Treatment of vasculitis: clinical guideline

Salford Royal NHS
NHS Foundation Trust
University Teaching Trust
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Who should read this document?

This protocol is applicable to all medical, nursing and pharmacy staff involved in the prescribing, dispensing and administration of immunosuppressant medication or plasma exchange therapy for renal vasculitis. The lead Consultant for renal vasculitis is Dr Edmond O'Riordan.

Key Messages

All patients under the care of the Renal Directorate who require therapy for renal vasculitis will ideally be treated in accordance with these protocols.

Any significant deviation from the standard protocol should be discussed with the vasculitis MDT and reasons documented in the patients notes

Background & Scope

This protocol and associated guidelines are designed to provide a safe effective framework for the prescription of immune therapy for pateints with vasculitis and anti-GBM disease while facilitating the physician to choose individualized regimes. They aim to maintain a high standard of care and enable rigorous audit of treatment in our centre.

This is the fourth edition. It has been extensively re-written to encompass developments in treatment based on recent guidelines and clinical trials. In particular, the K-DIGO glomerulonephritis guidelines and recent research combined to prompt this review.

Lupus nephritis management is outwith this guideline – please refer to the specific lupus nephritis document.

What is new in this version?

Main alteration is the division of lupus and vasculitis protocol into separate entities

Policy/ Guideline/ Protocol

PLEASE READ THIS COMPULSORY SECTION BELOW BEFORE TURNING TO SPECIFIC PROTOCOL

Informed Written Consent

INFORMED WRITTEN CONSENT should be obtained before prescribing cytotoxic therapy, in particular cyclophosphamide and rituximab due to the frequency and severity of the potential side effects.

Cytotoxic therapy is advised for treating patients with vasculitis as the benefits of therapy usually outweigh the risks.

Use the referral form (Appendix 3) to request outpatient treatment with cytotoxic/biologics.

NB Responsibility for patient care, especially timely provision of post discharge treatment remains with the referring team until review and/or acceptance of care by another specialist.

Vasculitis survival statistics
Without treatment, ANCA vasculitis with glomerulonephritis is associated with very poor outcomes. Early data showed that average time to death from AAV diagnosis was 9 months [1].

There is high quality evidence that treatment with corticosteroids and cyclophosphamide has dramatically improved the short and long term outcomes of ANCA associated vasculitis with systemic disease. However, despite this 5 year mortality still remains high at 25%[2].

Severe pulmonary haemorrhage affects about 10% of patients with ANCA vasculitis and GN and is associated with an increased risk of death.

Main adverse effects of Immunosuppressive treatment

Infections
Infection is the leading cause of death in patients with AAV in the first year following diagnosis.

Prophylaxis for specific common infections is advised. The most common infective complication is lower respiratory tract infections [LRTIs] but the risk of opportunistic infections such as Herpes Zoster, pneumocystis carinii pneumonia (PCP) and CMV are additionally increased.

Tumour Risk
The majority of cancer data in the vasculitis population arises from historical studies where cumulative cyclophosphamide doses were much higher.

However, the most recent data in this population suggests that this risk has significantly diminished with more recent standard incident rates of SIRs of 3.6- 7.2 reported for bladder cancer and SIR of only 1.1 for lymphoma [3].

There is in addition a significant increase in non-melanomatous skin cancer which the patient should be counselled about with regards to appropriate sun protection and skin monitoring (SIR 2-8-10.4)[3].

It is worth noting that the second NHS England publication removed the Cyclophosphamide threshold of 25g (for consideration of Rituximab) acknowledging that “There is therefore clinical and cost-effective justification for using rituximab at first relapse, before a threshold of 25g cyclophosphamide is reached.” [4]

Other assosciated risks can include:

- Nausea
- Vomiting
- Haemorrhagic cystitis (cyclophosphamide)
- Hair thining / Loss (transient)
- Loss of Fertility (Males and Females)
- Specific organ damage, most commonly lung or liver damage, although both rare, these may be life threatening if occur.
- Teratogenecity
- Infusion related reactions
- Progessive multifocal leucoencephalopathy (PML) (very rare but invariably fatal)
- Weight gain
- Osteoporosis
- Increased risk of diabetes

Despite the risks, cytotoxic therapy is advised for treating patients with vasculitis where the benefits of therapy outweigh the risks.

Patient must be fully informed and the following noted on the consent form:

For cyclophosphamide

1. Risk of infection (possibly life threatening)
2. Risk of loss of fertility (males and females)
3. Hair loss(rare)/thinning (common)
4. Haemorrhagic cystitis (rare (<5%) with iv common with oral)
5. Increased risk of bladder cancer (approx 1% at 10 years, increased risk of lymphoma and non-melanomatous skin cancer
6. Teratogenicity (males and females of child bearing age only).

For Rituximab

1. Risk of infection (possibly life threatening)
2. Significant reactions during infusions
3. Teratogenicity (females of child bearing age only).
4. Risk of Progressive Multifocal Leucoencephalopathy. This risk is impossible to quantify accurately with current data, however the risk probably lies in the range of 1 per several thousand to 1 per several tens of thousands patients treated.

Regimens

Regimen/ schedule selection

Clinician and patient choice should determine the regimen prescribed.

