IgA Nephropathy

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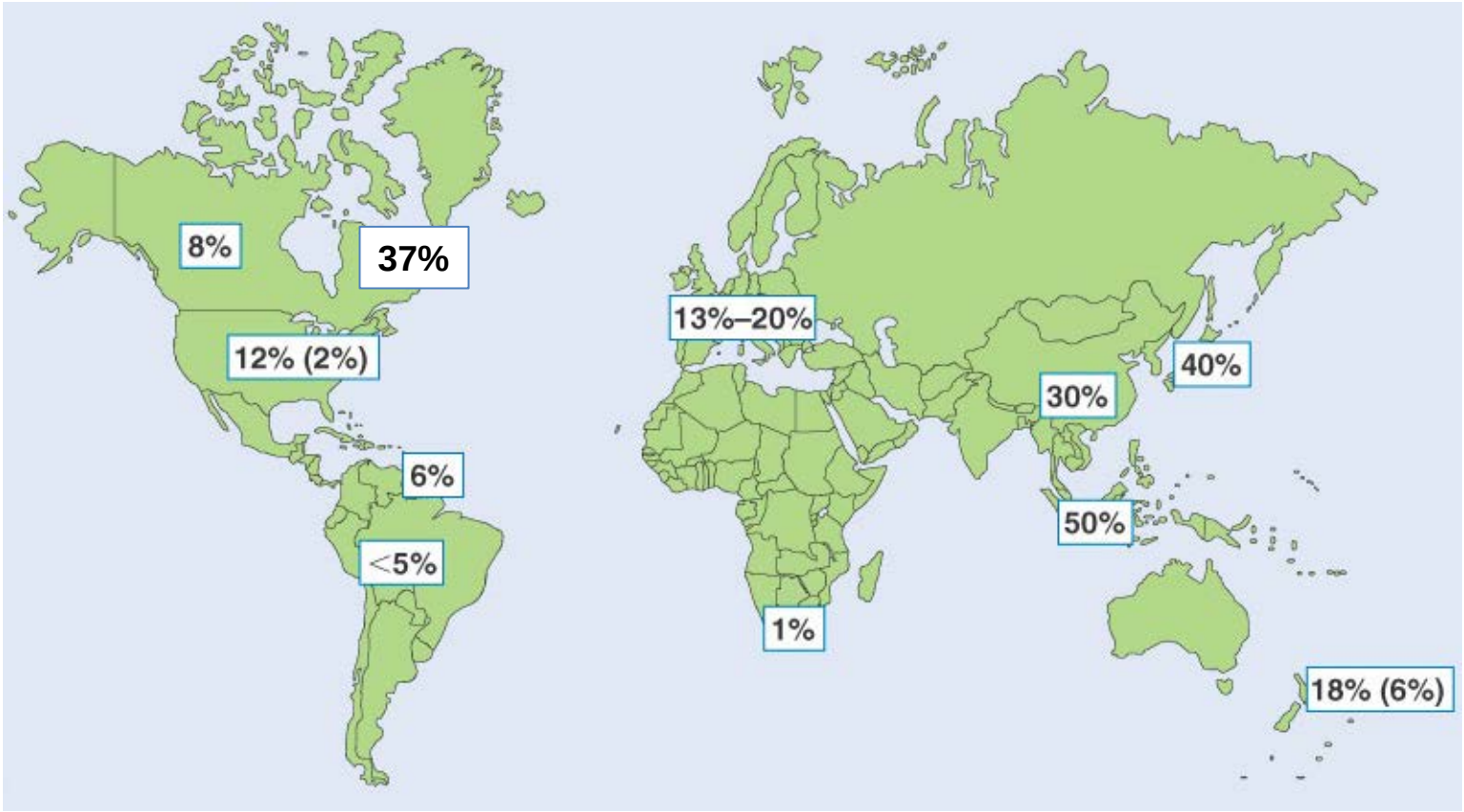
IgAN

- Worldwide is the most common type of GN
    - More common in Asia than Europe or N. America
    - Uncommon in Blacks
- Very important cause of ESRD in Asian countries
    - Childhood urine screening programs
- Typically presents in 20-30’s, equal male/female
- In Canada, may be increasing in prevalence
    - Now accounts for 36.7% of all biopsy-proven cases of GN

