Peripheral Edema from a nephrology perspective

Dr. Andrea Mazurat, MD FRCPC
Nephrologist, SOGH

Faculty/Presenter Disclosure

- **Faculty:** Andrea Mazurat

- **Relationships with commercial interests:**
  None

Objectives

1. Identify when peripheral edema is attributable to a renal cause
2. Outline initial investigations for a renal cause of peripheral edema
3. Diuretic dosing and use in Chronic Kidney Disease
4. When to refer to Nephrology

Mr. S

- 35 year old male (previously healthy) who presented to family MD in March 2019 with sudden onset peripheral edema

- Bloodwork March 2019:

Creatinine 77 eGFR 113 mL/min

TSH 7.21 Cholesterol 11.08

- Bloodwork repeated one month later:

Creatinine 73 eGFR 115 mL/min

TSH 6.89

Mr. S

Urinalysis (April 2019):

Protein > 3 g/L

Glucose negative

Ketones negative

WBC 6-10

RBC 11-20

Urinalysis (May 2019):

Protein > 3 g/L

Glucose negative

Ketones negative

WBC 0-2

RBC 11-20

Bacteria Few

Renal U/S (June 2019):

Negative renal and bladder ultrasound

- Referred to Urology for the microscopic hematuria
- Had a cystoscopy that was normal (July 2019)

- July 2019:

Urine Albumin/Creatinine (UACR): >500 mg/mmol

24 hour urine: 18 grams per day of protein

Referred to Nephrology and ultimately diagnosed with membranous nephropathy on biopsy

When is peripheral edema secondary to a renal issue?

- In the setting of significant proteinuria (glomerulonephritis, nephrotic syndrome)

- Chronic kidney disease (CKD) with impaired water/sodium handling

When is peripheral edema secondary to a renal issue?

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- Chronic kidney disease (CKD) with impaired water/sodium handling

Presenting complaints with nephrotic syndrome

- Acute onset edema
  - May be accompanied by periorbital edema, ascites
- Weight gain
  - Can be upwards of 20-50 lbs of fluid
- Fatigue/malaise
- There may be other symptoms depending on the disease

Questions to ask on history

- Past Medical History
  - Lupus, diabetes, multiple myeloma, previous episodes of nephrotic syndrome, Hep B/C/HIV
- Onset and duration of edema
- Weight gain

Questions to ask on history

- Associated symptoms:

  Red flags:

  - Systemic symptoms (fevers/chills)
  - Hemoptysis
  - Significant ENT symptoms (epistaxis, new hearing issues)
  - Purpuric rash
  - New joint abnormalities
  - “Tea” or “cola” coloured urine
  - Back pain
  - Symptoms of neuropathy

Questions to ask on history

- Associated symptoms:
  - **Red flags**:
  - Systemic symptoms (fevers/chills)
  - Hemoptysis (pulmonary-renal syndrome)
  - Significant ENT symptoms (epistaxis, new hearing issues) (pulmonary-renal syndrome)
  - Purpuric rash (vasculitis)
  - New joint abnormalities
  - "Tea" or "cola" coloured urine (proliferative GN)
  - Back pain (multiple myeloma)
  - Symptoms of neuropathy

Questions to ask on history

- New/change in medications:
  - NSAIDS (minimal change, membranous), bisphosphonates (FSGS),
  - Recently discontinued ACE-I/ARB (unmask proteinuria)
- Exposures:
  - Cocaine (vasculitis), heroine, anabolic steroids (FSGS)
- Recent infections (infection related GN)
  - Strep throat
  - Skin infections

Physical exam

- Weight
- Blood pressure
- Respiratory exam
- CV exam (looking for other causes of edema)
- Abdominal exam (ascites)
- Rheumatologic exam: Rashes, active joints
- Extremity exam: Wounds, peripheral edema

Initial investigations when considering renal cause of edema

Bloodwork:

Electrolytes

Urea/creatinine

Albumin

HgA1c

Urine:

Urinalysis

Urine ACR/PCR

Investigations

Bloodwork:

Electrolytes: Usually normal

Urea/creatinine: Creatinine may be elevated compared to baseline (or may be at baseline)

Albumin: Often lower than usual (can be <20 g/L)

HgA1C: ?Diabetes

Urine:

