SPRUN

SCOTTISH PAEDIATRIC RENAL AND UROLOGY NETWORK

Standard Operating Procedure for Rituximab in paediatric renal conditions

NOTE

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined based on all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

This guidance has been prepared by NHS National Services Scotland (NSS) National Networks. Accountable to Scottish Government, NSS works at the heart of the health service providing national strategic services to the rest of NHS Scotland and other public sector organisations to help them deliver their services more efficiently and effectively. Working across professional and organisational boundaries, National Networks support the delivery of safe, effective healthcare that's designed around patients, carers and families.

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Stakeholders involved	Consultant Paediatric Nephrologists Consultant Paediatricians Paediatricians with a renal interest Renal Nurse Specialists
Methodology used	Literature review of best current evidence – Pubmed search – terms “nephrotic syndrome” “Rituximab” “children/paediatrics” “steroid sensitive” Available Rituximab guidelines from other UK centres – including EMEESY Children’s Kidney Network
Rationale	The SPRUN network was established to support and develop Paediatric renal services throughout Scotland in improving standards of clinical care for patients. The network supports the delivery of evidence based, patient centred care through education, support, development and implementation of clinical guidelines, care pathways and information resources utilising a once for Scotland approach. Nephrotic Syndrome is a relatively common condition seen in paediatrics. However, the use of Rituximab remains under specialist guidance. Provision of a document outlining its indications, assessment, work-up and adverse effects, with means of administration, is vital to provide and support a continuing good standard of equitable clinical care for renal patients throughout the network.
Scope	Paediatricians and renal specialists throughout network, managing nephrotic syndrome and requiring the use of Rituximab.
Approval process	The guideline was approved by the SPRUN Steering Group on 22 July 2025. Membership available in Appendix 2.

Contents

1. Standard Operating Procedure Development

1.1 Membership of development group

Consultant Paediatric Nephrologist	Dr Deepa Athavale
Consultant Paediatric Nephrologist	Dr Ben Reynolds
Paediatric Renal Pharmacist	Angela Lamb
Renal Advanced Nurse Practitioner	Ursula Monachan

This document has been discussed and approved through the Scottish Paediatric Renal and Urology Network (SPRUN).

1.2 Patient population and target audience

This document provides information on the Standard Operating Procedure (SOP) for the investigation, treatment with rituximab and subsequent management of frequently relapsing or steroid dependent nephrotic syndrome in children. The SOP applies to children throughout Scotland with:

- frequently relapsing steroid sensitive nephrotic syndrome (FRSSNS)
- steroid dependent nephrotic syndrome (SDNS)

This document is intended for use by all health professionals (for example, doctors, nurses and pharmacists) who look after children receiving rituximab as part of treatment of their nephrotic syndrome within Scotland.

1.3 Objectives and clinical questions

- Describe eligibility criteria for rituximab use in FRSSNS and SDNS.
- Detail investigations required in preparation for administration of rituximab.
- Provide dosing guidelines.
- Follow up investigations.
- Provide adequate information for children and their families on the use of rituximab, its monitoring and planned follow up.

1.4 Methodology

This SOP has used the best evidence currently available including literature searches of PubMed, using the terms “paediatric” / “children”, “nephrotic syndrome”, “steroid sensitive” and rituximab. Evidence currently is predominantly from open labelled studies and expert opinion. Only articles written in English were included.

2. Introduction

Rituximab is a genetically engineered chimeric monoclonal antibody used to deplete the B cell population by targeting the surface marker CD20 antigen. Rituximab is not licenced to treat paediatric renal conditions but it has been used extensively in practice and shown to be effective. See off label drugs statement (Appendix 3).

Rituximab is used to provide a steroid sparing alternative treatment to relapsing nephrotic syndrome and potentially allows 6 months in remission and in some individual cases, up to 18 months.

SPRUN Rituximab patient information leaflet is available for patients and families from the SPRUN website: SPRUN Rituximab Patient Leaflet

2.1 Eligibility

Patients **must** be referred to and reviewed by a paediatric nephrologist before treatment is initiated.