IgAN prevalence world-wide

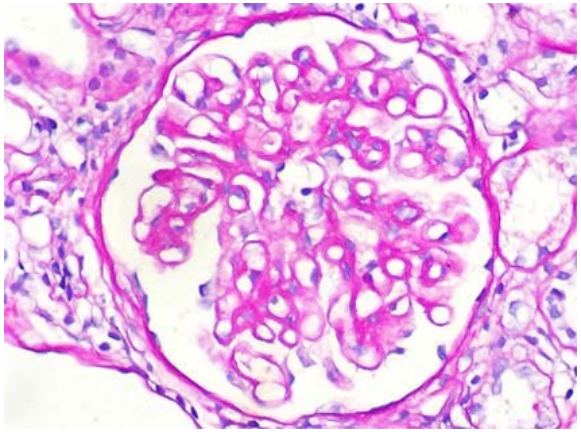
- Proportion of biopsy-proven GN cases due to IgAN:



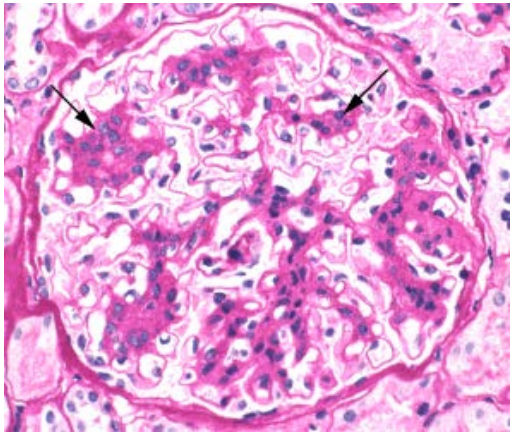
The percentage of biopsy-proven GN cases that are IgAN: Comprehensive clinical nephrology 3rd edition, Feehally

IgAN: diagnosis by kidney biopsy

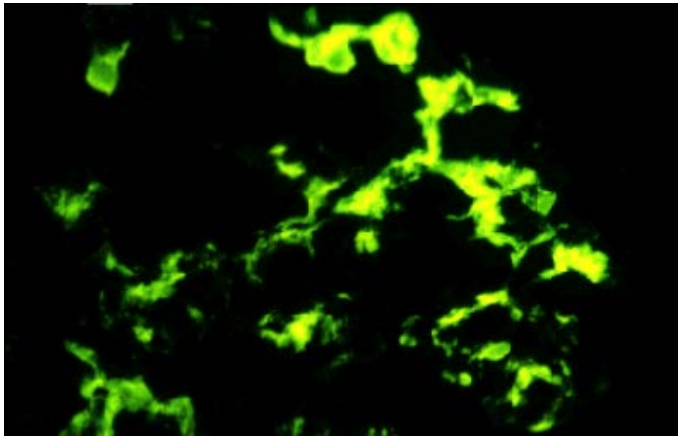
- Characterized by IgA deposits on the kidney biopsy
- Most commonly mild proliferative features



