UPDATE IN GLOMERULONEPHRITIS – TOOLS AND TIPS IN MANAGEMENT OF PATIENTS WITH GN

JUDITH MARIN AND JENNY NG

RPN EDUCATION DAY – OCTOBER 25TH, 2019

OBJECTIVES

- **Learn about the work being done by the ORN GN priority panel to improve care of patients with GN**
- **Become familiar with tools that are currently available for pharmacists in the care of patients with GN in Ontario and BC**
- **Review the MENTOR study**

GLOMERULONEPHRITIS STRATEGIC FRAMEWORK • 2019-2023 •

GOAL: | EFFECTIVE | Deliver kidney care using best evidence

STRATEGIC OBJECTIVE: Strengthen care delivery for patients with glomerulonephritis and women with chronic kidney disease requiring maternal healthcare

Increase patient access to standardized specialized GN care

Regional Partnerships

- Establish partnerships between Regional Renal Programs and GN Specialty Clinics to improve access to standardized, timely and high quality care

Renal Pathology

- Implement standards for the evaluation and reporting of renal biopsies to improve the state of access to diagnostic services across the province

Improve education and access to specialty drugs, diagnostics and lab monitoring tests

GN Drug Protocols & Guidelines

- Develop protocols and recommendations for managing immunosuppressive medications for patients with GN, to help providers deliver high quality care and contribute to better outcomes for patients

Diagnostic & Lab Monitoring Tests

- Improve access to tests used in diagnosing and monitoring of glomerular diseases to ensure optimal outcomes for patients

Implement professional education for healthcare providers

Professional Education for Healthcare Providers

- Support ongoing ORN GN Provincial Rounds to increase knowledge and expertise of glomerular diseases amongst healthcare providers across the province
- Develop and disseminate educational materials for healthcare providers to increase capacity and expertise in providing high-quality specialized care

Ensure patients and caregivers are supported to make informed decisions

Leverage ORN's Person-Centred Care portfolio to:

- engage patients and families in provincial initiatives
- enable peer support
- promote shared decision-making
- measure patient experience.

- Adapt and disseminate standard educational materials for patients and caregivers

Leverage data to enable planning, decision-making and monitoring of outcomes

Evaluation & Monitoring

- Leverage the GN minimum dataset to better understand the population of people with GN, their disease progression, healthcare utilization and outcomes.
- Institute performance indicators to drive quality improvement.
- Develop an evaluation framework to assess impact of implementing a provincial model of care aimed to increased access to specialized care

GN DRUG AND LAB ACCESS FRAMEWORK

Objective:
Improve education and access to specialty drugs, diagnostics and lab monitoring tests

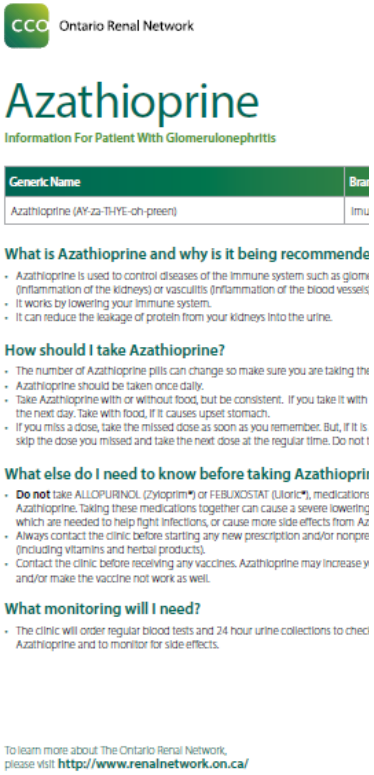
Patient Resources*	Provider Resources*	Provincial Drug Funding	Access to Lab Tests
✓ 7 Patient Medication fact sheets	✓ Drug access process map ✓ First two protocols/ guidelines ❑ Next six protocols/ guidelines	✓ Drug access jurisdictional scan ❑ EAP/CRP turnaround times ❑ EAP criteria expansion for rituximab	❑ PLA2R testing ❑ Complement testing ❑ CNI levels ❑ ANCA testing

* Resources developed in collaboration with GN Drug Access Task Group

PATIENT RESOURCES

GN DRUG ACCESS – PATIENT RESOURCES

Seven medication fact sheets for patients with GN



Ontario Renal Network

Azathioprine

Information For Patient With Glomerulonephritis

Generic Name	Bra
Azathioprine (AY-za-THYE-oh-preen)	Imu

What is Azathioprine and why is it being recommende

- Azathioprine is used to control diseases of the immune system such as glom (inflammation of the kidneys) or vasculitis (inflammation of the blood vessels
- It works by lowering your immune system.
- It can reduce the leakage of protein from your kidneys into the urine.

How should I take Azathioprine?

- The number of Azathioprine pills can change so make sure you are taking the
- Azathioprine should be taken once daily.
- Take Azathioprine with or without food, but be consistent. If you take it with the next day. Take with food, if it causes upset stomach.
- If you miss a dose, take the missed dose as soon as you remember. But, if it is skip the dose you missed and take the next dose at the regular time. Do not t

What else do I need to know before taking Azathiopri

- **Do not** take ALLOPURINOL (Zyloprim®) or FEBUXOSTAT (Uloric®), medications Azathioprine. Taking these medications together can cause a severe lowering which are needed to help fight infections, or cause more side effects from Az
- Always contact the clinic before starting any new prescription and/or nonpre (including vitamins and herbal products).
- Contact the clinic before receiving any vaccines. Azathioprine may increase y and/or make the vaccine not work as well.

What monitoring will I need?

- The clinic will order regular blood tests and 24 hour urine collections to chec Azathioprine and to monitor for side effects.

To learn more about The Ontario Renal Network, please visit **http://www.renalnetwork.on.ca/**

Ontario Renal Network

Cyclophosphamide

Information For Patient With Glomerulonephritis

Generic Name	Brand Name
Cyclophosphamide (SYE-kloe-FOS-fa-mide)	Cytoxan®, Procytox®

What is Cyclophosphamide and why is it being recommend

- Cyclophosphamide is used to control diseases of the immune system such as glome (inflammation of the kidneys) or vasculitis (inflammation of the blood vessels).
- It works by lowering your immune system.
- It can reduce the leakage of protein from your kidneys into the urine.

