Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis

Authors
John H Stone, MD, MPH
Andre A Kaplan, MD
Ronald J Falk, MD

Section Editor
Gerald B Appel, MD

Deputy Editor
Alice M Sheridan, MD

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NEW TERMINOLOGY — In January 2011, the Boards of Directors of the American College of Rheumatology, the American Society of Nephrology, and the European League Against Rheumatism recommended that the name Wegener’s granulomatosis be changed to granulomatosis with polyangiitis (Wegener’s), abbreviated as GPA [1-3]. This change reflects a plan to gradually shift from honorific eponyms to a disease-descriptive or etiology-based nomenclature. The parenthetic reference to Wegener’s will be phased out after several years as the new name becomes more widely known.

INTRODUCTION — Granulomatosis with polyangiitis (Wegener’s), which can be abbreviated as GPA, and microscopic polyangiitis (MPA) are related systemic vasculitides. Both are associated with antineutrophil cytoplasmic antibodies (ANCA), have similar features on renal histology (eg, a focal necrotizing, pauci-immune glomerulonephritis), and have similar outcomes. There are, however, several differences between these disorders. (See "Clinical manifestations and diagnosis of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis", section on 'Clinical presentation'.)

Therapy of GPA and MPA has two components: induction of remission with initial immunosuppressive therapy, and maintenance immunosuppressive therapy for a variable period to prevent relapse.

The initial immunosuppressive therapy of GPA and MPA will be reviewed here. Maintenance immunosuppressive therapy following induction of remission, the treatment of cyclophosphamide resistant or relapsing disease, the clinical manifestations and diagnosis of these disorders, and patient and renal outcomes are discussed elsewhere. (See "Maintenance immunosuppressive therapy in granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis" and "Treatment of cyclophosphamide-resistant granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis" and "Relapsing disease in granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis" and "Clinical manifestations
GENERAL PRINCIPLES

Assessment of disease activity — A variety of methods have been used to assess disease activity in patients with granulomatosis with polyangiitis (Wegener’s), abbreviated as GPA, or microscopic polyangiitis (MPA). As an example, the Birmingham Vasculitis Activity Score (BVAS) has been applied to patients with GPA (BVAS/GPA). The score includes both general symptoms (arthralgia, arthritis, and fever) and involvement of eight major organ systems. At each site, persistent symptoms or manifestations (eg, hematuria) are given one point and new or worse symptoms are given two points. (See "Overview of the management of the vasculitides in adults", section on 'Patient monitoring'.)

The BVAS/GPA score ranges from 0 (complete remission) to a maximum of 68. Major manifestations are defined as those that pose an immediate threat to the patient’s life or to the function of a vital organ. These include gangrene, alveolar hemorrhage, respiratory failure, nervous system involvement, sensorineural deafness, mesenteric ischemia, scleritis, retinal exudates or hemorrhage, red blood cell casts, and a rise in serum creatinine.

Immunosuppressive therapy is indicated in all patients with active GPA or MPA. Even patients with advanced renal disease at presentation are highly likely to benefit. In one report, for example, remission was induced in 72 percent of 240 patients with an estimated glomerular filtration rate (eGFR) ≤30 mL/min, 68 percent of 188 patients with an eGFR ≤20 mL/min, and 57 percent of 96 patients with an eGFR ≤10 mL/min [4].

Definition of complete remission — Induction of complete remission is the goal of immunosuppressive therapy in GPA or MPA and is defined as the absence of active disease. A number of definitions of complete remission have been used and the definitions have evolved over time.

In the 1992 National Institutes of Health study demonstrating the efficacy of cyclophosphamide, the criteria for complete remission included absence of systemic inflammatory disease such as serositis and fever, complete resolution of pulmonary infiltrates or stable scarring without signs of active inflammation, and an inactive urine sediment with stabilization of or improvement in renal function [5].
Similar criteria were used in a 1996 report from the University of North Carolina [6]. Complete remission was defined as stabilization of or reduction in the serum creatinine and resolution of extrarenal manifestations. Persistent proteinuria was not considered a sign of persistent disease activity.

The BVAS/GPA score described in the preceding section is more comprehensive, as it includes both systemic manifestations and involvement of eight organ systems [7,8]. Complete remission is defined as a score of 0. In terms of renal involvement, the BVAS/GPA score uses hematuria or red cell casts as a sign of active disease. Red cell casts are not present in some patients with hematuria due to vasculitis and there can be many false positive and false negative results if read by inexperienced observers.

**Renal remission** — If there is no active renal inflammation, then hematuria and, if present, red cell casts should remit, which is defined as 0 to 3 red cells per high power field. However, there are two other potential causes of hematuria that can occur in patients with GPA or MPA that are unrelated to active renal inflammation:

- Persistent hematuria at the time of apparent remission may reflect cyclophosphamide-induced cystitis. The red cells in this setting are typically isomorphic (normomorphic), not dysmorphic as with glomerular hematuria (picture 1A-B) and cystoscopy usually shows signs of bladder injury (70 percent in one series) [9]. (See "Hematuria: Glomerular versus extraglomerular bleeding", section on 'Red cell morphology'.)

In addition, the hematuria due to bladder injury should resolve within three to four weeks after the last cyclophosphamide dose. Persistent monomorphic hematuria raises the possibility of cyclophosphamide-induced bladder cancer, which is not typically seen with the usually short duration of cyclophosphamide therapy now used in patients with GPA or MPA [9]. (See "Epidemiology and etiology of urothelial (transitional cell) carcinoma of the bladder", section on 'Cyclophosphamide'.)

- Premenopausal women often have blood in the urine during menses due to contamination from menstrual bleeding. Short of bladder catheterization, the etiology of hematuria is best determined by repeat urinalysis after the cessation of menses. This is not a common issue in patients with GPA or MPA, since the mean age is over 50 years and most affected women are postmenopausal.
Active disease versus irreversible injury — Complete remission does NOT mean that all parameters have to return to baseline [5]. Many patients have persistent abnormalities that reflect irreversible injury induced during the period of active inflammation. As an example, a patient in whom systemic symptoms and signs resolve and the urinalysis becomes inactive (ie, no hematuria) is considered to be in remission, even if there is persistent proteinuria and persistent or even slowly worsening renal insufficiency. In addition, late progression of the renal disease can result from factors (eg, intraglomerular hypertension) that result from initial nephron loss rather than continuing disease activity. Angiotensin inhibition may be beneficial in such patients. (See "Secondary factors and progression of chronic kidney disease" and "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults".)

Partial remission — Partial remission is more difficult to define. In the kidney, partial remission refers to the persistence of dysmorphic (ie, glomerular) hematuria with or without red blood cell casts despite improvement in or stabilization of the serum creatinine and disappearance of extrarenal signs of active disease (picture 1A-B). This is a smoldering process that can lead to progressive renal injury and usually indicates the need for further therapy. On the other hand, persistent proteinuria may reflect irreversible glomerular injury and, as an isolated finding, is not indicative of active disease.

Dysmorphic hematuria must be distinguished from isomorphic hematuria, which is characteristic of extraglomerular bleeding and, in patients receiving initial immunosuppressive therapy, may reflect cyclophosphamide-induced bladder toxicity. (See "Hematuria: Glomerular versus extraglomerular bleeding", section on 'Red cell morphology'.)

Smoldering disease in the respiratory tract is a common and difficult problem. Active vasculitis in the upper respiratory tract must be distinguished from scarring, which can progress in the absence of active disease, and infection. Similarly, a nodule in the lung may represent active vasculitis, a scar, or infection.

Cyclophosphamide resistance — True cyclophosphamide resistance is uncommon in GPA and MPA and is discussed in detail elsewhere. (See "Treatment of cyclophosphamide-resistant granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis".)

Summarized briefly, a report from the University of North Carolina defined treatment resistance as one or both of the following despite immunosuppressive therapy for at least one month [6]:
• A progressive decline in renal function (ie, increase in serum creatinine) with persistence of an active urine sediment
• Persistence or new appearance of any extrarenal manifestations.

In some patients, resistance is incorrectly diagnosed with persistent manifestations being due to inadequate dosing of cyclophosphamide or to inactive disease rather than ongoing inflammation.

There are at least two disease manifestations that may be relatively unresponsive to cyclophosphamide (and to other systemic therapies), but are NOT considered to represent resistant disease: orbital pseudotumor (retrobulbar masses); and subglottic stenosis, which may reflect scar rather than ongoing inflammation, and may respond best to local therapies such as triamcinolone injections and dilatation procedures (avoiding laser therapies). (See 'Management of upper airway involvement' below.)

**Cannot take cyclophosphamide** — Occasional patients have a contraindication to cyclophosphamide therapy or refuse such therapy because of concerns about fertility, hair loss, the risk of malignancy, or other issues. Rituximab is the drug of choice for such patients since, in two randomized trials, rituximab was as effective as cyclophosphamide in inducing remission among patients with newly diagnosed or relapsing GPA or MPA [10,11]. A potential limitation is that the duration of follow-up was limited to six to twelve months compared with the extensive long-term experience with cyclophosphamide. (See 'Rituximab' below.)

**INITIAL THERAPY** — Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener’s), abbreviated as GPA, and MPA typically consists of cyclophosphamide and glucocorticoids. Rituximab may be used in patients who cannot, or refuse to take cyclophosphamide. Methotrexate may have a role in patients with mild disease, and selected patients with severe disease benefit from the addition of plasma exchange. (See 'Role of plasma exchange' below.)

The use of aggressive initial immunosuppression is justified because the mortality rate in untreated generalized GPA is as high as 90 percent at two years, usually due to respiratory or renal failure [5]. Mortality has markedly diminished with the introduction of initial therapy with cyclophosphamide and glucocorticoids.

**Choice of cyclophosphamide regimen** — Two cyclophosphamide dosing regimens, daily oral and monthly intravenous pulses, have been used for initial immunosuppressive therapy of GPA and MPA. Data from comparative trials have shown that the two regimens induce remission of active disease at a similar rate. Daily oral
therapy has the advantage of a lower rate of relapse and the disadvantages of more leukopenia and possibly infection [12-16].

Both regimens are used clinically. This was illustrated in a community-based cohort study of 350 patients who received a new diagnosis of ANCA-associated vasculitis between 1985 and 2003 and were followed by physicians in the Glomerular Disease Collaborative Network [4]. Among the patients treated with cyclophosphamide induction, 161 received monthly intravenous therapy and 112 received daily oral therapy. Patient preference may contribute to the choice of regimen once the advantages and disadvantages are described.

**Daily oral cyclophosphamide and glucocorticoids** — Many clinicians favor daily oral cyclophosphamide-glucocorticoid combination therapy in the initial treatment of patients with GPA or MPA. One of the largest nonrandomized, prospective single center studies reported the outcomes in 158 patients with GPA who were treated with varying regimens at the National Institutes of Health [5]. "Standard" low-dose cyclophosphamide plus prednisone, low-dose cyclophosphamide alone, non-cyclophosphamide cytotoxic agents plus steroids, or glucocorticoids alone were administered to 133, 8, 6, and 10 patients, respectively. Cyclophosphamide was administered for a mean of two years.

