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Cite this as: *BMJ* 2022;376:e064597
http://dx.doi.org/10.1136/bmj-2021-064597

RAPID RECOMMENDATIONS

Plasma exchange and glucocorticoid dosing for patients with ANCA-associated vasculitis: a clinical practice guideline

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ABSTRACT

CLINICAL QUESTIONS

What is the role of plasma exchange and what is the optimal dose of glucocorticoids in the first 6 months of therapy of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)? This guideline was triggered by the publication of a new randomised controlled trial.

CURRENT PRACTICE

Existing guideline recommendations vary regarding the use of plasma exchange in AAV and lack explicit recommendations regarding the tapering regimen of glucocorticoids during induction therapy.

RECOMMENDATIONS

The guideline panel makes a weak recommendation against plasma exchange in patients with low or low-moderate risk of developing end stage kidney disease (ESKD), and a weak recommendation in favour of plasma exchange in patients with moderate-high or high risk of developing ESKD. For patients with pulmonary haemorrhage without renal involvement, the panel suggests not using plasma exchange (weak recommendation). The panel made a strong recommendation in favour of a reduced dose rather than standard dose regimen of glucocorticoids, which involves a more rapid taper rate and lower cumulative dose during the first six months of therapy.

HOW THIS GUIDELINE WAS CREATED

A guideline panel including patients, a care giver, clinicians, content experts, and methodologists produced these recommendations using GRADE and in adherence with standards for trustworthy guidelines. The recommendations are based on two linked systematic reviews. The panel took an individual patient perspective in the development of recommendations.

THE EVIDENCE

The systematic review of plasma exchange identified nine randomised controlled trials (RCTs) that enrolled 1060 patients with AAV. Plasma exchange probably has little or no effect on mortality or disease relapse (moderate and low certainty). Plasma exchange probably reduces the one year risk of ESKD (approximately 0.1% reduction in those with low risk, 2.1% reduction in those with low-moderate risk, 4.6% reduction in those with moderate-high risk, and 16.0% reduction in those with high risk or requiring dialysis) but increases the risk of serious infections (approximately 2.7% increase in those with low risk, 4.9% increase in those with low-moderate risk, 8.5% increase in those with moderate-high risk, to 13.5% in high risk group) at 1 year (moderate to high certainty). The guideline panel agreed that most patients with low or low-moderate risk of developing ESKD would consider the harms to outweigh the benefits, while most of those with moderate-high or high risk would consider the benefits to outweigh the harms. For patients with pulmonary haemorrhage without kidney involvement, based on indirect evidence, plasma exchange may have little or no effect on death (very low certainty) but may have an important increase in serious infections at 1 year (approximately 6.8% increase, low certainty). The systematic review of different dose regimens of glucocorticoids identified two RCTs at low risk of bias with 704 and 140 patients respectively. A reduced dose regimen of glucocorticoid probably reduces the risk of serious infections by approximately 5.9% to 12.8% and probably does not increase the risk of ESKD at the follow-up of 6 months to longer than 1 year (moderate certainty for both outcomes).

UNDERSTANDING THE RECOMMENDATION

The recommendations were made with the understanding that patients would place a high value on reduction in ESKD and less value on avoiding serious infections. The panel concluded that most (50-90%) of fully informed patients with AAV and with low or low-moderate risk of developing ESKD with or without pulmonary haemorrhage would decline plasma exchange, whereas most patients with moderate-high or high risk or requiring dialysis with or without pulmonary haemorrhage would choose to receive plasma exchange. The panel also inferred that the majority of fully informed patients with pulmonary haemorrhage without kidney involvement would decline plasma exchange and that all or almost all (≥90%) fully informed patients with AAV would choose a reduced dose regimen of glucocorticoids during the first 6 months of therapy.

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which includes granulomatosis with polyangiitis and microscopic polyangiitis, is characterised by inflammation of small blood vessels (see box 1 for details of AAV).[4] Over the past few decades, with the evolution of disease awareness, diagnostic techniques, and improved treatments, mortality among patients with AAV has decreased.[5] However, it remains 2.6-fold higher than that in the general population due to complications from the underlying disease (such as kidney failure or pulmonary haemorrhage) and

complications from immunosuppressive therapy (such as serious infections or cancer).[6 7]

