

HeFSSA Practitioners Program 2019

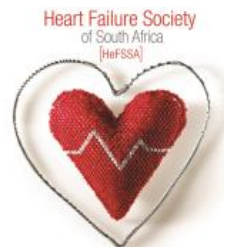
“Challenges in Heart Failure Management”

Dyspnoea and leg swelling, when is it heart failure?

Management of acute decompensated heart failure

Heart failure during pregnancy

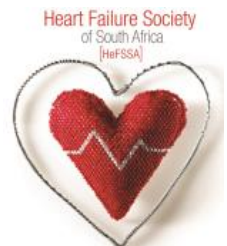
Refractory oedema in heart failure patient



Refractory oedema in heart failure

HF associated with prolonged hospital stay to achieve adequate decongestion and stability

Refractory oedema, diuretic resistance and cardiorenal syndromes may develop and pose additional challenges in HF management



Causes of refractory oedema

Refractory oedema

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graph TD; A[Refractory oedema] --> B[Heart failure]; A --> C[Liver cirrhosis]; A --> D[Nephrotic syndrome]; A --> E[Renal failure];
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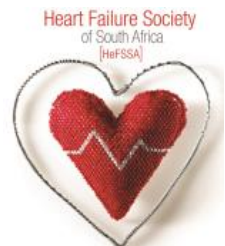
A flowchart with 'Refractory oedema' at the top, connected by a vertical line to a horizontal line. From this horizontal line, four vertical lines descend to four separate boxes: 'Heart failure', 'Liver cirrhosis', 'Nephrotic syndrome', and 'Renal failure'. The 'Heart failure' box is highlighted with a red border.

Heart failure

Liver cirrhosis

Nephrotic syndrome

Renal failure

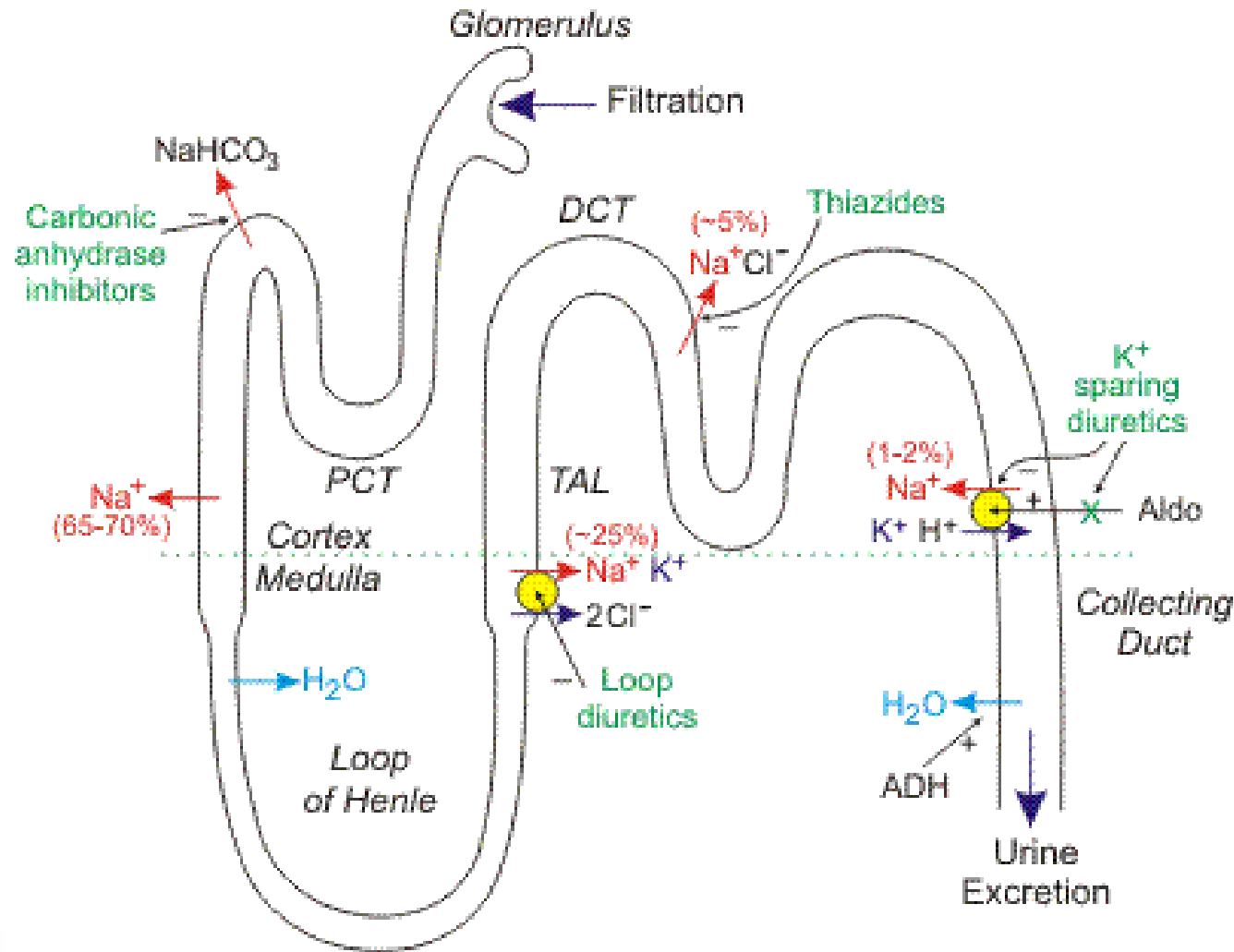


Definition

Refractory oedema is defined as oedema that is **refractory to typically effective doses of loop diuretics**

While this definition appears to be straightforward, it is often difficult to determine the optimal extracellular fluid volume status for an oedematous patient, as this process involves substantial clinical judgement and shared decision-making

How do diuretics work?



CASE STUDY:

Refractory oedema in heart failure patient

Mr SG, 68 year old man:

Hypertension, type 2 diabetes, chronic kidney disease, obesity (BMI 37kg/m²), prior stroke with good neurological recovery, prior anterior myocardial infarction, obstructive sleep apnoea and gout. Known with ischaemic LV dysfunction (LVEF 28%) and chronic heart failure.

In past 6 months, recurrent hospitalisation for HF decompensation despite increasing doses of diuretics and reported treatment adherence. Drinks <1.5L of fluid/day. Regularly adds salt to all meals, but no added salt recently.



CASE STUDY:

Refractory oedema in heart failure patient

Current medications: furosemide 160mg BD; hydrochlorothiazide 25mg daily; carvedilol 25mg BD; atorvastatin 20mg daily; Ecotrin 81mg daily; enalapril 10mg BD; ivabradine 7.5mg daily; allupurinol 300mg daily; metformin 850mg BD
(Spironolactone 25mg daily stopped due to renal dysfunction; regular NSAID use for gout)

On examination:

Obese; RR 24/min; HR 72/min, regular; BP 125/50 mmHg; warm peripheries, anasarca with 3+ pitting oedema, JVP elevated to angle of jaw. No pallor or jaundice.



CASE STUDY:

Refractory oedema in heart failure patient

CVS:

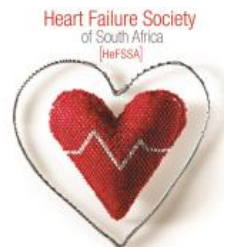
Displaced, diffused apex. Normal S1 and S2. S3 gallop. 3/6 pansystolic murmur louder on expiration, consistent with mitral regurgitation. No other murmurs.

