

Frequently Relapsing Nephrotic Syndrome

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Overview

- Definition
- Treatment algorithm
- Terminologies
- Drugs
- Fun facts

Definition

- ≥ 2 episodes in the first 6 months of initiation of treatment or ≥ 3 episodes in any 6 mo, ≥ 4 episodes in 1 year.
- Relapse means proteinuria 3+ or 4+ for 3 consecutive days.
- Can be precipitated with or without infection but is not counted as an episode if spontaneous remission occurs after treating the infection.

- Most relapses are precipitated by upper respiratory tract infection.
- **Steroid dependence** – Occurrence of two consecutive relapses on alternate day treatment or with 14 days of its discontinuation.
- Treatment – 1st episode
2mg/kg or 60mg/m² prednisolone daily for 6 weeks f/b 1.5mg/kg for 6 weeks.

Treatment

- **1st episode** - 2mg/kg or 60mg/m² prednisolone daily for 6 weeks f/b 1.5mg/kg or 40mg/m² for 6 weeks.
- **Relapse** - 2mg/kg or 60mg/m² daily till remission, then 1.5mg/kg or 40mg/m² alternate days for 1 month.

Frequently relapsing or steroid dependent nephrotic syndrome

↓
Prednisolone on alternate days; daily during infections

↓
Frequent relapses; steroid toxicity

↓
Steroid threshold >1 mg/kg on alternate days
>1 complicated relapse
Significant steroid toxicity

No

Yes

Levamisole
Mycophenolate mofetil

Frequent relapses

Mycophenolate mofetil
Cyclophosphamide

Difficult-to-treat disease

↓
Cyclosporine, tacrolimus

↓
Rituximab

Complicated Relapse

- Relapse associated with life threatening complications-
 1. Hypovolemia requiring inpatient care.
 2. Severe infection (peritonitis, cellulitis, meningitis), or
 3. Thrombosis

Significant steroid toxicity

- Hyperglycemia (fasting glucose $>100\text{mg/dl}$, post prandial $>140\text{mg/dl}$, or HbA1c $>5.7\%$)
- Obesity (BMI $>$ equivalent of 27kg/m^2 in adults)
- Short Stature – height $< -2\text{SDS}$ for age with height velocity $< -3\text{ SDS}$ for age
- Raised intra-ocular pressure, Cataract
- Myopathy, Osteonecrosis
- Psychosis

Difficult to treat steroid sensitive disease

- Both of the following-
 1. Frequent relapses, or significant steroid toxicity with infrequent relapses; and
 2. Failure of >2 steroid sparing agents (including levamisole, cyclophosphamide, MMF)

Long term Alternate Day Prednisolone

- Assess the minimum dose prednisolone at which relapse occurs.
- Small doses of 0.5 to 0.75mg/kg can be given on alternate days.
- This dose should be continued for 9 – 12months or longer as needed if there are no steroid side effects.
- Helps maintaining remission and does not seem to interfere with growth.

Levamisole

- It is an immunomodulatory agent.
- Dose – 2-2.5mg/kg every alternate day for 1-2 years or longer if effective.
- After inducing remission prednisolone is continued in a dose of 0.75 – 1mg/kg alternate day alongwith levamisole and then slowly tapered and stopped.

- Side effects of levamisole – mild gastrointestinal upset, flu like symptoms.
- Transient neutropenia particularly in HLA-B27 positive patients.
- Skin rash uncommon but can be associated with leucocytoclastic vasculitis.
- Leucocyte counts to be monitored every 2-4 months.

Cyclophosphamide

- It is an alkylating agent. (Immunosuppressant)
- Dose – 2- 2.5mg/kg daily alongwith steroids 1-1.5mg/kg on alternate days for 12 weeks.
- Avoid using in children <5-7 years and peri-pubertal due reduced efficacy and risk of steroid toxicity respectively.

- Side effects – leucopenia (leucocyte counts monitored every 15 days and therapy is withheld if counts are $<3000/\text{mm}^3$).
- Nausea, vomiting, hemorrhagic cystitis, alopecia.
- Gonadal toxicity is dose related and ovarian function is less affected than testicular function. (cumulative dosage of $168\text{mg}/\text{kg}$). Second course is avoided.

Mycophenolate Mofetil (MMF)

- It is reversible inhibitor of inosine monophosphate dehydrogenase (IMP) which is required in de novo purine synthesis.
- Usually used when once levamisole and cyclophosphamide have failed to benefit.
- This drug has no nephrotoxicity, hepatotoxicity, neurotoxicity or cosmetic side effects.
- Dose – 30mg/kg (600 – 750mg/m²) per day in 2 divided doses. Can give upto 1000-1200mg/m² per day.

- Side effects of MMF
- Gastro – intestinal symptoms, nausea, abdominal pain and diarrhoea are occasionally seen.
- Leucocyte counts and transaminases need to be monitored.

Rituximab

- It is anti CD20 monoclonal antibody.
- Dose – 375mg/m², 1-2 doses given at weekly intervals.
- Used more for SDNS than FRNS refractory to all previous medications.
- Cannot give to patients having hypogamaglobulinemia.

Fun Facts

- Measles infection can occasionally lead to spontaneous remission of nephrotic syndrome.
- Majority of the thromboembolic events occur in the first 3 months of onset of the syndrome and children >12 years are at a higher risk than younger children.

- Spontaneous remission occurs in 5% of the cases with 1-2 weeks of onset. Therefore can delay initial steroid therapy.
- Prednisolone is more water soluble than prednisone- hence its absorption and response with treatment can be erratic as compared to prednisone.

THANK YOU