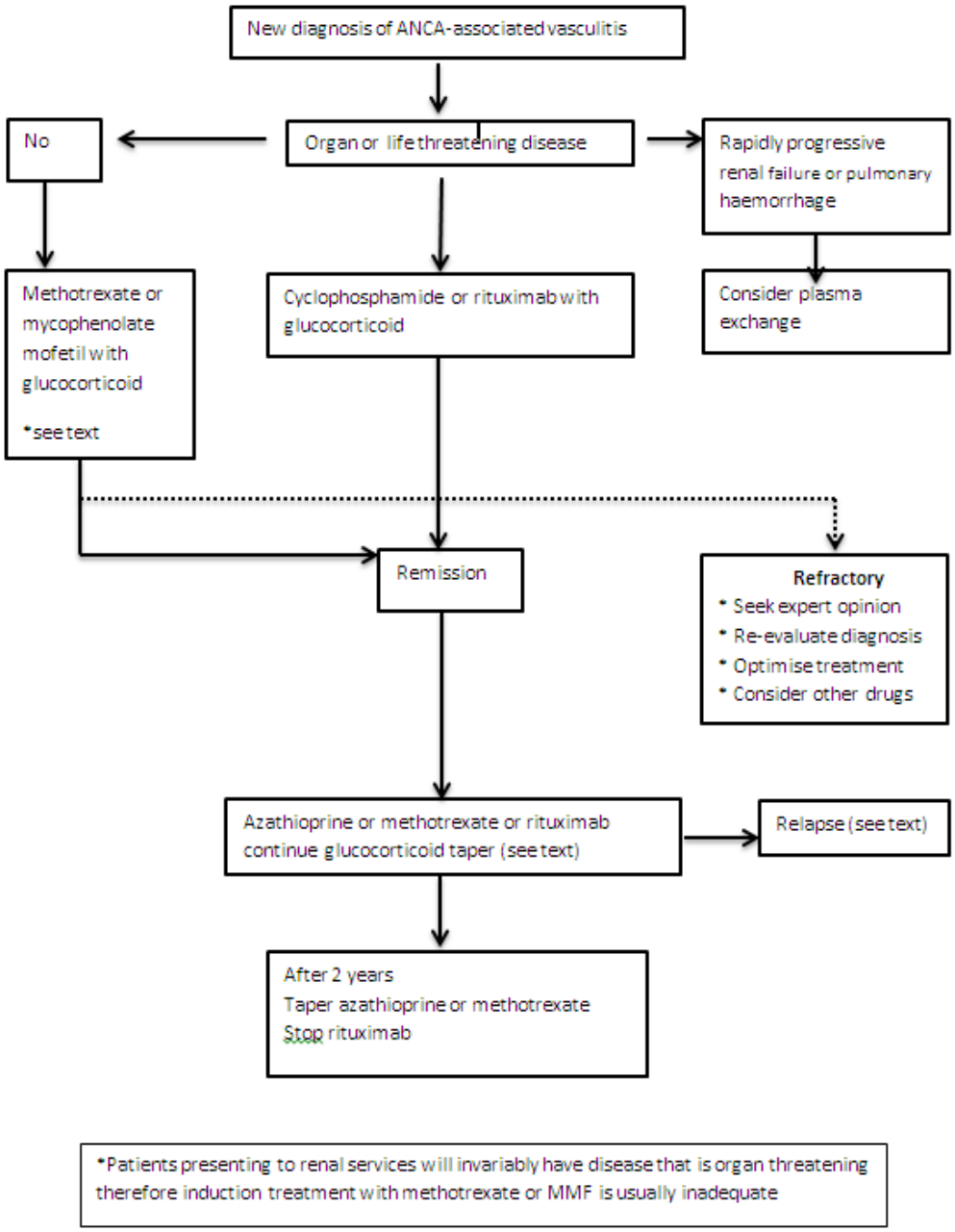
Patient Information

Complementary Trust-approved patient information leaflets are available for the treatment modalities described in this protocol. They can be downloaded from the Trust intranet: http://intranet.srht.nhs.uk/policies-resources/leaflets/ren/

Regimen adjustment

Minor changes have been made to the treatment schedules as originally described in clinical trials so there is relative homogeneity across the service. This should still facilitate clinician choice by providing a framework for different treatment schedules.

Standard therapy for vasculitis:



*Patients presenting to renal services will invariably have disease that is organ threatening therefore induction treatment with methotrexate or MMF is usually inadequate

A. <u>Vasculitis with rapidly progressive renal failure and/or serum creatinine >500µmol/L, or life- threatening disease (e.g. pulmonary haemorrhage)</u>

- Cyclophosphamide IV –CYCLOPS protocol
- Steroid therapy – IV followed by oral
- Plasma exchange

B. <u>Vasculitis where renal failure is severe eg with fibrosis on the biopsy suggesting little hope for renal recovery. If there is NO life- or organ threatening extra renal disease or in patients with milder disease</u>

- Monthly pulsed IV cyclophosphamide plus steroid.
- Short course of 3-6months therapy.

C. <u>Treatment resistant OR relapsing disease despite adequate standard therapy or in the context of approved clinical trials</u>

- Rituximab plus steroid
- Rituximab plus cyclophosphamide
- Plasma exchange
- Oral prednisolone and oral cyclophosphamide .
- IVIG in line with IVIG demand management guidelines from Department of Health

General considerations when prescribing cyclophosphamide for all regimens:

It is essential that the following information is recorded in patient notes prior to commencing therapy.

Regimen – with explanation as to choice and planned duration

Dose – with calculation

Patients starting weight

Patient's initial renal function and biopsy results

Organ involvement (consider BVAS)

<u>Important additional considerations when prescribing cylophosphamide</u>

1. Reductions for renal function and age are required – see individual regimens for details in the following sections.

2. Round cyclophosphamide i.v. doses should be dose banded to :

3. Multiples of 1000mg, 900mg, 750mg, 500mg or 200mg. Out of hours use dose bands – 500mg, 750mg, and 1000mg (rounding down). Round oral cyclophosphamide doses to the nearest 50mg over 3 days.

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4. Remember that cyclophosphamide is removed very efficiently by dialysis. All cyclophosphamide doses should be administered after dialysis and if possible further dialysis treatments withheld for 36-48 hours

5. Use **ideal** body weight to calculate doses. http://www.halls.md/body-surface-area/bsa.htm Recommended maximum cyclophosphamide pulse for vasculitis patients with impaired renal function (eGFR<60mls/min) is 1200mg.

6. IV cyclophosphamide is diluted in 0.9% sodium chloride and administered via a syringe. The dose should be given over 30 minutes through a large venflon or central line.

7. Mesna should be given with IV cyclophosphamide. The first dose of mesna is 20% of the cyclophosphamide dose given at the same time as the cyclophosphamide dose. This is followed by oral mesna, 40% of the cyclophosphamide dose 2 hours and 6 hours after the cyclophosphamide infusion. Total dose of mesna equivalent to 100% of the cyclophosphamide dose. If unable to take oral, give all IV mesna 20% of the cyclophosphamide dose, given with the cyclophosphamide and at 4 hours and 8 hours after cyclophosphamide. Total dose of i.v. mesna equivalent to 60% of the cyclophosphamide dose.

8. Prevention of emesis: Patients should be prescribed oral ondansetron 8mg twice daily for up to 3 days starting on the morning before the cyclophosphamide infusion.

9. Check Full blood count (FBC) on day of pulse or previous 72 hours. Only give dose if WBC >4 x 10^9/l

10. If white blood cell count (WBC) prior to pulse < 4 x 10^9/L, then postpone pulse until WBC > 4 x 10^9/L. Reduce dose of pulse by 25% and give reduced dose on subsequent cycles unless recovery of renal function.

11. With any further episodes of leucopenia, make equivalent dose reduction of 25%.

12. Check FBC between days 7 and day 10. If the leucocyte nadir (i.e. the lowest leucocyte count between two cyclophosphamide pulses) is < 3.0 x 10^9/L, even if the WBC prior to the next pulse is > 4 x 10^9/L, then reduce the dose of the next pulse by:
    - WBC nadir 1 - 2 x 10^9/L: Reduce CYC dose of next pulse to 50 % of previous dose.

- WBC nadir 2 – 4.0 x 10^9/L: Reduce CYC dose of next pulse to 75 % of previous dose.
- WBC nadir < 1 x 10^9/L: Seek haematology advice.

13. Monitor liver function tests (LFTs) monthly . Reduce dose by 50% if

Pulsed CYC dose reductions for renal function and age		
age (years)	**creatinine (umol/L)** **<300 (eGFR ≥20mls/min)**	**300+ (eGFR <20ml/min)**
< 60	15 mg/kg/pulse	12.5 mg/kg/pulse
> 60 and < 70	12.5 mg/kg/pulse	10 mg/kg/pulse
70 and over	10 mg/kg/pulse	7.5 mg/kg/pulse

bilirubin greater than 17 µmol/l (1 mg/100 ml); or serum transaminases or
alkaline phosphatase more than 2-3 times the upper limit of normal.

A: CYCLOPS regimen

Pulse Cyclophosphamide for ANCA-associated Systemic Vasculitis

Induction/consolidation regimen with pulsed Cyclophosphamide

Time (wk)	**Pulse no.**	**Body mass (Kg)**	**Route**	Dosage
0	1		intravenous (I.V.)	15 mg/kg##
2	2		I.V.	15 mg/kg##
4	3		I.V.	15 mg/kg##
7	4		Iv or oral	15mg/kg
10	5			15mg/kg
13	6			15mg/kg
16	7			15mg/kg
19	8			15mg/kg
22	9			15mg/kg
25	10			15mg/kg

Note: A prescription will be required for each pulse and must be signed by a SpR, Consultant or approved Non-medical prescriber within their competence.