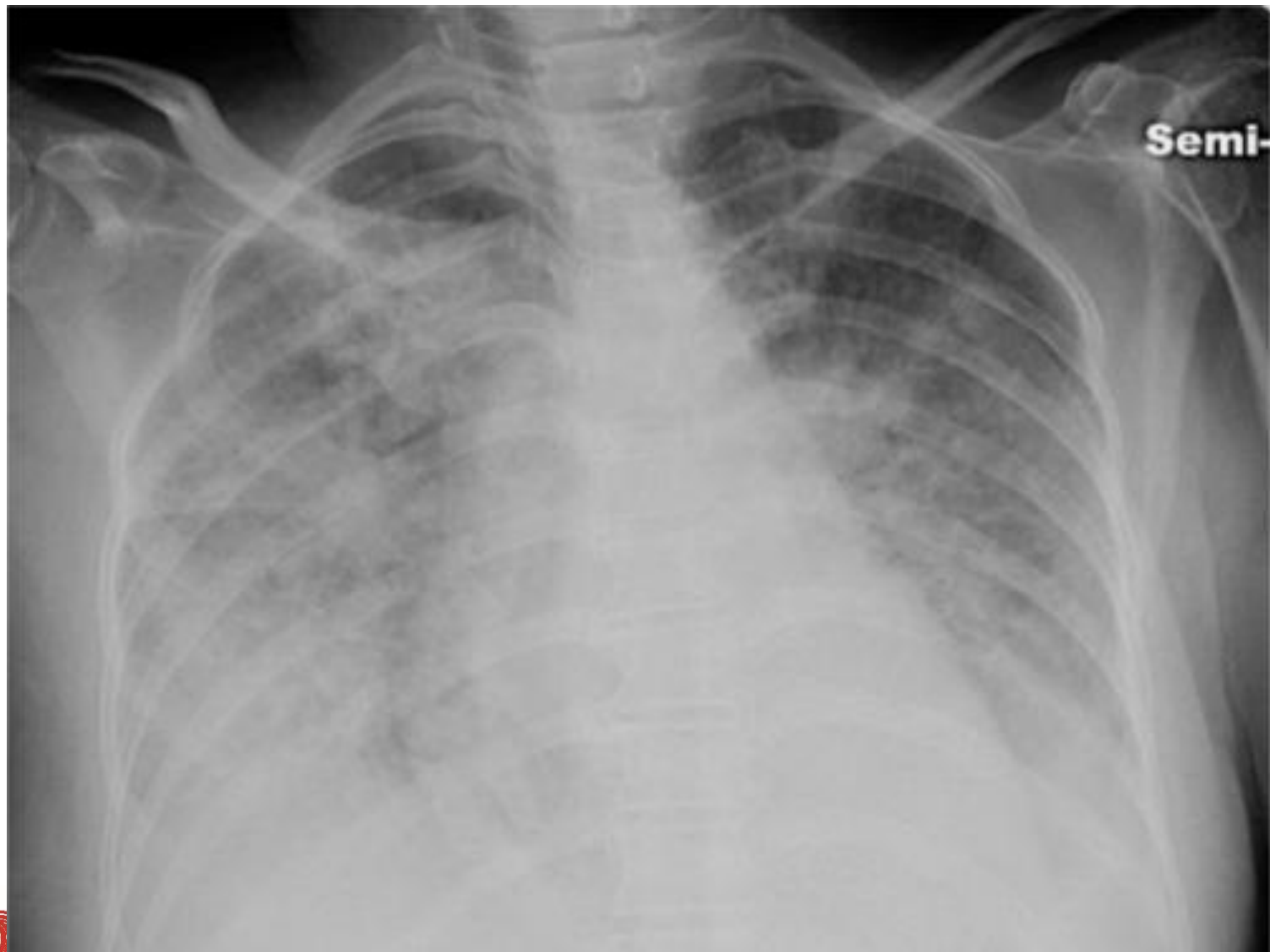
Chest:

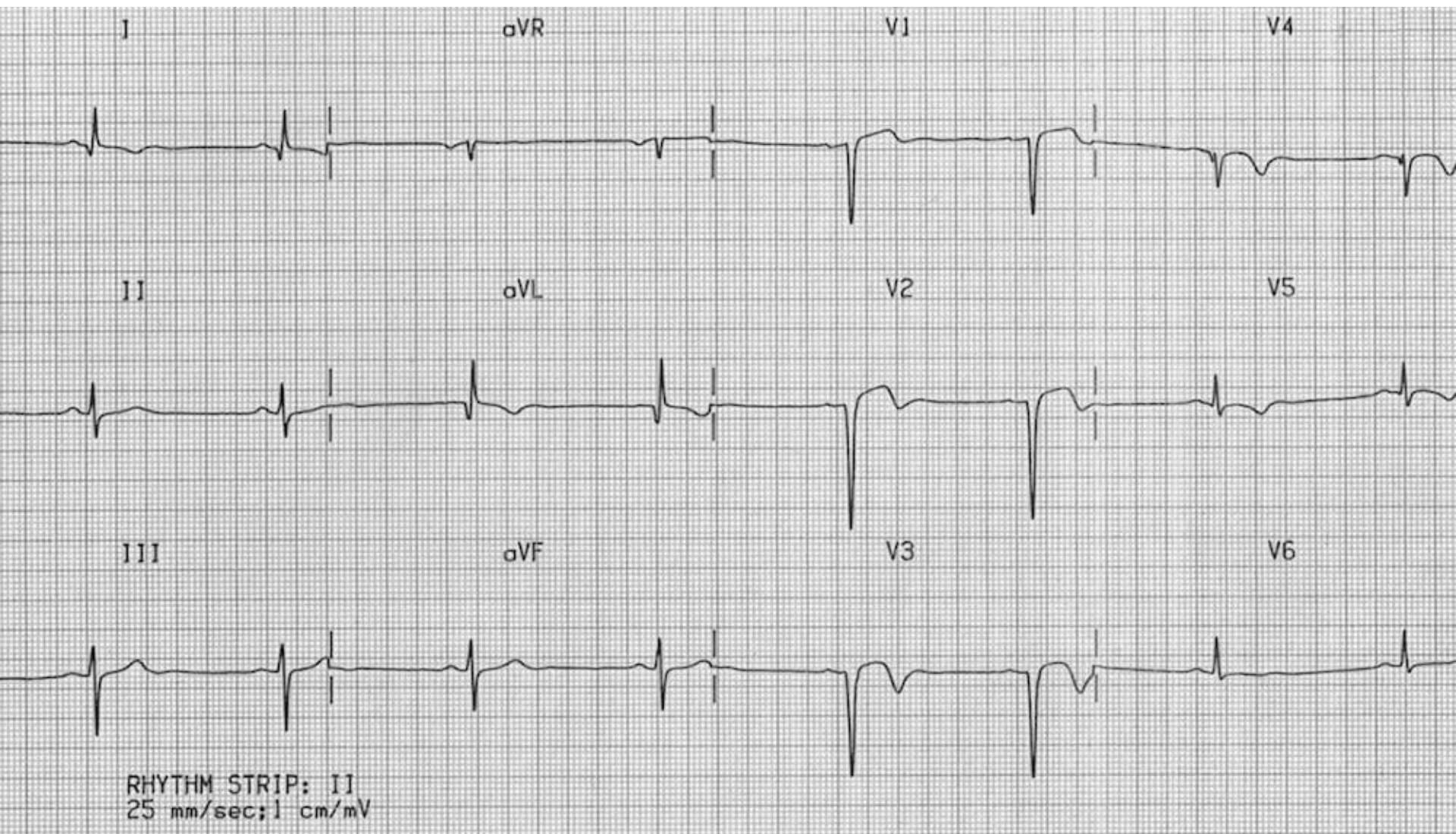
Bilateral inspiratory crackles and absent breath sounds and stony dullness in right lower zone.

