Norfolk and Norwich University Hospitals NHS Foundation Trust

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Joint Trust Guideline for the Administration of Ciclosporin for the Treatment of Ulcerative Colitis in Adults

A clinical guideline recommended for use

In:	Adult Acute Trust
By:	Registered nurses, Medical Staff, Pharmacists
For:	Patients with Ulcerative Colitis requiring the administration of ciclosporin
Division responsible for document:	Medicine – Division 1(NNUH)
Key words:	Ciclosporin, Ulcerative Colitis, Monitoring
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Approved by:	Clinical Guidelines Assessment Panel (CGAP) Chairs action ✓
Date of approval:	10th November 2022
Reported as approved to the:	Clinical Safety and Effectiveness Sub-board (NNUH) Clinical Governance (JPUH)
To be reviewed before:	10th November 2025
To be reviewed by:	Dr Mark Tremelling, Simon Nichols, Sarah Griffen
Reference/Trustdocs ID No:	JCG0064 v1 CA5058 – ID No: 8213
Version No:	4
Description of changes:	Updated prescribing on EPMA, monitoring, authors, administration via PVC-free set, & contact details for queries
Compliance links: **If Yes – does the strategy/policy deviate from the recommendations of NICE? If so, why?**	None

This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

The Trust's guidelines are made publicly available as part of the collective endeavour to continuously improve the quality of healthcare through sharing medical experience and knowledge. The Trust accepts no responsibility for any misunderstanding or misapplication of this document.

Joint Trust Guideline for the Management of: Administration of Ciclosporin for the Treatment of Ulcerative Colitis in Adults

Quick reference guideline/s

INDICATION

Severe steroid resistant colitis unresponsive to:

- IV methylprednisolone 40mg twice daily (NNUH)

  or

- IV hydrocortisone 100mg 6 hourly (JPUH)

This is an unlicensed indication and informed patient consent should be sought.

DOSE

2mg per kg body weight (total daily dose)

PRESCRIPTION

Prescribe 'CICLOSPORIN in 50mL SODIUM CHLORIDE 0.9% CONT. INFUSION' on EPMA and enter the correct dose by dividing the total daily dose into four 6-hour infusions, each one made in 50mL of sodium chloride 0.9%. For patients <50kg, the dilution volume is 25mL and you should select 'CICLOSPORIN in **25mL** SODIUM CHLORIDE 0.9% CONT. INFUSION on EPMA'.

e.g. 70kg patient total daily dose = 140 mg

∴35mg in 50mL made up with sodium chloride 0.9% given over 6 hours then repeated

ADMINISTRATION

Give each 6-hour infusion immediately after the previous one to form a continuous infusion.

Each time the infusion is changed the giving set should also be changed, and must be PVC-free.

MONITORING REQUIREMENTS

	Baseline	Frequency during IV	Frequency during PO
Abdominal X-ray	Y	N	N
Cholesterol	Y	N/A	N/A
U&Es, FBC, CRP, magnesium, LFTs	Y	Daily	Weekly for 6/52 or until levels stable, then monthly
Blood pressure	Y	QDS	
Ciclosporin levels	N/A	After 72hrs, then twice per week	
Blood glucose	Y	Random BMs (as per protocol for steroids)	
Blood lipids	Y	N	After 1 month of treatment
Stool chart	Whilst inpatient		

During Infusion

On day 1 of the infusion close observation for at least 30 minutes.
Temperature, pulse, and BP every 6 hours. As infusion is continuous, observations on subsequent days should continue at 6hrly intervals.

There is a **risk of anaphylaxis**, and so it is important that patients are observed for at least 30 minutes after starting infusion and at frequent intervals thereafter, with medicines to treat anaphylaxis available on the ward.

PROPHYLAXIS AGAINST PJP (PCP)

Clinicians should consider prescription of co-trimoxazole for the duration of ciclosporin therapy, at a dose of 960mg once a day three times a week although this is not mandatory.