TPMT (thiopurine methyl transferase) should be checked on commencement of cyclophosphamide to ensure results are available prior to introduction of azathioprine maintenance therapy. Exercise caution when interpreting results if recent blood transfusion.

The first 3 pulses are given at intervals of 2 weeks and must be given i.v. Subsequent pulses are usually given i.v., as a single dose on each pulse. If it is decided to give the subsequent pulses orally, the dose of cyclophosphamide should be divided over 3 days giving no more than 5 mg/kg each day

Consider conversion to azathioprine after remission achieved. (Initially 2mg/kg). Start at least 2 weeks after last cyclophosphamide dose after checking TPMT level.

B: NIH Monthly pulse cyclophosphamide for vasculitis

Two of the larger trials of cyclophosphamide used doses based on body surface area (BSA). Haubitz et al. recommended 0.75g/m^2 and the schedule is outlined below[6]. Guillevin used 0.7g/m^2 but patients received almost 3 times as much prednisolone with similar overall results[7].

Calculate dose according to body surface area
The following link will take you to Hall's calculator for BSA: http://www.halls.md/body-surface-area/bsa.htm (also contains equations for calculating lean body weight).

Dose adjustment for reduced renal function is as follows:
If GFR < 30ml/min then recommended dose is 0.5g/m2

Dialysis
Remember that cyclophosphamide is removed very efficiently by dialysis but accumulates in patients with a reduction of renal function. All cyclophosphamide doses should be administered after dialysis and if possible further dialysis treatments withheld for 36-48 hours.

********Recommended maximum single dose of cyclophosphamide for vasculitis patients with eGFR<60mls/min is 1200mg*******

Time (wk)	Pulse no.	BSA (m^2)	Route	Dosage (delete as appropriate)	
				eGFR >30	**eGFR ≤30**
0	1		intravenous (I.V.)	0.75g/m^2	0.5g/m^2
4	2		I.V.	0.75g/m^2	0.5g/m^2
8	3		I.V.	0.75g/m^2	0.5g/m^2
12	4		I.V.	0.75g/m^2	0.5g/m^2
16	5		I.V.	0.75g/m^2	0.5g/m^2
20	6		I.V.	0.75g/m^2	0.5g/m^2

Note: A prescription will be required for each pulse and must be signed by a StR or Consultant or approved non-medical prescriber within their competence.

In addition to general cyclophosphamide guide above:

- Pulse of cyclophosphamide is given every 28 days by IV infusion
- Check nadir of WCC by FBC between day 7 and day 14
- If converting to Azathioprine or mycophenolate wait for at least **2 weeks** after finishing the last dose of cyclophosphamide.

Gastric protection, osteoporosis prevention and Infection prophylaxis should be considered as above in general considerations section(see above).

Steroid Regimen

Where possible a steroid minimization regime is advised and is included with the protocol.

For poorly responding disease or relapse during induction the higher dose steroid regimens used in the trials are included in the appendix and may be considered.

Methylprednisolone for either cyclops or monthly NIH regimen

Pulsed methylprednisolone x 3 daily doses (dose reductions for weight and age)		
age (years)	**weight**	
	Less than 70kg	**70kg and above**
Less than 70	500mg	750mg
70 and over	500mg	500mg

Prednisolone regimen

Time (wk)	**Prednisolone dose (mg/kg/day)**
0 Day 4 following methylprednisolone	1
1	0.75
2	0.5
3	0.4
6	0.33
8	0.25
Aim for a maximum dose at the end of month 3	12.5 (BSR guidelines suggest 15mg at 3/12)
Aim for a maximum dose at the end of month 5	10

1. The usual maximum dose in first week is 80mg/day. This may be increased for patients >100Kg
2. Round initial prednisolone doses to the nearest 2.5mg
3. Single daily dose should be taken in the morning
4. Minimum dose in first three months is 10mg/day.

Rituximab

Rituximab is licensed for the treatment of ANCA positive vasculitis and treatment is commissioned by NHS England
https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/a13-ritux-anca-vascul.pdf

NHS England will routinely commission the use of rituximab for the treatment of ANCA-associated vasculitis as an option for inducing remission in adults, 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.

Dosing regimens are either the licensed dose of four infusions at weekly intervals of 375mg/m^2 or at two infusions of 1g, given two weeks apart

NHS England will commission the use of rituximab as maintenance therapy only when one of the following three clinical criteria, and all three additional centre criteria, is met.

1. The person is enrolled in a randomised trial that includes B cell suppression as maintenance therapy (e.g. RITAZAREM); OR.
2. Relapse requiring re-induction therapy has occurred after a previous rituximab induced remission; OR
3. Rituximab has been required to induce remission in Cyclophosphamide- refractory disease and future relapse would have a high risk of organ damage.

In addition

- The decision regarding rituximab maintenance has been made at, or in conjunction with, a specialised centre **AND**
- The person has been provided with the opportunity to be considered for any suitable clinical trials **AND**
- The person is registered on the UKIVAS database, to enable identification of use and outcome of treatment.

Maintenance therapy will be stopped after 2 years, or earlier if either treatment intolerance, a contraindication, or a major relapse occurs.

People receiving rituximab should be recruited to the UKIVAS study and data collected on a central platform. The specified outcomes will include BVAS

(disease activity) and VDI (disease damage), with assessment undertaken by clinicians who have certification of proficiency in using these outcome tools.

These will be measured at baseline, 6, and 12 months and annually thereafter (with the schedule modified if maintenance therapy is given so that assessment can be done at 6 and 12 months after each subsequent dose until a decision is made to discontinue rituximab therapy).

Prior to initiation of rituximab all patients must have the following screening:

- Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with Rituximab (at minimum this should include HBsAg-status and HBcAb-status)
- T and B lymphocytes and immunoglobulins should be checked.

There are two protocols that have been adopted locally:

Protocol A

- Rituximab 375mg/m2 body surface area, administered as an IV infusion once weekly for four weeks.

Protocol B

- Rituximab 1g on day 1 and day 14 administered as an IV infusion.
- Followed by Rituximab 1g every 6 months for two years regardless of clinical or serological quiesence or B cell count, and then stop.

Premedication

Patients will receive premedication with 100mg IV bolus over 15 minutes of methylprednisolone, 10mg IV bolus chlorphenamine or 8mg oral chlorphenamine and 1g oral paracetamol immediately before each rituximab infusion.
Patients with severe disease may require 1000mg IV methylprednisolone prior to the first rituximab infusion.

- Rituximab is removed by plasma exchange, therefore the timing of these two treatments needs to be carefully considered if used concomitantly.
- Rituximab is not removed by haemodialysis or haemofiltration.
- Gastric protection, osteoporosis prevention and infection prophylaxis should be considered as per the generl consideration section above'

Administration

Rituximab infusions are prepared in the Pharmacy Aseptic Unit. The dose of rituximab to be administered is diluted in 500ml of 0.9% sodium chloride.

