Nephrotic Syndrome Relapse

Inpatient & Outpatient

Center for Clinical Excellence

Inclusion criteria:
Patients with nephrotic syndrome (NS) and relapse (urine protein ≥ 3+ on urine dipstick x 3 days or ≥ 1+ for 7 days or edema with any degree of proteinuria)

- Start prednisone 2 mg/kg (max 60 mg) by mouth QAM for four weeks **or until remission** if sooner
- Nursing team to advise patient and family to check urine for protein daily. Call nephrology office when urine protein is negative or trace for three consecutive days. This means the patient is in remission.

Has the patient achieved remission?

No

- **IV methylprednisolone pulses** 500 mg/m² x 3 doses (max of 1 gram per dose) during weeks 5-6
- **Lisinopril** 0.1 mg/kg PO daily
- **Continue oral prednisone** 2 mg/kg (max 60 mg/day) on non-pulses days

Remission at end of 6 weeks?

Yes

No

Steroid Resistant Protocol

Yes

Has the patient had
- >1 relapse within 6 months

OR
- >3 relapses in 12 months?

No

Remission / Infrequent Relapses

Reduce prednisone to 1.5 mg/kg/dose (max of 40 mg) every other day for 6 weeks then stop the medication.

Yes

Remission / Frequent Relapses Steroid-Dependent

Start Mycophenolate Mofetil (first line option):
- 400 mg/m^2 per dose PO BID
- Increase to 600 mg /m^2 per dose PO BID in 2-4 wks if well tolerated (max dose is 1500 mg/dose)

Wean prednisone:
- 1.5 mg/kg (max 40 mg) QOD for 2 wks
- 1.25 mg/kg (max 30 mg) QOD for 2 wks
- 1 mg/kg (max 20 mg) QOD for 2 wks
- 0.75 mg/kg (max 10 mg) QOD for 2 wks

0.5 mg/kg (max 5 mg) QOD for 2 wks then off

If concerns for adherence, consider:
Rituximab

Long Term Management

Infrequent relapsing nephrotic syndrome: steroid-sensitive nephrotic syndrome with 0-1 relapses within 6 months, or ≤ 3 relapses within a 12-month period

Frequently relapsing nephrotic syndrome: steroid-sensitive nephrotic syndrome with 2 or more relapses within 6 months, or 4 or more relapses within a 12-month period.

Steroid sensitive nephrotic syndrome: complete remission within 4-6 weeks of daily prednisone

Steroid resistant nephrotic syndrome: patient unable to obtain remission after 6 weeks of prednisone +/- IV methylprednisolone pulses

Steroid-dependent nephrotic syndrome: steroid-sensitive nephrotic syndrome with 2 or more consecutive relapses during tapering or within 14 days of stopping steroids.

Rituximab

Treatment Guidelines:

- Start Rituximab while in remission if possible
- Extend Prednisone until first dose of Rituximab

Premedication:

- Cetirizine:
  - Children 6 months to <2 years: 2.5 mg PO daily
  - Children 2 to 5 years: 5 mg PO daily
  - Children >5 years:10 mg PO daily
- Acetaminophen: 15 mg/kg PO once prior to infusion (max 1000 mg/dose)
- Methylprednisolone 1 mg/kg IV (max 60mg)

Before initial dose, check:

- Hep B surface antigen
- Hep B surface antibodies
- Hep B core antibodies
- IgG
- Renal Function Panel
- Complete Blood Count with Differential
- Urinalysis
- Urine Protein/Creatinine ratio

Black box warning of Hepatitis B reactivation

If Hepatitis B titer negative, give Hepatitis B booster ≥ 6 months post Rituximab treatment

Energix-B ≤ 18 years
Heplisav B > 18 years

Rituximab Dosing:
375 mg/m^2 IV (max 1 gram /dose)
Give 2 doses 10-14 days apart

Lab Monitoring (Every 6 months):

- Total B Cell (CD 19, CD 20) Quantitation (first 2 years)
- IgG levels (first 2 years)
- Renal Function Panel
- Complete Blood Count with Differential
- Urine Protein/Creatinine Ratio
- Vitamin D 25 OH

Obtain Total B Cell (CD 19, CD 20) Quantitation at time of second dose

Is CD19+CD20+ B cells count < 5 B cells/mm3?

