PATHOPHYSIOLOGY AND MANAGEMENT OF OEDEMA IN NEPHROTIC SYNDROME

Nisha Krishnamurthy

Associate Consultant

Paediatric Nephrology

SRCC Childrens Hospital

ECHO India

Project ECHO®

KIDNEY FOUNDATION FOR CHILDREN

Oedema --- accumulation of fluid in the interstitial space

Four defining features of the nephrotic syndrome –

- Oedema
- Hypoalbuminemia
- Hyperlipidemia
- Proteinuria.

Symptom most commonly requiring intervention.

Peripheral oedema – uncomfortable

Restricted movements of limbs, mobility

Increased skin tension

Increased chances of skin breakage, secondary infections

Pulmonary congestion, pleural effusion, ascites – respiratory embarressment

Intestinal oedema - diarrhea

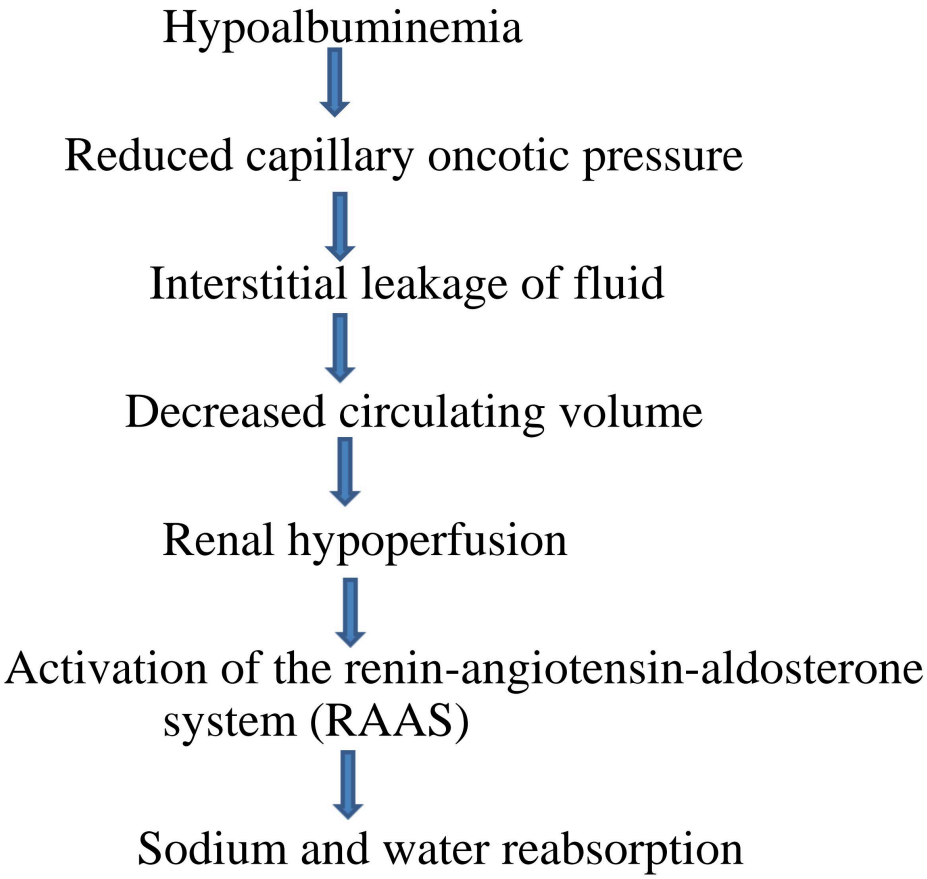
2 theories proposed –

1. Underfill theory
2. Overfill theory

Both result in sodium and water retention with interstitial fluid accumulation

Either of the mechanisms can be present in the same individual during the course of disease

Underfill theory


Hypoalbuminemia
Reduced capillary oncotic pressure
Interstitial leakage of fluid
Decreased circulating volume
Renal hypoperfusion
Activation of the renin-angiotensin-aldosterone system (RAAS)
Sodium and water reabsorption

Aldosterone - Distal collecting tubule, cortical and outer medullary collecting ducts - major sites of sodium reabsorption

Cortical collecting ducts - increased sodium retention --stimulation of basolateral Na+,K+-ATPase and apical epithelial sodium channel (ENaC)

If the under-fill theory was solely responsible then RAAS blockers or restoration of circulating volume would be curative treatment

Captopril (RAAS blocker) failed to change urinary sodium excretion despite successful inhibition of aldosterone secretion

Overfill theory

Capillary permeability – increased protein permeability :

- thickening of the basement membrane
- altered protein composition
- increased stiffness
- thickening of the basement membrane

Functional capillary surface area available for exchange increased

Capillary filtration capacity is increased almost twofold

Nephrotic ascites is likely to develop via similar mechanisms as interstitial fluid accumulation

Primary intrarenal defect in sodium handling is responsible for the occurrence of edema

Decreased filtration per nephron, increased tubular reabsorption, and decreased sensitivity to atrial natriuretic peptide, leading to fluid retention.