Abdomen:

Massive ascites.







CASE STUDY:

Refractory oedema in heart failure patient

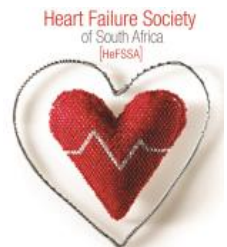
Echo is unchanged:

Dilated LV (LVEDD 6.5 cm). Dilated LA (4.7 cm). Severely impaired LV systolic function (EF 25-30%). Thinned, dyskinetic and aneurysmal anterior wall and apex.

Moderate mitral regurgitation.

Normal RV size. Mild tricuspid incompetence. PAP pressure 49 mmHg +JVP.

What would you do next to optimise treatment?

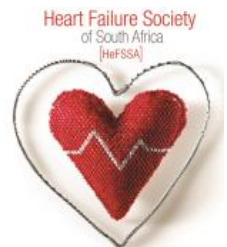


Causes of refractory oedema in HF

1. High salt intake (prevents net fluid loss)
2. Decreased loop diuretic secretion
3. Use of drugs that impair diuretic responsiveness (NSAIDs, thiazolidinediones, aminoglycosides)
4. Diuretic resistance (increased tubular sodium reabsorption)
5. Inadequate diuretic dose or frequency
6. Decreased intestinal perfusion, decreased intestinal motility and intestinal mucosal oedema



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Mechanisms of refractory oedema

1. High salt intake

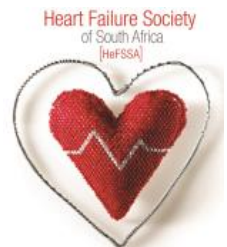
High sodium intake **prevents net sodium loss and increases extracellular fluid volume**, even if there is an appropriate natriuretic response to diuretics

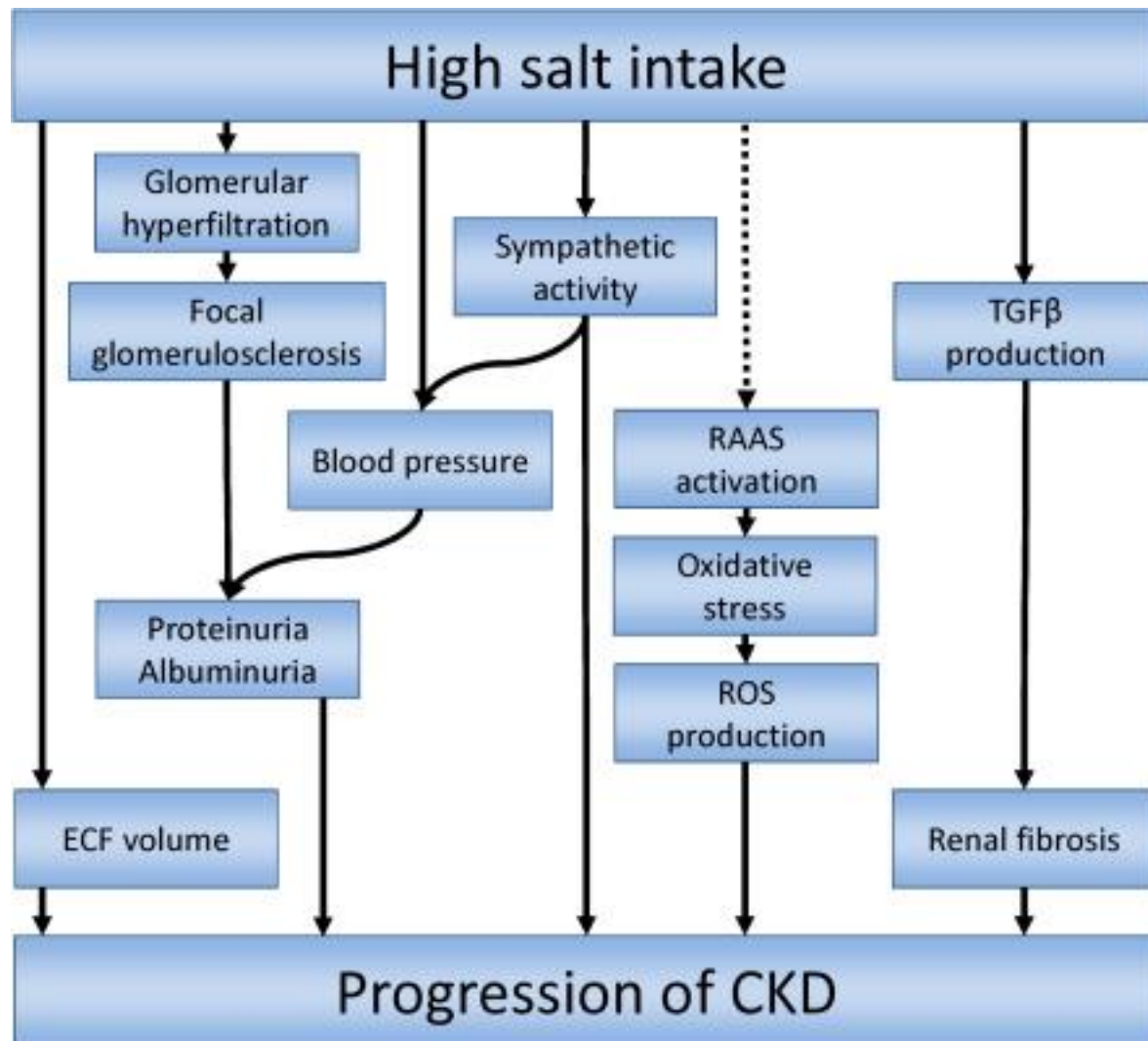
As diuretic effect wanes, there is postdiuretic sodium retention due to recovery of sodium reabsorption in the loop of Henle plus increased sodium reabsorption at other sites in the nephron

When sodium intake is high, postdiuretic sodium retention can counteract the diuresis that occurred while the diuretic was active