Normal glomerulus

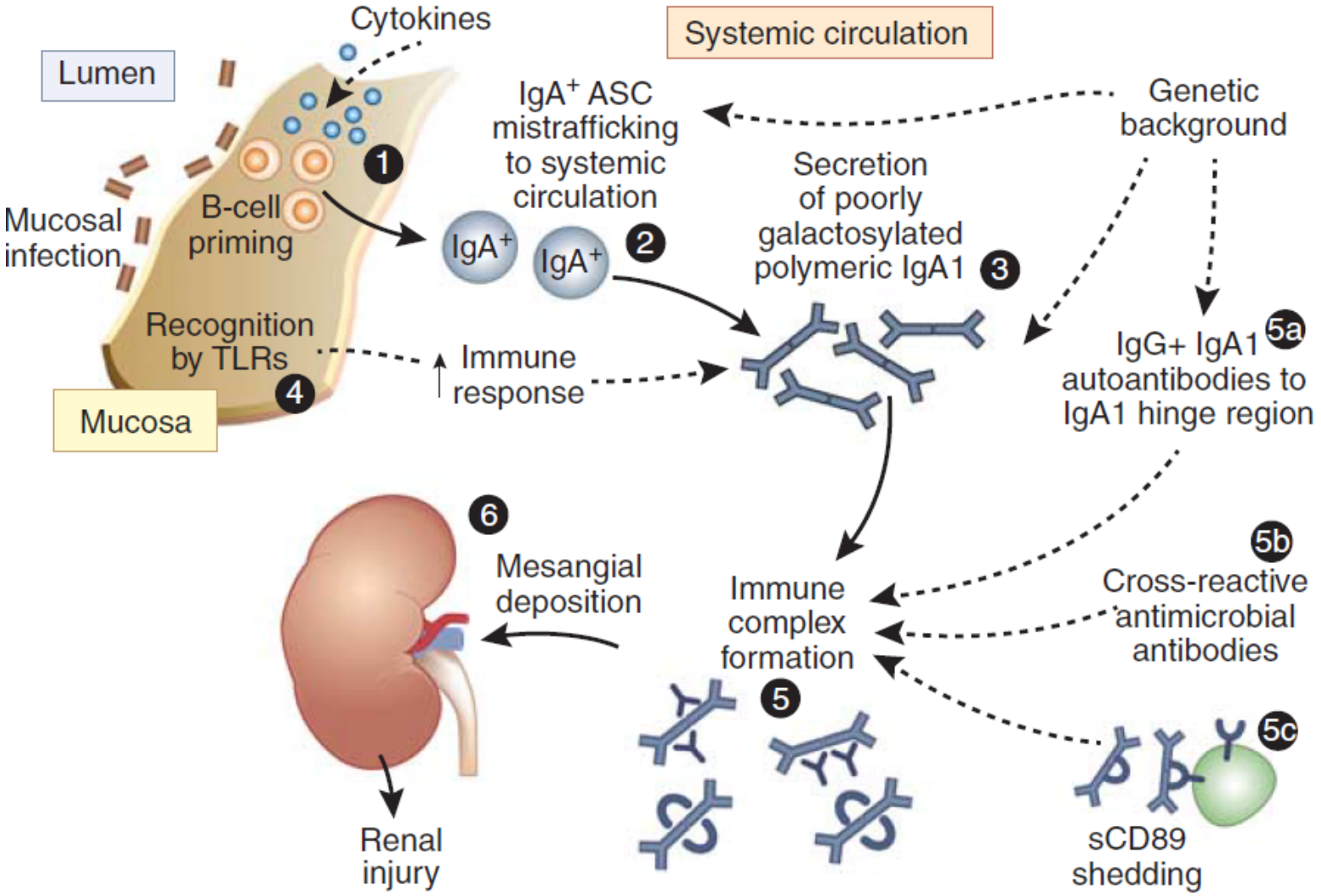


Mesangial hypercellularity
Mesangial expansion



Mesangial IgA deposits

IgAN: pathogenesis



Boyd, KI 2012

IgAN: clinical presentation

- Disease severity in IgAN is highly variable:

Asymptomatic hematuria Asymptomatic proteinuria	Slowly progressive proteinuric renal disease (MOST COMMON)	Rapidly progressive glomerulonephritis Severe nephrotic syndrome

- 40% have recurrent gross hematuria in context of viral infections (“synpharyngitic”)
- Most have asymptomatic slowly progressive proteinuric renal disease
- <10% have severe presentations:
    - RPGN or severe NS

IgAN is the most common type of GN in Canada

BC GN Registry data: March 2013 – March 2016:

	Total Number	Number per Year	Percent of yearly GN	Incidence per 100000/yr
All types of GN (N)	954	318	100%	8.24
IgA Nephropathy	186	62	19.5%	1.61
MCD	52	17	5.5%	0.44
Pauci-immune GN	134	45	14.0%	1.16
Membranous N.	100	33	10.5%	0.86
Lupus Nephritis	99	33	10.4%	0.86
FSGS (all)	148	49	15.5%	1.28
FSGS (idiopathic)	32	11	3.4%	0.27

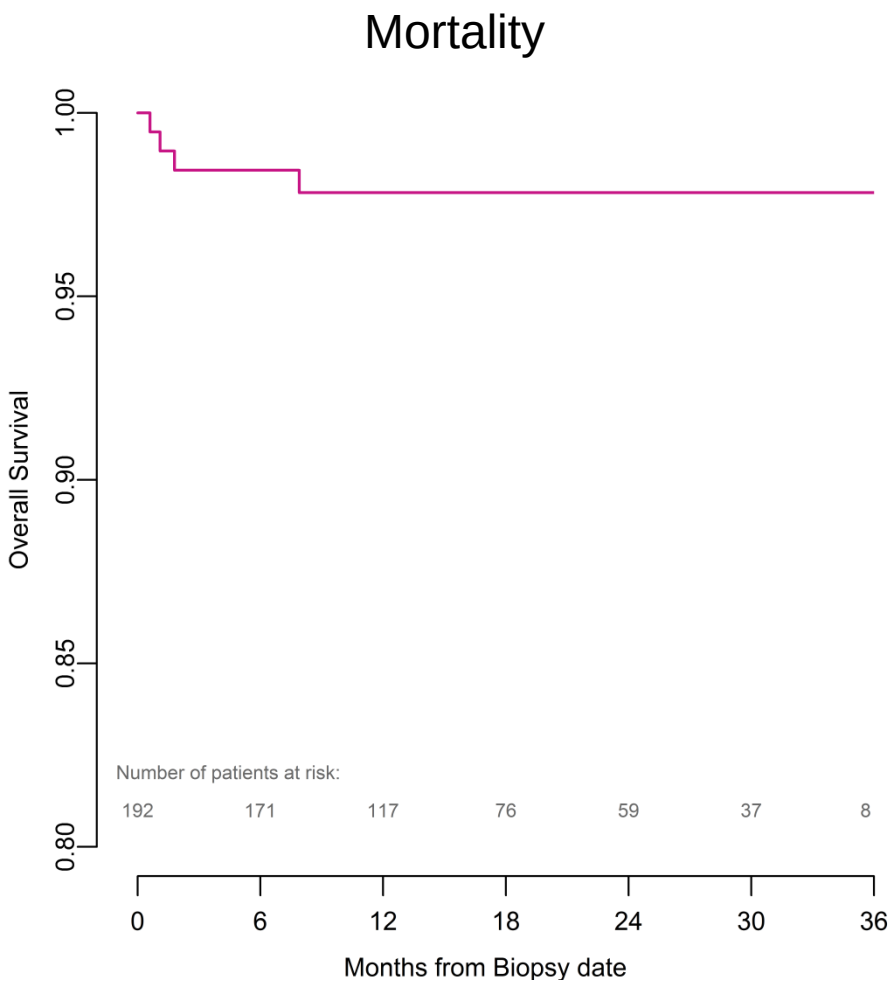
Incidence based on population estimates from BC Stats

