

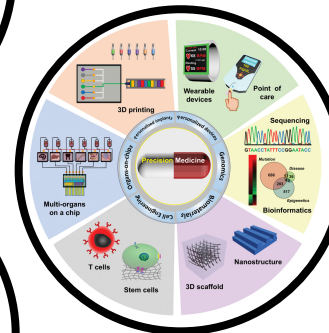
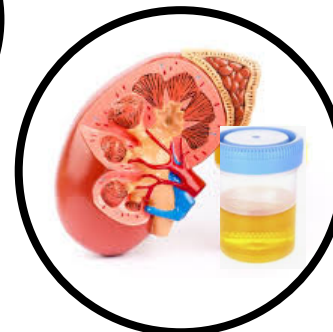
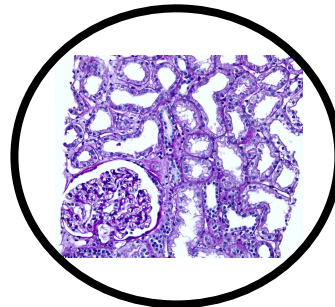
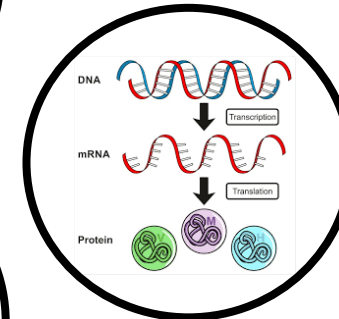
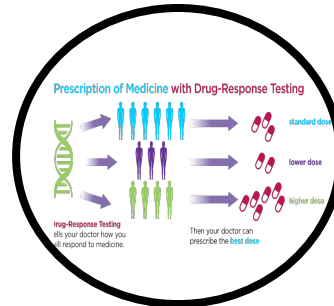
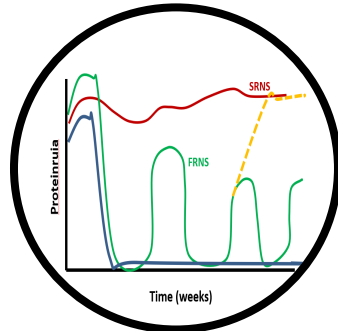
Rituximab 101

Dr. Susan Massengill, Levine Children's Hospital at Atrium
&
Dr. Debbie Gipson, University of Michigan

**Thanks to *The Nephrotic Syndrome Foundation* for
making this gathering possible.**

It is a great pleasure to spend this time together.

Improving NS Management is a Team Activity





FSGSrecurrencecollab.org



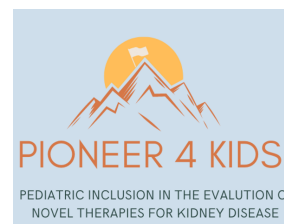
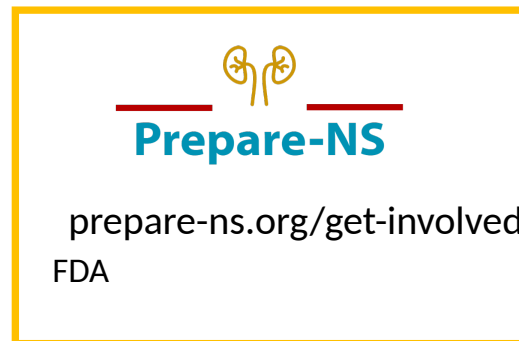
NEPTUNE-STUDY.ORG
NCATS/NIDDK/NIH



CureGN.org
NIDDK/NIH



KidneyResearchNetwork.org
Levine Children's Medical
Foundation/University of Michigan



Pioneer4Kids.org

Plan for today

1. Brief introduction to rituximab – type therapies

- What, when, why and how to use
- Labs and monitoring
- Long term safety and outcome

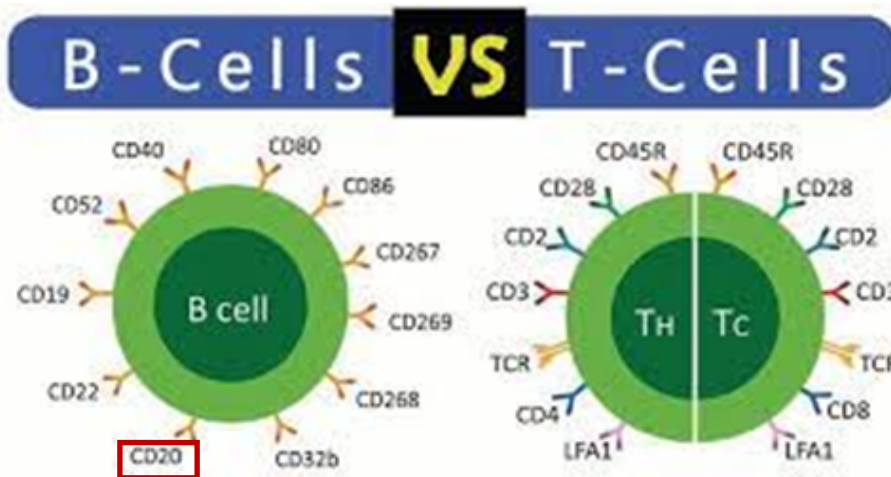
2. Discussion

- Use the chat
- Raise your hand
- Our moderators will read out a few questions that were submitted over the past few weeks, read questions typed in the chat and call on those raising hands.

