Supplementary Appendices: PCP Prophylaxis Guidelines

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Appendix 1: Antiproliferative Agents and Low Dose Prednisone

Search Strategy:

Medline 1946 to Present
Search executed on Dec 1, 2019

Search Terms:
Azathioprine AND prednisone AND Pneumocystis jirovecii pneumonia

- These are MESH headings, automatically mapped and exploded by Medline (e.g. PCP, Pneumocystis jirovecii pneumonia and Pneumocystis carinii pneumonia provided the same results).

Mycophenolate AND prednisone AND Pneumocystis jirovecii pneumonia

- These are MESH headings, automatically mapped and exploded by Medline

** note: this search is not exclusive for GN patients

Limits:

- Human
- English Language

Results:
Azathioprine AND prednisone AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=19
- Number of articles identified through review of reference: n=1
- Full-text papers selected for appraisal and analysis: n=2

Mycophenolate AND prednisone AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=5
- Number of articles identified through review of reference: n=1
- Full-text papers selected for appraisal and analysis: n=2

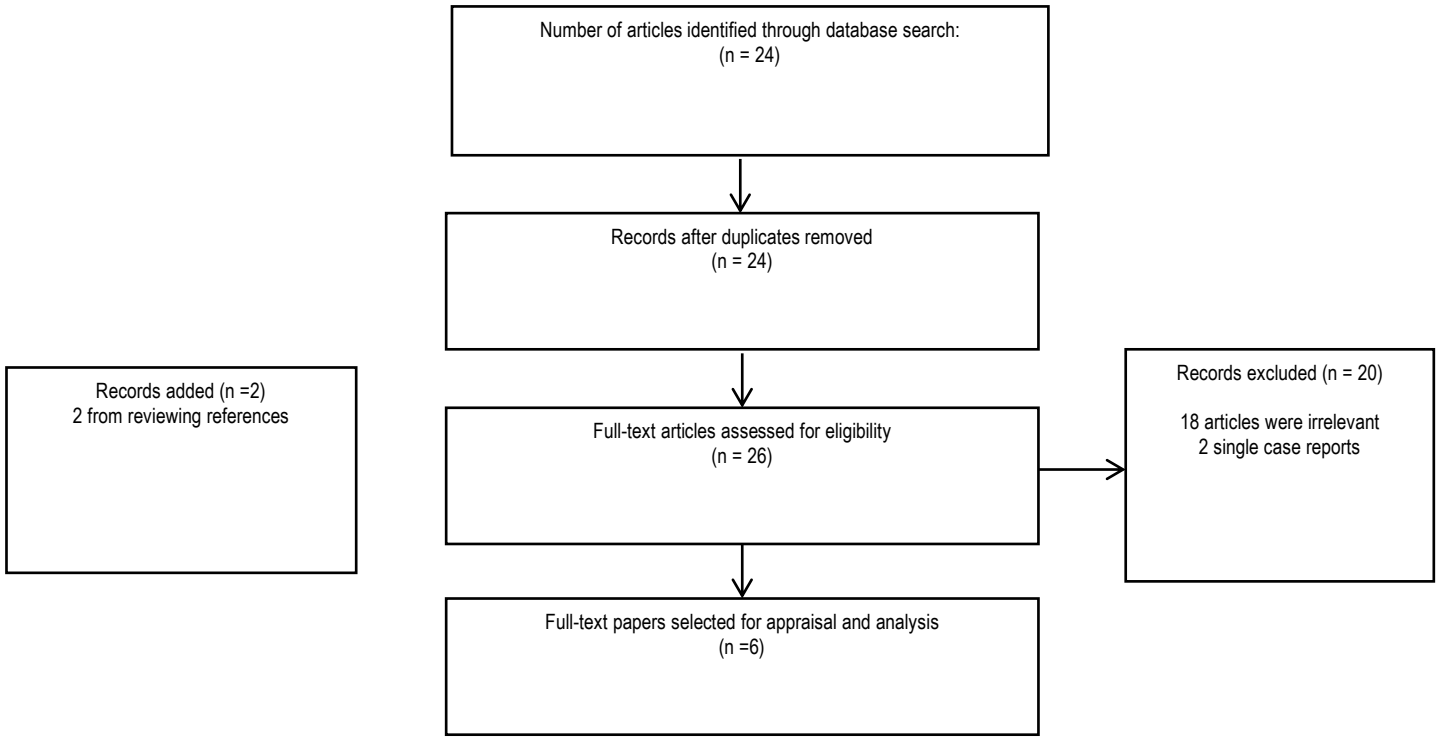
Number of articles identified through database search:
(n = 24)
Records after duplicates removed
(n = 24)
Records added (n =2)
2 from reviewing references
Full-text articles assessed for eligibility
(n = 26)
Records excluded (n = 20)
18 articles were irrelevant
2 single case reports
Full-text papers selected for appraisal and analysis
(n =6)

Table 1: Azathioprine AND prednisone AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
Decker et al. Cyclophosphamide or azathioprine in lupus glomerulonephritis. A controlled trial: results at 28 months. Ann Intern Med. 1975 Nov; 83(5): 606-15.	Prospective follow-up study after single center RCT looking at AZA, CYC or Pb added to low dose prednisone (≤ 0.5 mg/kg/d)	SLE patients with renal involvement (n=38); excluded pts with CrCl< 20 mL/min, SCr > 4 mg/100 mL No PCP prophylaxis given	Placebo (n=15) vs. CYC PO up to 4 mg/kg/d (n=10) vs. AZA up to 4 mg/kd/d (n=13) + all pts prednisone 0.5 mg/kg/d Mean follow-up: 32 months [range from 1 to 44 months]	-Primary outcome=> unfavorable outcome (death or HD start) **1 pt in CYC group died of PCP after 2.5 months -incidence = 10%** -	N/A	Not designed to look at adverse outcome.
Rifkind et al. Transplantation Pneumonia JAMA. 1964 Sep 14; 189 :808-12.	Retrospective study	6 kidney transplant pts with pneumonitis Onset within 42 to 102 days.	AZA and prednisone 1 mg/kg/day Age 3 to 30 y/o	6 out of the first 42 pts who have received a transplant at this center developed pneumonic process (higher prevalence in younger pts) 1 confirmed case of PJP: 16 y/o pt with kidney Tx on AZA + prednisone (200 mg/d) with gradual taper. On day 85th (was on prednisone 45 mg/d), started fever => died on day 97th. He was treated with penicillin G and chloramphenicol.		In 1964 there was no curative treatment for PCP, or an easy way to diagnose it (usually confirmed post mortem).
McGonigle et al. Does cyclosporin A adversely affect Pneumocystis carinii infection? Postgrad Med J. 1988 Sep; 64(755): 659-62.	Case series of PCP patients; descriptive comparison of patients who received CYC/AZA to those who received CsA	N=14 PCP pts in total • All pts received concomitant prednisolone 10-20 mg/d at time of PCP diagnosis • No pts received PCP prophylaxis <u>Group 1: 7 pts who received prednisolone + CYC/AZA (did not provide the number of pats who received CYC vs. AZA specifically):</u> • 2 pts with SLE, 5 pts with renal transplantation • CYC dose: 2-3 mg/kg/d adjusted according to leukocyte count • AZA dose: 2-2.5 mg/kg/d • Treatment with high-dose IV TMP-SMX (1920 mg 6-hourly) in all cases • All pts survived • Stable graft function in all 5 pts with renal transplantation <u>Group 2: 7 pts who received prednisolone + CsA:</u> • All pts were renal transplant recipients • CsA dose: 15 mg/kg/day orally initially, reduced to maintenance dose to keep trough levels within recommended therapeutic dose • Treatment with high-dose IV TMP-SMX (1920 mg 6-hourly) in all cases; 2 patients also received pentamidine 200 mg IV daily • 4 of 7 pts lived Stable graft function in 2 of the 3 pts who lived			Despite identical PCP treatment, pts who received CsA had worse outcomes compared to those who received CYC or AZA. This raises the question of prophylactic TMP-SMX in patients taking CsA+ prednisolone.	Numbers of pts who received specifically CYC or AZA were not provided. Difficult to draw valid conclusions from case series.

Abbreviations: AZA (azathioprine); CrCl (creatinine clearance); CsA (cyclosporine); sCr (serum creatinine); CYC (cyclophosphamide); HD (hemodialysis) PCP (Pneumocystis jirovecii pneumonia); pts (patients); RCT (randomized controlled trial); SLE (systemic lupus erythematosus); TMP-SMX (trimethoprim-sulfamethoxazole).

Table 2: Mycophenolate AND prednisone AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
Wan et al. Severe pneumonia in mycophenolate mofetil combined with low-dose corticosteroids-treated patients with immunoglobulin A nephropathy. Kaohsiung J Med Sci. 2015 Jan; 31(1): 42-6.	Retrospective chart review	Chinese pts with IgA (N=53) registered for follow up at a single center (Shenzhen Second People's Hospital in Guangdong China)	MMF + methylprednisolone 0.5 mg/kg/d) or prednisone (0.5 mg/kg/d), steroid initial dose x 2 months, then taper by 5 mg q2weeks until discontinued	Out of 53 pts, 9 pts developed severe pneumonia around 3rd month 4 pts diagnosed with PCP, MMF dose 1.5g/d for 3 pts and 1 g/d for 1 pt (Incidence rate = 7.5%)	Patients with severe pneumonia had a lower eGFR compared to those who didn't. (41.3 mL/min/1.73m^2 vs. 65.3 mL/min/1.73m^2) -lower renal function may increase MMF accumulation. MMF+ prednisone is safer than MMF+ methylprednisone. MMF is reported to be safe monotherapy, concerns are the addition of corticosteroid.	Small group of volunteer patients was followed.
Zhang Y1, Zheng Y. Pneumocystis jirovecii pneumonia in mycophenolate mofetil-treated patients with connective tissue disease: analysis of 17 cases. Rheumatol Int. 2014 Dec; 34(12): 1765-71.	Case-series	19 pts with CDT and PCP		Of 4120 pts, 17 cases of PCP identified (incidence = 0.4%) 6 SLE cases, 1 polymyositis,1 dermatomyositis, 1 RA case, 2 Wegener cases and 6 MPA cases 13 female pts. Mean age 58 ±13 yrs 16/17 pts were on CS (dose range 10-80 mg/d) 10 pts on MMF, 1 pt on AZA, 1 pt on MTX, 4 pts on CYC The 10 MMF pts and 5 non-MMF pts had	This study is the first report of PCP following MMF plus CS treatment in patients with CTD. CTD itself may be a risk factor for PCP. When CTD patients receiving MMF therapy have low lymphocyte counts and/or CD4 lymphocyte counts <250/μL, we should be careful of occurrence of PCP.	Small no. Cases. Wide steroid dose range used, and distribution not reported.

				lymphoctyes < 1,000/uL Out of 6 pts who died of PJP, 5 pts were on MMF, the other pt was on CS 6 out of 17 pts had complicating fungal infection at the time of PCP None of the patients with PCP received prophylaxis		
Schmajuk et al. Pneumocystis jirovecii pneumonia (PJP) prophylaxis patterns among patients with rheumatic diseases receiving high-risk immunosuppressant drugs. Sem in Arthritis and Rheum 2019; 48: 1087-1092.	Single-center retrospective cohort study using electronic health record data with mean follow-up 23.2 ± 14.2 months	N = 316 pts >18 years of age with diagnosis of GPA, MPA, dermatomyositis, polymyositis, or SLE who were new users of certain immunosuppressive agents Mean age 43 years, 15% GPA , 7% MPA, 56% SLE	Comparison of patients who received PCP prophylaxis (TMP-SMX, dapsone, atovaquone, or pentamidine) vs. patients who did not receive PCP prophylaxis <u>48 pts who received MMF + low-dose CS (< 20 mg prednisone equivalent):</u> 14 pts with prophylaxis vs. 34 without prophylaxis <u>27 pts who received AZA + low-dose CS (< 20 mg prednisone equivalent):</u> 9 pts with prophylaxis vs. 18 pts without prophylaxis	No pts received PCP diagnosis (as defined using diagnosis codes) Among all 192 study pts who received PCP prophylaxis: With mean follow-up 26 months, 9.7% had an ADE (serious/life-threatening in 1.5% of those taking TMP-SMX; 17.9% of those taking dapsone; 0% of those taking atovaquone or pentamidine)	No conclusions provided regarding PCP risk with MMF+ low-dose CS or AZA+ low- dose CS. The incidence of PCP is extremely low, and ADEs from antibiotics occur at a low but detectable rate. Evidence to guide more personalized risk assessment are needed to inform PCP prophylaxis.	Retrospective design. Pts had variable follow-up durations. Did not provide information on MMF+ CS or AZA+ CS regimens administered.

Abbreviations: ADE (adverse drug event); CS (corticosteroid); CTD (connective tissue disease); CYC (cyclophosphamide); GPA (granulomatosis with polyangiitis); MMF (mycophenolate mofetil); MPA (microscopic polyangiitis); MTX (methotrexate); PCP (Pneumocystis jirovecii pneumonia); pts (patients); RA (rheumatoid arthritis); SLE (systemic lupus erythematosus); TMP-SMX (trimethoprim-sulfamethoxazole).

Appendix 2: Antiproliferative Monotherapy

Search Strategy:

Medline 1946 to Present
Search executed on Dec 26, 2019

Search Terms:
Azathioprine AND Pneumocystis jirovecii pneumonia
These are MESH headings, automatically mapped and exploded by Medline (e.g. PCP, Pneumocystis jirovecii pneumonia and Pneumocystis carinii pneumonia provided the same results).

Mycophenolate AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline

** note: this search is not exclusive for GN patients

Limits:
- Human
- English Language

Results:
Azathioprine AND Pneumocystis jirovecii pneumonia
- Number of articles identified through database search: n=61
- Number of articles identified through review of reference: n=1
- Full-text papers selected for appraisal and analysis: n=1

Mycophenolate AND Pneumocystis jirovecii pneumonia
- Number of articles identified through database search: n=28
- Number of articles identified through review of reference: n=1
- Full-text papers selected for appraisal and analysis: n=1

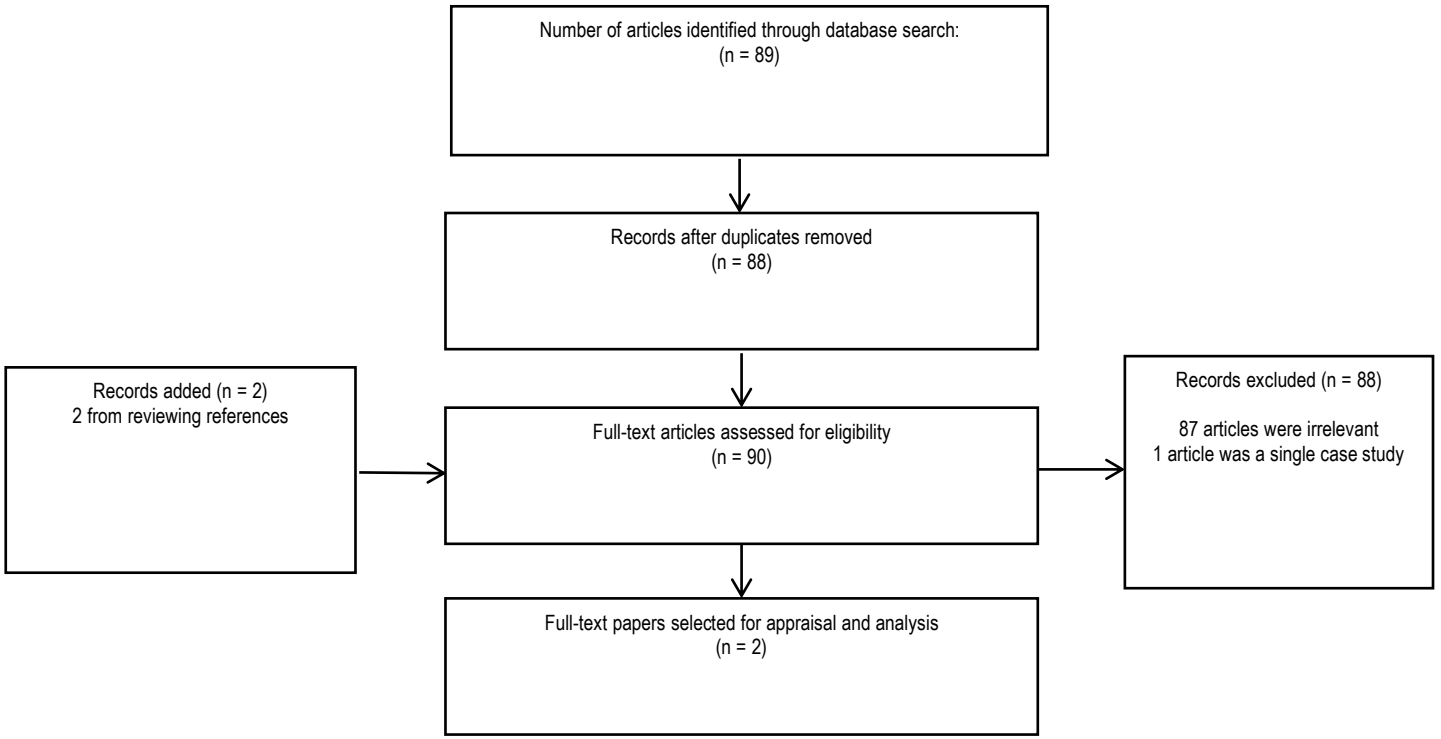
Number of articles identified through database search:
(n = 89)
Records after duplicates removed
(n = 88)
Records added (n = 2)
2 from reviewing references
Full-text articles assessed for eligibility
(n = 90)
Records excluded (n = 88)
87 articles were irrelevant
1 article was a single case study
Full-text papers selected for appraisal and analysis
(n = 2)

Table 3: Azathioprine AND Pneumocystis jirovecii pneumonia

Guillevin et al. Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis *MAINRITSAN trial*	Nonblinded RCT of AAV pts Follow-up until month 28 for all pts	N=118 AAV pts 18-75 years of age, in complete remission after a CYC-CS regimen. Enrolled within a maximum of 1 month after last CYC pulse. Mean age 55 years GPA 76%, MPO 20%, renal-limited AAV 4% Newly diagnosed AAV in 80%, relapsing AAV in 20%	AZA group: Maintenance therapy with AZA 2 mg/kg/day x 12 months, then 1.5 mg/kg/day x 4 months RTX group: Maintenance therapy with RTX 500 mg IV on days 0 and 14, then months 6, 12, and 18 after first infusion Ongoing CS: Mean prednisone dose at randomization 17.6 ± 7.3 mg/day; tapered and kept at a low dose (approx. 5 mg/day) for at least 18 months after randomization. Further tapering and decision to discontinue CS left to the investigator's discretion. PCP prophylaxis: TMP-SMX 80 mg/400 mg daily (or monthly pentamidine inhalation if sulfa allergy) for all patients with CD4+ T-lymphocyte count < 250/mm^3. At end of 18 months of maintenance treatment, TMP-SMX 800 mg/160 mg PO BID prescribed for patients with GPA, as recommended according to good clinical practice.	1 pt in RTX group developed PCP; survived No pt in AZA group developed PCP	No conclusions provided specific to PCP risk with AZA.	No information provided on the proportion of pt that received PCP prophylaxis.

