumab for remission maintenance on disease-related outcomes and treatment-related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:

  None

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission maintanance

- **PICO question 20:** In patients with non-severe EGPA who have entered remission, what is the impact of using mepolizumab vs. methotrexate /azathioprine/MMF for remission maintenance on disease-related outcomes and treatment related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

89. In patients with non-severe EGPA who have entered remission, what is the impact of using mepolizumab vs. methotrexate /azathioprine/MMF for remission maintenance on disease-related outcomes and treatment related adverse events?
No comparative data available

90. In patients with non-severe EGPA who have entered remission, what is the impact of using mepolizumab for remission maintenance on disease-related outcomes and treatment related adverse events?
No single arm data available

91. In patients with non-severe EGPA who have entered remission, what is the impact of using methotrexate /azathioprine/MMF for remission maintenance on disease-related outcomes and treatment related adverse events?
    - **Patient important outcomes:**

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Relapse	Metzler, 2004	Open label, prospective, single center	48 months, median	13 patients with CSS were treated with MTX during maintenance phase after having been induced with CYC. Two patients lost to follow up and not considered.	"MTX therapy was initiated at a dose of 7.5 mg i.v. once weekly and increased by 2.5 mg steps to a weekly dose of 0.3 mg/kg BW i.v., provided there were no contraindications to dose escalation, e.g., leucopenia. An equivalent dose of folinic acid was given on the day following MTX." Equivalent dose of folinic acid was given on day after dosing.	6/13 (46%) experienced a relapse.	Indirect.
Adverse Events	Metzler, 2004	Open label, prospective, single center	48 months, median	25 patients with CSS were treated with MTX. Two patients lost to follow up and not considered.	"MTX therapy was initiated at a dose of 7.5 mg i.v. once weekly and increased by 2.5 mg steps to a weekly dose of 0.3 mg/kg BW i.v., provided there were no contraindications to dose escalation, e.g., leucopenia. An equivalent dose of folinic acid was given on the day following MTX." Equivalent dose of	2 patients had to reduce MTX dose due to leukopenia (both had received CYC induction) 7 patients had upper respiratory infections No opportunistic infections or osteoporotic	Indirect. The induction of the remission regimen consisted of daily oral CYC in 11 patients, i.v. pulse CYC in 3, AZA in one, PRD in a further 2 (at daily doses of 25 and 40 mg PRD) and MTX in 8.

					folinic acid was given on day after dosing.	fractures were found during the observation period.	
Prednisone dose	Metzler, 2004	Open label, prospective, single center	48 months, median	25 patients with CSS were treated with MTX. Two patients lost to follow up and not considered.	"MTX therapy was initiated at a dose of 7.5 mg i.v. once weekly and increased by 2.5 mg steps to a weekly dose of 0.3 mg/kg BW i.v., provided there were no contraindications to dose escalation, e.g., leucopenia. An equivalent dose of folinic acid was given on the day following MTX." Equivalent dose of folinic acid was given on day after dosing.	"Prednisone could be reduced in the 12 patients who remained in remisssion throughout the study, from 7.5 mg/d at the study start (3 – 12.5 mg/d) to 4 mg/d at the study end (0 – 14 mg/d) (p= 0.056)."	Indirect. The induction of the remission regimen consisted of daily oral CYC in 11 patients, i.v. pulse CYC in 3, AZA in one, PRD in a further 2 (at daily doses of 25 and 40 mg PRD) and MTX in 8.

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies:

Author	Year	Title
Metzler	2004	Churg Strauss syndrome - Successful induction of remission with methotrexate and unexpected high cardiac and pulmonary relapse ratio during maintenance treatment

- Studies reviewed and excluded:

Author	Year	Title	Comment

Kim S	2010	Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome.	Exclude. Only has 7 subjects

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission maintanance

- **PICO question 21:** In patients with severe EGPA on remission maintenance therapy not using prednisone, what is the impact of continuing remission maintenance therapy for > 18 months vs. stopping remission maintenance therapy at or prior to 18 months on disease related outcomes and treatment related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, serious adverse events, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

92. In patients with severe EGPA on remission maintenance therapy not using prednisone, what is the impact of continuing remission maintenance therapy for > 18 months vs. stopping remission maintenance therapy at or prior to 18 months on disease related outcomes and treatment related adverse events?
    No comparative data available

93. In patients with severe EGPA on remission maintenance therapy not using prednisone, what is the impact of continuing remission maintenance therapy for > 18 months vs. stopping remission maintenance therapy at or prior to 18 months on disease related outcomes and treatment related adverse events?
    No single arm data available

94. In patients with severe EGPA on remission maintenance therapy not using prednisone, what is the impact of stopping remission maintenance therapy at or prior to 18 months on disease related outcomes and treatment related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:

  None

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission maintanance

- **PICO question 22:** In patients with severe EGPA on remission maintenance therapy and prednisone, what is the impact of continuing remission maintenance therapy for > 18 months with prednisone vs. stopping remission maintenance therapy at or prior to 18 months and continuing prednisone on disease related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, serious adverse events, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hyperglycemia, decreased bone mineral density)

95. In patients with severe EGPA on remission maintenance therapy and prednisone, what is the impact of continuing remission maintenance therapy for > 18 months with prednisone vs. stopping remission maintenance therapy at or prior to 18 months and continuing prednisone on disease related outcomes and treatment-related adverse events?
    No comparative data available

96. In patients with severe EGPA on remission maintenance therapy and prednisone, what is the impact of continuing remission maintenance therapy for > 18 months with prednisone on disease related outcomes and treatment-related adverse events?
    No single arm data available

97. In patients with severe EGPA on remission maintenance therapy and prednisone, what is the impact of stopping remission maintenance therapy at or prior to 18 months and continuing prednisone on disease related outcomes and treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies:

None

- Comments:

Author	Year	Title	Comments
L. Guillevin	1992	Lack of superiority of steroids plus plasma exchange to steroids alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome. A prospective, randomized trial in 78 patients	Excluded for EGPA PICO 22. No data available that informs the PICO.

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Remission maintanance

- **PICO question 23:** In patients with severe EGPA on remission maintenance therapy, what is the impact of using oral glucocorticoids for 6 months versus more than 6 months on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, toxicity leading to discontinuation (e.g., hyperglycemia, decreased bone mineral density)

98. In patients with severe EGPA on remission maintenance therapy, what is the impact of using oral glucocorticoids for 6 months versus more than 6 months on disease-related outcomes and treatment-related adverse events?
    No comparative data available

99. In patients with severe EGPA on remission maintenance therapy, what is the impact of using oral glucocorticoids for 6 months on disease-related outcomes and treatment-related adverse events?

