

Cyclophosphamide Therapy for Paediatric Rheumatology and Renal Patients (version 2)

This document is for paediatric patients who are receiving Cyclophosphamide therapy for rheumatological and/or renal diseases including Systemic Lupus Erythematosus, Juvenile Dermatomyositis, Wegener's Granulomatosis, Polyarteritis Nodosa, or Systemic Sclerosis. It is based on the existing protocols and supersedes those documents. Copies of earlier protocols should be destroyed.

Increasing numbers of children with rheumatological and renal diseases are being treated with Cyclophosphamide. This document details the 2 intravenous protocols to be used from now on. Each patient will be assigned to one or the other by the consultant in charge of the case and this should be clearly documented on all letters and prescriptions. **Schedule A** is similar to the one traditionally used to treat renal lupus, but **Schedule B** is more often used for those with more severe, life-threatening rheumatological conditions. Oral regimes of Cyclophosphamide are not dealt with specifically by this document, but the principles, particularly regarding infections are the same.

General Considerations

Cyclophosphamide has a number of side effects, both short and long-term. Short-term side effects include: nausea; hair loss; and, in particular, immunosuppression. The most notable long-term effects are the potential to cause fertility problems and, with higher doses, the risk of secondary malignancies. All of these should have been discussed before starting Cyclophosphamide and the following should be checked and noted

1. **Varicella and Measles status** – All patients should have serology sent to check for immunity to both these viruses, and the results should be clearly documented in the notes. In non-immune patients consideration should be given to immunisation before starting immunosuppression (although the timescale for doing this may often be impractical). You should be familiar with the protocol for dealing with subsequent Varicella or Measles contacts and disease. A copy of this is in the Rheumatology files on each paediatric ward and is also available on the intranet (<http://intranet/Policies/Launchtext.asp?launchit=2855>). Patients who develop chickenpox or shingles whilst immunosuppressed should be treated with IV Acyclovir and then have prophylactic acyclovir or valacyclovir until 2 months after their course of Cyclophosphamide is finished (see later).
2. **Tuberculosis (TB) status** – All patients should have a CXR and Quantiferon Gold test done to, as far as possible exclude, latent TB and the result recorded in the notes.
3. **Other Vaccinations:** All live vaccines are contraindicated in children on Cyclophosphamide. Inactivated vaccines may have reduced efficacy but should still, with the exception of Human Papilloma Vaccine (HPV), be given as part of the routine immunisation schedule. HPV vaccination has been associated with “flares” of autoimmune diseases and as such is not usually recommended until the patient is in remission. Annual Flu vaccine should be recommended to all children on cyclophosphamide as per the RCPCH Guidance (Immunisation in the immuno-compromised child (available at http://www.bspar.org.uk/downloads/clinical_guidelines/Immunocomp.pdf))
4. **Sperm banking** – in pubertal / post-pubertal boys this should be offered. Please contact Reproductive Medicine at the Centre For Life on 0191 219 4740 to arrange this. Referral letter should be sent to Prof Alison Murdoch / Dr Jane Stewart at: Reproductive Medicine, International Centre For Life, Times Square, Newcastle upon Tyne, NE1 4EP or faxed to 0191 219 4747 and urgent referrals can usually be accommodated

Infections:

Patients receiving Cyclophosphamide are highly vulnerable to all infections, and their immune system may work in such a way as to make the manifestations of infection less clinically obvious. This is particularly important in those patients with indwelling venous catheters.