2.2 Treatment contra-indications

- Active acute or chronic infection/ positive Mantoux
- Hypersensitivity to rituximab or other murine proteins
- Severe immunodeficiency – Hypogammaglobulinaemia or known low CD4/CD8 counts
- Clinically significant neutropenia/lymphopenia
- Serologic evidence of current or past HIV, Hepatitis B, or Hepatitis C infection
- Serologic or clinical evidence of current or recent viral infection (IgM +ve or +ve PCR): CMV, EBV, varicella infection. Serology/PCR for adenovirus infection or parvovirus infection only if clinically indicated.
- History of malignancy other than PTLD
- Pregnancy

2.3 Cautions

- Rituximab should be used with caution in patients with a history of cardiovascular disease or renal impairment (may require dose reduction).
- Vaccinations: (**refer to Green Book, Chapter 6, for up to date information** (Greenbook_chapter_6.pdf (publishing.service.gov.uk))
    - Live vaccines are contraindicated post rituximab for 12 months, or longer if B cells remain depleted.
    - Inactivated vaccines may be required to be repeated.
- Hypogammaglobulinaemia (recovery can be variable and in rare cases, permanent)
    - Increased susceptibility to infections especially varicella.
    - Increased risk with repeated administrations of rituximab.

2.4 Adverse effects

- Infusion reactions (rash, pruritus, wheeze, see Appendix)
    - Mild to moderate infusion reactions – 30-35% at 1st infusion; less with the 2nd
    - Severe infusion reactions are uncommon – frequency is reduced by the concomitant use of IV steroids and pre-medication

- Infections
    - Small increase in serious infections (not opportunistic infections e.g. TB)

2.5 Screening investigations

To be undertaken and reviewed at least 1 week before administration.

1. FBC + diff WBC
2. Renal (UEs and Bic), bone, liver profiles, CRP
3. Immunoglobulins (IgA, IgG and IgM)
4. Viral serology: IgG/IgM for CMV, EBV, Varicella, Hepatitis B and C ; Hepatitis B surface antigen (Note if repeat Rituximab – and IgG positive – only for IgM and Hep B SAg)
5. Viral serology for adenovirus or parvovirus ONLY IF recent symptomatic illness, (check local lab for sample requirements)
6. Viral PCR (check local lab for sample requirements): CMV and EBV
7. Lymphocyte subsets (CD19/20 count)
8. Consider Mantoux if any clinical suspicion or high risk

3. Ordering Rituximab infusion

- Rituximab needs to be prescribed as brand specific, as per your local health board.
- Within GG&C, the prescription should be sent to the Pharmacy Aseptic Unit at least 48 hours before the proposed infusion time; check with pharmacy prior to ordering. Document on prescription that request will be confirmed on the day of infusion following pre-infusion assessment.
- For other health boards, discuss with local pharmacy and follow standard procedures for ordering.
- It is the responsibility of the renal team to then advise the pharmacy to prepare the drug once all screening results are found to be satisfactory and the patient is fit and well on the day.
- Investigations **do not need to be repeated** on the day of attendance for treatment if these screening results are satisfactory.

3.1 Pre-infusion assessment

Prior to confirming rituximab order with pharmacy/aseptic unit, if applicable or prior to administration:

- Detailed history – including chronic or recent co-morbidity; recurrent infections; allergies
- Ensure normal physical examination and no active infection
- Urine for protein/creatinine ratio (P:CR)
    - Ideally administer when in remission – Urine P:CR <20mg/mmol
    - If patient has proteinuria, discuss with paediatric nephrology regarding administration. Consider administration on an individual basis if urine P:CR >50 - 200mg/mmol

- Presence of hypertension/current anti-hypertensive medication. (Rituximab may cause lower BP during infusion, and these medications may need review prior to administration)

4. Practical considerations on day of infusion

Rituximab should only be administered in an area with appropriately trained staff and full **resuscitation facilities** and close monitoring available. This is usually done on a day-case basis.

The first infusion may take between 6-7 hours to complete (i.e. IV cannula sited and pre-medication given 60 minutes prior. Infusion may take longer if the patient has any adverse reactions (see later section).

5. Treatment dose and co-medication

5.1 Regimen

- I.V. Rituximab 375mg/m^2 (max 500mg)

When calculating the SA, consider ideal body weight for age and gender.

5.2 Prescription

The doctor/ANP should prescribe on a kardex and infusion chart and check with paediatric pharmacist.