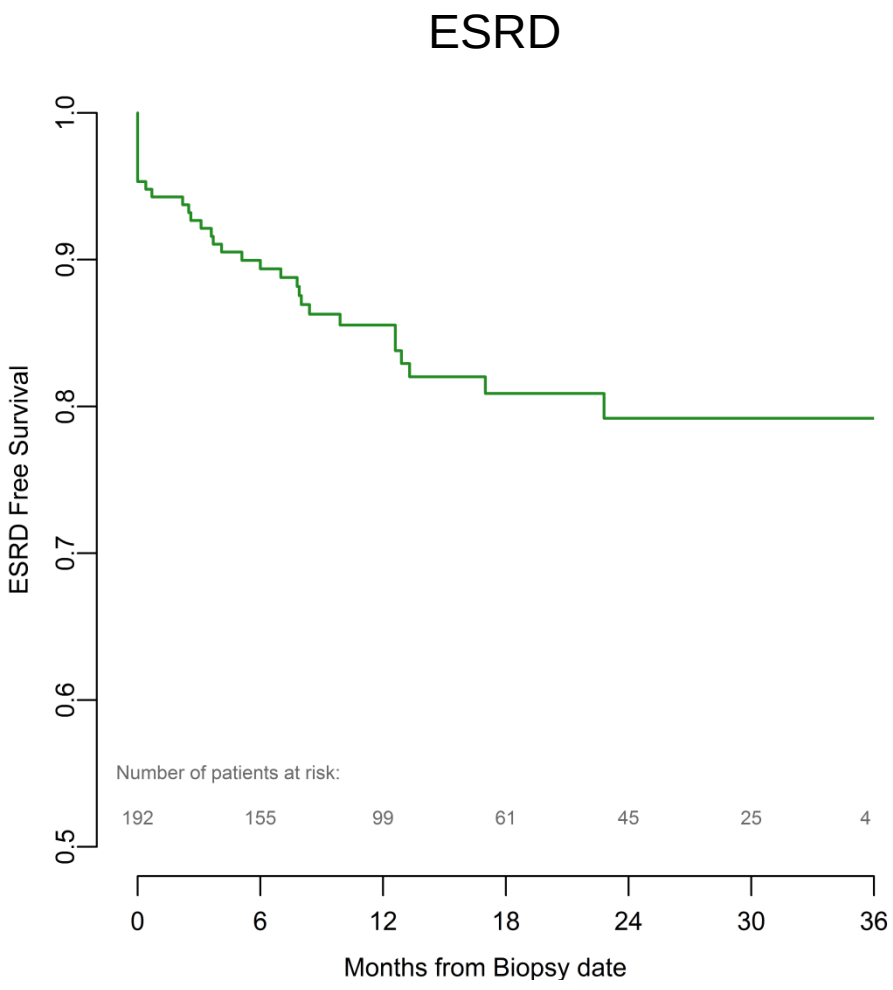
IgAN in BC: characteristics at biopsy

	IgAN	MN	FSGS (idiopathic)
Age (years)	44 [35 , 59]	61 [52 , 67]	52 [32 , 70]
Sex (% male)	66.2%	54.5%	56.5%
Creatinine (µmol/L)	154 [106 , 253]	95 [73 , 128]	83 [60 , 166]
eGFR (ml/min/1.73m^2)	38 [20 , 66]	64 [43 , 94]	81 [36 , 111]
Proteinuria (g/day)	1.3 [0.6 , 2.2]	3.8 [2.2 , 6]	4.3 [1.6 , 9.2]
<1g/d	37.8%	11.9%	14.3%
1-4g/d	50.4%	40.3%	28.6%
4-8g/d	9.2%	31.3%	28.6%
>8g/d	2.5%	16.4%	28.6%