The following outcomes were reported at a mean follow-up of eight years (range 6 months to 24 years):

- Survival was 80 percent, with most deaths being due to GPA and/or side effects of therapy.
- Significant clinical improvement was observed in more than 90 percent of patients, with 75 percent achieving complete remission.
- Among the 98 patients followed for more than five years, almost one-half experienced remissions lasting more than five years.

Similar findings have been noted in other studies [6,17-22].

**Cyclophosphamide regimen** — Cyclophosphamide is given orally in a dose of 1.5 to 2 mg/kg per day. Therapy is continued until a stable remission is induced, which is usually achieved within three to six months. The white blood cell count (WBC) should be closely monitored and the cyclophosphamide dose adjusted to avoid severe leukopenia. The WBC should remain above 3000/microL and the absolute neutrophil count above 1500/microL. (See "General principles of the use of cyclophosphamide in rheumatic and renal disease", section on 'Monitoring'.)
**Glucocorticoid regimen** — When initiating glucocorticoid therapy, there is disagreement among experts and among the authors as to whether therapy should begin with pulse methylprednisolone (7 to 15 mg/kg to a maximum dose of 500 to 1000 mg/day for three days) in all patients or only in those with necrotizing or crescentic glomerulonephritis or more severe respiratory disease. Oral glucocorticoid therapy, either from day one or from day four if pulse methylprednisolone is given, typically consists of 1 mg/kg per day (maximum of 60 to 80 mg/day) of oral prednisone (or its equivalent).

A variety of prednisone tapering schemes have been employed. In general, the initial dose is continued for two to four weeks. If significant improvement is observed at this time, the dose of prednisone is tapered slowly, with the goal of reaching 20 mg/day by the end of two months and an overall glucocorticoid course of between six and nine months unless needed for control of persistent systemic symptoms [17,23]. Alternate day glucocorticoid regimens, once recommended in GPA, are NOT generally employed now.

**Rate and time to remission** — The combination of oral cyclophosphamide and glucocorticoids induces remission in 85 to 90 percent of patients, with approximately 75 percent experiencing complete remission [5,6,12,13,17-22]. Most remissions occur between two and six months [12,22]. (See 'Definition of complete remission' above.)

Reasonable estimates of the rate and time to remission with common treatment regimens were provided by CYCAZAREM (Cyclophosphamide versus Azathioprine for the maintenance of Remission), a trial of 155 patients with ANCA-associated vasculitis [22], and WGET (Wegener’s Granulomatosis Etanercept Trial), a trial of 180 patients with GPA [17].

- In CYCAZAREM, 93 percent of patients achieved remission: 77 percent within three months, and an additional 16 percent between three and six months [22].
- In WGET, 91 percent achieved disease remission and 73 percent had a sustained complete remission lasting at least six months [17].

Relapses occurred after the induction of remission in both trials, although the rates were different: approximately 15 percent at 18 months in CYCAZAREM and approximately 50 percent at 27 months in WGET. (See "Relapsing disease in granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis".)

**Persistent disease-related morbidity** — In the NIH study cited above, 86 percent of patients had clinically important morbidity from the disease at a mean follow-up of
eight years despite adequate therapy [5]. Common extrarenal complications included hearing loss (35 percent), cosmetic and functional nasal deformities (28 percent), and tracheal stenosis (13 percent). In addition, 42 percent of patients had chronic kidney disease, with a median serum creatinine concentration of 2.6 mg/dL (229 micromol/L) at an average follow-up of seven to eight years. As expected, segmental sclerosis of previously active glomerular lesions was the most common finding on renal biopsy. Eleven percent progressed to end-stage renal disease. (See "Patient and renal outcomes in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis".)

**Monthly intravenous cyclophosphamide**—Monthly intravenous pulses of cyclophosphamide, which has been primarily used in systemic lupus erythematosus, has been evaluated in GPA and MPA in an attempt to lower the overall cumulative dose of cyclophosphamide. Randomized trials comparing the two approaches have shown that the rate of induction of remission with monthly intravenous cyclophosphamide compared to daily oral therapy is equivalent [12-16]. In almost all of these studies, monthly intravenous therapy had the advantages of lower total cyclophosphamide exposure and a lower rate of neutropenia and infection, but a higher rate of relapse.

The best data come from a randomized trial of 149 patients with ANCA-associated vasculitis [12]. The patients were treated prednisolone and either pulse cyclophosphamide (15 mg/kg every two to three weeks) or daily oral cyclophosphamide (2 mg/kg per day). The primary outcome was the time to remission and secondary outcomes included the relapse rate, change in renal function, adverse events, and cumulative dose of cyclophosphamide.

The following findings were noted:

- There was no difference in the time to remission or the percentage of patients who achieved remission by nine months (88 percent in both groups). Most remissions occurred between two and six months.
- The mean estimated glomerular filtration rate improved by a similar amount in both groups from about 30 mL/min per 1.73 m2 at study entry to 45 mL/min per 1.73 m2 at study end.
- Among the patients who achieved remission by nine months, 19 (14.5 percent) relapsed (10 major and 9 minor). There were more relapses in the intravenous pulse cyclophosphamide group (13 versus 6), a difference that was not statistically significant but the study was not designed or powered to assess an effect on relapse.
Pulse cyclophosphamide compared to daily oral cyclophosphamide was associated with a significantly lower cumulative cyclophosphamide dose (8.2 versus 15.8 g) and a lower rate of leukopenia (26 versus 45 percent).

These results are consistent with a prior meta-analysis that included 143 patients from three small randomized trials [16]. Intravenous cyclophosphamide was at least as effective as oral cyclophosphamide for inducing remission and was associated with a significantly lower rate of leukopenia and infection and a trend toward a higher rate of relapse.

Alternative regimens — Because of the toxicity associated with the prolonged administration of oral cyclophosphamide, several alternative regimens have been evaluated for initial therapy. None has supplanted the oral cyclophosphamide-glucocorticoid regimen, although rituximab is the preferred therapy for patients who cannot take or refuse cyclophosphamide.

Rituximab — Two randomized trials have suggested that rituximab may be an effective alternative to cyclophosphamide for the initial treatment of patients who have newly diagnosed disease or have relapsed following treatment with cyclophosphamide or other immunosuppressive therapy [10,11].

- A multicenter noninferiority trial (the RAVE trial) compared induction therapy with rituximab (375 mg/m2 per week for four weeks) or with oral cyclophosphamide (2 mg/kg per day) in 197 patients with GPA (75 percent of enrolled patients) or MPA (24 percent); 49 percent of patients were newly diagnosed and the remainder had relapsing disease [11]. All patients received one to three pulses of methylprednisolone (1000 mg) followed by prednisone (1 mg/kg per day). Rituximab was noninferior to cyclophosphamide in inducing remission by six months (64 versus 53 percent). However, in the 100 patients with relapsing disease, rituximab was superior to cyclophosphamide in inducing remission (67 versus 42 percent). There was no difference in the number of adverse events.

- In the second trial (RITUXVAS), 44 patients with newly diagnosed ANCA-associated renal vasculitis were assigned in a 3:1 ratio to receive methylprednisolone (1000 mg) followed by oral methylprednisolone (1 mg/kg per day with reduction to 5 mg per day by the end of six months) plus either rituximab (375 mg/m2 per week for four weeks) with two intravenous cyclophosphamide pulses (15 mg/kg), or intravenous cyclophosphamide for three to six months followed by azathioprine [10]. Patients who received
rituximab who had progressive disease within the first six months were given a third dose of cyclophosphamide (15 mg/kg per day). At 12 months, there was no difference in the rate of sustained remission (defined as the absence of disease activity for at least six months) between the rituximab and cyclophosphamide only groups (76 versus 82 percent). There was also no difference between groups in the rate of adverse events.

These studies suggest that rituximab is as effective as cyclophosphamide for the initial treatment of GPA and MPA or for patients with relapsing disease. However, both studies are limited in the duration of follow-up [24]. Longer-term results from the RAVE trial are expected in 2011. Until such data are available, we prefer cyclophosphamide to rituximab as initial therapy for GPA and MPA. However, rituximab is the preferred therapy for patients who cannot take or refuse cyclophosphamide.

**Methotrexate** — Low-dose weekly oral methotrexate has been used as initial therapy in patients with GPA who have non-organ threatening and non-life threatening disease [23,25-29] and, as discussed elsewhere, as maintenance therapy in patients treated initially with cyclophosphamide or methotrexate. (See "Maintenance immunosuppressive therapy in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis", section on 'Methotrexate'.)

The best data on the efficacy of methotrexate come from the randomized NORAM trial that compared methotrexate and cyclophosphamide for both induction and remission of ANCA-associated vasculitis without significant renal involvement (mean serum creatinine 1.0 mg/dL (85 micromol/L) and microscopic hematuria in only 28 percent) [27]. The trial enrolled 89 patients with newly diagnosed GPA and 6 with MPA, all of whom had "early generalized disease." The exclusion criteria were signs of potentially severe systemic disease as manifested by a serum creatinine greater than 1.7 mg/dL (150 micromol/L), red blood cell casts, severe hemoptysis, cerebral infarction due to vasculitis, orbital pseudotumor, or rapidly progressive neuropathy.

The patients were assigned to methotrexate (20 to 25 mg per week orally) or cyclophosphamide (2 mg/kg per day orally); all received prednisolone. Therapy was gradually tapered and withdrawn by 12 months.

The following findings were noted:

- At six months, 90 and 94 percent of patients in the methotrexate and cyclophosphamide arms, respectively, achieved remission, although time to remission was two months longer in the methotrexate group.
• Among the patients who achieved remission, the relapse rate at 18 months was significantly higher with methotrexate (70 versus 47 percent with cyclophosphamide).

• In terms of adverse outcomes, there was a higher incidence of leukopenia among those treated with cyclophosphamide and a higher incidence of liver function test abnormalities among those treated with methotrexate. Two patients in each group died.

Thus, methotrexate was as effective as cyclophosphamide for the induction of remission in patients with mild disease, but was associated with a significantly higher relapse rate. The 2008 European League Against Rheumatism (EULAR) guidelines recommended the combination of oral or parenteral methotrexate and glucocorticoids as a less toxic alternative than cyclophosphamide for induction of remission in non-organ threatening and non-life threatening ANCA associated vasculitis \[29\]. Rheumatologists have the most experience with methotrexate for induction therapy, while most nephrologists have little or no experience with this approach.

Given the higher relapse rate, methotrexate should probably be used primarily for limited disease not involving the kidney. It may also be used in selected patients who do not tolerate cyclophosphamide or rituximab. Given the risk of toxicity in patients with renal dysfunction, methotrexate should not be used when the estimated glomerular filtration rate is below 50 mL/min. (See "Major side effects of low-dose methotrexate").