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Relapse: 1 study with 17 EGPA patients with FFS≥1 with 18% relapse rate by 24 months. Comparison with	Maritati, 2017	Single-center randomized trial but functions as single	24 months	17 EGPA patients meeting ACR criteria and/or CHCC with FFS≥1 in remission within 9 months	Induction with IV methprednisolone followed by prednisone (initially 1mg/kg/d with taper down to 5mg/d by 6 months) + CYC (2mg/kg/d). Changed to MTX after remission achieved.	12 mon: 1/17(6%) 18 mon: 1/17 (6%) 24 mon: 3/17 (18%)	Indirect evidence: Patients were tapered to low dose (5mg/d), but not off, prednisone by 6 months.

longer term steroids is difficult because of differences in follow-up time.		arm for this PICO.		after CYC induction.			
Death: 1 study with 38 patients with EGPA, MPA or GPA with mortality rate of 3% by 24 months. This is higher than that seen with long term glucocorticoids.	Maritati, 2017	Single-center randomized trial but functions as single arm for this PICO.	24 months	38 GPA, MPA or EGPA patients meeting ACR criteria and/or CHCC in remission within 9 months after CYC induction.	Induction with IV methprednisolone followed by prednisone (initially 1mg/kg/d with taper down to 5mg/d by 6 months) + CYC (2mg/kg/d). Changed to MTX after remission achieved.	1/38 (2.6%) mortality rate by 24 months. Death was due to B-cell lymphoma	Indirect evidence: Patients were tapered to low dose (5mg/d), but not off, prednisone by 6 months.
Infections: 1 study with 38 EGPA, GPA and MPA patients with severe infection rate of 5% at 24 months.	Maritati, 2017	Single-center randomized trial but functions as single arm for this PICO.	24 months	38 GPA, MPA or EGPA patients meeting ACR criteria and/or CHCC in remission within 9 months after CYC induction.	Induction with IV methprednisolone followed by prednisone (initially 1mg/kg/d with taper down to 5mg/d by 6 months) + CYC (2mg/kg/d). Changed to MTX after remission achieved.	Total infections: 9/38 (23.7%) Severe infections: 2/38 (5.3%)	Indirect evidence: Patients were tapered to low dose (5mg/d), but not off, prednisone by 6 months.
Adverse events: 1 study with 38 EGPA, GPA and MPA with SAE rate of 13% at 24 months. Markedly lower than with long term glucocorticoids, however, this cohort has shorter follow-up by at least 1 year.	Maritati, 2017	Single-center randomized trial but functions as single arm for this PICO.	24 months	38 GPA, MPA or EGPA patients meeting ACR criteria and/or CHCC in remission within 9 months after CYC induction.	Induction with IV methprednisolone followed by prednisone (initially 1mg/kg/d with taper down to 5mg/d by 6 months) + CYC (2mg/kg/d). Changed to MTX after remission achieved.	SAE: 5/38 (13.1%)	Indirect evidence: Patients were tapered to low dose (5mg/d), but not off, prednisone by 6 months.

100. In patients with severe EGPA on remission maintenance therapy, what is the impact of using oral glucocorticoids for more than 6 months on disease-related outcomes and treatment-related adverse events?

- **Patient important outcomes:**

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Disease activity: 1 study with 14 EGPA patients with at least a partial response of 100% by 3 years.	Pagnoux, 2015	RCT; however, for PICO functions as single arm	3 years	14 EGPA patients with newly diagnosed disease, fulfilling 1990 ACR criteria and/or 1994 CHCC, and at least 65 years old.	Both treatment arms got IV CYC. Experimental arm got corticosteroids for about 9 months and max of six 500mg IV CYC every 2-3 weeks then changed to maintenance. Control arm got approx. 26 mon corticosteroids combined with 500mg/m2 IV CYC every 2-3 weeks until remission, then maintenance therapy for those with FFS≥1.	Complete or partial response in 14/14 (100%)	Direct: All got glucocorticoid therapy for > 6 months, however, 2 different regimens used.
Relapse: 1 study with 14 EGPA patients with a relapse rate of 36%. Differences in follow-up make direct comparisons with short term glucocorticoids difficult.	Pagnoux, 2015	RCT; however, for PICO functions as single arm	3 years	14 EGPA patients with newly diagnosed disease, fulfilling 1990 ACR criteria and/or 1994 CHCC, and at least 65 years old.	Both treatment arms got IV CYC. Experimental arm got corticosteroids for about 9 months and max of six 500mg IV CYC every 2-3 weeks then changed to maintenance. Control arm got approx. 26 mon corticosteroids combined with 500mg/m2 IV CYC every 2-3 weeks until remission, then maintenance therapy for those with FFS≥1.	5/14 (35.7%)	Direct: All got glucocorticoid therapy for > 6 months, however, 2 different regimens used
Death: 1 study with 14 EGPA patients with mortality rate of 0% by 3 years.	Pagnoux, 2015	RCT; however, for PICO functions as single arm	3 years	14 EGPA patients with newly diagnosed disease, fulfilling 1990 ACR criteria and/or 1994 CHCC, and at least 65 years old.	Both treatment arms got IV CYC. Experimental arm got corticosteroids for about 9 months and max of six 500mg IV CYC every 2-3 weeks then changed to maintenance. Control arm got approx. 26 mon corticosteroids combined with 500mg/m2 IV CYC every 2-3 weeks until remission, then maintenance therapy for those with FFS≥1.	0/14 (none)	Direct: All got glucocorticoid therapy for > 6 months, however, 2 different regimens used

