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Guidelines for the Management of ANCA-Associated Vasculitis with Renal Involvement

For use in:	Norfolk and Norwich University Hospitals
By:	Renal Unit Staff
For:	Patients with ANCA-associated vasculitis with renal involvement
Division responsible for document:	Medical
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Contents

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1.2	23/08/2021	Reviewed and amended , key people amended , references amended	A Chalisey and M Karim

This is a Controlled Document

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Definitions of Terms Used

ANCA	Anti-neutrophil cytoplasmic antibody
AAV	ANCA-associated vasculitis
AKI	Acute kidney injury
EGPA	Eosinophilic granulomatosis with polyangiitis
EULAR	European League Against Rheumatism
EUVAS	European Vasculitis Study Group
GPA	Granulomatosis with polyangiitis
HSP	Henoch-Schoenlein purpura
MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
PLEX	Plasma exchange
PR3	Proteinase 3
RPGN	Rapidly progressive glomerulonephritis

Objective

The objective of this document is to provide guidance for the **treatment of ANCA-associated vasculitis with renal involvement**. These guidelines may also be followed in other forms of crescentic nephritis due to vasculitis (e.g. Henoch-Schönlein Purpura, crescentic IgA nephropathy) although the evidence base in these situations is less secure.

Scope

These guidelines cover the management of primary ANCA-associated vasculitis. The guidelines may also be followed in other forms of crescentic glomerulonephritis due to vasculitis (e.g. HSP/IgA nephritis) although the evidence base is less secure.

Quick reference

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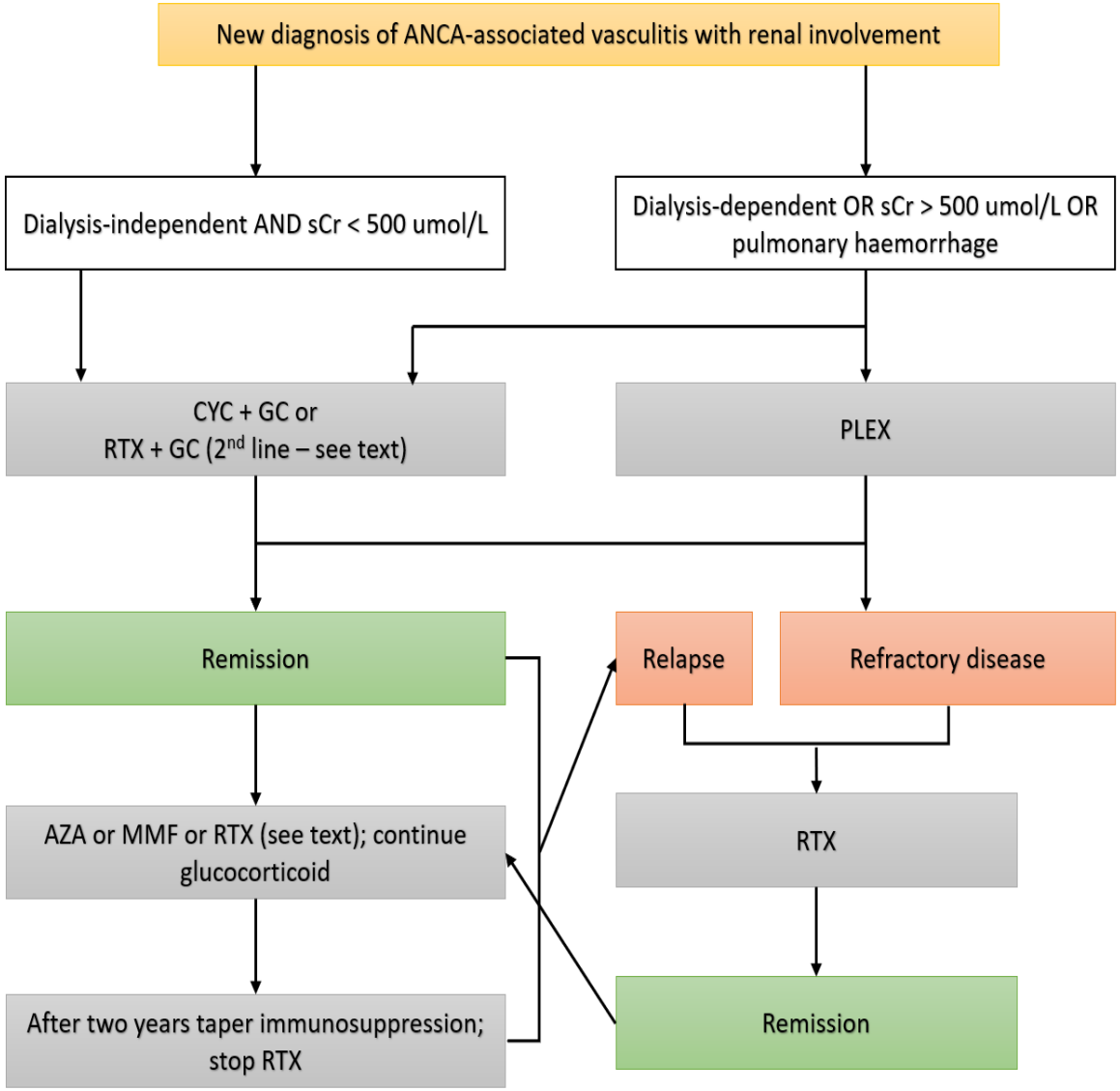

