REGIONAL GUIDELINE FOR THE USE OF CYCLOPHOSPHAMIDE IN AUTOIMMUNE DISORDERS (EAST MIDLANDS RHEUMATOLOGY AUTOIMMUNE NETWORK)

University Hospitals of Leicester NHS
NHS Trust

DEPARTMENT OF RHEUMATOLOGY

1. Introduction and Contents

There is an RCT evidence base for the use of pulse IV Cyclophosphamide (CYC) in the following situations:

- Remission Induction therapy in Primary Systemic Vasculitis e.g. granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), Eosinophilic GPA (eGPA).
- Scleroderma Lung Disease or Primary Cardiac Disease
- Remission Induction therapy in SLE (severe organ manifestations).

The protocols for each condition are different and should be adjusted by the treating Consultant according to disease and response to treatment.

These guidelines are based upon the combination of the:

- British Society of Rheumatology (BSR) and BHPR guidelines for the management of adults with ANCA-associated vasculitis
- EULAR recommendations for the management of ANCA- associated vasculitis - 2022 Update
- EULAR recommendations for the management of systemic lupus erythematosus: 2023 update
- The 2024 British Society for Rheumatology guideline for management of systemic sclerosis
- EUROLOUPUS
- NIH

Contents

2. Scope

This guideline applies to all Rheumatologists and physicians using Cyclophosphamide to treat the conditions stated in the introduction subsection.

3. Recommendations for use

3.1 Primary Systemic Vasculitis (GPA/ eGPA):

3.1.1 Indications (GPA/MPA)

For induction of remission in patients with new-onset or relapsing GPA or MPA with organ-threatening or life-threatening disease (see table 1), we recommend treatment with a combination of GCs and either RTX or CYC. RTX is preferred in relapsing disease.
(EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update | Annals of the Rheumatic Diseases (bmj.com))

Examples of organ/life-threatening and not organ/life-threatening manifestations in patients with AAV

Examples of potentially organ/life-threatening manifestations*	Examples of manifestations that are not ultimately organ/life-threatening*
Glomerulonephritis	Nasal and paranasal disease without bony involvement (erosion) or cartilage collapse or olfactory dysfunction or deafness
Pulmonary haemorrhage	Skin involvement without ulceration
Meningeal involvement	Myositis (skeletal muscle only)
Central nervous system involvement	Non-cavitating pulmonary nodules
Retro-orbital disease	Episcleritis
Cardiac involvement	
Mesenteric involvement	
Mononeuritis multiplex	

- *These are just examples of typical disease manifestations and many other manifestations of AAV exist. Assessment of severity in the individual patient may differ (eg, scleritis can become organ threatening under certain circumstances).
- AAV, antineutrophil cytoplasmic antibody-associated vasculitis.

Table 1: Definition of organ threatening disease (EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update | Annals of the Rheumatic Diseases (bmj.com))

3.1.2 Indications (eGPA)

Cyclophosphamide can be used to induce remission in severe disease. This would include patients with renal insufficiency, proteinuria, cardiomyopathy, GI tract involvement, CNS/PNS involvement or alveolar haemorrhage.

3.1.3 Administration – IV CYC including adjusted dosing

Protocol	Disease and activity stage	Dosing
Cyclophosphamide-Pulse* (CYCLOPS)	Life-/organ-threatening; remission induction	15 mg/kg** intravenously weeks 0, 2 and 4, then every 3 weeks until remission; maximum of 10 pulses

Table 2: [ard-2022-223764supp001.pdf] – From EULAR supplementary material

Cyclophosphamide is administered as 3 Infusions at 2 weekly intervals then 3 infusions at 3 weekly intervals. IV cyclophosphamide is typically administered at a dose of 15 mg/kg (up to a maximum of 1.2 grams per infusion). Dilute in 500mls of saline 0.9% or Dextrose 5%, given over 30 minutes to 1 hour.

In select cases with severe disease where rapid induction of remission is required, but Rituximab therapy is favoured long term, a combination induction of Rituximab and cyclophosphamide can be used. Examples where this might be used include pulmonary hypertension, alveolar haemorrhage or severe lupus nephritis. 2-3 pulses of cyclophosphamide can be given concurrently with the first cycle of rituximab in order to facilitate faster control of disease. Steroid doses from both cyclophosphamide and rituximab regimes will not need to be combined, steroids from just one regime will be sufficient.

Pulsed CYC dose reductions for renal function and age		
Age (years	Creatinine (µmol/L)	
	<300	300-500
< 60	15 mg/kg/pulse	12.5 mg/kg/pulse
60 – 70	12.5 mg/kg/pulse	10 mg/kg/pulse
> 70	10 mg/kg/pulse	7.5 mg/kg/pulse

Table 3: Dose modification as per CYCLOPS trial

Adjusted dosing: The dose may be reduced in elderly patients, those with renal impairment. Commonly, the dose is adjusted to 12.5 mg/kg for those over 60 years or with renal insufficiency

Duration: The induction treatment can continue for 3-6 months, depending on the patient's response to therapy and disease severity.)

- Remission should be achieved within 3 months and a further 3 months of pulsed CYC is given after entry into remission (i.e. 6 months in total).
- Should remission not be achieved by 3 months, continue CYC infusions at 3 week intervals until remission is reached, then give another 3 months of CYC pulse therapy before you proceed to the remission maintenance regimen.
- Remission should be reached by 9 months and the total duration of CYC should not exceed 12 months.

However, 10% of patients will have refractory disease, and if remission not achieved by 9 months consider alternative agents and consider asking a colleague for a second opinion.

- Lifetime exposure to CYC should not exceed 25 g.

eGPA: For eGPA the dose and administration of cyclophosphamide is the same as in GPA/MPA.