Resistance to the action of atrial natriuretic peptide and increased activity of Na+-K+ ATPase might contribute to increased tubular sodium resorption.

Management of oedema

Assess fluid status

Hypovolemia :

- Tachycardia
- Low normal or low blood pressure
- Features of dehydration
- Elevated blood levels of urea disproportionate to creatinine
- Measurement of urinary concentration and fractional excretion of sodium (FENa) assist in the evaluation of fluid status.

Normal urinary sodium concentration – 30 - 40 mEq/L

Values < 20 mEq/L indicate sodium-conserving states:

- Hypovolemia
- Dehydration
- Pre-renal ARF.

FENa (%) --- ratio of sodium excreted to that filtered by the renal tubules, is < 1% in sodium retaining conditions

$$\text{FENa\%} = \frac{(\text{urinary Na+}) \times (\text{serum creatinine}) \times 100}{(\text{serum Na+}) \times (\text{urinary creatinine})}$$

$$\frac{\text{Urinary K+}}{\text{(Urine K+ + Urine Na+)}}$$

Index of activation of the renin-angiotensin-aldosterone axis – s/o secondary hyperaldosteronism

A ratio of more than 0.6 or 60% -- renal potassium wasting

Patients with nephrotic syndrome and hypovolemia typically show low FENa (often < 0.2%) and high urinary $K^+/K^+ + Na^+$ (> 60%)

Such patients SHOULD NOT receive oral or intravenous diuretics, before correction of their intravascular volume with either crystalloids or colloids.

Patients with edema and no clinical or laboratory features of hypovolemia (normal levels of blood urea, FENa >1% and urinary $K^+/ K^+ + Na^+$ <60%) can safely be treated with potent diuretics.

sodium wasting due to prior therapy with diuretics often limits the practical utility of these indices

Sodium restriction

Patients with edema should consume unprocessed foods like vegetables, fruit, fish, chicken and meat, all of which contain small amounts of salt.

Use of table salt and items with high sodium content should be avoided

Sodium Content of Common Foods

High (more than 10 mEq/100 g)	Moderate (5-10 mEq/100 g)	Low (less than 5 mEq/100 g)
Bread, cornflakes, processed cheese, sauces.	Cornflour, oatmeal, green leafy and	Wheat flour,
Salted foods: butter, potato chips, biscuits, Nuts, popcorn, papad, pickles.	root vegetables, dried fruits, mutton, whole milk, cream, ice-cream	sago, rice, sugar, fruits, fruit-juices
Preserved foods: canned, tinned vegetables, soups, salted meat and fish		

1 mEq of Na+ = 23 mg Na+ or 58.3 mg common salt.