Adverse Events: 1 study with 14 EGPA patients with 71% SAE by 3 years. 1 study with 78 patients with EGPA, GPA or MPA with steroid AE in 8/78 (10.3%). The SAE rate is markedly higher then with shorter courses of glucocorticoids, however, the longer follow-up in this chort makes direct comparisons difficult.	Guillevin, 1992	Multicenter, prospective RCT (Single arm relavence)	~43 months, mean	***18 patients with CSS (part of a larger cohort of patients of n=78, the other portion of which is patients with PAN)	Prednisone 1mg/kg/d x 1 month, then decreased by 2.5mg every 10 days for 1 month, then decreased by 2.5mg every week until 0.5mg/kg/d. This was maintained for 3 weeks then decreased by 2.5mg every week until 20mg/day. Then decreased by 1mg every week until 10mg/day. This was maintained for 3 weeks then decreased by 1mg every week until at 5mg/day. Half of the patients received PLEX per RCT. CYC was used as rescue therapy in case of severe relapse. One year after start of therapy, mean steroid dose was 10mg/day and 13.7mg/day (PLEX vs no PLEX, not significant).	"Side effects of the steroid treatment were severe diffuse osteoporosis in 2 patients, aseptic necrosis of the femoral head in 2 patients, aseptic necrosis of the humeral head in 1 patient, duodenal ulcers in 2 patients, and pneumonia in 1 patient."	Very indirect. ***Very heterogenous population. Mostly PAN patients. Per authors, "Consistent with Fauci's classification system, PAN and CSS were not treated as separate diseases in this study, because we think that these two forms of necrotizing angiitis belong to the same disease group."
	Pagnoux, 2015	RCT; however, for PICO functions as single arm	3 years	14 EGPA patients with newly diagnosed disease, fulfilling 1990 ACR criteria and/or 1994 CHCC, and at least 65 years old.	Both treatment arms got IV CYC. Experimental arm got corticosteroids for about 9 months and max of six 500mg IV CYC every 2-3 weeks then changed to maintenance. Control arm got approx. 26 mon corticosteroids combined with 500mg/m2 IV CYC every 2-3 weeks until remission, then maintenance therapy for those with FFS≥1.	10/14 (71.4%) with SAE	Direct: All got glucocorticoid therapy for > 6 months, however, 2 different regimens used

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:

Author	Year	Title
Guillevin	1992	Lack of superiority of steroids plus plasma exchange to steroids alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome. A prospective, randomized trial in 78 patients
Pagnoux	2015	Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy.
Maritati	2017	Methotrexate versus cyclophosphamide for remission maintenance in ANCA-associated vasculitis: A randomised trial.

- Studies reviewed and excluded:

Author	Year	Title	Comments
N. Hattori	1999	Clinicopathological features of Churg-Strauss syndrome-associated neuropathy	Excluded for EGPA PICO23. No data on relavent population that informs the PICO.
C. Pagnoux	2015	Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy	Was also considered given its varying glucocorticoid protocols, but excluded here due to 9 of 14 EGPA patients having FFS=0 (and thus no maintenance therapy) and no patient level outcome data available on the remaining 5 patients.

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: refractory/smoldering disease

- **PICO question 24:** In patients with severe EGPA who have not entered remission with cyclophosphamide or rituximab therapy, what is the impact of adding mepolizumab vs. continued rituximab/cyclophosphamide therapy on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypogammaglobulinemia)

101. In patients with severe EGPA who have not entered remission with cyclophosphamide or rituximab therapy, what is the impact of adding mepolizumab vs. continued rituximab/cyclophosphamide therapy on disease-related outcomes and treatment-related adverse events?
No comparative data available

102. In patients with severe EGPA who have not entered remission with cyclophosphamide or rituximab therapy, what is the impact of adding mepolizumab therapy on disease-related outcomes and treatment-related adverse events?
No single arm data available

103. In patients with severe EGPA who have not entered remission with cyclophosphamide or rituximab therapy, what is the impact of continued rituximab/cyclophosphamide therapy on disease-related outcomes and treatment-related adverse events?

- **Patient important outcomes:**

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Remission/ Treatment Response: 2 study including 55 EGPA patients with 83-100% achieving at least a partial remission by 6 months. 1 study with 41 EGPA patients with full remission achieved in 34% by 6 months and 49% by 12 months.	Thiel, 2017	Retrospective, single center study	36 months	14 patients (5F, median age 54y) with EGPA treated with RTX (12 of 14 due to relapsing or refractory disease, 2/14 due to young age). Notably, 9/14 had received CYC before.	RTX 1 gram Day, Day 15 All patients received prednisone.	All patients showed a treatment response (at least partial remission) within 6 months.	Indirect. Treatment response was defined as 50% reduction in the BVAS and absence of new manifestations of vasculitis.
	Mohammad, 2014	Retrospective, single arm	12 months	41 EGPA treated with RTX between 2003-2013 meeting ACR criteria. 15/41 (37%) had refractory disease. 27/41 (66%) received prior induction with CYC.	Initial RTX 375mg/m2 x 4 (10) or 1,000mg x 2 (30) (19/41 only got a single course of RTX) 22/41 retreated with RTX at 6 mon, 17/22 got another cycle at 12 mon (375mg/m2 x 4, 1,000mg x 2 or 1,000mg x 1, 600mg x 1)	Partial response or remission: 6 mon: 34/41 (83%) 12 mon: 36/41 (88%) Remission: 6 mon: 14/41 (34%) 12 mon: 20/41 (49%)	Indirect: Not all the patients received CYC or RTX beforehand.
Relapse – One study of 14 patients with EGPA show that 28% of patients relapsed after being treated with second line RTX for induction.	Thiel, 2017	Retrospective, single center study	36 months	14 patients (5F, median age 54y) with EGPA treated with RTX (12 of 14 due to relapsing or refractory disease, 2/14 due to young age). Notably, 9/14 had received CYC before.	RTX 1 gram Day, Day 15 All patients received prednisone.	4/14 patients relapsed (one of these major – cardiac/pulmonary/neuropathy relapse).	Indirect. Relapse was defined as the occurrence of at least 1 BVAS item caused by vasculitis after previous remission. Major relapses were defined as potentially life-threatening disease activity that could not be treated with steroids only. All other