3.1.4 Treatment Pathways

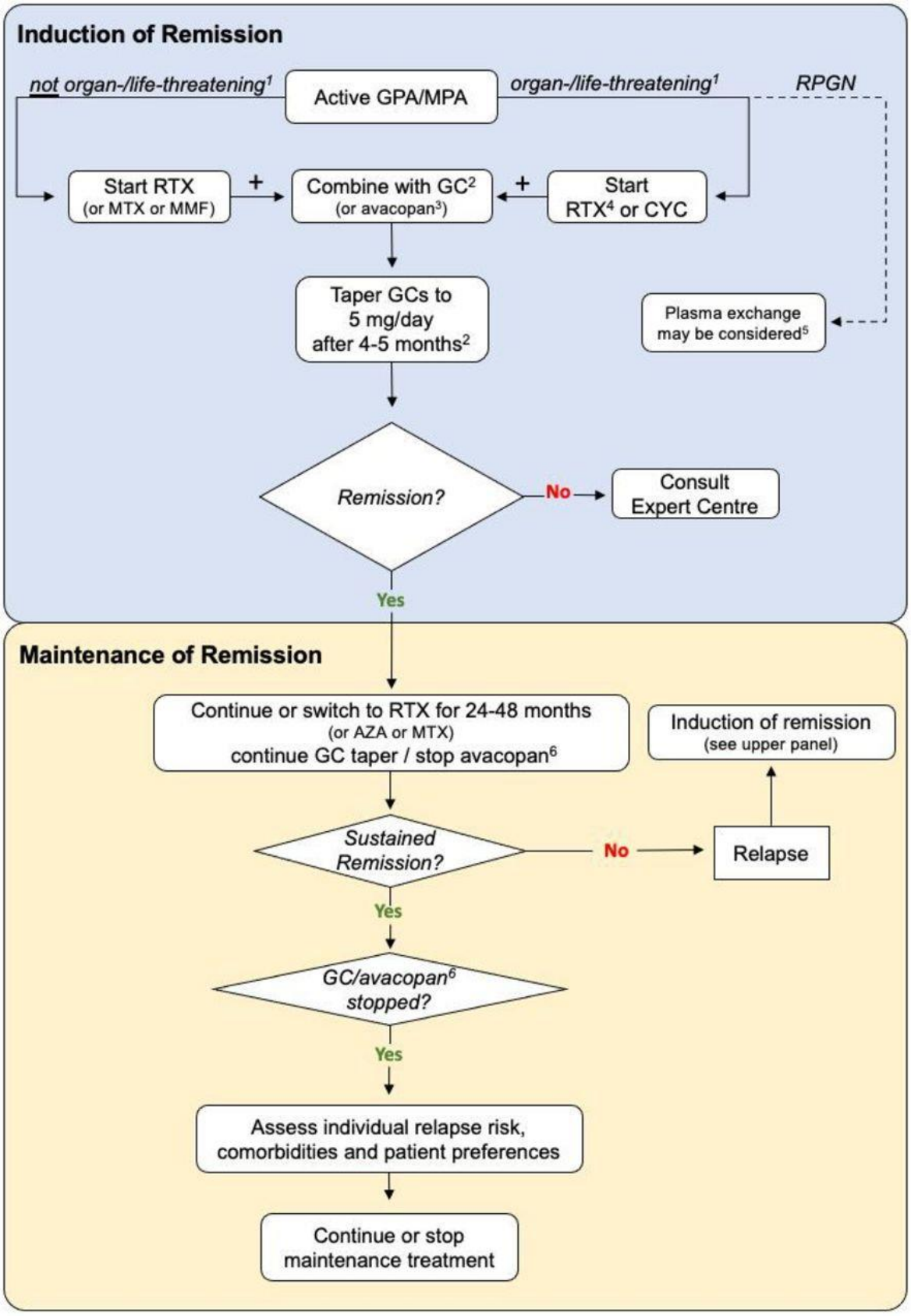
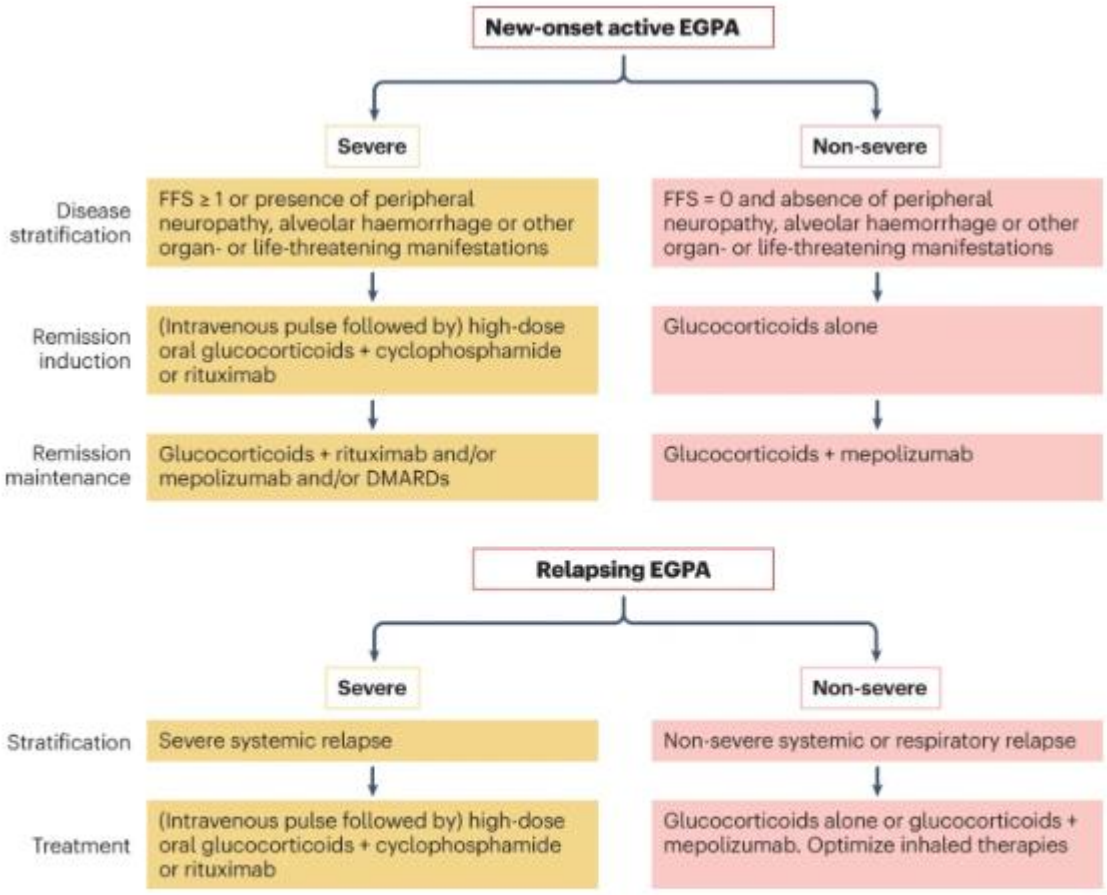


Figure 1 - Cyclophosphamide therapy in the GPA/MPA treatment pathway



This algorithm is based on the evidence-based statements and differentiates the treatment of patients with new-onset, active disease from that of patients with relapsing disease. The treatment approaches are also tailored on the basis of disease severity. EGPA, eosinophilic granulomatosis with polyangiitis; FFS, five-factor score.

Figure 2 – Proposed treatment algorithm for eGPA (https://www.nature.com/articles/s41584-023-00958-w#Sec7)

3.2 Scleroderma

3.2.1 Indication

- SSc-ILD - can be used following mycophenalate mofetil
- SSc-pHI – can be used following mycophenalate mofetil

3.2.2 Administration

The dosing of CYC for the above indications is as follows:

- 600mg/m2. (Maximum dose of 1 gm) for six 4-weekly infusions.
- Adjunct steroids: Oral prednisolone: 10 mg daily / 20 mg alternate days.

Lung function should be re-assessed at this stage, and decisions about whether CYC should be stopped and AZA commenced, or CYC continued, should be based on either symptomatic outcome or PFT results. Ideally, where such facilities exist, these decisions should be made in conjunction with a Respiratory physician, either separately or as part of an MDT discussion framework.