Diuretic therapy

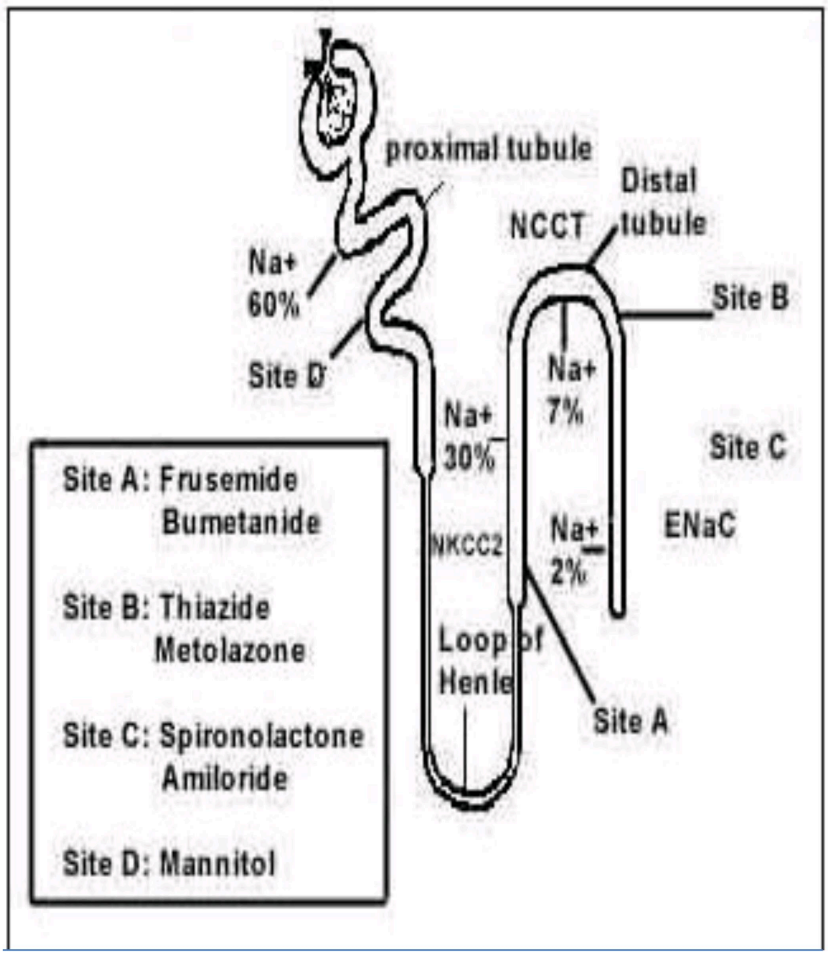
Diuretics :

Standard therapy for edema

Act by increasing urinary sodium excretion

Classified as per site of action

- Highly potent loop diuretics
- Moderately efficacious thiazide diuretics
- Potassium sparing diuretics
- Osmotic agents like mannitol and carbonic anhydrase inhibitors



Factors affecting response to diuretic

- ✓ Potency of diuretics is chiefly determined by its site of action in the nephron

- ✓ Loop diuretics increase FENa to 30%
  Thiazides to 5-10%
  Potassium sparing diuretics to 2-3%

- ✓ Dose response curve defines the intrinsic potency of a diuretic and is generally sigmoid shaped

- ✓ Using diuretics in two or three daily doses is rational only if each dose exceeds the diuretic threshold.

- ✓ Bioavailability varies widely between different loop diuretics
  50% for frusemide
  80% for torasemide
  90% for bumetanide

- ✓ Most diuretics act on the luminal surface of the renal tubule
- ✓ Loop diuretics are highly bound to proteins – Limiting them to the vascular space
- ✓ Marked hypoalbuminemia --- slower secretion into the tubules
- ✓ Renal failure results in impaired diuretic excretion
- ✓ Free drug that is secreted into tubular lumen may be bound to filtered intratubular albumin, rendering the former inactive

LOOP DIURETICS :

Frusemide
Bumetanide
Torasemide

- ✓ Rapid onset of action is rapid –
  within 30 minutes after oral
  5 minutes after intravenous administration

- ✓ Oral administration results in peak diuresis at 2 hr
  Duration of action of 6-8 hr.

- ✓ Oral dosing is preferred due to more sustained diuresis

- ✓ Intravenous administration of frusemide (bolus or infusion) : preferred in
  - Patients with intractable edema and/or
  - Reduced glomerular filtration rate
  - Continuous infusions - safer and more effective in refractory edema

- ✓ Intravenous boluses -- slowly over 10-15 minutes (not > 4 mg/min) to minimize the risk of ototoxicity, weakness, dizziness, nausea and vomiting

- ✓ After an initial bolus of 1-2 mg/kg, frusemide infusion is started at 0.1 mg/kg per hr and can be increased to 1 mg/kg per hr

- ✓ Patients who show no response, to intravenous bolus are unlikely to respond to an infusion

- ✓ Sodium, potassium and chloride wasting with diuresis

THIAZIDE DIURETICS :

Chlorthiazide
Hydrochlorthiazide
Metolazone

Metolazone --- effect on the proximal tubule
More potent than other thiazides
Onset of action - within one hr
Peak -- 4-6 hr
Duration of action -12 hr.
If thiazide + Loop diuretic combination – give Thiazide 1 hour prior

POTASSIUM SPARING DIURETICS :
Spironolactone
Triamterene, Amiloride
Delayed onset of action, often as long as 3-4 days.