ANCA	Anti-neutrophil cytoplasmic antibody
CYC	Cyclophosphamide
GC	Glucocorticoid
RTX	Rituximab
PLEX	Plasma exchange
AZA	Azathioprine
MMF	Mycophenolate Mofetil
VZV	Varicella zoster virus
PPI	Proton pump inhibitor
H2R	H2 receptor

Other considerations

- Pre-treatment viral screening for Hepatitis B/C, and ideally HIV (especially if requiring dialysis/PLEX – see Trust Documentation on Blood Borne Viruses).
- Screen for VZV immunity – if no immunity and exposed during treatment then consider aciclovir or VZIg.
- Co-trimoxazole prophylaxis for *P. jirovecii* infections.
- Consider bone protection (bisphosphonate/vitamin D/Ca)
- Gastric protection (PPI/H2R antagonist).

Rationale

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) comprise a group of inflammatory conditions affecting the small blood vessels, with potentially organ or life-threatening consequences. Treatment involves potent immunosuppressive agents, and full remission is often achieved, but relapse is common and the treatment strategies may have significant side effects.

The nomenclature of the AAV has changed over the years, but they are now classified as granulomatosis with polyangiitis (GPA, previously Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, previously Churg-Strauss syndrome). All three conditions share a form of necrotising small-vessel, although GPA and EGPA may additionally have granulomatous lesions. Distinguishing features of the three conditions are:

- GPA occurs in association with necrotising granulomatous inflammation with a predilection for involvement of the respiratory tract.
- EGPA occurs in association with asthma, eosinophilia and necrotising granulomatous inflammation. Nasal polyposis is a common feature.
- MPA is a necrotising small vessel vasculitis that occurs in the absence of features of GPA or EGPA.

The ANCA seen in the AAVS are predominantly IgG antibodies directed against components of neutrophilic lysosomes or granules. Indirect immunofluorescence of neutrophils demonstrates a cytoplasmic (cANCA) or perinuclear (pANCA) pattern of staining; the former correlates with proteinase-3 reactivity (PR3), whilst the latter correlates with reactivity towards myeloperoxidase (MPO). PR3-ANCA is associated predominantly with GPA, whereas MPO-ANCA is seen mainly in patients with MPA or EGPA.

Patients with ANCA may be categorised according to different levels of severity to assist treatment decisions [1]. Patients may change their category during the course of the disease.

Table 1: EUVAS categorisation of ANCA-associated vasculitis

Category	Definition
Localised	Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms
Early systemic	Any, without organ- or life-threatening disease
Generalised	Renal or other organ threatening disease, sCr < 500 µmol/L
Severe	Renal or other vital organ failure, sCr > 500 µmol/L
Refractory	Progressive disease unresponsive to glucocorticoids or cyclophosphamide

Diagnosis of AAV with renal involvement

A positive renal biopsy is the gold standard for diagnosis of AAV with renal involvement. However, sometimes the clinical situation may be such that a renal biopsy is either not possible, would delay treatment, or is associated with significant risk that outweighs any benefit. In these situations it is accepted that the diagnosis may be made on clinical and serological grounds.

The indirect immunofluorescence test for cANCA and pANCA have low specificity for an AAV diagnosis. However, a positive auto-antigen specific ELISA for PR3 and MPO in combination with a clinical suspicion of glomerulonephritis (e.g. AKI, haematuria), has >95% association with a positive histology [2]. It is important to note, however, that a false-positive ANCA, usually MPO-ANCA, can occur in the setting of other inflammatory conditions that also result in an active urinary sediment. These include lupus nephritis, endocarditis, other chronic infections, malignancy, and certain drugs (e.g., propylthiouracil, penicillamine, hydralazine).