							relapses were defined as minor.
Glucocorticoid dose – 2 studies of 55 patients with EGPA show that RTX allowed for decrease of prednisone.	Thiel, 2017	Retrospective, single center study	36 months	14 patients (5F, median age 54y) with EGPA treated with RTX (12 of 14 due to relapsing or refractory disease, 2/14 due to young age). Notably, 9/14 had received CYC before.	RTX 1 gram Day, Day 15 All patients received prednisone	Median daily prednisone dose declined from 22.5 mg (IQR, 13.75-32.5 mg) in RTX-treated patients at baseline to 7.5 mg (IQR, 6.25-12.5 mg) at 6 months (P=.0016) and 5 mg (IQR, 5-7.5) at 12 months(P<.0001 vs baseline and P=.0308 vs 6 months)	Indirect. Not on a uniform taper.
	Mohammad, 2014	Retrospective, single arm	12 months	41 EGPA treated with RTX between 2003-2013 meeting ACR criteria. 15/41 (37%) had refractory disease. 27/41 (66%) received prior induction with CYC.	Initial RTX 375mg/m2 x 4 (10) or 1,000mg x 2 (30) (19/41 only got a single course of RTX) 22/41 retreated with RTX at 6 mon, 17/22 got another cycle at 12 mon (375mg/m2 x 4, 1,000mg x 2 or 1,000mg x 1, 600mg x 1)	Median dose of prednisolone/prednisone at baseline 15mg/d (IQR 10-30mg) and decreased to 8mg/d (IQR 6.5-11) at 6 months (p<0.001) and to 8mg/d (IQR 6.9-10) at 12 months (p=0.001).	Indirect: Not all the patients received CYC or RTX beforehand.
Deaths: In 1 study of 41 EGPA patients mortality rate was 0% at 12 months	Mohammad, 2014	Retrospective, single arm	12 months	41 EGPA treated with RTX between 2003-2013 meeting ACR criteria. 15/41 (37%) had refractory disease. 27/41 (66%) received prior induction with CYC.	Initial RTX 375mg/m2 x 4 (10) or 1,000mg x 2 (30) (19/41 only got a single course of RTX) 22/41 retreated with RTX at 6 mon, 17/22 got another cycle at 12 mon (375mg/m2 x 4, 1,000mg x 2 or 1,000mg x 1, 600mg x 1)	No deaths at 12 months.	Indirect: Not all the patients received CYC or RTX beforehand.

Adverse Events – 2 study of 55 patients with EGPA treated with RTX with 0-15% developing severe infections. In one study of 41 patients 51% developed adverse events.	Thiel, 2017, 19148	Retrospective, single center study	36 months	14 patients (5F, median age 54y) with EGPA treated with RTX (12 of 14 due to relapsing or refractory disease, 2/14 due to young age). Notably, 9/14 had received CYC before.	RTX 1 gram Day, Day 15 All patients received prednisone (not on a uniform taper).	-No major infections and no opportunistic infections occurred. -3/14 developed hypogammaglobulinemia. -In 1 patient a seminoma and in a further patient a prostate carcinoma was diagnosed 1 and 2 years after RTX therapy, respectively.	Indirect.
	Mohammad, 2014	Retrospective, single arm	12 months	41 EGPA treated with RTX between 2003-2013 meeting ACR criteria. 15/41 (37%) had refractory disease. 27/41 (66%) received prior induction with CYC.	Initial RTX 375mg/m2 x 4 (10) or 1,000mg x 2 (30) (19/41 only got a single course of RTX) 22/41 retreated with RTX at 6 mon, 17/22 got another cycle at 12 mon (375mg/m2 x 4, 1,000mg x 2 or 1,000mg x 1, 600mg x 1)	Total AE: 21/41 (51.2%) Unclear how many had SAE Severe infections: 6/41 (14.6%)	Indirect: Not all the patients received CYC or RTX beforehand.

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:

Author	Year	Title

Theil	2017	Rituximab as Induction Therapy in Eosinophilic Granulomatosis with Polyangiitis Refractory to Conventional Immunosuppressive Treatment: A 36-Month Follow-Up Analysis
Mohammad	2014	Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss).

- Studies reviewed and excluded:

Author	Year	Title	Comments
S. Lovric	2009	Rituximab as rescue therapy in anti-neutrophil cytoplasmic antibody-associated vasculitis: a single-centre experience with 15 patients	Excluded for EGPA PICO 24. Only one patient with EGPA in the cohort.

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Relapse

- **PICO question 25:** In patients with EGPA who have relapsed with severe disease manifestations after prior remission induction with cyclophosphamide or rituximab, what is the impact of using the same agent vs. switching to the other agent for remission re-induction on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypogammaglobulinemia)

104. In patients with EGPA who have relapsed with severe disease manifestations after prior remission induction with cyclophosphamide or rituximab, what is the impact of using the same agent vs. switching to the other agent for remission re-induction on disease-related outcomes and treatment-related adverse events?
No comparative data available

105. In patients with EGPA who have relapsed with severe disease manifestations after prior remission induction with cyclophosphamide or rituximab, what is the impact of using the same agent for remission re-induction on disease-related outcomes and treatment-related adverse events?
No single arm data available

106. In patients with EGPA who have relapsed with severe disease manifestations after prior remission induction with cyclophosphamide or rituximab, what is the impact of switching to the other agent for remission re-induction on disease-related outcomes and treatment-related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies:

  None

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Relapse

- **PICO question 26:** In patients with EGPA who have relapsed with non-severe disease manifestations (asthma and/or sino-nasal disease) while on methotrexate/azathioprine/MMF, what is the impact of adding mepolizumab versus switching to another agent on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, infection, serious adverse events, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypersensitivity reaction)

107. In patients with EGPA who have relapsed with non-severe disease manifestations (asthma and/or sino-nasal disease) while on methotrexate/azathioprine/MMF, what is the impact of adding mepolizumab versus switching to another agent on disease-related outcomes and treatment-related adverse events?
No comparative data available

108. In patients with EGPA who have relapsed with non-severe disease manifestations (asthma and/or sino-nasal disease) while on methotrexate/azathioprine/MMF, what is the impact of adding mepolizumab on disease-related outcomes and treatment-related adverse events?

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments

Disease activity: 2 studies with the same 68 EGPA patients treated with Mepolizumab with 53% achiving BVAS 0 on ≤ 4mg/d prednisone by 52 weeks. Only 60% of population was on baseline immunosuppressive therapy. With mepolizumab versus placebo, 78% versus 32% of patients experienced clinical benefit 1, and 87% versus 53% of patients experience	Wechsler ME, 2017	Randomized, placebo-controlled double-blinded, parallel group, multicenter phase 3 trial	52 weeks	151 Relapsing or refractory EGPA defined as asthma, eosinophilia and 2 or more criteria (features typical of EGPA). Patients with life or organ threatening manifestations (i.e., severe manifestations) were excluded. Participants recruited from 2014 to 2015. Did not include patients with severe disease	300mg SQ monthly Mepolizumab versus placebo on top of standard of care. A total of 151 patients were recruited with 68 randomly assigned to Mepolizumab group.	Achieved remission (defined as BVAS of 0 and ≤ 4mg/d prednisone or prednisolone): 36/68 (52.9%)	Indirect: Only 60% of patients were on immunosuppressive agent at baseline.
	Steinfield, 2019	Randomized, placebo-controlled, double-blind, parallel-group trial recruited patients with relapsing/refractory EGPA receiving stable OGCs (prednisolone/prednisone, ≥7.5-50 mg/d) for 4 or more weeks	52 weeks	Patients received 300 mg of subcutaneous mepolizumab or placebo every 4 weeks for 52 weeks.	*Clinical benefit was defined post hoc as follows: remission at any time (2 definitions used), 50% or greater OGC dose reduction during weeks 48 to 52, or no EGPA relapses. The 2 remission definitions were Birmingham Vasculitis Activity Score of 0 plus OGC dose of 4 mg/d or less (remission 1/clinical benefit 1) or 7.5 mg/d or less (remission 2/clinical benefit 2)	With mepolizumab versus placebo, 78% versus 32% of patients experienced clinical benefit 1, and 87% versus 53% of patients experienced clinical benefit 2 (both P < .001)	Not all patients have non-severe disease manifestations

