PHARMACY BULLETIN

IN THIS ISSUE:

EDITORIAL TEAM:

NEPHROTIC SYNDROME

Prepared by: Shazana Daud

Nephrotic syndrome (NS) is a group of signs and symptoms due to kidney damage. These include:

Heavy Proteinuria- excretion of protein >3.5g/24hrs in urine (frothy urine)

Hypoalbuminemia

Hyperlipidemia

Edema with weight gain

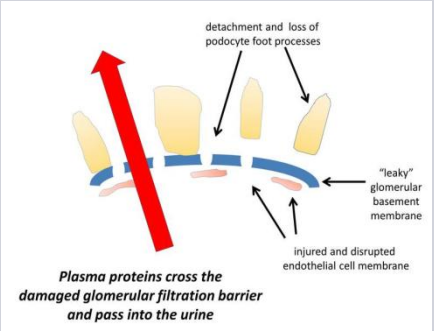
Others: tiredness, loss of appetite

Causes of Nephrotic Syndrome

The causes can be primary (affecting the kidney per se) or secondary (due to other systemic diseases):

Primary Causes

- **Focal segmental glomerulosclerosis (FSGS).** Damaged and scarred glomeruli causing leakage of albumin into urine
- **Membranous nephropathy (MN)** Autoimmune disease which results in disruption of the glomerular basement membrane's functional integrity and the protein filtration barrier of podocytes
- **Idiopathic Minimal change disease(Nil disease).** Abnormal secretion of lymphokines by T cells, causing structure alteration of podocyte and hence leakage of albumin into urine. This is the main cause of nephrotic syndrome in children.



Secondary Causes

- **Diabetic nephropathy** causing glomerular sclerosis and fibrosis
- **Lupus nephritis**. Autoimmune disease where autoantibodies forming immune complexes deposited in glomeruli and promote inflammatory response
- **Amyloidosis**. Buildup of the amyloid protein in kidney causing renal dysfunction.
- **Medications**: NSAIDs, lithium, interferon-alfa, bisphosphonates
- **Infection / Malignancy**

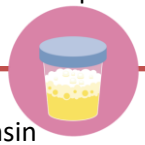
Diagnosing nephrotic syndrome:

1. **24-hour urine collection** (protein excretion measurement)
2. **Blood test** eg. renal profile, lipid profile, serum albumin
3. **Serologic studies: eg. antinuclear antibodies (ANA), complement (C3/ C4), syphilis serology, hepatitis serology**
4. **Kidney biopsy**.

Treatments for Nephrotic Syndrome?

- Differs between adult and children
- Would depend on the cause of the NS
- However, there are some non-specific therapies which target on complication of nephrotic syndrome:

1. Hypertension & Proteinuria.



- Angiotensin-converting enzyme inhibitors (ACEi) / Angiotensin Receptor Blocker (ARB)
- Lower intraglomerular pressure and hence protein excretion & rate of disease progression.
- Examples: Losartan, valsartan, Perindopril, Captopril
- If ACEi or ARB cannot be tolerated, direct rennin inhibitor or mineralocorticoid receptor antagonist (MRA), non-dihydrophyridine calcium channel blockers can be used

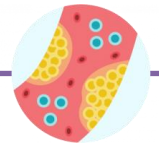
2. Edema

- Loop diuretics (first line), thiazide and potassium sparing diuretics (in combination with loop diuretics)
- Higher dose may be necessary in this population
- Natriuresis effect may be lesser than normal patients due to hypoalbuminemia (decreased delivery of protein bound drug to the loop of Henle) and albuminuria (binding the drug within the tubular lumen)
- IV albumin can be added to diuretic therapy in diuretic-resistant patient to improve intravascular volume, diuresis and natriuresis. However the effect may be transient due to rapid albumin excretion in urine.