How should I take Cyclophosphamide?

Cyclophosphamide is available as a tablet or by intravenous (IV) infusion given by a nur determine which formulation is most appropriate for you.

Tablets

- The number of Cyclophosphamide pills can change so make sure you are taking the
- Take Cyclophosphamide once daily in the morning with food and with lots of fluids
- Swallow tablets whole. Do not cut, crush or chew the tablets.
- If you miss a dose, take the missed dose as soon as you remember. But, if it is almost skip the dose you missed and take the next dose at the regular time. Do not take 2 d

Infusion

- Dose and schedule of this medication are dependent on your weight or specific to y
- You will have to go to a hospital day unit for administration of Cyclophosphamide.
- It is important that doses are not missed. Marking it on your calendar may be useful.

What else do I need to know before taking Cyclophospham

- To prevent a specific, serious lung infection called pneumocystis jiroveci pneumonia be prescribed an antibiotic. Most people will need to take this antibiotic for a period Cyclophosphamide infusion.
- Always contact the clinic before starting any new prescription and/or nonprescriptic (including vitamins and herbal products).
- Avoid pregnancy and breastfeeding while taking Cyclophosphamide.
- Speak to your doctor about birth control options before taking Cyclophosphamide.
- Contact the clinic before receiving any vaccines. Cyclophosphamide may increase yc infection and/or make the vaccine not work as well.

To learn more about The Ontario Renal Network, please visit **http://www.renalnetwork.on.ca/**

Ontario Renal Network

Rituximab

Information For Patient With Glomerulonephritis

Generic Name	Brand Name
Rituximab (ri-TUX-i-mab)	Rituxan®

What is Rituximab and why is it being recommended for me?

- Rituximab is used to control diseases of the immune system such as glomerulonephritis (inflammation of the kidneys) or vasculitis (inflammation of the blood vessels).
- Rituximab works by lowering your immune system.
- Specifically, it works by reducing the number of B-cells (white blood cells) in your body.
- It can reduce the leakage of protein from your kidneys into the urine.

How is Rituximab taken?

- Rituximab is given as an intravenous (IV) infusion by a nurse.
- You will have to go to a hospital day unit or a private infusion clinic for administration of Rituximab.
- Your first appointment to receive Rituximab will last about 6–8 hours.

What else do I need to know before starting Rituximab?

- To prevent a specific, serious lung infection called pneumocystis jiroveci pneumonia (PJP), you will be prescribed an antibiotic. Most people will need to take this antibiotic for at least 6 months after the last Rituximab infusion.
- Always contact the clinic before starting any new prescription and/or nonprescription medications (including vitamins and herbal products).
- Avoid pregnancy and breastfeeding with Rituximab. Although Rituximab is sometimes used in pregnant women, the long term effects on an unborn child are currently unknown.
- Speak to your doctor about birth control options before receiving Rituximab.
- Ensure that your vaccinations are all up to date before receiving Rituximab.
- Contact the clinic before receiving any vaccines. Rituximab may increase your chance of an infection and/or make the vaccine not work as well.

What monitoring will I need?

- The clinic will order regular blood tests and 24 hour urine collections to check your response to Rituximab and to monitor for side effects.
- During your follow-up visits, you may also have a blood test done called the "CD 19/20 cell count". This test may need to be done at a specific laboratory. It will help monitor your immune system function.

To learn more about The Ontario Renal Network, please visit **http://www.renalnetwork.on.ca/**

Ontario

Cancer Care Ontario

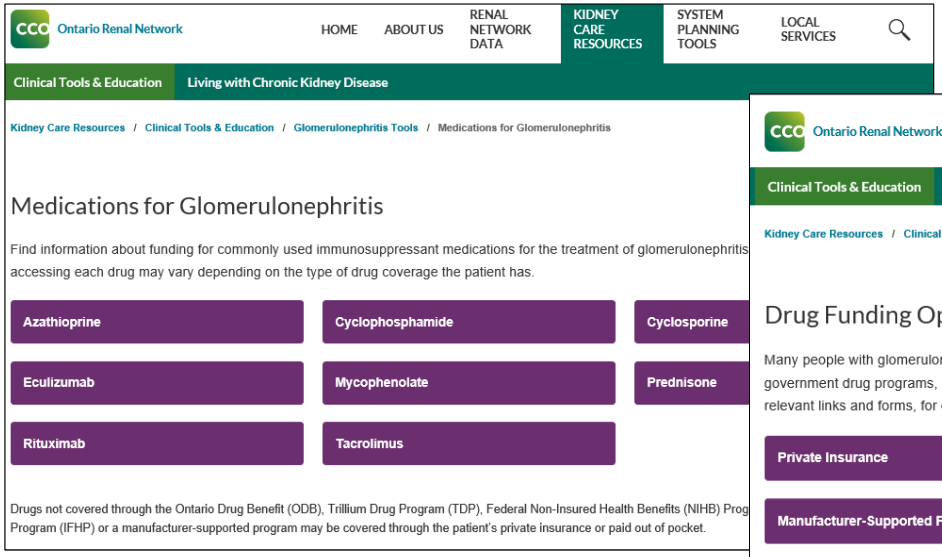
Other topics:

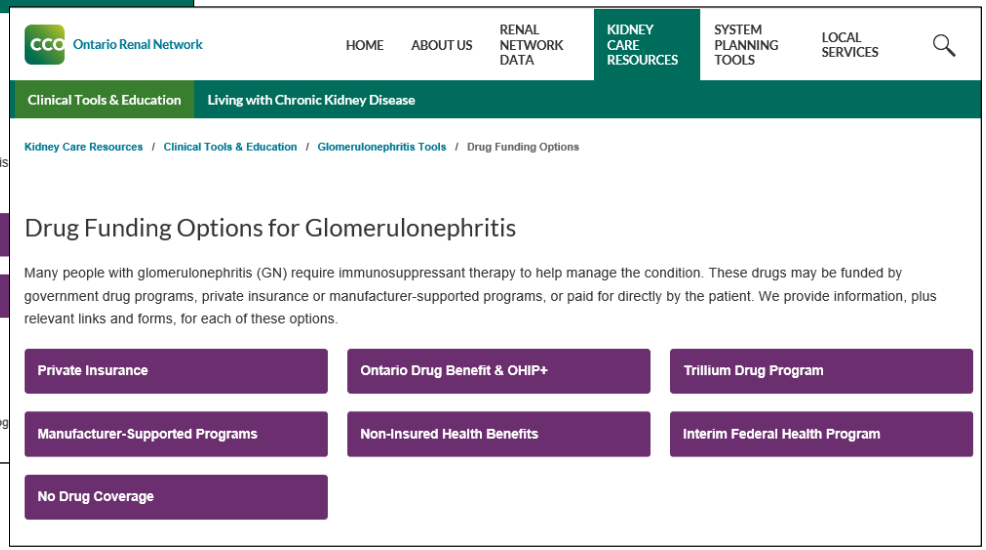
- Corticosteroids
- Cyclosporine
- Mycophenolate
- Tacrolimus
- https://www.ontariorenalnetwork.ca/en/kidney-care-resources/clinical-tools/glomerulonephritis/medications-for-glomerulonephritis

PROVIDER RESOURCES

Drug Access Process Map

- Purpose: To support healthcare providers in navigating the application process to obtain drug funding.
- Launched on Ontario Renal Network website in June 2018.
- View by drug or by funding option.





GN DRUG ACCESS – PROVIDER RESOURCES CONT'D

GN Drug Protocols and Guidelines

Purpose: Increase the comfort level among healthcare providers across the province when prescribing and managing the medications most commonly used in adult patients with GN

Two resources are complete:

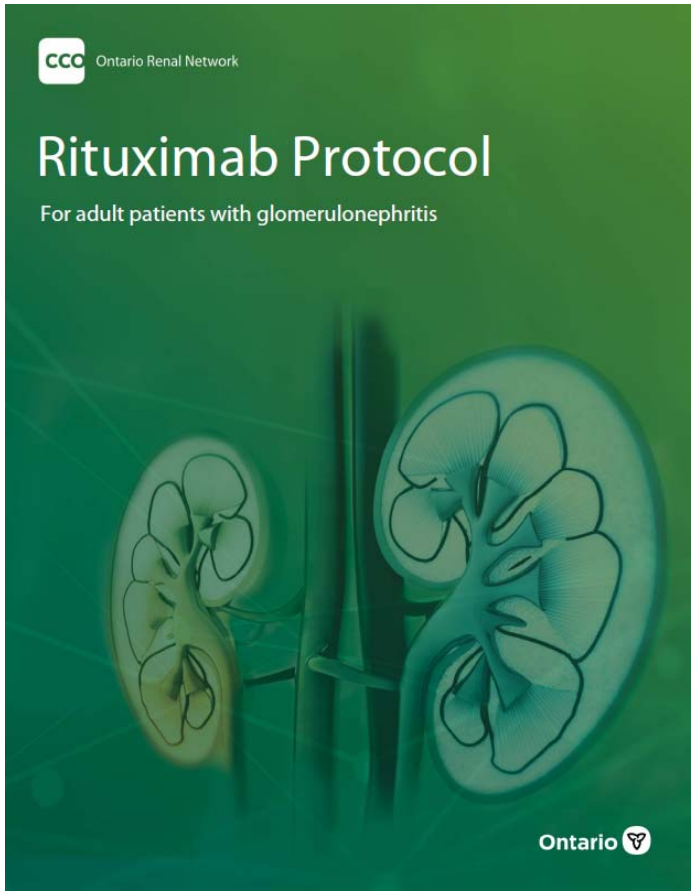
- ✓ **Rituximab** Protocol
- ✓ Considerations for **Immunization**

Six resources are under development:

- ❑ **Cyclophosphamide** Protocol
- ❑ **PCP Prophylaxis** Recommendations
- ❑ Recommendations for **Malignancy Screening** prior to Immunosuppressive Therapy
- ❑ Recommendations for **Infection Screening** relating to Immunosuppressive Therapy
- ❑ Strategies for **Fertility Preservation** for Patients Receiving Cyclophosphamide
- ❑ Recommendations for Prevention and Management of Glucocorticoid-Induced **Osteoporosis**

GN DRUG ACCESS – PROVIDER RESOURCES CONT'D

GN Drug Protocols and Guidelines Cont'd



RITUXIMAB PROTOCOL FOR GLOMERULONEPHRITIS (ADULT)

Protocol Development

The information contained in this protocol was derived from published evidence, clinical expert opinion, and existing institutional guidelines (University Health Network and Sunnybrook Health Sciences Centre).

Description

Rituximab (RITUXAN®) is a chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20.[1]

Indications

- To induce remission in patients with the following types of glomerulonephritis (GN) and who have organ and/or life-threatening disease:
  - Membranous Nephropathy (MN)[2]
  - Focal Segmental Glomerulosclerosis (FSGS)[3, 4]
  - Minimal Change Disease (MCD)[5]
  - Membranoproliferative glomerulonephritis (MPGN) with IgG deposits +/- complement)[6, 7]
- To induce or maintain remission in patients with the following types of Anti-Neutrophilic Cytoplasmic Autoantibody (ANCA)-associated vasculitides and who have organ and/or life-threatening disease:[1, 8, 9]
  - Granulomatosis with polyangiitis (GPA)
  - Microscopic polyangiitis (MPA)

Contraindications

- Known type 1 hypersensitivity or anaphylactic reactions to murine proteins, Chinese Hamster Ovary (CHO) cell proteins, or to any component of this product[1]
- Patients who have or have had progressive multifocal leukoencephalopathy[1]
- Severe, active infection[1]