Box 1: Details of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis

- *Classification*—ANCA-associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA).[1] An alternative approach to classification is based on ANCA serology (myeloperoxidase ANCA or proteinase 3 ANCA).
- *Clinical presentation*—Typical features of GPA include nasal crusting, stuffiness, and epistaxis; scleritis; upper respiratory tract involvement; and often, when in the context of an active urinary sediment, kidney involvement. Patients with MPA are typically older and present with more severe kidney disease than those with GPA.[2] All forms of AAV can involve pulmonary haemorrhage.
- *Pathophysiology*—Because both myeloperoxidase and proteinase 3 are sequestered from the immune system in primary granules and, after neutrophil degranulation at sites of tissue injury, are rapidly eliminated by specific inhibitors, it is unclear why autoantibodies to neutrophil self antigens develop. Defective neutrophil apoptosis or impaired clearance of apoptotic cell fragments may lead to prolonged exposure of the immune system to these antigens. Infection may also play a role through molecular mimicry.[1]
- *Treatment*—Initial therapy for AAV includes induction of remission with initial immunosuppressive therapy (treatment options include glucocorticoids, rituximab, cyclophosphamide, C5a inhibitors, mycophenolate mofetil, plasma exchange, intravenous immunoglobulin, and co-trimoxazole), and maintenance of remission with immunosuppressive therapy for a variable period to prevent relapse (treatment options include glucocorticoids, azathioprine, methotrexate, rituximab, and co-trimoxazole).[3]

This clinical practice guideline was triggered by publication of the PEXIVAS randomised controlled trial (RCT), holding the potential to change clinical practice.[8] The PEXIVAS trial failed to show a reduction in the composite outcome of death from any cause or end stage kidney disease (ESKD) in patients with severe AAV (defined by an estimated glomerular filtration rate (eGFR) of <50 mL/min/1.73 m^2 of body surface area or diffuse pulmonary haemorrhage) randomised to plasma exchange in addition to immunosuppressive therapy compared with immunosuppressive therapy alone (28.4% *v* 31.0%, hazard ratio 0.86 (95% confidence interval (CI) 0.65 to 1.13)).[8] This trial demonstrated that a reduced dose regimen of glucocorticoid (the cumulative dose was 40% of that in a standard dose regimen group at 6 months) reduced serious infections at 1 year compared with the standard dose regimen group (incidence rate ratio 0.69 (95% CI 0.52 to 0.93)).

Box 2: How these recommendations were developed

The *BMJ* Rapid Recommendations was initiated by the MAGIC Evidence Ecosystem Foundation (MAGIC, https://magicevidence.org/) together with *The BMJ* in 2016 to circumvent organisational barriers and to provide clinicians with guidance based on the most current practice-changing evidence.

The recent publication of PEXIVAS randomised controlled trial triggered this guideline.[8] The Rapid Recommendations team felt that the results of this study, interpreted in the context of existing evidence, might change practice.

Our international guideline panel included patient partners with AAV with or without experience of plasma exchange, a caregiver for a patient who has ESKD, rheumatologists, nephrologists, an intensivist specialised in pulmonary vasculitis and pulmonary haemorrhage, a paediatrician specialised in vasculitis and autoinflammatory diseases, general internists, and methodologists (see appendix 4 on bmj.com for details of panel members). No panel member had relevant financial conflicts of interest; intellectual and professional conflicts were minimised and transparently described (see appendix 4 for details of competing interests).

The panel decided the scope of the recommendation and rated the outcome importance to patients. The panel judged the following as patient-important outcomes for decision making: mortality, ESKD, remission of AAV, health related quality of life, relapse of AAV, and serious infections (defined as infection requiring intravenous antibiotics or hospitalisation) and other serious adverse events associated with plasma exchange or glucocorticoids.

The panel met online to discuss the evidence and to formulate recommendations. The panel followed the *BMJ* Rapid Recommendations procedures for creating trustworthy guidelines,[9] including using the GRADE approach to critically appraise the evidence and create recommendations (appendix 5 on bmj.com). The panel considered the balance of benefits, harms, and burdens and other practical issues related to plasma exchange and reduced dose regimen of glucocorticoids in the context of AAV, as well as typical and expected variations in patient values and preferences.[10] Within the GRADE approach, recommendations can be strong or weak (also known as conditional), for or against a course of action.[11]

We translated this new evidence for clinicians and patients using the GRADE approach and standards for trustworthy guidelines, as for previous *BMJ* Rapid Recommendations (see box 2). The guideline panel asked three key questions:

- Which patients with AAV and kidney involvement, if any, should receive plasma exchange?
- Should patients with AAV and pulmonary haemorrhage without kidney involvement receive plasma exchange?
- Should patients with AAV receive a reduced dose regimen of glucocorticoid during the first 6 months of therapy?

The recommendation is based on two linked systematic reviews on benefits and harms of plasma exchange and different dose regimens of glucocorticoids in patients with AAV.[12 13] The main infographic provides an overview of the relative and absolute benefits and harms of plasma exchange and reduced dose regimen of glucocorticoids in standard GRADE format. Box 3 shows articles linked to this guideline.