d clinical b enefit 2*							
Death: 1 study including 68 EGPA patients treatment with Mepolizumab with 2% mortality by 52 weeks.	Wechsler ME, 2017	Randomized, placebo-controlled double-blinded, parallel group, multicenter phase 3 trial	52 weeks	151 Relapsing or refractory EGPA defined as asthma, eosinophilia and 2 or more criteria (features typical of EGPA). Patients with life or organ threatening manifestations (i.e., severe manifestations) were excluded. Participants recruited from 2014 to 2015. Did not include patients with severe disease	300mg SQ monthly Mepolizumab versus placebo on top of standard of care. A total of 151 patients were recruited with 68 randomly assigned to Mepolizumab group.	Death: 1/68 (1.5%) which was due to cardiac arrest deemed not related to the trial regimen.	Indirect: Only 60% of patients were on immunosuppressive agent at baseline.
SAE: 1 study with 68 EGPA patients teated with Mepolizumab with 18% experiencing a SAE and 4% SAE related to drug.	Wechsler ME, 2017	Randomized, placebo-controlled double-blinded, parallel group, multicenter phase 3 trial	52 weeks	151 Relapsing or refractory EGPA defined as asthma, eosinophilia and 2 or more criteria (features typical of EGPA). Patients with life or organ threatening manifestations (i.e., severe manifestations) were excluded. Participants recruited from 2014 to 2015. Did not include patients with severe disease.	300mg SQ monthly Mepolizumab versus placebo on top of standard of care. A total of 151 patients were recruited with 68 randomly assigned to Mepolizumab group.	All SAE: 12/68 (18%) SAE related to trial agent: 3/68 (4%) Exacerbation or worsening of asthma as SAE: 2/68 (3%) which was less then seen in placebo (6%)	Indirect: Only 60% of patients were on immunosuppressive agent at baseline.

Toxicity leading to discontinuation: 1 study with 68 EGPA patients treated with Mepolizumab with 3% toxicity leading to discontinuation of drug.	Wechsler ME, 2017	Randomized, placebo-controlled double-blinded, parallel group, multicenter phase 3 trial	52 weeks	151 Relapsing or refractory EGPA defined as asthma, eosinophilia and 2 or more criteria (features typical of EGPA). Patients with life or organ threatening manifestations (i.e., severe manifestations) were excluded. Participants recruited from 2014 to 2015. Did not include patients with severe disease.	300mg SQ monthly Mepolizumab versus placebo on top of standard of care. A total of 151 patients were recruited with 68 randomly assigned to Mepolizumab group.	Events leading to trial agent discontinuation or trial withdrawal: 2/68 (3%)	Indirect: Only 60% of patients were on immunosuppressive agent at baseline.

109. In patients with EGPA who have relapsed with non-severe disease manifestations (asthma and/or sino-nasal disease) while on methotrexate/azathioprine/MMF, what is the impact of switching to another agent on disease-related outcomes and treatment-related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:

Author	Year	Title

Wechsler	2017	Mepolizumab or Placebo for Eosinophilic Granulomatosis with polyangiitis
Steinfield	2019	Evaluation of clinical benefit from treatment with mepolizumab for patients with eosinophilic granulomatosis with polyangiitis

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Relapse

- **PICO question 27:** In patients with EGPA and high IgE levels who have relapsed with non-severe disease manifestations (asthma and/or sino-nasal disease) while on methotrexate/azathioprine/MMF, what is the impact of adding omalizumab versus switching to another agent on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, infection, serious adverse events, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hypersensitivity reaction)

110. In patients with EGPA and high IgE levels who have relapsed with non-severe disease manifestations (asthma and/or sino-nasal disease) while on methotrexate/azathioprine/MMF, what is the impact of adding omalizumab versus switching to another agent on disease-related outcomes and treatment-related adverse events?
No comparative data available

111. In patients with EGPA and high IgE levels who have relapsed with non-severe disease manifestations (asthma and/or sino-nasal disease) while on methotrexate/azathioprine/MMF, what is the impact of adding omalizumab on disease-related outcomes and treatment-related adverse events?
- **Patient important outcomes:**

Outcomes (Name + Summary)	Author, year	Study type	Duration of follow up	Population (number and description)	Intervention used in relevant population (Describe the intervention)	Results	Comments
Treatment response (complete/ partial/BVAS) – One study of 17 patients	Jachiet, 2016	Nationwide, retrospective study	22 months, median	17 patients with EGPA (7F, mean age 45y, 29% ANCA+) who received omalizumab	Omalizumab was administered subcutaneously once or twice per month. Given the retrospective design of this study, the dosage for each patient was	Complete response - 6 patients (35%) Partial response - 5 patients (30%).	Indirect. Complete response was defined as the absence of asthma and/or ENT exacerbations with a prednisone dosage of 7.5