3.3 SLE

3.3.1 Indication

In patients with organ-threatening or life-threatening disease, intravenous cyclophosphamide should be considered. (EULAR guidelines)

Mild activity/flare	Moderate activity/flare	Severe activity/flare
Any number of BILAG C scores Single BILAG B score SLEDAI <6	2 or more systems with BILAG B scores SLEDAI 6-12	1 or more BILAG A scores SLEDAI >12

Table 4: BSR 2017 guidelines- CYC for severe disease, disease scores found in section 3.3.3)

3.3.2 Administration

Low dose regime (Euro-Lupus Nephritis Trial/ St. Thomas' Hospital)

- Intravenous CYC 500 mg in 100 mL N/saline over 30 mins, administered 2 weekly for 6 infusions.
- *Adjunct steroids:* see section 7.2

High dose regime (NIH Regimen) – Note, used less commonly

- The high dose NIH regimen can also be used at the supervising consultant's discretion:*7* Monthly IV CYC at 500-1000 mg/m2 body surface area for 6 months followed by 3 monthly IV CYC later for 2 years.
- *Adjunct steroids:* see section 7.2

Please also note that combination rituximab and cyclophosphamide can be used as described in 3.1.3.

Note: Lower doses have been proven to be more effective and safer for lupus nephritis in Europe than high dose regimens.

Cyclophosphamide	*"Initial" therapy in LN*: IV 500 mg on weeks 0, 2, 4, 6, 8 and 10 (Low-dose - Euro-Lupus regimen) *Organ- or life-threatening disease*: IV 0.75-1 g/m^2 BSA/month for 6 months (High-dose - NIH regimen)

Table 5: CYC protocol , EULAR 2023 guidelines (https://ard.bmj.com/content/annrheumdis/83/1/15/DC2/embed/inline-supplementary-material-2.pdf?download=truetgfyhv)

Maintenance therapy

- Either Azathioprine 1-2.5 mg/kg/day **or** Mycophenolate 500 mg–2 gm/day on completion of IV therapy.

3.3.3 SLE Activity Scores

SLEDAI-2K[1]

The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) was developed and validated as a clinical index for the measurement of disease activity in SLE (systemic lupus erythematosus).

Patient name: _____ **Date:** _____

Check the score column of each descriptor that is present at the time of the visit or in the preceding 10 days.

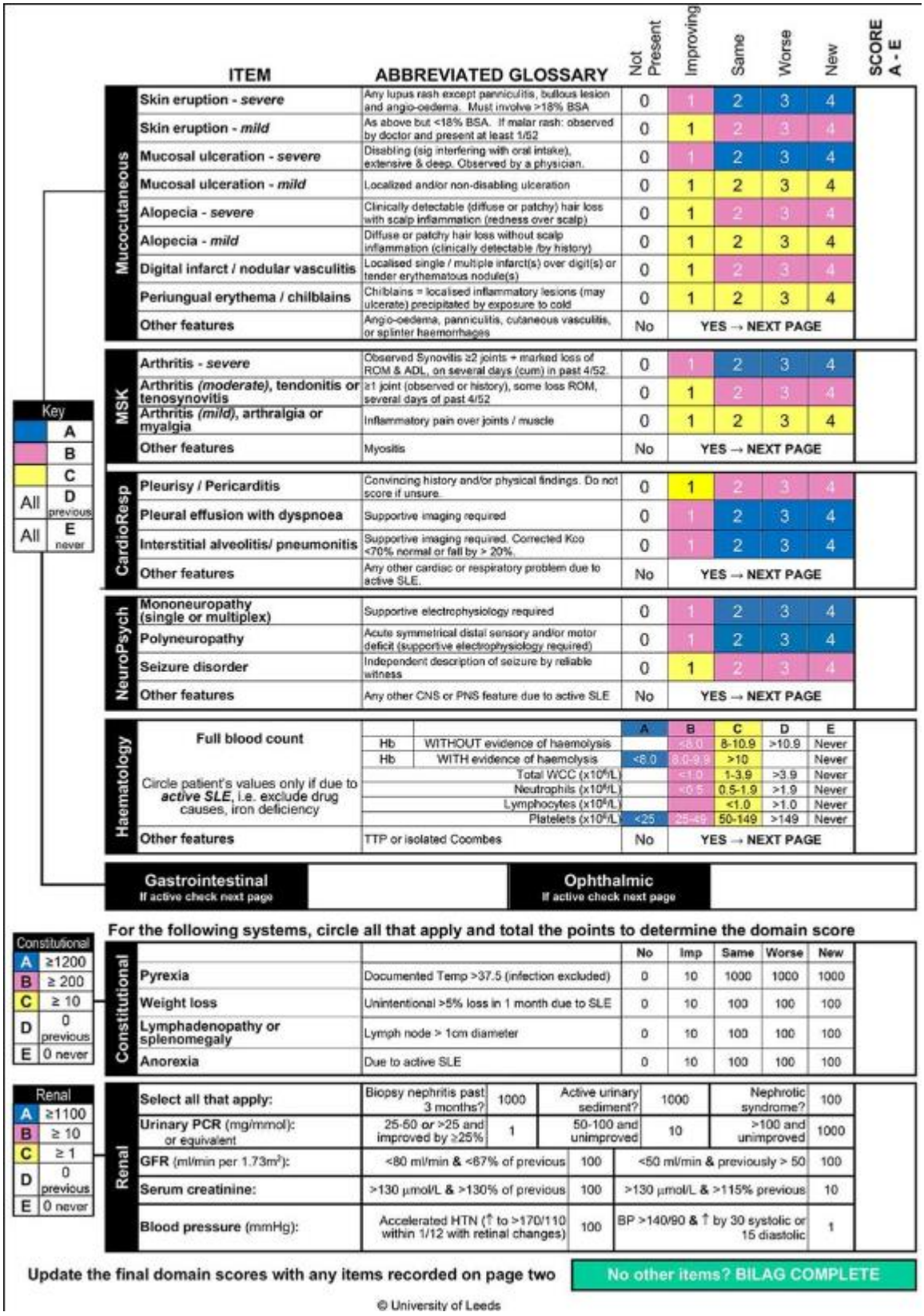
8	☐	**Seizure** - Recent onset, exclude metabolic, infectious or drug causes.
8	☐	**Psychosis** - Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	☐	**Organic brain syndrome** - Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia, or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	☐	**Visual disturbance** - Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate, or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	☐	**Cranial nerve disorder** - New onset of sensory or motor neuropathy involving cranial nerves.
8	☐	**Lupus headache** - Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	☐	**CVA** - New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	☐	**Vasculitis** - Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	☐	**Arthritis** - >2 joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion).
4	☐	**Myositis** - Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	☐	**Urinary casts** - Heme-granular or red blood cell casts.
4	☐	**Hematuria** - >5 red blood cells/high power field. Exclude stone, infection, or other cause.
4	☐	**Proteinuria** - >0.5 gram/24 hours.
4	☐	**Pyuria** - >5 white blood cells/high power field. Exclude infection.
2	☐	**Rash** - Inflammatory type rash.
2	☐	**Alopecia** - Abnormal, patchy, or diffuse loss of hair.
2	☐	**Mucosal ulcers** - Oral or nasal ulcerations.
2	☐	**Pleurisy** - Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	☐	**Pericarditis** - Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	☐	**Low complement** - Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	☐	**Increased DNA binding** - Increased DNA binding by Farr assay above normal range for testing laboratory.
1	☐	**Fever** - >38°C. Exclude infectious cause.
1	☐	**Thrombocytopenia** - <100,000 platelets / x10⁹/L, exclude drug causes.
1	☐	**Leukopenia** - <3,000 white blood cells / x10⁹/L, exclude drug cause.