Therapy

Overview

Combination therapy with glucocorticoids and cyclophosphamide is currently standard therapy for remission induction [3]. Plasma exchange is used as an adjunct to drug therapy in life- or organ-threatening disease [4]. Based predominantly on two large studies [5,6], Rituximab has also been licensed for AAV and many centres are now using this as an alternative or an addition to standard therapy. The European Vasculitis Study Group (EUVAS) and the EULAR/ERA-EDTA have published consensus recommendations [3] based on varying levels of evidence to try and harmonise therapy and refine treatment strategies.

Assessment prior to therapy

- FBC, U&E, LFT, CRP, and urinalysis for blood & protein with results checked prior to ordering the first treatment.
- History and examination to identify any contra-indications to cyclophosphamide-based immunosuppression. These include significant intercurrent infection (chest, throat or urine) and adverse reaction to past cyclophosphamide treatments. Any reaction to the previous infusions should be discussed with Consultant.
- In some circumstances (see below), a rituximab based regimen should be considered as an alternative.
- Pregnancy should be ruled out in female patients of childbearing age.
- All patients should be assessed for risk of active tuberculosis. Further testing with Interferon Gamma Release Assays (IGRA) may be appropriate in those at highest risk of latent infection – those born in areas of where it is endemic and in the UK for < 5 years; those of African, Asian, South American or Eastern European decent; and those with a history of contact with smear positive TB.
- Baseline viral immunity: all patients should have screening of Hepatitis B and C serology and Varicella Zoster immunity and ideally HIV status. Those not immune

to Varicella (chicken pox) should be warned to avoid contact with infectious individuals, but in case of exposure to chicken pox, or shingles, they should know to contact their relevant hospital clinicians as soon as possible to consider administration of hyperimmune globulin (VZIg) or prophylactic aciclovir (under expert guidance).

Counselling and consent

Because of the potential short- and long-term toxicity of cyclophosphamide, counselling regarding side effects of cyclophosphamide treatment should be provided. This should be documented in the notes, as should a discussion of the risks and side effects of steroids. Written consent should be obtained before the first treatment.

Table 2: Minimum recommendation for counselling and consent of corticosteroids and cyclophosphamide

For corticosteroids	For cyclophosphamide
Weight gain Bone loss Diabetes Increased risk of infection	Hair loss Infertility & teratogenicity Consider sperm banking Avoid pregnancy Neoplasia: small risk of skin, bladder, cervical or haematological malignancy Marrow suppression, neutropenia & increased risk of infection

Remission induction therapy

Based on work from the early seventies, the standard remission induction regime remains a combination of cyclophosphamide and glucocorticoids [3,7]. However, Rituximab is now recognised as being as effective as cyclophosphamide for remission induction in previously untreated patients [5, 6]. NHS England will routinely fund the use of rituximab for the treatment of ANCA-associated vasculitis as an option for inducing remission in adults [8], only if:

- The disease has remained active or progressed, or has relapsed, despite a course of cyclophosphamide lasting 3-6 months; OR
- Cyclophosphamide is contraindicated (as defined in the summary of product characteristics) or not tolerated; OR
- The person has not completed their family and treatment with cyclophosphamide may materially affect their fertility; OR
- The person has had uroepithelial malignancy

The licensed rituximab dosing protocol is 375 mg/m^2/week for 4 weeks, however, 1 g repeated after 2 weeks is equally effective and acceptable.

Rituximab therapy has become standard remission re-induction therapy in cases of major disease relapse (see section on relapse, below). Where rituximab is used instead of cyclophosphamide, glucocorticoids are still used at standard doses but should also be used as pre-medication for rituximab.

Glucocorticoid therapy

High dose oral prednisolone is suitable in most situations, but the use of parenteral steroids may be considered if either rapid induction is needed or there is intolerance of or inability to take oral medication. If given orally, prednisolone is normally started at a dose of 1 mg/kg to a maximum dose of 60 mg. The current EULAR guidelines suggest weaning prednisolone to achieve a target of 7.5-10 mg after 3 months of treatment [3], although many centres follow variations of the protocol used in the MYCYC trial [9] which used a slower wean lasting 6 months, after which a maintenance dose of 5 mg was used. The more recent PEXIVAS study has suggested non-inferiority of a regiment using lower steroid doses [21].