Precautions/Warnings

- Active infection[1]
- Reactivation of chronic, latent infections such as hepatitis B or tuberculosis[1]
- Malignancy concerns

Pregnancy and Lactation

Rituximab should not be administered to pregnant women unless the possible benefit outweighs the potential risk. It is recommended that women of childbearing age employ effective contraceptive methods during and for up to 12 months after treatment with rituximab.[1]

- The information available on use of rituximab during pregnancy is limited, but does not suggest an increased risk for major congenital malformations above the baseline risk in the general population.[10, 11]

Ontario

4

GN DRUG ACCESS – PROVIDER RESOURCES CONT'D

VACCINATIONS FOR ADULTS WITH GLOMERULONEPHRITIS

Relative to the immunocompetent patient population, GN patients are at increased risk for infection. GN patients with at least one of the following circumstances should be considered for immunization:

- **Current proteinuria greater than 3 grams per day or nephrotic syndrome**
- **May start immunosuppressant therapy**
- **Receiving immunosuppressant therapy**

GENERAL PRINCIPLES

1. Vaccine immunogenicity decreases with increasing proteinuria, treatment with immunosuppressant therapy, and decreased kidney function.
2. Up-to-date routine immunizations, including the annual influenza vaccine, are recommended for GN patients, household members, and other close contacts.
3. GN patients taking immunosuppressant medication should not receive any live vaccines due to risk of disease caused by the live strain.

GENERAL PRINCIPLES

4. Immunization and immunosuppressant therapy:

- If immunization cannot be completed prior to initiating immunosuppressant therapy, a period of at least three months should elapse between therapy cessation and the administration of inactivated vaccines or live vaccines.
- Consider vaccination with inactivated vaccines during immunosuppressant therapy, for those with a long projected duration of immunosuppression and high risk of acquisition for disease based on exposure risk.

GENERAL PRINCIPLES

5. Immunization post-corticosteroid therapy:

- **Immunization can occur as early as 4 weeks following discontinuation of high-dose systemic steroid therapy.**
- **Corticosteroid therapy is not a contraindication to immunization when steroid therapy is short-term (i.e. less than 14 days); or a low-to-moderate dose of prednisone or equivalent (less than 20 mg/day); or long-term, alternate-day treatment with short-acting preparations; or maintenance physiologic replacement therapy; or administered topically, inhaled or locally injected (e.g. joint injection).**

GENERAL PRINCIPLES

6. Immunization post-rituximab therapy:

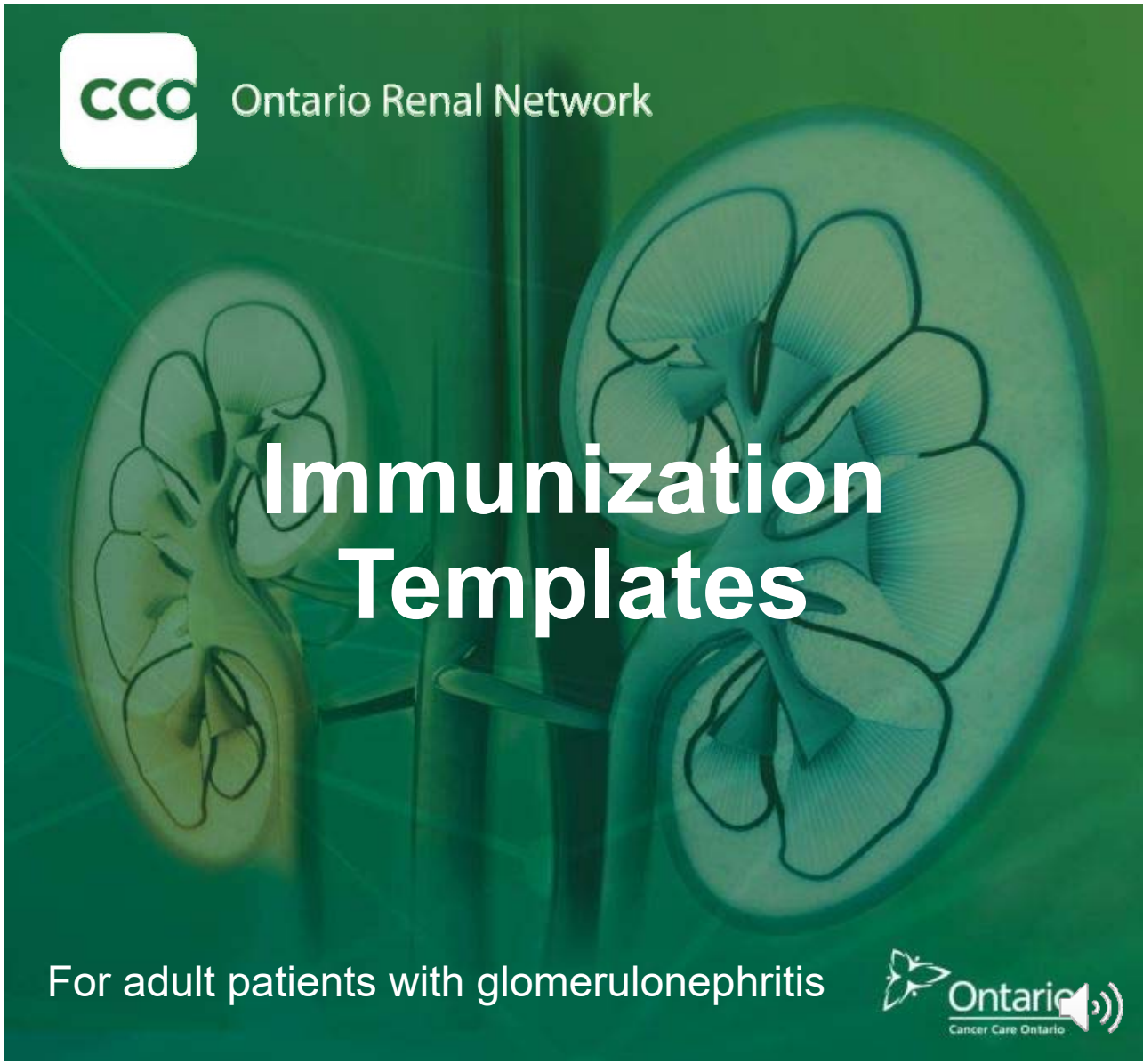
- **If immunization cannot be completed prior to initiation of rituximab, generally a period of 6-12 months should elapse between rituximab cessation and the administration of inactivated or live vaccines. B cell enumeration should be reviewed prior to immunization.**

1. Patient Handout: Vaccines for Patients with Glomerulonephritis

2. Notification of Vaccine Administration

3. Immunization Recommendations

4. Immunization Prescription



Ontario Renal Network

Vaccines for Patients with Glomerulonephritis

Why do I need to get vaccines?