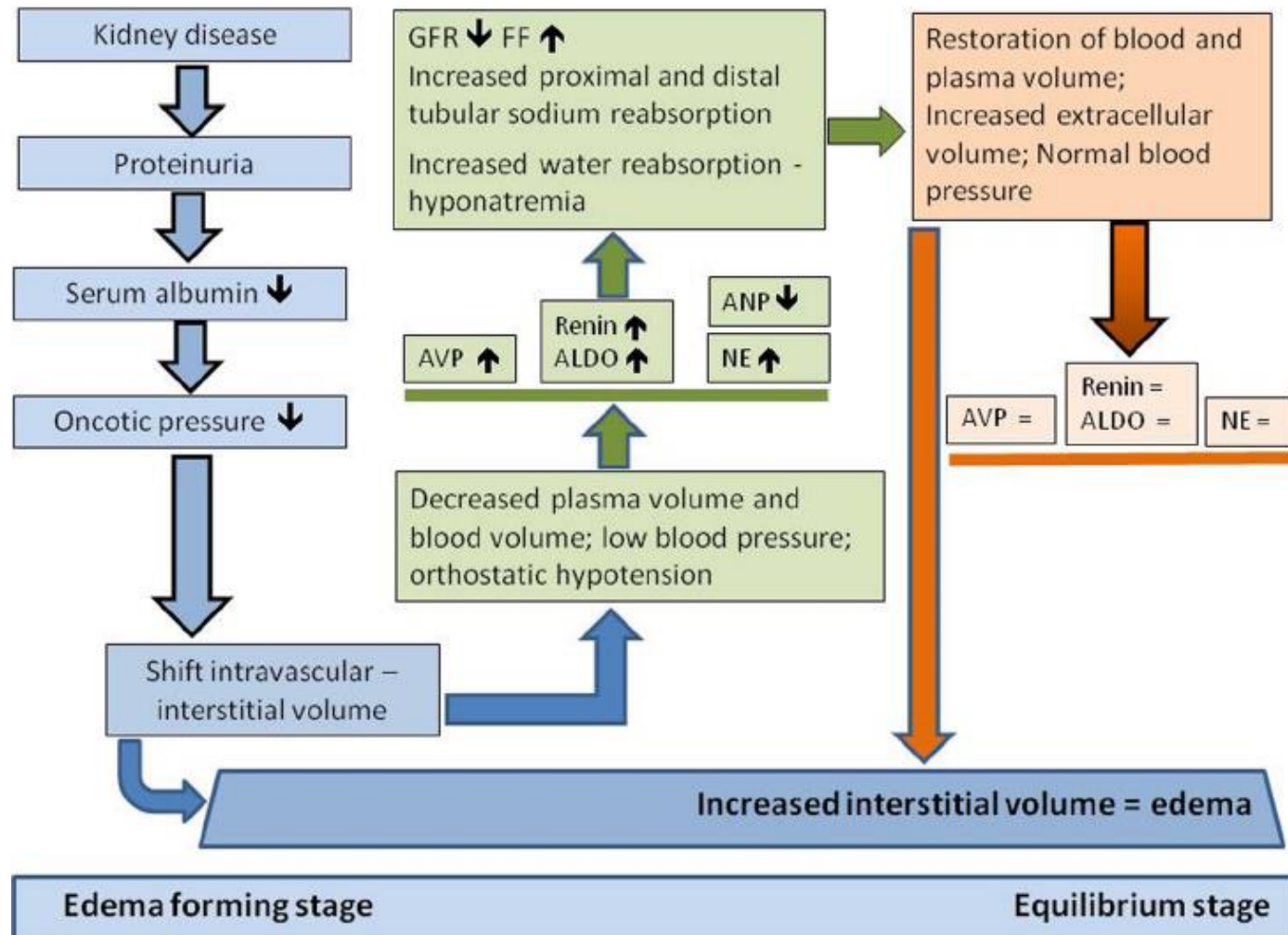


Ellison DH. Ann Intern Med 1991;114(10):886-894.
Wilcox CS, et al. J Pharmacol Exp Ther 1979;210(23):450-458.





Consequences of high salt intake



Mechanisms of refractory oedema

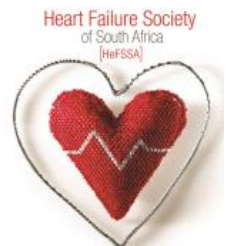
1. High salt intake

2010 Heart Failure Society of America (HFSA) and 2016 European Society of Cardiology Guidelines: recommend sodium intake of **less than 2g/day** in decompensated heart failure

24 hour urine: a value >100 mEq Na/day indicates non-adherence to sodium intake recommendations



HFSA. J Card Fail 2010;16:475-539.
Ponikowski P, et al. Eur Heart J 2016;18(8):891-975.





If your Blood pressure is normal, need not to worry about sodium intake, but try to consume less than 1500mg of salt daily. **1.**



Do not eliminate sodium altogether from your Diet, it's an essential nutrient, you need the right amount for good health. **2.**



Try spices, herbs and citrus, it enriches the flavor of food. **3.**

LEARN THE SIX LOW SALTY HABITS THIS SALT AWARENESS WEEK

Go for Low-Sodium Foods,
they have more Taste &
Good for Heart Health!



Do you know Sea salt contains 40 percent of sodium in comparison with table salt? **4.**



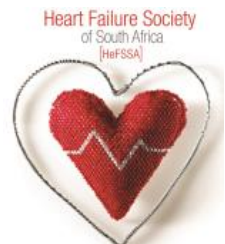
While buying the packed foods always check the nutritional panel and choose the foods lowest in Sodium. **5.**



Say No to Breads, Pizza, Soup and Cheese, they add a lot of Sodium to your diet. **6.**



#CHANGEYOURSALTYWAYS



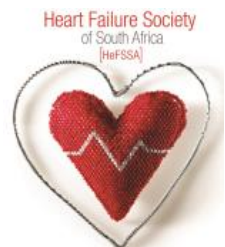
Mechanisms of refractory oedema

2. Decreased loop diuretic secretion

Loop diuretics must enter the tubular fluid in order to exert their diuretic effect

Loop diuretics are highly ($\geq 95\%$) protein bound; consequently, they primarily enter the tubular lumen by secretion by the proximal tubule, not by glomerular filtration

Decreased diuretic secretion into the tubular lumen results from decreased renal perfusion in patients with heart failure (due to the reduced cardiac output)



Mechanisms of refractory oedema

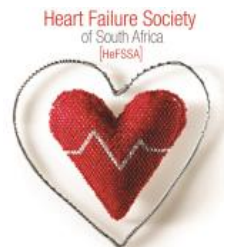
2. Decreased loop diuretic secretion

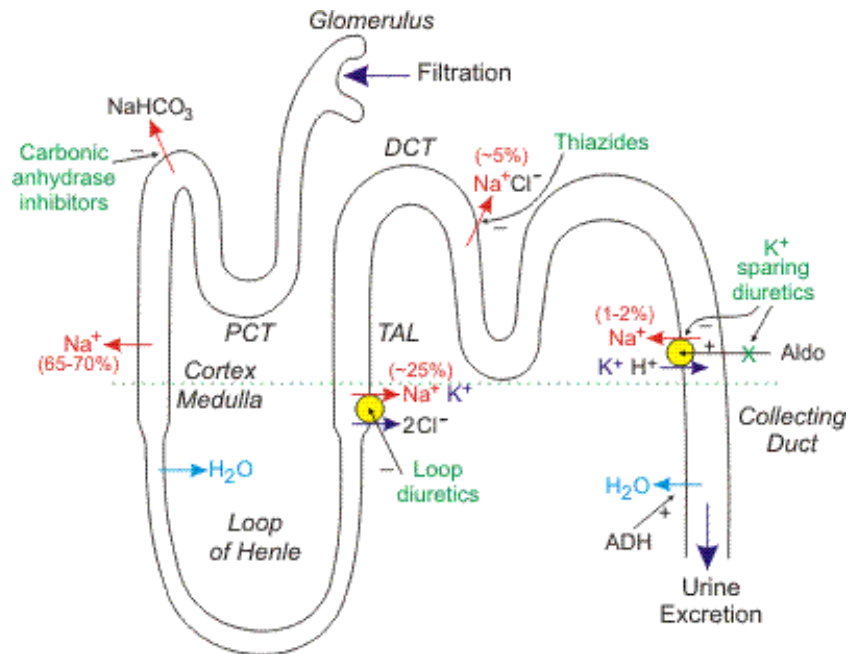
Patients with HF and nephrotic syndrome may also be unresponsive to diuretics due to decreased tubular secretion (as loop diuretics are highly protein bound, severe hypoalbuminemia reduces the delivery of diuretic to the renal tubule)