Cyclophosphamide therapy

The use of cyclophosphamide in the treatment of GPA and MPA is well established [7]. The grade of evidence for use in EGPA is lower as no randomised controlled trials have been performed in this group.

Both oral and IV cyclophosphamide may be used. Due to concerns about cumulative exposure, pulsed intravenous regimens have been tested, the largest study being the CYCLOPS trial [10]. This concluded that pulsed cyclophosphamide was more likely to achieve remission and was associated with fewer side effects than oral cyclophosphamide. However, long-term follow-up of the cohort revealed no differences in overall survival, renal survival or long-term adverse events. However, pulsed regimens continue to be favoured due to the reduced dose of cyclophosphamide overall.

Oral cyclophosphamide is given daily, usually for 3 months, but can be for up to six months if no remission. The first three doses of pulsed cyclophosphamide are given fortnightly after which the interval is increased to three-weekly for 6 doses in total. This may be extended further if remission is not achieved at the end of the 6th cycle. The local dosing regimen is shown below:

Table 3: Cyclophosphamide dosing regimen (based on EUVAS vasculitis protocol)

	Oral cyclophosphamide (mg/kg)	IV cyclophosphamide (mg/kg)	
eGFR (mL/min/1.73m^2)		**> 30**	**< 30**
Age			
<60	2	15	12.5
60-75	1.5	12.5	10
>75	1	10	7.5
Notes and Monitoring	Maximum dose 200 mg FBC weekly for the 1st month, two-weekly for 2nd and 3rd months, and monthly thereafter. Stop therapy if: • WCC < 3 or neutrophils < 1.5 • Platelets < 150	Maximum dose 1.2 g FBC on day before or of pulse. • If WCC < 4, then postpone until > 4 and reduce dose by 25% Check FBC 10-14 days after a pulse; if the nadir is < 3 (even if on the day of the pulse it is > 4) then adjust dose as follows: • If WCC 1-2 reduce dose by 40% • If WCC 2-3 reduce dose by 20%	

Rituximab therapy

Rituximab in AAV has been tested in two RCTs (RAVE [6] and RITUXVAS [5]) which compared it to standard Cyclophosphamide-based therapy. In both trials, rituximab was non-inferior to cyclophosphamide; in the RAVE trial, Rituximab appeared to be more effective for relapsing disease.

Two IV Rituximab protocols exist - 375 mg/m2/week for 4 weeks and 1000 mg repeated after 2 weeks. These appear equally effective for induction of remission, but have not been formally compared and both are recognised by NHS England although only the 4 week regimen is licensed.

Cyclophosphamide is not usually given concurrently with rituximab but may be considered in severe, life or organ-threatening presentations such as rapidly progressive glomerulonephritis in order to achieve rapid disease control.

As with cyclophosphamide, rituximab runs the risk of opportunistic infections and reactivation of latent infections - as such the viral screens suggested for cyclophosphamide should also be performed prior to administration of rituximab; in particular reactivation of latent HBV is a concern and specialist input should be sought if serology is suggestive of this. Reports of progressive multifocal leukoencephalopathy (PML) due to reactivation of JC virus have also been described in patients given

Rituximab, but whether this is due to Rituximab or the underlying auto-immune disease is unclear. Other adverse events to consider include:

- Late-onset neutropenia (>4 weeks after Rituximab)
- Sustained hypogammaglobulinaemia – may require treatment with IVIg
- Pulmonary parenchymal toxicity manifesting as interstitial pneumonitis - frequency is undetermined and most cases resolve with discontinuation of Rituximab
- Its risk in pregnancy is undetermined

Plasma exchange

Plasma exchange (PLEX) should be used in patients with AAV who develop an RPGN that renders them dialysis-dependent, results in a serum creatinine >500 umol/L or who develop severe diffuse alveolar haemorrhage [4,11]. The MEPEX trial, which showed PLEX reduced ESRD and death at 3 months [4] but long-term follow-up revealed no statistically significant benefit [12]. The PEXIVAS trial did not show a benefit from PLEX with regard to incidence of death or end stage renal disease [21] but this remains controversial.

Plasma exchange should also be considered in patients with AAV who are also anti-glomerular basement membrane positive, particularly if there is linear staining of IgG on the glomerular basement membrane [13,14].

Trust guidelines for Plasma Exchange in patients with renal conditions may be found at Trustdocs ID13347.