Glucocorticoids alone — Glucocorticoid monotherapy is NOT generally considered for remission induction, since the reported remission rate is much lower than in combination with cyclophosphamide (56 versus 85 percent), and the rate of relapse much higher \[6\]. This is particularly true for patients with severe disease manifestations, such as glomerulonephritis. Among 57 patients evaluated at the National Institutes of Health who were initially treated with prednisone alone, none of those with renal disease (45 patients) experienced sustained improvement, and 55 of the 57 (96 percent) eventually required cytotoxic therapy \[30\].

Role of plasma exchange — Several controlled trials of patients with GPA, MPA, or the related disorder segmental necrotizing glomerulonephritis with no immune deposits on pathologic examination (which is thought to represent renal-limited vasculitis) have demonstrated no overall benefit for the renal disease from plasma exchange, with the possible exception of patients who one or more of the following \[19,31-37\]:

• Severe renal disease, which has been variably defined
Concurrent anti-glomerular basement membrane (GBM) antibody disease

Severe pulmonary hemorrhage

Severe active renal disease — Two trials have evaluated the efficacy of plasma exchange in patients with GPA or MPA who have severe active renal disease. Potential efficacy of plasma exchange was evaluated in an initial randomized trial in which 48 patients with focal necrotizing glomerulonephritis were assigned to immunosuppressive therapy with or without plasma exchange; pulse methylprednisolone was not given \[31\]. There was no difference in outcome among the 17 patients with a serum creatinine concentration of less than 5.7 mg/dL (500 micromol/L) or the 12 with higher serum creatinine concentrations in whom dialysis was not required. In contrast, plasma exchange appeared to be of benefit in the patients who required dialysis.

The role of plasma exchange in patients with severe renal disease was also addressed in the randomized Methylprednisolone versus Plasma Exchange (MEPEX) trial \[37\]. This trial enrolled 137 patients with a new diagnosis of GPA or MPA, pauci-immune glomerulonephritis, and a serum creatinine concentration above 5.7 mg/dL (500 micromol/L). The mean serum creatinine at presentation was 8.3 mg/dL (735 micromol/L) and 69 percent required dialysis which, in the preceding trial, identified patients who benefited from plasma exchange.

The patients were assigned randomly to receive either seven sessions of plasma exchange over the first two weeks after diagnosis or methylprednisolone 1 g/day for three days. In addition to these therapies, patients received prednisolone (1 mg/kg per day, tapered over six months) and cyclophosphamide (2.5 mg/kg per day for three months), followed by azathioprine for remission maintenance.

The major results of the MEPEX trial are as follows:

- Plasma exchange was associated with a significantly higher likelihood of being alive and having independent renal function at three months (69 versus 49 percent in the methylprednisolone group).
- Plasma exchange was associated with a significant reduction in the risk of progression to end-stage renal disease at one year (19 versus 43 percent).
- The mortality rate was high in both groups (27 and 24 percent at one year). The majority of deaths occurred in the first three months of treatment. Of the 35 deaths in the trial, 19 were related to infection, 6 to pulmonary hemorrhage, and 4 to cardiovascular events.

The MEPEX trial had a number of important shortcomings:
• The trial was not blinded and was not optimally designed. A preferable trial
design would have provided pulse methylprednisolone to both treatment
groups at the outset of therapy and then randomly assigned patients to
either plasma exchange or sham plasma exchange.
• The plasma exchange regimens varied significantly from site to site.
• The mortality rate at one year appears excessive compared to other trials, even
allowing for the fact that patients in MEPEX had more severe renal disease at
baseline than in other trials. (See "Patient and renal outcomes in
granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis",
section on ‘Mortality’.)

Despite these limitations, the results of the MEPEX trial support the notion that the
addition of plasma exchange to cyclophosphamide and glucocorticoid therapy may
enhance the recovery of renal function among patients who present with severe renal
dysfunction (serum creatinine above 5.7 mg/dL (500 micromol/L)) during the acute
phase of disease.

In a meta-analysis of nine trials (of which the MEPEX was by far the largest) and
including 387 patients, the addition of plasma exchange to standard care decreased
the pooled risk of end-stage renal disease or death (RR 0.8, 95% CI, 0.65-0.99) and of
end-stage renal disease alone (RR 0.64, 95% CI 0.47-0.88) [38]. The serum creatinine
of participants ranged from 3.2 to 13.5 mg/dL (283 to 1193 mmol/L).

However, although these results were statistically significant, the calculated optimal
information size (sample size) required to be confident of a risk reduction of roughly 25
percent is 1478 patients. Thus, reliable conclusions cannot be drawn from this
underpowered analysis, although it supports the role of plasma exchange as a
promising adjunctive therapy.

For patients with advanced renal dysfunction without concurrent anti-GBM antibody
disease, we suggest seven sessions of plasma exchange over two weeks (60 mL/kg at
each session). Albumin is the preferred replacement fluid in patients without bleeding
or a recent renal biopsy. For patients with bleeding or a recent biopsy, we suggest that
one to two liters of fresh frozen plasma should be substituted for albumin at the end of
the procedure to reverse pheresis-induced depletion of coagulation factors.

Among patients who develop severe infection in the setting of plasma exchange, a
single infusion of intravenous immune globulin (100 to 400 mg/kg) can be given to
partially replenish antibody levels.
Concurrent anti-GBM antibodies — Based entirely upon presumed benefits in patients with anti-GBM antibody disease alone, plasma exchange is usually used in combination with immunosuppressive therapy in patients with ANCA-associated vasculitis who also have anti-GBM antibodies [39,40]. (See "Treatment of anti-GBM antibody (Goodpasture's) disease", section on 'Plasmapheresis' and "Clinical spectrum of antineutrophil cytoplasmic antibodies", section on 'Anti-GBM antibody disease'.)

Pulmonary hemorrhage — Although randomized controlled trials have not been performed, patients with pulmonary hemorrhage should be treated with plasma exchange [40,41]. This strategy is based upon the theoretical benefit of removing ANCA by plasma exchange and the observed efficacy of plasma exchange in patients with pulmonary hemorrhage due to anti-GBM antibody disease.

Benefits from plasma exchange in this setting were suggested in a retrospective review of 20 patients who presented between 1995 and 2001 with diffuse alveolar hemorrhage (DAH) and ANCA-associated small vessel vasculitis [41]. Fourteen of the patients presented with impaired renal function, with the average serum creatinine concentration being 4.7 mg/dL (415 micromol/L).

All patients underwent daily full plasma volume plasma exchange until DAH improved, which was then changed to alternative day apheresis therapy until the DAH resolved. The replacement fluid was 5 percent albumin and two units of fresh frozen plasma at the end of apheresis. All patients also received intravenous methylprednisolone (7 mg/kg per day) for three days, and all but two received intravenous cyclophosphamide (0.5 g/m² of body surface area). Additional therapy included ventilatory support and hemodialysis for nine and seven patients, respectively.

DAH resolved in all 20 patients, with the mean number of apheresis treatments being 6.15 (range of 4 to 9). There were no complications due to apheresis. One patient died because of a pulmonary embolism. Among the seven patients who did not require dialysis, the serum creatinine fell significantly by the time of discharge (4.5 to 2.4 mg/dL (398 to 212 micromol/L)).

The results of this study must be interpreted in light of its retrospective design and lack of a control group. In addition, because all patients in the review received conventional therapies (generally cyclophosphamide and glucocorticoids) in addition to plasma exchange, independent effects of plasma exchange are impossible to delineate.

For patients with pulmonary hemorrhage, we suggest seven sessions of plasma exchange over two weeks (60 mL/kg at each session). Fresh frozen plasma is the
preferred replacement fluid, with one to two liters being given at the end of the procedure to reverse pheresis-induced depletion of coagulation factors.

Among patients who develop severe infection in the setting of plasma exchange, a single infusion of intravenous immune globulin (100 to 400 mg/kg) can be given to partially replenish antibody levels.

**Treatment-associated toxicity** — The cyclophosphamide plus glucocorticoid regimen is associated with important toxicity and does not reverse tissue necrosis. In addition to the toxicities discussed below, cytotoxic agents are toxic to the fetus. (See "Pregnancy in women with underlying renal disease" and "Use of antiinflammatory and immunosuppressive drugs in rheumatic diseases during pregnancy and lactation" and "General principles of the use of cyclophosphamide in rheumatic and renal disease").

In the 1992 NIH study cited above, cyclophosphamide therapy resulted in a 57 percent incidence of either amenorrhea lasting more than one year or inability to become pregnant; gonadal function in men was not evaluated. Other reported toxicities included cystitis (50 percent), bladder cancer (5.6 percent), myelodysplasia (2 percent), and lymphoma (0.7 percent) [5]. A detailed discussion of the measures available to minimize toxicity associated with this regimen can be found in a separate topic review. (See "General toxicity of cyclophosphamide and chlorambucil in inflammatory diseases").

Reported toxicities of extended glucocorticoid therapy in the NIH study were cataracts (21 percent), diabetes mellitus (8 percent), osteopenia, fractures (11 percent), and aseptic necrosis of bone (3 percent). In addition, severe gastritis may develop and result in gastrointestinal bleeding in patients at increased risk. (See "Major side effects of systemic glucocorticoids").

**PCP prophylaxis** — Pneumocystis carinii (jiroveci) pneumonia (PCP) and other opportunistic infections are potentially fatal complications of immunosuppressive therapy in GPA or MPA. In one series, for example, PCP developed in 11 of 180 (6 percent) patients with GPA, all of whom were treated with daily glucocorticoids and a second immunosuppressive drug [42]. (See "Epidemiology, clinical manifestations, and diagnosis of Pneumocystis pneumonia in non-HIV-infected patients").

Prophylaxis may be both cost-saving and life-prolonging in this setting. We administer prophylaxis during induction therapy; the suggested regimen varies with the regimen used for initial immunosuppression:

- For patients treated with cyclophosphamide and glucocorticoids, we use trimethoprim-sulfamethoxazole (one single strength (80 mg/400 mg) tablet
daily or one double strength tablet (160 mg/800 mg) three times per week. Atovaquone is preferred in patients who are allergic to sulfonamides or do not tolerate trimethoprim-sulfamethoxazole.

- For patients treated with methotrexate and glucocorticoids, the addition of trimethoprim-sulfamethoxazole is associated with an increased risk of pancytopenia. Atovaquone may be used for prophylaxis in such patients.
- After cyclophosphamide is discontinued and maintenance immunosuppressive therapy is initiated, we continue PCP prophylaxis until the CD4-positive T cell count exceeds 300/microL. This empiric threshold is derived from that used for HIV-infected patients (200/microL) with an extra margin for safety since patients with ANCA-associated vasculitis have more severe disease and higher mortality rates with PCP than HIV-infected patients [43]. (See "Treatment and prevention of Pneumocystis pneumonia in non-HIV-infected patients", section on 'Outcomes'.)

Among patients who have been treated with trimethoprim-sulfamethoxazole for prophylaxis during induction, we continue trimethoprim-sulfamethoxazole when azathioprine is used for maintenance therapy and switch to atovaquone when methotrexate is used for maintenance therapy.