Abbreviations: AZA (azathioprine); PO (microscopic polyangiitis); PCP (Pneumocystis jirovecii pneumonia); PO (oral); pts (patients); RCT (randomized- controlled trial); RTX (rituximab); TMP-SMX (trimethoprim/sulfamethoxazole).

Table 4: Mycophenolate AND Pneumocystis jirovecii pneumonia

Schmajuk et al. Pneumocystis jirovecii pneumonia prophylaxis patterns among patients with rheumatic diseases receiving high-risk immunosuppressant drugs. Sem in Arthritis and Rheum 2019; 48: 1087-1092.	Single-center retrospective cohort study using electronic health record data with mean follow-up 23.2 ± 14.2 months	N = 316 pts >18 years of age with diagnosis of GPA, MPA, dermatomyositis, polymyositis, or SLE who were new users of certain immunosuppressive agents Mean age 43 years, GPA 15%, 7% MPA, 56% SLE	Comparison of patients who received PCP prophylaxis (TMP-SMX, dapsone, atovaquone, or pentamidine) vs. patients who did not receive PCP prophylaxis <u>19 pts who received MMF monotherapy:</u> 1 with prophylaxis vs.18 without prophylaxis <u>6 pts who received AZA monotherapy:</u> 2 with prophylaxis vs. 4 without prophylaxis	No patients received PCP diagnosis (as defined using diagnosis codes) <u>Among all 192 study pts who received PCP prophylaxis:</u> With mean follow-up 26 months, 9.7% had an ADE (serious/life-threatening in 1.5% of those taking TMP-SMX; 17.9% of those taking dapsone; 0% of those taking atovaquone or pentamidine)	No conclusions specific to MMF or AZA monotherapy and PCP risk were provided. The incidence of PCP is extremely low, and ADEs from antibiotics occur at a low but detectable rate. Evidence to guide more personalized risk assessment are needed to inform PCP prophylaxis.	Retrospective design. Patients had variable follow-up durations. Did not provide information on MMF or AZA regimens administered.

Abbreviations: ADEs (adverse drug events); azathioprine (AZA); GPA (granulomatosis with polyangiitis); MPA (microscopic polyangiitis); Pneumocystis jirovecii pneumonia (PJP); pts (patients); SLE (systemic lupus erythematosus); TMP-SMX (trimethoprim/sulfamethoxazole).

Appendix 3: Dual Antiproliferative Therapy

Search Strategy:

Medline 1946 to Present
Search executed on Dec 1, 2019

Search Terms:
Azathioprine AND mycophenolate AND Pneumocystis jirovecii pneumonia

- These are MESH headings, automatically mapped and exploded by Medline (e.g. PCP, Pneumocystis jirovecii pneumonia and Pneumocystis carinii pneumonia provided the same results).

** note: this search is not exclusive for GN patients

Limits:

- Human
- English Language

Results:
Azathioprine AND mycophenolate AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=3
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=0

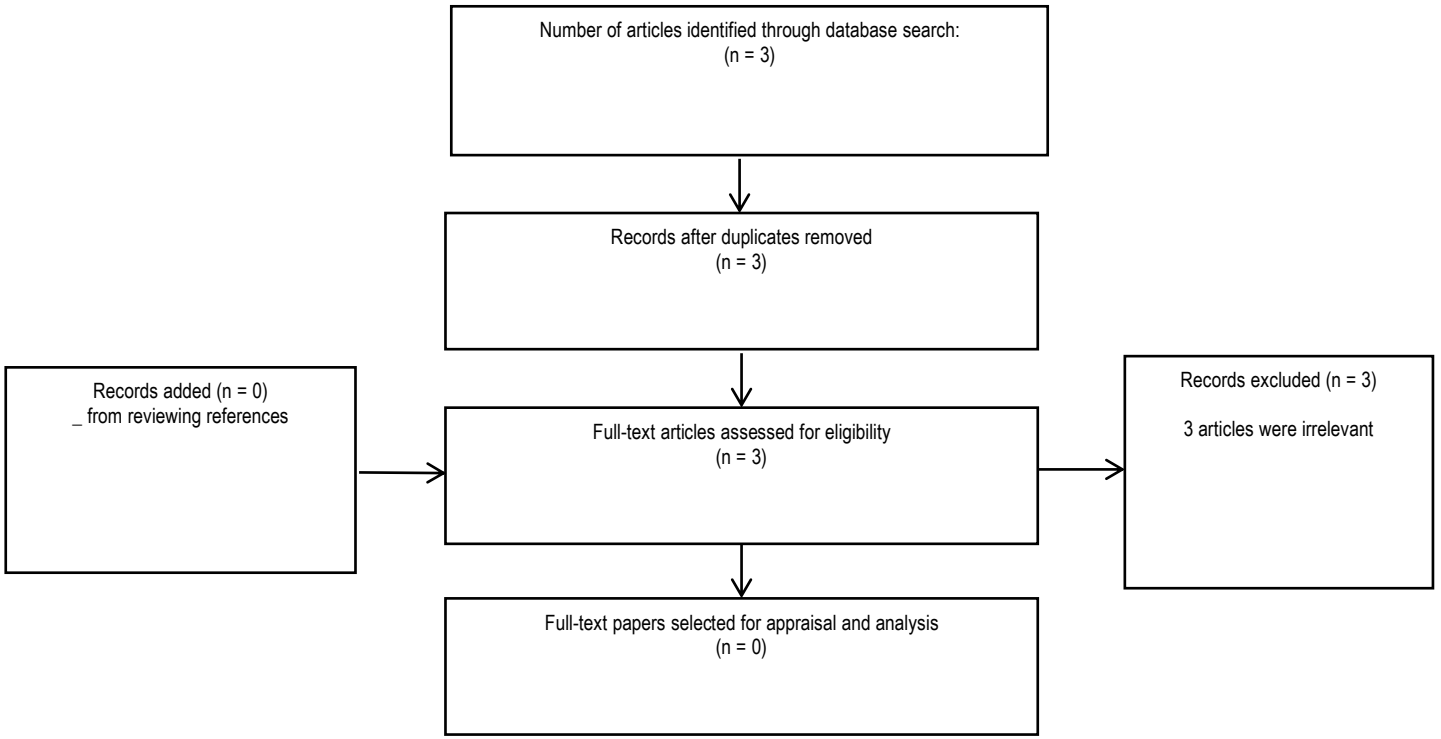
Number of articles identified through database search:
(n = 3)
Records after duplicates removed
(n = 3)
Records added (n = 0)
_ from reviewing references
Full-text articles assessed for eligibility
(n = 3)
Records excluded (n = 3)
3 articles were irrelevant
Full-text papers selected for appraisal and analysis
(n = 0)

Table 5: Azathioprine AND mycophenolate AND Pneumocystis carinii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
No papers						

Appendix 4: Calcineurin Inhibitor Monotherapy

Search Strategy:

Medline 1946 to Present
Search executed on Dec 26, 2019

Search Terms:
Tacrolimus AND Pneumocystis jirovecii pneumonia

- These are MESH headings, automatically mapped and exploded by Medline (e.g. PCP, Pneumocystis jirovecii pneumonia and Pneumocystis carinii pneumonia provided the same results).

Cyclosporine AND Pneumocystis jirovecii pneumonia

- These are MESH headings, automatically mapped and exploded by Medline
- Page 3

** note: this search is not exclusive for GN patients

Limits:

- Human
- English Language

Results:
Tacrolimus AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=45
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=2

Cyclosporine AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=96
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=2

- Full-text papers selected for appraisal and analysis: n=3

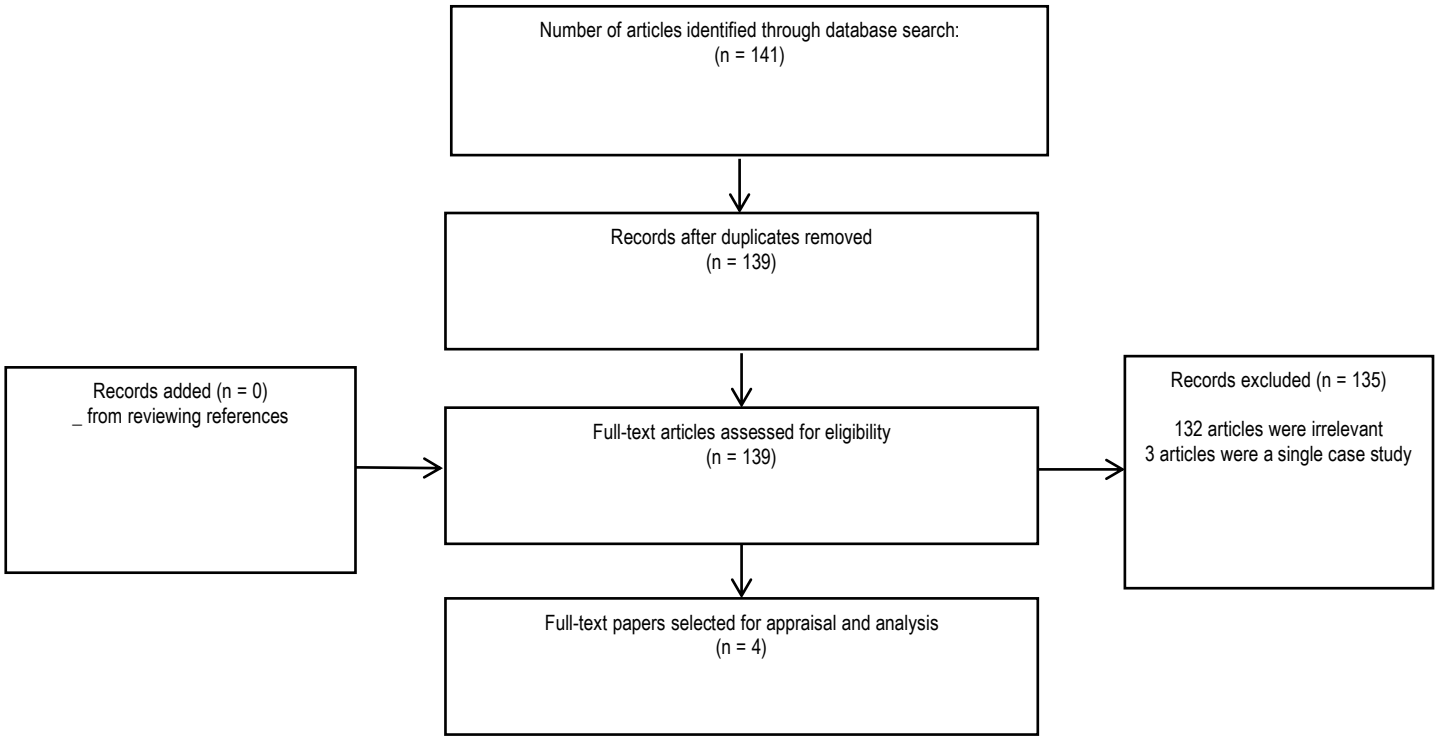

Table 6: Tacrolimus AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention		Outcome	Conclusion	Limitations
Escher M, Stange EF, Herrlinger KR. Two cases of fatal Pneumocystis jirovecii pneumonia as a complication of tacrolimus therapy in ulcerative colitis--a need for prophylaxis. J Crohns Colitis. 2010 Nov;4(5):606-9.	Single case study ➔ exclude Both cases CNI + CS (one with triple therapy)		<u>Case 1 CNI+ CS:</u> 72 y/o man with UC x 3 months. Severe rectal bleeding and abdominal pain despite high dose CS (unknown duration), so TAC was initiated at 0.01 mg/kg. Six days after TAC initiation, pt developed respiratory insufficiency. TPM-SMX was initiated, with piperacillin, combactam, levofloxacin and fluconazole. Pt died 23 days after starting TAC. <u>Case 2 CNI + CS + 6-mercaptopurine:</u> 74 y/o man with resistant UC diagnosis. Two years after initiation of triple therapy, pt developed respiratory insufficiency and sepsis. High dose TMP-SMX was initiated. Pt died 2 weeks later.		For their program (Germany), 200 cases over 10 years of patients treated with TAC for steroid resistant UC flare. These are the only 2 cases of PCP (incidence 1%).		
Orlando et al. Ab initio calcineurin inhibitor-based monotherapy immunosuppression after liver transplantation reduces the risk for Pneumocystis jirovecii pneumonia. Transpl Infect Dis. 2010 Feb;12(1):11-5.	Retrospective study of all patients who received a Liver Tx at their center (Vertaga University in Rome) between 2001 and 2008.	203 Liver Tx pts, CNI monotherapy		No PCP prophylaxis given to pts, No CS given at baseline. C2 target 700-800 ng/mL for first 2 months, then 500-700 ng/mL Trough TAC level 6-8 ng/mL x first 2 months, than target 4-6 ng/mL. CS only used for severe acute rejection. MMF or rapamycin given if increased sCr.	No PCP case reported at 1 and 5 years. 10.2% of pts had bacterial infection, 3.9% CMV and 0.6% fungal infection. Rate of acute rejection 4.5% with less than 1/3 of episodes requiring additional IS.		

Other abbreviations: CMV (cytomegalovirus); CNI (calcineurin inhibitor); CS (corticosteroid); IS (immunosuppressant); MMF (mycophenolate mofetil); PCP (Pneumocystis jirovecii pneumonia); sCr (serum creatinine); TAC (tacrolimus); TMP-SMX (trimethoprim/sulfamethoxazole); Tx (transplant); UC (ulcerative colitis).

Table 7: Cyclosporine AND Pneumocystis jirovecii pneumonia (PCP)

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
Santos et al. Efficacy of intravenous cyclosporine for steroid refractory attacks of ulcerative colitis. J Clin Gastroenterol. 1995 Jun;20(4):285-9.	Retrospective open label cohort study Case CsA +CS => added to appropriate table	21 UC pts with refractory UC hospitalized and failed to improve despite methylprednisone 1 mg/kg/24h and TPN x 10 days. Exclusion: colonic stenosis, toxic megacolon, concomitant infections, CKD, treatment with other IS, gestation, mental deficit. 15 men/6women; mean age 30 y/o [15 to 74 y/o]	IV CsA (5 mg/kg/24 hrs), administered as continuous infusion for 4-6 hours, target trough level 100-400 ng/mL Pt who improved stated PO diet and CS tapered off. If improvement persisted, CsA was switched to PO and maintained for a mean period of 8.4 months [range 1-48 months]	-One of the pt who entered remission while on CsA died of PCP -16/21 pts improved in 9 days; 10 pts entered into remission, 7 discontinued CS.		-No information about CS dosage while developed PCP.
Kay et al. Infections after bone marrow transplantation using cyclosporine. Transplantation. 1983 Nov;36(5):491-5.	Single-center retrospective open label cohort study	N=86 consecutive BMT patients Baseline characteristics not provided	CsA as a preventive of GVHD reactions (dosing not provided) TMP-SMX as PCP prophylaxis from 30-180 days after transplant	PCP diagnosed in only 1 patient 15 weeks after BMT, when PCP had been discontinued due to a skin sensitivity	Lack of PCP infection can be attributed to PCP prophylaxis	Retrospective design Description of CsA regimen(s) administered not provided

Abbreviations: BMT (bone marrow transplant); CKD (chronic kidney disease); CsA (cyclosporin); CS (corticosteroid); GVHD (graft versus host disease); IS (immunosuppressant); IV (intravenous); PCP (Pneumocystis jirovecii pneumonia); PO (oral); pt (patient); TMP-SMX (trimethoprim/sulfamethoxazole); TPN (total parenteral nutrition); UC (ulcerative colitis).

Appendix 5: Calcineurin Inhibitor and Low-dose Prednisone

Search Strategy:

Medline 1946 to Present
Search executed on Dec 1, 2019

Search Terms:
Tacrolimus AND prednisone AND Pneumocystis jirovecii pneumonia

- These are MESH headings, automatically mapped and exploded by Medline (e.g. PCP, Pneumocystis jirovecii pneumonia and Pneumocystis carinii pneumonia provided the same results).

Cyclosporine AND prednisone AND Pneumocystis jirovecii pneumonia

- These are MESH headings, automatically mapped and exploded by Medline

** note: this search is not exclusive for GN patients

Limits:

- Human
- English Language

Results:
Tacrolimus AND prednisone AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=4
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=0

Cyclosporine AND prednisone AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=9
- Number of articles identified through review of reference: n=1
- Full-text papers selected for appraisal and analysis: n=3

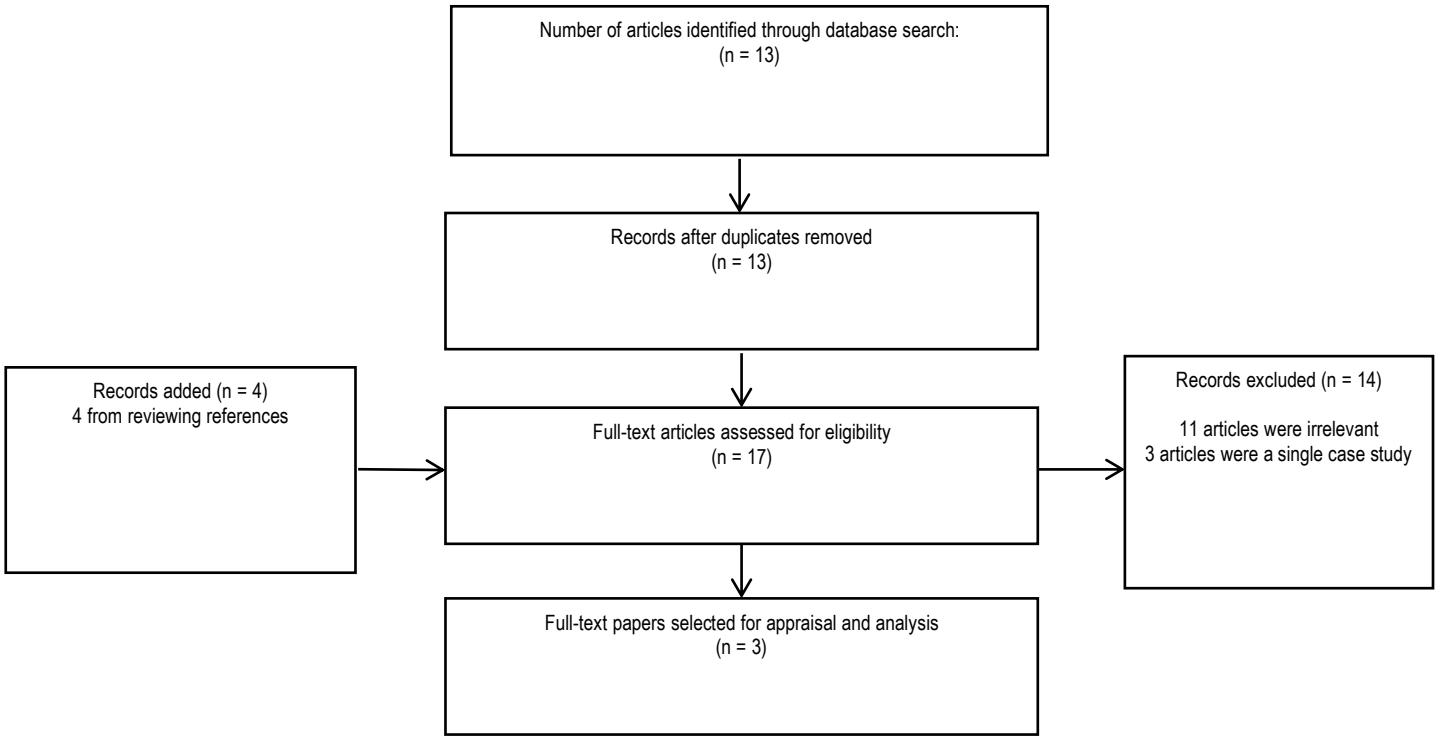
Number of articles identified through database search:
(n = 13)
Records after duplicates removed
(n = 13)
Records added (n = 4)
4 from reviewing references
Full-text articles assessed for eligibility
(n = 17)
Records excluded (n = 14)
11 articles were irrelevant
3 articles were a single case study
Full-text papers selected for appraisal and analysis
(n = 3)