FURTHER INFORMATION

For further information refer to full protocol below, manufacturer's literature, contact your ward pharmacist or Gastroenterology.

Objective/s

The aim of this document is to ensure the safe administration of ciclosporin in patients receiving treatment for ulcerative colitis.

Rationale

Ciclosporin is an unlicensed drug in the treatment of ulcerative colitis. The drug itself has a narrow-therapeutic range, requires therapeutic drug monitoring, and has complex requirements for prescription and administration.

This guideline is based on the current CONSTRUCT trial protocol, the Leeds Teaching Hospital Policy 2010 and evidence from clinical trials.

Broad recommendations

1. WHAT IS CICLOSPORIN

Ciclosporin is a potent immunosuppressant, commonly used to prevent organ transplant rejection. There is evidence (Grade A) that intravenous ciclosporin can be effective for patients with severe corticosteroid resistant ulcerative colitis, with initial response rates of 80%[1,2,3]. In reported case series the likelihood of avoiding colectomy over 2-3 years is 40-50%[4].

2. INDICATIONS FOR USING CICLOSPORIN

IV ciclosporin is indicated in acute severe ulcerative colitis refractory to IV corticosteroids, where surgery would not be the first choice therapy. This is an unlicensed indication, and informed patient consent should be sought.

Ciclosporin should be considered after 3 days of IV steroids where improvement is not being seen (stool frequency >8/day or CRP >45mg/L at 3 days has been shown to predict the need for surgery in 85% of cases[5])

Those patients who respond favourably to IV ciclosporin will normally be switched to oral ciclosporin (see later for dose conversion).

3. CONTRA-INDICATIONS

- Known hypersensitivity to ciclosporin or any excipients
- Concomitant use of tacrolimus
- Known hypersensitivity to polyethoxylated castor oils (anaphylaxis risk)
- Low serum cholesterol (high likelihood of side effects)
- Uncorrected hypomagnesaemia (likelihood of seizures)

4. DOSAGE AND ADMINISTRATION

Total daily dose = 2 mg / kg

The total daily dose (or closest approximation) should be equally divided into four 6-hour infusions, given continuously. Each dose should be given in 50ml of sodium chloride 0.9%, unless the patient is less than 50kg. In this case make up to 25ml with sodium chloride 0.9%.

e.g. 70kg patient, total daily dose = 140 mg

∴ 35mg in 50ml made up with sodium chloride 0.9% given over 6 hours then repeated

Ciclosporin is not compatible with polyvinyl chloride (PVC) and therefore the infusion must be prepared and administered with non-PVC lined administration sets. **Polyethylene (PE) lined sets must be used instead. These are commonly used to administer heparin and insulin and are available on all wards.** (NB. The packaging for PE lined administration sets may also reference PVC; however this describes the PVC component on the outside of the tubing – the inner lining of the set is PVC free).

5. CONCOMITANT IBD THERAPY

Corticosteroids

Patients should normally be maintained on

- IV methylprednisolone 40mg twice daily (NNUH)

  or

- IV hydrocortisone 100mg 6 hourly (JPUH)

during initial ciclosporin dosing until clinical improvement allows conversion to oral steroid dosing and then steroid dose reduction to commence.

Oral mesalazine

Patients already taking oral mesalazine therapy should have their current dose continued during ciclosporin therapy.

Rectal Therapy

Rectal therapy with corticosteroids and/or mesalazine preparations may also be continued during ciclosporin therapy if appropriate.

6. DRUG INTERACTIONS

Drugs known to have nephrotoxic effects should be used with extreme caution in patients on ciclosporin. Commonly used potentially nephrotoxic drugs include:

- NSAIDs (e.g. aspirin, diclofenac etc)
- aminoglycosides (e.g. gentamicin)
- ciprofloxacin

A number of drugs may increase or decrease the plasma or whole blood levels of ciclosporin within the body, and ciclosporin can affect the clearance of other medicines. Interactions should be checked when initiating treatment using the BNF or by referring to the summary of product characteristics.

