Evaluation and Management of Edema

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Pathophysiology and etiology of edema
- Alteration in capillary hemodynamics
- Sodium/water retention by the kidneys

Clinical manifestations and diagnosis of edema
- Peripheral edema, pulmonary edema, ascites, idiopathic edema
- Differential diagnosis of edema

Treatment of edema
- General principles of treatment
- Diuretics
- treatment of refractory edema

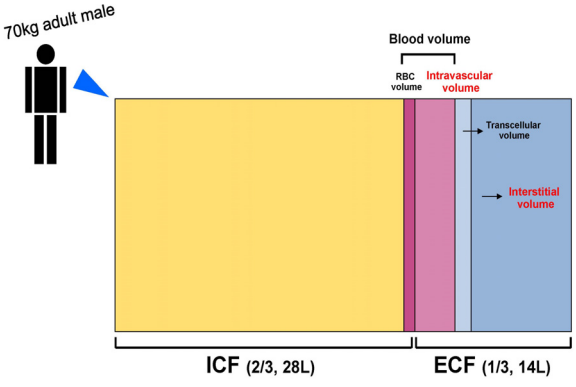
Introduction

Definition of edema
- Palpable swelling produced by expansion of the interstitial fluid volume

Two basic steps – fluid shifting and retention
Alteration in capillary hemodynamics
movement of fluid from the vascular space into the interstitium
Retention of dietary or intravenously administered sodium and water by the kidneys

Clinically apparent edema > interstitial volume increased by 2.5-3L
Normal plasma volume 3L

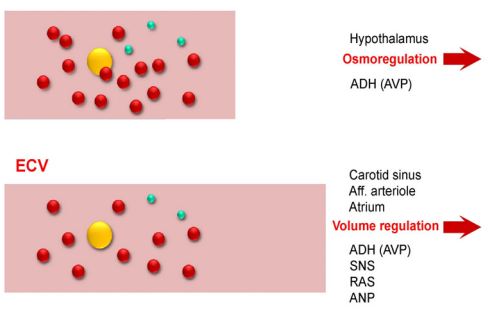
Distribution of total body water



Osmolality ≈ Tonicity

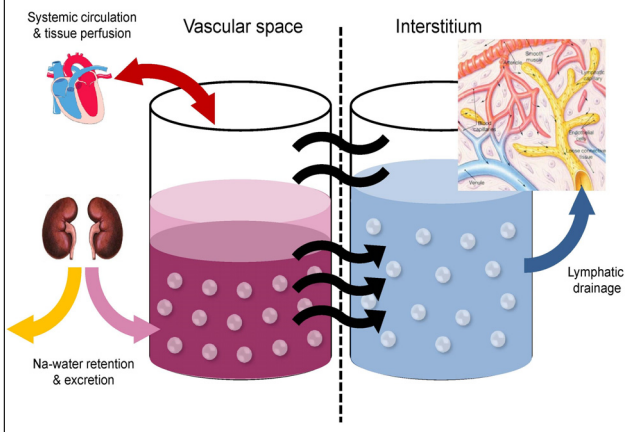
number of particles in 1L (1kg) water

osmolality of ECF vs. ICF
effective osmolality
driving force of fluid shifting



Major sensors and effectors of osmo- & volume regulation pathways

	Osmoregulation	Volume regulation
What is sensed	Plasma osmolality (Posm)	Effective tissue perfusion (ECF)
Sensors	Hypothalamus	Carotid sinus Afferent arteriole Macula densa Atrium
Effectors	ADH (thirst)	RAS, SNS (NE), ADH, ANP
What is affected	Urine osmolality (water)	Urine sodium



Major causes of edema according to primary mechanism

Increased capillary hydraulic pressure
- Increased plasma volume due to renal Na+ retention
  1. Heart failure, including cor pulmonale
  2. Primary renal sodium retention
     - Renal disease (NS), refeeding edema, early LC
     - Drugs: Vasodilator (minoxidil), TZDs, CCBs, NSAIDs, fludrocortisone, estrogens
  3. Pregnancy and premenstrual edema
  4. Idiopathic edema, when diuretic-induced
- Venous obstruction – LC (hepatic v. obstruction), acute pulmonary edema

Increased capillary permeability
- Burns, trauma, inflammation, sepsis, allergic reaction (angioedema)
- Adult respiratory distress syndrome
- Diabetes mellitus, IL-2 therapy, malignant ascites, idiopathic edema

Hypoalbuminemia (decreased capillary oncotic pressure)
- Protein loss – Nephrotic syndrome, protein-losing enteropathy
- Reduced albumin synthesis – Liver disease, malnutrition

Lymphatic obstruction (increased interstitial oncotic pressure)
- LN dissection, LN metastasis, malignant ascites
- Hypothyroidism

Uncertain mechanism – Docetaxel, Pramipexole

Pathophysiology – capillary hemodynamics

↑ vascular injury
burn, ARDS, DM
IL-2, VEGF

↑ venous expansion
venous obstruction

↓ hypoalbuminemia

Net filtration = cap.permeability x (Δ hydraulic pr. – Δ oncotic pr.)