What: Steroid-Sparing Agents

- **Mycophenolate mofetil (CellCept)**
- **Calcineurin inhibitors (Cyclosporine, Tacrolimus)**
- **Cyclophosphamide / Chlorambucil**
- **CD20 Monoclonal Antibodies (Rituximab, Riabni, Ruxience, Truxima, Ofatumamab, Obinutuzumab, etc.)**

How: Mechanism of Action



- NS has been hypothesized to be a disorder of T cells
- New information provides insight that some NS may be caused by self-directed immune proteins
- Rituximab:
 - B cell depletion by binding to CD20 receptor
 - Indirect and direct effects on T cells
 - Decrease in production of immune proteins
 - Binds to the surface of podocytes to potentially stabilize structure and function

Whom: Nephrotic Syndrome

- **Diagnosis: Child or adult onset, MCD, FSGS, IgM, child onset not biopsied**
- **Frequently relapsing NS**
- **Steroid dependent NS**
- **Complex or burdensome disease and medication regimen**
- **Uncommonly, in treatment resistant patients**

Both the rituximab dose and maintenance immunosuppression in steroid-dependent/ frequently-relapsing nephrotic syndrome have important effects on outcomes.

Design

Retrospective cohort

511 children

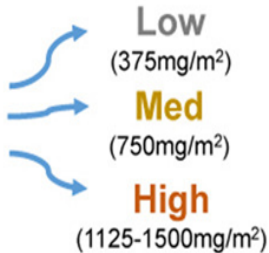


11 centres



Intervention

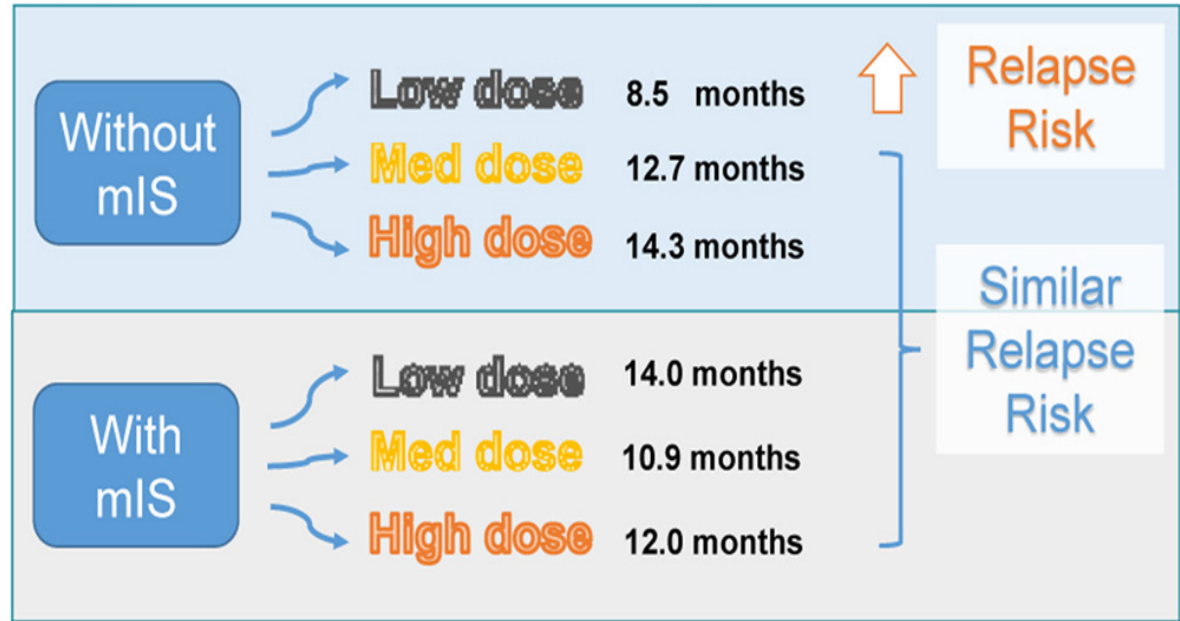
Rituximab doses



± mIS (IS at relapse or given ≥ 6 months)

Outcomes

Median relapse-free period



Conclusion:

Children receiving low-dose rituximab without maintenance immunosuppression had the shortest relapse-free period. Both rituximab dose and maintenance immunosuppression have important effects on long-term control of SD/FRNS

Monitoring

- **Evidence of B cell recovery**
 - CD 19 levels

- **Anti-rituximab antibody levels**

Safety of Repeated Rituximab in children with Frequently Relapsing or Steroid Dependent NS

- Safety with median follow up 5.9 years
- 51% Low Immunoglobulin G (disease or therapy related)
 - 7% doses Low IgG levels < 200 mg/dL, infections or used IgG replacement therapy
 - 4% doses neutropenia
 - 2% doses agranulocytosis
 - 14% patients infections
 - 14% short-term and fully resolved; <1% long-term virus (EBV, hepatitis B)
 - Side effects did not increase with more treatments or higher total dose