Patients should be advised to avoid grapefruit juice during oral ciclosporin dosing as it has been reported to increase bioavailability.

7. ADVERSE REACTIONS

There is a **risk of anaphylaxis**, and so it is important that patients are observed for at least 30 minutes after starting infusion and at frequent intervals thereafter, with medicines to treat anaphylaxis available on the ward.

Side effects are usually dose-dependent and responsive to dose reduction.

A frequent and potentially serious complication is a dose-dependent and reversible increase in serum creatinine and urea during the first few weeks of therapy. Less frequently renal structural changes may develop - this is more common with long term treatment and is therefore less likely to be a problem in our patients.

Apart from impaired renal function, the most frequently observed side effects include hirsutism, tremor, hypertension, hepatic dysfunction, fatigue, gingival hypertrophy, gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhoea) and burning sensations of the hands and feet (usually during the first week of treatment).

A full list of side effects can be found in the product monograph[6].

8. MONITORING REQUIREMENTS

<table>
<tr><th></th><th>Baseline</th><th>Frequency during IV</th><th>Frequency during PO</th></tr>
<tr><td>Abdominal X-ray</td><td>Y</td><td>N</td><td>N</td></tr>
<tr><td>Cholesterol</td><td>Y</td><td>N/A</td><td>N/A</td></tr>
<tr><td>U&Es, FBC, CRP, magnesium, LFTs</td><td>Y</td><td>Daily</td><td rowspan="4">Weekly for 6/52 or until levels stable, then monthly</td></tr>
<tr><td>Blood pressure</td><td>Y</td><td>QDS</td></tr>
<tr><td>Ciclosporin levels</td><td>N/A</td><td>After 72hrs, then twice per week</td></tr>
<tr><td>Blood glucose</td><td>Y</td><td>Random BMs (as per protocol for steroids)</td></tr>
<tr><td>Blood lipids</td><td>Y</td><td>N</td><td>After 1 month of treatment</td></tr>
<tr><td>Stool chart</td><td colspan="3">Whilst inpatient</td></tr>
</table>

Magnesium

Hypomagnesemia is a common finding of ciclosporin treated patients and has been proposed as both a cause and a consequence of induced nephrotoxicity. Hypomagnesemia should be

corrected before commencing ciclosporin. Refer to policy on management of hypomagnesaemia.

Cholesterol

Ciclosporin is a highly lipophilic drug. Studies in transplant patients have suggested that the risk of neurotoxicity is increased in patients with hypocholesterolaemia (the other major risk factor being ciclosporin toxicity itself)[7].

Patients being considered for IV ciclosporin therapy should therefore have a pre-treatment cholesterol level measured. A level of >3 mmol/L is considered acceptable for dosing at 2mg/kg/day IV. A level of <3mmol/L does not preclude the patient from treatment but the risk of neurotoxicity may be increased. This should be a Consultant decision.

If a patient develops signs of neurotoxicity on ciclosporin a dose reduction or discontinuation of therapy should alleviate the symptoms.

Renal Function (serum creatinine, urea and potassium)

Ciclosporin can impair renal function. This is a frequent and potentially serious complication of therapy. Close monitoring of creatinine and urea is required and dose adjustment may be necessary. Increases in these values during the first few weeks of therapy are usually dose-dependent and respond to dosage reduction. The dose should be reduced if serum creatinine increases by 30% above baseline. Ciclosporin also enhances the risk of hyperkalaemia, especially in patients with renal dysfunction or those taking other medicines that can cause hyperkalaemia. Therefore serum potassium should be monitored and hyperkalaemia treated if this occurs.

Liver Function

Ciclosporin may affect liver function, and dosage adjustment based on the results of bilirubin and liver enzyme monitoring may be necessary. The dose should be reduced if serum liver enzyme values increase by 50% from base line.