BC GN Registry data: March 2013 – March 2016

IgAN in BC: outcomes





IgAN: monitoring disease activity

- Mostly asymptomatic
- Laboratory values:
  - Renal function trends over time (Cr, eGFR): expected pattern is slow change over years
  - Urine: RBC on urinalysis
  - Proteinuria: ACR, PCR or 24 hour urine
- Monitor:
  - Disease progression over time
  - Response to treatments

IgAN: treatment

- Following does not apply to rare and more aggressive variants that may be treated differently
- First address conservative measures:
    - BP target <130/80
    - Weight loss, exercise
    - OSA: start CPAP
    - Low salt diet
    - ACEi or ARB, maximize dose for proteinuria <1g/day
    - Dyslipidemia
    - Fish oil: controversial
- Continue conservative measures for at least 6 months or longer

IgAN: treatment

- Consider immunosuppression with prednisone in patients:
    - Have already optimized conservative therapy for at least 6 months
    - Proteinuria >1g/d
    - Have treatable lesions on kidney biopsy (ie not all scarring)
    - Are at lower risk of steroid complications
    - Understand the risk/benefit of treatment
    - Are not beyond the point of no return (ie eGFR <30-40)
- Goal of immunosuppression:
    - Long-term: reduce the risk of progression to ESRD, slow rate of renal function decline
    - Short-term: reduce proteinuria (surrogate outcome)

IgAN: KDIGO treatment recommendations

10.2: Antiproteinuric and antihypertensive therapy

10.2.1: We recommend long-term ACE-I or ARB treatment when proteinuria is >1 g/d, with up-titration of the drug depending on blood pressure. (*1B*)

10.2.2: We suggest ACE-I or ARB treatment if proteinuria is between 0.5 to 1 g/d (in children, between 0.5 to 1 g/d per 1.73 m^2). (*2D*)

10.2.3: We suggest the ACE-I or ARB be titrated upwards as far as tolerated to achieve proteinuria <1 g/d. (*2C*)

10.2.4: In IgAN, use blood pressure treatment goals of <130/80 mm Hg in patients with proteinuria <1 g/d, and <125/75 mm Hg when initial proteinuria is >1 g/d (see Chapter 2). (*Not Graded*)

10.3: Corticosteroids

10.3.1: We suggest that patients with persistent proteinuria ≥1 g/d, despite 3-6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR >50 ml/min per 1.73 m^2, receive a 6-month course of corticosteroid therapy. (*2C*)

Really no other IS agents used in IgAN except in rare cases

IgAN: prednisone treatment

Table 26 | Corticosteroid regimens in patients with IgAN

References	Pozzi C *et al.*[509]	Manno C *et al.*[510]; Lv J *et al.*[511]
Regimen	i.v. bolus injections of 1 g methylprednisolone for 3 days each at months 1, 3, and 5, followed by oral steroid 0.5 mg/kg prednisone on alternate days for 6 months	6-month regime of oral prednisone[a] starting with 0.8–1 mg/kg/d for 2 months and then reduced by 0.2 mg/kg/d per month for the next 4 months

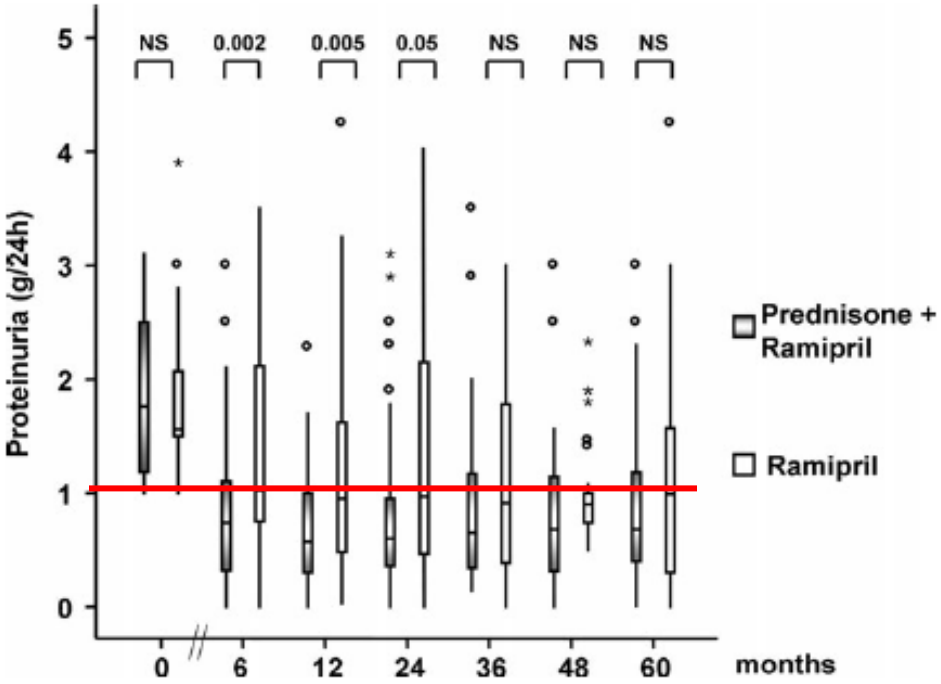
IgAN, immunoglobulin A nephropathy.
[a]Prednisone and prednisolone are equivalent and can be used interchangeably with the same dosing regimen.