Some patients have low CD4-positive T cell counts for prolonged periods after the cessation of cyclophosphamide and require prolonged PCP prophylaxis, with glucocorticoids being tapered to the lowest possible dose. If patients treated with trimethoprim-sulfamethoxazole develop neutropenia, which is a possible side effect, we switch to atovaquone.

**MANAGEMENT OF UPPER AIRWAY INVOLVEMENT** — The consequences of upper airway involvement are often not improved by initial immunosuppressive therapy and are NOT considered resistant disease.

Nasal ulcers and crusting are common manifestations of upper airway disease in ANCA-associated vasculitis, particularly in GPA. It is often difficult to determine if these lesions are attributable to vasculitis, infection, or both. Although oral antibiotics are frequently required to treat more severe infections in the upper respiratory tract, some experts prefer a trial of topical therapy for nasal ulcers and crusting. This approach may involve either direct application of antibiotic ointment just inside of the nares and/or nasal irrigation with a saline solution to which topical antibiotics have been added. Nasal saline sprays are available over the counter or may be made up as one quart of water with one teaspoon of brine or pickling salt and one teaspoon of baking soda.
Lesions of the tracheobronchial tree can cause a variety of problems. The most serious complications include tracheal or bronchial stenosis that can lead to respiratory failure or postobstructive pneumonia. Treatment options for these problems include airway dilation with or without stenting. For subglottic stenosis, intraluminal injection of glucocorticoids in combination with endoscopic dilation may avoid the need for more invasive surgical procedures [44,45].

Tracheostomy should be avoided whenever possible. When tracheostomy is necessary, most patients are able to have the tracheostomy tube removed. This was illustrated in a retrospective report of 27 patients with ANCA-associated vasculitis: 11 required tracheostomy and 3 could not be decannulated [46]. (See "Diagnosis and management of central airway obstruction").

Stenosing lesions of the nasal passages and destructive lesions of the nasal cartilage and bones may cause discomfort and/or be disfiguring. Reconstructive surgery may provide a functional airway and can restore a more nearly normal appearing nose [47]. Grafts prepared from a patient's costal or auricular cartilage, iliac or other bone, or dura have been used with varying success.

**MANAGEMENT IN PREGNANCY** — There is only limited information on pregnancy complicated by GPA or MPA, although both newly diagnosed and relapsing GPA can occur during pregnancy or in the postpartum period [48,49]. As with active disease in nonpregnant patients, prednisone alone is relatively ineffective, particularly for moderate to severe disease, while remission can be induced by combined therapy with cyclophosphamide.

The major challenges in treating active disease during pregnancy are that potentially serious adverse effects can occur with both cyclophosphamide and with alternative therapies such as mycophenolate. In addition, there are insufficient data to assess the safety of rituximab, (which has been used for non-pregnant patients who cannot tolerate cyclophosphamide) in pregnancy. (See "Treatment of cyclophosphamide-resistant granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis", section on 'Mycophenolate mofetil' and "Use of antiinflammatory and immunosuppressive drugs in rheumatic diseases during pregnancy and lactation", section on 'Rituximab'.)

Fetal cyclophosphamide exposure during the first trimester has been associated with a high risk of skeletal and palatal defects, as well as malformations of the limbs and eyes. The fetal risk is much smaller with cyclophosphamide therapy during the second and third trimesters, but pancytopenia and impaired fetal growth can occur. (See "Use of antiinflammatory and immunosuppressive drugs in rheumatic diseases during
pregnancy and lactation", section on 'Cyclophosphamide' and "General toxicity of cyclophosphamide and chlorambucil in inflammatory diseases", section on 'Teratogenicity'."

Mycophenolate mofetil (MMF) increases the risk of miscarriage and congenital malformation such as cleft lip and palate. As a result, MMF has a boxed warning for these complications and some consider MMF to be contraindicated in pregnancy. (See "Use of antiinflammatory and immunosuppressive drugs in rheumatic diseases during pregnancy and lactation", section on 'Mycophenolate mofetil'.)

As a result, there are three major therapeutic approaches in women with significant active disease during pregnancy: the use of safer immunosuppressive drugs; therapeutic abortion prior to initiation of cyclophosphamide-based therapy, and the use of rituximab, which has insufficient safety data for use in pregnancy.

The safer immunosuppressive drugs that have been effective in GPA and MPA include glucocorticoids, azathioprine, and cyclosporine (or tacrolimus), particularly in mild to moderate disease. These drugs can also be tried for severe disease. Alternatives that could be considered include cyclophosphamide or rituximab in the second or third trimester once organogenesis is complete.

MAINTENANCE THERAPY — Once remission is induced with cyclophosphamide therapy (which usually occurs within three to six months), patients are switched to maintenance therapy with less toxic immunosuppressive drugs, usually azathioprine or methotrexate. This issue is discussed in detail separately. (See "Maintenance immunosuppressive therapy in granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient
education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Beyond the Basics topic (See "Patient information: Vasculitis").

SUMMARY AND RECOMMENDATIONS — Granulomatosis with polyangiitis (Wegener’s), which can be abbreviated as GPA, and microscopic polyangiitis (MPA) are related systemic vasculitides that are associated with antineutrophil cytoplasmic antibodies (ANCA). GPA and MPA have similar features on renal histology and similar outcomes. Therapy of GPA and MPA has two components: the induction of remission; and maintenance immunosuppressive therapy to prevent relapse. Induction of complete remission, defined as the absence of active disease, is the goal of initial immunosuppressive therapy. (See 'Definition of complete remission' above.)

Cyclophosphamide or rituximab — Initial therapy with cyclophosphamide and glucocorticoids, which is preferred in the great majority of patients, induces remission in 85 to 90 percent of patients, usually with two to six months. Two randomized trials have suggested that rituximab may be an effective alternative to cyclophosphamide for the initial treatment of patients who have newly diagnosed disease but both studies are limited in the duration of follow-up. (See 'Rate and time to remission' above and 'Rituximab' above.)

- For all patients with newly diagnosed organ-threatening or life-threatening disease, we recommend initial immunosuppressive therapy with glucocorticoids plus either cyclophosphamide (either oral or intravenous) or rituximab rather than other therapies or glucocorticoids alone (Grade 1A).
- Until long-term data on the effectiveness and safety of rituximab are available, for patients with newly diagnosed organ-threatening or life-threatening disease who do not have a contraindication to, and do not refuse to take cyclophosphamide, we suggest initial immunosuppressive therapy with the combination of cyclophosphamide (either oral or intravenous) and glucocorticoids rather than rituximab and glucocorticoids (Grade 2B).

There are two cyclophosphamide regimens: daily oral and monthly intravenous. Data from comparative trials have shown that the two regimens induce remission of active disease at a similar rate. Daily oral therapy has the advantage of a lower rate of relapse and the disadvantages or more leukopenia and possibly infection. Patient preference may contribute to the choice of regimen once the advantages and disadvantages are described.
Regardless of the regimen chosen, close follow-up and monitoring for the development of neutropenia are indicated. (See 'Choice of cyclophosphamide regimen' above.)

- If oral cyclophosphamide is given, the preferred dose is 1.5 to 2 mg/kg per day. Therapy is continued until a stable remission is induced, which is usually achieved within three to six months. (See 'Daily oral cyclophosphamide and glucocorticoids' above.)
- If pulse intravenous cyclophosphamide is given, the preferred regimen is 0.5 to 1.0 g/m² body surface area monthly for three to six months, until a stable remission is induced. (See 'Monthly intravenous cyclophosphamide' above.)
- Among patients treated with cyclophosphamide, the white blood cell count (WBC) should be closely monitored and the cyclophosphamide dose adjusted to avoid severe leukopenia. The WBC should remain above 3000/microL and absolute neutrophil count above 1500/microL. (See "General principles of the use of cyclophosphamide in rheumatic and renal disease", section on 'Monitoring'.)

- For all patients with organ-threatening or life-threatening disease who cannot or refuse to take cyclophosphamide, we recommend initial immunosuppressive therapy with rituximab and glucocorticoids rather than other therapies (Grade 1B). (See 'Cannot take cyclophosphamide' above.) The preferred regimen is that used in the RAVE trial:
  - Rituximab 375 mg/m² per week for four weeks given with methylprednisolone (1000 mg) followed by oral prednisone 1 mg/kg per day. (See 'Rituximab' above.)

Glucocorticoid therapy

- We recommend glucocorticoid therapy in all patients with active GPA or MPA (Grade 1B). The decision to initiate glucocorticoids with intravenous pulse methylprednisolone depends upon the severity of the disease. (See 'Glucocorticoid regimen' above.)

- For patients with necrotizing or crescentic glomerulonephritis or severe respiratory disease, we suggest pulse methylprednisolone followed by oral prednisone or its equivalent (Grade 2C). The preferred regimen is 7 to 15 mg/kg to a maximum dose of 500 to 1000 mg/day for three days followed by
oral prednisone on day four at a dose of 1 mg/kg per day (maximum of 60 to 80 mg/day).

- For patients who do not have necrotizing glomerulonephritis or severe respiratory disease, we suggest oral prednisone or its equivalent rather than initial pulse intravenous therapy (Grade 2C). A suggested dose is 1 mg/kg per day (maximum of 60 to 80 mg/day) beginning on day one. However, some clinicians prefer pulse methylprednisolone for three days in such patients.
- Oral prednisolone or its equivalent is continued at the initial dose for two to four weeks. If significant improvement is observed at this time, the dose of prednisone is tapered slowly, with the goal of reaching 20 mg/day by the end of two months and an overall glucocorticoid course of between six and nine months. We suggest NOT using alternate day glucocorticoid regimens (Grade 2C).

**Methotrexate therapy**

- Methotrexate given with glucocorticoid therapy is an alternative to cyclophosphamide for highly selected patients with non-organ-threatening and non-life-threatening disease such as those with pulmonary nodules or infiltrates without respiratory compromise, and/or ocular disease. Methotrexate should NOT be given to patients with an estimated glomerular filtration rate less than 50 mL/min. (See 'Methotrexate' above.)

- A suggested regimen is oral methotrexate at an initial dose of 0.3 mg/kg (but not exceeding 15 mg) once per week, with increases of 2.5 mg each week to a maximum dose of 25 mg once per week. Since methotrexate is a structural analogue of folic acid that can competitively inhibit the binding of dihydrofolic acid (FH2) to the enzyme dihydrofolate reductase (DHFR), folic acid (1 to 2 mg/day) or folinic acid (2.5 to 5 mg per week, 24 hours after methotrexate) should be given concurrently to reduce potential toxicity.

**Plasma exchange**

- The addition of plasma exchange to cyclophosphamide and glucocorticoid therapy may enhance the recovery of renal function among patients who present with severe renal dysfunction during the acute phase of disease. We suggest plasma exchange for patients with GPA or MPA who have anti-GBM antibodies as well as ANCA; for patients with severe pulmonary hemorrhage on presentation or those with worsening pulmonary hemorrhage despite the combination of high-dose glucocorticoids and cyclophosphamide; and for
patients who have advanced renal dysfunction at presentation, as defined by a serum creatinine level above 5.7 mg/dL (500 micromol/L) and/or dialysis dependence (Grade 2C). (See 'Role of plasma exchange' above.)