= LpS x [(Pcap - Pif) – s(πcap – πif)]

Starling's forces in different organs

	Skeletal muscle	Alveoli
Hydraulic pressure		
Capillary (mean)	17.3	8
Interstitium	-3.0	-2
Mean gradient	20.3	10
Oncotic pressure		
Capillary (mean)	28	26
Interstitium	8	18
Mean gradient	20	8
Net gradient favoring filtration	0.3	2

Muscle – small net gradient

Alveoli – low Pcap, high πif
more permeable to proteins

Liver – highly permeable to proteins
roughly equal πcap, πif

Safety factors

Protective response

There must be at least 15 mmHg gradient increase favoring filtration before edema can be detected.

1) lymphatic flow and contractility
- influenced by individual factors and acuteness of hemodynamic change

2) interstitial hydraulic pressure
- fluid entry eventually raise interstitial hydraulic pressure

3) interstitial oncotic pressure
- fluid entry also lowers interstitial oncotic pressure by dilution and lymphatic removal of interstitial proteins

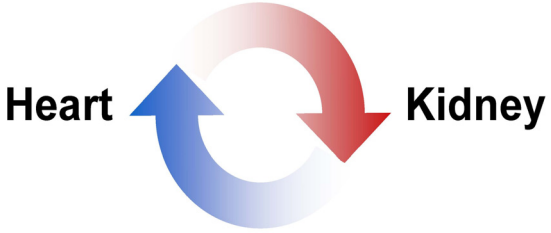
Safety factors

Nephrotic syndrome
- interstitial oncotic pressure (subcutaneous tissue) 12-15 mmHg
- urinary albumin loss – gradual fall in plasma oncotic pressure
  → parallel decline in interstitial oncotic pressure (less albumin entry)
  → initially maintained with little tendency to edema formation
  → /s severe hypoAlb, edema is primarily d/t renal Na retention

Pulmonary edema
- high alveolar capillary permeability, high interstitial oncotic pressure 18 mmHg
  → /s concurrent LA, PCP increase,
  pulmonary edema is not usually seen with hypoAlb, even at low plasma Alb enough to peripheral edema

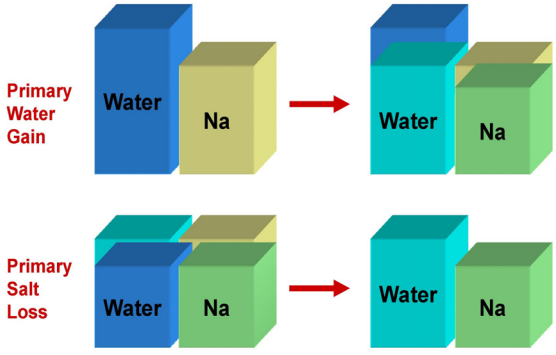
Rapid administration of large volume of saline to marked hypovolemic patients
- acute dilutional hypoAlb without time for interstitial Alb to fall
  → peripheral edema can occur before restoration of intracardiac filling pressure

Pathophysiology – renal Na retention

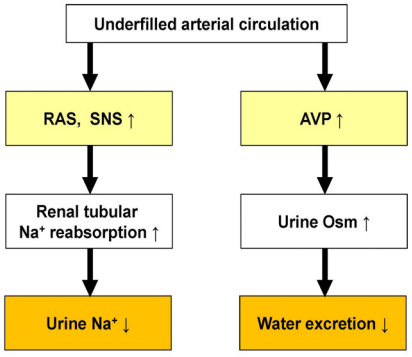


Function – regulation, adjustment
→ appropriate compensation for effective circulating volume
Dysfunction – deterioration, failure
→ inappropriate manifestation of renal disease