with EGPA treated with omalizumab show that BVAS improves and many patients can achieve a partial or complete response.					defined by the practitioner in charge. The dosage was calculated according to the patient's IgE levels and body weight as suggested for severe asthma treatment, in accordance with the EMA recommendations.	Both outcomes were mainly 3–6 months after treatment initiation. Median BVAS dropped from 2.5 at baseline to 1, 1, and 0.5 at months 3, 6, and 12, respectively.	mg/day,and partial response was defined as the absence of asthma and/or ENT exacerbations with a prednisone dosage of 7.5 mg/day. BVAS was also used.
Adverse Events – One study of 17 patients with EGPA treated with omalizumab reported no serious adverse events. There were two curious relapses with a rare disease manifestation noted.	Jachiet, 2016	Nationwide, retrospective study	22 months, median	17 patients with EGPA (7F, mean age 45y, 29% ANCA+) who received omalizumab	Omalizumab was administered subcutaneously once or twice per month. Given the retrospective design of this study, the dosage for each patient was defined by the practitioner in charge. The dosage was calculated according to the patient's IgE levels and body weight as suggested for severe asthma treatment, in accordance with the EMA recommendations.	No serious adverse event was observed. Adverse events included erythema and pruritus at the injection site (n=1), myalgia (n=1), and asthenia 1 day after injection (n=1). 2 patients developed retrobulbar optic neuritis after 12 and 15 months on the drug. The optic neuritis was deemed to be disease relapse in both cases.	Indirect.
Glucocorticoid dosage – One study of 17 patients	Jachiet, 2016	Nationwide, retrospective study	22 months, median	17 patients with EGPA (7F, mean age 45y, 29% ANCA+) who	Omalizumab was administered subcutaneously once or twice per month. Given the retrospective design	Median prednisone dosage decreased from 16 mg/day at baseline to 10 mg/day, 11 mg/day,	Indirect.

with EGPA treated with omalizumab showed that prednisone dose can be lowered modestly while on the treatment.				received omalizumab	of this study, the dosage for each patient was defined by the practitioner in charge. The dosage was calculated according to the patient's IgE levels and body weight as suggested for severe asthma treatment, in accordance with the EMA recommendations.	and 9 mg/day at months 3, 6, and 12, respectively.	

112. In patients with EGPA and high IgE levels who have relapsed with non-severe disease manifestations (asthma and/or sino-nasal disease) while on methotrexate/azathioprine/MMF, what is the impact of switching to another agent on disease-related outcomes and treatment-related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies:

Author	Year	Title
Jachiet	2016	Anti-IgE Monoclonal Antibody (Omalizumab) in Refractory and Relapsing Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss): Data on Seventeen Patients

- Studies reviewed and excluded:

Author	Year	Title	Comments

A. Detoraki	2016	Omalizumab in patients with eosinophilic granulomatosis with polyangiitis: a 36-month follow-up study	Excluded for EGPA PICO 27. Less than 10 patients.
Z. Celebi Sozener	2018	Omalizumab in the treatment of eosinophilic granulomatosis with polyangiitis (EGPA): single-center experience in 18 cases.	Almost all patient were not treated with immunosuppression for induction/maintenance treatment. Only 5 subjects had Azathioprine as "add-on". Omalizumab was only added after subjects failed corticosterdoids. Does not really fit the patient population for PICO question 27

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Treatment: Relapse

- **PICO question 28:** In patients with EGPA who have relapsed with non-severe disease manifestations (asthma and/or sino-nasal disease) while on low dose glucocorticoids and no other therapy, what is the impact of increasing the dose of glucocorticoids versus adding methotrexate/azathioprine/MMF/mepolizumab on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, infection, serious adverse events, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hyperglycemia, decreased bone mineral density, hypersensitivity reaction)

113. In patients with EGPA who have relapsed with non-severe disease manifestations (asthma and/or sino-nasal disease) while on low dose glucocorticoids and no other therapy, what is the impact of increasing the dose of glucocorticoids versus adding methotrexate/azathioprine/MMF/mepolizumab on disease-related outcomes and treatment-related adverse events?
No comparative data available

114. In patients with EGPA who have relapsed with non-severe disease manifestations (asthma and/or sino-nasal disease) while on low dose glucocorticoids and no other therapy, what is the impact of increasing the dose of glucocorticoids on disease-related outcomes and treatment-related adverse events?
No single arm data available

115. In patients with EGPA who have relapsed with non-severe disease manifestations (asthma and/or sino-nasal disease) while on low dose glucocorticoids and no other therapy, what is the impact of adding methotrexate/azathioprine/MMF/mepolizumab on disease-related outcomes and treatment-related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:

  Non

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Other: role of continued prednisone use

- **PICO question 29:** In patients with EGPA in remission and currently only on prednisone, what is the impact of continuing with low dose prednisone long-term (e.g., > 18 months) vs. stopping low dose prednisone on disease-related outcomes and treatment related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, toxicity leading to discontinuation (e.g., hyperglycemia, decreased bone mineral density)

116. In patients with EGPA in remission and currently only on prednisone, what is the impact of continuing with low dose prednisone long-term (e.g., > 18 months) vs. stopping low dose prednisone on disease-related outcomes and treatment related adverse events?
No comparative data available

117. In patients with EGPA in remission and currently only on prednisone, what is the impact of continuing with low dose prednisone long-term (e.g., > 18 months) on disease-related outcomes and treatment related adverse events?
No single arm data available

118. In patients with EGPA in remission and currently only on prednisone, what is the impact of stopping low dose prednisone on disease-related outcomes and treatment related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:

  None

- Single arm studies:

  None

- Studies reviewed and excluded:

Author	Year	Title	Comments
A. Hara	2018	Risk Factors for Relapse of Antineutrophil Cytoplasmic Antibody-associated Vasculitis in Japan: A Nationwide, Prospective Cohort Study	Exclude. Does not answer the PICO question. Data not available for the small group of patients with EGPA.
M. M. Boomsma	2002	Prevalence of reduced bone mineral density in patients with anti-neutrophil cytoplasmic antibody associated vasculitis and the role of immunosuppressive therapy: a cross-sectional study	Exclude. Does not answer the PICO question. Data not stratified for the different diagnoses. 6/99 patients had EGPA and data results are only available for the whole group.
L. Guillevin	1999	Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients.	Excluded. This study is a follow up study on 4 clinical trials for induction therapy for EGPA. Per article, all patients received 1 mg/k/d for induction therapy, then was progressively tapered to 10 mg per day at year 1 (per protocol or clinical indication). Thereafter, it was not clearly specified during the long-term follow-up how many patients were on chronic low dose prednisone or how many stopped taking prednisone. Follow-up period was as long as 22 years. Moreover, it was not specified if all patients were only taking prednisone during remission period (PICO 29 queries EGPA patients only taking Prednisone during remission). Therefore, this article cannot provide clear answer for PICO 29.