Urinalysis: >3 g/L protein, +/- RBC and RBC casts

Urine ACR: >200 mg/mmol

Urine PCR: >200 mg/mmol

Proteinuria

- Unlike hematuria, proteinuria is always **renal** in origin
- Urine Albumin/Creatinine Ratio (UACR) measures albumin
  - So does the urinalysis
- Urine Protein/Creatinine Ratio (UPCR) measures non-albumin protein
  - The values are usually similar
  - Notable exception is free light chains in multiple myeloma (non-albumin proteins)

Proteinuria

- UACR or UPCR > 3mg/mmol to 150 mg/mmol have implications for kidney disease and progression, but **shouldn't** be associated with **nephrotic syndrome**

- Quick "conversion" of UACR or UPCR to 24 hour urine is to multiply by 10
  - UACR: 100 mg/mmol = 1000 mg/day = 1 gram/day
  - UACR: 200 mg/mmol = 2000 mg/day = 2 grams/day

- "Glomerular range" when >2 grams/day
- "Nephrotic range" when >3 grams/day

Do you need to do 24 hour urine collection?

- **No**

- UACR and UPCR are sufficient to make the diagnosis

- 24 hour urine collection has specific collection instructions, notoriously error-prone (over- or under-collection), cumbersome
  - May be useful for making treatment decisions in Nephrology clinic

Different types of glomerulonephritis

- I've included the tables, but this is WAY too much information to review
- I've highlighted the conditions that usually cause sudden-onset edema/nephrotic syndrome without other obvious abnormalities on investigations and history/physical
- I've included a slide of what I call the "Nephro Stamp" – if you ordered all those investigations you have ordered almost everything to rule-in or out a specific etiology

Non-proliferative/nephrotic GNs Classically cause nephrotic syndrome

GN	Secondary causes	Investigations
Membranous	Lupus Malignancy Drugs (NSAIDs) Hepatitis B Syphylis	ANA, dsDNA Hepatitis B serology
Minimal change disease	Lymphoma Drugs (NSAIDs, lithium)	
Focal Segmental Glomerulosclerosis (FSGS)	Drugs (heroin, pamidronate) HIV Scarring: chronic reflux, obesity	HIV serology
Paraprotein **(amyloid)**	Multiple myeloma Amyloid	SPEP Free light chain ratio
Diabetes		HgA1c

PROLIFERATIVE/NEPHRITIC GNS DON'T CLASSICALLY CAUSE NEPHROTIC SYNDROME

GN	Secondary causes	Investigations
ANCA	Vasculitis	ANCA
Anti-GBM	Vasculitis	Anti-GBM
IgA nephropathy		
Infection-related	Any infection Classically after strep throat	ASOT Usually low C3
Lupus		ANA, dsDNA C3 and C4 may be low
Membrano proliferative GN		Hepatitis C

These GN's tend to cause hematuria/RBC casts

ANCA/anti-GBM are often rapidly progressing and can cause death or dialysis-dependence if not treated

Initial investigations summary: "Nephro Stamp"

- HgA1c
- Viral serology: Hepatitis B, Hep C, HIV
- Autoimmune serology: ANA, dsDNA, C3, C4, ANCA, anti-GBM
- SPEP, Free light chain ratio
- Renal ultrasound
- Urinalysis
- Urine ACR/PRC
- +/- ASOT (anti-streptolysin O titer)

Initial investigations summary: "Nephro Stamp"

- HgA1c (Diabetes)
- Viral serology: Hepatitis B (membranous), Hep C (membranoproliferative), HIV (FSGS)
  - Implications regarding treatment with immunosuppression
- Autoimmune serology: ANA, dsDNA (SLE), C3 (low in infection related or SLE), C4 (low in SLE), ANCA (ANCA-GN), anti-GBM (anti-GBM disease)
- SPEP, Free light chain ratio (Mulitple myeloma, amyloid)
- Renal ultrasound (kidney size, number, cysts, stones)
- Urinalysis (hematuria, protein)
- Urine ACR/PRC (protein quantification)
- +/- ASOT (anti-streptolysin O titer) (post-infectious GN)

When to consult nephrology

- Anytime there is significant proteinuria
  - UACR >100 mg/mmol
- Urgent referral if:
  - UACR >200 mg/mmol and signs of nephrotic syndrome
- Call Nephrology if:
  - Red flags on history
  - Rapidly worsening creatinine (may be best managed as an inpatient)

Initial management of nephrotic syndrome

- Fluid restriction
  - <2L per day, often <1.5L per day “all sources”
- Salt restriction
  - CKDpathway.ca under “medical management” has a good handout on sodium restriction

Avoid

These foods are high in sodium.