Also, filtered albumin and proteases may bind or degrade loop diuretics in the tubular lumen, thereby interfering with their absorption and function

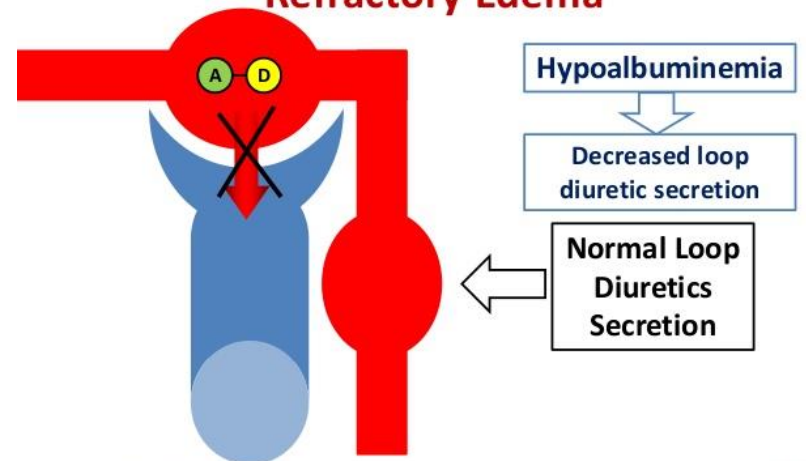


Bohnert BN, et al. Kidney Int 2018;93(1):159-172.



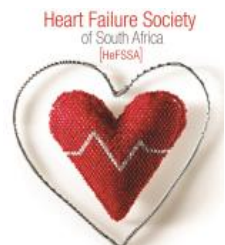


Mechanism of Development of Refractory Edema



NephroTube
www.nephrotube.com

M.Gawad. www.NephroTubeCNE.com
Opie LH, Kaplan NM, Pool-Wilson P, eds. Drugs for the Heart. 5th edition. Diuretic therapy.



Mechanisms of refractory oedema

3. Use of drugs that impair diuretic responsiveness (NSAIDs, thiazolidinediones, aminoglycosides)

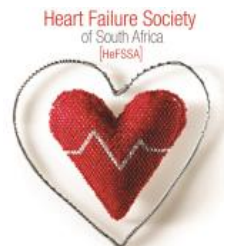
Refractory oedema may result from drugs that interfere with the action of diuretics

NSAIDs reduce the synthesis of vasodilator and natriuretic prostaglandins and impair diuretic responsiveness

Thiazolidinediones increase renal salt retention as a result of upregulation of the ENaC in the collecting ducts and also increase proximal tubule sodium reabsorption



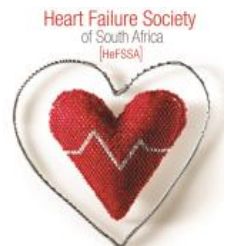
Ellison DH. Am J Kidney Dis 1994;23(5):623-643.
Fu Y, et al. PPAR Res 2015;646423.



Mechanisms of refractory oedema

3. Use of drugs that impair diuretic responsiveness (NSAIDs, thiazolidinediones, aminoglycosides)

Aminoglycosides increase the risk of nephrotoxicity and ototoxicity of diuretics



Drugs that exacerbate oedema

Direct arterial vasodilators (antihypertensive)	Hydralazine Clonidine Methyldopa α -blockers
Calcium channel blockers (antihypertensive)	Amlodipine
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Ibuprofen Diclofenac
Hormones	Glucocorticoids Anabolic steroids Estrogens Progestins Growth hormone
Thiazolidinediones (oral hypoglycemics)	Rosiglitazone Pioglitazone
Anti-depressants	MAO inhibitors

Mechanisms of refractory oedema

4. Diuretic resistance (increased tubular sodium reabsorption)

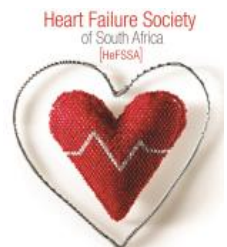
Some patients have partial or relatively complete resistance to a loop diuretic despite adequate secretion of the diuretic into the tubular fluid (i.e., despite having the same rate of urinary diuretic excretion as normal controls)

Due to **increased tubular sodium reabsorption by nephron segments other than the loop of Henle**

Phenomenon called '**diuretic braking**'



Rao V, et al. J Am Soc Nephrol 2017;28(11):3414-3424.
Loon NR, et al. Kidney Int 1989;36(4):682-689.

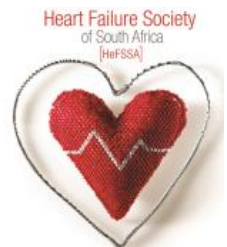


Diuretic resistance

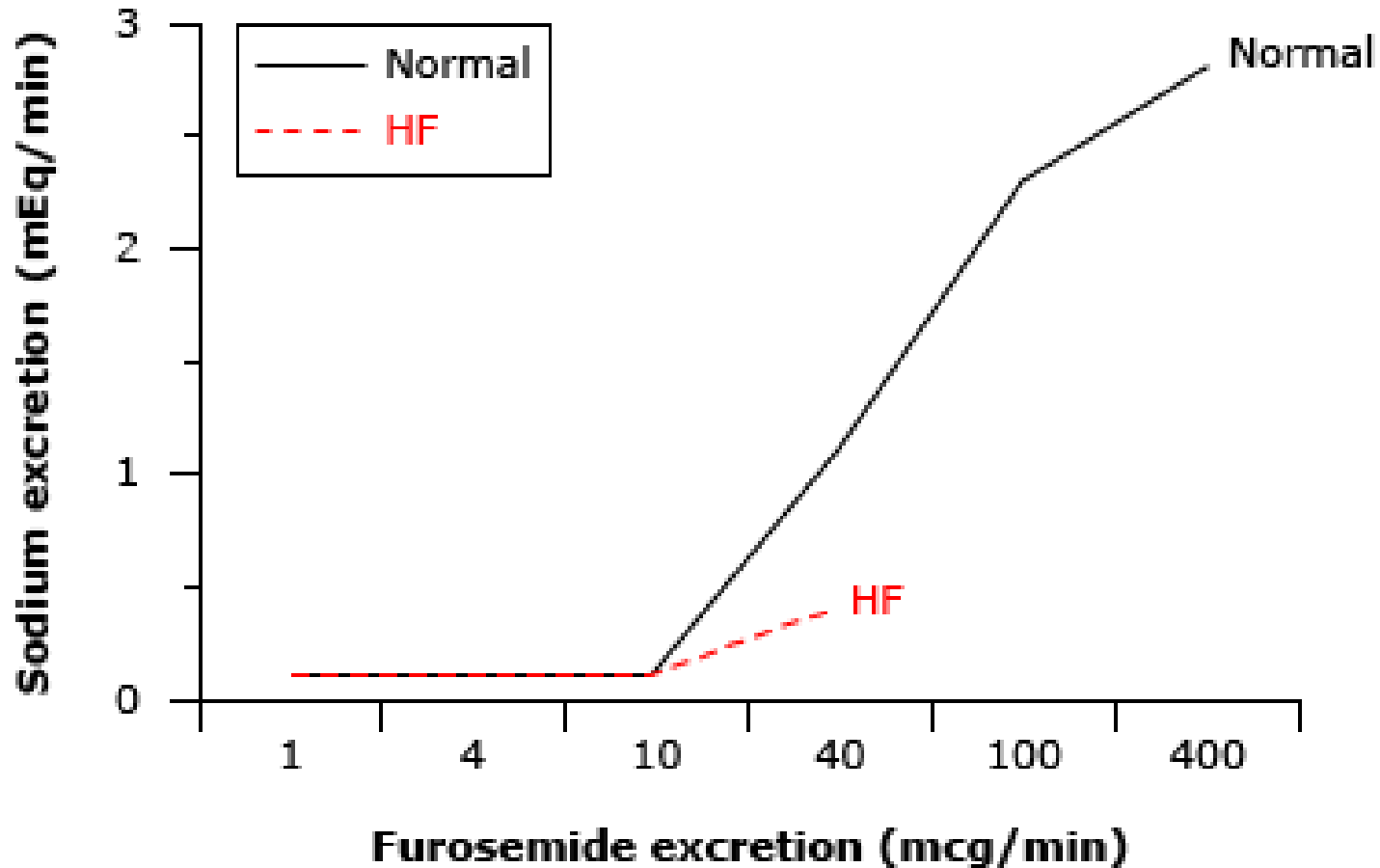
1. In the proximal tubule: enhanced activity of angiotensin II and norepinephrine
2. In the distal tubule: flow-dependent hypertrophy resulting from chronic loop diuretic therapy, which increases sodium delivery and reabsorption at this thiazide-sensitive site
3. In the collecting tubules: increased mineralocorticoid activity
4. Additionally, filtered proteases may cleave the epithelial sodium channel (ENaC), which increases its conductance for sodium