Prophylaxis: This should be commenced at the start of therapy and should only be discontinued after discussion with the consultant paediatric rheumatologist / nephrologist, and not within 2 months of finishing treatment:

1. **Bacterial:** All patients on Cyclophosphamide should be taking bacterial prophylaxis in the form of once-daily Co-Trimoxazole (Septrin) (Children under 5yrs should receive 240mg od, and those over 5yrs 480mg od). Patients unable to take Co-Trimoxazole should be offered once-daily Azithromycin 10mg/kg (max 250mg) as an alternative.
2. **Fungal:** All patients with SLE on cyclophosphamide should receive once-daily Itraconazole prophylaxis 5mg/kg/day, but other children with complex immunosuppression, especially if neutropaenic (total neutrophil count <1.0) may also benefit. This should be discussed with the relevant consultant.
3. **Viral:** Prophylaxis against Herpes viruses with Acyclovir is not routinely needed but non-immune children with complex immunosuppression, especially if lymphopaenic (<1) may benefit. This should be discussed with the relevant consultant. Children in contact (same room for >15mins, or face to face contact) with Varicella or Measles should be dealt with as follows:
 - a. **Known immunity:** no treatment but child must be fully undressed and examined by parent/carer twice a day and if spots develop admitted to hospital as above. For children who are very heavily immunosuppressed with a Varicella contact consider giving prophylactic oral Acyclovir 10mg/kg/dose qds for 7 days (discuss with consultant first).
 - b. **Unknown / non-immune:** within 72 hrs of exposure these children may be given either of the following:
 - i. **Varicella**
 1. Zoster immunoglobulin (ZIG) - consider IVIG if child is thrombocytopenic as IM ZIG may cause excessive bruising
 - a. <5yrs of age: 250mg
 - b. 5-10yrs: 500mg
 - c. >10yrs: 750mg
 2. Oral Acyclovir 10mg/kg/dose QDS for 7 days
 - ii. **Measles:** Children are infectious from 3 days before onset of rash until desquamation (usually ~4days). Children within 6 days (most effective if within 3 days) of contact should receive Normal Human Immunoglobulin (available from Public Health Laboratory Service, contact Virologist on-call). Measles is a notifiable disease so the index case must be notified to PHLS.
 1. Normal Human Immunoglobulin
 - a. <1yr: 250mg IM
 - b. 1-2yr: 500mg IM
 - c. >2yr: 750mg IM
 2. Standard Immunoglobulin may be used only if Normal Human Immunoglobulin is not available. Dose is 0.2mg/kg given IV

Acute Infections

All patients taking Cyclophosphamide are advised to contact ward 5 (or the ward at their local hospital to which they have open access) in the following circumstances:

1. Single episode of fever >38C
2. Two episodes of fever between 37.5 and 38C within 24hrs
3. Close contact with infectious disease (esp. Varicella). This normally refers to “kissing contacts” such as close family members rather than school friends, but patients are also at risk if they have been in the same room as an infectious person for longer than 15mins. If in doubt parents should seek advice from ward 5.
4. Parental / patient concern. Especially in the presence of symptoms that may indicate infection (even without documented pyrexia) such as nausea, vomiting, diarrhoea, cough, coryza, etc.
5. Any evidence (even 1 spot) of chickenpox, Zoster (Shingles), or Herpes Simplex (cold sore)

In all circumstances where an acute infection is suspected the patient MUST be reviewed on the paediatric ward as soon as possible (ideally within the hour) and the following checked:

1. FBC (note however that, although profoundly immunosuppressed the WCC may be: normal, low due to previous cyclophosphamide, or raised due to steroid therapy)
2. ESR and CRP
3. U+E, Creatinine and LFT's
4. Blood cultures
5. Urine cultures

Other investigations such as throat swabs, cough swabs, viral PCR, lumbar puncture etc should be done if clinically indicated but are not routine, however if respiratory signs are present (hypoxia, tachypnoea etc) then Pneumocystis infection must be considered and CXR and BAL may be necessary.