Salt, sea salt, or seasonings that contain salt

Hot cereals, instant, with added salt

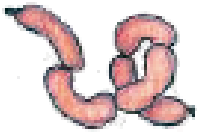
Soup, packaged or canned

Packaged dinners

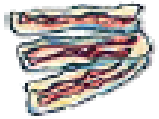
Processed lunch meat and frozen meats

Pickled products

Ham



Sausage



Bacon

Salted nuts or seeds

Processed cheese or cheese spreads

Hot dog

Salted chips, pretzels, or popcorn

Pizza

Pancakes or waffles, frozen or from mix

Soya, fish, or steak sauce and marinades

Packaged rice, noodle, and sauce mixes

Salt substitutes with potassium*

***Ask your dietitian or doctor if you can use salt substitutes.**

French fries, salted

Canned vegetables, salt added

Canned pasta sauce, tomato sauce, canned tomatoes with added salt

Tomato juice, vegetable cocktail

Initial management of nephrotic syndrome

- Diuretics
  - Often need high doses to be effective
  - Can start with furosemide 40 mg and titrate up to as much as 160 mg po BID
- Daily weights
  - Same time each day, record weight
  - Goal diuresis 1-2 lbs per day
- ACE-I/ARB inhibition if normal renal function (and you feel comfortable)
  - Start on lowest dose of chosen agent
  - Titrate based on blood pressure
  - Electrolytes, creatinine 1-2 weeks after starting

Complications

- Elevated TSH
  - Decrease in thyroxine-binding globulins
- Infectious complications
  - Immunosuppressed
- Hypercoagulable
  - Arterial and venous clots
- Hyperlipidemia
  - Most patients are treated with a statin

Please refer!

- Refer earlier rather than later
- These patients need to be assessed and renal biopsy considered

FYI:

Antiplatelets and NSAIDs need to be held 7 days prior to renal biopsy

When is peripheral edema secondary to a renal issue?

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- **Chronic kidney disease (CKD) with impaired water/sodium handling**

Loop Diuretics in CKD

- Furosemide, bumetanide, torsemide, ethacrynic acid
- Inhibit the sodium-potassium-chloride transorter in the thick ascending limb of the loop of Henle
- Ethacrynic acid has a higher rate of ototoxicity compared to the other loop diuretics
  - Can be used in patients allergic to the sulfonamide group in the other loop diuretics

Loop diuretics in CKD

- Diuretics are **not** nephrotoxic
- Increased creatinine is usually not a direct result of the diuretics
  - Increasing creatinine often reflects the underlying pathology
  - Sometimes patients are massively volume overloaded and creatinine is slightly diluted

- If patient is hypovolemic as a result of diuretics they can be held
- If patient is being over-diuresed, the dose can be lowered

Loop diuretics in CKD

- Loop diuretics must be un-metabolized and in the tubular fluid to be effective
- They gain access to the tubular fluid by secretion in the proximal tubule
- In CKD, there is a reduced fraction of an administered dose that is presented to the kidney because of a reduction in renal blood flow

Wilcox, C. *J Am Soc Nephrol*. 2002; 13: 798-805

Loop diuretics in CKD

- Loop diuretics are weak organic anions and compete for peritubular uptake and secretion of other organic anions
  - Such as the organic anions that accumulate in CKD

- All of this to say:
  - Patients with CKD often need much higher doses of diuretics to achieve adequate effect

Loop Diuretics in nephrotic syndrome

- Loop diuretics are strongly bound to plasma albumin
- Even moderate hypoalbuminemia diminishes the renal clearance of active furosemide
  - Limits the proximal secretion of furosemide
  - Increase the volume of distribution
- Filtered albumin in nephrotic syndrome binds loop diuretics in tubular fluid and impairs the effect