Requires IV infusions
No RASB used in trial
Used less often

Easier to administer
Trial done on background RASB
Used more often

IgAN: prednisone treatment

- 8 year risk of doubling serum creatinine in Manno trial:
  - 25% in placebo group
  - 5% in steroid group
- 75% of steroid-treated patients have proteinuria reduce to <1g/day



Manno, NDT 2009

IgAN: prednisone treatment controversies

- STOP-IgAN and TESTING trials:
  - 10-15% risk of serious complications
  - Optimal conservative treatment can be very effective
  - Risk/benefit ratio of steroids is unclear
- Not all nephrologists may want to treat IgAN with steroids given the controversies
- Evidence may change over the next few years

Complications of steroids

Major Side Effects Associated with Corticosteroid Therapy

Dermatologic and soft tissue
- Skin thinning and purpura
- Cushingoid appearance
- Alopecia
- Acne
- Hirsutism
- Striae
- Hypertrichosis

Eye
- Posterior subcapsular cataract
- Elevated intraocular pressure/glaucoma
- Exophthalmos

Cardiovascular
- Hypertension
- Perturbations of serum lipoproteins
- Premature atherosclerotic disease
- Arrhythmias with pulse infusions

Gastrointestinal
- Gastritis
- Peptic ulcer disease
- Pancreatitis
- Steatohepatitis
- Visceral perforation

Renal
- Hypokalemia
- Fluid volume shifts

Genitourinary and reproductive
- Amenorrhea/Infertility
- Intrauterine growth retardation

Bone
- Osteoporosis
- Avascular necrosis

Muscle
- Myopathy

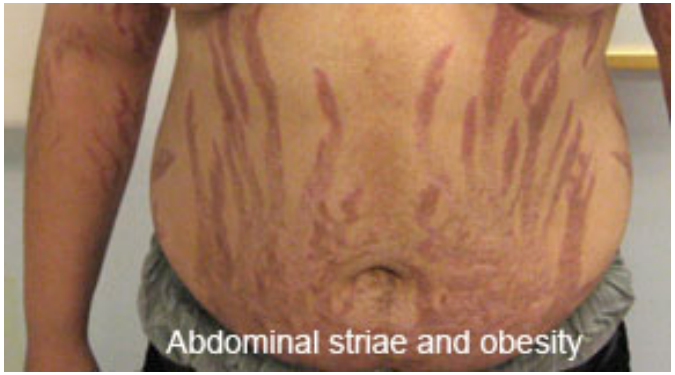
Neuropsychiatric
- Euphoria
- Dysphoria/depression
- Insomnia/akathisia
- Psychosis
- Pseudo tumor cerebri

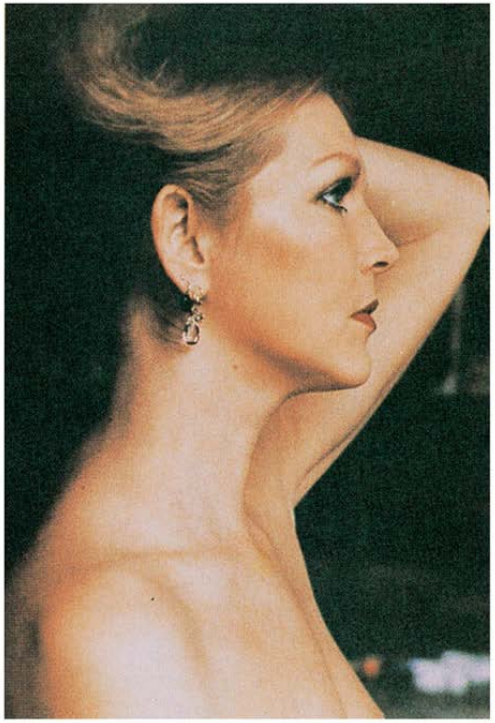
Endocrine
- Diabetes mellitus
- Hypothalamic-pituitary-adrenal insufficiency