No → Recheck again in 2 weeks. If not < 5 B cells/mm3, give:
Rituximab:
375 mg/m^2 IV (max 1 gram/ dose)

Yes

Failed Rituximab:
Relapse or persistent proteinuria < 6 months after Rituximab course

- If starting second line agent Tacrolimus/ Mycophenolate Mofetil (MMF) for a minimum 12- 24 months then consider weaning over 3-6 months
- Wean prednisone off per algorithm

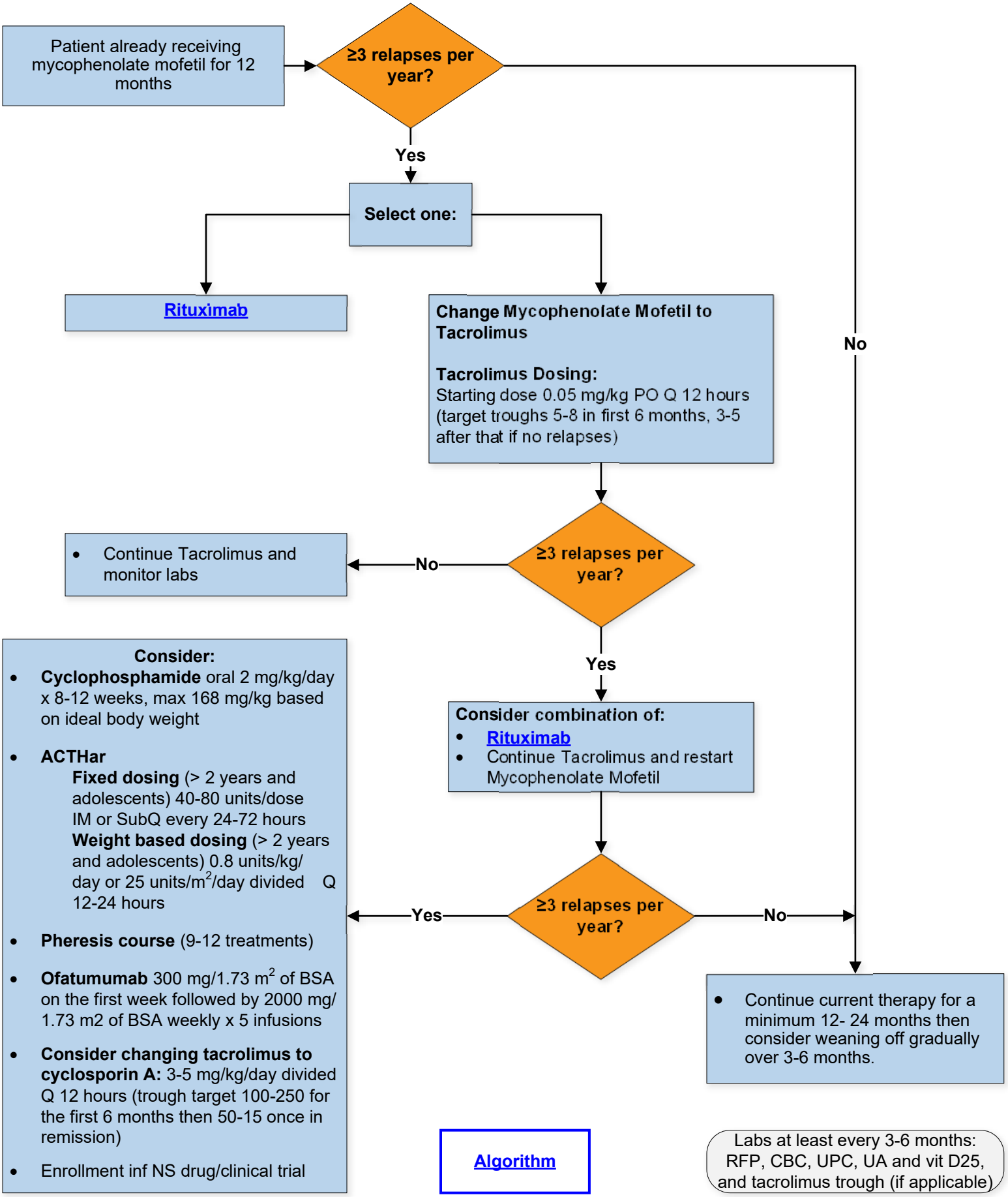
Remission achieved within 6 months post Rituximab?