The initial rate of the first infusion is 50 mg/hr. After the first 30 minutes if there has been no allergic or infusion related reaction the rate can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

Subsequent doses of rituximab, where the initial dose was tolerated, can be infused at an initial rate of 100 mg/hr and increased by 50mg/hr increments at 30 minutes intervals, to a maximum of 400 mg/hr.

First infusion

time	rate	cumulative dose given
0-30 mins	50mg/hour	25
30-60	100mg/hour	75
60-90	150mg/hour	150
90-120	200mg/hour	250
120-150	250mg/hour	375
150-180	300mg/hour	525
180-210	350mg/hour	700
210-240	400mg/hour	900
240-255	400mg/hour	1000

total time for first 1000mg = 4.25hrs

Second infusion

0-30 mins	100mg/hour	50
30-60	150mg/hour	125
60-90	200mg/hour	225
90-120	250mg/hour	350
120-150	300mg/hour	500
150-180	350mg/hour	675
180-210	400mg/hour	875
210-230	400mg/hour	1000

total time for 1000mg - just under 4 hours

Rituximab is administered peripherally via a dedicated venflon (a second venflon must be sited for the other IV medications).

Monitoring

A full blood count, and biochemistry profile (including liver function tests) should be performed for all patients before each course of rituximab and regularly thereafter (initially monthly). Immunoglobulins should be checked before commencing rituximab, one month after completing the course and then every three months thereafter.
During the infusion patients should have their observations recorded every 15 minutes for the first hour and then, if stable, hourly until the infusion stops.
Infection should be excluded before giving rituximab, and patients reporting signs and symptoms of infection following rituximab therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of rituximab patients should be re-evaluated for any potential risk for infections.

Precautions and side effects

Patients treated with rituximab must be given the patient alert card with each infusion

Treatment with rituximab is generally well tolerated.However there is a risk of infusion reactions due to cytokine or other chemical mediator release.

- Mild infusion reactions such as fever, chills and rigors are relatively common and usually prevented by premedication with hydrocortisone, paracetamol and chlorphenamine.
- Moderate infusion reactions are usually reversible with a reduction in rate or interruption of infusion and administration of chlorphenamine, hydrocortisone and occasionally oxygen, IV 0.9%Sodium chloride or salbutamol nebulised. In most cases the rituximab infusion can be resumed at a 50% reduction in rate when symptoms have completely resolved.
- More severe hypersensitivity reactions are rare but have been reported and should be treated with intramuscular adrenaline and intravenous chlorphenamine and hydrocortisone as per Trust anaphylaxis protocol.
- As hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications for 12 hours prior to giving rituximab.
- Repeated administration of rituximab may lead to hypogammaglobulinaemia.
- Vaccination should be completed at least four weeks prior to initiation of rituximab. Live vaccines are not recommended in patients while B cell depleted.
- Patients with a history of hepatitis B infection should be carefully monitored for signs of active hepatitis B infection when rituximab is used in association with cytotoxic chemotherapy.
- Women of childbearing potential should use effective contraceptive methods during treatment and up to 12 months following rituximab therapy.
- There have been reports of fatal progressive multifocal leukoencephalopathy (PML) in patients treated with rituximab. Patients should be counselled to seek urgent medical advice if they experience any new neurological symptoms or signs, including major changes in vision; unusual eye movements; loss of balance or coordination disorientation or confusion, as these could be warning signs of PML.

Protocol A Rituxvas dosing schedule

Induction/consolidation regimen for rituximab

Time (weeks)	Rituximab pulse number	IV rituximab dose	Cyclophosphamide pulse number
0	1	375mg/m^2	1
1	2	375mg/m^2	
2	3	375mg/m^2	2
3	4	375mg/m^2	

NB: Consideration can be given to using the fortnightly Rituximab regime outlined above above if clinically appropriate.

Steroid Dosing regimen used as part of the Rituxvas trial

Time (week)	Prednisololne dose mg/kg/day
0	1 (max 60mg)
1	0.75
2	0.5
3	0.4
6	0.33
8	0.25
	Prednisolone dose mg/day
Reduce at end of month 3	Maximum 12.5
Reduce at end of month 4	Max 10
Reduce at end of month 5	Max 7.5
Reduce at end of month 6	Max 5
18-24 months	Reduce from 5 to zero

Prophylaxis

Routine prophylaxis

Routine prophylaxis should be given to all patients prescribed cyclophosphamide, rituximab, and/ or high dose steroid therapy.

Note: High dose steroid therapy is defined as a daily dose of prednisolone greater than or equal to 20mg.

1. Gastric protection: ranitidine 150mg twice a day or omeprazole 20mg daily for 6 months while on steroids.

2. Pneumocystis jiroveci (carinii) pneumonia:

   Sulfamethoxazole/trimethoprim (Co-trimoxazole) 480mg daily during cyclophosphamide and for a minimum of 3 months after last cyclophosphamide infusion. All patients recieving Rituximab should be prescribed PjP prophylaxis for 6 months following the last infusion. Second line options include dapsone, atovaquone and nebulised pentamadine. If using dapsone there should be awareness of the possible side- effect of methaemogloginaemia , and this should be screened for if there is any clinical suspicion (symptoms or an unexplained drop in haemoglobin). There is very little data directly comparing the effectiveness of these alternative prophylactic agents, with no evidence in favour of a particular agent in the small number of comparisons that have been made. G6-PD should be checked prior to initiation of dapsone and preferably before the prescription of co-trimoxazole.

3. Advice on prophlaxis should be sought from microbiology and pharmacy for patients intolerant of co-trimoxazole.

4. Awareness should be maintained of the potential serious interaction between methotrexate and co-trimoxazole, with fatalities due to cytopaenias reported

5. Routine fungal prophylaxis is not indicated for all patients with vasculitis.
   For high risk patients* consider oral fluconazole 100-200mg daily (depending on renal function) for up to 12 weeks while prednisolone dose is 20mg/day or more.
   ***High risk patients may be those identified as having previous fungal infection or other opportunistic infection or other risk factors for infection (frailty, older age, severe renal impairment, leucopenia, hypogammaglobulinaemia)**

6. Patients with a previous history of tuberculosis or who are suspected to have latent infection should be discussed with the TB team however treatment for vasculitis should not be delayed. See NICE guidelines for further information (www.nice.org.uk/guidnace/ng33)[5]

7. Prophylaxis against osteoporosis:
   Weekly oral biphosphonate e.g. Alendronate 70mg weekly should be given for men and post menopausal women with eGFR>30mls/min.

   Patients with eGFR < 30ml/min, consider reduction of frequency to fortnightly and metabolic bone expert review.

   Pre-menopausal women may not require bisphosphonate prophylaxis.
   Adcal d3 2 daily should be given to all patients unless also requiring any Vitamin D supplementation or hypercalcaemia.

8. Patients with an episode of neutropenia with duration of more than 7 days may require additional prophylaxis and should be discussed with a Consultant Nephrologist and Microbiologist in addition to reduction in immunosuppressive dose.

9. Patients known to be Cytomegalovirus (CMV) positive or where patients have prolonged neutopenia consideration should be given to testing for CMV or other viral infections. Routine prophylaxis for the general population is not suggested but may be given on an individual basis at Consultant discretion.

10. All patients should have an immunoglobulin screen at presentation. This should be reviewed and advice sought from Consultant Immunologist if necessary.