Add all the checked scores above to calculate the total score.

Total SLEDAI-2K Score: _____

Reference: 1. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. Journal of Rheumatology 2002; 29(2):288–91. CA-8366E

Fig 2: SLEDAI 2K score: a score >12 denotes severe disease



ITEM	ABBREVIATED GLOSSARY	Not Present	Improving	Same	Worse	New	SCORE A - E
Mucocutaneous							
Skin eruption - *severe*	Any lupus rash except panniculitis, bullous lesion and angio-oedema. Must involve >18% BSA	0	1	2	3	4	
Skin eruption - *mild*	As above but <18% BSA. If malar rash: observed by doctor and present at least 1/52	0	1	2	3	4	
Mucosal ulceration - *severe*	Disabling (sig interfering with oral intake), extensive & deep. Observed by a physician.	0	1	2	3	4	
Mucosal ulceration - *mild*	Localized and/or non-disabling ulceration	0	1	2	3	4	
Alopecia - *severe*	Clinically detectable (diffuse or patchy) hair loss with scalp inflammation (redness over scalp)	0	1	2	3	4	
Alopecia - *mild*	Diffuse or patchy hair loss without scalp inflammation (clinically detectable /by history)	0	1	2	3	4	
Digital infarct / nodular vasculitis	Localised single / multiple infarct(s) over digit(s) or tender erythematous nodule(s)	0	1	2	3	4	
Periungual erythema / chilblains	Chilblains = localised inflammatory lesions (may ulcerate) precipitated by exposure to cold	0	1	2	3	4	
Other features	Angio-oedema, panniculitis, cutaneous vasculitis, or splinter haemorrhages	No	YES → NEXT PAGE				
MSK							
Arthritis - *severe*	Observed Synovitis ≥2 joints + marked loss of ROM & ADL, on several days (cum) in past 4/52	0	1	2	3	4	
Arthritis *(moderate)*, tendonitis or tenosynovitis	≥1 joint (observed or history), some loss ROM, several days of past 4/52	0	1	2	3	4	
Arthritis *(mild)*, arthralgia or myalgia	Inflammatory pain over joints / muscle	0	1	2	3	4	
Other features	Myositis	No	YES → NEXT PAGE				
CardioResp							
Pleurisy / Pericarditis	Convincing history and/or physical findings. Do not score if unsure.	0	1	2	3	4	
Pleural effusion with dyspnoea	Supportive imaging required	0	1	2	3	4	
Interstitial alveolitis/ pneumonitis	Supportive imaging required. Corrected Kco <70% normal or fall by > 20%.	0	1	2	3	4	
Other features	Any other cardiac or respiratory problem due to active SLE.	No	YES → NEXT PAGE				
NeuroPsych							
Mononeuropathy (single or multiplex)	Supportive electrophysiology required	0	1	2	3	4	
Polyneuropathy	Acute symmetrical distal sensory and/or motor deficit (supportive electrophysiology required)	0	1	2	3	4	
Seizure disorder	Independent description of seizure by reliable witness	0	1	2	3	4	
Other features	Any other CNS or PNS feature due to active SLE	No	YES → NEXT PAGE				

Haematology			A	B	C	D	E
Full blood count	Hb	WITHOUT evidence of haemolysis		≤8.0	8-10.9	>10.9	Never
Circle patient's values only if due to ***active SLE***, i.e. exclude drug causes, iron deficiency	Hb	WITH evidence of haemolysis	<8.0	8.0-9.9	>10		Never
		Total WCC (x10⁹/L)		<1.0	1-3.9	>3.9	Never
		Neutrophils (x10⁹/L)		<0.5	0.5-1.9	>1.9	Never
		Lymphocytes (x10⁹/L)			<1.0	>1.0	Never
		Platelets (x10⁹/L)	<25	25-49	50-149	>149	Never
Other features	TTP or isolated Coombes		No	YES → NEXT PAGE			

Gastrointestinal	Ophthalmic
If active check next page	If active check next page

Key	
	A
	B
	C
All	D previous
All	E never

For the following systems, circle all that apply and total the points to determine the domain score

Constitutional			No	Imp	Same	Worse	New
Constitutional							
Pyrexia	Documented Temp >37.5 (infection excluded)		0	10	1000	1000	1000
Weight loss	Unintentional >5% loss in 1 month due to SLE		0	10	100	100	100
Lymphadenopathy or splenomegaly	Lymph node > 1cm diameter		0	10	100	100	100
Anorexia	Due to active SLE		0	10	100	100	100

Constitutional	
A	≥1200
B	≥ 200
C	≥ 10
D	0 previous
E	0 never

Renal							
Renal							
Select all that apply:	Biopsy nephritis past 3 months?	1000	Active urinary sediment?	1000	Nephrotic syndrome?	100	
Urinary PCR (mg/mmol): or equivalent	25-50 or >25 and improved by >25%	1	50-100 and unimproved	10	>100 and unimproved	1000	
GFR (ml/min per 1.73m²):	<80 ml/min & <67% of previous	100	<50 ml/min & previously > 50	100			
Serum creatinine:	>130 µmol/L & >130% of previous	100	>130 µmol/L & >115% previous	10			
Blood pressure (mmHg):	Accelerated HTN (↑ to >170/110 within 1/12 with retinal changes)	100	BP >140/90 & ↑ by 30 systolic or 15 diastolic	1			

Renal	
A	≥1100
B	≥ 10
C	≥ 1
D	0 previous
E	0 never

Update the final domain scores with any items recorded on page two

No other items? BILAG COMPLETE

Fig 3: EASY BILAG page 1; a BILAG A criteria is sufficient for CYC

	ITEM	ABBREVIATED GLOSSARY	Nil	Imp	Same	Worse	New
Gastrointestinal	Lupus peritonitis	Serositis presenting as acute abdomen with rebound/guarding.	0	1	2	3	4
	Abdominal serositis or ascites	Not presenting as acute abdomen.	0	1	2	3	4
	Lupus enteritis / colitis	Vasculitis or inflammation of small or large bowel, with supportive imaging &/or biopsy.	0	1	2	3	4
	Malabsorption	Diarrhoea + abnormal D-xylose absorption / ↑faecal fat losses. Exclude Coeliac & gut vasculitis.	0	1	2	3	4
	Protein-losing enteropathy	See detailed glossary.	0	1	2	3	4
	Intestinal pseudo-obstruction	Subacute intestinal obstruction due to intestinal hypomotility.	0	1	2	3	4
	Lupus hepatitis	Raised transaminases, without AIH specific autoantibodies. Exclude drug- & viral hepatitis.	0	1	2	3	4
	Acute lupus cholecystitis	Exclude gallstones or infection.	0	1	2	3	4
	Acute lupus pancreatitis	Usually associated with multisystem involvement.	0	1	2	3	4
Ophthalmic	Orbital inflam / myositis / proptosis	Orbital inflammation + myositis / extra-ocular muscle swelling / proptosis. Imaging required.	0	1	2	3	4
	Keratitis - severe	Sight-threatening. Includes corneal melt and peripheral ulcerative keratitis.	0	1	2	3	4
	Keratitis - mild	Not sight-threatening.	0	1	2	3	4
	Anterior uveitis		0	1	2	3	4
	Post. uveitis/retinal vasculitis - severe	Sight-threatening and/or retinal vasculitis not due to vaso-occlusive disease.	0	1	2	3	4
	Post. uveitis/retinal vasculitis - *mild*	Not sight-threatening. Not due to vaso-occlusive disease.	0	1	2	3	4
	Episcleritis		0	1	2	3	4
	Scleritis - severe	Necrotising anterior scleritis. Ant &/or post scleritis requiring systemic therapy.	0	1	2	3	4
	Scleritis - mild	Anterior/posterior scleritis not requiring systemic steroids.	0	1	2	3	4
	Retinal / choroidal vaso-occlusive disease	See detailed glossary table.	0	1	2	3	4
	Isolated cottonwool spots	Also known as cystoid bodies.	0	1	2	3	4
	Optic neuritis	Exclude anterior ischaemic optic neuropathy.	0	1	2	3	4
	Anterior ischaemic optic neuropathy	Visual loss with pale swollen optic disc due to occlusion of posterior ciliary arteries.	0	1	2	3	4