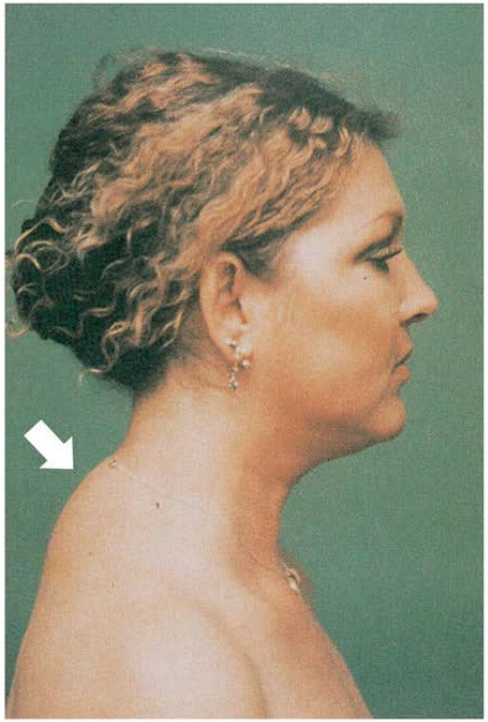
Infectious disease
- Heightened risk of typical infections
- Opportunistic infections
- Herpes zoster

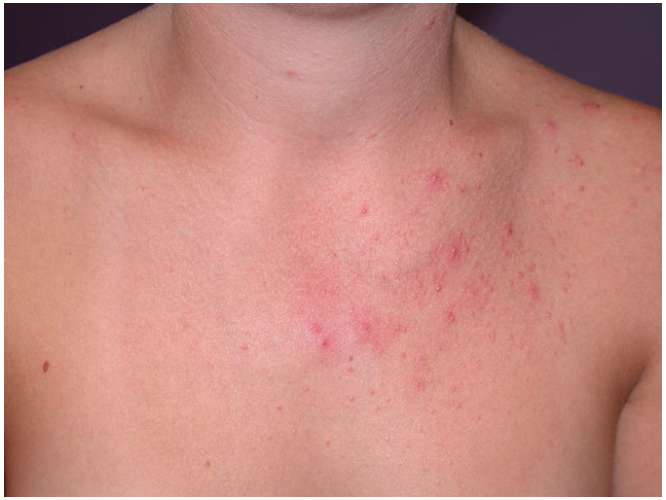
Complications of steroids

Complications of steroids









Complications of steroids

- Medications used to prevent complications:
    - Ranitidine or PPI: gastritis
    - Calcium (between meals), Vitamin D, +/- bisphosphonate: osteoporosis

BCPRA resources

- Available on-line: BCPRA > Health Professionals > Clinical Resources > Glomerulonephritis
- Steroid treatment protocols: Manno/Lv, Pozzi regimens
- Supporting documentation
- Prednisone: information sheet for patients

BCRenal
an agency of the Provincial Health Services Authority

IgA Nephropathy:
CORTICOSTEROID REGIMEN
Pozzi Protocol

To obtain prednisone coverage under the BCPRA GN Formulary:

- Ensure the patient is registered in PROMIS
- Fax this prescription along with an application form to Macdonald's Pharmacy at **1-866-685-0305**

1. 6-month corticosteroid regimen (Pozzi protocol):

- **METHYLPREDNISONE** IV x 3 days at the beginning of months 1, 3 and 5 (follow medical short stay orders on page 3)

WITH

- **PREDNISONE** 0.5 mg/kg _____ mg PO q2days x 6 months **THEN** taper **PREDNISONE** as below:

_____

_____

_____

_____

Quantity: New prescription fill quantity shall be for 90 days and if tolerated, may repeat times one.

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IgA Nephropathy:
CORTICOSTEROID REGIMEN
Pozzi Protocol

- **Admit to medical short stay under Dr.** _____
- **Insert IV in non-dominant arm**
- **Vital signs x 1, then PRN**

☐ **METHYLPREDNISONE 1000 mg IV x 3 days at the beginning of months 1, 3 and 5**
☐ **METHYLPREDNISONE _____ mg IV x 3 days at the beginning of months 1, 3 and 5**

The patient is to receive the above methylprednisone doses on the following consecutive dates:

Month 1: _____

Month 3: _____

Month 5: _____

- **Remove IV**
- **Discharge home**

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IgA Nephropathy: CORTICOSTEROID REGIMEN Manno/Lv Protocol

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1. 6-month corticosteroid regimen (Manno/Lv protocol):

☐ **PREDNISONE**_____ mg (recommended: 1 mg/kg/day to a max of 60 mg) PO daily for
☐ 60 days (recommended)
OR ☐_____

✹ **THEN** taper **PREDNISONE** (recommend: reduce dose by 5 mg/day/week until 20 mg PO daily then reduce dose by 2.5 mg/day/week until off):