No →
- No further rituximab
- Consider other options (see Long Term management)

Yes →
- Repeat Rituximab per protocol above
- Max of 6 Rituximab courses
- Or consider other options (see Long Term management)

Algorithm

Long Term Management
(for Frequently Relapsing or Steroid Dependent Nephrotic Syndrome)

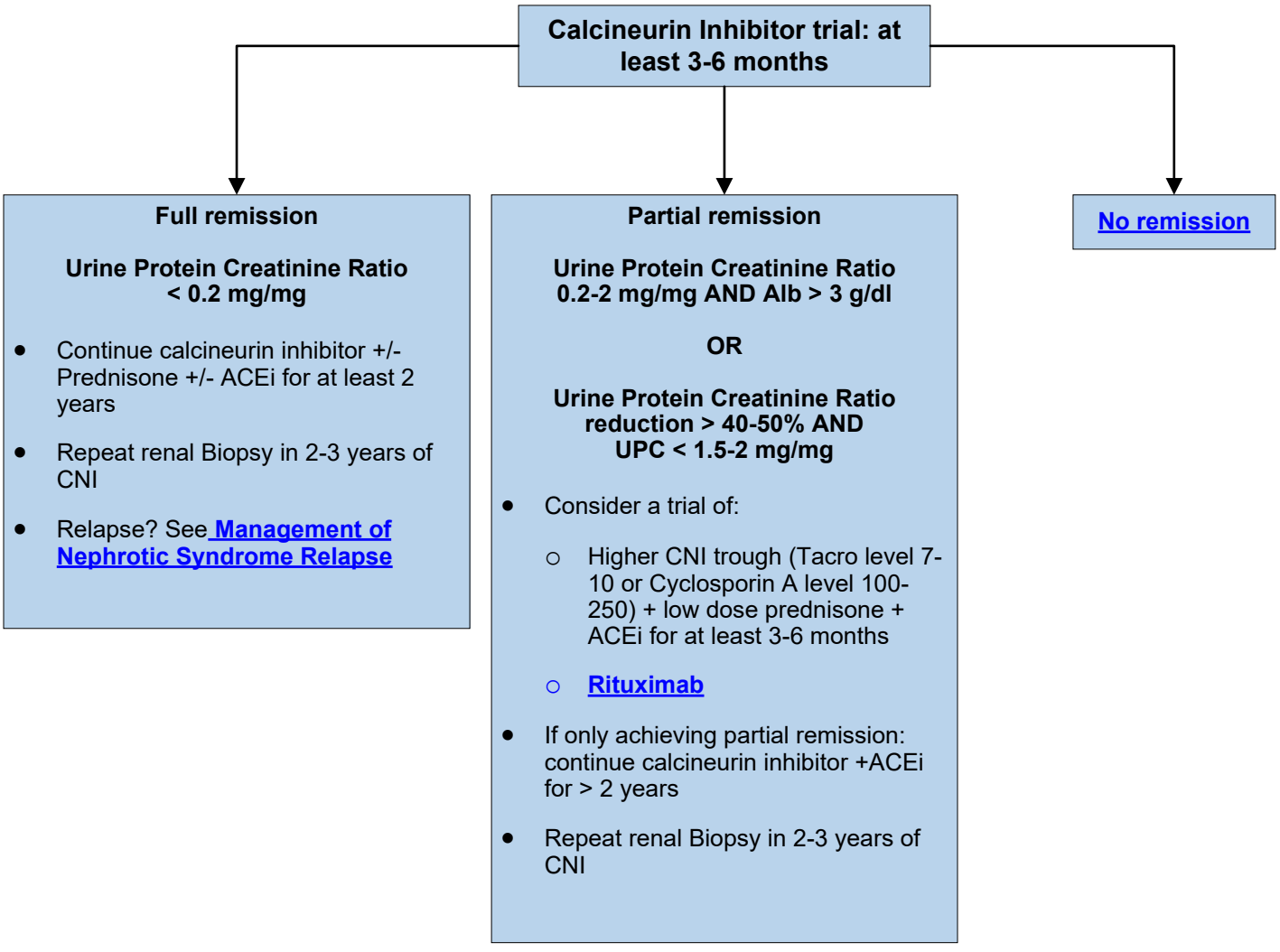


Steroid-Resistant Nephrotic Syndrome Protocol

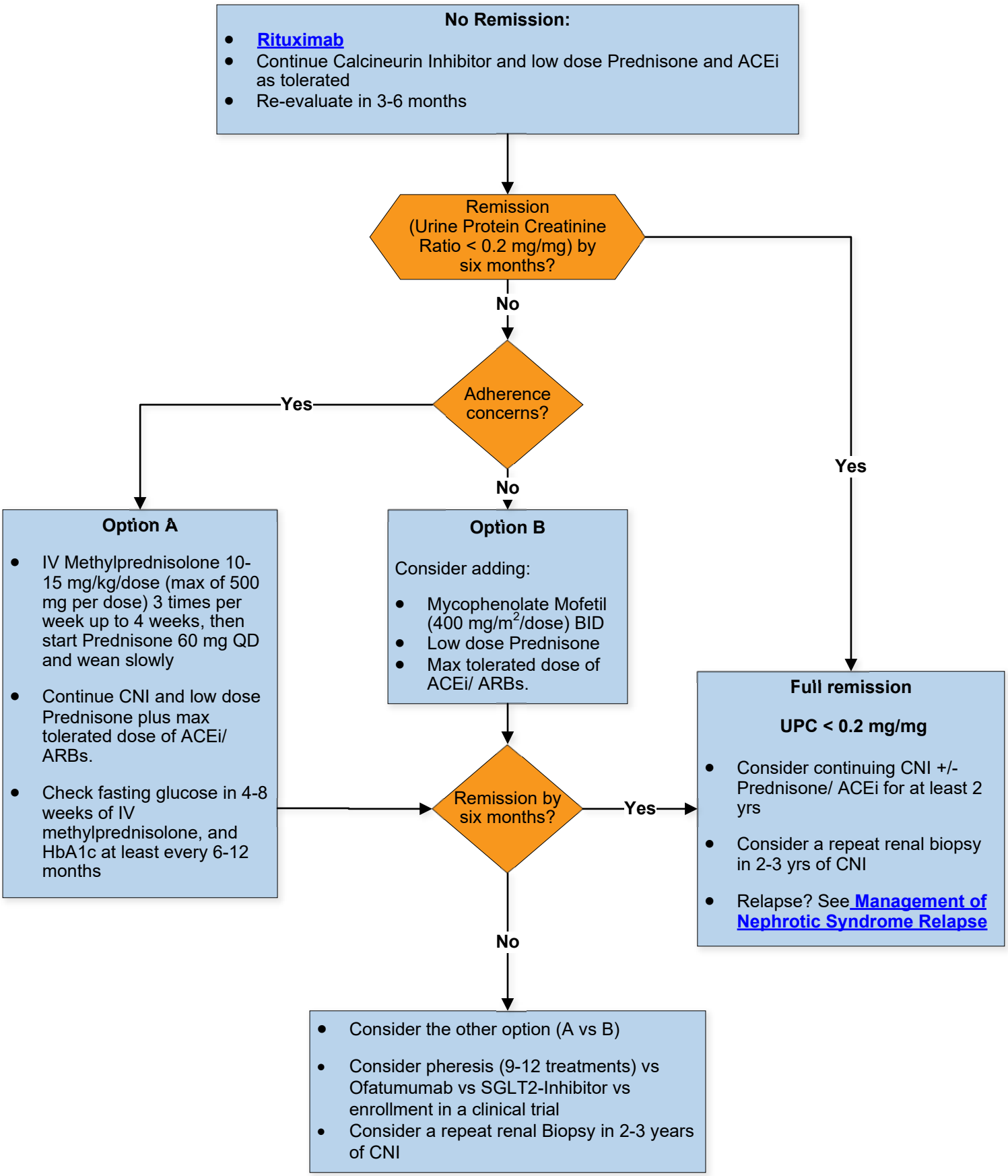
Definition:
Proteinuria despite 6 weeks of Prednisone 2mg/kg/day max of 60 mg/day, +/- IV Methylprednisolone pulses