Box 3: Linked resources for this BMJ Rapid Recommendations cluster

- Zeng L, Walsh M, Guyatt GH, et al. Plasma exchange and glucocorticoid dosing for patients with ANCA-associated vasculitis: a clinical practice guideline. *BMJ* 2022;376:e064597
  - Summary of the results from the Rapid Recommendation process
- Walsh M, Collister D, Zeng L, et al. The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis. *BMJ* 2022;376:e064604
  - Review and meta-analysis of randomised trials that assess effects of plasma exchange for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).
- Xiao Y, Guyatt G, Zeng L, et al. The comparative efficacy and safety of alternative glucocorticoids regimens in patients with ANCA-associated vasculitis: a systematic review. *BMJ Open* 2022; doi:10.1136/bmjopen-2021-050507
  - Review and meta-analysis of randomised trials that assess effects of alternative glucocorticoids regimens for AAV.
- Walsh M. Predicting the 1-year risk of kidney failure in ANCA associated vasculitis. *BMC Medicine* (forthcoming)
  - Prediction model of risk of kidney failure in AAV.

- MAGICapp (https://app.magicapp.org/#/guideline/4218)
  - Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices.

Current practice

Who should use plasma exchange?

Most existing guidelines recommend in favour of plasma exchange in patients with severe kidney impairment (serum creatinine ≥500 µmol/L) or with active vasculitis despite ongoing remission induction therapy (see table 1).[14 -21] However, guidelines vary in the recommendation for patients with severe diffuse pulmonary haemorrhage, with some guidelines recommending in favour of plasma exchange, while others conclude there is insufficient evidence to support plasma exchange in these patients.

What is the tapering regimen of glucocorticoids for the first six months of therapy?

In guidelines that have a recommendation on the dose regimen of glucocorticoids, the initial dose of prednisolone or equivalent is 0.5-1 mg/kg/day. There is, however, no standard for the taper rate of glucocorticoids after initial treatment. A guideline from the British Society for Rheumatology/British Health Professionals in Rheumatology recommends a "rapid reduction" of glucocorticoids after the initial dose.[21] The recommended taper rate is, however, slower than the reduced dose regimen in the PEXIVAS trial.

Table 1 | Current recommendations for plasma exchange and dose regimen of glucocorticoids in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV)

Organisation and year of publication	Recommendation of plasma exchange (PLEX) in		Recommendation of tapering regimen of glucocorticoids in induction therapy
	AAV and kidney involvement	AAV and pulmonary haemorrhage	
ASFA 2020[14]	*For patients with creatinine ≥500 µmol/L:* In favour of PLEX as accepted second line therapy alone or as adjuvant; support use of PLEX in select patients with biopsy proven RPGN (strong recommendation based on moderate quality evidence). *For patients with creatinine <500 µmol/L:* Optimal role not established, decision should be individualised (weak recommendation based on low or very low quality evidence)	Consider PLEX for pulmonary haemorrhage a class I indication (accepted first line therapy) (strong recommendation based on low quality evidence)	No recommendation
KDIGO 2020[15]	Against routine use of PLEX for patients with GFR <50 mL/min/1.73 m2; PLEX can be considered for more severe presentations (serum creatinine >500 µmol/L, especially if oliguric)	In favour of PLEX for AAV and diffuse alveolar haemorrhage plus hypoxaemia	No explicit recommendation, but commented that (*a*) in most RCTs oral glucocorticoids started at 1 mg/kg/day; (*b*) PEXIVAS trial showed more rapid reduction was as effective but safer than "standard" corticosteroid tapering regimen
ARCH 2020[16]	In favour of PLEX for AAV and rapidly progressive glomerulonephritis	In favour of PLEX for AAV and pulmonary haemorrhage	No recommendation
Japan Research Committee of the Ministry of Health, Labour, and Welfare 2017[17]	In favour of PLEX for AAV and severe renal impairment	No recommendation	No recommendation
BSR 2017[18]	In favour of PLEX for AAV and rapidly progressive glomerulonephritis with serum creatinine >5.8 mg/dL	Insufficient evidence to support PLEX for AAV presenting with pulmonary haemorrhage, PLEX possibly beneficial	Prednisone or prednisolone prescribed at initial dose of 0.5-1.0 mg/kg/day (max 80 mg/day) for 1-4 weeks followed by tapering 10 mg every 2-4 weeks until 20 mg/day. Then taper dose 2.5-5.0 mg every 2-4 weeks until complete withdrawal
EULAR/ERA-EDTA 2016[19]	In favour of PLEX for AAV and serum creatinine level ≥500 mmol/L due to rapidly progressive glomerulonephritis in new or relapsing disease	In favour of PLEX for AAV and severe diffuse pulmonary haemorrhage	No recommendation
CanVasc 2016[20]	Against PLEX as first line therapy for AAV and severe renal involvement (GFR <50 mL/min). PLEX may be a reasonable adjuvant therapy if patients clinically deteriorate	Against PLEX as first line therapy for AAV and pulmonary haemorrhage. PLEX may be a reasonable adjuvant therapy if patients clinically deteriorate	No recommendation
BSR/BHPR 2014[21]	In favour of PLEX for AAV and severe renal failure (serum creatinine >500 mmol/L)	In favour of PLEX for AAV and pulmonary haemorrhage	Glucocorticoids usually given as daily oral prednisolone, initially at high doses (1 mg/kg up to 60 mg) with dose rapidly reduced to 15 mg prednisolone at 12 weeks