Vaccines lower your risk of getting certain infections.

You are more likely to get seriously ill from infections when you have glomerulonephritis (GN). This is because:

- Your body loses protein in the urine, but can also lose antibodies that fight infection in the urine.
- To treat GN, you may need to take or are already taking medicines that lower your body's ability to fight infections (immunosuppressant medication).
- You may have decreased kidney function. This can make your white blood cells weaker and less able to fight infections.

What vaccines do I need to get?

The most important vaccines are listed first.

Vaccine	Why the vaccine is important
Influenza (Flu)	• This vaccine protects you from getting the flu during flu season (early October to late May). • You have a higher risk of getting seriously ill and having to stay in the hospital if you get the flu. **Get the flu vaccine:** every year in October.
Pneumococcal	• These vaccines protect you from bacteria that cause pneumonia, meningitis, and blood infections. • You have a higher risk of getting seriously ill and having to stay in the hospital if you get a pneumococcal infection. **Get the Prevnar® 13 vaccine.** **Get the Pneumovax® 23 vaccine:** at least 8 weeks after getting the Prevnar® 13 vaccine, a booster dose 5 years later, and when you are 65 years old.
Herpes zoster (Shingles)	• This vaccine protects you from the herpes zoster virus (shingles). • You can get shingles more than once. **Get the SHINGRIX® vaccine** 2 times over the next 2 to 6 months. Get the first dose and then again 2 to 6 months afterwards. If you have had shingles or the Zostavax® II vaccine, wait 1 year before getting SHINGRIX®.
Hepatitis B	• This vaccine protects you from the hepatitis B virus. Hepatitis B can cause liver disease and GN. **Get the high dose (40 mcg) hepatitis B vaccine:** 4 times over the next 6 months. Get first dose and then again 1 month, (2 months), and 6 months afterwards. (The number of doses depends on which vaccine you receive).
Human papillomavirus (HPV)	• This vaccine protects you from certain types of the human papillomavirus (HPV). HPV can cause genital warts and some types of cancers. • You have a higher risk of getting genital warts and some types of cancers from an HPV infection if you are taking immunosuppressant medication. **Get the HPV vaccine:** if you are female and under 46 years old, or male and under 27 years old.

For your safety: **Do not get any live vaccines** (a vaccine that has a weakened form of the virus/bacteria in it) **if you are taking immunosuppressant medications.** You would be at risk of getting that infection. All of the recommended vaccines in this handout are inactivated (non-live) vaccines.

When should I get these vaccines?

Get these vaccines as soon as possible. They work best if you get them before starting immunosuppressant medication and when your kidneys are still working normally.

Where can I get these vaccines?

Some of these vaccines will require a prescription. Take this handout to your family doctor or nurse practitioner to obtain vaccine supply and then these may be injected at your local pharmacy or at your family doctor's office.

What side effects should I expect?

Most vaccine side effects are mild and only last for a few days. Side effects include:

- pain, redness, or swelling where you got your shot
- a mild fever (between 37°C and 38°C)
- feeling tired (fatigued)
- headache
- muscle and joint pain

What should I do after I get a vaccine?

You, your doctor, or your local pharmacist should tell the clinic right away.

- Send vaccine documentation to your clinic at _____.
  (clinic fax number)

Who can I ask if I have questions?

Call the clinic at _____.
(clinic phone number)

Ontario Renal Network

Date: _____

Notification of Vaccine Administration

Dear Dr. _____,
(physician name)

Our mutual patient _____ _____
(patient name) (date of birth)

received the following vaccination(s) in the Glomerulonephritis Clinic at

_____ .
(hospital)

Vaccine	Date Administered

Sincerely,

_____
(name)

_____
(signature)

Ontario Renal Network

Immunization Recommendations

Dear Dr. _____, **Date:** _____
(physician name)

It is recommended that _____ _____
(patient name) (date of birth)
receive the following immunizations due to (potential) immunosuppressant therapy:

- ☐ **Pneumococcal conjugate 13 (Prevnar® 13)** 0.5 mL IM, followed by **pneumococcal polysaccharide 23 (Pneumovax® 23)** 0.5 mL IM administered at least 8 weeks later.
  Patients who require immunosuppressant therapy qualify for Public Health supply of Pneumovax® 23. Patients age 50 or greater who require immunosuppressant therapy qualify for Public Health supply of Prevnar® 13.

- ☐ **Pneumococcal conjugate 13 (Prevnar® 13)** 0.5 mL IM x 1 dose.
  Patients age 50 or greater who require immunosuppressant therapy qualify for Public Health supply of Prevnar®13.

- ☐ **Pneumococcal polysaccharide 23 (Pneumovax® 23)** 0.5 mL IM x 1 dose.
  Patients who require immunosuppressant therapy qualify for Public Health supply of Pneumovax® 23.

- ☐ **Recombinant zoster vaccine (Shingrix®)*** 0.5 mL IM administered at month 0 and between 2-6 months after first injection.

- ☐ **Recombinant monovalent hepatitis B*:**
  Engerix®-B 40 mcg administered IM at months 0, 1, 2 and 6 **OR**
  Recombivax-HB® 40 mcg administered IM at months 0, 1 and 6.