OTHER PAGE 1 FEATURES: Record here and update the score for that domain on page one:

Mucocutan	Angio-oedema - severe	Urticaria variant in subcut, submucosal &deep dermal tissues. Potentially life-threatening.	0	1	2	3	4
	Angio-oedema - mild	As above but not life-threatening.	0	1	2	3	4
	Panniculitis/ bullous lupus - severe	See detailed glossary table.	0	1	2	3	4
	Panniculitis/ bullous lupus - mild	Affects <9% BSA & does not fulfil any criteria for severe panniculitis.	0	1	2	3	4
	Major cutaneous vasculitis/thrombosis	Cutaneous vasculitis/thrombosis → extensive gangrene /ulceration / skin infarction.	0	1	2	3	4
	Splinter haemorrhages		0	1	2	3	4
MSK	Myositis - *severe*	Significantly ↑ muscle enzymes with significant muscle weakness.	0	1	2	3	4
	Myositis – *mild*	Significantly ↑muscle enzymes + myalgia but no significant muscle weakness.	0	1	2	3	4
Cardiorespiratory	Myocarditis - mild	↑ cardiac enzymes &/or ECG changes. No heart failure/arrhythmia/valve dysfunction.	0	1	2	3	4
	Myo /Endocarditis + cardiac failure	See detailed glossary table.	0	1	2	3	4
	Arrhythmias	Due to myocarditis / non-infective inflammation. ECG evidence required.	0	1	2	3	4
	New valvular dysfunction	Due to myocarditis / non-infective inflammation. Supportive imaging required.	0	1	2	3	4
	Cardiac tamponade	Supportive imaging required.	0	1	2	3	4
	Pulmonary haemorrhage/vasculitis	With haemoptysis &/or dyspnoea &/or pulmonary HTN. Imaging &/or histology required.	0	1	2	3	4
	Shrinking lung syndrome	Acute ↓ lung volumes (< 70% predicted) + normal corrected Kco. Diaphragmatic dysfunction.	0	1	2	3	4
	Aortitis	+/- dissection with supportive imaging, claudication, bruits or BP discrepancy >10 mmHg.	0	1	2	3	4
	Coronary vasculitis	Imaging evidence of non-atheromatous coronary narrowing/ obstruction /aneurysm.	0	1	2	3	4
Neuropsychiatric	Aseptic meningitis	See detailed glossary table.	0	1	2	3	4
	Cerebral vasculitis	With features of vasculitis in another system. Supportive imaging &/or biopsy required.	0	1	2	3	4
	Demyelinating syndrome	Discrete white matter lesion + neurological deficit. Ideally ≥1 prior recorded event. Exclude MS.	0	1	2	3	4
	Myelopathy	Acute onset, rapidly evolving paraparesis, quadriparesis and/or sensory level. Exclude SOL.	0	1	2	3	4
	Acute confusional state	See detailed glossary table.	0	1	2	3	4
	Psychosis	Delusions &/or hallucinations. Excludes primary psychotic disorder, drugs or during delirium.	0	1	2	3	4
	Acute inflammatory demyelinating polyradiculoneuropathy	See detailed glossary table.	0	1	2	3	4
	Cranial neuropathy	Exclude optic neuropathy which is classified under ophthalmic system.	0	1	2	3	4
	Plexopathy	Supportive electrophysiology study required.	0	1	2	3	4
	Cognitive dysfunction	Sufficient to impair ADLs. Includes attention, memory, language, visuospatial, psychomotor.	0	1	2	3	4
	Status epilepticus	A seizure or seizures lasting >30 minutes without full recovery to baseline.	0	1	2	3	4
	Cerebrovascular disease	Not vasculitis. See detailed glossary table.	0	1	2	3	4
	Movement disorder	Exclude drug-induced.	0	1	2	3	4
	Autonomic disorder	See detailed glossary table.	0	1	2	3	4
	Cerebellar ataxia	Cerebellar ataxia in isolation of other CNS features. Usually subacute presentation.	0	1	2	3	4
	Severe lupus headache	Unremitting, Disabling, unresponsive to narcotics, >3 days. Exclude SOL and CNS infection.	0	1	2	3	4
	Headache from intracranial hypertension	Exclude cerebral sinus thrombosis.	0	1	2	3	4
Haem	TTP	Micro-angiopathic haemolytic anaemia + thrombocytopenia. Other causes excluded.	0	1	2	3	4
	Coombes positive (isolated)	Without evidence of haemolysis.	Negative		Positive		

Fig 4: EASY BILAG page 2; a BILAG A criteria is sufficient for CYC

4.Discussions Prior to Use

Because of the potential short and long term toxicity of CYC, decisions on initiating treatment should be made and documented by the treating Consultant and include the rationale for choosing CYC (rather than an alternative agent).

4.1 Informed Consent

Requirements are

1. Substantial benefits include
    a. Improved Survival
    b. Disease control
    c. Prevention/amelioration of permanent organ damage
2. Serious Complications and concerns related to treatment with cyclophosphamide
    a. Infection
    b. Infertility, early menopause (circa 50%)
        i. Dependent on cumulative dose and age
    c. Teratogenicity – contraceptive advise as appropriate
    d. Malignancy – Related to cumulative dose of CYC >30g
        i. Lymphoma risk 4-11 fold increase
        ii. Skin cancer 4-10 fold increase
        iii. Bladder cancer 4-33 fold increase
    e. Hair loss
    f. GI upset
3. Steroid Side effects
    a. Mood disturbance, change in appearance, weight gain
    b. Diabetes Mellitus, Bone disease, infection, GI disease
    c. Secondary hypoadrenalism

4.2 Information Provided to Patients

1. How and when to seek advise
    a. Monitoring booklets, steroid card
        i. Symptoms and signs of infection
        ii. Symptoms and signs of on-going disease activity
    b. Rheumatology nurse-led help line
2. Vaccination / screening advice
    a. Live vaccinations should be avoided until ≥ 3 months after stopping immunosuppression
    b. Vaccinations should be completed before treatment if feasible. Otherwise they should be postponed until after induction therapy completed (≥ 4 months after rituximab)
    c. Annual influenza vaccination
    d. Pneumococcal vaccination
    e. HPV vaccination

f. Cervical screening following cyclophosphamide
    i. Annual for 3 years
    ii. Every 3 years thereafter