General guidance:

- Obtain Genetic testing (Prevention Genetics NEPHROTIC SYNDROME- FSGS PANEL, test code: 10417)
- Obtain a renal biopsy within 2-4 weeks
- Start calcineurin inhibitor (CNI):
  Tacrolimus 0.1 mg/kg/dose Q 12 hours (target troughs 5-8 for first 6 months and then 3-5 once in remission)
  or
  Cyclosporin A 3-5 mg/kg/day divided Q 12hrs (target troughs 100-250 for first 6 months and then 50-150 once in remission)
- Consider keeping on a low dose of Prednisone for the first 6 months. (2.5-5 mg PO QAM or QOD), especially if had some steroid sensitivity initially (late SRNS)
- Start ACE inhibitor (ACEi) or Angiotensin Receptor Blocker in all patients, especially if hypertensive, target BP ≤ 50-75% as tolerated.
- Check RFP, CBC, CNI trough level, lipid panel (preferred fasting) and vit D 25 level at least every 3 months and manage them accordingly.



Steroid-Resistant Nephrotic Syndrome Protocol: No Remission



Clinical Updates for Nurses

Nurses to use dot phrase: .nephroticsyndrome when calling the family / patient.

If patient in relapse or new onset- call weekly for updates
If patient is on taper- every 2 weeks for updates

Questions to ask:
- Urine protein levels
- Remission or relapse?
- Swelling: Y/N
- Weight recently
- Remind low salt diet
- Patient seen in ER – admitted since last visit / call?
- Any recent albumin/ Lasix infusions?
- Any fevers or new sick symptoms
- Current dose of steroids
- Any missed doses of steroids- if yes how many and the reason why
- Any side effects of steroids
- Total dose of prednisone for this relapse ?

When should a NS patient be evaluated by MD (PCP / Nephrologist):
- Has unexplained fever (no obvious source such as URI)
- Might have peritonitis (any combination of vomiting, pain, fever, etc.)
- Parent is not experienced enough to judge severity of edema
- Where appropriate, call the local MD to discuss specific concerns/issues

Should be admitted if:
- Peritonitis is suspected after evaluation by local MD (or if reported signs & symptoms are obvious)
- Edema is severe enough so that child is clearly uncomfortable
- Child has skin breakdown/cellulitis from their edema
- Child is having profuse vomiting / diarrhea, suggesting poor absorption of PO meds
- Any suggestion of respiratory distress/compromise

Algorithm

References

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Algorithm

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Clinical Pathway Development

This clinical pathway was developed using the process described in the NCH Clinical Pathway Development Manual Version 6, 2022. Clinical Pathways at Nationwide Children's Hospital (NCH) are standards which provide general guidance to clinicians. Patient choice, clinician judgment, and other relevant factors in diagnosing and treating patients remain central to the selection of diagnostic tests and therapy. The ordering provider assumes all risks associates with care decisions. NCH assumes no responsibility for any adverse consequences, errors, or omissions that may arise from the use or reliance on these guidelines. NCH's clinical pathways are reviewed periodically for consistency with new evidence; however, new developments may not be represented, and NCH makes no guarantees, representations, or warranties with respect to the information provided in this clinical pathway.

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Algorithm