- For patients with advanced renal dysfunction, we suggest seven sessions of plasma exchange over two weeks (60 mL/kg at each session). A more prolonged regimen is used in patients with anti-GBM disease. (See "Treatment of anti-GBM antibody (Goodpasture's) disease").
- Among patients who have had a recent renal biopsy or have pulmonary hemorrhage, we suggest that one to two liters of fresh frozen plasma should be substituted for albumin at the end of the procedure to reverse pheresis-induced depletion of coagulation factors. For patient who have no evidence of hemorrhage or who are not at risk for bleeding, we suggest that albumin be used as the replacement fluid.
- Among patients who develop severe infection in the setting of plasma exchange, a single infusion of intravenous immune globulin (100 to 400 mg/kg) can be given to partially replenish antibody levels.

**Role of PCP prophylaxis** — Pneumocystis carinii (jiroveci) pneumonia (PCP) and other opportunistic infections are potentially fatal complications of immunosuppressive therapy in GPA. The estimated incidence of PCP is approximately 6 percent. The suggested approach to prophylaxis against PCP infection during initial immunosuppressive therapy is discussed above. (See 'PCP prophylaxis' above.)

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REFERENCES


NEW TERMINOLOGY — In January 2011, the Boards of Directors of the American College of Rheumatology, the American Society of Nephrology, and the European League Against Rheumatism recommended that the name Wegener’s granulomatosis be changed to granulomatosis with polyangiitis (Wegener’s), abbreviated as GPA [1-3]. This change reflects a plan to gradually shift from honorific eponyms to a disease-descriptive or etiology-based nomenclature. The parenthetic reference to Wegener’s will be phased out after several years as the new name becomes more widely known.

INTRODUCTION — Granulomatosis with polyangiitis (Wegener’s), abbreviated as GPA, and microscopic polyangiitis (MPA) are related systemic vasculitides. Both are associated with antineutrophil cytoplasmic antibodies (ANCA), have similar features on renal histology (eg, a focal necrotizing, pauci-immune glomerulonephritis), and have similar outcomes. There are, however, several differences between these disorders. (See "Clinical manifestations and diagnosis of granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis", section on 'Clinical presentation'.)

Therapy of GPA and MPA has two components: induction of remission with initial immunosuppressive therapy; and maintenance immunosuppressive therapy for a variable period to prevent relapse.

Maintenance immunosuppressive therapy of GPA and MPA will be reviewed here. Initial immunosuppressive therapy, the treatment of cyclophosphamide resistant or relapsing disease, clinical manifestations and diagnosis, and patient and renal outcomes are discussed elsewhere. (See "Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis" and "Treatment of cyclophosphamide-resistant granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis" and "Relapsing disease in granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis" and "Clinical manifestations and diagnosis of granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis" and "Patient
and renal outcomes in granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis”.

**GENERAL PRINCIPLES** — Long-term cyclophosphamide has significant treatment-related toxicity [4,5]. Thus, after attainment of remission, almost all patients with granulomatosis with polyangiitis (Wegener’s) or microscopic polyangiitis (GPA or MPA) are switched to a less toxic non-cyclophosphamide maintenance regimen, most often azathioprine or methotrexate, to reduce the risk of relapse. A notable exception is drug-induced ANCA-associated vasculitis in which relapse should not occur if the responsible drug is discontinued. (See “Clinical spectrum of antineutrophil cytoplasmic antibodies”, section on ‘Drug-induced ANCA-associated vasculitis’.)

**Assessment of disease activity** — Disease activity can be assessed by use of the Birmingham Vasculitis Activity Score (BVAS) that has been applied to patients with GPA [6]. Complete remission is defined as a BVAS/GPA score of 0, which generally means there is no clinical, radiologic, or pathologic evidence of active disease [6,7].

Complete remission does NOT mean that all parameters have to return to baseline, since persistent abnormalities may reflect irreversible injury induced during the period of active inflammation. As an example, a patient in whom the systemic symptoms and signs resolve and the urine sediment becomes inactive is considered to be in remission, even if there is persistent proteinuria or persistent or even slowly worsening renal insufficiency. (See “Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis”, section on ‘Definition of complete remission’.)

Monitoring serum ANCA titers alone is NOT helpful in assessing disease activity. In the largest prospective study, the correlation between changes in disease activity and ANCA levels was evaluated in 156 patients with GPA enrolled during periods of active disease [8]. Changes in ANCA levels explained less than 10 percent of the variation in disease activity. In addition, only about 40 percent of patients relapsed within one year of an increase in PR3-ANCA. (See “Relapsing disease in granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis”, section on ‘ANCA titers’.)

Some clinicians monitor changes in the ANCA titer along with changes in the ESR and CRP levels as indicators of disease activity.

The combination of oral cyclophosphamide and glucocorticoids induces remission in 85 to 90 percent of patients, with approximately 75 percent experiencing complete remission, usually within three to six months after the initiation of cyclophosphamide and glucocorticoid therapy. Patients in whom remission is not attained within six
months may be maintained on cyclophosphamide for a few more months unless toxicity is limiting. (See "Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis", section on 'Rate and time to remission'.)

**MAINTENANCE THERAPY** — The preferred drugs for maintenance therapy in patients who have attained a complete or remission with a cyclophosphamide-based regimen are methotrexate and azathioprine, which seem to have equal efficacy. Glucocorticoids do not appear to provide benefit during maintenance therapy, and tapering should begin once there is a significant response to initial immunosuppressive therapy. (See 'Glucocorticoid therapy' below.)

Some patients who present with or develop dialysis-dependent renal failure show no evidence of return of renal function after two to three months of immunosuppressive drug therapy. In such patients, excess immunosuppression should be AVOIDED to minimize morbidity and mortality unless indicated for extrarenal manifestations. (See "Patient and renal outcomes in granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis".)

**Methotrexate** — Weekly oral methotrexate can be used for maintenance therapy after induction of remission with a cyclophosphamide-based regimen [9-13]. The potential efficacy of methotrexate was illustrated in a series of 42 patients in whom remission was induced with cyclophosphamide and glucocorticoids (at a median period of three months) [11]. Patients with a persistent serum creatinine above 2.5 mg/dL (221 micromol/L) at the time of remission were excluded from the study.

Methotrexate was started within one to two days of the last cyclophosphamide dose at an oral dose of 0.3 mg/kg per week (maximum dose 15 mg). If tolerated, the dose was increased in 2.5 mg increments each week to a dose of 20 to 25 mg per week. Patients were also treated with leucovorin (5 to 10 mg) once per week given 24 hours after methotrexate. If remission was sustained for two years or longer, methotrexate was tapered by 2.5 mg each month until discontinuation.

The following findings were noted at a median follow-up of 32 months [11]:

- One patient died from a cause unrelated to vasculitis, two were withdrawn because of methotrexate pneumonitis, and one was lost to follow-up.
- Relapse occurred in 22 (58 percent) of the remaining 38 patients. Among 16 patients with a renal relapse, only four had elevations in serum creatinine, all of whom returned to baseline kidney function following retreatment.
• Of the 16 patients who did not relapse, 15 were in remission a median period of 16 months after all immunosuppressive therapy had been discontinued. The remaining patient was being tapered off methotrexate after two years of remission.

The effectiveness of methotrexate in maintaining remission is lower in patients who are not treated initially with cyclophosphamide. This was illustrated in the randomized NORAM trial, which used methotrexate and cyclophosphamide for both induction and maintenance of remission in patients with early clinical disease [14]. Patients with a serum creatinine ≥1.7 mg/dL (150 micromol/L) were excluded. Treatment with oral methotrexate for 12 months was associated with a significantly higher relapse rate at 18 months than cyclophosphamide for 12 months (70 versus 47 percent).

In summary, methotrexate appears to be reasonably effective in maintaining a remission in patients with no or mild renal disease who are initially treated with cyclophosphamide. However, prolonged treatment is required. In addition, use of methotrexate for both induction and maintenance immunosuppression is associated with a high relapse rate.

Given the risk of methotrexate toxicity in patients with impaired renal function, azathioprine is preferred to methotrexate in patients with an estimated GFR less than 50 mL/min. The major side effects of low-dose methotrexate therapy are discussed separately. (See "Major side effects of low-dose methotrexate".)

Azathioprine — A number of studies have evaluated the efficacy of oral azathioprine for maintenance of remission in patients with granulomatosis with polyangiitis (Wegener's), abbreviated as GPA, or MPA [7,15-17]. This was best shown in the CYCAZAREM trial of 155 patients with ANCA-positive vasculitis who received induction therapy with oral cyclophosphamide (2 mg/kg per day) plus prednisolone (initial 1 mg/kg per day and tapered to 0.25 mg/kg per day by 12 weeks) for a minimum period of three months [15]. The 144 patients in whom remission was achieved (77 and 16 percent in three months and between three and six months, respectively) were randomly assigned to either continued cyclophosphamide (1.5 mg/kg per day) or azathioprine (2 mg/kg per day); prednisolone was also given at 10 mg/day in each regimen. At one year, both groups were treated with azathioprine (1.5 mg/kg per day) plus prednisolone (7.5 mg/day).

At 18 months, the rates of relapse were not significantly different with azathioprine and cyclophosphamide (15.5 versus 13.7 percent) and, during the
maintenance phase, both groups had a similar number of severe adverse events (eight and seven patients, respectively).

In contrast to these findings, the rate of relapse with either azathioprine or, in patients with a serum creatinine concentration less than 2.0 mg/dL (177 micromol/L), methotrexate was much higher (57 percent) in the Wegener's Granulomatosis Etanercept Trial (WGET) [7]. The proportion of relapses that were severe was also higher than in CYCAZAREM (22 versus 7 percent). The addition of etanercept to azathioprine or methotrexate had no effect on the rate of relapse.

A number of factors may have contributed to the higher rate of relapse in WGET [7]:

- A relapse in WGET required only one minor manifestation compared to three minor manifestations in CYCAZAREM.
- MPA, which is less likely to relapse than GPA, was present in 39 percent of patients in CYCAZAREM compared to none in WGET.
- Not all patients received induction therapy with cyclophosphamide, as those with limited disease were treated with methotrexate.
- The duration of follow-up was longer in WGET (27 versus 18 months in CYCAZAREM).
- Patients continued to receive 7.5 mg/day of prednisolone in CYCAZAREM. In contrast, glucocorticoid therapy was terminated after six months in WGET if the patients were in clinical remission.