For patients age 19 yrs or younger requiring Recombivax-HB®, the recommended dose is 10 mcg IM.

- ❑ **Human Papillonmavirus 9-valent recombinant vaccine (GARDASIL®-9) *** 0.5 mL IM at month 0, 2 and 6

*Engerix®-B, Recombivax-HB®, Shingrix® and Gardasil®-9 are not covered by Public Health. The patient is aware that he/she will need to inquire about coverage through private insurance or pay out of pocket.

The patient has been asked to contact your office to arrange an appointment to receive these immunizations. As each vaccine is administered, please notify the GN Clinic _____.
(clinic fax number)

Sincerely,

_____
(name)

_____
(signature)

Ontario Renal Network

Patient Name:

Date of Birth:

Immunization Prescription

Date: _____

Drug allergies: _____ ☐ No known drug allergy

Pneumococcal 13-valent conjugate vaccine (PREVNAR®-13)
Sig: Inject 0.5 mL IM **x 1 dose**
Qty:**0.5 (Zero Point Five) mL**
Refill: **0 (Zero)**

Pneumococcal polyvalent vaccine (PNEUMOVAX®-23)
Sig: Inject 0.5 mL IM **x 1 dose**
Administer at least 8 weeks after receiving Prevnar 13
Qty: **0.5 (Zero Point Five) mL**
Refill: **0 (Zero)**

Herpes zoster non-live recombinant vaccine (SHINGRIX®)
Sig: Inject 0.5 mL IM **x 2 doses**
Administer first dose at month 0 and second dose at 2-6 months
Qty: **0.5 (Zero Point Five) mL**
Refill: **1 (One)**

Hepatitis B recombinant vaccine (ENGERIX®-B) 20 mcg/mL
Sig: Inject 2 mL (40 mcg total) IM **x 4 doses**
Administer at months 0, 1, 2 and 6
Note to pharmacy: Give 2 x 20 mcg (1 mL) vials for 40 mcg (2 mL) dose
Qty: **2 (Two) mL**
Refill: **3 (Three)**

Hepatitis B recombinant vaccine (RECOMBIVAX®-HB) 40 mcg/mL
Sig: Inject 1 mL (40 mcg total) IM **x 3 doses**
Administer at months 0, 1 and 6
Qty: **1 (One) mL**
Refill: **2 (Two)**

Human papillomavirus 9-valent recombinant vaccine (GARDASIL®-9)
Sig: Inject 0.5 mL IM **x 3 doses**
Administer at months 0, 2 and 6
Qty: **0.5 (Zero Point Five) mL**
Refill: **2 (Two)**

Meningococcal A,C,Y and W-135 quadrivalent conjugate vaccine – CHOOSE ONE

(☐MENACTRA® or ☐ MENVEO® or ☐ NIMENRIX®)
Sig: Inject 0.5 mL into the muscle **x 2 doses**
Administer at weeks 0 and 8
Qty: **0.5 (Zero Point Five) mL**
Refill: **1 (One)***

Meningococcal multicomponent serogroup B vaccine (BEXSERO®)
Sig: Inject 0.5 mL IM **x 2 doses**
Administer at weeks 0 and 4
Qty: **0.5 (Zero Point Five) mL**
Refill: **1 (One)***

Haemophilus influenza type b conjugate vaccine – CHOOSE ONE

(☐Act-HIB® or ☐ HIBERIX®)
Sig: Inject 0.5 mL IM **x 1 dose**
Qty:**0.5 (Zero Point Five) mL**
Refill: **0 (Zero)**

Prescriber Name (PRINT):_____ CPSO Number: _____

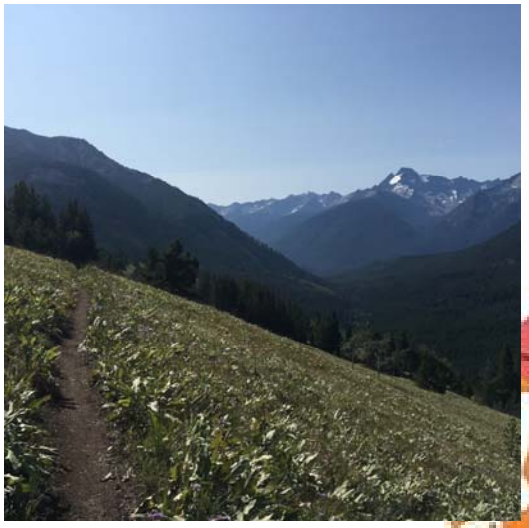
Prescriber Signature:_____ GN Clinic Tel: _____
(clinic telephone number)

□ Rx PROVIDED to **Patient** □ Rx FAXED to **Pharmacy:** _____

***** If vaccine is administered in the pharmacy, please notify the GN Clinic as each vaccine is administered (Fax: _____)*****
(clinic fax number)

GN DRUG ACCESS TASK GROUP

Name	Title/Affiliation
Jenny Ng (Chair)	Pharmacist, Sunnybrook Health Sciences Centre
Dr. Todd Fairhead (Chair)	Nephrologist, The Ottawa Hospital
Alison Shipley	Pharmacist, St. Joseph's Healthcare Hamilton
Anna Babej	Pharmacist, Trillium Health Partners
Brandi Grozell	Nurse Practitioner, Sunnybrook Health Sciences Centre
Lisa Zhu	Pharmacist, Sunnybrook Health Sciences Centre
Melissa Lan	Pharmacist, University Health Network
Clara Korenvain	Pharmacist, London Health Sciences Centre
Kiet-Nghi Cao	Pharmacist, The Ottawa Hospital
Caitlin Jones	Pharmacist, Kingston Health Sciences Centre
Ontario Renal Network – Core Team	
Mayuri Mahentharan	Analyst, Clinical Programs
Catherine Bacik	Senior Specialist, Clinical Programs
Jessie Wong	Team Lead, Clinical Programs
Daphne Sniekers	Group Manager, Clinical Programs
Rohini Naipaul	Senior Pharmacist, CCO Drug Programs