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Other: role of continued prednisone use

- **PICO question 30:** In patients with EGPA in remission on remission maintenance therapy and prednisone, what is the impact of continuing low dose prednisone long-term (e.g., > 18 months) vs. stopping low dose prednisone and continuing remission maintenance therapy on disease-related outcomes and treatment related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, infection, serious adverse events, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity, hyperglycemia, decreased bone mineral density)

119. In patients with EGPA in remission on remission maintenance therapy and prednisone, what is the impact of continuing low dose prednisone long-term (e.g., > 18 months) vs. stopping low dose prednisone and continuing remission maintenance therapy on disease-related outcomes and treatment related adverse events?
No comparative data available

120. In patients with EGPA in remission on remission maintenance therapy and prednisone, what is the impact of continuing low dose prednisone long-term (e.g., > 18 months) on disease-related outcomes and treatment related adverse events?
No single arm data available

121. In patients with EGPA in remission on remission maintenance therapy and prednisone, what is the impact of stopping low dose prednisone and continuing remission maintenance therapy on disease-related outcomes and treatment related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:

  None

- Studies reviewed and excluded:

Author	Year	Title	Comments

M. M. Boomsma	2002	Prevalence of reduced bone mineral density in patients with anti-neutrophil cytoplasmic antibody associated vasculitis and the role of immunosuppressive therapy: a cross-sectional study	Exclude. Does not answer the PICO question. Data not stratified for the different diagnoses. 6/99 patients had EGPA and data results are only available for the whole group.

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Other: Role of nasal rinses

- **PICO question 31:** In patients with sino-nasal involvement in EGPA, what is the impact of using nasal rinses vs. not using nasal rinses on disease related outcomes and treatment-related adverse events?

- **Critical Outcomes:** sino-nasal symptoms, disease activity, disease damage, relapse, infection, toxicity leading to discontinuation, patient reported outcomes

122. In patients with sino-nasal involvement in EGPA, what is the impact of using nasal rinses vs. not using nasal rinses on disease related outcomes and treatment-related adverse events?
No comparative data available

123. In patients with sino-nasal involvement in EGPA, what is the impact of using nasal rinses on disease related outcomes and treatment-related adverse events?
No single arm data available

124. In patients with sino-nasal involvement in EGPA, what is the impact of not using nasal rinses on disease related outcomes and treatment-related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:

None

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Other: Pneumocystis prophylaxis

- **PICO question 32:** In patients with EGPA on cyclophosphamide or rituximab, what is the impact of using Pneumocystis prophylaxis vs. not using Pneumocystis prophylaxis on pneumocystis infection and treatment-related adverse events?

- **Critical Outcomes:** Pneumocystis infection, death, other infection, serious adverse events, toxicity leading to discontinuation (e.g., adverse reaction to prophylaxis)

125. In patients with EGPA on cyclophosphamide or rituximab, what is the impact of using Pneumocystis prophylaxis vs. not using Pneumocystis prophylaxis on pneumocystis infection and treatment-related adverse events?
- No Comparative Data Avaliable

126. In patients with EGPA on cyclophosphamide or rituximab, what is the impact of using Pneumocystis prophylaxis on pneumocystis infection and treatment-related adverse events?

- **Patient Important Outcomes:**

  Effect of TMP-SMX prophylaxis on 1-year PCP incidence and 1-year PCP-related mortality in propensity score-matched population (n=470)

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	New Comparison	placebo	Relative (95% CI)	Absolute (95% CI)	
1 year PCP incidence											
1	observational studies	not serious	not serious	not serious	not serious	none	-/0	-/0	**HR 0.07** (0.01 to 0.53)	**0 fewer per 1,000** (from 1 fewer to 0 fewer)	⊕⊕◯◯ LOW
1-year PCP related mortality											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	New Comparison	placebo	Relative (95% CI)	Absolute (95% CI)	
1	observational studies	not serious	not serious	not serious	not serious	none	-/0	-/0	**HR 0.07** (0.01 to 0.65)	**0 fewer per 1,000** (from 1 fewer to 0 fewer)	⊕⊕◯◯ LOW

- **References:**

- Randomized controlled trials:

  None

- Comparative Observational Studies:

  None

- Single Arm Studies:

Author	Year	Title
J. W. Curtis	2018	Prophylactic effect of trimethoprim-sulfamethoxazole for pneumocystis pneumonia in patients with rheumatic diseases exposed to prolonged high-dose glucocorticoids

- Studies reviewed and excluded:

  The table below includes clinical trials in EGPA and Pneumocystis prophylaxis was checked in these RCTs to check for indirect evidence:

Author	Year	Title	Comments
X. Puechal	2017	Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial	Prophylaxis against Pneumocystis jiroveci pneumonia (cotrimoxazole or aero- solized pentamidine if cotrimoxazole was not tolerated) was compulsory for patients with CD4 T lymphocyte counts of <300/mm3. No other information provided.
L. Guillevin	1997	Treatment of glomerulonephritis in microscopic polyangiitis and Churg-Strauss syndrome. Indications of plasma exchanges, Meta-analysis of 2 randomized studies on 140 patients, 32 with glomerulonephritis	Metanalaysis, no mention of Prophylaxis against Pneumocystis jiroveci

L. Guillevin	1997	Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis. A prospective, randomized trial in sixty-two patients	It was strongly recommended that CD4 lymphocyte counts be monitored every 3 months, or every month if the CD4 count was found to be <300/mm3. In the latter situation, prophy-lactic treatment against Pneumocystis carinii pneumonia (cotrimoxazole, 1 tabletjday) was prescribed. No other information provided.
L. Guillevin	1994	Treatment of polyarteritis nodosa and Churg-Strauss syndrome: indications of plasma exchanges	No mention of Prophylaxis against Pneumocystis jiroveci
L. Guillevin	1992	Treatment of polyarteritis nodosa and Churg-Strauss syndrome. A meta-analysis of 3 prospective controlled trials including 182 patients over 12 years	Metanalaysis, no mention of Prophylaxis against Pneumocystis jiroveci
L. Guillevin	1991	Longterm followup after treatment of polyarteritis nodosa and Churg-Strauss angiitis with comparison of steroids, plasma exchange and cyclophosphamide to steroids and plasma exchange. A prospective randomized trial of 71 patients. The Cooperative Study Group for Polyarteritis Nodosa	No mention of Prophylaxis against Pneumocystis jiroveci
L. Guillevin	1990	Treatment of polyarteritis nodosa and Churg-Strauss angiitis: indications of plasma exchange. Results of three prospective trials in 162 patients. The Cooperative Study Group for the Study of Polyarteritis Nodosa	No mention of Prophylaxis against Pneumocystis jiroveci
M. E. Wechsler	2017	Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis	No mention of Prophylaxis against Pneumocystis jiroveci
R. B. Jones	2015	Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial	No mention of Prophylaxis against Pneumocystis jiroveci
L Guillevin	1991	The absence of superiority of the association of plasma exchanges and corticosteroids versus corticosteroids during polyarteritis nodosa or Churg-Strauss syndrome. Final analysis of a prospective study in 78 patients.	No mention of Prophylaxis against Pneumocystis jiroveci
C Pagnoux	2012	Treatment of systemic necrotizing vasculitides in patients >65 years old: results of the multicenter randomized cortage trial	Patients receiving CYC were given mesna for bladder protection at each pulse and cotrimoxazole (800 mg sulfamethoxazole/160 mg trimethoprim, 3 times per week) prophylaxis against *Pneumocystis jiroveci* infection, until 3 months after their last CYC pulse (17–19). No pulmonary