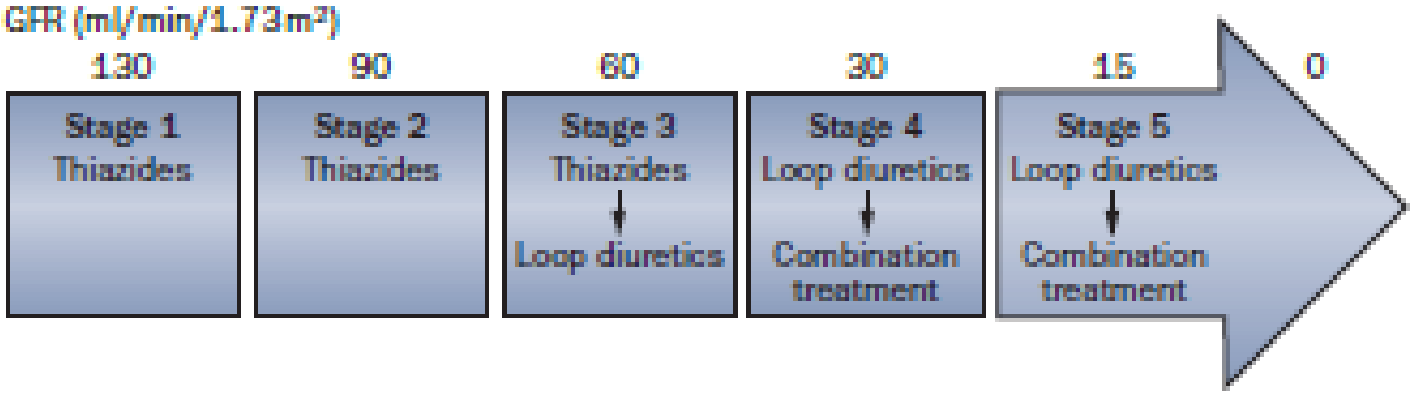
Thiazide diuretics in CKD

- Thiazide monotherapy is relatively ineffective in patients with GFR <30 mL/min
  - Every patient is different, so if it seems to be working can continue
- Thiazide diuretics used in high doses can be effective particularly when used in combination with loop diuretics
  - Although effective at promoting fluid loss, there may be further rise in urea and creatinine
  - High risk for electrolyte disturbances
- Combination therapy should be held off until ceiling doses of loop diuretics are reached

Potassium-sparing diuretics

- Use cautiously in patients with CKD

Practical dosing of diuretics in CKD



Sica, D. A. *Nat. Rev. Nephrol.* 8, 100-109 (2012)

My approach to managing edema in CKD

- What drug and dose is the patient on (if any)?
- If on a thiazide:
  - Consider switching to a loop diuretic (furosemide)
- If on furosemide, increase either the dose or frequency:
  - Loop diuretics have a very narrow threshold (when the drug starts to work) and ceiling dose (maximal effect)
  - Consider increasing frequency rather than the dose
  - When ordering BID, consider morning and noon

Practical dosing of diuretics in CKD

- Continue to titrate the dose as needed (requires frequent assessment)
  - Maximum dose usually ~160 mg po BID
  - The monograph has a maximum dose listed as 600 mg per day!
  - Higher doses put patients at risk of ototoxicity
- Once doses of furosemide are at the maximum, consider adding metolazone
  - Takes a couple days to achieve full effectiveness
  - Start with 2.5 mg daily, can increase to 10 mg daily

Practical dosing of diuretics in CKD

- Once diuresis has been achieved, can decrease the metolazone dose for maintenance
  - Depends on the initial dose that the patient required
  - Can use 2.5 mg 2-3 times a week

- If resistant to PO furosemide/metolazone, consider admission for IV furosemide
  - Metolazone is only available PO

Practical dosing of diuretics in CKD

- Diuretics should always be accompanied by sodium and fluid restriction

- Renal function and clinical response need to be monitored closely while actively diuresing
  - Q1-2 weeks clinical assessment
  - Q1-2 week bloodwork after diuretic dose increase

Mr. C

- CKD patient followed in Nephrology clinic
  - CKD presumed secondary to diabetes and HTN
  - Baseline Cr 271, eGFR 21 mL/min, UACR 2.4 (July 2019)
  - Chronically on Furosemide 120 mg po BID

- Seen by his Cardiologist and told to contact Renal clinic to be seen urgently
  - Significant peripheral edema, dyspnea and orthopnea

Mr. C

- Bloodwork:

Creatinine 302, eGFR 18, UACR 4.9

- Seen in Nephrology clinic, not in any acute distress
- Weight 128 kg (July 2019 130 kg)

- Added metolazone 2.5 mg po daily with clinical and blood work follow-up in 2 weeks

Thank you!