3. Prevention of Infection with vaccination.

- NS increase risk of pneumococcal infection
- Pneumococcal vaccine has to be given
- Live vaccines has to be avoided during relapse and while on daily immunouppresive medications

4. Hypolipidemic agents.



- Indicated for primary and secondary prevention of cardiovascular disease (CVD)
- Treatment considered by weighing the indication, potential benefits and risks of treatment (ie. nephrotic syndrome resolution, indication for primary/ secondary CVD prevention, lipid profile)
- Lipid abnormality due to nephrotic syndrome may reverse with resolution of the disease, hence treatment of underlying cause is needed
- Example: statins (first line), ezetimibe, fibrates (second line)

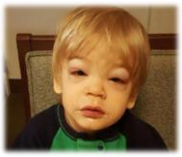
5. Anticoagulants

- Nephrotic syndrome cause patients to be in hypercoagulable state, putting patient in risk of Deep vein thrombosis (DVT), Renal vein thrombosis (RVT), and pulmonary embolism (PE)
- The necessity of primary prevention (prophylactic anticoagulation) is decided based on:
  - a.bleeding risk
  - b. type of NS (higher thromboembolism risk in MN)
  - c. serum albumin level (inversely related to risk of thromboembolism)
  - d. additional risk factors of thrombosis eg. thrombosis history, genetic predisposition, immobility, malignancy, pregnancy or surgery
- Full anticoagulation is indicated for patients with thromboembolic event occurring in nephrotic syndrome
- Examples: warfarin, low molecular weight heparin, DOACs (only minimal experience of usage for this indication)

Immunosuppresant Therapy in Adult?

- In adults, not all patients require treatment with immunosuppressant.
- For example, those with MN, proteinuria <3.5g/d and eGFR >60ml/min/1.73m^2 has good outcome and only requires conservative therapy; those with MCD & Primary FSGS require treatment with corticosteroid, or other immunosuppressant such as cyclophospamide, calcineurin inhibitors, rituximab, & mycophenolate (if there is contraindication/disease is frequently relapsing or steroid-dependent or steroid resistant)

Treatment of Children Idiopathic Nephrotic Syndrome (INS)



1. Edema Management
   - No added salt diet
   - Daily weights, daily urine dipstick
   - Strict fluid balance with close attention to volume status
   - Albumin and Frusemide
     - Albumin: 20% Albumin 5 mL/kg (1 g/kg) over 4 hours IV
     - Frusemide: 1 mg/kg max 40 mg over 20 minutes IV (if not hypovolemic)

2. Steroid therapy
   - Children most likely have MCD, which would be steroid-sensitive
   - Initial treatment with Prednisolone: to induce remission, followed by a slow wean to reduce risk of relapse:
     - 60 mg/m2/day (max 60 mg) for 4 weeks,
     - then 40 mg/m2/day (max 40 mg) on alternate days for 4 weeks,
     - then 20 mg/m2/day on alternate days for 10 days,
     - then 10 mg/m2/day on alternate days for 10 days,
     - then 5 mg/m2/day on alternate days for 10 days,
     - Then cease.

   - Treatment of relapses (proteinuria 3+ or 4+ for 3 consecutive days)
     - Re-introduction of full dose prednisolone should be prompted:
     - Prednisolone 60 mg/m2/day (max 60 mg) until urine protein is 0, trace or + for 3 consecutive days
     - Then weaning regimen:
       - 40 mg/m2/day on alternate days for 2 weeks,
       - 20 mg/m2/day on alternate days for 2 weeks,
       - 15 mg/m2/day on alternate days for 2 weeks,
       - 10 mg/m2/day on alternate days for 2 weeks,
       - 5 mg/m2/day on alternate days for 2 weeks
     - The total time of weaning regimen can be shortened if the child relapses infrequently (2–3 relapses in any 12-month period) and responds to treatment quickly. If edema recurs, penicillin prophylaxis should also be restarted.