ASFA = American Society for Apheresis; Kidney Disease: KDIGO = Improving Global Outcomes; ARCH = Arthritis Research and Collaboration Hub; BSR = Brazilian Society of Rheumatology; EULAR/ERA-EDTA = European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association; CanVasc = Canadian Vasculitis Research Network; BSR/BHPR = British Society for Rheumatology/British Health Professionals in Rheumatology; GFR = glomerular filtration rate, RCT = randomised controlled trial.

A review of the prednisolone dose regimen in trials compared the dose in the PEXIVAS trial with those in other key trials. On average, a dose of 10 mg was achieved after 19 weeks in the standard dose regimen group of the PEXIVAS trial and in other trials, and after 13 weeks in the reduced dose regimen group of PEXIVAS. The standard dose regimen achieved a dose of 7.5 mg after 21 weeks, while the reduced dose regimen achieved this dose four weeks earlier (after 17 weeks) (see appendix 1 for more details). A cross sectional survey

among 34 hospitals in England revealed a large variation in the initial dose and taper rate of glucocorticoids in patients with AAV.[22]

The evidence

What are the benefits and harms of plasma exchange in patients with AAV, with or without kidney involvement?

We incorporated the PEXIVAS trial into a linked systematic review to generate pooled estimates of effect (see infographic). The review included nine RCTs and 1060 patients with AAV comparing plasma exchange in addition to standard care (that is, immunosuppression and glucocorticoids) versus standard care alone. Table 2 provides an overview of the trials and participants. PEXIVAS, the largest of the nine trials, evaluated the effect of plasma exchange in 704 patients with severe AAV. The systematic review analysed mortality and ESKD separately, rather than as composite.

Table 2 | Characteristics of 9 randomised controlled trials (1060 patients) included in systematic review of plasma exchange in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV), with or without kidney involvement

	Values
Trial characteristics	Mean (range) of means across trials
No of patients enrolled	118 (14-704)
Length of follow-up (months)	Median 36 (12-127)
Dose regimen of plasma exchange	Centrifugation or filter separation; 8 trials used albumin and/or crystalloid replacement solution for a median 8 treatments; exchange volume ranged from 1 to 1.5 plasma volumes (or 40 to 60 mL/kg or fixed volume of 3.5-4 L)
Setting	Multiple centres internationally including Europe, North America, and Australasia
Funding	Public funding only (4 trials) In-kind supplies from industry partner (1 trial) Public funding and in-kind supplies from three industry partners (1 trial) Not reported (3 trials)
Patient involvement	No trial reported patient involvement in design or conduct
Patient characteristics	Mean (range) of means across trials
Age (years)	56 (47-67)
Sex (% women)	35 (22-44)
ANCA positive	84% in 6 trials that measured ANCA
Kidney function (serum creatinine concentration µmol/L)	Median 716 (256-1176)
Presence of pulmonary haemorrhage	Patients with pulmonary haemorrhage included (4 trials) Patients with severe pulmonary haemorrhage included (1 trial)

We used the control group event rates in the systematic review to estimate the baseline risks for outcomes of mortality, serious infections, and relapse of AAV, and used the data from seven multinational RCTs conducted by the European Vasculitis Study Group with 798 patients to estimate the baseline risk for the outcome of ESKD.[23-29] The systematic review found no credible evidence that the relative effect of plasma exchange would vary on the basis of kidney function or pulmonary haemorrhage.[12] We therefore used the baseline risks, along with the pooled relative risk for overall patients at the timeline of one year and long term follow-up (median 3 years) from the systematic review, to calculate the absolute effect estimates presented in our evidence summaries.