			Pneumocystis jiroveci infection occurred. One pa- tient in the experimental arm died 2.5 years after his granulomatosis with polyangiitis (Wegener's) diagnosis, of lung tuberculosis with esophageal–bronchial fistulas.
C Pagnoux	2003	Treatment of Churg Strauss syndrome (css) with poor prognosis factor(s): a prospective, randomized, multicenter trial comparing corticosteroids (cs) and 6 vs 12 cyclophosphamide	For CD4+ lymphocyte counts <300/mm^3, cotrimoxazole (400 mg of trimethoprim/80 mg of sulfamethoxazole per day) therapy as prophylaxis against *Pneumocystis jiroveci* pneumonia was required. The dosage has never been demonstrated to modify the course of vasculitis.

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Other: Role of leukotriene inhibitors

- **PICO question 33:** In patients with newly diagnosed EGPA and on leukotriene inhibitors what is the impact of discontinuing leukotriene inhibitors versus continuing leukotriene inhibitors on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** asthma control, disease activity, disease damage, death, serious adverse events, toxicity leading to discontinuation

127. In patients with newly diagnosed EGPA and on leukotriene inhibitors what is the impact of discontinuing leukotriene inhibitors versus continuing leukotriene inhibitors on disease-related outcomes and treatment-related adverse events?
   - No Comparative Data Available

128. In patients with newly diagnosed EGPA and on leukotriene inhibitors what is the impact of discontinuing leukotriene inhibitors on disease-related outcomes and treatment-related adverse events?
   - No Data Avaliable

129. In patients with newly diagnosed EGPA and on leukotriene inhibitors what is the impact of continuing leukotriene inhibitors on disease-related outcomes and treatment-related adverse events?
   - **Patient Important Outcomes**

Outcomes	Author, year	Study type	Duration of follow up	Population	Intervention used in relevant population	Results	Comments

Risk of of EGPA onset with patients taking montelukast	Hauser T, 2008	Case-crossover design	1999-2004	78 patients with EGPA 43 males 35 females 20 pts exposed to montelukast and 58 not exposed to the drug	Case-crossover analysis Retrospective review of data from prospective patients enrolled in another study Exposure rates to montelukast and other classes of asthma meds during 15 months before EGPA onset Beside montelukast, other drugs for asthma were evaluated: inhaled long acting B2 agonists, inhaled corticosteroids, and oral corticosteroids.	20/78 pts were exposed to montelukast (26%) Mean interval from starting the medication to EGPA onset: 11.3 months(median 8.4) Montelukast treatment was associated with a statistically significant 4/5 fold increased risk of developing EGPA within 3 months. All asthma medications also incurred with an increased risk but not all statistically significant . ORs for 3-months periods: Montelukast: 6.7 (95% CI 1.3-34.1) Inhaled long acting b2 agonists: 2.9 (0.6-13.3) Inhaled CS: 1. (0.2-4.8) Oral CS: 4.2 (1.2-14.6)	The result of the study was not able to distinguish a true association between Montelukast and increased risk of EGPA from montelukast being a proxy measure for gradually worsening asthma at an individual level.
	Harrold L, 2006	Population based, nested case-control study		Source of population: 3 US managed care organizations and UnitedHealthCare enrollees followed in the Ingenix Research Data Mart	32 definite/probable and 15 possible cases of EGPA were matched to 4700 controls.	In the 2-6 months prior to the diagnosis of EGPA, only 6/47 cases were exposed to leukotriene modifiers After adjustment for the effects of all the drug exposures, use of	Small number of patients and exposure limits power to detect an association. Largest population based study of EGPA to date of publication

				381,459 asthma drug users		leukotriene modifiers (OR 1.32, 95% CI 0.90-1.72) was not associated with EGPA	Only 47 cases of EGPA and of those only 6 exposed to leukotriene modifiers.

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies: (2)

Author	Year	Title
T. Hauser	2008	The leucotriene receptor antagonist montelukast and the risk of Churg-Strauss syndrome: a case-crossover study
L. R. Harrold	2007	Asthma drug use and the development of Churg-Strauss syndrome (CSS)

Eosinophilic Granulomatosis with Polyangiitis (EGPA; Churg-Strauss)

Other: Role of leukotriene inhibitors

- **PICO question 34:** In patients with EGPA and active asthma and/or sino-nasal disease what is the impact of adding leukotriene inhibitors versus not adding leukotriene inhibitors on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** asthma control, disease activity, disease damage, relapse, death, serious adverse events, toxicity leading to discontinuation

130. In patients with EGPA and active asthma and/or sino-nasal disease what is the impact of adding leukotriene inhibitors versus not adding leukotriene inhibitors on disease-related outcomes and treatment-related adverse events?
No comparative data available

131. In patients with EGPA and active asthma and/or sino-nasal disease what is the impact of adding leukotriene inhibitors on disease-related outcomes and treatment-related adverse events?
No single arm data available

132. In patients with EGPA and active asthma and/or sino-nasal disease what is the impact of not adding leukotriene inhibitors on disease-related outcomes and treatment-related adverse events?

No single arm data available

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies:

  None

- Studies reviewed and excluded:

Author	Year	Title	Comments
T. Hauser	2008	The leucotriene receptor antagonist montelukast and the risk of Churg-Strauss syndrome: a case-crossover study	Exclude. Does not address PICO question.
L. R. Harrold	2007	Asthma drug use and the development of Churg-Strauss syndrome (CSS)	Exclude. Does not address PICO question.