5.3 Pre-Medication Drugs

• IV Methylprednisolone 60 minutes before rituximab infusion
(Continue oral prednisolone dose as prescribed)

1-5years - 50mg
6 years and above - 100mg

• Paracetamol 15mg/kg (max. 1gm) orally - 60 minutes prior to infusion
• Chlorphenamine orally 60 minutes prior to infusion

1-5 years – 1mg
6 -12 years – 2mg
12 years+ - 4mg

5.4 Infusion Therapy*- see Appendix 1 for Administration Advice

The following prescription is based on 2mgs/ml

Rituximab can be classified as a cytotoxic since it destroys B cells. Since the drug product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed during preparation of the infusion solution.

Rituximab does not require any special handling precautions beyond those described and is subject to the same considerations as any other preparation for intravenous use, including other monoclonal antibodies.

5.5 Rituximab Infusion

- I.V. Rituximab (calculated dose) in sodium chloride 0.9% (2mg/ml dilution)
- **Use ideal body weight to calculate rate NOT actual weight, up to a max of 50kg.**

INFUSION RATE

Time	mg/hour	ml/hour
1st 30 minutes	1**mg**/kg/hour	0.5**ml**/kg/hour (max 25ml/hr)
2nd 30 minutes	2**mg**/kg/hour	1**ml**/kg/hour (max 50ml/hr)
Thereafter the rate can be increased by 1**mg**/kg/hour (0.5ml/kg/hour) every 30 minutes to a **maximum** rate of 8**mg**/kg/hour (4mls/kg/hour – max 200ml/hr) **providing no adverse reactions occur (see below)**		

- In the event of any adverse reaction, stop infusion, give a further dose of chlorphenamine.
- Depending on the severity of the infusion-related reaction (IRR) and the required interventions, temporarily or permanently discontinue rituximab.
- In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved.

6. Follow-up

Adequate B-cell depletion is indicated by an absence of CD19/CD20 +ve cells. Most studies assume <1% is adequate depletion with a further dose recommended if there is persistence of B-cells. Normally one dose of 375mg/m^2 is necessary to achieve B cell depletion though a further dose may be administered.

CD20 recovery may occur between 6 and 12 + months after the initial treatment, but this is very individual. No predictive factors as to when this may occur have been identified.

6.1 Withdrawal of immunosuppressants and prednisolone after rituximab administration

Plan to reduce steroids as per nephrotic syndrome guideline and stop all other immunosuppressants. It may be appropriate to continue on Mycophenolate Mofetil or introduce it post-rituximab as per nephrology advice.

6.2 Monitoring after Rituximab

1. CD19/20 count (lymphocyte subsets – LSS)
2. Immunoglobulins (IgA, IgG and IgM)
3. FBC + diff WBC
4. Renal, bone, liver profiles
5. Urine tests for protein/creatinine ratio (uP:CR)

All above tests to be repeated 2 weeks following the 1st dose of rituximab. If B cells >1% on LSS, a further dose should be repeated as soon as practically possible with a further LSS count 2 weeks after.

6.3 Subsequent doses

For repeat treatment a single dose of Rituximab can be given as before. Further repeat lymphocyte subsets will depend on individual clinical course and requirement for further doses and any risk of hypogammaglobulinaemia.

Rituximab runs the risk of inducing a prolonged hypogammaglobulinaemia; which may need regular and long term IVIG replacement therapy. This risk increases particularly after repeated courses.

7. References

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Appendix 1

Administration Advice

ADMINISTRATION
On the day of the rituximab infusion:
The nurse should: -

- Check pre-assessment has been performed
- Check that the patient has not received analgesics containing paracetamol within the last 4 hours and that if the patient is on anti-hypertensive medication, this has been discussed and omitted if felt necessary.
- Take and record Temperature, Pulse, Blood Pressure and O2 Saturation levels as baseline
- Insert IV cannula
- Administer pre-infusion medications as prescribed, commencing 60 minutes before rituximab is given

INFUSION RATE

- **Use ideal body weight to calculate rate NOT actual weight, up to a max of 50kg.**

***added this in here in case this is the page that is read**

Time	mg/hour	ml/hour
1st 30 minutes	1**mg**/kg/hour	0.5**ml**/kg/hour (max 25ml/hr)
2nd 30 minutes	2**mg**/kg/hour	1**ml**/kg/hour (max 50ml/hr)
Thereafter the rate can be increased by 1**mg**/kg/hour (0.5ml/kg/hour) every 30 minutes to a **maximum** rate of 8**mg**/kg/hour (4mls/kg/hour – max 200ml/hr) **providing no adverse reactions occur (see below)**		

Clinical observations DURING INFUSION
1st hour – Blood pressure, Pulse, Temperature and SaO_2 every 15 minutes
Thereafter, every 30 minutes prior to increasing the rate of infusion and throughout the course of the infusion once maximum rate is reached.