Table 8: Cyclosporine AND prednisone AND Pneumocystis jirovecii pneumonia (PCP)

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
Suffredini et al. Acute respiratory failure due to Pneumocystis carinii pneumonia: clinical, radiographic, and pathologic course. Crit Care Med. 1985 Apr;13(4):237-43.	Case series of patients who received renal transplantation between 1981-1982	12 renal Tx pts treated with CsA+ prednisone who developed PCP: • Mean age 40 years (range 20-65 years) • Onset of PCP was 10-49 weeks after Tx (mean 17 weeks) • Cumulatively from time of transplantation to PCP diagnosis: Mean daily CsA dose 13.5 ± 1./9 mg/kg/d, mean daily CS dose (in prednisone dose equivalents) 0.6 ± 0.2 mg/kg/d • At time of PCP diagnosis: CsA tapered to 6-12 mg/kg/d (mean 10.3 mg/kg/d), prednisone tapered to 15-20 mg/d (mean 16.4 mg/d) • Lymphopenia (< 1.5 x 10^3 cell/mm^3) in 8 pts, which persisted throughout illness in 5 patients • All 12 pts had concomitant or subsequent infection by various pathogens (including Streptococcus fecalis, E. coli, H. Zoster, Klebsiella, Candida, CMV, Staphylococcus aureus, Pseudomonas aeruginosa) • 4 pts grew CMV from lung biopsy material, 1 of which also had CMV esophagitis; clinical course suggested that CMV pneumonia contributed in only a minor degree to the course of respiratory failure, but may have been a predisposing factor for PCP infection • All patients received TMP-SMX; 2 had pentamidine added due to persistent fever and respiratory failure • 2 patients died Comparison of renal Tx pts with PCP (n=12) vs. matched renal Tx pts without symptoms of infection (n=98) • Lower doses of Cs • Higher incidence of symptomatic and asymptomatic CMV infection • Increased occurrence of HLA-DR6 antigen Comparison of PCP pts with less severe illness (required supplemental oxygen but did not require invasive hemodynamic monitoring or >24 h mechanical ventilation after lung biopsy) (n=6) vs. those with more severe illness (required mechanical ventilation with positive end-expiratory pressure > 6 days after lung biopsy) (n=6): • None of the studied factors that potentially affect host response (including dosage of cyclosporine and steroids, presence of CMV infection, and HLA-DR6 antigen) explained the differences in pulmonary impairment.			No conclusions provided with regards to PCP risk with CsA + prednisone Pts in this case series may have a genetic predisposition to PCP, as they had a higher incidence of HLA-DR6 antigen compared to matched pts without infection.	Retrospective design Analyses limited by small number of pts who developed PCP. Difficult to draw conclusions from case series.
McGonigle et al. Does cyclosporin A adversely affect Pneumocystis carinii infection? Postgrad Med J. 1988 Sep;64(755):659-62.	Case series of PCP pts; descriptive comparison of patients who received CYC/AZA to those who received cyclosporine	N=14 PCP pts in total • All pts received concomitant prednisolone 10-20 mg/d at time of PCP diagnosis • No patients received PCP prophylaxis Group 1: 7 pts who received prednisolone + CYC/AZA (did not provide the number of pts who received CYC specifically): • 2 patients with SLE, 5 patients with renal Tx • CYC dose: 2-3 mg/kg/d adjusted according to leukocyte count • AZA dose: 2-2.5 mg/kg/d • Treatment with high-dose IV TMP-SMX (1920 mg 6-hourly) in all cases • All pts survived • Stable graft function in all 5 pts with renal Tx Group 2: 7 pts who received prednisolone + CsA: • All patients were renal Tx recipients			Despite identical PCP treatment, pts who received CsA had worse outcomes compared to those who received CYC or AZA. This raises the question of prophylactic TMP-SMX in patients taking CsA.	Numbers of patients who received specifically CYC or AZA were not provided. Difficult to draw conclusions from case series.

		• CsA dose: 15 mg/kg/day orally initially, reduced to maintenance dose to keep trough levels within recommended therapeutic dose • Treatment with high-dose IV TMP-SMX (1920 mg 6-hourly) in all cases; 2 pts also received pentamidine 200 mg IV daily • 4 of 7 pts lived • Stable graft function in 2 of the 3 pts who lived				
Santos et al. Efficacy of intravenous cyclosporine for steroid refractory attacks of ulcerative colitis. J Clin Gastroenterol. 1995 Jun;20(4):285-9.	Retrospective open label cohort study	21 pts with refractory UC hospitalized and failed to improve despite methylprednisone 1 mg/kg/24h) and TPN x 10 days. Exclusion criteria: colonic stenosis, toxic megacolon, concomitant infections, CKD, treatment with other IS, gestation, mental deficit. 15 men/6women; mean age 30 y/o [15 to 74 y/o]	IV CsA (5 mg/kg/24 hrs), administered as continuous infusion for 4-6 hours, target trough level 100-400 ng/mL Pt who improved stated PO diet and steroid tapered off. If improvement persisted, CsA was switched to PO and maintained for a mean period of 8.4 months [range 1-48 months]	-One of the pt who entered remission while on CsA died of PCP -16/21 pts improved in 9 days; 10 pts entered into remission, 7 discontinued steroids		-No information about CS dosage while developed PCP.

Abbreviations: AZA (azathioprine); CKD (chronic kidney disease); CMV (cytomegalovirus); CS (corticosteroid); CsA (cyclosporin); CYC (cyclophosphomide); IS (immunosuppressant); IV (intravenous) CP (Pneumocystis jirovecii pneumonia); PO (oral); pts (patients); SLE (systemic lupus erythematosus); TMP-SMX (trimethoprim/sulfamethoxazole); TPN (total parenteral nutrition); Tx (transplantation); UC (ulcerative colitis).

Table 8: Tacrolimus AND prednisone AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
No papers						

Appendix 6: Calcineurin Inhibitor and Mycophenolate

Search Strategy:

Medline 1946 to Present
Search executed on Dec 1, 2019

Search Terms:
Tacrolimus AND mycophenolate AND Pneumocystis jirovecii pneumonia

- These are MESH headings, automatically mapped and exploded by Medline (e.g. PCP, Pneumocystis jirovecii pneumonia and Pneumocystis carinii pneumonia provided the same results).

Cyclosporine AND mycophenolate AND Pneumocystis jirovecii pneumonia

- These are MESH headings, automatically mapped and exploded by Medline

** note: this search is not exclusive for GN patients

Limits:

- Human
- English Language

Results:
Tacrolimus AND mycophenolate AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=13
- Number of articles identified through review of reference: n=1
- Full-text papers selected for appraisal and analysis: n=1

Cyclosporine AND mycophenolate AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=3
- Number of articles identified through review of reference: n=
- Full-text papers selected for appraisal and analysis: n=0

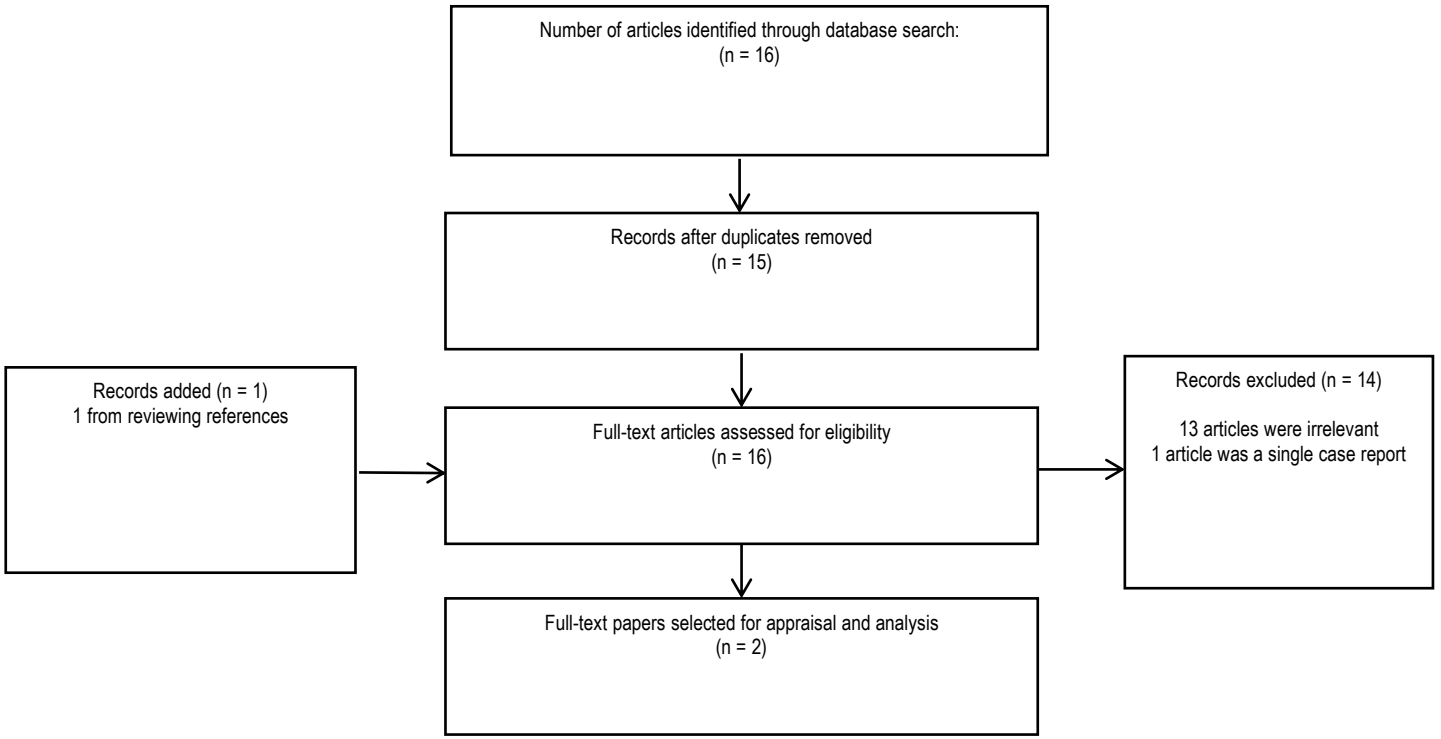
Number of articles identified through database search:
(n = 16)
Records after duplicates removed
(n = 15)
Records added (n = 1)
1 from reviewing references
Full-text articles assessed for eligibility
(n = 16)
Records excluded (n = 14)
13 articles were irrelevant
1 article was a single case report
Full-text papers selected for appraisal and analysis
(n = 2)

Table 9: Tacrolimus AND mycophenolate AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
Neff et al. Analysis of USRDS: incidence and risk factors for Pneumocystis jiroveci pneumonia. Transplantation. 2009 Jul 15;88(1):135-41.	Retrospective cohort studies pooling data from USRDS	Renal Transplantation between Jan 1st 2000 and July 31st 2004 (n=32,575 pts), mean age 51.27±14.1 yrs old, 51% male	Factors related to PCP	-SIR +MMF associated with more PCP - No significant association of PCP in pts who took CS, MMF, TAC, or AZA for discharge immunosuppression. There was no association with type or lack of induction therapy. - By using TAC + MMF as comparison group, the combination regimens, SIR and TAC (AHR 3.60, 95% CI 2.03–6.39), SIR and MMF (AHR 2.77, 95% CI 1.40 –5.47), and CsA and MMF (AHR 2.09, 95% CI 1.31–3.31), were associated with increased risk of PCP disease. All other regimens were not statistically significant.	PCP infections are rare but serious, especially in pts who are on SIR as part of the immunosuppressive regimen.	-No specification on PCP prophylaxis therapy used.
Azevedo et al. Mycophenolate mofetil may protect against Pneumocystis carinii pneumonia in renal transplanted patients. Rev Inst Med Trop Sao Paulo. 2005 May-Jun;47(3):143-5. Epub 2005 Jul 12.	Retrospective study	Kidney Tx from January 1998 to June 2002	AZA/CS/CNI or MMF/CS/ CNI AZA + TMP/SMX (n=135); AZA no TMP/SMX (n=11); MMF no TMP/SMX (n=126)	No case of PCP reported.	MMF may have an effective protective role against PCP as no patient under MMF, despite not receiving TMP/SMX coverage, developed PCP.	Small retrospective study, missing details on type of pts, pred dosage, CNI level.

Abbreviations: AZA (azathioprine); CNI (calcineurin inhibitor); CS (corticosteroid); CsA (cyclosporin); MMF (mycophenolate mofetil); PCP (Pneumocystis jirovecii pneumonia); pts (patients); SIR (sirolimus); TAC (tacrolimus); TMP-SMX (trimethoprim-sulfamethoxazole); Tx (transplantation).

Table 10: Cyclosporine AND mycophenolate AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
No papers						

Appendix 7: Cyclophosphamide Monotherapy

Search Strategy:

Medline 1946 to Present
Search executed on Nov 24, 2019

Search Terms:
Cyclophosphamide AND glomerulonephritis AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline (e.g. PCP, Pneumocystis jirovecii pneumonia and Pneumocystis carinii pneumonia provided the same results).

Cyclophosphamide AND vasculitis AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline

Cyclophosphamide AND lupus AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline

Cyclophosphamide AND IgA nephropathy AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline

Cyclophosphamide AND focal segmental glomerulosclerosis AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline

Cyclophosphamide AND minimal change disease AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline

Cyclophosphamide AND membranous nephropathy AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline

Limits:
- Human
- English Language

Results:
Cyclophosphamide AND glomerulonephritis AND Pneumocystis jirovecii pneumonia
- Number of articles identified through database search: n=20
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=4

Cyclophosphamide AND vasculitis AND Pneumocystis jirovecii pneumonia
- Number of articles identified through database search: n=30
- Number of articles identified through review of reference: n=17
- Full-text papers selected for appraisal and analysis: n=19

Cyclophosphamide AND lupus AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=20
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=12

Cyclophosphamide AND IgA nephropathy AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=1
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=1

Cyclophosphamide AND focal segmental glomerulosclerosis AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=0
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=0

Cyclophosphamide AND minimal change disease AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=0
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=0

Cyclophosphamide AND membranous nephropathy AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=1
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=1

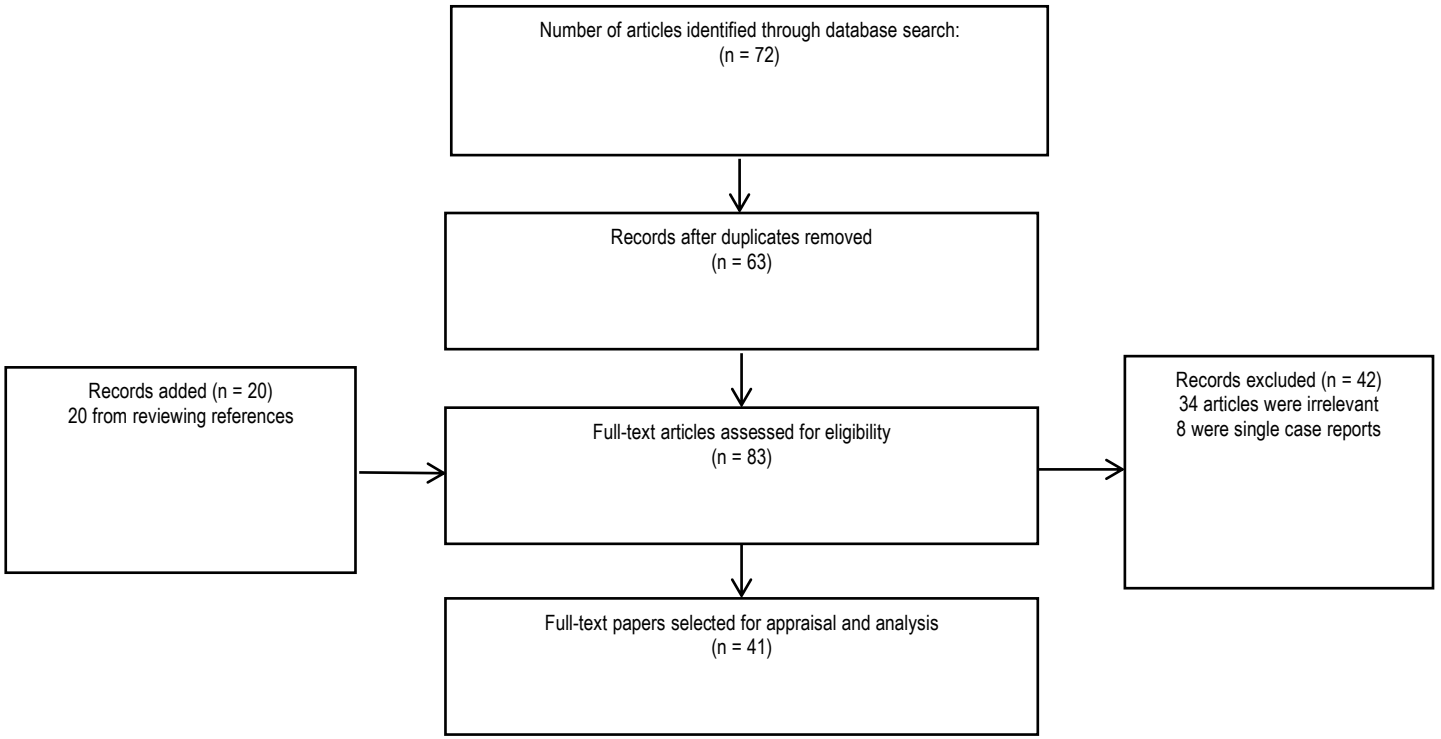
Number of articles identified through database search:
(n = 72)
Records after duplicates removed
(n = 63)
Records added (n = 20)
20 from reviewing references
Full-text articles assessed for eligibility
(n = 83)
Records excluded (n = 42)
34 articles were irrelevant
8 were single case reports
Full-text papers selected for appraisal and analysis
(n = 41)