Mortality and relapse of AAV

Plasma exchange probably has little or no effect on mortality (risk difference (RD) 0.8% reduction (95% CI 3.9% reduction to 3.6% increase) at 1 year; RD 1.3% reduction (5.5% reduction to 3.6% increase) at long term follow-up; both moderate certainty due to imprecision). Plasma exchange may reduce relapse of AAV (RD 2.1% reduction (11.6% reduction to 13.9% increase) at long term follow-up; low certainty due to very serious imprecision; no data available at 1 year).

End stage kidney disease and serious infections

The absolute effects of plasma exchange in ESKD and serious infections vary significantly with baseline risks. The panel, therefore, decided to use risk of developing ESKD at 1 year (that is, baseline risk) as a stratification variable to present the absolute effects of plasma exchange on ESKD and serious infections, and then discussed the tradeoff between benefits and harms in each of the risk groups.

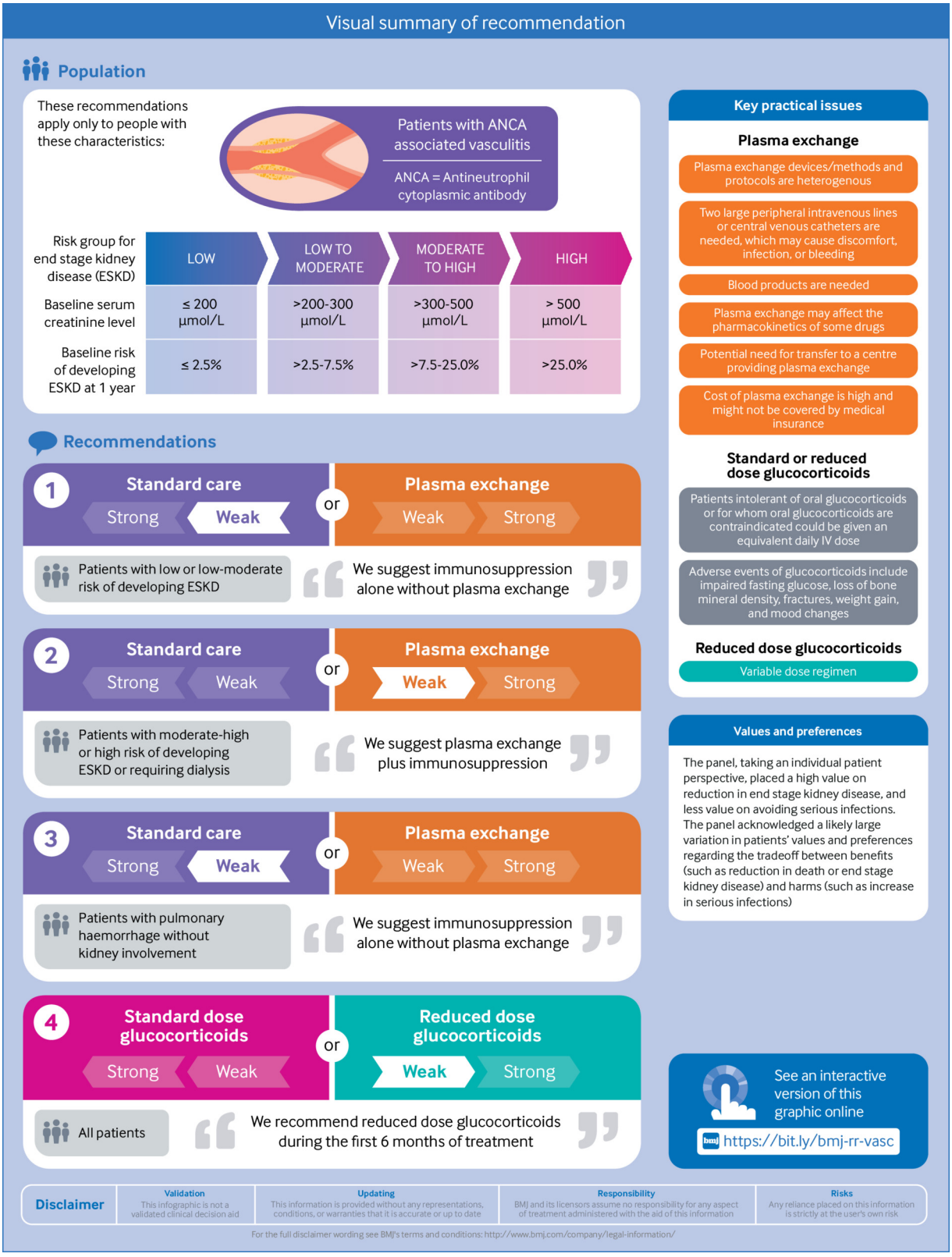
The panel stratified the risks of developing ESKD for four groups (see infographic). A linked prognostic study demonstrates that serum creatinine, as a single predictor, can provide robust estimates of the risk of developing ESKD.[30] Patients with serum creatinine ≤200 µmol/L, >200-300 µmol/L, >300-500 µmol/L and >500 µmol/L fall, respectively, into low, low-moderate, moderate-high, and high risk groups (see infographic).[30] The panel recognised that, although serum creatinine level could well predict the risk of ESKD,[30] using serum creatinine as a single predictor has limitations (for example, the serum creatinine might change rapidly or the prognosis may be modified by tests such as kidney biopsy).