   - Steroid-dependent Nephrotic syndrome
     - If >2 consecutive relapses occur during steroid taper or within 14 days of the cessation of steroid, re-induce steroid therapy and maintain on as low a dose of alterate day prednisolone as possible.
     - If patient is steroid toxic (short stature, striae, cataractsm glaucoma, severe cushingoid features), steroid sparing agents such as cyclophosphamide, calcineurin inhibitors, mycophenolatate, rituximab may be necessary.

3. Prophylaxis against complications:
    - Infection: Routine prophylaxis is not indicated unless there is risk of pneumococcal infection (e.g.; gross or symptomatic edema, unimmunized). If indicated, it can be managed with oral penicillin V (phenoxymethylpenicillin) 125 mg BD (> 5 years), or 250 mg BD (≥ 5 years). Cease after edema subsides.
    - Gastritis: use of acid suppressing therapies is not indicated unless there are upper gastrointestinal symptoms while on steroid therapy.

Lifestyle for Nephrotic Syndrome Patients

Choose lean sources of protein. Plant-based protein is preferred.

Reduce the amount of fat and cholesterol in diet to help control blood cholesterol levels.

Eat a low-salt diet to help control swelling.

Control the amount of liquid taken

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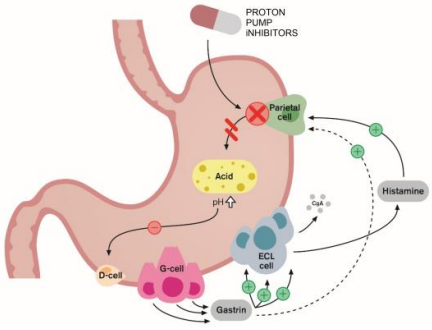
PROTON PUMP INHIBITORS

Prepared by: Su Yi Xiang & Ainaa Izzati Jalani

WHAT ARE PROTON PUMP INHIBITORS (PPIs)?

PPIs are drugs used to treat a wide variety of pathologies related to the stomach's acid production. They work by irreversibly binds to H^+/K^+ ATPase Pump in parietal cells of stomach to prevent acid secretion into the stomach.



They are indicated for the following acid-related disorders (based on FUKKM, MOH Malaysia):

Disorder	Types of Oral PPI (- Prazole)					
	Panto	**Ome**	**Esome**	**Lanso**	**Dexlanso**	**Rabe**
H.pylori eradication (with antibiotics)	40mg BD x 1-2/52	20mg BD x 1-2/52	40mg OD x 10/7	30mg BD x 1-2/52	-	20-40mg BD
Peptic Ulcer Disease (PUD)	40mg OD x 2-4/52	20mg OD x 4-6/52	-	30mg OM x 4/52 (duodenal); 8/52 (gastric) Maintenance: 15mg OD	-	20mg OD x 4-8/52
Gastro-esophageal Reflux Disorder (GERD)	20-40mg OD x 4/52	20-80mg OD-BD x 8-12/52	20mg OD x 4-8/52	30mg OM x 8/52 Maintenance: 15mg OD	Erosive Esophagitis (EE) treatment: 60mg OD x 8/52 Maintenance of healed EE: 30mg OD x 6/12 Symptomatic non-erosive GERD: 30mg OD x 4/52	20mg OD x 8/52
Zollinger Ellison Syndrome	80mg daily, titrate as needed	20-120mg OD (based on patient's response)	-	60mg OM (adjust as required)	-	60mg OD, titrated up to 60mg BD

IV PPIs (-Prazole)	**Indication**	**Dose**
Panto	Short term use for symptomatic improvement and healing of GI diseases which require acid secretion reduction	40mg BD until oral administration can be resumed
Ome	Reflux esophagitis	40mg IV OD (when oral therapy is inappropriate)
	Eradication of H. pylori infection	
	Benign PUD	
	ZE syndrome	
	Endoscopically confirmed peptic ulcer	40-160mg IV in single/ divided doses
Esome	Acute erosive/ ulcerative oesophagitis	20-40mg OD x 2-5/7
	Non-variceal upper GI bleed	80mg IV bolus, then 8mg/hr infusion x 72hrs