5. Assessments Prior to Therapy

1. FBC, U&E, LFT and urinalysis for blood & protein with results checked prior to ordering the first treatment.
2. History and examination to elicit any **contra-indications** to treatment which include intercurrent significant infection (chest, throat or urine) and adverse reaction to past CYC treatments. Any reaction to the previous infusions should be discussed with Consultant.
3. Pregnancy should be ruled out by careful history in every female patient of childbearing age.
4. Baseline pulse and blood pressure should be recorded. ≥
5. All patients should be assessed for risk of tuberculosis by taking a full history, physical examination and performing a chest X-ray
6. Disease activity should be assessed before the treatment is commenced and assessed at regular intervals, using standard outcome measures:
    a. BVAS
    b. BILAG/ SLEDAI
7. Vaccinations (as above).

5.1 Baseline Investigations Prior to Administration

The below checks need to be performed prior to the first infusion of cyclophosphamide:

FBC and CRP	Ensure • WBC ≥3.5x10^9/L but ≤11x10^9/L (unless high WBC is due to corticosteroids and **NOT** infection) • Neutrophils ≥1.5x10^9/L • Platelets ≥50x10^9/L • No clinical evidence of infections – Discuss raised CRP with Consultant/SpR
Urea, Electorlytes and Creatinine	As previously stated, adjusted doses can be found in the vasculitis protocol
Infection Screen • HIV • Hepatitis B • Hepatitis C	Discuss with HIV team/Hepatologist if positive

Table 6: Baseline investigations prior to CYC infusions

Postpone infusion if:

- WBC prior to infusion <4.03.5

- neutrophil count <2.01.5,
- platelets < 50

Then check the FBC weekly.

If the platelet count is 50 -100 then reduce dose by 50%.

If persistent cytopaenia: reduce dose of infusion by 25%.

- With any further episodes of leukopenia/neutropenia make equivalent dose reduction.

5.2 Clinical Assessment Prior to Administration

Temperature	To exclude active infection.
Urinalysis	To exclude active infection and haematuria. Remember to check for pregnancy in women of child bearing age.
Check for any new signs and symptoms	Check for sore throat or cough to help exclude active infection. There should be no clinical evidence of infection before proceeding with scheduled dose. Assess disease symptoms. Assess hydration (check sodium and urea)
Check how previous cycles were tolerated.	If patient had nausea despite taking domperidone after the last treatment, then arrange for an outpatient prescription to be written for ondansetron.
Check that patient has stopped any other immunosuppressant drugs.	This should be done prior to the first infusion.
Confirm that consent, ID and cannulation policies have been followed.	

Table 7: Clinical Assessment prior to CYC administration

5.3 Post Infusion Checks

After the first infusion of CYC check FBC between days 10 and on day of next infusion. If:

- Leucocyte count 1–2.0 or neutrophil count 0.5–1.0
    - Reduce CYC infusion by 40% of previous dose
- Leucocyte count 2–3.0 or neutrophil nadir 1–1.5
    - Reduce CYC infusion by 20% of previous dose.

Thereafter check the FBC on the day of the infusion or previous day unless there is an adjustment made to the dose of CYC administered or interval period between infusions, in these cases the FBC should be additionally checked at day 10.

Renal function should be measured on the day of infusion or previous day and adjustments be made to CYC dose as per table above.

6. Logistics

CYC should usually only be infused in either a Cytotoxic designated Day Case area or a designated ward. It should only be prescribed by the consultant or by a SpR who has been signed off as competent to prescribe chemotherapy. The infusion can only be administered by a nurse who has completed the chemotherapy module. Medical staffs are not allowed to infuse.

FBC, U&E, LFT & urine dipstick should be done as per protocol and infection should be excluded. The results should be reviewed before CYC is administered. If CYC is prescribed before the bloods are taken then the responsible clinician should authorise in writing its administration after reviewing the results.

Response to treatment should be assessed at regular intervals.

LGH – Ward 17 and 19 Medical Day Case Unit (MDCU)

N.B. Patients must be clinically stable to attend MDCU

- Clinician to call nurse in charge on MDCU on 0116 258 4012/4013
- Followed up with email confirmation to MDCU mailbox ward1mdcu@uhl-tr.nhs.uk
- Rheumatology doctor to complete and send hard copy of prescription chart with MDCU form in advance
- Medical/Rheumatology team need to have done biologic pre-screening tests prior to referral
- Patient to attend MDCU for treatment if medically stable within 48 hours of referral
- Please ensure proceeding instructions and document have been followed (Appendix 1)
- Spillage kits to be on ward and purple lidded sharps bin need to be available

GGH – RRCV

ITU patients

- Rheumatology doctor to contact Dianna Russel - Charge Nurse (0116 258 8044) or Helen Skeete (07950861856) or, if no response, RRCV matron of the day via RRCV flow coordinator's (07921545525) to discuss referral
- Email confirmation of referral to contact discussed with as above
- Prescription completed by rheumatology doctor via nerve centre including pre-medications
- Medical/Rheumatology team need to have done biologic pre-screening tests prior to referral
- Renal nurse to attend ITU to administer drug within 48 hours of referral

Renal ward

- If patient is a rheumatology patient only then rheumatology doctor to provide prescription via nerve centre including pre-medications. If joint care patient then renal will use their own protocol
- Renal ward follow own protocol
- Spillage kits to be on ward and purple lidded sharps bin need to be available

Respiratory ward

- Rheumatology doctor to contact Dianna Russel –Charge Nurse (0116 258 8044) or Helen Skeete - Matron (07950861856) or if no response RRCV matron of the day via RRCV flow coordinator's (07921545525)
- Rheumatology doctor to provide prescription via nerve centre including pre-medications
- Pharmacy to check prescription on ward
- Medical/Rheumatology team need to have done biologic pre-screening tests prior to referral
- Renal nurse to attend ITU to administer drug within 48 hours of referral
- Spillage kits to be on ward and purple lidded sharps bin need to be available

LRI – any ward including ITU

- Rheumatology doctor to contact Clair Burroughs, Lead Nurse on (07950893545)– then Karen Pedley Oncology Matron (07949743660), Becky Brennan

Haematology Matron (07950884157) and then CHUGGS flow co for matron of the day (07970940124) with 24-48 hours' notice

- Rheumatology doctor to write in notes patient requires cyclophosphamide
- Rheumatology doctor provide cyclophosphamide prescription via nerve centre including pre-medications
- Pharmacy to check prescription on ward
- Medical/Rheumatology team need to have done biologic pre-screening tests prior to referral
- Pre-medication at 10AM for chemo administration at midday
- Spillage kits to be on ward 24 and purple lidded sharps bin need to be available
- Nurse to attend ward to administer drug within 48 hours of referral

Cyclophosphamide is the standard remission induction agent, and is usually given for 3-6 months, adjusted for age, body weight, and renal function. The majority of people treated with Cyclophosphamide will attain remission. However, 15% will not, and will continue to have active or progressive disease that is refractory to conventional treatment. Cyclophosphamide has significant side effects including gonadal toxicity inducing premature ovarian failure, bone marrow depression and infection, haemorrhagic cystitis, and an increased risk of future uroepithelial (bladder) cancer

7. Adjunctive Therapies

7.1 Avacopan

7.1.1 Indications

NICE Guidance

- Avacopan with cyclophosphamide or rituximab regimen is recommended, within its marketing authorisation, as an option for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis in adults

EULAR 2022 update

- Avacopan, in combination with RTX or CYC, may be considered for induction of remission in GPA or MPA as part of a strategy to substantially reduce exposure to steroids.