Renal adaptation to Na change

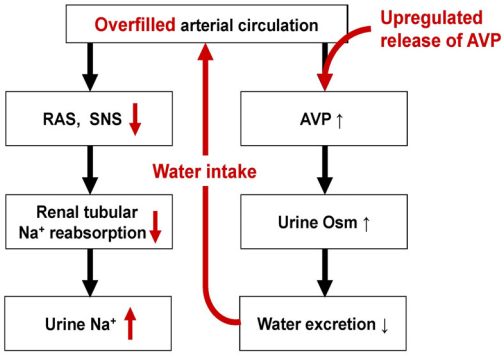


Hemodynamic stimuli for AVP

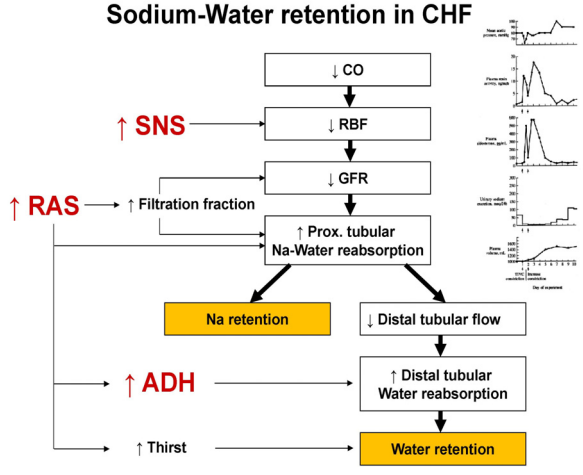


Na-Water retention

SIADH (Syndrome of inappropriate secretion of ADH)



Sodium-Water retention in CHF



Clinical manifestations

Peripheral edema
- pitting (>5 sec), movement of excess interstitial fluid in response to pressure
- low tissue pressure area (periorbital, pretibial, sacral)
- grading (1+ ~ 4+), weight change

Pulmonary edema
- SOB, orthopnea, chest pain (AMI-induced PE), confirmed by CXR
- cardiac (TMC), renal disease, ARDS
- PCWP (>18-20 mmHg) in cardiac, renal disease vs. PCWP normal in ARDS
- not occur in uncomplicated LC, hypoalbuminemia alone

Ascites
- abdominal distention, shifting dullness, fluid wave
- SOB d/t pressure on diaphragm

Clinical manifestations

Unilateral edema
- Venous insufficiency or thrombosis
  - limited to lower extremities, unilateral, DVT excluded
  - CVP normal
  - poor response to diuretics, signs of hypoperfusion
  - limited to arms and hands (catheter-induced venous thrombosis)
- Lymphedema
  - LN dissection, filariasis
  - limited to ipsilateral arm or leg
  - cutaneous and subcutaneous thickening, Stemmer sign

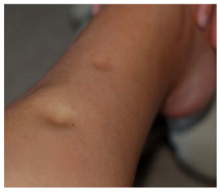
Nonpitting edema
- Lymphedema (moderate to severe)
- Pretibial myxedema (hypothyroidism)

Case 1

- 52-yo male
- Edema – pretibial pitting edema, scrotal swelling

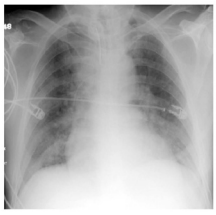
- Urinalysis – protein (4+), RBC 3-5/HPF
- Spot urine PCR – 3900 mg/g
- Spot urine ACR – 3650 mg/g

- Serum albumin – 2.4 g/dL
- Serum total cholesterol – 312 mg/dL



Case 2

- 52-yo male
- Edema, then dyspnea



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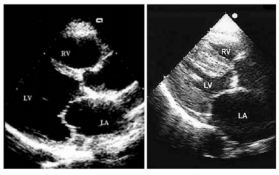
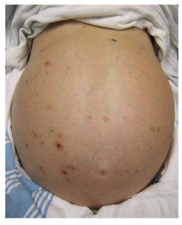


- Chest PA
- Echocardiography

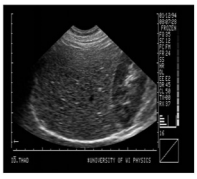
Case 3

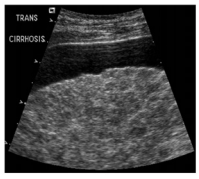
- 68-yo male
- Edema – Ascites
- Chronic hepatitis B



- Hb – 9.8 g/dL, Platelet – 87,000/mm^3
- Serum AST/ALT – 68/127 U/L

- USG Abdomen





Diagnostic workup

History taking
- any disorders or drugs
- edema location
- intermittent or persistent?