**Other sources may use different dose for the aforementioned indication.*

PHARMACOKINETICS OF PPIs

PPIs	Oral bioavailability	Time to peak (hours)	Half-life (hours)	Metabolism	Excretion
Pantoprazole	77%	2-2.5	1	Hepatically by CYP2C19 & CYP3A4	Inactive metabolites excreted in urine and faeces via bile
Omeprazole	45% in single dose, increased after multiple doses	0.5-3.5	0.5-3		
Esomeprazole	64% in single dose, 90% in multiple doses Food reduced ~50% of bioavailability	1-1.6	1.2-2.5		
Lansoprazole	85% Food reduces ~50% of bioavailability	1.5-3	0.9-1.5		
Dexlansoprazole	Similar bioavailability taken with/without food	1-2 (peak 1) 4-5 (peak 2)	1-2		
Rabeprazole	52%	2-5	1-2		

ADMINISTRATION OF PPIs

- Oral formulations need to be taken 30-60 minutes before meal to exert its maximum effect.
- The tablets or capsules contain enteric coated granules or pellets. They should not be ground or chewed in order to protect the drugs from stomach acid, before they reach small intestine for disintegration and absorption
- For patients who cannot swallow tablets/capsules, Pantoprazole, omeprazole, and lansoprazole can be formulated into oral suspension; whereas esomeprazole tablet can be disperse into water without crushing.
- For once-daily dosing, take PPI the first thing in the morning. (H^+/K^+ATPase present in greatest amount in the parietal cell after prolonged overnight fast)
- For twice-daily dosing, second dose can be taken 30 minutes before dinner.
- Intravenous formulations provide immediate acid suppression.

CHOOSING A SUITABLE PPI

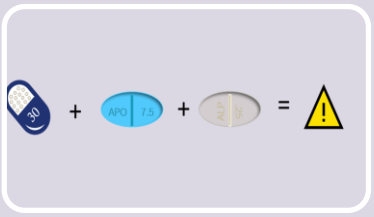
PPIs are used in various standard dosages for inhibition of acid secretion in acute and maintenance treatment of acid-related disorders.

Systemic review of RCTs examining the relative effectiveness of different PPI doses and dosing regimens found no consistent difference in symptom resolution and esophagitis healing rates. At equipotent doses, all PPIs are equally effective.

Hence, the selection of PPI can be based on:

Cost

- The most **cost effective** treatment will most likely be selected



Drug Interactions

- Eg. esomeprazole and omeprazole (strong CYP2C19 inhibitors) **SHOULD NOT** be used in patients taking **clopidogrel** as it may result in decreased effectiveness of the later and hence increased risk of negative Cardiovascular- related outcomes.
- Rabeprazole or pantoprazole with weaker CYP2C19 inhibition properties may be lower-risk alternatives

Patient's ability to swallow medication

- Patient who can't take tablet/ capsule as a whole may require PPIs which can be formulated into other dosage forms
- Pantoprazole, omeprazole, and lansoprazole can be formulated into **oral suspension**
- Esomeprazole tablets/ capsule can be **disperse in water** prior to administration

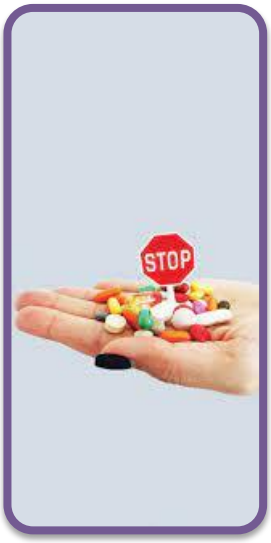
LONG TERM COMPLICATIONS OF PPIs

Complications from Reduced or Modified Absorption of Nutrients	• Vitamin B12 deficiency • Reduced Calcium absorption with risk of osteoporosis • Hypomagnesemia • Reduced iron absorption
Complications from Altered pH of Gastric Contents	• Increased enteric infections (including Clostridium difficile) • Increased risk of community and hospital acquired pneumonia • Increased development of fundic gland polyps
Others	• Dementia • Acute interstitial nephritis and possibly other kidney disease