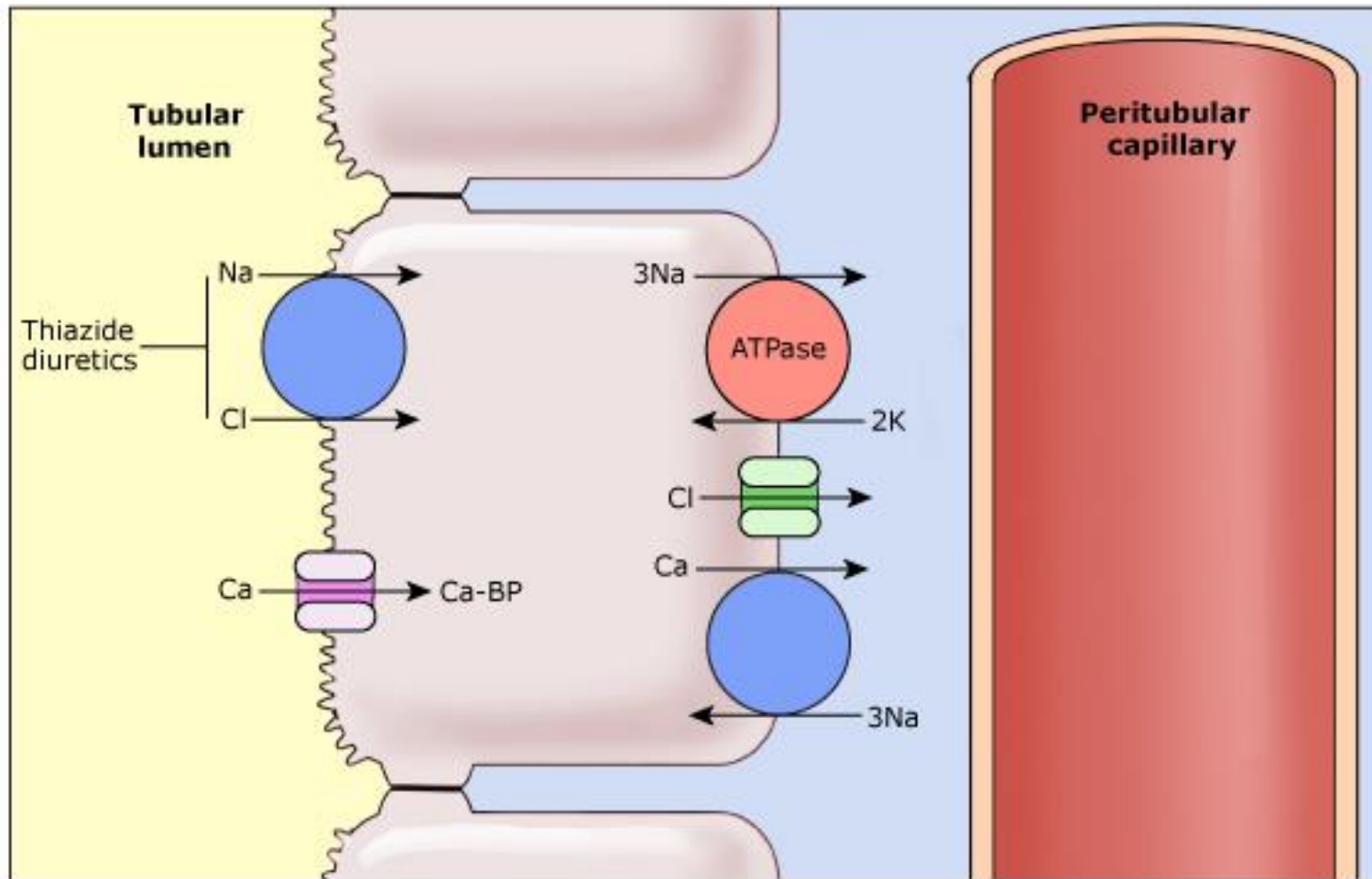
Wald H, et al. *Cir Res* 1991;68(4):1051-1058.
Saritas T, et al. *Cell Rep* 2018;25(10):2668-2675.



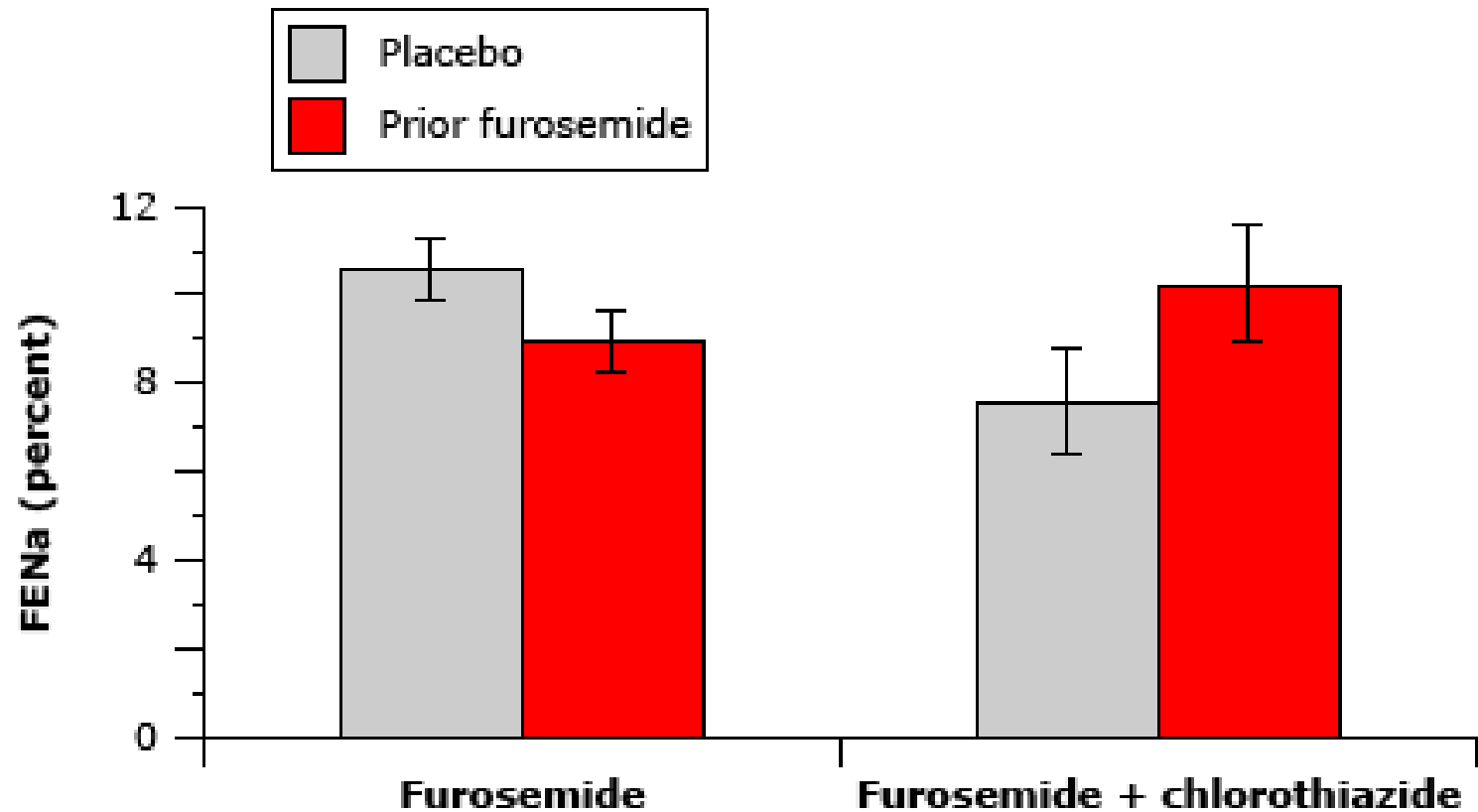
Dose response relationship: diuretics & Na excretion