Oral Cyclophosphamide

Considerable clinical experience exists for using oral cyclophosphamide to treat vasculitis. It is undoubtedly more toxic but may be more efficacious. In particular, it is not possible to give mesna bladder protection. In general intravenous pulse therapy is preferred. Oral cyclophosphamide may be used in cases where there is frequent disease relapse, disease recalcitrant to intravenous therapy or severe difficulty with venous access.

The most efficient method of monitoring oral therapy is poorly described as are the appropriate reductions for age or reduced renal function. The following represents a regimen drawing on the best elements of the regimens described in the papers by Haubitz, Guillevin and Fauci.[3, 11, 12, 22]

The steroid regimen will be adjusted according to patient response. The described one was used in combination with oral cyclophosphamide. Steroid regimens used in combination with oral cyclophosphamide vary considerably.

Week	**Cyclophosphamide (CYC) oral daily dose CrCL <30 ml/min**	**CYC oral daily dose CrCL ≥30 ml/min**
1 and 2	**1.5mg/Kg**	**2.0mg/kg**
3 and 4	**2.0mg/kg (If WCC >4x10^9/L)**	**2.0mg/kg (If WCC >4x10^9/L)**
5-8	**2.5mg/kg (If WCC >4x10^9/L)**	**2.5mh/kg (If WCC >4x10^9/L)**
9-12	**3.0mg/kg (If WCC >4x10^9/L)**	**3.0mg/kg (If WCC >4x10^9/L)**
Maintain on oral cyclophosphamide until in remission for 3 months. Monitor WCC and adjust dose as below. Then wean oral cyclophosphamide as below.		
For 4 weeks	**Maintenance dose 0.5mg/kg**	**Maintenance dose 0.5mg/Kg**
For 4 weeks	**Maintenance dose 1.0mg/kg**	**Maintenance dose 1.0mg/Kg**
For 4 weeks	**Maintenance dose 1.5 mg/kg**	**Maintenance dose 1.5 mg/Kg**
Continue wean to zero		

Monitoring

Alternate day FBC for the first two weeks and then weekly for 4 weeks and then fortnightly. In particular observe the slope of the WCC.

If WCC <4x10^9/L then reduce the dose by 0.5mg/Kg

If WCC <2.5 then withhold until WCC > 4 and reduce dose by 50%
Round oral cyclophosphamide doses to the nearest 50mg over 3 days.

Remember that cyclophosphamide is removed very efficiently by dialysis. All cyclophosphamide doses should be administered after dialysis.

Monitor LFTs monthly. Bilirubin greater than 17 µmol/l (1 mg/100 ml); or serum transaminases or alkaline phosphatase more than 2-3 times the upper limit of normal. In all such cases, dosage should be reduced.

Use **ideal** body weight to calculate doses. http://www.halls.md/body-surface-area/bsa.htm

Maintenance therapy - Azathioprine, Mycophenolate mofetil or Rituximab

Disease relapse occurs in ~50% of patients with 5 years[8,9]. Therefore standard regimens include the use of induction agents for 3-6 months followed by tapering dose maintenance with oral immunopsuppression therapy and steroids.

A number of trials inform the use of cyclophosphamide, azathioprine, mycophenolate and rituximab to prevent relapse. Cyclophosphamide has no advantage over azathioprine as a maintenance agent and is more toxic (Cyzarem)[10]. The IMPROVE trial compared starting doses of 2mg/kg/day of Azathioprine versus Mycophenolate 2g/day in a randomized trial[11]. The Azathioprine arm had a lower relapse rate albeit with a non-significant increase in adverse events. Immunosuppression was weaned over 42 months.

Azathioprine is therefore the currently preferred oral agent, though a low TPMT level or the presence of gout and patient preference should be considered as part of the decision making process.

A recent study demonstrated that Rituximab can be used as an effective maintenance.agent. After initial induction a further 3 x 6 monthly doses of 500 mg resulted in a lower relapse rate compared with a weaned dose of azathioprine[12]. Further trials are necessary.

When to initiate maintenance therapy is not well studied. We recommend to start approx. 3 weeks to 3 months after the final induction therapy is administered to reduce the risk of neutropenia yet prevent relapse. Starting early allows small initial doses with gradual titration and may improve tolerability.

Azathioprine

Azathioprine is licensed for the treatment of systemic lupus erythematosus and has been widely used off- license in patients with vasculitis.

Prior to commencing azathioprine therapy, it is good practice to measure individual thiopurine methyl transferase enzyme levels. (TPMT). This test is used to assess the potential toxicity of azathioprine and to identify patients who may require higher doses.

Samples may be taken at any time however must not be measured within 3 months of a red cell blood transfusion as this may give inaccurate results.

Samples should be sent to biochemistry in a “red tube” and will be sent to the Purine Reference laboratory in London.

Results will take 2-4 weeks and will appear on the EPR results section.

Normal range 69-150mU/L
Patient may be prescribed standard doses

High activity >150mU/L
Patient may need higher doses

Low activity <68mU/L
Patient may need lower doses

Very low activity **PATIENT SHOULD NOT RECEIVE AZATHIOPRINE AS THEY WILL BE UNABLE TO ADEQUATELY METABOLISE AND CLEAR DRUG.**

NOTE
Measuring TPMT levels does not negate the need for regular LFT and FBC on commencement of therapy. There remains a risk of bone marrow suppression even in patients with normal levels of enzyme activity.

Short term toxicity

Nausea
Short term, dose dependent toxicity should be anticipated. It is usually self limiting and spontaneously resolves within a few weeks without dose reduction.

To reduce this effect, we recommend gradual dose escalation over the first 2-4 weeks of therapy.

Moderate nausea may be controlled by splitting the daily dose and administration with food.

Hypersensitivity
Hypersensitivity may occur although the incidence is not clear. Symptoms include generalised or organ specific symptoms such as fever, myalgia, arthralgia, nausea and rarely, hepatitis and interstitial nephritis or renal failure. Pneumonitis has been reported infrequently and pancreatitis is rare.

Myelotoxicity
Bone marrow suppression is a potentially fatal adverse effect usually due to neutropenic sepsis.

Infection risk
Azathioprine increases the risk of infection, irrespective of neutropenia.

Hepatotoxicity
Mild derangement of liver function tests can be anticipated and is not uncommon.

Rarely, acute idiosyncratic drug induced liver injury and nodular regenerative hyperplasia may be observed. The later has been mainly observed in patients with inflammatory bowel disease and/or organ transplantation.

Acute idiosyncratic drug induced liver injury associated with mild derangement of liver function tests is often self limiting with LFTs returning to normal range without dose change.

Transaminase rise of more than twice the upper limit of normal should prompt a 50% dose reduction.

Long term toxicity - Cancer
Skin cancer and lymphoma have been associated with prolonged use of azathioprine.

Dosing
Treatment of vasculitis regimens suggest a dose of 1-2.0mg/kg per day.
In patients with renal disease, doses should be initiated at a maximum of 1mg/kg/day and titrated (see notes on tolerability).

Baseline Blood Tests
TPMT
Full blood count
Liver function tests including alanine aminotransferase.

Follow up blood tests
BNF suggests that monitoring for azathioprine should be weekly for up to 8 weeks and monthly thereafter. Three monthly testing can be allowed in long term stable patients.

Fertility
Azathioprine does not appear to affect male fertility.