**Azathioprine versus methotrexate** — Azathioprine and methotrexate provide comparable efficacy and are similarly safe when administered for maintenance therapy. In the only well-designed trial (WEGENT) that directly compared these agents, 126 patients with GPA or MPA who were in remission after treatment with cyclophosphamide and oral glucocorticoids were randomly assigned to azathioprine (2 mg/kg per day) or methotrexate (0.3 mg/kg per week, progressively increased by 2.5 mg every week to a maximum of 25 mg per week) for 12 months followed by gradual withdrawal over three months [18]. The mean serum creatinine was approximately 2.0 mg/dL (176 micromol/L) at baseline and 1.5 mg/dL (129 micromol/L) at randomization.

At a mean follow-up of 29 months, both drugs were associated with a similar number of adverse effects that required drug discontinuation (11 and 19 percent for azathioprine and methotrexate, respectively) and a similar relapse rate (36 and 33 percent). The majority of relapses (73 percent) occurred after the cessation of maintenance therapy.
Azathioprine versus mycophenolate mofetil — Azathioprine appears to be more effective than mycophenolate mofetil (MMF) in maintaining remission. This was shown in an open-label, randomized multicenter trial (IMPROVE) that included 156 patients with newly diagnosed ANCA-associated vasculitis [19]. After induction of remission with cyclophosphamide and glucocorticoids, patients received either azathioprine (starting at 2 mg/kg per day, then reduced to 1.5 and 1.0 mg/kg per day after 12 and 18 months, respectively) or MMF (starting at 2000 mg per day and reduced to 1500 and 1000 mg per day after 12 and 18 months respectively). Both agents were withdrawn after 42 months of treatment. At a median follow-up of 39 months, relapses were significantly less frequent among those who received azathioprine (38 versus 55 percent, adjusted hazard ratio 0.56, 95% CI 0.34-0.91). The rate of adverse events was not significantly different for those who received azathioprine (16 versus 8 percent, respectively).

Choice of maintenance agent — As indicated by the preceding observations, methotrexate and azathioprine appear to have equivalent efficacy for maintaining remission in patients with GPA or MPA and appear to be associated with a similar rate of adverse effects [18]. Mycophenolate mofetil does not appear to be as effective as azathioprine in maintaining remission and no trials have directly compared MMF and methotrexate [19].

Most nephrologists prefer azathioprine, in part because they have limited or no experience with methotrexate. In contrast, rheumatologists have extensive experience with methotrexate in rheumatoid arthritis and other rheumatic diseases and are therefore comfortable with both drugs.

Azathioprine is preferred in women who want to become pregnant, since methotrexate is contraindicated in pregnancy. The choice between these drugs may also be affected by renal function, since methotrexate requires dose adjustment and is more difficult to use in patients with a substantially reduced glomerular filtration rate (GFR). (See "Use of methotrexate in the treatment of rheumatoid arthritis", section on 'Dosing of MTX'.)

In different studies, patients were excluded from methotrexate therapy if the serum creatinine was above 1.7 mg/dL (150 micromol/L) [14], 2.0 mg/dL (177 micromol/L) [7,12], or 2.5 mg/dL (221 micromol/L) [11], and, in the trial directly comparing methotrexate to azathioprine for maintenance therapy, there was no mentioned exclusion criteria for serum creatinine, but almost all patients had a serum creatinine less than 2.5 mg/dL (221 micromol/L) at randomization [18].
It is difficult to use the serum creatinine to determine which patients should be treated with azathioprine rather than methotrexate, since the relationship between the serum creatinine and GFR varies importantly with muscle mass. This and other factors are partially taken into account with estimation equations, such as MDRD (calculator 1) and Cockcroft-Gault (calculator 2). These equations can only be used in patients with a stable serum creatinine. (See "Assessment of kidney function: Serum creatinine; BUN; and GFR", section on 'Estimation equations'.)

We suggest using azathioprine rather than methotrexate for maintenance therapy in patients with an estimated GFR below 50 mL/min. In patients who cannot tolerate azathioprine, we suggest switching to methotrexate if the estimated GFR is greater than 30 to 40 mL/min. Although data are limited, mycophenolate mofetil is preferred if neither azathioprine nor methotrexate can be used. (See "Alternative agents in the treatment of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis", section on 'Mycophenolate mofetil'.)

**Initiation of maintenance therapy** — Cyclophosphamide induction therapy is usually continued for one to two months after the first documentation of remission, as defined above. (See 'Assessment of disease activity' above.)

Maintenance therapy should not be started until cyclophosphamide has been discontinued, since excess immunosuppression can lead to neutropenia and infection. The risk of infection is increased when the absolute neutrophil count is less than 1000 cells/microL (table 1). The absolute neutrophil count is equal to the product of the total white blood cell count and the fraction of polymorphonuclear cells and band forms noted on the differential analysis (calculator 3).

The time period between cessation of cyclophosphamide and initiation of maintenance therapy varies with the cyclophosphamide induction regimen that was used:

- For patients treated with daily oral cyclophosphamide for induction of remission, maintenance therapy can be started as soon as the following criteria are met after the cessation of cyclophosphamide: the white blood cell count is >4000 cells/microL; and the absolute neutrophil count is >1500 cells/microL. In some patients, maintenance therapy can be started the day after oral cyclophosphamide is stopped.
- For patients treated with monthly intravenous cyclophosphamide, maintenance therapy, maintenance therapy is started at two to four weeks (the time of the leukocyte nadir) after the last dose of cyclophosphamide if the above criteria are met.
Duration of maintenance therapy — Maintenance therapy in patients with newly diagnosed GPA or MPA is usually given for 12 to 18 months after stable remission has been induced [7,15,18]. However, there are no randomized trials that have compared different durations of maintenance therapy. Furthermore, risk factors for relapse have been identified. (See "Relapsing disease in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis", section on 'Risk factors'.)

The magnitude of the effect of risk factors was evaluated in a series of 258 patients with newly diagnosed ANCA-associated vasculitis who attained remission [20]. Antiproteinase-3 (PR3)-ANCA compared to anticytoplasmic (MPO)-ANCA, and upper respiratory tract and/or pulmonary involvement were each associated with a significantly increased risk of relapse (hazard ratio 1.71 to 1.87). Upper respiratory tract involvement was considered likely with clinical or radiologic studies showing sinusitis, otitis media, nasal crusting and/or subglottic disease, Pulmonary involvement was defined by the presence of hemoptysis, pulmonary hemorrhage, respiratory failure, nodules, and/or cavities without evidence of infection.

The rate of relapse was much higher in patients with all three of these risk factors compared to those with none (73 percent at a median of 17 months versus 26 percent at a much longer median of 62 months). The duration of cyclophosphamide induction therapy (≤6 versus >6 months) was NOT a significant risk factor for relapse, even in patients at high risk.

Based upon such observations, some experts would vary the duration of maintenance therapy, based upon the estimated risk of relapse. As an example, some suggest continuing maintenance therapy after induction of remission in new onset disease for three years or more in patients with PR3-ANCA. In addition, prolonged or even indefinite immunosuppressive therapy may be warranted in patients with multiple relapses.

Some clinicians believe that a shorter duration of maintenance therapy (eg, six to nine months) can be given to patients at very low risk for relapse, such as those with MPO-ANCA and no upper respiratory tract or pulmonary involvement as confirmed by chest CT scan. However, we are concerned about the ability to replicate these findings outside of centers with expertise in ANCA-associated vasculitis.

Patients who progress to end-stage renal disease and are treated with chronic dialysis have a substantially lower rate of relapse than the same patients before they reached end-stage renal disease or patients with preserved renal function. In addition, maintenance therapy is associated with an increased risk of infection in dialysis patients. As a result, a shorter duration of maintenance therapy is suggested in such
patients. The rate of relapse is even lower in patients who receive a renal transplantation, presumably due to the immunosuppressive therapy given to prevent rejection. These issues are discussed in detail elsewhere. (See "Relapsing disease in granulomatosi"s with polymyalgia (Wegener’s) and microscopic polyangiitis", section on 'Chronic renal replacement therapy'.)

**Glucocorticoid therapy** — Low-dose oral **prednisone** (or its equivalent) is initially continued in most patients receiving maintenance therapy. The goal is to attain the minimum prednisone dose required for control of systemic symptoms, and varies among patients. We strongly prefer daily to alternate day prednisone therapy, since most patients develop aches and pains on the off day. However, some patients tolerate alternate day therapy, which is begun when the daily prednisone dose is 5 to 10 mg/day.

Patients who remain asymptomatic can be slowly tapered off **prednisone**. Once the prednisone dose reaches 5 mg/day, tapering should proceed at a rate of 1 mg/day reduction in dose every four weeks.

The median duration of glucocorticoid therapy is less than six to eight months \[7,21\]. However, some experts recommend long-term, low dose maintenance therapy in patients who have had multiple relapses. (See "Relapsing disease in granulomatosis with polymyalgia (Wegener’s) and microscopic polyangiitis".)

**Other drugs** — A number of drugs other than **methotrexate** and **azathioprine** have been evaluated for maintenance therapy in GPA and MPA. These include **mycophenolate mofetil** (MMF), **rituximab**, and, in selected patients, possibly **trimethoprim-sulfamethoxazole**.

The main indications for the use of MMF or **rituximab** for maintenance therapy are an inability to tolerate or relative contraindications to both **azathioprine** and **methotrexate** or continued relapses despite use of these drugs. Based upon the available data, the authors of this topic prefer MMF ahead of rituximab due in part to uncertain long-term dosing and higher cost, but some of the reviewers prefer rituximab. (See "Alternative agents in the treatment of granulomatosis with polymyalgia (Wegener’s) and microscopic polyangiitis".)

The efficacy of **trimethoprim-sulfamethoxazole** as maintenance therapy is unproven, but a trial may be reasonable in patients with disease limited to the upper respiratory tract \[22\]. An appreciable proportion of patients treated with trimethoprim-sulfamethoxazole maintenance (20 percent in one trial) discontinue therapy due to side effects, most of which are minor (anorexia, nausea, rash) \[22\]. (See "Alternative
agents in the treatment of granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis", section on 'Trimethoprim-sulfamethoxazole'.

Etanercept should NOT be used for maintenance therapy, since there was no benefit in the WGET trial mentioned above [7].

PCP prophylaxis — In patients treated with cyclophosphamide for induction of remission, we continue PCP prophylaxis until the CD4-positive T cell count exceeds 300/microL. The suggested regimens are discussed elsewhere. (See "Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis", section on 'PCP prophylaxis'.)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Beyond the Basics topic (See "Patient information: Vasculitis".)

SUMMARY AND RECOMMENDATIONS — The treatment of granulomatosis with polyangiitis (Wegener's), abbreviated as GPA, and microscopic polyangiitis (MPA) usually begins with cyclophosphamide and glucocorticoid therapy to induce remission. (See "Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis".)

Cyclophosphamide is discontinued one to two months after complete remission is achieved, which usually occurs within three to six months. (See 'Assessment of disease activity' above.)

After cyclophosphamide has been discontinued:
• Maintenance therapy should not be started until the white blood cell count is >4000 cells/microL and the absolute neutrophil count is >1500 cells/microL. If these criteria are met, maintenance can be begun within days after cessation of oral cyclophosphamide and within two to four weeks after the last monthly dose of intravenous cyclophosphamide (the time of the leukocyte nadir). (See 'Initiation of maintenance therapy' above.)