Because of availability of baseline risk strata, the linked systematic review provided the absolute effects of plasma exchange in ESKD and serious infections in a time frame of 1 year rather than a longer time frame.[12] Plasma exchange probably reduces the 1 year risk of ESKD (the absolute risk reduction approximately 0.1% in low risk group, 2.1% reduction in low-moderate risk group, 4.6% reduction in moderate-high risk group, and 16.0% in high risk group or patients requiring dialysis) but increases the risk of serious infections (the absolute risk increase approximately 2.7% in low risk group, 4.9% in low-moderate risk group, 8.5% increase in moderate-high risk group, and 13.5% in high risk group or patients requiring dialysis) at 1 year (moderate to high certainty). See infographic for more details.

What are the benefits and harms of plasma exchange in patients with AAV and pulmonary haemorrhage without kidney involvement?

In patients with pulmonary haemorrhage without kidney involvement, the key benefit outcome becomes risk reduction in death, and the key harm outcome remains an increase in serious infections. Because we have limited data regarding the baseline risks of death and serious infections in this group of patients, we estimated the baseline risk for outcome of mortality in a time frame of 1 year using the average mortality (20.8%) in patients with pulmonary haemorrhage in the control group of the PEXIVAS trial. The estimate comes from a mix of patients with or without kidney involvement. Thus, this mortality (20.8%) might overestimate mortality for the average patient with pulmonary haemorrhage without kidney involvement. We estimated the baseline risk of serious infections as similar to the risk in the entire control group of the RCTs (25%).

We are uncertain whether plasma exchange has an effect on death at 1 year (RD 1.5% reduction (95% CI 7.1% reduction to 6.4% increase); very low certainty due to indirectness and very serious imprecision). It may have an important increase in serious infections at 1 year (RD 6.8% increase (95% CI 0.8% increase to 14% increase); low certainty due to indirectness and imprecision).



What are the benefits and harms of reduced dose regimen of glucocorticoids?

The linked systematic review of comparative efficacy and safety of alternative glucocorticoids regimen included two RCTs at low risk of bias. One trial included 704 patients with severe AAV; the other included 140 patients with newly diagnosed AAV (of which 134 patients completed the trial).[28 31] Due to the heterogeneity in the population and in the regimens of glucocorticoids, the systematic review authors descriptively presented the two trials and did not combine the results using meta-analysis.

Compared with standard dose regimen of oral glucocorticoids, the reduced dose regimen of oral glucocorticoids probably has an important reduction in serious infections at a follow-up of 6 months to 1 year (RD 5.9% to 12.8% reduction; moderate certainty due to imprecision), and may reduce death from any cause at long term follow-up (RD 1.7% to 2.1% reduction; low certainty due to very serious imprecision) without increasing the risk of ESKD (RD 1.5% reduction to 0.4% increase; moderate certainty due to imprecision). The reduced dose regimen probably has little or no effect on disease remission, relapse, or health related quality of life (moderate to high certainty).

Values and preferences

To elicit the guideline panel's view of patients' values and preferences (primarily the relative value patients would place on avoiding ESKD and avoiding serious infections) we conducted two formal panel surveys. In the first survey, conducted before the panel reviewed the evidence of benefits (that is, reduction in ESKD), the panel members (including four patients and one care giver partner), presented with the harms associated with plasma exchange, expressed their view of the magnitude of reduction in ESKD that patients would require to choose plasma exchange (see appendix 2 for details of the survey process and results). In that survey and the subsequent discussion, the panel concluded that patients would place a high value on reduction in ESKD, and less value on avoiding serious infections.

For making a judgment about how patients with varying risks of developing ESKD would view the trade-off between benefit (that is, reduction in ESKD) and harm (increase in serious infections) of plasma exchange, the panel completed a second survey. In this survey, they considered the estimated absolute effects of plasma exchange on the key benefit and the key harm from the linked systematic review (see appendix 3 for details of the survey process and results). Based on the survey and panel discussion, the panel agreed that, for patients with low or low-moderate risk of developing ESKD, the harms of serious infections outweighed the benefits in terms of reduction in ESKD; but, because it was a close balance, the majority of patients but not all (50-90%) would decline plasma exchange. The panel agreed that, for patients with moderate-high or high risk of developing ESKD or requiring dialysis, the benefits outweigh the harms, such that the majority of patients would choose plasma exchange.