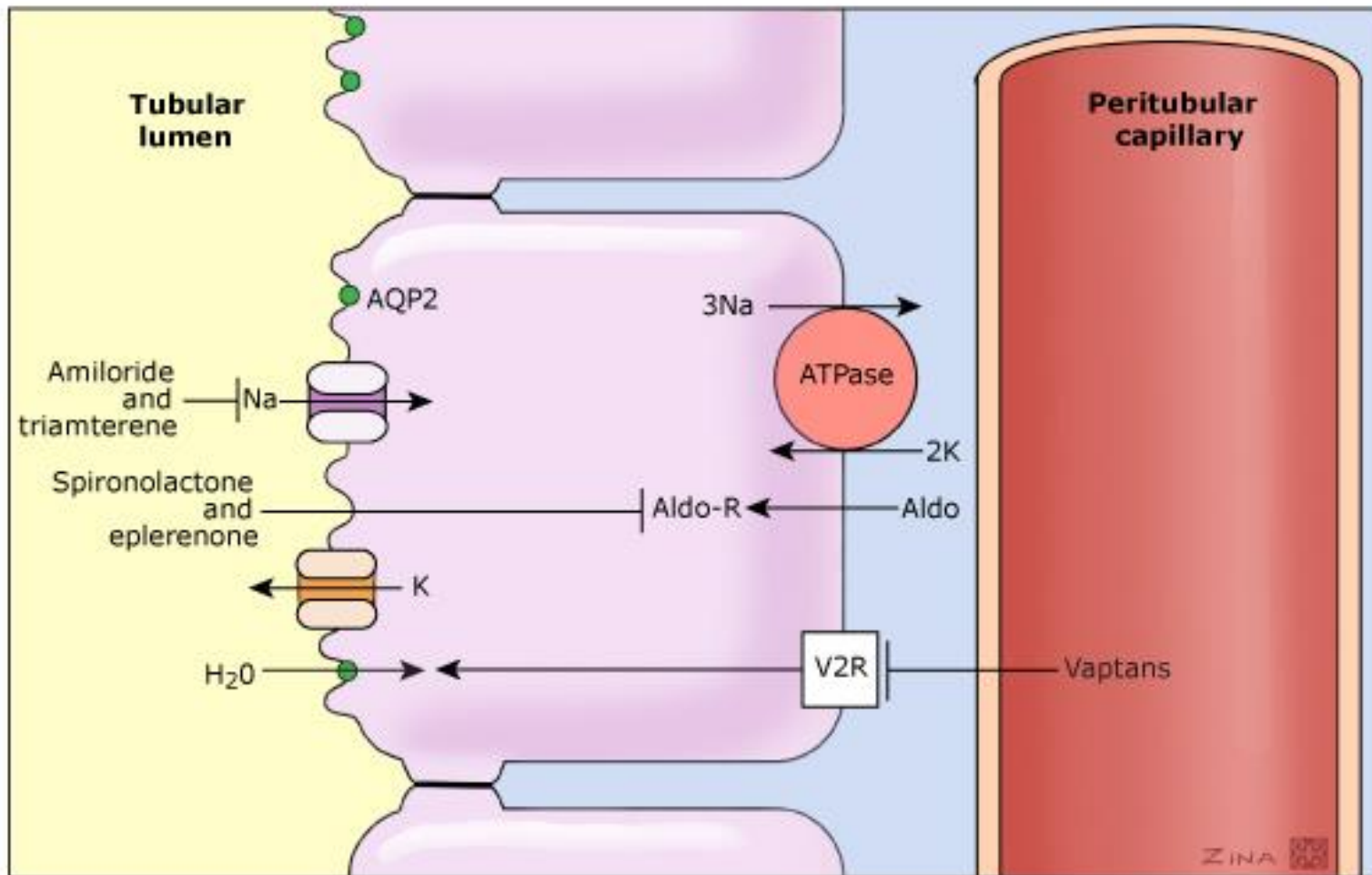
Ion transport in the DCT



Loop diuretic-induced increase in DCT Na reabsorption



Ion transport in the collecting tubule



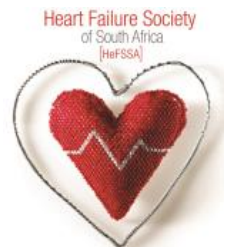
Diuretic resistance

Diuretic resistance may be overcome by:

1. Increasing doses of loop diuretic
2. Adding second and third diuretics from different classes



Almeshari K, et al. J Am Soc Nephrol 1993;3(12):1878-1883.
Rudy DW, et al. Ann Intern Med 1991;115(5):360-366.



Mechanisms of refractory oedema

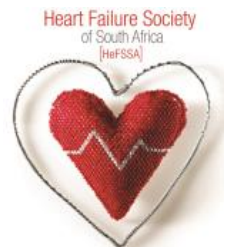
5. Inadequate diuretic dose or frequency

Commonly related:

1. Patient non-adherence to prescribed therapy
2. Physician inertia to target optimal drug doses or treatment titration



Gawad MA. Urol Nephrol Open Access J 2014;1(2):47-54.



Mechanisms of refractory oedema

6. Decreased intestinal perfusion, decreased intestinal motility and intestinal mucosal oedema

Patients with HF may have decreased intestinal perfusion, reduced intestinal motility, and also intestinal mucosal oedema, which will reduce the diuretic absorption, and hence diuretic delivery to the kidney and diuretic excretion rate



Gawad MA. Urol Nephrol Open Access J 2014;1(2):47-54.