Blood Pressure

Ciclosporin can cause hypertension and regular monitoring of blood pressure is required during therapy. If hypertension develops, appropriate antihypertensive therapy must be instituted. The dose of ciclosporin should be reduced where diastolic blood pressure remains consistently over 90 mm Hg despite antihypertensive therapy.

Other Tests

Abdominal X-Ray at baseline, then as indicated
Daily CRP and stool chart
Daily FBC due to risk of blood dyscrasias, such as leucopenia and thrombocytopenia
Blood glucose due to risk of hyperglycaemia
Lipids due to risk of hyperlipidaemia at baseline and after 1 month of treatment

Ciclosporin Levels

The measurement of ciclosporin levels is recommended to give an indication of appropriate dosing and to inform dose adjustment as appropriate.

Levels Aim for 150-250nanograms/millilitre[2]. Ciclosporin toxicity can occur above 300 nanograms/millilitre.

Timing Steady state will not have been reached until approximately 72hrs. Levels should not be taken until at least the middle of the 3rd day (approx 60hrs)

Frequency Ciclosporin levels should be taken twice weekly while on IV therapy and week 1 of oral therapy, then once weekly thereafter until levels are stable or for six weeks. Thereafter levels can be taken monthly until ciclosporin is stopped. Should doses need to be adjusted the frequency should return to weekly again until stable.

9. THE NURSE'S RESPONSIBILITY WHEN GIVING CICLOSPORIN

Ciclosporin injection contains polyethoxylated castor oil which has been reported to cause anaphylactoid reactions. These reactions consist of flushing of the face and upper thorax, acute respiratory distress with dyspnoea and wheezing, blood pressure changes and tachycardia. Special caution is therefore necessary in patients who have previously received IV injections or infusions containing polyethoxylated castor oils, or in patients with allergic conditions.

On day 1 of the infusion, closely observe patient for at least 30 minutes. Monitor temperature, pulse, and BP every 30 minutes for the first 2 hours, then every 6 hours. As infusion is continuous, monitoring should continue every 6 hours on subsequent days.

If anaphylaxis occurs, the infusion should be discontinued and the patient managed in accordance with common clinical practice.

Side effects are usually dose dependent and responsive to dose reduction. Any adverse effects or changes in the above clinical observations must be reported to the medical team.

10. CONVERSION TO ORAL THERAPY

IV ciclosporin will normally be given for up to 7 days depending on response (unresponsive patients are likely to require surgical intervention), following which patients will routinely be converted to oral therapy.

The brand **CAPIMUNE** has a more predictable bioavailability than the older NEORAL brand and should be prescribed by brand name.

For patients **not** previously treated with IV ciclosporin CAPIMUNE should be initiated at a total daily dose of 5.5 mg/kg. The total daily dose should be given in **two equal divided doses**, morning and evening.

For patients previously receiving IV ciclosporin with appropriate drug therapeutic levels the correct total daily oral dose is 3 x the total daily IV dose. The total daily oral dose should be given in **two equal divided doses**, morning and evening.

Monitoring

Regular weekly monitoring (blood pressure, renal and hepatic function, magnesium and trough ciclosporin levels) should continue for the first 6 weeks of ciclosporin therapy, thereafter monthly monitoring if all parameters are stable[8]. Ciclosporin levels should fall into the range quoted previously.

11. PNEUMOCYCTIS JIROVECI PNEUMONIA (PJP) PROPHYLAXIS

Most patients should receive prophylaxis against PJP with co-trimoxazole at a dose of 960mg once a day three times a week. This is a decision for the consultant responsible for the patients care.

12. FURTHER INFORMATION

For further information regarding the use of ciclosporin or for clarification of any part of these guidelines contact gastroenterology, your ward pharmacist or consult the manufacturer's literature.

13. REFERENCES

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This guideline was adapted from the Leeds Hospital protocol for administration of ciclosporin for ulcerative colitis.