Understanding the recommendations

Recommendation 1. We suggest immunosuppression alone rather than adding plasma exchange for patients with AAV and low or low-moderate risk of developing ESKD, with or without pulmonary haemorrhage (weak recommendation)

This recommendation applies to adult patients with AAV and with low or low-moderate risk of ESKD with or without pulmonary haemorrhage. Following GRADE guidance, a weak recommendation implies that the majority (50-90%) of patients would decline plasma exchange, but a minority (<50%) would, depending on individual shared decision making, choose to receive plasma exchange.

The panel made this recommendation on the basis that, for the majority of patients, moderate to high certainty evidence of a reduction in ESKD (0.1% to 2.1% reduction) in patients with low or low-moderate risk of ESKD does not counterbalance the increase in serious infections (2.7% to 4.9% increase) over a timeframe of 1 year.

Recommendation 2. We suggest plasma exchange plus immunosuppression rather than immunosuppression alone for patients with AAV and moderate-high or high risk of developing ESKD or requiring dialysis, with or without pulmonary haemorrhage (weak recommendation)

This recommendation applies to adult patients with AAV and with moderate-high or high risk of ESKD or requiring dialysis with or without pulmonary haemorrhage. A weak recommendation implies that most patients (50-90%) would choose plasma exchange; a minority (<50%) would, depending on individual shared decision making, decline plasma exchange.

The panel made this recommendation on the basis of moderate to high certainty evidence of an important reduction in ESKD (4.6% to 16.0% reduction) and an important increase in serious infections (8.5% to 13.5% increase) in patients with moderate-high to high risk of ESKD or requiring dialysis. The panel considered patients would generally place more value on avoiding ESKD and less value on avoiding risk of serious infections.

Recommendation 3. We suggest immunosuppression alone without plasma exchange in patients with AAV and pulmonary haemorrhage without kidney involvement (weak recommendation)

This recommendation applies to adult patients with AAV and pulmonary haemorrhage without kidney involvement, and does not apply to those with kidney involvement. For the latter, please refer to recommendations 1 and 2 in this guideline.

A weak recommendation for immunosuppression alone reflects the panel's view that the majority (50-90%) of patients with AAV and isolated pulmonary haemorrhage without kidney involvement would decline plasma exchange; a minority (<50%) of patients would, depending on individual shared decision making, choose plasma exchange.

The panel made this recommendation based on indirect evidence that plasma exchange may increase the risk of serious infections (6.8% increase) but uncertainty about the effect on death (1.5% reduction with very wide confidence interval) over a timeframe of 1 year.

Recommendation 4. We recommend reduced dose regimen of glucocorticoids rather than standard dose regimen of glucocorticoids during the first six months of therapy in patients with AAV (strong recommendation)

The panel recognised that the evidence that supports the reduced dose regimen of glucocorticoids is based on the systematic review of reduced dose versus standard dose of glucocorticoids in patients with severe AAV and patients with newly diagnosed AAV.[13]

The panel made this recommendation on a basis of moderate certainty evidence of an important reduction in serious infections (5.9% to 12.8% reduction) and no increase in death or ESKD (2.1% reduction for death and 0.4% increase for ESKD) in patients with severe AAV over a timeframe of 1 year, and similar findings in

patients with newly diagnosed AAV. The panel considered the strong recommendation mandated by the decreased harm and no decreased benefit. Standard dose regimen of glucocorticoids may be appropriate for patients who do not respond to a reduced dose regimen.

Practical issues

Tables 3 and 4 outline the key practical issues regarding the use of plasma exchange and reduced dose regimen of glucocorticoids in patients with AAV. The protocols for either plasma exchange or dose regimen of glucocorticoids might vary largely between medical institutions. Patients using plasma exchange need intravenous lines or central venous catheters that may cause discomfort or increase the risk of infection, clotting, or bleeding, and might need blood transfusions.

Cost and resources

In some jurisdictions the cost of plasma exchange might not be covered by medical insurance, and access might be limited.