Table 11: Cyclophosphamide AND glomerulonephritis AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention (CYC- focused)	Outcome (PCP-focused)	Conclusion (PCP and CYC-focused)	Limitations (PCP and CYC-focused)
Lv et al. Delayed severe pneumonia in mycophenolate mofetil-treated patients with IgA nephropathy. NDT (2008) 23:2868-2872	Retrospective cohort study with mean follow-up 25.0 months (range 3-70 months)	N=47 (this table refers only to pts who received CYC) IgAN with: impaired renal function (SCr > 1.5 mg/dL); persistent proteinuria (>3.5 g/d) regardless of RAAS blockade; and/or renal histology lesions of segmental glomerular necrotizing or focal small crescent formation Baseline characteristics only reported for pts with eGFR < 60 mL/min/1.73 m^2 (n=19): Mean age 32 years, eGFR 42 mL/min/1.73 m^2, daily prednisone 50 mg/day	<u>Immunosuppressive therapies:</u> CYC 100 mg/day, or 50 mg/day if eGFR < 30 mL/min/1.73 m^2; accumulated dose 6-8 grams Concurrent prednisone 40-60 mg/day, tapered after 6-8 weeks <u>PCP prophylaxis:</u> Not specified whether PCP prophylaxis was prescribed to patients on CYC	No pt who received CYC developed severe pneumonia (defined as diffuse bilateral lung infiltrate with respiratory failure, and including PCP).	No conclusions specific to CYC and PCP risk were provided.	Retrospective design Pts had variable follow-up durations and immunosuppression regimens. Small number of pts who received CYC. Baseline characteristics not fully reported and not specified whether pts on CYC received PCP prophylaxis.
Jarrousse et al. Increased risk of Pneumocystis carinii pneumonia in patients with Wegener's granulomatosis. Clin and Exp Rheum. (11) 1993:615-621	Case series of patients who developed PCP during a multicenter controlled clinical trial	23 pts with biopsy-proven WG and RPGN were randomized to intermittent high-dose pulse IV CYC or daily PO low-dose CYC, in combination with PO prednisone	Pulse steroid + IV CYC 0.7 g/m^2 x 1 dose, then PO prednisone 1 mg/kg/day with tapering after complete remission. Also randomized to: 1) CYC 0.7 g/m^2 IV Q3 weeks until 1 year after complete remission, then CYC tapered (n=15) 2) CYC 2 mg/kg PO daily x 1 year, then CYC tapered (n=8) Note: CYC was adjusted to WBC count from trial initiation to target neutrophil count 1500-3000/mm^3, but adjusted to renal function only after the first 13 pts were enrolled due to observations of severe cytopenia and opportunistic infections. In addition, systematic PCP prophylaxis was recommended after the first 13 pts.	<u>6 pts developed PCP:</u> Mean age 51 years 3 pts in pulse IV CYC group, 3 pts in daily PO CYC group 5 of 13 pts developed PCP before the protocol modification, 1 of 10 pts after the protocol modification (not specified whether this pt received PCP prophylaxis) Mean of 2.5 months of therapy (range 1.25-5 months) prior to development of PCP No pts were leukopenic or neutropenic at time of diagnosis; inverted CD4/CD8 ratios in 2 pts	Higher rates of PCP than previously thought in pts treated with daily prednisone + pulse IV or PO CYC. Recommendations for PCP prophylaxis are needed.	Case series taken from a trial with a small sample size.

				Renal function significantly was impaired compared to pts without PCP (SCr 494 umol/L vs. 195 umol/L, p=0.03)		

Abbreviations: CYC (cyclophosphamide); PCP (Pneumocystis jirovecii pneumonia); IV (intravenous); PO (oral); pts (patients); RAAS (renin-angiotensin-aldosterone-system); RPGN (rapidly progressive glomerulonephritis); sCr (serum creatinine); WG (Wegener's granulomatosis).

Table 12: Cyclophosphamide AND vasculitis AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention (CYC- focused)	Outcome (PCP-focused)	Conclusion (PCP and CYC-focused)	Limitations (PCP and CYC-focused)
Mecoli et al. Pneumocystis jiroveci pneumonia in rheumatic disease: a 20-year single-centre experience. CLIN 2017 Jul-Aug; 35(4): 671-673.	Retrospective review of all pts with rheumatic disease who received a PJP or PCP ICD-9 code from Jan 1996-Oct 2015 in a single academic center	<u>21 pts with rheumatologic conditions diagnosed with PCP:</u> • Mean age 52 years at time of diagnosis • No PCP prophylaxis at time of diagnosis • Most common underlying rheumatologic conditions were inflammatory myopathy (17%), SLE (17%), GPA (14%) • Average prednisone dose on admission 36 mg/day (range 1-60 mg/day) o 18 (86%) were receiving ≥ 20 mg/day prednisone o Of the 3 patients taking < 20 mg/day prednisone, all were receiving concomitant immunosuppression; 2 were receiving CYC • No patients were taking < 20 mg/day prednisone monotherapy at time of diagnosis • Most common concomitant non-prednisone immunosuppressant medications were MTX (n=6, 29%) and CYC (n=6, 29%) o CYC doses in the 6 patients: 50 mg TID; 25 mg daily; 50 mg daily; and not reported in 3 patients • All but 3 patients were lymphopenic at presentation (defined as ALC < 1100 cells/mm^3; normal is 1100-4800 cells/mm^3) o Average ALC 558 cells/mm^3 o ALC range 0-1580 cells/mm^3		PCP is more commonly observed in inflammatory myopathies, SLE, and GPA compared to other rheumatic diseases, but reason(s) for this are still unclear. PCP prophylaxis should be considered for pts receiving prednisone ≥ 20 mg/day x ≥ 4 weeks and for those receiving any dose of prednisone + CYC.	Retrospective design. Pts had variable follow-up durations and immunosuppression regimens. Small total number of PCP cases.
Schmajuk et al. Pneumocystis jirovecii pneumonia (PJP) prophylaxis patterns among patients with rheumatic diseases receiving high-risk immunosuppressant drugs. Semin Arthritis Rheum 2019; 48(6): 1087-1092.	Single-center retrospective cohort study using electronic health record data with mean follow-up 23.2 ± 14.2 months	N = 316 pts >18 years of age with diagnosis of GPA, MPA, dermatomyositis, polymyositis, or SLE who were new users of certain immunosuppressive agents Mean age 43 years, GPA 15%, 7% MPA, 56% SLE	Comparison of pts who received PCP prophylaxis (TMP-SMX, dapsone, atovaquone, or pentamidine) vs. pts who did not receive PCP prophylaxis <u>30 pts who received CYC:</u> CYC alone (n=8): 5 with prophylaxis vs. 3 without prophylaxis CYC + high-dose CS (n=13): 9 with prophylaxis vs. 4 without prophylaxis CYC + RTX (n=9): 9 with prophylaxis vs. 0 without prophylaxis	No pts received PCP diagnosis (as defined using diagnosis codes) <u>Among all 192 study pts who received PCP prophylaxis:</u> With mean follow-up 26 months, 9.7% had an ADE (serious/life-threatening in 1.5% of those taking TMP-SMX; 17.9% of those taking dapsone; 0% of those taking atovaquone or pentamidine)	No conclusions specific to CYC and PCP risk were provided. The incidence of PCP is extremely low, and ADEs from antibiotics occur at a low but detectable rate. Evidence to guide more personalized risk assessment are needed to inform PCP prophylaxis.	Retrospective design. Pts had variable follow-up durations. Did not provide information on CYC regimens administered.

Huynh-Do et al. Pneumocystis carinii Pneumonia During Immunosuppressive Therapy for Antineutrophil Cytoplasmic Autoantibody—Positive Vasculitis. Arch Intern Med. 1995;155(8):872-874	Case series of pts with AAV who developed PCP	<u>2 HIV-negative pts with AAV who developed PCP:</u> • Both 71 years old, malnourished, with COPD • Received prednisone > 40 mg/d for > 6 weeks • Not specified, but presumably no PCP prophylaxis Pt 1: • Admitted to hospital and diagnosed with WG and glomerulonephritis • Underwent HD and treated with CYC 100 mg/d + prednisone 100 mg/d, reduced to 50 mg/d after 3 weeks • Developed PCP 5 weeks after admission Pt 2: • Admitted to hospital and diagnosed with AAV and glomerulonephritis • Responded well to initial immunosuppression. 3 weeks later, discharged from hospital on CYC 100 mg/d and prednisone 30 mg/d. 6 weeks later, prednisone dose was increased to 50 mg/d for recurrent COPD exacerbations. • 4 months after first admission, developed PCP. Prednisone had been tapered down to 20 mg/d by this time	No conclusions specific to CYC and PCP risk were provided PCP prophylaxis could be beneficial in a select group of patients receiving immunosuppression for AAV (i.e. elderly pts with clinical signs of malnutrition, or in patients with persistent vasculitis activity requiring longer duration of high-dose steroid therapy (eg. prednisone > 20 mg/d)	Difficult to draw valid conclusions from case series
Sen et al. Pulmonary Complications of Combination Therapy with Cyclophosphamide and Prednisone. CHEST Volume 99, Issue 1, January 1991, Pages 143-1	Case series of pts with various medical conditions treated with oral CYC + prednisone during a 15-month period in 1 institution Comparison to pts within a similar time period with the same conditions who were treated with prednisone without CYC	<u>4 HIV-negative patients with various medical conditions treated with oral CYC + prednisone during a 15-month period who developed PCP:</u> • Not specified, but presumably no PCP prophylaxis • None of the pts were leukopenic or neutropenic at time of PCP diagnosis • 3 pts had severe lymphopenia (< 500 lymphocytes per cubic millimeter); 4th pt had chronic lymphocytic leukemia Pt 1 (56 years old): • Started prednisone (no dose provided) + CYC 150 mg/d for WG with no renal involvement • At 2 months, unable to taper prednisone below 20 mg. Developed PCP Pt 2 (71 years old): • On prednisone x 2 years for malignant left pleural effusion secondary to malignant thymoma, then diagnosed with bronchiolitis obliterans with organizing pneumonia that failed to respond to prednisone 60 mg/d • Regimen changed to CYC 125 mg/d + prednisone 30 mg/d. Developed PCP 2 months later Pt 3 (60 years old): • Diagnosed with necrotizing glomerulitis and presumed polyarteritis nodosa • Started CYC 150 mg/d + prednisone 80 mg/d (tapered to 40 mg/d). Developed PCP within 3 months Pt 4 (61 years old): • Six-year history of chronic lymphocytic leukemia • Received CYC 100 mg/d + prednisone 40 mg/d. Developed PCP within 6 weeks <u>Analysis Results:</u> • In the institution, 4 of 6 pts with systemic vasculitis, bronchiolitis obliterans, or chronic lymphocytic leukemia receiving CYC + prednisone during this 15-month period developed PCP	Convincing evidence that the combination of daily doses of CYC + prednisone contributed to the development of PCP. Prophylactic TMP-SMX should be considered in patients receiving CYC + prednisone.	Difficult to draw valid conclusions from case series and from comparisons of a non-controlled study.

		• None of the 32 pts with the same conditions receiving prednisone without CYC had PCP (p=0.002) • None of the patients with PCP between 1986-1990 at the institution had received prednisone alone		

Arend et al. Pneumocystis carinii pneumonia in patients without AIDS, 1980 through 1993. An analysis of 78 cases. Arch Intern Med. 1995 Dec 11-25;155(22):2436-41.	Single-center retrospective chart review of pts who were admitted with PCP between 1980-1993	<u>76 HIV-negative pts aged ≥ 16 years who developed PCP:</u>
		• Mean age 49.7 years
		• None received adequate PCP prophylaxis
		• Most pts (49%) had hematologic malignancy
		• Included 17 pts (22%) with systemic vasculitis/autoimmune diseases (8 patients with WG, 1 pt with SLE)
		• 33 of the pts received CYC prior to PCP development
		  ○ Many of these pts likely received additional chemotherapeutic agents
		• 72 of the pts received CS prior to PCP development
		  ○ 47% of these pts were on continuous high-dose CS
		
		<u>Risk factors for mortality included, among others:</u>
		• Previous CYC treatment (p=0.01)
		• Perhaps, previous CS use (p=0.06)
			No conclusions specific to CYC and PCP risk were provided.
			
			PCP occurred at all levels of immunosuppression; no threshold level could be defined.
				Retrospective design.
				
				Pts were on variable immunosuppressive agents, including chemotherapeutic agents.

Godeau et al. Factors associated with Pneumocystis carinii pneumonia in Wegener's granulomatosis. Ann Rheum Dis. 1995 Dec;54(12):991-4.	Case-control study of WG pts from 4 medical centers	No patients received PCP prophylaxis
		
		<u>WG with PCP group (n=12):</u>
		• Mean age 51 years
		• PCP developed after a mean of 128 days from immunosuppressive therapy initiation (median 90 days, range 50-510 days)
		• Majority (8 of 12 pts) developed PCP within first 3 months of immunosuppressive therapy
		
		<u>WG without PCP group (n=32):</u>
		• Mean age 49 years
		
		<u>Comparison of pts with PCP vs. without PCP:</u>
		• Similar initial clinical presentations of WG
		  ○ Only statistically significant difference was pre-treatment lymphocyte count, which was lower in PCP group (1060/mm^3 vs. 1426/mm^3; p=0.04)
		• Similar parameters after start of treatment
		  ○ Only statistically significant difference was lymphocyte count; minimum counts were significantly lower in the PCP group during the 1st, 2nd, and 3rd months of treatment
		  ○ Lymphocyte count threshold that best discriminated between PCP and control groups was 600/mm^3 during the first 3 months of treatment
		• Immunosuppressive treatment
		  ○ All pts received daily CS and CYC, but doses and routes were not standardized
		  ○ Similar mean cumulative doses of CS between groups
		  ○ Mean cumulative CYC dose was greater in PCP group at end of 2nd and 3rd months of treatment (respectively: 1.55 mg/kg/d vs. 0.99 mg/kg/d; 1.67 mg/kg/d vs. 0.97 mg/kg/d)
			Study suggests that the dose of CYC is an important contributor to the risk of PCP; however, cannot affirm this due to the retrospective study design.
			
			Results suggest that primary PCP prophylaxis is indicated most appropriately for patients whose lymphocyte count decreases to less than 600/mm^3 during the first 3 months of treatment; however, further studies are required to define these limits more clearly.
				Retrospective design.
				
				Small sample size.
				
				Patients had variable follow-up durations.
				
				Multiple comparisons increased risk of false positive results.

		▪ Significant negative correlation between cumulative CYC dose and lymphocyte count <u>Multivariate analysis comparing patients with PCP vs. without PCP:</u> • Only 2 factors associated with PCP were pre-treatment lymphocyte count (cutoff of 800 mm^3; p=0.018) and lymphocyte count at month 3 (cutoff of 600 mm^3; p=0.014)				
Yoda et al. Clinical evaluation of patients with inflammatory connective tissue diseases complicated by cytomegalovirus antigenemia. Mod Rheumatol. 2006;16(3):137-42.	Single-center retrospective review to evaluate the incidence of CMV disease from Oct 2002 to May 2004 in patients with refractory inflammatory connective tissue diseases under intensive immunosuppressive therapies	N=23 pts aged 19-87 years with refractory inflammatory connective tissue diseases (including 9 with SLE, 1 with MPA)	Intensive immunosuppressive therapy consisting of ≥ 4 weeks of oral prednisolone 30-60 mg/d, ± oral CsA 150-300 mg/d or pulse IV CYC 500 mg/d; some patients received pulse IV methylprednisolone 500 mg/d x 3 days as well Note: 5 pts received pulse IV CYC; no information provided on pulse IV CYC regimens that were administered Not specified whether patients received PCP prophylaxis	10 of 23 pts developed CMV antigenemia, and incidence was markedly higher in pts who received pulse IV methylprednisolone + pulse IV CYC (4 out of 4 pts) No data provided on incidence of PCP overall, but presumably, all cases occurred in pts with CMV antigenemia 4 of the 10 pts with CMV antigenemia simultaneously developed PCP <u>2 of these 4 pts who developed PCP were taking CYC:</u> Pt 1 - 66 years old; Pulse IV CYC 500 mg/d + prednisolone 30 mg/d; lymphocyte count 1860/uL Pt 2 - 52 years old; adult-onset Still's disease; Pulse IV methylprednisolone 500 mg/d x 3 days + pulse IV CYC 500 mg/d + prednislone; lymphocyte count 740/uL	Pts with connective tissue diseases under intensive immunosuppressive therapies (IV steroid pulse in combination with additional IV CYC) are highly susceptible to CMV infection and disease. CMV antigenemia patients are susceptible to concurrent PCP.	Retrospective design. Small sample size. Pulse IV CYC regimens administered were not specified, and not specified whether patients received PCP prophylaxis.
De Souza et al. Wegener's granulomatosis: experience from a Brazilian tertiary center. Clin Rheumatol. 2010 Aug;29(8):855-60.	Single-center retrospective study of WG pts between 1999-2009 with follow-up period of 3 years after initial diagnosis	N=134 consecutive WG pts Mean age at WG diagnosis 43 years Renal involvement (Scr > 1.8 mg/DL, hematuria, or red cell casts in urinary sediment or proteinuria >0.5 g/d) in 75.4%	<u>Immunosuppressive therapies:</u> 97 pts (72.4%) received CYC (2 mg/kg PO daily, or 0.5-1.0 mg/kg m^2 IV monthly) + prednisone 1 mg/kg PO daily x 2 months followed by tapering over the next 6 months; methylprednisolone 1 g IV x 3 days given initially prior to PO prednisone if there was immediate threat to a critical organ or patient life Other immunosuppressive	None of the patients developed PCP	Concomitant use of TMP-SMX may explain the fact that no case of PCP was observed.	Retrospective design. Use of PCP prophylaxis not specified, though TMP-SMX was used at WG treatment dose in most patients. Higher TMP-SMX dose used for PCP prophylaxis than usual practice.

			agents (MTX, AZA, and MMF) given if CYC was contraindicated or not tolerated <u>TMP-SMX therapy:</u> 82 patients (61.2%) received TMP-SMX 800/160 mg PO BID Not specified whether any of the remaining patients received TMP-SMX at PCP prophylaxis doses			
Guillevin et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. Arthritis Rheum 1997;40:2187-98.	Multicenter RCT with mean follow-up of 24.9-30.6 months	N=50 pts aged > 15 years with newly diagnosed systemic WG Mean age 54 years 74% with glomerulonephritis	All pts received IV methylprednisolone 15mg/kg/d x 3 days, then prednisone 1 mg/kg/d x 6 weeks, which was then tapered gradually if remission was achieved. All also received IV CYC 0.7 g/m^2 x 1 dose after the last methylprednisolone dose. <u>Group A (n=27):</u> Pulse IV CYC, at mean dose of 0.7 g/m^2 (adjusted for renal function and PMN count to target 10-day nadir of 1500-3000/mm^3), given Q3weeks until remission achieved + for 1 year thereafter. Intervals between pulse treatments then increased to Q4weeks x 4 months, then Q5weeks x 4 months, then Q6weeks for 2 years of total treatment <u>Group B (n=23):</u> Daily PO CYC at dose of 2 mg/kg/d (dose adjusted for renal function and PMN count	PCP developed in 10 pts and was the cause of death in 6 pts overall Presumably, all PCP cases occurred before the protocol amendment to provide PCP prophylaxis to all pts (this is based on a comment in the Discussion section stating that PCP has not been observed since the initiation of systematically prescribing TMP-SMX to lymphopenic patients). Therefore, PCP presumably occurred in 10 of the first 12 pts recruited. <u>Group A:</u> PCP in 3 patients (11.1%) 2 pts died due to PCP (for both, occurred 3 months after study inclusion) <u>Group B:</u> PCP in 7 patients (35%) 4 pts died due to PCP; 1 had concomitant CMV (occurred at 6 months, 7 months, 17 months, and 23 months after study inclusion)	PCP occurred frequently, especially in the PO CYC-treated group, and was often the cause of death. Systematic PCP prophylaxis should therefore be prescribed.	Small sample size.

			to target 1500-3000/mm^3) starting on day 10 following initial CYC pulse, after the PMN nadir had been reached. 1 year after remission reached, CYC dose tapered by 25% Q4months until discontinuation. Protocol was amended to include TMP-SMX 400 mg/d for all pts due to the high frequency of PCP observed in the first 12 pts recruited.			