• We recommend initiation of maintenance therapy with either methotrexate or azathioprine to sustain the remission (Grade 1A). These drugs are preferred to long-term cyclophosphamide therapy, which is associated with significantly greater toxicity. (See 'Azathioprine versus methotrexate' above.)

• We suggest using azathioprine rather than methotrexate for initial maintenance therapy in patients with an estimated GFR less than 50 mL/min (Grade 2B). (See 'Choice of maintenance agent' above.)

• Azathioprine is administered at an initial dose of 2 mg/kg per day in most patients. The dose can be lowered to 1.5 mg/kg per day at one year from the time of initiation of induction therapy [15]. (See 'Azathioprine' above.)

• If methotrexate is used, one regimen consists of an initial dose of 0.3 mg/kg once per week (maximum 15 mg) that is progressively increased by 2.5 mg per week to a maximum dose of 25 mg once per week. Because methotrexate is a structural analogue of folic acid that can competitively inhibit the binding of dihydrofolic acid (FH2) to the enzyme dihydrofolate reductase (DHFR), folic acid (1 to 2 mg/day) or folinic acid (2.5 to 5 mg/week, 24 hours after methotrexate) should be given concurrently to reduce potential toxicity. (See 'Methotrexate' above.)

• Maintenance immunosuppressive therapy should be continued for 12 to 18 months. Longer term or indefinite maintenance therapy may be warranted in patients with multiple relapses. (See 'Duration of maintenance therapy' above.)

• We recommend concurrent glucocorticoid therapy (prednisone or equivalent), using the lowest dose required for control of extrarenal symptoms (Grade 1C). Patients who remain asymptomatic can be slowly tapered off glucocorticoid therapy. (See 'Glucocorticoid therapy' above.)

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REFERENCES


NEW TERMINOLOGY — In January 2011, the Boards of Directors of the American College of Rheumatology, the American Society of Nephrology, and the European League Against Rheumatism recommended that the name Wegener’s granulomatosis be changed to granulomatosis with polyangiitis (Wegener’s), abbreviated as GPA [1-3]. This change reflects a plan to gradually shift from honorific eponyms to a disease-descriptive or etiology-based nomenclature. The parenthetic reference to Wegener’s will be phased out after several years as the new name becomes more widely known.

INTRODUCTION — Granulomatosis with polyangiitis (Wegener’s), which can be abbreviated as GPA, and microscopic polyangiitis (MPA) are related systemic vasculitides. Both are associated with antineutrophil cytoplasmic antibodies (ANCA), have similar features on renal histology (eg, a focal necrotizing, pauci-immune, crescentic glomerulonephritis), and have similar outcomes. There are, however, several differences between these disorders. (See "Clinical manifestations and diagnosis of granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis", section on 'Clinical presentation'.)

For patients with life-threatening or organ-threatening disease, cyclophosphamide in combination with glucocorticoids is the standard of care for initial immunosuppressive therapy, although two randomized trials with limited follow-up have shown that rituximab was as effective as cyclophosphamide in inducing remission of patients with newly diagnosed or relapsing GPA or MPA [4,5].

The treatment of cyclophosphamide-resistant GPA or MPA will be reviewed here. Initial and maintenance immunosuppressive therapy, the clinical manifestations and diagnosis of these diseases, the treatment of relapsing disease, and patient and renal outcomes are discussed elsewhere. (See "Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis" and "Maintenance immunosuppressive therapy in granulomatosis with polyangiitis".
DEFINITION — True cyclophosphamide resistance in granulomatosis with polyangiitis (Wegener’s), abbreviated as GPA, and MPA is defined as the presence of active disease affecting a major organ despite optimal initial immunosuppressive therapy with cyclophosphamide and glucocorticoids. (See “Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis”.)

Studies from the University of North Carolina defined treatment resistance as one or both of the following despite immunosuppressive therapy for at least one month [6,7]:

- A progressive decline in renal function (ie, increase in serum creatinine) plus persistence of an active urine sediment (ie, dysmorphic hematuria with or without red cell casts)
- Persistence or new appearance of extrarenal manifestations of active vasculitis.

Some patients are incorrectly considered to be cyclophosphamide-resistant. An important cause is failure to distinguish correctly between active disease and signs of permanent damage induced by previous inflammatory injury. As an example, an elevated serum creatinine with or without proteinuria that can reach the nephrotic range can reflect chronic injury with scarring and is not considered a sign of active renal disease in the absence of dysmorphic (glomerular) hematuria (picture 1A-B). (See "Hematuria: Glomerular versus extraglomerular bleeding”, section on 'Red cell morphology'.)

Other factors that can lead to an incorrect diagnosis of persistent active disease include the presence of other diseases, noncompliance, an inadequate induction regimen, and the development of medication toxicities (eg, infection) that may present with manifestations similar to active disease. Thus, clinical judgment is essential when deciding that a patient is resistant to cyclophosphamide.

Cannot take cyclophosphamide — Occasional patients have a contraindication to cyclophosphamide therapy or refuse such therapy because of concerns about fertility, hair loss, the risk of malignancy, or other issues. Rituximab is the drug of choice for such patients since, in two randomized trials, rituximab was as effective as cyclophosphamide in inducing remission among patients with newly diagnosed or relapsing GPA or MPA [4,5]. A potential limitation is that the duration of follow-up was
limited to six to twelve months compared with the extensive long-term experience with cyclophosphamide. (See "Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis", section on 'Rituximab'.)

**Unresponsive but not resistant** — There are at least two disease manifestations that may be relatively unresponsive to cyclophosphamide (and to other systemic therapies), but are NOT considered resistant disease:

- Orbital pseudotumor (retrobulbar inflammatory masses).
- Subglottic stenosis, which may reflect scar rather than ongoing inflammation, and may respond best to local therapies such as triamcinolone injections and dilatation procedures (avoiding laser therapies). (See "Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis", section on 'Management of upper airway involvement'.)

**INCIDENCE AND RISK FACTORS** — The incidence of true cyclophosphamide resistance appears to be lower in clinical trials than clinical practice. In three major randomized clinical trials in ANCA-associated vasculitis, approximately 90 percent of patients in each of the trials achieved disease remission within six months of treatment and 10 percent are resistant [8-10]. By comparison, higher rates of resistant disease have been observed in clinical practice. This was illustrated in a community-based cohort study of 350 patients who received a new diagnosis of ANCA-associated vasculitis between 1985 and 2003 and were followed by physicians in the Glomerular Disease Collaborative Network [6].

The following findings were noted:

- Resistance, as defined in the preceding section, occurred in 23 percent of patients; 82 percent of these patients were treated with a cyclophosphamide-based regimen and the remaining patients were treated with glucocorticoids alone or with other drugs such as azathioprine or mycophenolate mofetil.
- The likelihood of resistance was significantly lower with cyclophosphamide compared to glucocorticoids alone (adjusted odds ratio 0.43).
- Resistance was more likely in patients with severe kidney disease at presentation (odds ratio 1.28 per 1.13 mg/dL [100 micromol/L] elevation in serum creatinine). However, although treatment resistant patients had a higher mean serum creatinine than responders (6.7 versus 4.0 mg/dL [590 versus 353 micromol/L]), therapy was effective in the majority of these
patients. Remission was induced in 72, 68, and 57 percent of patients with an estimated glomerular filtration rate of ≤30, ≤20, and ≤10 mL/min, respectively.

- Other significant risk factors included female sex and black ethnicity.

Other risk factors included MPO-ANCA compared to PR3-ANCA, advanced age, and renal biopsy findings of chronic disease (eg, glomerular and vascular sclerosis).

**PROGNOSIS** — Patients with cyclophosphamide-resistant granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis (GPA or MPA) have a much worse prognosis than patients who respond. The rate of progression to end-stage renal disease according to the response to cyclophosphamide induction therapy was evaluated in the above series of 350 patients from the Glomerular Disease Collaborative Network [6]. The renal prognosis was poor as 60 of 76 such patients (79 percent) developed end-stage renal disease at a median of two months after the initiation of therapy. The rate of end-stage renal disease was much lower in patients who attained remission with initial immunosuppressive therapy (19 percent at 9 years in patients who did not relapse and 28 percent at 5.5 years in those who relapsed).

Patient and renal outcomes in patients with GPA or MPA are discussed separately. (See "Patient and renal outcomes in granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis").

**TREATMENT OF CYCLOPHOSPHAMIDE-RESISTANT DISEASE** — The first step in the management of the patient suspected of being cyclophosphamide-resistant is to ensure that the clinical abnormalities are not due to drug toxicity, noncompliance, an inadequate regimen, progression of chronic inactive disease, infection, and/or pathogenic processes other than ongoing inflammation.

The optimal cyclophosphamide regimens and the role of plasma exchange in selected patients are discussed in detail separately. (See "Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis", section on 'Choice of cyclophosphamide regimen' and "Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis", section on 'Role of plasma exchange'.)

A number of drugs have been examined in small numbers of patients with resistant disease. In many cases, an accurate interpretation of the results is difficult due to the presence of one or more of the following:
• Manifestations of non-major organ involvement, such as constitutional features, upper airways disease, and/or arthralgias.
• Features suspicious for chronic sequelae rather than active disease.
• Subglottic stenosis which, as noted above, is often unresponsive to immunosuppressive therapy and may respond best to local therapies such as triamcinolone injections and dilatation procedures (avoiding laser therapies). (See 'Unresponsive but not resistant' above.)

Possibly effective therapies — No therapy for cyclophosphamide-resistant disease has been proven to be effective in randomized controlled trials. Observational studies have suggested efficacy for rituximab, mycophenolate mofetil and rituximab.

Rituximab — Two randomized trials cited above found that rituximab was as effective as cyclophosphamide in inducing remission of patients with newly diagnosed or relapsing granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis (GPA or MPA) at a follow-up of six to twelve months [4,5]. However, these trials did not include patients with resistant disease. (See 'Cannot take cyclophosphamide' above and "Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis", section on 'Rituximab'.)

Rituximab plus glucocorticoids have been beneficial in patients with cyclophosphamide resistance in observational studies [11-19]. The largest reported experience in resistant disease comes from a retrospective multicenter survey of 65 patients with cyclophosphamide-resistant ANCA-associated vasculitis [11]. The following findings were noted:

• The rates of complete and partial remission in 75 and 23 percent, respectively. The median time to remission was two months (range one to five months).
• Among the 49 patients who attained complete remission, 28 (57 percent) relapsed at a median of 12 months. Relapse was preceded by recovery of B cell counts in about one-half of cases. The likelihood of relapse appeared to be unrelated to the rituximab regimen (either four weekly infusions of 375 mg/m2 or two 1 g infusions given two weeks apart).
• A second course of rituximab was given to 33 patients because of relapse or preemptive therapy to avoid relapse and to five patients because of persistent disease. Complete remission was induced or maintained in 32 of these patients (84 percent).
• Monitoring ANCA titers and B cell counts were not sufficiently sensitive to guide the timing of retreatment. Although ANCA titers fell after rituximab therapy,
relapse was not associated with either ANCA positivity or a rise in ANCA titers.