COMPLICATIONS :

- Hypovolemia
- Azotemia
- Hyponatremia
- Hypokalemia
- Metabolic alkalosis
- Hyperuricemia and hypomagnesemia.
- Use of diuretics must be avoided in patients with diarrhea and/or persistent vomiting.

Dosage of Diuretics

Drugs	Dosage
Frusemide	PO. 2-4 mg/kg/dose 8-12 hr; maximum 8 mg/kg/day
	IV. 1-2 mg/kg/dose 8-12 hr; maximum 3 mg/kg/dose
	IV infusion. Initial bolus 1-2 mg/kg, then infuse at
	0.1-1 mg/kg per hr
Metolazone*	0.1-0.2 mg/kg/dose every 12-24 hr
Hydrochlorthiazide**	2-4 mg/kg/day every 12-24 hr
Spironolactone	2-3 mg/kg/day in single dose
Bumetanide	0.02-0.04 mg/kg/day 12-24 hr

Refractory oedema

Management of Refractory Edema

Problem	Comments, Action
Excess sodium intake	Persistent edema suggests inadequate sodium restriction
	24 hr urinary sodium >100 mEq/day indicates an adequate diuretic response
	Restrict sodium intake
Decreased or delayed intestinal drug absorption	Bowel wall edema impairs oral drug absorption
	Intravenous administration of frusemide if high dose oral therapy ineffective
Decreased drug entry into tubular lumen	Increase to maximum effective dose of frusemide
	Albumin infusion along with loop diuretic if marked hypoalbuminemia
Increased distal sodium reabsorption	Administer multiple daily doses of frusemide
	Partial response, add thiazide diuretics; spironolactone
Decreased tubular sodium due to low glomerular	Oral corticosteroids increase tubular sodium delivery
filtration rate	Dialysis or hemofiltration in renal failure

Synergistic therapy

Albumin Infusion –

Presentation with hypovolemia –

- Correction of intravascular volume deficit gets precedence over management of edema
- Initial replacement of fluids may be achieved using normal saline or 5% albumin at 10-20 ml/kg over 30-60 minutes in such patients

Combination of 20% albumin and frusemide –

- Restricted to patients who show refractory edema or ascites despite maximized doses of diuretics
- Severe hypoalbuminemia.

20% albumin (at a dose of 1g/kg over 1-4 hr) (rate of infusion < 2-3 mL/min) with frusemide (2 mg/kg)

Frusemide may be given as a bolus either midway or at the end of therapy with similar results

Effect of albumin infusion is transient

Repeated infusions -- usually on alternate days for sustained reduction in edema.

Risk of aggravating pulmonary edema and congestive heart failure

Monitoring of vital signs and volume status during and after the infusion is recommended

Step 1 Assess volume status*

Step 2*a* If features of hypovolemia, give 5% or 20% albumin infusion**

Step 2*b* If normovolemia or hypervolemia, administer frusemide 2-8 mg/kg daily orally. Add spironolactone 2-3 mg/kg/day at higher frusemide doses. Restrict sodium intake. If inadequate response, add metolazone (0.1-0.3 mg/kg/d) or hydrochlorothiazide (2-3 mg/kg/d)

III sustained response to above measures, hospitalize

Step 3 Administer IV frusemide 1-3 mg/kg/dose every 12 hr

Step 4 Consider frusemide infusion at 0.1-1.0 mg/kg/hr if the effect of IV boluses not sustained

Step 5 Significant edema persisting despite these measures, give albumin infusion 20% with frusemide, over 1-4 hr, on alternate days.

*Assess volume status clinically by heart rate, blood pressure and hydration. In patients with hypovolemia blood urea may be raised, fractional excretion of sodium <0.2% and urinary K^+/ K^+ + Na^+ > 60%.

**20% albumin may be diluted in normal saline or 5% dextrose solution to increase the infusate volume especially in patients with hypovolemia.

Fig. 2. Management of edema due to nephrotic syndrome. Response is considered inadequate if weight loss is less than 1% per day.

- ✓ In steroid responsive nephrotic syndrome -- treatment with daily corticosteroids usually leads to diuresis within 7-10 days
- ✓ Treatment for minimal periorbital puffiness or pedal edema not required
- ✓ Patients showing moderate to severe edema need specific treatment for its control
- ✓ Most such patients show reduction of edema with modest restriction of sodium intake and oral administration of frusemide
- ✓ Aggressive therapy for edema is required in less than 10% patients.

THANK YOU