DEPRESCRIBING PPIs

PPIs should be prescribed at the lowest dose and for the shortest duration appropriate to the condition being treated. Deprescribing involves reducing and/or stopping PPI after considering therapeutic indication, benefits and risk. Nevertheless, there are certain conditions where PPI may need to be continued for long term.

Situation in which deprescribing of PPIs can be considered	Situation in which PPI shall not be ceased
• Mild to moderate esophagitis • GERD treated for 4-8 weeks (esophagitis healead, symptoms controlled) • Peptic ulcer disease (from NSAIDs or H. pylori) treated for 2-12 weeks • Upper GI symptoms without endoscopy, asymptomatic for 3 consecutive days • ICU stress ulcer prophylaxis treated beyond ICU admission • Uncomplicated H. pylori treated for 2 weeks and asymptomatic	• Barrett's esophagus, eosinophilic esophagitis or idiopathic pulmonary fibrosis • Hypersecretory states (eg. Zollinger-Ellision syndrome) • History of upper GI bleeding • High risk of GI bleed such as taking multiple antithrombotics or on chronic NSAIDs (with other risk factors such as old age, concomitant corticosteroid/ antithrombotic)



- Consider deprescribing by dose tapering or stop and use on demand (medication is taken daily when symptoms recur and discontinued when it resolves)
- Follow up at 4 & 12 weeks after deprescribing. To assess symptoms control (heartburn, dyspepsia, epigastric pain, loss of appetitte, weight loss and agitation) and frequency of on-demand use
- While discontinuing PPI, to minimize rebound effects, advise patient on non-pharmacological measures such as:
  - avoid meals 2-3 hours before bedtime
  - elevate head of bed
  - weight loss
  - avoid dietary triggers
- OTC antacids & H2-Antagonist can be used on demand to manage occasional symptoms

PPI Discontinuation strategies:

Currently there is no single agreed upon discontinuation strategy. Some experts suggest in patients who have received continuous therapy for >6 months, may gradually taper therapy until discontinuation to avoid worsenior rebound symptoms. This includes:

- Decrease dose by 50% every week and discontinue after patient is on the lowest dose for 1 week
- Decrease dose by 50% over 2-4 weeks, then discontinue

American Gastroenterological Association (AGA) suggests that tapering or abrupt discontinuation is reasonable. In either case, patients should be advised to be mindful of developing recurrent upper GI symptoms as a consequence of rebound acid hypersecretion (RAHS), and should try to manage with lower-potency options such as H_2-antagonist or antacids for symptom control.

If symptoms relapse after discontinuation, which persist for 3–7 days and interfere with normal daily activity, patient should be:

- Tested and treated for H. pylori
- Consider return to previous PPIs dose

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RESPIMAT Reusable

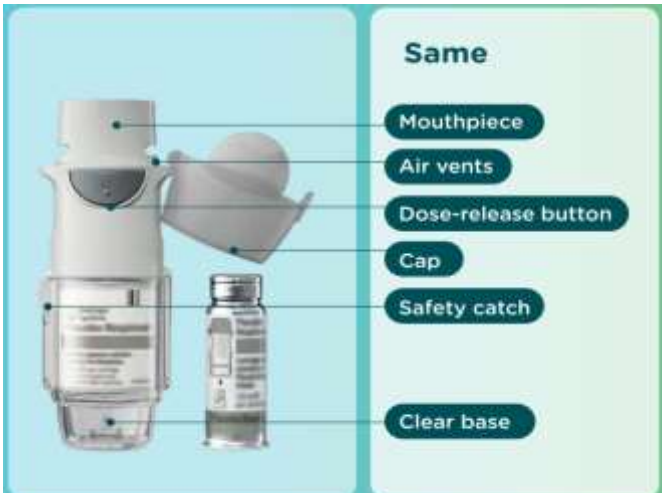
Prepared by: Cassandra Eva Charles

Respimat inhaler is a handheld, propellant-free device that produces a slow-moving, long-lasting mist of drug for inhalation. It offers the benefits of easier inhalation and higher lung deposition of drug compared with dry-powder inhalers or pressurized metered-dose inhalers.