Table 3 | Practical issues regarding use of plasma exchange in patients with antineutrophil cytoplasmic antibody-associated vasculitis

Practical issues	Plasma exchange + standard care	Standard care
Procedure and device	Heterogeneity in plasma exchange protocols	Null
Coordination of care	Need for an intravenous line with plasma exchange, which may cause discomfort, infection, or bleeding	Null
Coordination of care	Potential need for blood products with plasma exchange.	Null
Adverse effects, interactions, and antidote	Plasma exchange may affect the pharmacokinetics of some drugs	Null
Costs and access	Potential need for transfer to another centre to get plasma exchange Cost of plasma exchange is high and might not be covered by medical insurance	Null

Table 4 | Practical issues regarding use of reduced dose regimen of oral glucocorticoids (prednisone or prednisolone) in patients with antineutrophil cytoplasmic antibody-associated vasculitis

Practical issues	Reduced dose regimen	Standard dose regimen
Medication routine	• Initial dose in 1st week is same as that in standard dose regimen • In 2nd week, dose is reduced by ~50% • In 3rd to 6th weeks, dose is reduced by 5 mg in every 2 weeks • In 7th to 14th weeks, dose is reduced by 2.5-1 mg every 2 weeks until reaches 5 mg/day at 15th week • At 6 months, cumulative dose of oral glucocorticoids is <60% of that in standard dose regimen group	• Initial dose in first 2 weeks is: Patients <50 kg weight, 50 mg/day Patients 50-75 kg: 60 mg/day Patients >75 kg, 75 mg/day • From 3rd to 6th week, dose reduced by 10 mg every 2 weeks • From 7th to 22nd week, dose is reduced by 5-2.5 mg every 2-4 weeks until reaches 5 mg/day at 23rd week
Medication routine	Patients intolerant of oral glucocorticoids or for whom oral glucocorticoids are contraindicated could be given an equivalent daily intravenous dose	
Adverse effects, interactions, and antidote	Adverse events of glucocorticoids including impaired fasting glucose, loss of bone mineral density, fractures, weight gain, mood changes, etc	

Uncertainty

- The process of determining the threshold at which the recommendation changes from immunosuppression alone to adding plasma exchange proved challenging.
- The uncertainty in the estimates of risk of ESKD: although the linked prognostic study showed that serum creatinine as a single predictor can effectively predict the risk of ESKD in patients with AAV,[30] a prognostic model with multiple and more stable predictors is likely to improve prediction and thus risk stratification.
- The uncertainty in patients' values and preferences regarding the trade-off between benefit (reduction in ESKD) and harm (increase in serious infections). A broader patient survey would be helpful in ascertaining patients' values and preferences.
- The extent to which the safety and efficacy of the recommended regimen, which included intravenous glucocorticoids before beginning the reduced dose regimen, to regimens that do not include intravenous glucocorticoids is uncertain
- Very limited data proved available to estimate risk of death or serious infections in patients with AAV and pulmonary haemorrhage without kidney involvement.
- The benefits and harms of plasma exchange and reduced dose regimen of glucocorticoids in patients with both antineutrophil cytoplasmic and anti-glomerular basement membrane antibodies was not evaluated in this review, and these recommendations do not apply to them.
- Other than infections, serious adverse events associated with plasma exchange (such as allergic reactions, cardiovascular events) remain uncertain. As the rate of these serious adverse events is low, current RCTs are under-powered to detect differences.

- The dose regimens of glucocorticoids vary in clinical practice. The comparative efficacy and safety of regimens other than those tested remain uncertain.

Update to this article

Table 5 shows evidence that has emerged since the publication of this article. A group will assess new evidence as it becomes available and make a judgment as to whether it might alter recommendations.

Table 5 | New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article				

How patients were involved in the creation of this article

Four patient partners with ANCA-associated vasculitis with or without experience of plasma exchange and a caregiver for a patient who has end stage kidney disease were full panel members. These panel members identified important outcomes, participated in the teleconferences and email discussions on the evidence and recommendation. They also contributed to the identification of practical issues related to the decision of plasma exchange and glucocorticoids regimen and met all authorship criteria for the present article. We thank them for their time and contribution.

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Funding: This guideline was not funded.

Competing interests: All authors have completed the *BMJ* Rapid Recommendations interest disclosure form and a detailed, contextualised description of all disclosures is reported in appendix 4. As with all *BMJ* Rapid Recommendations, the executive team and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests were minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions.

Participation in the panel and authorship of this manuscript does not constitute organisational endorsement of the recommendations.

Transparency: L Zeng and A Mahr affirm that the manuscript is an honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned have been explained.

This *BMJ* Rapid Recommendations article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between the MAGIC group (www.magicevidence.org) and *The BMJ*. A summary is offered here, and the full version including decision aids is on the MAGICapp (www.magicapp.org), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation of recommendations to allow contextualisation of recommendations and to reduce duplication of work. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact *The BMJ* for permission to reuse content in this article.

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Appendices 1-5

Infographic