INFUSION REACTIONS
• Acute infusion reactions may occur within 1-2 hrs of the first rituximab infusion. These consist of fever, headache, rigors, flushing, nausea, rash, and URTI symptoms.
• Transient hypotension and bronchospasm are usually related to the infusion rate

Mild to moderate reactions e.g. low grade fever; hypotension <30mmHg from baseline

- Stop infusion
- Administer further dose of chlorphenamine
- Depending on the severity of the infusion-related reaction (IRR) and the required interventions, temporarily or permanently discontinue rituximab.
- In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved
- Infusion rate may need to be left at a lower rate throughout the infusion to avoid reactions.
- If necessary the infusion can be run at a slow rate over 24 hours (this requires ward admission).

Moderate to severe reactions e.g. fever >38.5ºC; chills; mucosal swelling; shortness of breath; hypotension by >30mmHg from baseline

- **STOP the infusion and treat the symptoms.**
- **Contact the doctor/ANP**
- If necessary the infusion can be run at a slow rate over 24 hours (this requires ward admission).

POST INFUSION

1. Remove IV cannula
2. Advise parent/patient to seek medical help if they have any symptoms that could be due to an infection e.g. fever in the hours or days after the infusion – ensure they have appropriate contact numbers for the Renal Unit or otherwise to contact GP and / or attend Emergency Department
3. Advise parent/patient to restart any anti-hypertensive drugs the day after infusion

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1. Enter rituximab prescription details in Renal database (SERPR) or send details of treatment to link nephrologist if administered in other network centre.

Appendix 2

SPRUN Steering Group Membership

Name	Designation	Role	Area representing
Deepa Athavale	Consultant Paediatric Nephrologist	Lead Clinician/Chair	NHS Greater Glasgow & Clyde
Rozi Ardill	Consultant Paediatrician	Member	NHS Lothian
Susan Burns	Renal Data Manager	Member	NHS Greater Glasgow & Clyde
Claire Cowe	Renal Nurse Specialist	Member	NHS Grampian
Sheena Dunsmore	Trustee	Member	Third Sector (Kidney Kids Scotland)
Karen Elrick	Paediatric Renal Dietician	Member	NHS Greater Glasgow & Clyde
Fiona Graham	Paediatric Renal Dietician	Member	NHS Greater Glasgow & Clyde
Claire Haggerty	Renal Nurse Specialist	Member	NHS Greater Glasgow & Clyde
Liz Hunter	Consultant Clinical Psychologist	Member	NHS Greater Glasgow & Clyde
Angela Lamb	Paediatric Renal Pharmacist	Member	NHS Greater Glasgow & Clyde
Boma Lee	Consultant Surgeon / Urologist	Member	NHS Greater Glasgow & Clyde
Karen McFarlane	Manager	Member	Third Sector (Kidney Kids Scotland)
Ursula Monachan	Advanced Renal Nurse Practitioner	Member	NHS Greater Glasgow & Clyde
Robin Oswald	Consultant Paediatrician	Member	NHS Tayside
Peter Schulga	Consultant Paediatric Nephrologist	Member	NHS Greater Glasgow & Clyde
Jan Vedarajan	Specialty Doctor/ Link Paediatrician	Member	NHS Highland

Appendix 3

Off label drugs statement

Prescribing of medicines outwith their marketing authorisation
Recommendations within this pathway are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off-label' use. Medicines may be prescribed 'off-label' in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration, via a different route
- for administration
- for a different dose for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans. Generally, 'off-label' prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".

The General Medical Council (GMC) recommends that when prescribing a medicine 'off-label', doctors should:

- be satisfied that there is no suitably licensed medicine that will meet the patient's need
- be satisfied that there is sufficient evidence or experience of using the medicine to show its safety and efficacy
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine, and any follow-up treatment, or ensure that arrangements are made for another suitable doctor to do so.

Make a clear, accurate and legible record of all medicines prescribed and when not following common practice, the reasons for prescribing an unlicensed medicine. Non-medical prescribers should ensure that they are familiar with the legislative framework and Royal Pharmaceutical Society's Competency Framework for all Prescribers.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics (www.medicines.org.uk). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.