7.1.2 Administration including steroid weaning guidance

Avacopan is a tablet given at a dose of 30mg twice a day. Its use is currently recommended for up to 1 year however can be used long term. Avacopan allows a faster steroid wean.

7.2 Glucocorticoids

As per the advocate trial, it is recommended steroids be weaned off by 21 weeks. Methylprednisolone at a cumulative dose of 1-3g on days 1-3 can be considered in patients with severely active disease. Indications for this include but are not limited to renal involvement with an eGFR <50 and/or diffuse alveolar haemorrhage. The use is at the discretion of the responsible clinician.

Current EULAR 2022 guidelines recommend a glucocorticoid wean from 1mg/kg/day with aim of cessation by week 21.

Week	*Glucocorticoid dose*
1-4	*Flexible – usually day 1-3 the patient is given 1g of methylprednisolone OD, followed by 1mg/kg/day of oral prednisolone. The dose is weaned to 40mg no later than week 4.*
5-6 (or from reaching 40mg OD prednisolone)	*40mg*
7-8	*30mg*
9-10	*20mg*
11-12	*15mg*
13-14	*10mg*
15-16	*7.5mg*
17-18	*5mg*
19-20	*2.5mg*
21	*0mg*

RAVE Trial Protocol: https://nejm.org/doi/suppl/10.1056/NEJMoa0909905/suppl_file/nejmoa0909905_appendix.pdf

If the patient has been started on avacopan and the disease is well controlled, steroids can be initiated at 40mg and weaned down by 10mg per week, stopping completely after week 4.

The steroids should be weaned more gradually for SLE patients as shown below:

Weeks	Weight <50kg (dose of steroid in mg)	Weight 50-75kg (dose of steroid in mg)	Weight >75kg (dose of steroid in mg)
1	50	60	75
2	25	30	40
3-4	20	25	30
5-6	15	20	25
7-8	12.5	15	20
9-10	10	12.5	15
11-12	7.5	10	12.5
13-14	6	7.5	10
15-18	5	5	7.5

19-52	5	5	5
>52	Individual Taper	Individual Taper	Individual Taper

7.3 Mesna

7.3.1 Indications

Mesna (2-mercaptoethane sulphonate sodium) should be considered for protection against urothelial toxicity in all patients receiving CYC, and especially in those receiving oral CYC. It is given with each pulse of CYC.

7.3.2 Administration

The oral dose of mesna should be 40% of the CYC dosage = 400mg.

If given intravenously, the dose should be 20% that of the CYC dosage = 200mg.

Given 2 h prior to the pulse of cyclophosphamide and repeated 2 and 6h after the pulse of cyclophosphamide.

In patients receiving oral CYC, mesna is given for as long as the patient receives CYC treatment.

7.4 Prophylaxis against Pneumocystis Jiroveci:

Patients receiving CYC and GCs should be considered to receive trimethoprim/sulphamethoxazole 960 mg thrice weekly as prophylaxis against pneumocystis jiroveci. Atovaquone 750mg BD or dapsone 100mg OD can also be considered.

7.5 Fluids:

Patients should be encouraged to drink at least 2 L of water on the day of infusion.

7.6 Antiemetic Therapy

PO Ondansetron 4-8 mg BD at the start of infusion, and for 2-3 days post- infusion. Depending on local practice, PO Metoclopramide 10 mg TDS for 48 hours could also be used.

7.7 Bone Protection

Should be considered in accordance with Royal College of Physicians guidelines.

7.8 GnRHa therapy to prevent ovarian failure

Cyclophosphamide can lead to ovarian failure. GnRH agonists are typically given injections once every 4 weeks during (Goserelin acetate 3.6 is stocked in UHL), with the first dose starting 2 weeks prior to initiation of cyclophosphamide and continuing for the duration of treatment with cyclophosphamide.

8.Drug Interactions

This list is not exhaustive; please refer to the **British National Formulary** or **Summary of Product Characteristics** available from Medicines Information.

Increased risk of myelosuppression following concurrent administration of other marrow depressant drugs.

The Consultant must assess the risk/benefit of further myelosuppression and allow an adequate wash out period (usually one week) when switching from mycophenolate or azathioprine. Patients must be counselled on how to recognise signs and symptoms of myelosuppression and what action to take if these develop (see under Febrile Neutropenia – above). Patients must be issued with a medicines monitoring booklet.

Manufacturer advises avoid concomitant use of cyclophosphamide with clozapine (increased risk of agranulocytosis).

If this situation arises the consultant must assess the risk/benefit in conjunction with the consultant psychiatrist managing clozapine therapy. Clozapine therapy requires strict blood monitoring and if the FBC is abnormal, clozapine therapy may need to be stopped.

Allopurinol may increase risk of myelosuppression with cyclophosphamide.

There is some evidence that the incidence of serious bone marrow suppression can be increased but this has not been confirmed in a controlled study and the interaction is not established with clear certainty. No additional action required as increased toxicity would be detected as part of pre-treatment investigations.

Itraconazole: may enhance adverse effects of cyclophosphamide

No additional action required as increased toxicity would be detected as part of pre-treatment investigations.

Sulphonylureas: enhanced hypoglycaemic effect.

Patients should be advised that hypoglycaemia may occur and to monitor blood glucose if they experience signs and symptoms of hypoglycaemia and treat accordingly.

9. Advice for staff caring for patient following administration of IV Cyclophosphamide

Pregnant staff

- If a staff member becomes pregnant, it is imperative that the manager is informed at the earliest opportunity. This allows for an individual risk assessment for pregnant and breastfeeding mothers to be completed.
- Risks should be mitigated to an acceptable level by, for example ensuring they are allocated to care for a team of patients that does not include the patient having Cyclophosphamide. If risks cannot be mitigated to an acceptable level then consideration should be given to redeploying the member of staff until the risk is nullified. Evidence is scant as to the risk to this group of staff, but risk will be minimised by the wearing of appropriate PPE of apron and gloves.

Patient care

- Cytotoxic substances can be excreted in all bodily fluids -urine, vomit, faeces and even sweat. Most cytotoxic drugs are cleared within 48-72 hrs but some take longer – up to 7 days following administration so it is important to take appropriate precautions.

- Cyclophosphamide can cause irritation of the bladder. It is important to encourage the patient to drink plenty of fluids during the 24 hrs post administration. It is important to observe urine for evidence of haematuria – it is beneficial to perform urinalysis whilst in hospital. It is recommended that the patient uses a bed pan or urinal in order to monitor for abnormalities. If there is any evidence of blood, please inform the medical team as it may be necessary to administer further IV Mesna which helps to protect the bladder and reduce any irritation. It is also necessary to advise the patient to empty their bladder frequently to avoid retaining urine.