Remission maintenance therapy

After remission induction, the first-line choice for maintenance therapy is azathioprine at a target dose of 2 mg/kg/day (max 200 mg OD, rounded to nearest 25 mg). This may be reduced to 1.5 mg/kg/day after 12 months or in patients >60 years. In patients >75 years, 1 mg/kg may be considered.

Measurement of patient's thiopurine S-methyltransferase (TPMT) status prior to initiating therapy is at the prescriber's discretion, but monitoring of myelotoxicity and hepatotoxicity should be according to national and local guidelines.

Table 4: safety monitoring for Azathioprine

Check FBC and ALT or AST (for hepatotoxicity):

- Every two weeks for one month.
- Every two months for the first year.
- Then three monthly.

Stop if WBC < 4 x 10^9/L, OR neutrophils < 2 x 10^9/L, OR platelets < 150 x 10^9/L:

- Restart when counts above these levels with AZA dose reduced by at least 25mg
- Monitor weekly for one month.

For falling WBC (fall of > 2 x 10^9/L over previous count), re-check in one week and reduce dose of AZA by 25mg.

Long-term therapy with cyclophosphamide has been used to maintain remission, but the toxicity associated with this makes it an unattractive option. Azathioprine at a dose of 2 mg/kg has been shown to be as effective at 18 months as cyclophosphamide in preventing relapse [15,16]. Methotrexate should not be used in those with organ-threatening or renal disease

Mycophenolate Mofetil (MMF) may be used for remission maintenance if there is intolerance to azathioprine, but the IMPROVE [17] trial showed a greater rate of relapse in patients treated with MMF, and so it should not be used as first-line for remission maintenance.

Remission maintenance with rituximab is also an option. The MAINRITSAN trial showed that low dose rituximab was more effective than tapering dose azathioprine in maintaining systemic and renal remission at 28 months [18]. NHS England [8] will commission the use of rituximab as maintenance therapy if one of the following three clinical criteria and all three centre criteria detailed below are met. If used, regional practice is to retreat with rituximab 1g once every six months for 2 years in total.

Table 5*: Criteria for remission maintenance of ANCA-associated vasculitis with Rituximab*

Clinical criteria (one must be met)	**Centre criteria (all three must be met)**
The patient is enrolled in a randomised control trial that includes B cell suppression as maintenance therapy (e.g. RITAZAREM)	The decision regarding rituximab maintenance has been made at, or in conjunction with, a specialised centre
Relapse requiring re-induction has occurred following a previous rituximab-induced remission	The patient has been provided with the opportunity to consider enrolment in a suitable clinical trial
Rituximab has been required to induce remission in cyclophosphamide-refractory disease and future relapse would have a high risk of organ damage	The patient is registered on the UKIVAS database, to follow-up outcome of treatment

Duration of maintenance therapy and risk of relapse

There have been no published randomised control trials comparing duration of maintenance therapy regimens, but we advocate remission maintenance therapy should continue for at least 24 months *following* induction of sustained remission. Reduction of glucocorticoids should be made prior to tapering of immunosuppressive agents. Ideally, there should be a 6-month interval between withdrawing glucocorticoids and tapering other immunosuppressants.

Treatment withdrawal may be associated with relapse, and this should be carefully monitored for. Higher relapse rates are seen in patients with PR3-ANCA positivity or cardiovascular/lung involvement [19, 20]. In these patients, the supervising consultant may wish to consider a longer duration of maintenance therapy.

Management of relapsed disease

Factors associated with increased risk of relapse include:

- A diagnosis of GPA, and/or PR3-ANCA serology at presentation
- ANCA +ve after remission induction, or a subsequent increase in ANCA titre
- ENT involvement, or better renal function (creatinine < 200 µmol/L)
- Lower total cyclophosphamide dose, or recent withdrawal of immunosuppression or steroids

Relapses may be divided into minor or major relapses, and different trials have different definitions. Broadly speaking, a major relapse is defined as the reoccurrence or new onset of a potentially organ- or life-threatening disease (one or more major BVAS items), and a minor relapse as the reoccurrence or new onset of disease which is neither life nor organ-threatening (at least three BVAS items). Typical treatment of relapses is based on the management used in the EUVAS trials:

Table 6: Management of minor and major relapses of ANCA-associated vasculitis

Minor relapse management	Major relapse management
increase in prednisolone dose to 30mg then gradual taper with optimisation of immunosuppressive therapy	Rituximab is now the standard of care for remission re-induction for major relapses (based on the RAVE trial) with increase or reintroduction of prednisolone to doses of at least 30 mg/day
for relapses on azathioprine, consider switch to MMF	IV methylprednisolone or plasma exchange may be considered as discussed in the induction section