Yukon
Northwest Territories
Nunavut
British Columbia
Alberta
Saskatchewan
Manitoba
Ontario
Quebec
Newfoundland and Labrador
Prince Edward Island
Nova Scotia

GN MANAGEMENT IN BC

- **Mostly managed by nephrologists in their office**

- **2nd opinion case referred to one nephrologist operating in 2 mutidisciplinary GN clinics (Dr. Sean Barbour)**

- **Progression to ESRD => referred to KCC clinic**
  - Minimum management of immunosuppressants

BCRA GN NETWORK

- **Collection and standardized data for CKD patients**
- **Help to facilitate access to immunosuppressive therapy**
- **Standardized therapy**
  - Immunosuppressants
  - Adjunctive therapy
  - Conservative therapy
  - Tools for patients and clinicians

BCRA GN NETWORK

http://www.bcrenalagency.ca/health-professionals/clinical-resources/glomerulonephritis#Protocols--&--tools

MENTOR STUDY

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy

F.C. Fervenza, G.B. Appel, S.J. Barbour, B.H. Rovin, R.A. Lafayette, N. Aslam, J.A. Jefferson, P.E. Gipson, D.V. Rizk, J.R. Sedor, J.F. Simon, E.T. McCarthy, P. Brenchley, S. Sethi, C. Avila-Casado, H. Beanlands, J.C. Lieske, D. Philibert, T. Li, L.F. Thomas, D.F. Green, L.A. Juncos, L. Beara-Lasic, S.S. Blumenthal, A.N. Sussman, S.B. Erickson, M. Hladunewich, P.A. Canetta, L.A. Hebert, N. Leung, J. Radhakrishnan, H.N. Reich, S.V. Parikh, D.S. Gipson, D.K. Lee, B.R. da Costa, P. Jüni, and D.C. Cattran, for the MENTOR Investigators

NEJM July 2019; 381 (1): 36-46.

MENTOR STUDY

- **Open-label RCT, multicenter (North America), non-inferiority trial**
- **IMN patients with proteinuria > 5 g/d, CrCl > 40 mL/min on RAAS blockade for > 3 months**
- **RTX 1 g Q2weeks x 2 dose (can repeat at 6 months if partial response) vs. CsA targeting trough 125 to 175 ng/mL x 12 months; F/U x 24 months**
  - CsA taper over 2 months
- **1º outcome => Complete or partial remission or proteinuria at 24 months**

MENTOR STUDY

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Rituximab (N=65)	Cyclosporine (N=65)
Age — yr	51.9±12.6	52.2±12.4
Male sex — no. (%)	47 (72)	53 (82)
Blood pressure — mm Hg		
Systolic	125.7±14.8	123.3±13.4
Diastolic	74.7±10.1	76.5±9.8
Height — m	1.7±0.1	1.7±0.1
Weight — kg	96±23	90±20
Body-mass index†	31.8±6.3	29.3±5.6
History of immunosuppressive therapy — no. (%)	19 (29)	20 (31)
Cholesterol — mg/dl		
Low-density lipoprotein	114.1±57.7	122.3±63.0
Total	145.1±61.6	144.8±69.8
Anti-PLA2R — U/ml		
Median	409	413
Interquartile range	163–834	206–961
Anti-PLA2R positive — no. (%)‡	50 (77)	46 (71)
Serum albumin — g/dl		
Median	2.5	2.5
Interquartile range	2.1–2.9	2.1–2.9
Serum creatinine — mg/dl	1.3±0.4	1.3±0.4
Urinary protein — g/24 hr		
Median	8.9	8.9
Interquartile range	6.8–12.3	6.7–12.9
Urinary creatinine — g/24 hr	1.7±0.5	1.8±0.6
Creatinine clearance — ml/min/1.73 m^2	84.9±29.8	87.4±34.4
Protein:creatinine§	6.2±2.6	6.2±3.3

MENTOR STUDY

Evaluation Time Point	Rituximab (N=65)	Cyclosporine (N=65)	Risk Difference (95% CI)	P Value for Noninferiority	P Value for Superiority
	no. with complete or partial remission (%)		*percentage points*		
End of treatment period at 12 mo	39 (60)	34 (52)	8 (–9 to 25)	0.004	—
End of follow-up at 24 mo	39 (60)	13 (20)	40 (25 to 55)	<0.001	<0.001

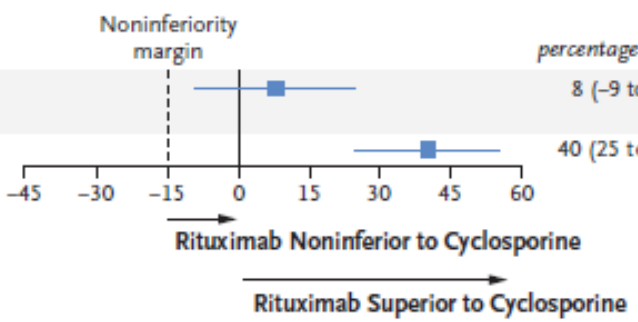


Figure 1. Composite Outcome of Complete or Partial Remission at 12 and 24 Months.

Point estimates and two-sided 95% confidence intervals are shown for the treatment effect, defined as the risk difference for complete or partial remission between groups in the intention-to-treat analysis. The noninferiority margin for rituximab as compared with cyclosporine was –15 percentage points. The lower end of the two-sided 95% confidence interval of the risk difference in the secondary composite of complete remission or partial remission at 12 months was above –15 percentage points, and the P value for noninferiority of 0.004 was significant, which met the prespecified alpha level of a P value of less than 0.0125 after Bonferroni correction. Per the statistical analysis plan, no test for superiority was performed for the secondary outcome of complete or partial remission at 12 months. The lower limit of the two-sided 95% confidence interval for the risk difference in the primary composite outcome of complete remission or partial remission at 24 months was above 0 percentage points; both the criterion for noninferiority and the criterion for superiority of rituximab were met at a P value of less than 0.001, which met the prespecified alpha levels specified for noninferiority ($P<0.025$) and superiority ($P<0.05$). P values for noninferiority are one-sided, and the P value for superiority is two-sided.