- Staff handling patient's bodily fluids during this time should wear PPE – apron and gloves –preferably Nytraguard ChemoPure (Purple gloves).

- Any contaminated patient clothing should be removed and placed in a sealed plastic bag until it can be laundered. Gloves need to be worn when handling contaminated clothing.
    - If you become contaminated with cytotoxic bodily fluids – it is important to wash skin with soap and water for at least 15 seconds. If bodily fluids splash into the eyes, remove contact lenses immediately if worn, and rinse eyes for 15 minutes with

water. If eyes or skin become red or irritated for more than 1 hour, you need to seek medical advice.
- Hospital linen, including towels, should be dealt with as infected linen.
- Disposable pads should be changed and disposed of immediately and the surrounding skin cleansed thoroughly with soap and water.
- Cytotoxic spillage kits should be used to deal with any spillages of either Cyclophosphamide or contaminated body fluids – this should be available in the ward area.

10. Post administration advice for patients whilst in hospital

Cytotoxic substances can be excreted in all bodily fluids -urine, vomit, faeces and even sweat. Most cytotoxic drugs are cleared within 48-72 hrs but some take longer – up to 7 days following administration so it is important to take appropriate precautions:

- Hands should be thoroughly washed with water and soap following use of the toilet.
- We recommend that during this period of time that men sit down when using the toilet to pass urine, to avoid splashes.
- It is important to place the lid down when flushing the toilet.
- Any contaminated clothing / bedding / towels should be placed in a sealed plastic bag until it can be laundered. Gloves need to be worn when handling contaminated clothing.
- Once at home any bedding /towels should be treated in the same way as contaminated clothing.
- Avoid sharing towels.
- Laundry should be at maximum possible temperature as a single garment on a full cycle, not a quick wash.

Appendix

Standard GP Letter for Cyclophosphamide – IV/Oral

After discussing the risks and benefits of Cyclophosphamide using the ARC information sheet, *(name of patient)* has consented to treatment.

He/She is aware that this is an immunosuppressive drug that has a potential to increase the risk of infections and knows to seek urgent medical advice if any symptoms of infection occur (e.g. sore throat, fever, cough, diarrhoea, and discomfort on passing urine). If she/he does consult you, please consider that *he/she* may be neutropenic and require intravenous antibiotics and therefore, admission to (name of hospital) via the medical take.

Immunisation with pneumovax and an annual flu vaccine is recommended and we have advised contacting your surgery to organise this.

He/She has been screened for varicella zoster antibodies and *has/does not have* chicken pox immunity *(remove this statement depending on local policy for checking)*.

(Women)

She is aware that Cyclophosphamide can adversely affect a developing foetus and it is essential to avoid pregnancy during, and for 6 months after, treatment. She is aware of the need for adequate contraception and she may seek your further advice. Cyclophosphamide can potentially cause an earlier menopause with associated loss of fertility.

(Men)

He knows to avoid fathering a child during, and for 6 months after treatment, and is aware of the need for adequate contraception. Cyclophosphamide is cytotoxic and could reduce future fertility; we have discussed sperm banking which has been *arranged/ declined.*

Ondansetron has been used to prevent nausea, but if this does occur and oral or sublingual drugs cannot be tolerated then I.M. Metoclopramide or Prochlorperazine may be helpful. Mesna has been given to reduce the risk of bladder irritation/cystitis. Cotrimoxazole has been started to reduce the risk of pneumocystis jirovecii (PCP) infection having ascertained no history of sulphonamide allergy.

Key References

Lapraik C, Watts R, Bacon P et al. BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis. Rheumatology 2007;46:1–11

Mukhtyar C, Guillevin L, Cid MC et al. EULAR Recommendations for the management of primary small and medium vessel vasculitis. Annals Rheum Dis 2009;68:310-317.

Hellmich B, Sanchez-Alamo B, Schirmer JH*, et al* EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update *Annals of the Rheumatic Diseases* 2024;**83:**30-47.

Fanouriakis A, Kostopoulou M, Andersen J*, et al* EULAR recommendations for the management of systemic lupus erythematosus: 2023 update *Annals of the Rheumatic Diseases* 2024;**83:**15-29

Christopher P Denton, Lorenzis, Roblin, Goldman, Alcacer-Pitarch, Blamont, Buch, Carulli, Cotton, Del Galdo, Derrett-Smith, Douglas, Farrington, Fligelstone, Gompels, Griffiths, Herrick, Hughes, Pain, Pantano, Pauling, Prabu, O'Donoghue, Renzoni, Royle, Samaranayaka, Spierings, Tynan, Warburton, Ong, The 2024 British Society for Rheumatology guideline for management of systemic sclerosis, *Rheumatology*, 2024;, keae394, https://doi.org/10.1093/rheumatology/keae394

de Groot K, Harper L, Jayne D et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis. A randomized trial. . Ann Intern Med.2009;150:670-80.

de Groot K, Rasmussen N, Bacon PA et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52(8):2461-9.

BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF treatment. Thorax 2005;60:800–5.

BSR (2002) Vaccinations in the immunocompromised person. Guidelines for the patient taking immunosuppressant, steroids and biologic therapies. www.rheumatology.org.uk

Gluck T. Vaccinate your immunocompromised patients. Rheumatology 2006;45:9–10

Hoyles, RK, Ellis, RW, Wellsbury, J, et al. A multicenter, prospective, randomized, double- blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum 2006; 54:3962.

Tashkin DP et al, Cyclophosphamide versus Placebo in Scleroderma Lung Disease. NEJM 2006;354:2656-2666

Houssiau, FA, Vasconcelos, C, D'Cruz, D, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons

from long-term follow up of patients in the Euro-Lupus Nephritis Trial. Arthritis Rheum 2004; 50:3934.

Gourley MF, Austin HA III, Scott D et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. Ann Intern Med 1996; 125: 549– 557

Stamp L, Hust M. Is there a role for Consensus Guidelines for PCP prophylaxis in immunosupressed patients with rheumatic diseases?. J Rheumatol 2010;374:686-688

Easy-BILAG: a new tool for simplified recording of SLE disease activity using BILAG-2004 index Lucy M Carter, Caroline Gordon, Chee Seng Yee, Ian Bruce, David Isenberg, Sarah Skeoch, Edward M Vital medRxiv 2021.07.30.21261385; doi: https://doi.org/10.1101/2021.07.30.21261385

John H. Stone, Peter A. Merkel, Robert Spiera, Philip Seo, Carol A. Langford, Gary S. Hoffman, Cees G.M. Kallenberg, for the RAVE−ITN Research Group* Published July 15, 2010, N Engl J Med 2010;363:221-232, DOI: 10.1056/NEJMoa0909905

Emmi, G., Bettiol, A., Gelain, E. et al. Evidence-Based Guideline for the diagnosis and management of eosinophilic granulomatosis with polyangiitis. Nat Rev Rheumatol 19, 378–393 (2023). https://doi.org/10.1038/s41584-023-00958-w