Abbreviations: ADE (adverse drug reaction); ALC (absolute lymphocyte count); AAV (ANCA-associated vasculitis); AZA (azathioprine); CMV (cytomegalovirus); COPD(chronic obstructive pulmonary disease); CS (corticosteroid); CsA (cyclosporin); CYC (cyclophosphamide); GPA (granulomatosis with polyangiitis); HD (hemodialysis); MMF (mycophenolate mofetil); MPA (microscopic polyangiitis); MTX (methotrexate); PCP (Pneumocystis jirovecii pneumonia); PMN: polymorphonuclear leukocytes; pts (patients); RTX (rituximab); SLE (systemic lupus erythematosus); TMP-SMX (trimethoprim-sulfamethoxazole).

Table 13: Cyclophosphamide AND lupus AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention (CYC- focused)	Outcome (PCP-focused)	Conclusion (PCP and CYC-focused)	Limitations (PCP and CYC-focused)
Banerjee et al. Low incidence of opportunistic Infections in Lupus Patients treated with Cyclophosphamide and Steroids in a Tertiary care setting. Med Res Arch. 2017 Mar;5(3).	Single-centre retrospective chart review of SLE pts from 2004-2014; data from the 6 months following induction treatment with CYC was recorded	N=31 SLE pts who received ≥ 6 infusions of IV CYC in the induction phase of treatment Mean age 37.9 years 26 (84%) received CYC for lupus nephritis	<u>Induction immunosuppressive therapies:</u> IV CYC regimens administered not specified 7 pts received multiple CYC cycles (1 pt received 4 cycles. 2 pts received 3 cycles, 4 pts received 2 cycles); overall, 42 cycles received by 31 pts overall Pts were on variable doses of CS during CYC induction 7 of 31 pts received RTX 1000 mg x ≥ 2 doses <u>Maintenance immunosuppressive therapies:</u>	1 pt developed PCP (details not provided); incidence rate 1.29 per 100 person-years (95% CI 0.037-44.28) Significantly higher cumulative CS at time of PCP case, compared to non-PCP cases: 23305 prednisone equivalent vs. 11554 prednisone equivalent (p=0.015 in time-dependent multivariate analysis; total of 42 courses of	Found a very low incidence of PCP in CYC-treated SLE patients. Findings do not support PCP prophylaxis in SLE patients on CYC treatment.	Retrospective design. Small sample size. Short follow-up duration. CYC regimens administered were not specified. Cannot draw firm conclusions from the comparison of PCP vs. non-PCP cases, as there was only 1 PCP case.

			Not described in detail, but included quarterly CYC, MMF, or AZA <u>PCP prophylaxis:</u> No pt received PCP prophylaxis	CYC was used as the denominator)		
Gupta et al. Prophylactic antibiotic usage for Pneumocystis jirovecii pneumonia in patients with systemic lupus erythematosus on cyclophosphamide: a survey of US rheumatologists and the review of the literature. J Clin Rheumatol 2008; 14(5):262-72	1) Systematic review using Ovid and PubMed for manuscripts from all dates to July 2007 (MESH terms systemic lupus erythematosus, Pneumocystis carinii pneumonia, and cyclophsophamide) 2) Survey of US rheumatologists via email	1) Systematic review: Identified 18 original manuscripts from 1987-2006 which addressed SLE pts > 18 years of age treated with relevant immunosuppressive agents (10 retrospective observational case series, 2 retrospective case-control studies, 6 RCTs) • 121 cases of PCP identified in 76,156 SLE patients, giving frequency of 15.88 per 10,000 (0.1588%) patients 2) Survey of US rheumatologists: Response rate of 16.63%; 264 responses included in the final analysis • 264 rheumatologists had 4742 years of cumulative experience • 5174 patients received PO or IV CYC over the last 5 years, mean of 20 pts (range 0-250) per rheumatologist • For SLE pts on CYC: 133 rheumatologists (50.37%) prescribed routine PCP prophylaxis, of which 17 (6.43%) prescribed it only with PO CYC; 131 (49.63%) did not prescribe any PCP prophylaxis; 2 prescribed it if CD4 < 200 cells/uL • 32 PCP cases were detected by the respondents who prescribed PO or IV CYC to SLE patients, giving a rate of 67.48 per 10,000 years of cumulative practice experience		The frequency of PCP in SLE patients treated with CYC is low. It is questionable whether sufficient data is available to support routine use of PCP prophylaxis in SLE patients treated with CYC, and one must weigh whether prophylactic TMP-SMX therapy in this setting is justified. It is proposed to reserve therapy to those at highest risk of PCP. Further studies are consensus guidelines are needed to address this issue.	1) Systematic review: • Of the 18 manuscripts included, most made no of mention PCP, though pneumonia was often mentioned. Therefore, cannot exclude the possibility that PCP occurred and was simply not reported. • Many of the manuscripts did not mention the use of CYC, and if PCP occurred, it was not specified whether patient was on CYC. • Most studies were retrospective. • Studies and patients included in studies had variable follow-up times. 2) Survey: • Low response rate. • Reliance on respondent recall to determine rate of PCP overall. • No data provided to compare CYC and PCP prophylaxis usage in patients with and without PCP.

Liam et al. Pneumocystis carinii pneumonia in patients with systemic lupus erythematosus. Lupus. 1992 Dec;1(6):379-85	Case series of SLE patients who developed PCP from a single-centre prospective study between 1974-1988	<u>Of the 351 SLE pts who required hospitalization, 9 developed PCP:</u>
		• Mean age 27 years (ranged 14-34 years)
		• All Chinese females
		• 5 pts had SLE for several years and were being treated for several years; 4 pts were newly diagnosed with PCP
		• All had active SLE at time of developing PCP
		• 8 pts had lymphopenia (<1.5 x 10^9/L) when they developed PCP; lymphocyte count was not available for 1 patient
		• 6 pts had elevated SCr when they developed PCP
		• Immunosuppression:
		  ○ Within the month prior to developing PCP, 8 pts were receiving prednisolone in doses ranging from 10-60 mg daily; 4 of these pts were also on CYC 100 mg PO daily
		  ○ 1 pt was only taking traditional Chinese medication
		  ○ The 5 pts who developed more extensive PCP as seen on their chest radiographs were on the whole receiving more
				Pts who were on more intensive immunosuppressive therapy (i.e. higher doses of prednisolone ± CYC 100 mg/d) developed more severe PCP.	Difficult to draw valid conclusions from case series.
					
					No information provided to compare SLE pts who developed PCP to those who did not at this institution.

		intensive immunosuppression (i.e. higher doses of prednisolone ± CYC 100 mg/d) • PCP prophylaxis: o Not specified, but presumably none of the 9 pts received PCP prophylaxis				
Decker et al. Cyclophosphamide or azathioprine in lupus glomerulonephritis. A controlled trial: results at 28 months. Ann Intern Med. 1975 Nov;83(5):606-15.	RCT of SLE pts with diffuse GN with mean 2.5 years of follow-up	N=38 pts with diffuse GN of SLE; excluded pts with SCr >4 mg/100 mL or CrCl < 20 mL/min Renal involvement defined as: Erythrocyte casts, cellular casts, and either hematuria or pyuria; or High anti-DNA antibodies, low complement, and positive renal biopsy Age range 12.2-58.5 years	<u>Randomized to:</u> 1) Continuation of CS at a dose ≤ prednisone 0.5 mg/kg/d (n=15); 2) CS regimen of (1) + PO CYC up to 4 mg/kg/d (n=10, later 11 due to pt being intolerant to AZA); or 3) CS regimen of (1) + PO AZA up to 4 mg/kg/d (n=13) Note: 10 pts had treatment re-assignments at 12 weeks (including 2 pts on CYC who were switched to prednisone and 5 pts on prednisone who were switched to one of the other assignment categories), but may have returned to their original assignments at approximately 12 months <u>PCP prophylaxis:</u> Not specified, but presumably, PCP prophylaxis was not included in the study protocol	<u>1 pt developed PCP and died after 2.5 months of CYC:</u> • 48.2 years old at study entry • 7 years of renal disease and early crescent formation on renal histology at study entry • Mean daily dose of PO CYC was 1.2 mg/kg/d • Mean daily dose of PO prednisone was 0.5 mg/kg/d	No conclusions provided with regards to PCP.	Small sample size. Difficult to draw conclusions about the frequency of PCP with each regimen due to the study design allowing for re-assignments.

Abbreviations: AZA (azathioprine); CrCl (creatinine clearance) CS (corticosteroid); CYC (cyclophosphamide); GN (glomerulonephritis) IV (intravenous); MMF (mycophenolate mofetil); PCP Pneumocystis jirovecii pneumonia; PO (oral); pts (patients); RCT (randomized-controlled trial); RTX (rituximab); sCr (serum creatinine); SLE (systemic lupus erythematosus); TMP-SMX (trimethoprim/sulfamethoxazole).

Table 14: Cyclophosphamide AND IgA nephropathy AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
No papers						

Table 15: Cyclophosphamide AND membranous nephropathy AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
No papers						

Table 16: Additional studies from reviewing references on cyclophosphamide AND vasculitis AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention (CYC- focused)	Outcome (PCP-focused)	Conclusion (PCP and CYC-focused)	Limitations (PCP and CYC-focused)
Charlier et al. Risk factors for major infections in Wegener granulomatosis: analysis of 113 patients. Ann Rheum Dis 2009;68:658-63.	Single-centre retrospective chart review of WG pts with median of 6 years of follow-up (range 0-22 years)	N=113 WG pts >12 years of age followed at least once between 1984-2006 Median age 49 (range 13-79 years) 62 (55%) with GN 33 pts diagnosed with WG before 1996, 80 diagnosed after 1996	Both before and after 1996, administration of 1-3 methylprednisolone infusions could be prescribed at the onset of induction therapy, depending on the severity of WG <u>Before 1996:</u> Induction therapy with daily high-dose CS (1 mg/kg x 6 weeks, then slow taper) + daily PO CYC (2 mg/kg) PO CYC usually continued for up to 18 months to maintain remission <u>Since 1996:</u> Induction regimen modified to PO CS (1	No PCP was reported	Study confirmed the efficacy of PCP prophylaxis.	Retrospective design.

			mg/kg x 4 weeks, then quick taper) + IV CYC (0.6 g/m^2 on days 0, 15, and 30, then 0.7 g/m^2 Q3weeks until remission) Maintenance therapy consisted of AZA 2 mg/kg/d or MTX 0.3 mg/kg/week x ≥12-18 months <u>PCP prophylaxis:</u> Since 1993, all pts received prophylaxis with TMP-SMX 400/80 mg/d, or with monthly pentamidine if intolerant or allergic to TMP-SMX. Prophylaxis was withdrawn after immunosuppressants were stopped and lymphocyte counts normalized <u>Therapies that patients received:</u> Induction therapy with CS (n=100, 97%) and PO CYC (n=16, 14%) or IV CYC (n=92, 81%); 3 pts only received TMP-SMX 1600 mg/d Maintenance therapy with PO CYC (n=13, 12%), AZA (n=64, 57%), and/or MTX (n=29, 26%); 2 pts received no maintenance therapy 52 pts experienced ≥ 1 relapse and were treated with 1 or several drugs, sometimes in combination: IV CYC (n=20, 18%), PO CYC (n=45, 40%), IVIg (n=18, 16%), infliximab (n=10,			

			9%), RTX (n=9, 8%), plasma exchanges (n=8, 7%). Maintenance treatment after relapse included MTX (n=15, 13%), AZA (n=24, 21%), MMF (n=19, 17%), and etanercept (n=2, 2%) PCP prophylaxis in 104 pts			
Godeau et al. Pneumocystis carinii pneumonia in the course of connective tissue disease: Report of 34 cases. J Rheumatol 1994;21: 246–51.	Retrospective analysis of all PCP cases that were observed in HIV-negative pts with CTD in 10 medical units in the previous 10 years	<u>34 cases of PCP in HIV-negative pts with CTD were studied:</u> • Included patients with WG, SLE, polyarteritis nodosa, poly/dermatomyositis, and "others" • Not specified, but presumably, none of the pts received PCP prophylaxis prior to the onset of PCP • PCP usually occurred soon after the diagnosis of CTD (mean of 16 months after diagnosis date, and during the first 8 months in 74%) • WG pts (n=12, out of an estimated total of 100 WG pts): o Age 28-75 years at PCP presentation o Prior to PCP, CS duration of 2-3 months in most pts; ranged 2-18 months o Mean CS dose during 2 months prior to PCP ranged 0.75-1.9 mg/kg/d o All pts received CYC in 2 months prior to PCP; mean dose in the 2 months ranged 0.7-3.3 mg/kg/d o 11 pts had lymphocyte count ranging 0-0.8 x 10^9/L, 1 had lymphocyte count 1.5 x 10^9/L o 6 pts died • SLE pts (n=6, out of an estimated total of 750 SLE pts): o Age 24-55 years at PCP presentation o Prior to PCP, CS duration of 5-32 months in 4 pts; no prior CS in 2 pts o Mean CS dose during 2 months prior to PCP ranged 0.6-1.3 mg/kg/d; no prior CS in 2 patients o 3 pts received CYC in 2 months prior to PCP; mean dose in the 2 months ranged 0.3-2.5 mg/kg/d o 5 pts had lymphocyte count 0.2 x 10^9/L; 1 pt had lymphocyte count 1.5 x 10^9/L o 5 pts died • BAL was repeated in 13 pts at a mean of 17 days after beginning PCP treatment o No PCP was found except in 1 pt who died of *Pseudomonas aeruginosa* infection • 10 of the 23 survivors overall received secondary PCP prophylaxis o After mean follow-up of 28 months, none had PCP recurrence • 13 of the 23 survivors overall did not receive secondary PCP prophylaxis o All received immunosuppressive agent(s) after PCP, with or without modification of previous regiments o After mean follow-up of 18 months, none had PCP recurrence	Incidence of PCP in WG was very high in this study (estimate of ~12%); the interest of PCP prophylaxis must be evaluated in these pts. The estimated incidence of PCP in the other CTD included in this study is low (less than 2%); further studies are required to determine the pt characteristics and/or treatments characterizing patients at high risk of PCP. Results suggest that secondary PCP prophylaxis is not absolutely required for HIV-negative patients with CTD; however, further studies are needed to clarify this issue due to the small number of pts in the study.	Retrospective design. Small number of PCP cases were observed and described.

Bligny et al. Predicting Mortality in Systemic Wegener's Granulomatosis: A Survival Analysis Based on 93 Patients. Arthritis Rheum 2004; 51:83-91.	Retrospective chart review of 93 WG pts who were diagnosed with WG between 1984 and 1999 (including 49 pts of a previous multicenter trial and 44 additional pts) with mean follow-up of 4.5 years	N=93 WG pts <u>At diagnosis:</u> Mean age 52 years Median SCr 124 umol/L (range 49-1730 umol/l) 58 (62%) with GN (microscopic hematuria or red cell casts in urinary sediment with either proteinuria >0.5 g/d or SCr >140 umol/L); median SCr 157 umol/L (range 52-1730 umol/L) in GN pts Median lymphocyte count 1.3 x 10^9/L (range 0.1-9.1 x 10^9/L)	<u>Immunosuppression:</u> Initially, 88 (95%) pts received CS + PO CYC/intermittent IV CYC; mean duration of CYC treatment was 18.5 months (see 1997 study by Guillevin et al. for the CS + PO/IV CYC regimens received by 49 pts included in this chart review) All, with the exception of perhaps 1, of the remaining patients eventually received CYC <u>PCP prophylaxis (with TMP-SMX or aerosolized pentacarinat):</u> Prescribed to most pts taking CYC after 1991; systematically prescribed to all pts taking CYC after 1997	<u>12 pts developed PCP:</u> All PCP occurred during induction therapy without PCP prophylaxis 5 pts died with PCP as a contributing factor Note: Number of pts that did not receive PCP prophylaxis was not specified; therefore, cannot determine risk of PCP without prophylaxis from this study	No conclusions provided regarding PCP.	Retrospective design.
Chung et al. Cost-effectiveness of prophylaxis against Pneumocystis carinii pneumonia in patients with Wegener's granulomatosis undergoing immunosuppressive therap. Arthritis Rheum. 2000; 43(8):1841-8.	Markov state-transition model to follow hypothetical cohort of WG pts over their lifetimes starting from time of initial exposure to immunosuppressive therapy Effect of PCP prophylaxis on life expectancy, QALY, ADLC, and incremental cost-effectiveness estimated based on data from literature review; direct medical costs examined from societal perspective; costs and benefits discounted at 3% annually	Annual incidence of PCP estimated from study by Ognibene et al.: • 11 PCP cases among 180 WG pts receiving immunosuppressive therapy over 7.2 years; annual incidence rate estimated to be 0.85% Other studies that reported on occurrence of PCP used to establish reasonable range for sensitivity analyses. 13 studies included in literature review: • All studies were comprised of HIV-negative patients with inflammatory diseases (SLE, systemic vasculitis, RA, derrmatomyositis/polymyositis, polyarteritis nodosa, giant cell arteritis, pemphigus, pemphigoid, sarcoid) • Incidence of PCP not reported in 5 studies; mortality from PCP not reported in 2 studies • Time to PCP not reported in 6 studies • CYC was reported as an immunosuppressant used in 8 of the studies Incidence of ADR estimated from an RCT of TMP/SMX given BID x 24 months to prevent relapses	<u>No PCP prophylaxis</u>: Life-expectancy of 13.36 QALY; ADLC of $4538 <u>TMP-SMX alone for PCP prophylaxis:</u> Life-expectancy of 13.54 QALY; ADLC of $3304 <u>TMP-SMX followed by pentamidine (due to ADR from TMP-SMX) for PCP prophylaxis:</u> Life-expectancy of 13.61 QALY; ADLC of $7428. Increased quality-adjusted life expectancy compared to TMP-SMX until incidence of PCP exceeded 7.5% Both the TMP-SMX and TMP-SMX followed by pentamidine prophylaxis	Compared to no PCP prophylaxis, using TMP-SMX alone increased life expectancy and reduced cost of patients with WG receiving immunosuppressive therapy. Advantage persists as long as the annual PCP risk is > 0.2%. Replacing TMP-SMX with monthly aerosolized pentamidine in cases of ADR further increased life expectancy, although at an increased cost. Decision to add	Values used in Markov-state transition model may not be valid: • Annual incidence of PCP estimated from Ognibene et al. study is likely incorrect, as 7.2 years was not the follow-up duration of the 180 WG pts [unclear where authors obtained these numbers; perhaps from a statement that 10 (not 11) of the cases occurred from 1984 to June 1992]. • Studies included pts with inflammatory conditions other than WG. • Many studies used for sensitivity analyses did not provide complete data (incidence of PCP, mortality from PCP, time to PCP).