Physical exam
- pattern of distribution of edema
  : capillaries with altered hemodynamics
- central venous pressure
- presence or absence of pulmonary edema

Major physical findings in edematous states

Disorder	Pulmonary edema	Central venous pressure	Ascites and/or pedal edema
Left-sided heart failure	+	Variable	-
Right-sided heart failure	-	↑	+
Cirrhosis	-	↓-Normal	+
Renal disease	Variable	↑	+
Nephrotic syndrome	-	Variable	+
Idiopathic edema	-	↓-Normal	+
Venous insufficiency	-	Normal	+, edema may be asymmetric

Differential Diagnosis

Idiopathic edema
- similar to volume depletion state,
  because of exaggerated fall in plasma volume in the erection position
  and concomitant effect of diuretics
- exclusion diagnosis only in menstruating women, normal S-Alb, normal CVP,
  no cardiac, hepatic, renal disease

Drug-induced edema
- vasodilator (minoxidil) – RAS, SNS activation after BP decline → Na retention
- TZD (rosiglitazone) – collecting duct Na channel activation → Na retention
- CCB (DHP) – dilation of precapillary sphincter (aff. arteriole) → capillary leak
- NSAIDs – inhibition of renal PGs synthesis
- Fludrocortisone – synthetic mineralocorticoid
- Estrogens (oral contraceptives) – Na retention
- Pramipexole – dopamine agonist (Parkinsonism, restless legs syndrome)

General principles of treatment

Aims

1. Reversal of underlying disorder (if possible)
2. Dietary Na restriction to minimize fluid retention
3. Diuretic therapy

Considerations

1. Timing – when must edema be treated ?
2. Result – what are the consequences of edema removal ?
3. Speed – how rapidly should edema be removed ?

General principles of treatment

When must edema be treated?

Pulmonary edema is the only form of life-threatening edema

Others (esp. liver cirrhosis with ascites) – slow treatment

- hypoK, Met. Alkalosis, rapid fluid shift induced by diuretics
- can precipitate hepatic encephalopathy or hepatorenal syndrome

What are the consequences of removal of edema fluid?

Na-water retention

– appropriate compensation vs. inappropriate response

Diuretic Tx of appropriate compensatory fluid retention in CHF, LC

→ effective circulating volume↓, venous return↓, cardiac filling pr↓

→ cardiac output↓ (tolerable, even if CO↓ by 20%)

→ tissue perfusion↓ (esp. in severe CHF, rapid fluid removal in LC)

→ should be monitored with BUN, SCr

General principles of treatment

How rapidly should edema fluid be removed?

diuretics remove fluid initially from intravascular space

→ venous pressure↓, capillary hydraulic pressure↓

→ mobilization of edema fluid into vascular space

→ restoration of plasma volume

Generalized edema d/t CHF, NS (primary Na retention)

→ rapid mobilization of edema fluid (most capillary beds involved)