- **Rituximab** was well tolerated. Two patients developed neutropenia at three and five months after the second course, and no other adverse event was directly attributable to rituximab.

Systemic and vasculitis-related symptoms may completely resolve within days to weeks [11,13]. In contrast, manifestations due to granuloma formation improve more slowly (over several weeks to months) or do not respond [13,17]. One report, for example, evaluated the efficacy of rituximab in eight patients (five with retrobulbar granuloma, one with pulmonary/sinus granuloma, and two with subglottic stenosis) who had not responded to prednisone in combination with cyclophosphamide, methotrexate, or mycophenolate mofetil, or to anti-tumor necrosis factor-alpha therapy [17]. Improvement in disease manifestations was noted in the patient with pulmonary/sinus granuloma and one of the patients with subglottic stenosis, but in none of the patients with retrobulbar disease. (See "Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis", section on 'Management of upper airway involvement'.)

Benefit has also been noted in patients with ophthalmic manifestations (eg, scleritis and/or granulomas causing optic nerve compromise) that were resistant to cyclophosphamide therapy [18,19].

Further study of rituximab in patients with GPA or MPA is needed in order to better understand its role in the management of these disorders, and whether development of antibodies limits its long-term usefulness.

**Mycophenolate mofetil** — Mycophenolate mofetil (MMF) has shown possible efficacy for maintenance immunosuppression and the treatment of relapses in patients with GPA or MPA. These data are presented separately. (See "Alternative agents in the treatment of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis", section on 'Mycophenolate mofetil'.)

A number of small observational studies have evaluated MMF in patients who were resistant to or could not tolerate cyclophosphamide [20-22].

With respect to patients who are resistant to cyclophosphamide, a pilot study of non-life-threatening disease included four patients who failed to improve after at least six months of cyclophosphamide-based induction therapy and two patients who had been treated with azathioprine because cyclophosphamide could not be given [20]. After cyclophosphamide was discontinued, the glucocorticoid dose was maintained and the
patients were started on MMF (500 mg twice daily, which was increased by 250 mg twice daily every two weeks to a maximum dose of 1500 mg twice daily in patients who showed no evidence of response to 1000 mg twice daily). Six other patients had frequently relapsing disease and were included in the analysis. Among the 10 patients who completed the study (target dose given for 24 weeks), improvement in disease activity occurred in all patients and six had at least a transient complete remission.

MMF was also evaluated for remission induction in 32 consecutive patients who had ANCA-associated vasculitis for a median of six years, had a median of four relapses prior to the current relapse, and could not be treated with cyclophosphamide [22]. Cyclophosphamide was considered contraindicated for a variety of reasons including previous hemorrhagic cystitis on cyclophosphamide, treated bladder cancer, bone marrow depression, patient refusal, and, in six patients, an incomplete response to or relapse during cyclophosphamide therapy.

Complete or partial remissions were induced in 78 and 19 percent, respectively. Relapse during follow-up occurred in 19 of 25 patients (76 percent) who attained complete remission and in all six who attained partial remission. The patients who had been treated unsuccessfully with cyclophosphamide had a worse response than those had previously responded (complete remission 50 versus 84 percent, relapse 100 versus 50 percent).

The possible efficacy of MMF for maintenance therapy after remission of active disease has been induced by cyclophosphamide is discussed elsewhere. (See "Alternative agents in the treatment of granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis", section on 'Mycophenolate mofetil'.)

**Therapies of unproven efficacy**

**Anti-TNF-alpha therapy** — Insights into the role of Th1 cytokines in the pathogenesis of GPA have led to on-going trials involving therapy with antagonists to tumor necrosis factor-alpha (TNFa) and inhibitors of monocyte function, such as interleukin-10 [23]. The rationale for such therapy is discussed separately. (See "Pathogenesis of granulomatosis with polyangiitis (Wegener’s) and related vasculitides", section on 'Role of T cells'.)

Data are limited on the possible efficacy of these agents in GPA or MPA and there is possible harm. In a major randomized trial of patients with GPA who were not resistant to cyclophosphamide (Wegener’s Granulomatosis Etanercept Trial), etanercept was ineffective in maintaining remission and was associated with a higher rate of malignancy [8].
In an open label study, infliximab was added to standard immunosuppressive therapy in 16 patients with acute ANCA-associated vasculitis at first presentation or relapse and in 16 with persistent disease despite multiple immunosuppressive regimens [24]. Fourteen patients in each group (88 percent) achieved remission within a mean of 6.4 weeks. Serious infections and death were reported in seven and two patients, respectively, while five patients (three with persistent disease) had a relapse at a mean of 27 weeks. (See "Tumor necrosis factor-alpha inhibitors: An overview of adverse effects").

The role, if any, of TNFα inhibitors for the treatment of GPA or MPA remains unproven.

**Anti-T cell antibodies** — The observation that active systemic vasculitis is mediated in part by T cell-induced injury has led to the evaluation of anti-T cell antibodies in patients with GPA who are resistant to or cannot tolerate cytotoxic therapy [25-27]:

- In one study, the administration of a combination of two humanized monoclonal antibodies (one directed against an antigen on all mononuclear cells and one directed against CD4) led to long-lasting remission in four patients with different forms of refractory vasculitis [25]. This was also accompanied by toxicity that included infusion reactions, infection, autoimmune events, and prolonged lymphocyte depletion.
- Among 15 patients with refractory disease (seven unresponsive to and eight intolerant of cyclophosphamide), anti-thymocyte globulin (ATG) resulted in a partial or complete remission in 9 and 4 patients, respectively [27]. However, two patients died one and three days after the first administration of ATG (due to pulmonary hemorrhage and infection).

The role of these experimental therapies remains to be determined.

**Intravenous immune globulin** — Intravenous immune globulin has been studied in only a limited fashion in ANCA-associated vasculitis, and none of the available studies provide clear answers regarding potential efficacy [28-31]. The best data come from a randomized, placebo-controlled trial of 34 patients with ANCA-associated systemic vasculitis and persistent disease activity despite previous immunosuppressive therapy [31]. Improvement occurred in 6 of 13 who had lung involvement but no information was provided regarding the presence or response of renal manifestations of the disease. The uncertain efficacy of intravenous immune globulin has led many investigators to be hesitant about its use in ANCA-associated systemic vasculitis. A review of the mechanisms of action and potential side effects associated with this
modality can be found elsewhere. (See "General principles in the use of immune globulin").

**Intravenous azathioprine** — There are anecdotal reports of using high dose intravenous azathioprine to treat a variety of immune-mediated diseases. In one report, four patients with GPA who had not responded to oral cyclophosphamide (2 mg/kg per day) were treated with monthly infusions of azathioprine [32]. Two had remission of disease, one of whom developed renal involvement during relapse, which responded to retreatment.

In the absence of further data, high dose intravenous azathioprine should NOT be used for the treatment of ANCA-associated systemic vasculitis.

**15-Deoxyspergualin** — 15-deoxyspergualin (gusperimus), which has an antiproliferative effect on antigen-stimulated B cells, has been evaluated in a small number of patients with cyclophosphamide-resistant disease or contraindications to the use of cyclophosphamide:

- Among 20 such patients, the administration of 15-deoxyspergualin resulted in complete or partial remission in six and eight cases, respectively [33]; every patient experienced transient leukopenia with each treatment cycle.
- In a series of seven patients treated with 15-deoxyspergualin and glucocorticoids, all had complete or partial remission, but prolonged treatment (up to four years) was required [34].

Careful monitoring of the white blood count is required to avoid excessive leukopenia. The role of this agent remains to be determined.

**Radiation therapy** — Radiation therapy for the treatment of airway involvement in GPA has been evaluated in case reports [35,36]. Nasal and sinus involvement in one instance was treated with two courses of 20 and 26 Gy, administered in 2 Gy fractions given a month apart [36]. Plastic stents were placed in the nasal passages to prevent stenosis due to radiation-induced fibrosis.

The use of ionizing radiation for nonmalignant disease is always controversial. Current data do NOT support its use in a systemic disorder like GPA.

**Stem cell transplantation** — High-dose, myeloablative chemotherapy with stem cell transplantation has been utilized for the treatment of refractory severe vasculitis. There are case reports of successful treatment of vasculitis with renal involvement, including a few patients with GPA [37]. Much more study is required to determine if
there is a role for stem cell transplantation in the management of resistant ANCA-associated systemic vasculitis.

**SUMMARY AND RECOMMENDATIONS**

- **Cyclophosphamide** resistance in patients with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis (GPA or MPA) is defined as one or both of the following despite therapy for at least one month: progressive decline in renal function (ie, increase in serum creatinine) plus persistence of an active urine sediment (ie, dysmorphic hematuria with or without red cell casts); and persistence or new appearance of extrarenal manifestations of active vasculitis. (See 'Definition' above.)

- True **cyclophosphamide** resistance must be distinguished from signs of permanent damage induced by previous active disease (eg, an elevated serum creatinine with or without proteinuria in the absence of dysmorphic hematuria), the presence of other diseases, and the development of medication toxicities (eg, infection) that may present with manifestations similar to active disease. (See 'Unresponsive but not resistant' above.) The incidence of cyclophosphamide resistance has been approximately 10 percent in clinical trials, but higher in clinical practice (23 percent in one series). Significant risk factors for resistance include female sex, black ethnicity, and severe kidney disease at presentation. (See 'Incidence and risk factors' above.)

- Patients with **cyclophosphamide** resistance have a poor prognosis, as 79 percent in one series developed end-stage renal disease at a median of two months after the initiation of therapy. The rate of end-stage renal disease was much lower in patients who attained remission with initial immunosuppressive therapy. (See 'Prognosis' above.)

- In the patient with true **cyclophosphamide**-resistant active inflammation, the first step is to ensure that the cyclophosphamide regimen has been optimized and, if indicated, plasma exchange has been administered. These issues are discussed in detail separately. (See "Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis", section on 'Role of plasma exchange'.)

- Among patients with definitive evidence of persistent active disease involving a major organ, and in whom optimal **cyclophosphamide** dosing is ineffective or not tolerated, we suggest a trial of **rituximab** (Grade 2C). The suggested dose of rituximab is 375 mg/m2 per week for four weeks given with
methylprednisolone (1000 mg) followed by oral prednisone 1 mg/kg per day. (See "Initial immunosuppressive therapy in granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis", section on 'Rituximab'.)

- Among patients with definitive evidence of persistent active disease involving a major organ, and in whom both cyclophosphamide and rituximab are ineffective or not tolerated, we suggest a trial of mycophenolate mofetil (Grade 2C). The suggested dose of mycophenolate mofetil is 500 mg twice daily which is increased, if there is no response, by 250 mg twice daily every two weeks to a maximum dose of 1500 mg twice daily. (See 'Mycophenolate mofetil' above.)

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REFERENCES