		in WG; lower rates of ADRs examined in sensitivity analyses due to the likely lower rate of ADRs with PCP prophylaxis doses PCP mortality rate (40.8%) estimated from an aggregate of all inflammatory conditions in the 13 aforementioned studies		strategies dominated the no prophylaxis strategy until the annual PCP incidence fell below 0.2% and 2.25%, respectively	pentamidine in cases of ADRs depends on estimated incidence of PCP (conventional threshold of ~$50,000 per QALY is reached when annual PCP incidence exceeds 0.93%).	
Booth et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. Am J Kidney Dis. 2003; 41(4):776-84.	Retrospective, multicenter sequential cohort study of patients newly diagnosed with ANCA-associated renal vasculitis between 1995 and 2000 with median 3.1 years of follow-up	N=246 pts newly diagnosed with ANCA-associated renal vasculitis from 7 hospitals (120 with MPA, 82 with WG, 33 with renal-limited vasculitis, 11 with Churg-Strauss angiitis) Renal involvement defined as hematuria ± red blood cell casts, increased SCr attributable to disease, or histological evidence of pauci-immune necrotizing GN <u>At presentation:</u> Median age 66 years At presentation, median SCr at presentation 342 umol/L and ANCA present in 92%	<u>Immunosuppression:</u> CS: All pts received PO prednisolone x 18-48 months CYC: Administered to 214 pts (88%), with mean cumulative dose of 10.3 g 2 centers administered CYC by IV bolus; remaining 5 used PO therapy Azathioprine: Used as initial therapy in 2 centers, but otherwise introduced at 3 months or at time of remission Other: Plasma exchange in 40 patients, TMP-SMX in 12 pts, MTX in 4 pts, MMF in 11 pts, IVIg in 11 pts, TAC in 4 pts, immunoadsorption in 1 pt <u>PCP prophylaxis:</u> Not specified whether pts received PCP prophylaxis, though 12 pts received TMP-SMX for vasculitis treatment	1.4% developed PCP (shown in Fig. 8 pie chart) Details of pts who developed PCP was not provided	No conclusions provided regarding PCP.	Retrospective design. Cannot draw conclusions regarding PCP or PCP prophylaxis due to lack of information provided.
Little et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. Ann Rheum Dis. 2010; 69(6):1036-43.	Assessment of mortality in the first year of pts prospectively recruited to 4 European AAV clinical trials using individual data records	<u>MEPEX trial (n=140):</u> Inclusion criteria included severe renal involvement with SCr > 500 umol/L Induction: CYC 2.5 mg/kg + prednisolone 1 mg/kg tapering Adjuvant: Plasma exchange x 7 or methylprednisolone 3 g total Maintenance: AZA 2 mg/kg + low dose prednisolone		<u>Within 1 year of trial enrollment, 5 pts developed PCP (3% of all infections, 0.9% of total population):</u> 2 had coexistent CMV infection	Study supports EUVAS guidelines advocating PCP prophylaxis (which is cost-effective in patients with AAV).	Different immunosuppressive regimens (including CYC regimens) were used in each trial; cannot determine from this study whether certain CYC regimens are associated with higher PCP risk than others.

	(Upon review, only 1 of the trial manuscripts reported on the occurrence of PCP)	PCP prophylaxis: Suggested but not mandatory <u>CYCAZERAM trial (n=153):</u> Inclusion criteria included renal involvement but SCr < 500 umol/L and no imminent loss of vital organ function Induction: CYC 2 mg/kg + prednisolone 1 mg/kg tapering Maintenance: CYC 1.5 mg/kg or AZA 2 mg/kg, + low dose prednisone PCP prophylaxis: Recommended but not mandatory <u>CYCLOPS trial (n=149):</u> Inclusion criteria included renal involvement but SCr < 500 umol/L Induction: CYC 2 mg/kg to remission + 2 months of 1.5 mg/kg, or pulsed IV CYC 15 mg/kg Q2-3 weeks x 6 months; prednisolone 1 mg/kg tapering Maintenance: AZA 2 mg/kg + low dose prednisone PCP prophylaxis: Recommended for all patients <u>NORAM trial (n=100):</u> Inclusion criteria included active disease but no imminent loss of vital organ function, SCr < 150 umol/L Induction: CYC 2 mg/kg or MTX 15-25 mg/week, + prednisolone 1 mg/kg tapering Maintenance: CYC 1.5 mg/kg or MTX 20-25 mg/week; prednisolone discontinued by 12 months PCP prophylaxis: Optional, but was ultimately not used	Only 1 was receiving PCP prophylaxis at the time of infection No other information provided on details of PCP cases, or on which trials these pts were enrolled in; upon review of manuscripts, 1 of the pts was enrolled in CYCLOPS trial		
Li et al. Pneumocystis carinii pneumonia in patients with connective tissue disease. J Clin Rhumatol. 2006;12(3):114-7.	Case series of CTD patients in a single center who were diagnosed with PCP between 2004-2005 (clinical laboratory had just begun to detect PCP beginning 2003)	<u>N=7 HIV-negative pts with CTD who developed PCP:</u> • 2 with SLE (out of approximately 150-200 new cases per year); 2 with MPA (out of approximately 15-20 new cases per year), 2 with dermatomyositis (out of approximately 30-40 new cases per year), 1 with polymyositis (out of approximately 30-40 new cases per year) • None received PCP prophylaxis • 4 pts received CS + CYC; 3 pts received CS + MTX <u>The 4 pts who received CYC (all had SLE or MPA):</u> Pt 1 (36 years with SLE, died): • Prednisone 30 mg/d + CYC 100 mg/d + CsA 150 mg/d • CD4 count 48/uL • Complicated by *Aspergillus fumigatus* infection Pt 2 (67 years old with MPA, died): • Prednisone 60 mg/d + CYC 100 mg/d; also received methylprednisolone 1 g/d x 3 d prior to PCP diagnosis • CD4 count 20/uL		Frequency of PCP in patients with CTD is low, but it is a serious complication with high mortality. Propose that patients with CTD receiving high doses of immunosuppressive therapy (e.g. pulsed methylprednisolone) and CD4 counts < 250/uL receive PCP prophylaxis; however, further studies are needed to determine the role of PCP	Difficult to draw valid conclusions from case series.

		• Complicated by *Aspergillus fumigatus* infection Pt 3 (47 years old with MPA, died): • Prednisone 60 mg/d + CYC 100 mg/d • CD4 count 38/uL • Complicated by *Candida albicans* infection Pt 4 (28 years old with SLE, survived): • Prednisone 50 mg/d + CYC 100 mg/d; also received methylprednisolone 1 g/d x 3 d prior to PCP diagnosis • CD4 count 91/uL			prophylaxis in CTD patients.	

Noel et al. Risk factors and prognostic influence of infection in a single cohort of 87 adults with systemic lupus erythematosus. Ann Rheum Dis 2001;60: 1141-4.	Case-control study of SLE pts to determine risk factors for infection	N=87 SLE pts > 16 years old who were seen at least once a year by the same team between 1960-1997
		
		Median age 33.7 years (16-80 years) at diagnosis
		
		Median duration of follow-up since diagnosis of 9.4 years (range 1-37 years)
			<u>Of the 87 pts:</u>
			• 43 with SLE GN
			• No details provided about the immunosuppressive regimens that pts received overall
			• 7 pts receiving immunosuppressive treatment received PCP prophylaxis (daily TMP-SMX in 3 patients, monthly aerosolized pentamidine in 4 pts)
			• 35 (40%) had ≥ 1 infectious episode, yielding 57 episodes
			  ○ 81% of the infections were community-acquired
			  ○ Bacteria responsible for 82% of the infectious
			• 52 (60%) had no infectious episodes
			• None developed PCP
					Although there were no cases of PCP during the entire study period, other studies have reported occurrence of PCP. Thus, TMP-SMX prophylaxis may be warranted in heavily immunosuppressed pts with lymphopenia.	Retrospective design.
						
						Immunosuppressive regimens not described.

Contreras et al. Sequential Therapies for Proliferative Lupus Nephritis. NEJM 2004;350:971-80.	Single-center, open-label RCT of lupus nephritis patients, with 72- month follow-up reported	N=59 pts ≥ 18 years old with lupus nephritis; excluded if CrCl < 20 mL/min, received >7 doses of IV CYC, or received AZA x >8 weeks 12 in WHO class III, 46 in class IV, 1 in class Vb Mean age 33 years	<u>Induction:</u> All received maximum of 7 monthly CYC IV boluses (0.5-1.0 g/m^2) + CS <u>Maintenance:</u> All received PO prednisone (up to 0.5 mg/kg/d) and Randomized to: 1) IV CYC 0.5-1.0 g/m^2 Q3 months n=20); 2) AZA 1-3 mg/kg PO daily (n=19); or 3) MMF 500-3000 mg PO daily (n=20) <u>PCP prophylaxis:</u>	<u>Rate of infection:</u> AZA 29% MMF 32% CYC 77% (p-value vs. AZA 0.002, vs. MMF 0.005) <u>Rate of major infection:</u> AZA 2% MMF 2% CYC 25% (p-value vs. AZA 0.01, vs. MMF 0.02) <u>PCP:</u> 1 patient in MMF group died of PCP Patient had received MMF x 10 months, then treatment was changed to MTX because of sluggish response of necrotic vasculitis. Died 5 months later due to PCP.	No conclusions provided regarding PCP. The incidence of severe infection was significantly lower in the AZA and MMF groups, compared to the long-term IV CYC group.	Small sample size. Infection was not the primary outcome; increased risk of false-positive results due to multiple comparisons. Incidence of PCP not specified.

			Not specified whether patients received PCP prophylaxis	Not specified whether any other patients developed PCP. <u>Rate of pneumonia (may have included PCP, but not specified):</u> AZA 2% MMF 2% CYC 15% (p-value vs. AZA 0.05, vs. MMF 0.06)		
de Groot 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(10):670-80.	Multicenter, open-label, RCT of AAV pts with median follow-up 18 months (range 0.25-18 months)	N=149 pts aged 18-80 years with newly diagnosed generalized AAV (WG, MPA, or renal-limited MPA) with renal involvement but not immediately life-threatening disease Renal involvement defined as SCr >150-500 umol/L, biopsy demonstrating necrotizing GN, erythrocyte casts, and/or hematuria Mean age 56.5-58.2 years WG in 56 pts, MPA in 71 pts, renal-limited MPA in 22 pts	<u>Induction:</u> All pts received prednisolone 1 mg/kg PO daily, tapered to 12.5 mg at end of month 3 and to 5 mg at end of the study (month 18) Randomized to: 1) Pulse CYC (n=76): CYC 15 mg/kg IV 2 weeks apart, then either CYC 15 mg/kg IV Q3weeks or CYC 5 mg/kg PO daily x 3 days given Q3weeks (dose reduced for age, SCr, and leukocyte nadir) Treatment continued until remission, then for another 3 months or 2) Daily PO CYC (n=73) CYC 2 mg/kg /d until remission, then 1.5 mg/kg/d x another 3 months (dose reduced for age, SCr, and leukocyte nadir) <u>Maintenance:</u> All received AZA 2 mg/kg PO daily until 18 months <u>PCP prophylaxis:</u>	<u>1 episode of PCP identified:</u> • Occurred in PO CYC group • Pt had not received PCP prophylaxis • Fatal outcome • No other details of PCP episode provided	No conclusions provided regarding PCP.	Details of PCP episode not provided. As a result, difficult to draw meaningful conclusions about PCP.

			Recommended for all patients, but given at the discretion of the local investigator Number of pts who received PCP prophylaxis was not specified			
Mahr et al. Analysis of factors predictive of survival based on 49 patients with systemic Wegener's granulomatosis and prospective follow-up. Rheumtatology (Oxford). 2001;40(5)492-8.	Prospective study of WG pts enrolled in a previous RCT (see 1997 study by Guillevin et al.) with to determine factors predictive of survival Previous RCT is 1997 study by Guillevin et al.	See data provided for 1997 study by Guillevin et al. No additional data regarding PCP cases was provided in this manuscript.				
Hoffman et al. Wegener Granulomatosis: An Analysis of 158 Patients. Ann Intern Med. 1992;116(6):488-98.	Single-center, retrospective study of WG pts Follow-up of 6 months to 24 years (total of 1229 pt-years); mean follow-up of 8 years	N=158 WG pts referred to National Institute of Allergy and Infectious Diseases Mean age 41 years (range 9-78 years), 15% <19 years of age <u>GN:</u> 18% presented with features of GN; symptomatic in all cases 77% later developed GN, usually within first 2 years of disease onset	133 (84%) received NIH protocol, comprised of low-dose CYC + CS; 8 (5%) received only low-dose CYC; 6 (4%) received other cytotoxic agents + CS; 10 (6%) received only CS <u>NIH protocol:</u> <u>NIH protocol CYC therapy:</u> 2 mg/kg PO daily (some patients received 3-5 mg/kg daily for fulminant and rapidly progressive disease); subsequent doses adjusted for WBC count CYC continued for ≥ 1 year after pt achieved complete remission, then tapered by 25 mg decrements Q2-3 months until discontinuation or until disease recurrence required dose increase <u>NIH protocol prednisone therapy:</u>	<u>6 episodes of PCP occurred:</u> • No details provided	No conclusions provided regarding PCP.	Unable to draw conclusions about PCP due to lack of information provided about the cases.

			If fulminant or rapidly progressive disease, received prednisone (or parenteral equivalent) 2-15 mg/kg x first few days. All pts received prednisone 1 mg/kg x ~4 weeks, then 60 mg on alternate days x 1-2 months. Then tapered gradually until discontinuation and patient was only on CYC <u>PCP prophylaxis:</u> Not specified, but presumably, pts did not routinely receive PCP prophylaxis			
Gottenberg et al. Long-term outcome of 37 patients with Wegener's granulomatosis with renal involvement. Presse Med 2007;36:771-8.	Subgroup analysis of the pts with renal involvement who were enrolled in the 1997 study of 50 WG pts by Guillevin et al. (see above for details)	N = 37 pts in the 1997 study by Guillevin et al. who had renal disease at diagnosis Renal disease either histologically proven or diagnosed with proteinuria >0.5 g/d and/or SCr >140 umol/L Median age 57 years (range 2-75 years) Median CrCl 22.8 mL/min (range 6.3-84.6 mL/min)	All pts received IV methylprednisolone 15mg/kg/d x 3 days, then prednisone 1 mg/kg/d x 6 weeks, which was then tapered gradually if remission was achieved. Also, all received IV CYC 0.7 g/m^2 x 1 dose after the last methylprednisolone dose. <u>Group A (n=23):</u> Pulse IV CYC, at mean dose of 0.7 g/m^2 (adjusted for renal function and PMN count to target 10-day nadir of 1500-3000/mm^3), given Q3weeks until remission achieved + for 1 year thereafter. Intervals between pulse treatments then increased to Q4weeks x 4 months, then Q5weeks x 4 months, then Q6weeks for 2 years of total treatment <u>Group B (n=14):</u>	<u>5 pts from the subgroup of pts with renal involvement developed PCP (out of 10 pts overall who developed PCP):</u> • None received PCP prophylaxis • All had severe lymphopenia • From the description, appears that all 5 of these PCP cases occurred in the first 10 pts with renal involvement that were enrolled • All 5 pts died (2 from PCP; 1 from PCP and bacterial pneumonia; 1 from PCP and CMV pneumonia; 1 from PCP, CMV pneumonia, and multifactorial thromobopenia) • No information on whether these patients were randomized to Group A or B	PCP prophylaxis is necessary for WG patients receiving CYC.	Small sample size.

			Daily PO CYC at dose of 2 mg/kg/d (dose adjusted for renal function and PMN count to target 1500-3000/mm^3) starting on day 10 following initial CYC pulse, after the PMN nadir had been reached. 1 year after remission reached, CYC dose tapered by 25% Q4months until discontinuation. Protocol was amended to include TMP-SMX 400 mg/d for all pts due to the high frequency of PCP observed in the first 12 pts recruited to the overall study (appears that this included the first 10 pts with renal involvement)			
Cohen et al. Infection and immunosuppression: a study of the infective complications of 75 patients with immunologically-mediated disease. QJM 1982; 51: 1-15.	Single-center retrospective review of pts with immunologically-mediated disease who required high-dose immunosuppression between 1974-1978	N=75 pts with immunologically-mediated disease 22 with GBM (mean age 38 years); 19 with SLE (mean age 31 years); 18 with WG (mean age 54 years); 16 with other forms of systemic vasculitis, including 3 with rapidly progressive GN (mean age 40 years) Mean age overall 40 years (range 9-67 years)	<u>PCP prophylaxis:</u> Not specified, but presumably, PCP prophylaxis was not routinely prescribed <u>SLE patients (n=19):</u> Initially received prednisolone 60 mg/d. Prednisolone dose usually reduced to 20 mg/d by end of week 3, then reduced by 5 mg decrements weekly 11 also treated with AZA, 6 with methylprednisolone, 5 with plasma exchange, 5 with CYC (highest total dose given to a single patient was 1.2 g) Mean length of immunosuppression 40.4 days	<u>2 pts developed PCP:</u> Immunosuppressive regimens that the pts received were not described Pt 1: • SLE • 24 years old • Required dialysis • Death due to pneumonia (*Klebsiella*, *Pneumocystis*) Pt 2: • "Other" systemic vasculitis • 45 years old • Required dialysis • Death due to pneumonia (*Aspergillus fumigatus*, *Pneumocystis*)	No conclusions provided regarding PCP.	Retrospective design. Unable to draw conclusions about risk factors for PCP, as pts who developed PCP were not compared to those who did not.