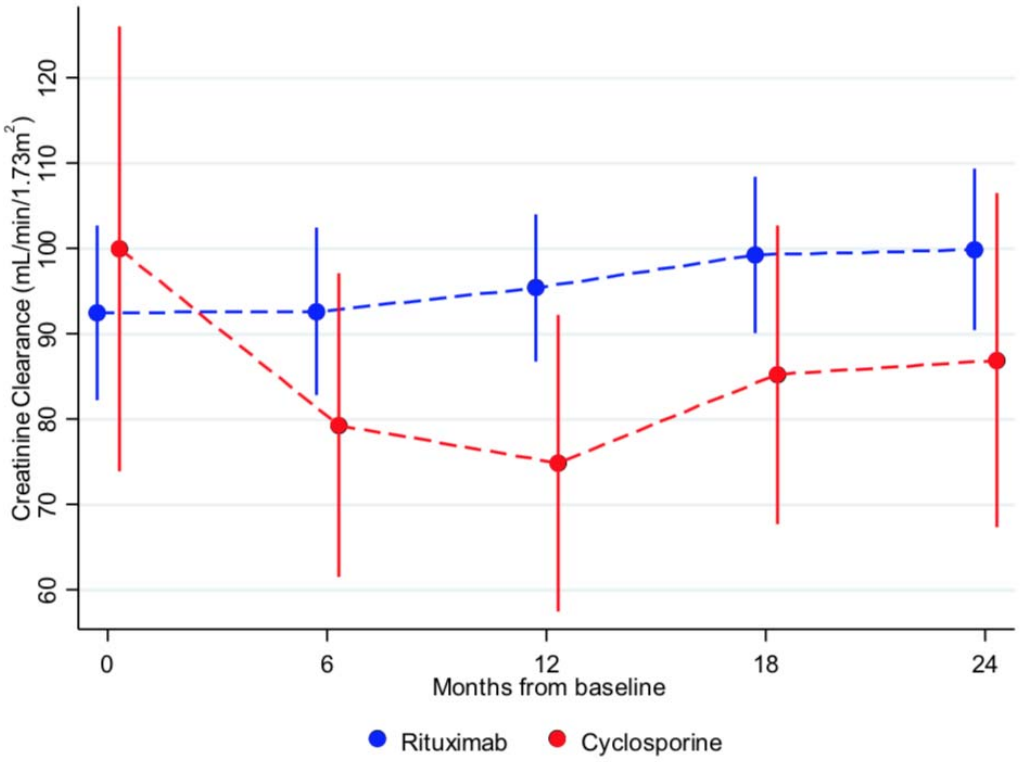
MENTOR STUDY

Table 3. Adverse Events.

Event	Rituximab (N=65)		Cyclosporine (N=65)		P Value*
	Patients	Events	Patients	Events	
	no. (%)	*no. of events (rate per 100 patients)*	*no. (%)*	*no. of events (rate per 100 patients)*	
Any adverse event	46 (71)	179 (275)	51 (78)	218 (335)	0.31
Grade ≥3	11 (17)	14 (22)	23 (35)	27 (42)	0.02
Grade <3	44 (68)	165 (254)	45 (69)	191 (294)	0.85
Serious adverse event	11 (17)	13 (20)	20 (31)	22 (34)	0.06
Fatal	0	0	0	0	1.00
Nonfatal	11 (17)	13 (20)	20 (31)	22 (34)	0.06
Adverse event occurring in ≥4 patients					
Hypertension	0	0	5 (8)	6 (9)	0.06
Hyperkalemia	1 (2)	1 (2)	4 (6)	12 (18)	0.37
Gastrointestinal pain	1 (2)	2 (3)	9 (14)	9 (14)	0.02
Gingival event	1 (2)	1 (2)	4 (6)	4 (6)	0.37
Nausea or vomiting	2 (3)	4 (6)	9 (14)	15 (23)	0.03
Chills	1 (2)	1 (2)	5 (8)	5 (8)	0.21
Edema	4 (6)	5 (8)	5 (8)	6 (9)	1.00
Fatigue	5 (8)	6 (9)	8 (12)	8 (12)	0.38
Influenza-like symptoms	6 (9)	8 (12)	3 (5)	3 (5)	0.49
Infusion-related reaction	16 (25)	22 (34)	0	0	<0.001
Gastrointestinal infection	4 (6)	4 (6)	4 (6)	4 (6)	1.00
Pneumonia	1 (2)	1 (2)	6 (9)	6 (9)	0.12
Other respiratory tract infection	9 (14)	12 (18)	9 (14)	10 (15)	1.00
Skin infection	4 (6)	5 (8)	0	0	0.12
Muscle cramps	6 (9)	9 (14)	4 (6)	5 (8)	0.74
Myalgia	4 (6)	4 (6)	6 (9)	8 (12)	0.74
Pain	2 (3)	3 (5)	4 (6)	7 (11)	0.68
Dizziness	2 (3)	3 (5)	4 (6)	5 (8)	0.68
Headache	4 (6)	5 (8)	7 (11)	8 (12)	0.34
Paresthesia or dysesthesia	2 (3)	2 (3)	4 (6)	5 (8)	0.68
Anxiety or depression	1 (2)	1 (2)	4 (6)	6 (9)	0.37
Increased creatinine level†	4 (6)	5 (8)	15 (23)	17 (26)	0.01
Cough	7 (11)	9 (14)	2 (3)	4 (6)	0.16
Dyspnea	2 (3)	2 (3)	3 (5)	3 (5)	1.00
Pruritus	7 (11)	8 (12)	0	0	0.01

* P values are for the difference in proportions of patients having a specific type of event. P values were not adjusted for multiple comparisons.
† End-stage renal disease developed in one patient in the cyclosporine group.

MENTOR STUDY



QUESTIONS?