Pregnancy
Azathioprine and its metabolites do cross the placenta however the literature does not suggest a teratogenic effect. Use should be limited to patients where the risks outweigh the benefits.

Drug interactions
Allopurinol and febuxostat must never be given in combination with azathioprine and may result in fatal toxicity

Mycophenolate Mofetil

Use of Mycophenolate Mofetil (MMF) for Vasculitis
Recent evidence has accrued that vasculitis may be kept in remission with MMF in combination with steroid after standard induction treatment.

Mycophenolate mofetil (MMF) Dose and monitoring schedule

	Dose	**Monitoring**	**Activity**	**Aim**
Week one	500mg twice a day	***Time***	Clinic visit	START THERAPY DRUG EDUCATION
Week two	750mg twice a day If NOT tolerated in week one – continue with 500mg twice a day	FBC Monday/Tuesday	Virtual clinic review of bloods	
Week three	1000mg twice a day	FBC Monday/Tuesday	Clinic visit	Patient review check tolerability
Week four	1000mg twice a day	FBC		
Patients should continue to have FBC every 4 weeks with virtual review for a further 4 months				

Supply of medicines

*****Prescriptions should not exceed four months supply at any one time*****

Note, this is an unlicensed indication and therefore is classed as a “red drug” – should be supplied and monitored by secondary care only.

Dose modifications
If patients do not tolerate 1000mg twice a day due to side-effects, reduce to 500mg twice a day and increase to 750mg twice a day after 4 weeks and 1000mg twice a day after a further 4 weeks.

If side effects preclude dose escalation, frequency may be increased, e.g. to 500mg three times a day or four times a day

Prophylaxis (Recommended)

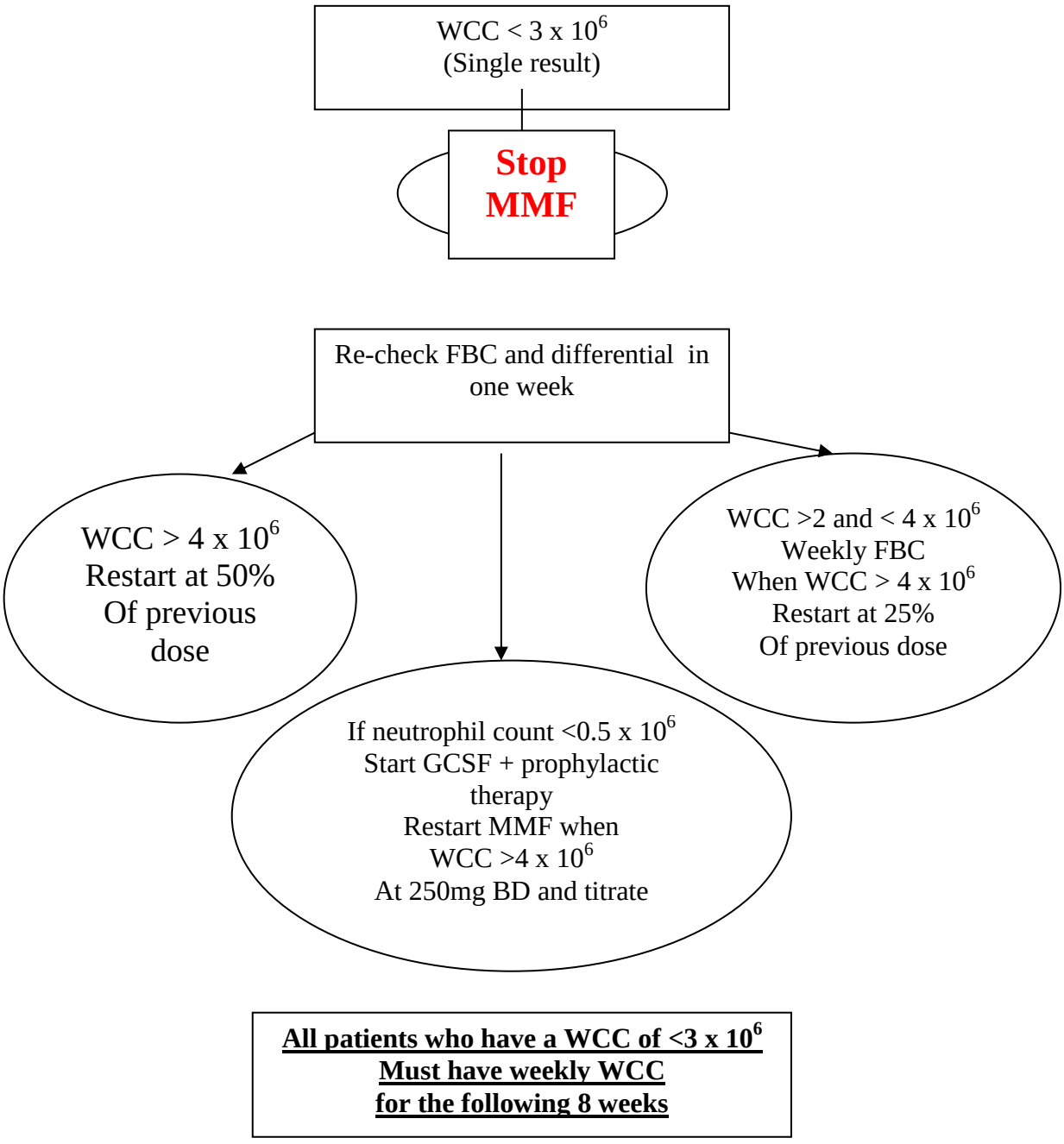
Peptic ulceration omeprazole 20mg daily
Fungal infection if concurrent steroids > 20mg per day and high risk e.g. fluconazole 100-200mg od depending on renal function
Pneumocystis carinii during initial 12 weeks of therapy and /or if WCC<4 x 10^6 Co-trimoxazole 480mg daily

Concurrent Infections

Mild bacterial or viral infections, continue MMF and treat with antibiotics or antiviral medication (to be decided by Consultant).

Severe infections, temporary cessation of MMF therapy during treatment of infection. Resume therapy at a reduced dose, at least 500mg per day lower than the previous dose.

Leucopenia (assosciated with MMF)



All patients who have a WCC of <3 x 10^6
Must have weekly WCC
for the following 8 weeks

Gastro Intestinal Intolerance

Many of the gastric side effects listed previously may be minimized or avoided by introducing therapy at a low dose and slowly increasing.

For patients who do not tolerate standard dose increases listed above, doses will be changed to:

250mg three times a day
250mg four times a day
500mg three times a day
500mg four times a day

Once the target of 2g daily is achieved some patients will tolerate 1g twice a day and may be switched to this to aid compliance. However if patients prefer, they may be maintained on 500mg four times a day.

While initiating treatment, should a patient experience diarrhoea, it may be useful to reduce the dose of mycophenolate by 50% and monitor symptoms. If the GI symptoms do not improve after 4 weeks at the reduced dose patients may be switched to Myfortic for a month trial.

If patients develop diarrhoea during mycophenolate therapy, other causes should be excluded e.g. C*lostridium difficile* or other drug therapy.

If there are no contraindications, a short trial (up to 3 weeks) of loperamide 2mg up to four times a day may be added.

Patient's weight must be monitored during episodes of severe gastric intolerance to ensure that patients do not begin to lose weight.

Taking mycophenolate with food reduces peak plasma concentrations by up to 40%. There is no effect on the total amount of drug absorbed.