			<u>GBM, WG, and systemic vasculitis:</u> Induction therapy included prednisolone 60 mg/d, CYC 3 mg/kg/d x 6 weeks, and AZA 1 mg/kg/d (no azathioprine if > 55 years old) Prednisolone dose usually reduced to 20 mg/d by end of week 3, then reduced by 5 mg decrements weekly <u>GBM (n=22):</u> Mean total CYC 4.56 g (range 1.6-14.1 g) 4 also treated with methylprednisolone, 21 with plasma exchange Mean length of immunosuppression 42.9 days <u>WG (n=18):</u> Mean total CYC 6.24 g (range 0-43.06 g) 3 also treated with methylprednisolone, 13 with plasma exchange Mean length of immunosuppression 63.6 days <u>"Other" systemic vasculitis (n=16):</u> Mean total CYC 2.41 (range 0-11.2 g) 2 also treated with methylprednisolone, 11 with plasma exchange			

			Mean length of immunosuppression 73.5 days			
Bradley et al. Infectious complications of cyclosphosphamide treatment for vasculitis. Arthritis Rheum 1989;32:45-53.	Single-center retrospective chart review of vasculitis patients treated with CYC between 1984-1987, to determine risk of infection over 201 pt-months of CYC therapy	N=15 pts with vasculitis treated with CYC 6 with WG, 4 with isolated cerebral vasculitis, 5 with systemic necrotizing vasculitis (definition of the latter not provided) Mean age 49.1 years (range 17-85 years); WG subgroup older with mean age 30.2 years (range 36-85 years)	<u>Typical immunosuppressive regimen:</u> CYC 1-2 mg/kg PO daily, then increased by 25 mg every 2 weeks until clinical response or serious toxic effects (WBC count < 3000/ mm^3, or neutrophil count <1000-1500/ mm^3); continued x 1 year after complete remission, then reduced by 25 mg Q2-3 months +/- CS therapy (regimen unclear; appears that most patients received prednisone 1 mg/kg/d x 2-3 weeks, with conversion to alternate-day regimen over 1-2 months and subsequent tapering) <u>PCP prophylaxis:</u> Not specified, but presumably, PCP prophylaxis was not routinely prescribed	10 of 15 pts developed infection (17 infectious episodes overall); 2 died of infection Higher prevalence of infection in pts with WG (12 episodes in 6 pts; 0.12 episodes/patient-month of CYC treatment), compared to isolated cerebral vasculitis (2 episodes in 4 pts; 0.03 episodes/pt-month of CYC treatment) or systemic necrotizing vasculitis (3 episodes in 5 patients; 0.07 episodes/pt-month of CYC treatment). Not clearly attributed to difference in total CYC duration or myelosuppression Neither incidence of leukopenia nor dosage/duration of CYC or of CS correlated well with infection <u>2 pts developed PCP:</u> Pt 1 (died) – • Systemic necrotizing vasculitis • 63 years old • Pneumonia with *Pneumocystis*, *H. influenza*, *Enterobacter* isolates • At onset of pneumonia, CYC 100 mg/d + prednisone 30 mg/d • At onset of pneumonia, WBC 2700/mm^3 and neutrophil 1900/mm^3	No conclusions provided regarding PCP. High rate of infectious complications observed using this CYC +/- CS regimen. Pts with WG appear to be at greater risk of infection than those with other forms of vasculitis (i.e. isolated cerebral vasculitis and systemic necrotizing vasculitis).	Retrospective design. Small sample size. Unable to draw conclusions about risk factors for PCP, as patients who developed PCP were not compared to those who did not.

				Pt 2 (died) – • WG • 65 years old • Numerous infections at diagnosis of PCP: disseminated candidiasis; disseminated herpes simplex; *Staph. aureus* bacteremia; pneumonia with *Psuedomonas multophila, Serratia marsescens, and Pneumocystis* isolates • At onset of pneumonia, CYC 175 mg/d + prednisone 30 mg/d • At onset of pneumonia, WBC 3200/mm^3 and neutrophil 3000/mm^3		
Pohl et al. Plasmapheresis Does Not Increase the Risk for Infection in Immunosuppressed Patients with Severe Lupus Nephritis. Ann Intern Med 1991;114:924-9.	Multicenter RCT of severe diffuse proliferative lupus nephritis pts to determine whether plasmapheresis increases risk of infection in immuosuppression patients	N=86 pts >16 years old with severe diffuse proliferative lupus nephritis (WHO class III or IV with >50% glomeruli involved, or class V with superimposed diffuse or severe segmental proliferation) Exclusion criteria included SCr > 533 umol/L, neutrophil count <1500/mm^3 Mean age 32 years Mean 38.9 months since lupus nephritis diagnosis Mean SCr 180 umol/L	<u>Standard therapy (n=46):</u> Prednisone 60 or 80 mg daily (depending on body size) x 4 weeks. If lupus process table or improving, tapered to 50 mg x 4 weeks. Then tapered according to standardized medical management protocols. + CYC 2 mg/kg/d (max 150 mg/d) x 5 weeks, then 1 mg/kg/d x 3 weeks <u>Stardard therapy + plasmapheresis (n=40)</u> Above therapy + plasmapheresis (3 per week x 4 weeks) <u>PCP prophylaxis:</u>	<u>5 pts developed PCP:</u> • 3 in Standard therapy group • 2 in Standard therapy + plasmapheresis group	No conclusions provided regarding PCP	No details regarding PCP cases were provided

			Not specified, but presumably, PCP prophylaxis was not included in the study protocol			

Ognibene et al. Pneumocystis carinii pneumonia a major complication of immunosuppressive therapy in pts with Wegener's granulomatosis. Am J Respir Crit Care Med 1995	Case series of WG pts followed at the National Institute of Allergy and Infectious Diseases and National Institutes of Health between 1968-1992 who developed PCP
	
	Over 1300 pt-years of follow-up
		<u>Of 180 WG pts followed at the institution, 11 developed PCP:</u>
		• Mean age at diagnosis 54 years
		• 8 (73%) had previous pulmonary disease secondary to WG; 10 (91%) had underlying renal disease; 1 had previous renal transplantation
		• None received PCP prophylaxis
		• All developed PCP during the initial course of treatment or during treatment for recurrent WG
		  ○ 6 of 11 pts developed PCP within a year of WG diagnosis and during their first courses of immunosuppressive therapy; other 5 developed PCP between 3-14 years after diagnosis but during treatment for recurrent disease
		  ○ All were receiving daily CS therapy (doses ranging 60 mg alternating with 5 mg every other day to 60 mg daily); 10 were on tapering doses
		  ○ All pts were receiving a second immunosuppressive agent (doses not provided):
		  ▪ 5 pts on CYC
		  ▪ 1 pt on CYC + CsA
		  ▪ 3 pts on MTX
		  ▪ 1 pt on AZA
		  ▪ 1 pt on CsA
		• Total lymphocyte count at time of PCP ranged 61-658 cell/uL (not available for 1 pt)
		• 1 pt died
			Data indicate that in pts with WG, the highest risk for developing PCP is during treatment with daily CS + other immuonosuppressive agents (have not seen PCP in pts on alternate-day prednisone + other immmunosuppressive therapy, or in those receiving cytotoxic therapy alone).
			
			All pts had absolute lymphocytopenia. Raises possibility that increased PCP risk with CYC + CS is due to combination of lymphocytopenia from the cytotoxic agent in addition to lymphocyte and monocyte functional abnormalities induced by CS therapy.
			
			Authors raise issue of whether PCP prophylaxis should become standard. Authors' approach is to place all pts with WG who are receiving daily CS on TMP-SMX for PCP prophylaxis.
				Retrospective design.
				
				Unable to draw conclusions about risk factors for PCP, as pts who developed PCP were not compared to those who did not.
				
				No descriptions provided of CYC regimens that patients with PCP received.

Abbreviations: ADR (adverse drug reaction); AAV (ANCA-associated vasculitis); ADLC (average discounted lifetime cost); AZA (azathioprine); BAL (brochoalveolar lavage); CS (corticosteroid); CsA (cyclosporin); CTD (connective tissue disease); CrCl (creatinine clearance); CYC (cyclophosphamide); GBM (antiglomerular basement membrane disease); GN (glomerulonephritis); HIV (human immunodeficiency virus); IV (intravenous); IVIg (intravenous immunoglobulin); MMF (mycophenolate mofetil); MTX (methotrexate); PCP (Pneumocystis carinii pneumonia); PMN (polymorphonuclear neutrophil); PO (oral); pts (patients); QALY (quality-adjusted life years); RA (rheumatoid arthritis); RCT (randomized controlled trial); RTX (rituximab); sCr (serum creatinine); SLE (systemic lupus erythematosus); TAC (tacrolimus); TMP-SMX (trimethoprim-sulfamethoxazole); WBC (white blood cell); WG (Wegener's granulomatosis).

Table 17: Additional studies from reviewing other literature searches

	Design	Patient(s)	Intervention (CYC- focused)	Outcome (PCP-focused)	Conclusion (PCP and CYC-focused)	Limitations (PCP and CYC-focused)
McGonigle et al. Does cyclosporin A adversely affect Pneumocystis carinii infection? Postgrad Med J. 1988 Sep;64(755):659-62.	Case series of PCP pts; descriptive comparison of pts who received CYC/AZA to those who received CsA	N=14 PCP pts in total • All pts received concomitant prednisolone 10-20 mg/d at time of PCP diagnosis • No pts received PCP prophylaxis <u>Group 1: 7 pts who received prednisolone + CYC/AZA (did not provide the number of pts who received CYC specifically):</u> • 2 pts with SLE, 5 pts with renal transplantation • CYC dose: 2-3 mg/kg/d adjusted according to leukocyte count • AZA dose: 2-2.5 mg/kg/d • Treatment with high-dose IV TMP-SMX (1920 mg 6-hourly) in all cases • All pts survived • Stable graft function in all 5 pts with renal transplantation <u>Group 2: 7 pts who received prednisolone + CsA:</u> • All pnts were renal transplant recipients • CsA dose: 15 mg/kg/day orally initially, reduced to maintenance dose to keep trough levels within recommended therapeutic dose • Treatment with high-dose IV TMP-SMX (1920 mg 6-hourly) in all cases; 2 pts also received pentamidine 200 mg IV daily • 4 of 7 pts lived • Stable graft function in 2 of the 3 pts who lived			Despite identical PCP treatment, pts who received CsA had worse outcomes compared to those who received CYC or AZA. This raises the question of prophylactic TMP-SMX in patients taking CsA.	Numbers of pts who received specifically CYC or AZA were not provided. Details about patients' prednisolone regimens and relevant characteristics affecting PCP risk (eg. lymphocyte counts) not provided. Difficult to draw valid conclusions from case series.

Suryaprasad et al. When Is It Safe to Stop Pneumocystis jiroveci Pneumonia Prophylaxis? Insights From Three Cases Complicating Autoimmune Diseases. Arthritis Rheum 2008; 59(7):1034-9.	Case series of PCP pts	N=3 pts with rheumatic disease who developed PCP after discontinuation of CYC and high-dose CS
		
		Pt 1 (70 years old with WG, lymphocyte count nadir 158/mm^3):
		• Treated 3 years earlier with CYC and high-dose CS that were tapered off
		• Developed pachymeningitis that required reinstitution of immunosuppression
		  ○ CYC 125 mg/day + prednisone 60 mg/day
		  ○ PCP prophylaxis with atovaquone 750 mg BID due to sulfa allergy; patient was non-adherent to this
		• After 6 months of CYC and prednisone taper of 6 months' duration, disease was in remission
		  ○ CYC, prednisone, and atovaquone were stopped
		  ○ Started on MTX 20 mg/week for remission maintenance
		• Developed PCP 5 months after starting MTX
		  ○ Prior to this, duration of immunosuppression was 438 days
		  ○ Total lymphocyte count 158/mm^3 (normal range 1100-4800/mm^3)
		  ○ Treated with clindamycin + primaquine
		  ○ After 3 weeks hospitalization, total lymphocyte count increased to 1260/mm^3 and was discharged in stable condition
		
		Pt 2 (36 years old with SLE, lymphocyte count nadir 89/mm^3)
		• Treated for newly diagnosed SLE
					Common features among these pts were: autoimmune diseases associated with systemic inflammation; immunosuppression with CYC + high-dose CS; persistence of CD4 lymphocytopenia after discontinuation of immunosuppression; lapsed PCP prophylaxis.
					
					Important to prescribe PCP prophylaxis and ensure that it is maintained.
					
					These cases suggest that the need for PCP prophylaxis can extend for months beyond the time of intensive immunosuppressive therapy.
					
					The mean CD4 count in the group of patients infected was 281/mm^3, indicating that many pts developed their PCP at CD4 counts well above
						Difficult to draw valid conclusions from case series.

		○ 3-days pulse of methylprednisolone (1 g/day) + 1 dose IV CYC 500 mg/m^2, with plan to complete a full CYC course based on National Institutes of Health regimen. ○ PCP prophylaxis with TMP/SMX 1 double strength tablet 3x/week; switched to atovaquone 750 mg BID due to cholestasis thought to be due to TMP/SMX • Hospitalized over next 10 weeks for neutropenic fevers, central line infections, pulmonary infiltrates, cholestatic jaundice ○ Received another CYC dose within this period • Due to no signs of renal recovery, CYC discontinued, prednisone tapered to 10 mg/day, atovaquone discontinued • Developed PCP 1 month after stopping CYC and while on prednisone 10 mg/d ○ Prior to this, duration of immunosuppression was 114 days ○ Total lymphocyte count 160 mm^3 (normal range 1100-4800/mm^3) ○ Treated with methylprednisolone 100 mg TID + IV pentamidine 4 mg/kg Q2days • Lymphocyte count improved to 3373/mm^3 in following 5 weeks, but died from intracranial hemorrhage during week 6 of PCP treatment Patient 3 (64 years old with WG, lymphocyte count nadir 0/mm^3) • Treated for necrotizing, pauci-immune glomerulonephritis with crescents ○ Urgent dialysis started ○ CYC 150 mg/day + prednisone 80 mg/day, followed by CS tapering regimen • 5 months later while on CYC 150 mg/day and prednisone 30 mg/day, disease was in remission ○ Still very leukopenic (white blood cell count 2200/mm^3) ○ CYC stopped; prednisone planned to taper over next 2 months • Appears that PCP prophylaxis was initiated when CYC was stopped ○ Initially received TMP/SMX 1 single strength tablet daily was initiated, but switched to dapsone 100 mg/day due to diffuse skin rash with mucous membrane involvement ○ Patient was non-adherent to PCP prophylaxis • Developed PCP 2 months after stopping CYC; was not on any immunosuppression ○ Lymphocyte count was 0/mm^3 ○ Underwent TMP/SMX desensitization and completed TMP/SMX treatment for PCP • Lymphocyte count improved to 500/mm^3 in hospital and pt recovered			the guideline for the termination of prophylaxis in patients with HIV. Suggest that clinicians consider checking CD4 lymphocyte counts in pts for whom the discontinuation of PCP prophylaxis is considered. If the CD4 count is < 200/mm^3, clinicians should consider continuing prophylactic treatment until the counts are consistently above this level for 6 months. However, recognize that this measure is unlikely to be a perfect surrogate for immunocompetence relating to PCP, in contrast to its utility in HIV pts.	
Pryor et al. Risk factors for serious infection during treatment with cyclophosphamide and high-dose corticosteroids for systemic lupus erythematosus. Arthritis Rheum 1996; 39(9):1475-82	Retrospective chart review of a series of SLE patients treated with CYC (with concomitant steroid) Comparison done with patients treated with high-dose CS alone	N=100 SLE patients treated with CYC Mean age 34.7 years 40% had renal indication for CYC	<u>Treatment:</u> • No uniform treatment protocol • Mean duration was 11.5 months (range of 1 IV CYC infusion to 96.5 months of therapy)	<u>45 of 100 pts on CYC therapy developed infection:</u> • 82% were taking a lower dose of CS than their course maximum at the time of infection (half were taking	No conclusions provided regarding PCP.	Retrospective design. No details regarding PCP cases were provided.

	(≥60 mg/day x ≥14 days) to determine relative contribution of steroids to risk of serious infection among CYC-treated patients		• All patients received concomitant CS therapy with CYC (mean max CS dose of 195 mg/day, max range 30-2500 mg/day) • 3 patients received concomitant cytotoxic therapy (1 vinblastine, 1 vincristine, 1 CsA) <u>CYC therapy:</u> • PO in 40% • IV in 41% • Sequential IV and PO in 19% <u>PCP prophylaxis:</u> • Not specified whether any patients received PCP prophylaxis	≤40 mg/day of prednisone, quarter were taking <25 mg/day) • 3 patients developed PCP; 1 died (this patient also had CMV adrenalitis) <u>Factors associated with infection in pts on CYC therapy:</u> • In multivariate analysis, factors significantly associated with infection were use of sequential PO and IV CYC (OR 2.3, 95% CI 1.4-4.3) and WBC nadir of ≤ 3000 cells/uL (OR 2.8, 95% CI 1.4-5.5) • In univariate analyses, factors significantly associated with <u>opportunistic</u> infection were higher maximum CS dose (p=0.04) and lower WBC nadir at some time during treatment course (p=0.02) <u>Comparison of patients treated with CYC + CS vs. high-dose CS alone:</u> • Infection occurred in significantly more patients treated with CYC+CS than with high-dose CS alone (45% vs. 12%, p=0.001)		

				• No PCP cases reported in high-dose CS alone group		
Lertnawapan et al. Risk factors of Pneumocystis jeroveci pneumonia in patients with systemic lupus erythematosus. Rheumatol Int 2009; 29:491-6	Retrospective, single-center case-control study comparing non-HIV Thai SLE patients with and without PCP between 1994-2004 Controls were age-and sex-matched, and were selected from the same period after treatment for comparison	15 PCP cases: 60 controls (mean age 37 years): • Not specified whether any patients had received PCP prophylaxis, but presumably, none had <u>PCP cases (n=15):</u> • Marked reduction in lymphocyte count observed before onset of PCP in all cases (mean 710 ± 377 cells/mm^3) • 3 pts died (20% mortality rate) • All had been treated with prednisolone <u>Comparison of PCP vs. non-PCP (univariate analyses):</u> • Higher activity index by MEX-SLEDAI (13.6 ± 5.83 vs. 6.73 ± 3.22) • More renal involvement (86 vs. 11.6%, p<0.01) • Higher mean cumulative dose of CS in the 6 months prior to infection (49 ± 29 vs. 20 ± 8 mg/day, p<0.01) • Lower lymphocyte count during 6-7 months after initiation of SLE treatment (520 ±226 vs. 1420 ± 382 cells/mm^3, p<0.01), though lymphocytopenia in both groups • Similar mean CYC, AZA, and chloroquine doses in the 6 months prior to infection		The high mortality rate of 20% signifies the importance of PCP prophylaxis in high-risk SLE pts. Authors recommend a profound decrease in lymphocyte count at or below 750 cells/mm^3 at any time during treatment to necessitate primary PCP prophylaxis; estimated that using CD4 count < 200 could also be used as a threshold for prophylaxis, given that CD4 count can be calculated from 15-20% of lymphocytes. Additional factors that can be helpful in selecting LSE pts who need PCP prophylaxis include higher disease activity, higher dose of CS, and renal involvement. The finding regarding prednisolone dose is in agreement with the recommendation to start PCP prophylaxis in pts who receive >20 mg prednisolone equivalent per day. Could not find significant correlation between PCP infection and doses of immunosuppressive agents other than prednisolone, such as CYC and AZA.	Retrospective design. Small number of PCP cases. Only univariate analyses performed to determine factors associated with PCP; multivariate analyses perhaps would have produced different results. Exact immunosuppressive regimens had pts received were not described. Unclear whether any of the pts (cases or controls) had received PCP prophylaxis.

Abbreviations: AZA (azathioprine); CMV (cytomegalovirus); CS (corticosteroid); CsA (cyclosporin); CYC (cyclophosphamide); IV (intravenous); MTX (methotrexate); PCP (Pneumocystis carinii pneumonia); PO (oral); SLE (systemic lupus erythematosus).