Respimat inhaler has been updated to improve its usability and environmental impact while preserving the pharmaceutical performance and basic functions of the disposable Respimat inhaler. Patients prefer the new features of the **reusable inhaler** and find it easier to use than the disposable one.

Respimat vs Respimat reusable

What stays the same?



Patients already know how it works:

No changes in daily use

What's new in Respimat Reusable?

RESPIMAT REUSABLE INHALER

Key features

- Familiar Turn, Open, Press technique
- Larger dose indicator
- Simple cartridge replacement

How will you benefit?

- Designed for multiple uses: **up to 6 cartridges**
- Straightforward cartridge replacement: automatically detaching clear base

RESPIMAT Reusable

Prepared by: Cassandra Eva Charles

Preparing your RESPIMAT inhaler for first-time use

•REMOVE CLEAR BASE

- •keep the cap closed
- •Press the safety catch while pulling off the clear base with your other hand

•INSERT CARTRIDGE

- •insert the cartridge
- •place the inhaler on a firm surface and push down until it clicks into place

•TRACK CARTRIDGE

- •mark the check-box on the inhaler's label to track the number of cartridges
- •put the clear base back into place until it clicks

•TURN

- •keep the cap closed
- •Turn the clear base in the direction of the arrows on the label until it clicks (half a turn)

•OPEN

- •Open the cap until it snaps fully open

•PRESS

- •Point the inhaler towards the ground
- •press the dose-release button
- •Close the cap
- •Repeat steps 4-6 until a cloud is visible
- •Then repeat steps 4-6 three more times

References

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Daily use of the Respimat inhaler

TURN

- keep the cap closed

- TURN the clear base in the direction of the arrows on the label until it clicks (half a turn)

OPEN

- OPEN the cap until it snaps fully open

PRESS

-breathe out slowly & fully, then close your lips around the mouthpiece

- while taking in a slow, deep breath,

PRESS the dose-release button; keep breathing in slowly

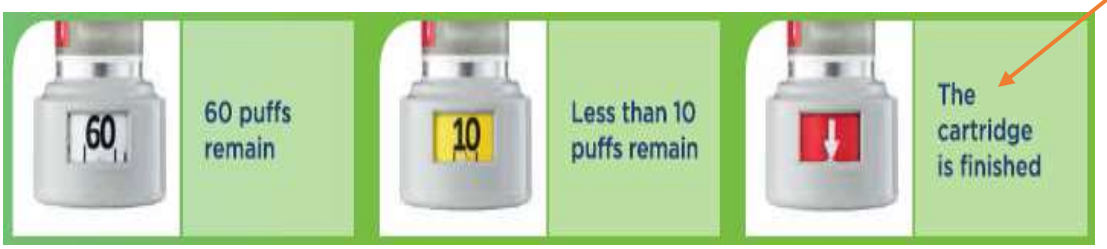
- hold your breath for 10 seconds or for as long as comfortable

-close the cap

Repeat **TURN, OPEN, PRESS** for a total of 2 puffs

When should I replace my Respimat cartridge?

The easy-to-read dose indicator shows how many puffs remain in the cartridge



Cartridge replacement is straightforward

The cartridge is finished when the dose indicator shows the white arrow on a red background.

Once the cartridge is finished turn the clear base to loosen it, and remove the clear base. Pull the cartridge out of the inhaler and insert a new one (as shown in 'Preparing your Respimat inhaler for first-time use' section.'.