1. _____ mg PO daily x 1 week
2. _____ mg PO daily x 1 week
3. _____ mg PO daily x 1 week
4. _____ mg PO daily x 1 week
5. _____ mg PO daily x 1 week
6. _____ mg PO daily x 1 week
7. _____ mg PO daily x 1 week
8. _____ mg PO daily x 1 week
9. _____ mg PO daily x 1 week
10. _____ mg PO daily x 1 week
11. _____ mg PO daily x 1 week
12. _____ mg PO daily x 1 week
13. _____ mg PO daily x 1 week
14. _____ mg PO daily x 1 week
15. _____ mg PO daily x 1 week

Quantity: New prescription fill quantity shall be for 90 days and if tolerated, may repeat times one.

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IgA Nephropathy:
CORTICOSTEROID REGIMEN
Pozzi Protocol

The prescriptions on this page can be filled at any community pharmacy.

2. Osteoporosis prevention while on corticosteroids:

CALCIUM: The recommended daily intake with diet plus supplements is 1500 mg of elemental calcium. Supplement as necessary to reach this target.

☐ **CALCIUM CARBONATE** 1250 mg (500 mg elemental) 1 tab PO daily
☐ **CALCIUM CARBONATE** 1250 mg (500 mg elemental) _____ tabs PO _____

VITAMIN D: The recommended daily intake is 800 to 1000 units:

☐ **VITAMIN D_3** 800 units PO daily
☐ **VITAMIN D_3** _____ units PO daily

ALENDRONATE: Is recommended for all postmenopausal women, for men greater than 50 years old, and for premenopausal women and men less than 50 years old with a previous fragility fracture, if no contraindications exist.

☐ **ALENDRONATE** 70 mg PO weekly
☐ _____ mg PO _____

3. GI Prophylaxis while on corticosteroids:

☐ **RANITIDINE** 150 mg PO bid
☐ **RANITIDINE** 150 mg PO daily if eGFR less than 50 ml/min/1.73 m^2
☐ **PANTOPRAZOLE MAGNESIUM** 40 mg PO daily (note: special authority required)

Quantities: New prescription fill quantity shall be for 90 days and if tolerated, may repeat times one. It is recommended that calcium and vitamin D be purchased over the counter.

Prednisone

MEDICATION INFO SHEET

WHAT IS PREDNISONE?

- A corticosteroid medication used in combination with other medications to control swelling from diseases of the immune system such as vasculitis (inflammation in the blood vessels) or glomerulonephritis (inflammation of the kidneys).
- Prednisone lowers your body's harmful response to diseases of the immune system. It is often used with other medications, such as cyclosporine, tacrolimus, mycophenolate or cyclophosphamide.
- Available as 1mg, 5mg and 50mg tablets. The tablets are scored and can be split in half if required.

HOW DO I USE IT?

- Take the medication regularly, usually once daily or every other day.
- Prednisone is best taken in the morning (e.g. 8:00 or 9:00 am) to match the normal production of a natural steroid hormone in the body called cortisol.
- Prednisone should be taken with food to minimize stomach upset.
- If you have been taking prednisone for a long time, do not stop taking it suddenly. If prednisone is to be stopped, the dose is usually decreased slowly to ensure no flare-ups and/or to allow your own body to produce cortisol again.
- The starting dose of prednisone is based on your weight and is specific to your medical condition. Do not change your dose without talking to your doctor or pharmacist.

WHAT DO I DO IF I MISS A DOSE?

- If you take prednisone once daily, take the missed dose as soon as you remember unless it is already the next day. Do not "double-up" the dose.
- If you take prednisone every other day, take the missed dose as soon as you remember unless it is already the day of your next dose. Go back to your normal schedule. Do not "double-up" the dose.

WHAT SHOULD I EXPECT?

- Common side effects that can occur early include nausea, stomach upset, increased appetite, weight gain, mood swings (a feeling of high spirits/depression), water retention (swollen ankles), increase in blood pressure, or increase in blood sugars.
- These side effects are often related to the dose and will decrease once the dose is lowered. If these symptoms continue or become bothersome, talk to your doctor or pharmacist.
- Other side effects include stomach ulcers/bleeding, anxiety and/or problems sleeping, cataracts, glaucoma, slow wound healing, electrolyte changes, weak bones, damage to the hip joints (rarely), change in body fat (more on the face and neck), easy bruising, stretch marks and decreased production of cortisol by the body.
- Since prednisone lowers your body's ability to fight off infections, wash your hands often and stay away from people with infections, colds or flu. Contact your doctor right away if you feel you may have a cold or other infection, e.g. if you experience high fever, chills, very bad sore throat, chest congestion, pain with

Questions?