These patients will almost always need admission and IV antibiotics. They must be discussed with the consultant paediatric rheumatologist / nephrologist if admitted during normal working hours. Out-of hours there is no paediatric rheumatologist on call and the paediatric immunologist on-call (available via switchboard) should be contacted. Antibiotic regimes may vary according to individual circumstances but in general the following regimes are applicable in patients with normal renal function (For patients with impaired renal function this **must** be discussed with the Nephrologist on-call before starting treatment)

1. **Central line in situ: Teicoplanin 6mg/kg 12hrly for 3 doses then once-daily and Meropenem 20mg/kg tds (max 2g)**
2. **No Central line: Ceftazidime 50mg/kg tds (max. 2g) and Gentamycin 5mg/kg od, or Meropenem 20mg/kg tds (Max 1g) and Gentamycin 5mg/kg od**
3. **Varicella (Chickenpox or Shingles): IV Acyclovir 500mg/m²/dose 8-hrly for at least 5 days, and then prophylaxis with oral acyclovir 10mg/kg/dose twice a day until at least 2 months after finishing Cyclophosphamide.**

Schedule A: Modified NIH Renal Lupus Protocol

Cyclophosphamide

Dose: **750 – 1000mg/m²/dose** by IV infusion over 15mins once a month for, initially, a total of 6months. **This will be prescribed by the consultant paediatric rheumatologist or nephrologist only** and ordered in advance.

Starting dose is usually 750mg/m². A lower starting dose of 500mg/m² may be used for Nephrotic Syndrome, significant HSP/IgA Nephropathy, or when a patient has severe renal failure and is dialysis-dependent as bone-marrow toxicity may be greater. If the patient is dialysis-dependent the dose should be given 8hrs before dialysis and subsequent doses varied as below.

Subsequent doses are dependent on the change in White Cell Count (WCC) 10-14 days after the dose. The dose is increased by 25% if the WCC has not fallen by 25% or more by this time, and decreased by 25% if the WCC falls to <3 (or neutrophil count <1.5).

Fluids

All patients should receive IV fluids **unless they are dialysis dependent** (these patients' need for fluids will be determined individually in conjunction with the paediatric nephrology staff).

0.18%Saline / 4%Dextrose should be given at a rate of **80mls/ m²/hr** for 2hrs before and 6 hours after the Cyclophosphamide.

MESNA

Patients receiving these doses do not need MESNA in their pre or post-hydration fluids. If higher doses of Cyclophosphamide are given (>1g/m²) then MESNA to give a **total dose equivalent to 100% of the Cyclophosphamide dose** should be added to the hydration fluids to run over the whole 8hrs of pre and post-hydration.

Ondansetron

Ondansetron at a dose of 5mg/ m²/dose (max.8mg) should be given IV or Orally 1hr before the Cyclophosphamide and 8hrly for up to 2days afterwards as needed.

Prednisolone

60mg/m²/ day for 6 weeks from start of Cyclophosphamide therapy, then 40mg/m² alt.days for 6 weeks, before tapering to 0.25mg/kg alt.days. Deflazacort may be considered if patient is very steroid-toxic

Monitoring

All patients need the following blood tests taken before each dose of Cyclophosphamide. Cyclophosphamide must not be given without prior discussion with the consultant paediatric rheumatologist / nephrologist if the patient is Leukopaenic (WCC<3), Neutropaenic (WCC< 1.5), or has a febrile illness:

FBC / ESR / U+E / Creatinine / LFT

Early morning urine sample sent for **albumin:Creatinine ratio**

10-14 days after each Cyclophosphamide dose an FBC needs to be checked

In addition:

Patients with SLE need C3, C4, ANA, dsDNA, checked before every dose and Lupus Anticoagulant, and anti-cardiolipin antibodies checked every 3 months

Patients with Juvenile Dermatomyositis need CK and LDH checked each month.

Patients with Wegener's need ANCA titres checked every month.

Patients taking concomitant Anti-TNF therapy need an Autoantibody screen (to include anti-dsDNA) every 3 months.

Schedule B: Birmingham Vasculitis Protocol

Cyclophosphamide

Dose: 15mg/kg every 2 weeks for 3 doses, then every 3 weeks for 3 doses, then every 4 weeks until disease remission achieved. **This will be prescribed by the consultant paediatric rheumatologist /nephrologist only** and ordered in advance.