Appendix 8: Rituximab

Search Strategy:

Medline 1946 to Present
Search executed on Dec 28, 2019

Search Terms:
Rituximab AND glomerulonephritis AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline (e.g. PCP, pneumocystis jirovecii pneumonia and pneumocystis carinii pneumonia provided the same results).

Rituximab AND vasculitis AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline

Rituximab AND lupus AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline

Rituximab AND IgA nephropathy AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline

Rituximab AND focal segmental glomerulosclerosis AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline

Rituximab AND minimal change disease AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline

Rituximab AND membranous nephropathy AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline

Rituximab AND prednisone AND Pneumocystis jirovecii pneumonia
- These are MESH headings, automatically mapped and exploded by Medline
- ** note: this search is not exclusive for GN patients

Limits:
- Human
- English Language

Results:
Rituximab AND glomerulonephritis AND Pneumocystis jirovecii pneumonia
- Number of articles identified through database search: n=3
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=0

Rituximab AND vasculitis AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=7
- Number of articles identified through review of reference: n=7
- Full-text papers selected for appraisal and analysis: n=3

Rituximab AND lupus AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=5
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=2

Rituximab AND IgA nephropathy AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=1
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=0

Rituximab AND focal segmental glomerulosclerosis AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=1
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=0

Rituximab AND minimal change disease AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=1
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=0

Rituximab AND membranous nephropathy AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=0
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=0

Rituximab AND prednisone AND Pneumocystis jirovecii pneumonia

- Number of articles identified through database search: n=22
- Number of articles identified through review of reference: n=0
- Full-text papers selected for appraisal and analysis: n=2

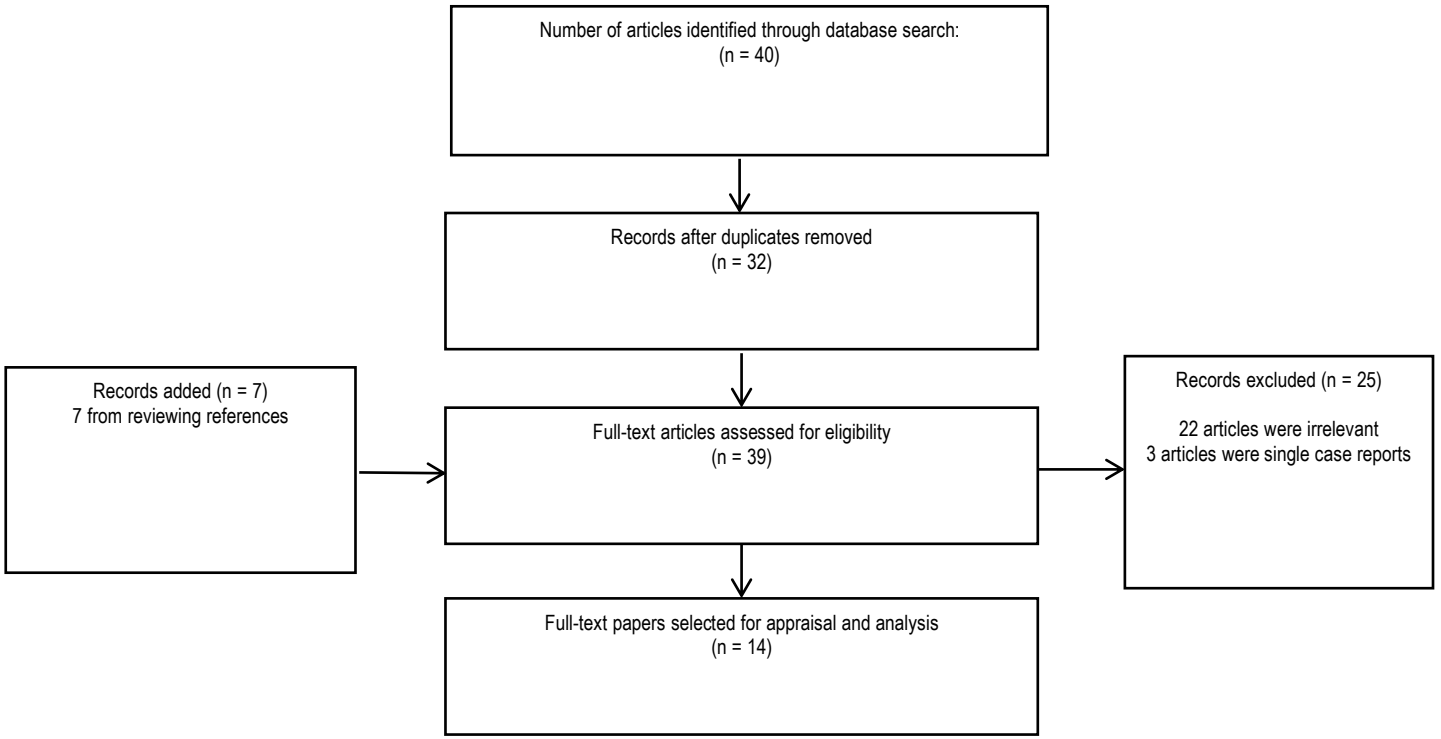
Number of articles identified through database search:
(n = 40)
Records after duplicates removed
(n = 32)
Records added (n = 7)
7 from reviewing references
Full-text articles assessed for eligibility
(n = 39)
Records excluded (n = 25)
22 articles were irrelevant
3 articles were single case reports
Full-text papers selected for appraisal and analysis
(n = 14)

Table 18: Rituximab AND glomerulonephritis AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
No papers						

Table 19: Rituximab AND vasculitis AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
King et al. The complications of vasculitis and its treatment. Best Pract Res Clin Rheumatol. 2018 Feb;32(1):125-136.	Narrative	Pts with AAV	N/A	Prophylaxis with TMP/SMX (800/160 mg on alternative days or 400/80 mg daily) is recommended for all pts undergoing CYC or RTX treatment (referencing: EULAR, ERA-EDTA recommendation for ANCA and BSR and BHPR guidelines for ANCA vasculitis)		The EULAR guidelines recommend prophylaxis for patients on CYC. The BSR guidelines recommend prophylaxis for patients on CYC or CS. King et al. should not have extrapolated this to RTX.
Besada et al. Should Pneumocystis jiroveci prophylaxis be recommended with Rituximab treatment in ANCA-associated vasculitis? Clin Rheumatol. 2013 Nov;32(11):1677-81.	Single case-report and then literature review.	79 y/o man PR3-ANCA GPA, relapsed with sinus and lung activity while on MMF 1.5 g/d and pred 5 mg/d; switched to RTX 1 g Q2weeks x 2 doses and prednisone 40 mg/d with gradual taper (MMF was d/ced).		3 months post RTX, pt developed PCP while on prednisone 15 mg/d. Pt treated with PCP with TMP/SMX dosage adjusted for reduced kidney function x 21 days. Pt recovered. Lit review Out of 516 AAV pts treated with RTX in different cohorts (from 10 studies), at least 6 pts (1.2%) developed PCP and 2 pts died.	Some experts in AAV have recommended maintaining PCP chemoprophylaxis in patients treated with RTX for at least the duration of B cells depletion [33]. If the PCP incidence in AAV/GPA patients is close to 1 %, this recommendation is not supported by the general principles of PCP prophylaxis. Even though PCP prophylaxis is effective and reduced the PCP mortality rate, the risk for PCP must be over 3.5 % to outweigh the ADRs chemoprophylaxis [6]. Others concerns are that	Calculated PCP incidence rate of 1.2% with RTX use in AAV is likely very inaccurate for the following reasons: • The total number of pts who received RTX in 10 studies was 487 (not 516). • 5 pts (not 6) had confirmed PCP from the 10 studies, and 1 (not 2) of these pts died. • PCP prophylaxis was reported as recommended/prescribed in 3 of the studies; in the remainder, PCP prophylaxis was not routinely prescribed, prescribed to only select pts, or not specified. • 5 of the studies simply did not report on PCP, which does not exclude the possibility that PCP occurred. • 8 of the studies were retrospective, and PCP likely was not systematically diagnosed/reported.

					neither primary nor secondary PCP prophylaxis is perfect [3] and that bacterial resistance to TMP-SMX can occur [6].	Of note, most pts in the 10 studies received concomitant immunosuppressive agents with RTX, so this group of studies cannot be used to calculate the PCP incidence with RTX monotherapy.
Nixon et al. Infectious complications of rituximab therapy in renal disease. Clin Kidney J. 2017 Aug;10(4):455-460.	Narrative		"The addition of rituximab to chemotherapy in lymphoma pts significantly increases the risk of PCP infections [43]. In the RAVE trial, opportunistic infections were not reported in the RTX arm but 3 fatal cases were seen in the CYC arm [4]. Elsegeinyet al. [44] very elegantly demonstrate the effect of RTX alone on T lymphocyte cytokines, as well as the role of T-lymphocytes in the development PCP infection. We do not see this effect in the RA population, highlighting that pt and disease factors are important in determining the risk of infection with RTX treatment. Nonetheless, even in lymphoma pts, PJP prophylaxis is highly effective in preventing infection."			
Schmajuk et al. Pneumocystis jirovecii pneumonia (PJP) prophylaxis patterns among patients with rheumatic diseases receiving high-risk immunosuppressant drugs. Semin Arthritis Rheum 2019; 48(6): 1087-1092.	Single-center retrospective cohort study using electronic health record data with mean follow-up 23.2 ± 14.2 months	N = 316 pts >18 years of age with diagnosis of GPA, MPA, dermatomyositis, polymyositis, or SLE who were new users of certain immunosuppressive agents Mean age 43 years, GPA 15%, 7% MPA, 56% SLE	Comparison of pts who received PCP prophylaxis (TMP-SMX, dapsone, atovaquone, or pentamidine) vs. pts who did not receive PCP prophylaxis <u>20 pts who received RTX:</u> RTX monotherapy (n=13): 11 with prophylaxis vs. 2 without prophylaxis RTX + CS (not indicated whether low- or high-dose) (n=23): 16 with prophylaxis vs. 7 without prophylaxis RTX + other(s) ("other" not specified) (n=5): 1 with prophylaxis vs. 4 without prophylaxis		No pats received PCP diagnosis (as defined using diagnosis codes). <u>Among all 192 study pts who received PCP prophylaxis:</u> With mean follow-up 26 months, 9.7% had an ADE (serious/life-threatening in 1.5% of those taking TMP-SMX; 17.9% of those taking dapsone; 0% of those taking atovaquone or pentamidine).	No conclusions specific to RTX and PCP risk were provided. The incidence of PCP is extremely low, and ADEs from antibiotics occur at a low but detectable rate. Evidence to guide more personalized risk assessment are needed to inform PCP prophylaxis.
Jones et al. Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. N Engl J Med 2010; 363:211-20.	Open-label, two-group, parallel-design, RCT with 3:1 randomization of AAV patients involving 8 centers in Europe and Australia; 12-month follow-up	N=44 pts with new diagnosis of AAV, ANCA positivity, and renal involvement (defined as necrotizing GN on biopsy or red cell casts or hematuria on urinalysis)	Before enrollment, pts allowed to undergo plasma exchange to receive max of 2 grams IV methylprednisolone All pts received methylprednisolone 1 gram + oral CS regimen of 1 mg/kg/d initially, with a reduction to 5 mg/day at the end of 6 months Both groups had CYC dose reductions for age ≥60 years and renal function (creatinine >300μmol/L) <u>RTX group (n=33):</u>		No PCP developed in any of the pts.	No conclusions specific to PCP risk with RTX or CYC were provided.

		Median age 68 years, GFR 18 mL/min/1.73 m^2	RTX 375 mg/m^2 weekly x 4 weeks + IV CYC 15 mg/kg with 1st and 3rd RTX infusions One additional IV CYC dose of 15 mg/kg permitted if progressive disease within first 6 months No AZA to maintain remission Control group (n=11): IV CYC 15 mg/kg Q2weeks x 3 doses, then Q3weeks thereafter until stable remission (minimum 6, max 10 doses) Maintenance therapy with PO AZA 2 mg/kg/d introduced after CYC withdrawal PCP prophylaxis: Recommended for all pts (no particular agent recommended); in protocol, max of 6 months of PCP prophylaxis was permitted for Control group (unclear duration for RTX group) 22 pts (67%) in RTX Group and 8 pts (73%) in control group received antibiotic prophylaxis (presumably PCP prophylaxis)		

Abbreviations: ADE (adverse drug events); AAV (ANCA-associated vasculitis); AZA (azathioprine); BHPR (British Health Professionals in Rheumatology); BSR (British Society for Rheumatology); CS (Corticosteroid); CYC (cyclophosphamide); ERA- EDTA (European Renal Association- European Dialysis and Transplant Association); EULAR (European Alliance of Associations for Rheumatology); GPA (granulomatosis with polyangiitis); MMF (mycophenolate mofetil); MPA (microscopic polyangiitis); PCP (pneumocystis jirovecii pneumonia); pts (patients); RA (rheumatoid arthirtis); RTX (rituximab); SLE (systemic lupus erythematosus); TMP-SMX (trimethoprime-sulfamethoxazole).

Table 20: Rituximab AND lupus AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
Bonilla-Abadia et al. Pneumocystis jirovecii pneumonia in two patients with systemic lupus erythematosus after rituximab therapy. Clin Rheumatol. 2014 Mar;33(3):415-8.	Case series (2 pts with SLE)	**Case 1:** 20 y.o female with LN IV. **Case 2:**	**Case 1:** RTX 1g IV x 2 doses q2weeks every 9 months x 4 years Also, on AZA 50 mg/day and prednisone 5 mg/day **Case 2:** RTX 1g IV x q2weeks 2 doses	**Case 1:** PCP 1 mo after the last dose of RTX Treated with 21 days of primaquine and clindamycin. (regimen not given). Recovered. **Case 2:** PCP 6 weeks after the last dose of RTX	Increased vigilance for PCP required.	It is unclear how many other SLE patients at this hospital received RTX without issue.

		19 y.o female with SLE treated x 2 years with PO prednisone 25 mg/day.		Given TMP/SMP 800/160 mg but died 12h later.		
Tsai et al. Pneumocystis jiroveci pneumonia in patients with systemic lupus erythematosus after rituximab therapy. Lupus. 2012 Jul;21(8):914-8.	Case series (2 pts with SLE)	**Case 1:** 20 y.o female with SLE. PCP x 2 occasions (7 months apart) **Case 2:** 39 y.o female with SLE treated x 6 years with PO methylprednisonlone (12-16 mg/day), CsA and MMF (regimen not provided).	**Case 1:** RTX 500 mg IV x 2 doses 1 month apart. **Case 2:** RTX 500 mg IV x 2 doses. It is unclear if other immunosuppressants were stopped, and if so, the timing of this.	**Case 1:** PCP 6 weeks after the 2nd dose of RTX. Treated with primaquine and clindamycin. Recovered (regimen not given). **Case 2:** Salmonella bacteremia 2 days after RTX. Then PCP 17 days after RTX. The pt died despite broad spectrum antibiotics.	PCP may occur sporadically in pts with autoimmune disease after RTX treatment, but the relation between PCP and RTX remains unclear.	It is unclear how many other SLE pts at this hospital received RTX without issue.

Abbreviations: AZA (azathioprine); CsA (cyclosporin); LN (lupus nephritis); MMF (mycophenolate mofetil); pts (patients); PCP (pneumocystis jirovecii pneumonia); PO (oral); RTX (rituximab); SLE (systemic lupus erythematosus).

Table 21: Rituximab AND IgA nephropathy AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
No papers						

Table 22: Rituximab AND focal segmental glomerulosclerosis AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
No papers						

Table 23: Rituximab AND minimal change disease AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
No relevant papers						

Table 24: Rituximab AND membranous nephropathy AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
No search results						

Table 25: Rituximab AND prednisone AND Pneumocystis jirovecii pneumonia

	Design	Patient(s)	Intervention	Outcome	Conclusion	Limitations
Alexandre et al. Pneumocystis jirovecii pneumonia in patients treated with rituximab for systemic diseases: Report of 11 cases and review of the literature. Eur J Intern Med. 2018 Apr;50:e23-e24	Retrospective case series through a call for cases through the French Society of Internal medicine	11 cases of. PCP in non-HIV pts exposed to RTX for an autoimmune disease (other than RA) between Jan 2005 and Dec 2015. Before RTX infusion: Median lymphocyte	RTX regimens not provided Not specified whether patients received PCP prophylaxis 10 of 11 pts were also on prednisone (median dose	Time to PCP from last RTX infusion: 0 to 11 weeks Overall mortality rate 27%	PCP appears uncommon in context of RTX, but incidence is difficult to assess accurately due to non-exhaustive reports and heterogeneity of PCP prophylaxis use.	Retrospective design. Information on RTX regimens and PCP prophylaxis (if any) not provided.

		count 1 x 10^9/L (0.5-3.2 x 10^9/L); Median CD4+ count (available for 8 patients) 487/mm^3 (84-2440/ mm^3)	30 mg, range of 0-85 mg/day) 8 pts were on prednisone > 20 mg/day.		Almost all cases were associated with concomitant CS therapy. PCP can occur even if patients have CD4+ cell above 350/mm^3. PCP occurred 3-6 months after last infusion, corresponding to the time of maximal B lymphocyte depletion. PCP prophylaxis can be discussed with patients receiving RTX, especially if they are also taking prednisone > 20 mg/day.	
Martin-Garrido et al. Pneumocystis pneumonia in patients treated with rituximab. Chest. 2013 Jul;144(1):258-265	Retrospective case series	Patients > 18 y/o diagnosed with PCP between Jan 1998 and Aug 2011 at the Mayo Clinic, Rochester N=30 Mean age =70	All patients given RTX Typical dose = 375 mg/m^2 at 1 to 2-week intervals, either alone in or in combo with other agents Mean # of RTX cycles = 4 2 pts (7%) developed PCP after 1 course of RTX	RTX administration was documented in 14.5% of total non-HIV PCP cases. 27 of 30 pts with PCP (90%) received a CS or cytotoxic therapy 11 of 30 (37%) pts received CS only (in addition to RTX). 15 pts (51%) received RTX as part of diffuse large B-cell lymphoma therapy **3 pts (10%) received RTX**	In conclusion, PCP can occur in association with RTX alone, but most cases have also received either chemotherapy or significant doses of CS. Primary prophylaxis should be considered in RTX-treated pts. Importantly, secondary prophylaxis against recurrent PCP should be provided unless immune reconstitution is assured.	It is unknown how many pts received RTX and did not develop PCP (incidence rate is unknown).

				monotherapy; 1 for GPA (Wegener's) who was not lymphocytopenic, 1 for diffuse large B-cell lymphoma who was not lymphocytopenic, and 1 for chronic lymphotopenic lymphoma.		

Abbreviations: CS (corticosteroid); pts (patients); GPA (granulomatosis with polyangiitis); HIV (human immunodeficiency virus); PCP (pneumocystis jirovecii pneumonia); RA (rheumatoid arthritis); RTX (rituximab); SLE (systemic lupus erythematosus).