Once remission is re-established, options include a return to optimised immunosuppressive therapy or maintenance with rituximab

Prophylaxis

- In all patients treated with cyclophosphamide or rituximab, prophylaxis should be given against *Pneumocystis jirovecii.*
    - First-line prophylaxis is with Co-trimoxazole 960 mg three times a week.
    - Where Co-trimoxazole is contraindicated, consideration should be given to either 300 mg nebulized pentamidine monthly, or 50-100 mg dapsone daily.
    - Prophylaxis should continue for at least two weeks after discontinuation of cyclophosphamide.
    - Prophylaxis should be prolonged after rituximab therapy, but no clear external guidance exists on the exact duration. We advocate treatment for 6 months, or until B cell recovery whichever is longer.

  - However, if the patient is to be commenced on azathioprine-based maintenance therapy, there is an increased risk of haematotoxicity, and this requires consideration/monitoring.

- Prophylactic anti-fungal agents such as nystatin should be considered in those receiving remission induction therapy.
- If past history of TB, or previous household contact with a TB case, seek expert advice from a specialist with an interest in the treatment of TB.
- Fracture risk should be assessed using the FRAX tool. All patients receiving standard therapy should be considered for bisphosphonate therapy with calcium and vitamin D supplementation, although bisphosphonate use in renal failure is not established. We recommend the following:
  - Calculated MDRD GFR > 35 ml/min: alendronate 70 mg or risedronate 35 mg once weekly.
  - Calculated MDRD GFR < 35 mL/min: discuss with consultant. Options include bisphosphonate, alfacalcidol / calcitriol, or calcium and vitamin D supplementation.
- All patients on long-term steroids should receive gastric protection with a H2-receptor blocker or proton pump inhibitor.
- For individuals due to commence immunosuppressive treatments, inactivated vaccines should ideally be administered at least two weeks before commencing the immunosuppression. This is likely to be unfeasible in vasculitis and therefore vaccination may be carried out at any time and re-immunisation considered after treatment is finished and recovery has occurred. Recommended inactivated vaccines include:
  - 23 valent PPV (polysaccharide pneumococcal vaccine).
  - Hib / Men C vaccine (which should be followed at least one month later by the conjugate Men ACWY vaccine).
  - Annual influenza vaccinations.
- Live vaccines should be postponed until at least 3 months after stopping cyclophosphamide therapy.

Screening during follow-up

- Urothelial screening:
  - Use reagent strip testing (not urine microscopy) to screen periodically for persistent non-visible haematuria.
  - A test result of blood +1 or more, in someone who has previously been negative, warrants further evaluation. Two out of 3 positive dipstick tests (blood +1, or more) count as persistent non-visible haematuria, and such patients should be referred to urology for investigation of urothelial pathology.
  - If a patient has persistent haematuria but has already been investigated, they may be reassured unless the clinical situation suggests otherwise.

- Cervical screening recommendations are based on national guidance:
    - If a woman's cervical screening history is incomplete at the time she commences a course of cytotoxic drugs, then a screening test (cervical cytology) should be performed with immediate referral to colposcopy for any screening abnormality.
    - All women aged 25 to 64 years with renal failure requiring dialysis or any other disease with a high chance of needing organ transplantation must have cervical cytology at or shortly after diagnosis. Women with an abnormal result should be referred to colposcopy.
    - All women who receive immunosuppression should be considered for HPV vaccination.
    - All women between 25-64 should be on the national screening programme.

Relevant ongoing trials

The following trial is ongoing and the above guidelines may require adjustment depending on their outcomes:

- RITAZAREM trail - RCT in relapsing patients. After remission re-induction by Rituximab (by trial protocol) patients are randomised to either maintenance AZA or fixed interval rituximab.

Clinical audit standards

This document is a guideline so there are no formal standards to audit against

Summary of development and consultation process undertaken before registration and dissemination

The authors listed above drafted this document on behalf of the Renal Consultants who have agreed the final content. During its development it has been circulated for comment to: Drs Mark Andrews, Calum Ross, Matt Todd, Ravi Varma (Consultant Nephrologists) and Nicholas Weavers (Renal Pharmacist).

The revised version was modified by Mahzuz Karim and endorsed by Drs Mark Andrews, Ravi Varma, and Anna Friedla (Consultant Nephrologists).

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