Chan E, et al, JASN, 2022; International (16 centers; 9 countries)
1154 RTX courses / 346 children

Safety From 6 Clinical Trials of Rituximab in Steroid Sensitive NS

- Safety summary, compared with control group
 - No difference in severe infection
 - 5% risk for joint pain
 - 5% risk for RTX infusion reaction (moderate/severe)

Rituximab Response – Steroid Sensitive NS

- Following initial dosing
 - 85-90% Relapse Free @ 6 months
 - 70% Relapse Free @ 12 months
- Improving the Relapse Free period duration
 - Use moderate treatment dose, or
 - Add low dose maintenance immunosuppression medication
 - And: Repeat dosing, eg 6 month interval
- Relapse free duration is variable, ranging from 0 months (no effect) to permanent

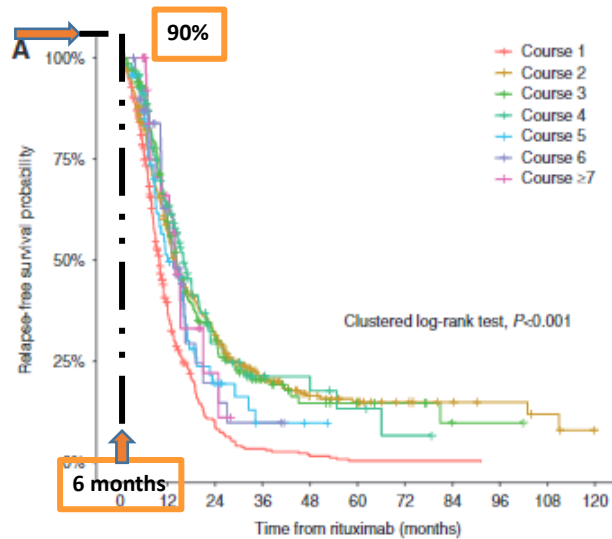
Rituximab Response – Steroid Resistant NS

- Following initial dosing
 - 15-25% Remission
- Improving the Remission
 - Rituximab, consider:
 - moderate to high treatment dose
 - different response by agent in same CD20 MAB drug class
 - adding low dose maintenance immunosuppression
 - Combination with other therapies, eg ACEi/ARB
 - Control blood pressure and body weight

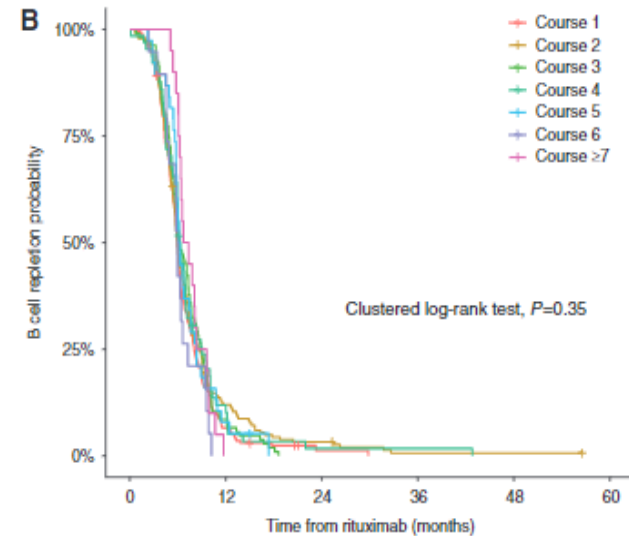
Limited data

Long-term View

Relapse Free response is consistent with multiple doses



B cell recovery times are consistent with multiple doses



- The frequency or severity of side effects did not worsen with up to 8 courses of rituximab repeated dosing or higher lifetime total dose of rituximab

Chen, 2022; n = 346

Let's have a discussion

- Use the chat
- Raise your hand
- Our moderators will read out a few questions that were submitted over the past few weeks and alternate with calling on those raising hands.

Remember to talk with your doctor about what is right for you.

Intentionally left blank

Factors Observed in Relapses after Rituximab

- Older age at rituximab⁵¹⁻⁵⁴
- White children⁵¹
- Use of maintenance immunosuppression after rituximab, e.g., MMF⁶⁹
- Repeated courses of rituximab⁵⁰
- Lower mitogen-stimulated T-cell subsets at baseline²⁵

Lower risk of relapse



Histology^{7,41,48} and high-dose rituximab⁵⁰
do not alter relapse risk

Higher risk of relapse

- East Asian, South Asian, and Black children⁵¹
- History of steroid resistance^{48,51}
- Multidrug dependence^{50,51}
- Low-dose rituximab without maintenance therapy⁵⁰
- Repopulation of total memory B cells, especially switched memory B cells¹⁴⁻¹⁶

Clinical and immunological factors that determine the treatment outcomes after rituximab therapy in children with frequently relapsing, steroid-dependent nephrotic syndrome. MMF, mycophenolate mofetil.