Anti GBM (Glomerular basement membrane) Disease

General consideration

Advanced renal failure is still not generally reversible by any current available treatment. Hammersmith data suggest only 1/38 who presented with a creatinine >600umol/l was dialysis independent at 1 year[13]. Those who also have severe nephritis (100% crescents) on biopsy and oliguria have a poor outcome. The K-DIGO guidelines advocate no treatment for those with these findings and no pulmonary haemorrhage.

Plasma exchange is probably of no benefit as a sole agent. The report with the best outcome used PE plus oral cyclophosphamide and steroid. Only 8% of those who required dialysis at presentation were dialysis free at 1 year. Pulse IV steroid will probably be as effective but less toxic. Relapse does occur but recurrence of disease after periods of remission is rare.
Relapse should be treated as initial disease but there is usually an agent provocateur such as a line sepsis that needs to sought and eradicated.

Treatment

Anti-GBM, expert opinion (Oxford Textbook of Nephrology) recommends:

1. 4 litre daily exchanges for 14 days or until Anti-GBM antibody level is suppressed. Replacement is 4.5% albumin. 1 Litre of FFP is given at the end of therapy in cases of pulmonary haemorrhage or if within 48 hours **(pre OR post)** of a procedure (renal biopsy). Levy's (2001) study used PE with a volume of 50ml/kg to max of 4L and used daily exchanges for at least 14 days or until antibody undetectable.
2. Steroids were given at a dose of 1/mg/kg and weaned to zero over 6-9 months.
3. Cyclophosphamide was given orally at a dose of 3mg/kg day for 3 months.
4. Long-term treatment is not recommended as there is a low risk of recurrence.[18]

Suggested protocol

A. PLASMA EXCHANGE for ANTI-GBM

Daily

Dose 50ml/kg to maximum of 4L (aim for maximum if tolerated).
Replacement Fluid is 4.5% albumin unless renal biopsy or invasive procedure planned, or pulmonary haemorrhage. Then use FFP 1 litre at end of therapy for previous 2 days and 2 days post procedure (also recommended by K-DIGO).

Omit Plasma Exchange on day of biopsy.

Daily exchanges for at least 14 days or until anti-GBM titre in normal range.
Blood flow probably optimal at 180ml/min and TMP of 40 mmHg
Anticoagulate with Heparin, 1000iu loading and 1000iu/hour. Reduce if bleeding diathesis present. Note that FFP contains citrate as anticoagulant (which results in more severe hypocalcaemia)

Supplement calcium as 10mls of 10% calcium chloride over 5 minutes for every hour on PE. (usually 2 doses).[20]
Femoral access is preferred. (max 5 days)

Pre Plasma Exchange bloods
Check clotting and FBC, Renal profile, Calcium, phosphate, Mg, prior to PE.
If PT/APTT are >1.5 times normal consider adding FFP to replacement.
Measure the substance (ANCA, Anti GBM) to be removed before Rx

Other considerations for patients receiving PE
Stop ACE inhibitors for 24 hours pre and post PE.

B. MONTHLY PULSE CYCLOPHOSPHAMIDE for ANTI-GBM

Calculate dose according to body surface area. The following link will take you to Hall's calculator for BSA: http://www.halls.md/body-surface-area/bsa.htm (also contains equations for calculating lean body weight).

Dose adjustment for reduced renal function is as follows:

If GFR < 30ml/min then recommended dose is 0.5g/m^2 and

Dialysis. Remember that cyclophosphamide is removed very efficiently by dialysis but accumulates in patients with a reduction of renal function. All cyclophosphamide doses should be administered after dialysis and if possible further dialysis treatments withheld for 36-48 hours.

Maximum single dose of cyclophosphamide is 1200mg

Time (wk)	**Pulse no.**	**BSA (m^2)**	**Route**	Dosage (delete as appropriate) GFR>30	GFR≤30
0	1		intravenous (I.V.)	0.75g/m^2	**0.5g/m2**
4	2		I.V.	0.75g/m^2	**0.5g/m2**
8	3		I.V.	0.75g/m^2	**0.5g/m2**

Note: A prescription will be required for each pulse and must be signed by a SpR or Consultant or approved non-medical prescriber within their competence.

Dosage is given monthly
Check nadir of WCC by FBC at day 10 and day 14.
LFT's need to be monitored monthly

C. STEROIDS

A. Pulsed Methylprednisolone (if given)

Pulsed methylprednisolone x 3 daily doses (dose reductions for weight and age)		
age (years)	**weight**	
	Less than 70kg	**70kg and above**
Less than 70	500mg	750mg
70 and over	500mg	500mg

B. Prednisolone regimen (rapid taper)

Time (wk)	**Prednisolone dose (mg/kg/day)**
0	1
1	0.75
2	0.5
3	0.4
6	0.33
8	0.25
	Prednisolone DAILY dose mg
aim for maximum dose at the end of month 3	12.5
aim for maximum dose at the end of month 5	10
month 6-9	0

Prednisolone

- Maximum dose in first week is 80mg/day.
- Round prednisolone doses to the nearest 2.5mg
- Single daily dose
- Minimum dose in first three months is 10mg/day.

Fertility

Female ovary protection

A comprehensive systematic review of the effectiveness of gonadotropin-releasing hormone agonist (GnRHa) therapy for women undergoing chemotherapy for breast cancer or lymphoproliferative disorders or those receiving cyclophosphamide for SLE was undertaken in 2010. This included a meta-analysis of 19 prospective studies[14]. Fifteen of these, including 681 patients, evaluated "fertility preservation" as defined by regular menses or by FSH levels, following GnRHa. This analysis yielded a significant benefit for GnRHa in preserving the menstrual cycle (RR 0.26, 95% CI 0.22–0.34). However, the three RCTs that included pregnancy rates as outcomes failed to show an advantage for the use of GnRHas. This review acknowledged though that the studies included had many limitations including lack of stratification by age, different chemotherapy regimens and inaccurate definitions of preservation of ovarian reserve[14].

Consider GnRH analogue (Leuprorelin Acetate 3.75mg every 4 weeks (Prostap) as an SC or I.M injection. Start first dose 4 weeks before 1st or 2nd pulse cyclophosphamide. (Due to urgency of treatment will usually be before the 2nd pulse). Following 4 weeks of GnRH therapy start an estradiol patch to maintain estrogen levels and reduce symptoms of hormonal withdrawal.

Pregnancy

Recommend Depot three monthly Medroxyprogesterone I.M. injections to prevent pregnancy

Risks of baldness/ tumour/ infection death with cyclophosphamide

These should be consented for and documented in the patient record.

1. Recommend annual or bi annual cervical cancer screening. This is more frequent than recommended as part of the National Cervical Screening program
2. Hair thinning occurs in 20% who get cyclophosphamide with severe hair loss in <10%.
3. The effect on male fertility is uncertain but it is likely to result in sterility in a proportion of patients.
4. Premature ovarian failure (POF) occurs in a large proportion of patients. The incidence is related to the age of the patient and the cumulative cyclophosphamide dose.[13, 23]

Dose	Age of patient	% with POF
6 x monthly pulses	<25yrs	0%
	26-30	12%
	>31	25%
15 x Pulses	<25	17%
	26-30	43%
	>31	100

Sperm Banking

http://www.cmft.nhs.uk/saint-marys/our-services/andrology/arranging-sperm-banking Information taken directly from CMFT

Male patients who require immunosupresssant or cytotoxic therapy for their renal disease should be considered for sperm banking referral to Central Manchester University Hospital NHS Foundation Trust.