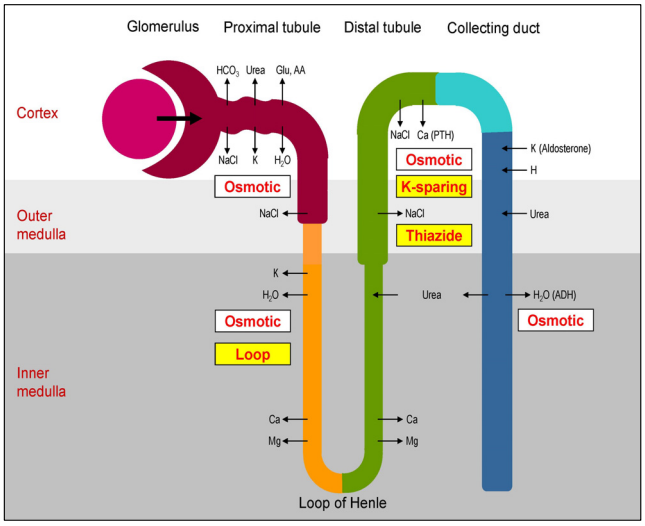
→ >2-3 L/day removal

LC and ascites with no peripheral edema

→ limited mobilization of excess ascitic fluid via peritoneal capillaries

→ max 300-500 mL/day removal

→ rapid removal is associated with azotemia, hepatorenal syndrome



Renal tubular transporter

Site	Luminal	Basolateral
Proximal tubule	Na^+-H^+ exchanger (NHE-3) Cotransporter (Na^+-glucose, phosphate, aminoacid, lactate,urea) AQP1	Na^+-HCO_3^- cotransporter (NBC) Na^+-K^+ ATPase HCO_3^- - Cl^- exchanger(AE1)
Loop (TAL)	Na^+-K^+ - 2Cl^- cotrasnporter (BSC)	Na^+-K^+ ATPase
Distal tubule	Na^+-Cl^- cotransporter (TSC) Ca^{++} ATPase	Na^+-K^+ ATPase
Collecting duct	<Principal cell> Na^+ channel (ENaC) K^+ channel AQP2	Na^+-K^+ ATPase AQP3, AQP4
	<Intercalated cell, A type> H^+-ATPase H^+-K^+-ATPase	HCO_3^- - Cl^- exchanger(AE1)
	<Intercalated cell, B type> HCO_3^- - Cl^- exchanger(AE1)	H^+-ATPase
	<IMCD cell> AQP2 Urea transporter(UT)	AQP4

Choice of diuretics

First choice – loop diuretics (furosemide)

Monitoring – degree of diuresis,

hypoK, met alkalosis, hypoNa, hyperUA, BUN, SCr

LC – slow diuresis with loop diuretic + spironolactone

CHF – diuresis rate is usually not a limiting issue

NS – higher dose of loop diuretic

(diuretic+tubular albumin binding, reduced functioning nephron)

Idiopathic edema – D/C diuretic for at least 2-3 weeks

Resistant edema – high-dose iv loop diuretics

diuretic combination acting at different sites of nephron

Diuretic dose

Normal renal function
- Initial diuresis – furosemide 10 mg iv
- Max diuresis – furosemide 40 mg iv (no further diuresis with >40 mg)

CHF, LC (advanced), Renal failure – ↓ diuretic effect → higher dose
- ↓ renal perfusion (↓drug delivery to kidneys)
- ↓ drug secretion into lumen (retention of competing anion)
- ↑ Na-retaining activity (RAS)

Max diuretic response with the first dose
- If diuresis (+)/hours → effective dose, short-lived → same dose x 2/day
- If diuresis (−)/hours → doubling dose (to 320-400 mg po, 160-320 mg iv)

Diuretic response

Time limitation
- max diuresis with the first dose
- gradual decline over 1-2 weeks
- new steady state (solute-water excretion = intake)

Initial solute-water excretion
- → intravascular fluid loss (↓ECF)
- → ↓BP, ↑Na-retaining factors (AT-II, aldosterone, norepinephrine)
- → Na-retaining forces = Na-losing activity (diuretics)
- → New steady state (Na intake = Na excretion)

→ Higher diuretic dose or combination therapy is required

Refractory edema

Factors of persistent fluid retention

1. inadequate diuretic dose
2. excess Na intake
3. delayed intestinal absorption of oral diuretics
4. decreased diuretic excretion into urine (tubular secretion)
5. increased Na reabsorption at other sites in the nephron

6. NSAIDs - ↓synthesis of vasodilator and natriuretic PGs
7. Allergy to sulfa (sulfonamide loop diuretics) → ethacrynic acid

CA inhibitors, Loop diuretics

Thiazides, Thiazide-like diuretics

Management of refractory edema

Initial iv diuretic therapy
- ← ↓intestinal diuretic absorption
- ← ↓intestinal perfusion, ↓intestinal motility, mucosal edema

Oral torsemide > furosemide – more predictably absorbed, longer half-life
iv infusion > iv bolus – less ototoxic, more constant

Resistance to diuretics
- ↓diuretic secretion into tubular lumen → max effective dose
- ↑tubular Na reabsorption (at sites other than loop of Henle)
- → repeating dose twice or three times daily
- → adding thiazide diuretic

Management of refractory edema

Continuous infusion
- significant 30% increase in Na excretion (Urine Na)
- significant higher urine volume

- should not be tried in non-responder to max bolus doses

- loading dose : 40-80 mg furosemide over 5 min
- starting rate
  - eGFR < 30 mL/min → 20 mg/h → second bolus → 40 mg/h
  - eGFR > 75 mL/min → 5 mg/h → second bolus → 10 mg/h
- higher infusion rate up to 240 mg/h

Summary

Pathophysiology
- capillary hemodynamic change – hydraulic -oncotic pressure
- renal Na-water retention – appropriate-inappropriate response

Clinical manifestations and Diagnosis
- DDx – pitting edema, non-pitting edema
- DDx – CHF, LC, Renal disease (NS, RF)
- pumonary edema, ascites, peripheral edema, CVP

Management
- timing, consequences, rapidity of treatment according to pathogenesis
- diuretics – choice, dose, response
- refractory edema – repeating dose, combination