Methylprednisolone

After each dose of Cyclophosphamide the patient should receive 30mg/kg of Methylprednisolone (Maximum 1g) over 4hrs. A separate protocol is available to detail nursing requirements regarding blood pressure monitoring and a copy should be on each ward. Patients should take their usual oral steroids between each admission; the consultant in charge of the case sets the dose of this individually.

Fluids

All patients should receive IV fluids **unless they are dialysis dependent** (these patient's need for fluids will be determined individually in conjunction with the paediatric nephrology staff).

0.18%Saline / 4%Dextrose should be given at a rate of **80mls/ m²/hr** for 2hrs before and 6 hours after the Cyclophosphamide. The rate should be decreased to allow the Methylprednisolone to go through the same line.

MESNA

Patients receiving 15mg/kg Cyclophosphamide do not need MESNA in their pre or post-hydration fluids.

Ondansetron

Ondansetron at a dose of 5mg/ m²/dose (max.8mg) should be given IV or Orally 1hr before the Cyclophosphamide and 8hrly for up to 2days afterwards as needed.

Monitoring

All patients need the following blood tests taken before each dose of Cyclophosphamide. Cyclophosphamide must not be given without prior discussion with the consultant paediatric rheumatologist / nephrologist if the patient is leukopaenic (WCC<3), neutropaenic (WCC< 1.5), or has a febrile illness:

FBC / ESR / U+E / Creatinine / LFT

Early morning urine sample sent for **Albumin:Creatinine ratio**

In addition:

Patients with SLE need C3, C4, ANA, and dsDNA, checked every month and Lupus Anticoagulant, and anti-cardiolipin antibodies checked every 3 months

Patients with Juvenile Dermatomyositis need CK and LDH checked each month.

Patients with Wegener's need cANCA titres checked every month.

Patients taking concomitant Anti-TNF therapy need an Autoantibody screen (to include anti-dsDNA) every 3 months.

Cyclophosphamide Record Sheet - Record of attendance for therapy

(To be filled in by ward SHO)

Name:
Hospital Number:
Date of Birth

Schedule: A (modified NIH renal lupus)
 B (modified Birmingham Vasculitis)

Date	Treatment number	Dose (Total)	Dose (mg/m ² or mg/kg)	WCC	Neutrophil count	Side-effects
	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					

Plan for Admission (1st dose usually as an inpatient, but most subsequent doses as day-case on ward 5).

1. Patient admitted. Clerked by SHO on ward. This must include checking for intercurrent infections and involve a full physical examination, documented in the notes. Paediatric Rheumatology or Nephrology SpR (or consultant if not available) informed of arrival and of any problems **before** Cyclophosphamide started.
2. IV line inserted (or central line accessed) and bloods taken as per protocol above (please check disease - specific bloods are also done). Urine checked for presence of Haematuria / Proteinuria / Glycosuria
3. IV fluids started as per regime
4. After 1 hr of pre-hydration give Ondansetron as prescribed
5. After 2 hrs of pre-hydration, **if FBC normal**, IV Cyclophosphamide given over 15mins (if FBC not normal this **must** be discussed with SpR or Consultant before giving as dose may need to be decreased or even omitted).
6. Once Cyclophosphamide is finished, Methyl Prednisolone started if on Schedule B. This can run concurrent with post-hydration fluids (Total fluid rate to not exceed 80mls/m²/hr)
7. 6hrs post-hydration as per protocol. Patient can go home once total 8hrs hydration completed.
8. Make sure patient has adequate supplies of medications needed at home, especially oral steroids, Ondansetron, and prophylactic antibiotics.
9. If on Schedule A, arrangement made for FBC to be checked in 10-14days time.
10. Plain urine bottle for early-morning albumin:creatinine ratio given for next admission.
11. Patient booked to be re-admitted at appropriate time for next dose of Cyclophosphamide depending on schedule being followed. Copy of schedule to be kept in the notes.