Patients must be medically fit enough to undertake masturbation for sperm collection.

Patients should be referred directly to the andrology team for sperm banking before facing imminent sterile inducing treatments eg chemotherapy/ radiotherapy.

Tests required:

Negative screening results within the preceding 3 months must be available before the referral can be taken:
HIV –anti HIV- 1 &2
HTLV 1 and 2
Hepatitis B surface antigen and core antibody HBsAg and Anti-HBc
Hepatitis C antibody. Anti HCV-Ab

These results must be printed and faxed to the andrology service.

The faxed results must clearly state the patients name and NHS number and date of birth.

Hospital In-patients who are well enough to attend Andrology

Only morning appointments are available to these patients.

They must be accompanied by a registered nurse who stays in the Andrology department with the patient and escorts them back to the ward at the end of the appointment.

They must be transferred by taxi/ambulance (transport arranged by referring centre).

Referral

A signature from a registered medical practitioner, stating the diagnosis of the patient may cause infertility is required by the Andrology team before sperm banking can be undertaken

Prior to making referral
Consider nature of diagnosis/ treatment – is infertility associated
Is patient fit enough to undertake masturbation?
Discuss possible referral for sperm banking
Ensure screening tests are undertaken and results available

Fax over negative screening results to 0161 276 6609.
Then telephone Andrology on 0161 276 6473 to make referral
(between 8.30 am - 4.00 pm, Monday-Friday).

All relevant patient details will be taken over the phone (see below).
The referral will be faxed to you for a medical practitioner to sign.
Fax the signed declaration back to Andrology on 0161 276 6609.
A patient appointment will be given to you over the telephone.
Inform the patient of appointment time in Andrology.

Advise the patient that 2-7 days abstinence from sexual activity is preferable for sperm storage

Ensure that you tell them to ask for Andrology in the Department of Reproductive Medicine on Oxford Road (*Do not tell them to ask for St Mary's hospital because they will be directed to the new hospital complex).*

Information that Andrology will ask you at the time of referral:

- Patient's identification details (Full names; Date of Birth; NHS/Passport number; Address).
- Patient's GP and address.
- Diagnosis and any relevant history (e.g. undescended testicles).
- Whether the patient has had chemotherapy or radiotherapy before, and when.
- Whether this is a relapse.
- When chemotherapy/radiotherapy is planned to start.
- Whether the patient is on any medication with side effects of decreased libido or potency.
- Any co-morbidities and/or difficulties/disabilities that may affect the patient's visit to the department.
- Any known allergies (**especially latex allergy**).
- Whether an interpreter is required.

What to tell the patient

- The time and date of their appointment with Andrology.
- Tell the patient that if they need any more information about the service, they can phone us on 0161 276 6473.
- 2-7 days abstinence from sexual activity is preferable for sperm storage.
- Explain that more than one sample may be required.

- They need to ask for **Department of Reproductive Medicine** on Oxford Road, **not** Saint Mary's Hospital.

For more information search for Andrology on the Trust website: www.cmft.nhs.uk
Maps, directions and car parking (on Hathersage Road) can be found on the left hand side of the web page under planning your visit.

There is an information booklet for patients: **Long Term Semen Storage** that can be found in the related downloads section on the front page of the CMFT website.

Information leaflets are available from St Marys/ CMFT website

- Long Term Semen Storage Information for Patients
- Sperm Banking Pathway (FRM/DRM/AND/198)
- How to Refer Patients for Long Term Semen Storage (FRM/DRM/AND/028)

Explanation of terms & Definitions

Vasculitis: A local or systemic disease characterized by inflammtion of blood vessels.

ANCA: The presence of abnormal anti-neutrophil cytoplasmic antibodies detectable by immunofluorescence

References and Supporting Documents

Key documents
https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/a13-ritux-anca-vascul.pdf

http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-GN-Guideline.pdf

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Appendices

Appendix 1 Assessment of day case patients attending for cyclophosphamide infusions

Assessment maybe carried out by advanced nurse practitioner, specialist renal pharmacist with clinical skills (independent prescriber) or specifically trained junior doctor or senior doctor.

A full history must be taken of:

- Fever
- Sore throat
- Cough/Sputum/dysuria
- Unexplained weight Loss
- Feeling unwell
- Uncontrolled nausea/vomiting after last dose and anti-emetics taken.

Blood tests

Review bloods (FBC, U&E, LFT) at day 10 and pre treatment results (within previous 72 hours) Any deterioration consider reduced dose of cyclophosphamide or withdrawal of therapy.

Physical examination/ observations:

- Temperature
- Pulse (compare with previous)
- Blood Pressure
- Examine relevant system if symptomatic

ACTION

- Document if fit for treatment
- Plan next treatment date (Use protocol)
- Ensure patient has a follow up appointment in out-patient clinic with medical team.

Appendix 2

Trust approved patient information leaflets may be downloaded from the intranet.

Steroids:
http://intranet.srht.nhs.uk/policies-resources/leaflets/ph/ren-2-09/

Cyclophosphamide
http://intranet.srht.nhs.uk/policies-resources/leaflets/ph/ren-4-09/

Azathioprine
http://intranet.srht.nhs.uk/policies-resources/leaflets/ren/ren-5-09/

Mycophenolate
http://intranet.srht.nhs.uk/policies-resources/leaflets/ph/ren-3-09/

Plasma exchange
http://intranet.srht.nhs.uk/policies-resources/leaflets/ph/ren-6-09/

Appendix 3

Referral to Vasculitis & Lupus clinic inc. OPD Cyclophosphamide

Form to be sent to Dr O'Riordan's secretary xt 60138 and referral documented on EPR

Patient name	**DOB/ward**	**Hosp/NHS number**

Diagnosis (circle) Vasculitis Lupus

Disease Classification Date of first diagnosis/relapse

Diagnosis established by biopsy (Y/N)(date) Imaging Clinical

Date of planned discharge

Immunosuppression commenced as in-patient (Y/N) date

Cyclophosphamide protocol: Cyclops Monthly (NIH) Eurolupus Other

Date of first treatment: Date most recent dose: Cycle number completed:

Date next treatment due: Last dose administered (mg):

Rituximab last dose administered (mg) date of last dose Last cycle number

Protocol Fortnightly x 2 Weekly x 4

Oral immunosuppression Type dose date started

If iv immunosuppression needed as outpatient within 2 weeks of discharge please organize from ward with a RUSS referral form and liaise directly with pharmacy

Prednisolone reducing plan provided until:

Other medications at discharge:

Allergies and intolerances : None Known / details

Is patient receiving dialysis Y/N – location……

Does patient require transport to attend hospital appointments/ for treatment
Other co-morbidities/ diagnosis

Referrer name…… Date…… Ward

Consultant……..

For Vasculitis/ Lupus MDT use only:

Referral received date: _____

Reviewed at MDT date: yes/no when? _____

Clinic appointment scheduled: yes/no when? _____

Cyclophosphamide scheduled: yes/no when? _____

Tracker updated: yes/no when? _____

RUSS Drugs completed: yes/no when? _____

Pre-admitted: yes/no when? _____