Mechanisms of refractory oedema

6. Decreased intestinal perfusion, decreased intestinal motility and intestinal mucosal oedema

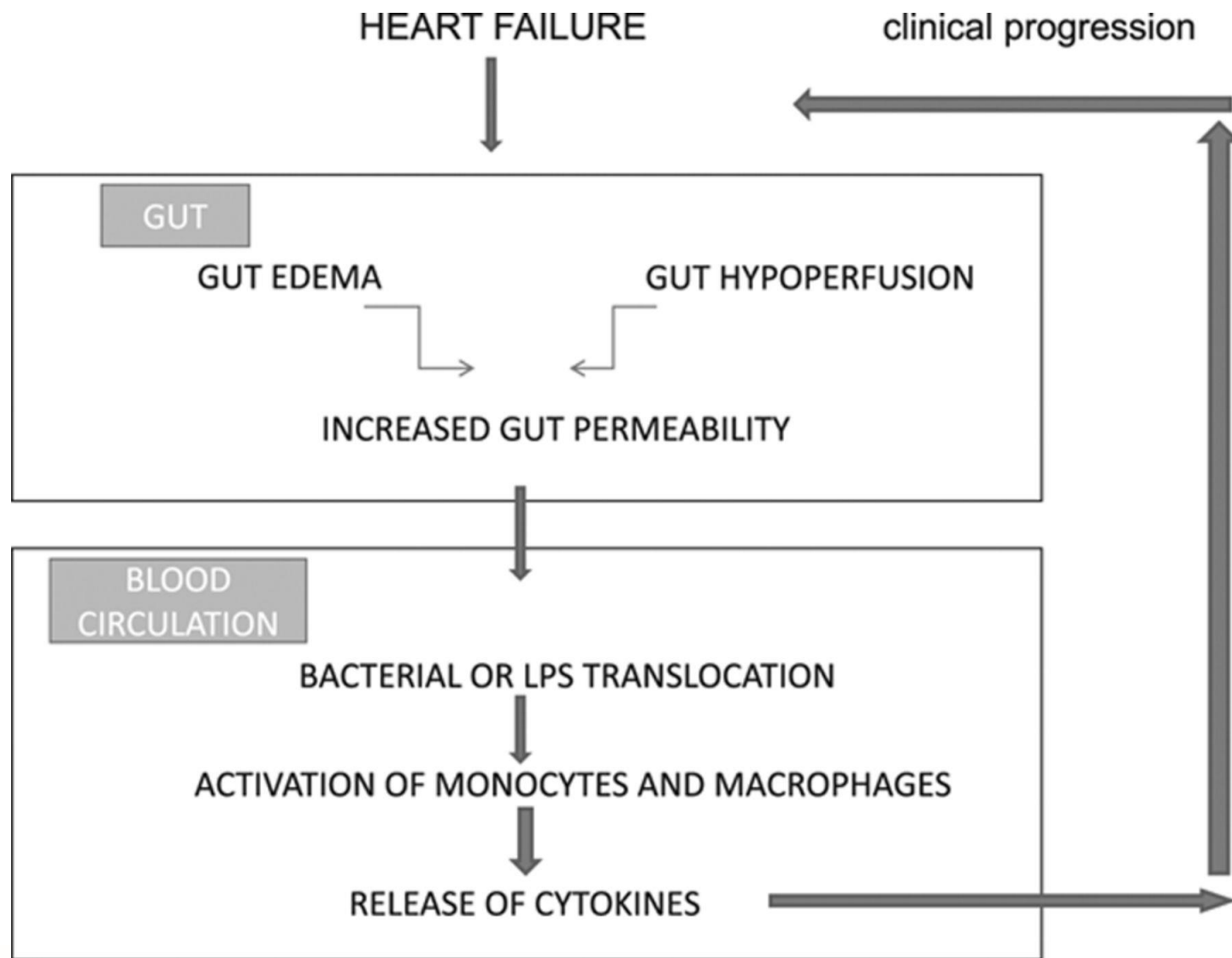
Patients with decompensated HF typically require initial intravenous (IV) therapy

The defect in diuretic absorption is often reversible, resulting in more effective oral therapy following removal of some of the oedema fluid with IV diuretics and stabilisation of cardiac function



Brater DC, et al. *Kidney Int* 1984;26(2):183-189.
Kramer BK, et al. *Am J Med* 1999;106(1):90-96.





Management of refractory oedema in HF

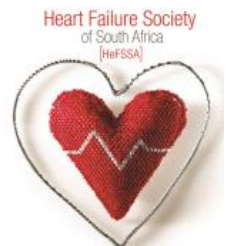
Before intensifying diuretic therapy, the following steps should be taken:

1. Exclude excessive sodium intake
24-hour urine should be collected

A value above 100 mmol in 24 hours (i.e., 2.3 g of sodium) suggests nonadherence with sodium restriction; a value above 100 to 120 mmol in 24 hours also suggests that the diuretic response is adequate since true diuretic resistance is manifested by intense renal sodium retention



Gawad MA. Urol Nephrol Open Access J 2014;1(2):47-54.



Management of refractory oedema in HF

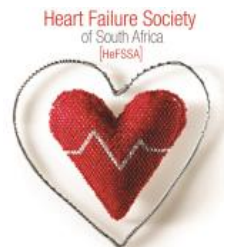
2. Confirm that the patient requires a reduction in extracellular fluid volume

While the mere presence of residual oedema or pulmonary congestion is suggestive, the decision to further reduce the extracellular fluid volume requires careful clinical judgement

Aggressive diuresis may be needed, and guidance from ultrasonography (e.g. IVC collapse) and serum biomarkers (e.g. brain natriuretic peptides)



Kaptein MJ, et al. Int J Nephrol 2017;2017:3756857.



Management of refractory oedema in HF

3. Fluid restriction

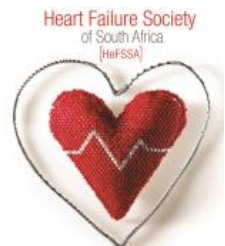
Aim for 1 to 1.5L/day

4. Avoid drugs that may interfere with diuretic responsiveness

5. Daily weight diary

Should be performed at the same time each day, usually in the morning, prior to eating and after voiding

Patient education and reporting of adverse events

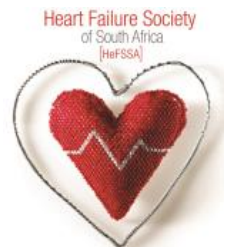


Stepwise approach to refractory oedema

Step 1: Intensification of oral loop diuretic therapy

Most patients can achieve adequate control of signs and symptoms of extracellular fluid volume expansion with typical diuretic doses given orally

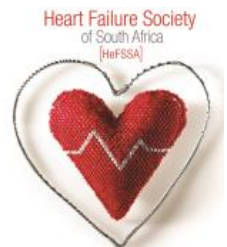
Patients who do not have an adequate response to oral loop diuretic therapy should have the dose increased until either a clinically significant diuresis is attained or the maximum daily dose has been reached



Stepwise approach to refractory oedema

Loop diuretics act rapidly, and therefore the patient should experience a notable increase in urine output within hours of an effective dose; if this does not occur, and especially if the body weight does not decline to indicate a reduction in extracellular volume, then doses can be escalated weekly, as long as adequate patient monitoring is available

When the diuretic response to oral loop diuretics is partial but inadequate (an increase in urine volume but little to no decrease in body weight), the net effect may be improved by repeating the same dose two or three times per day



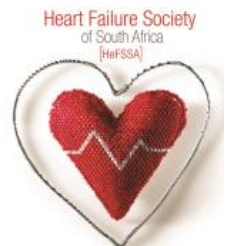
Stepwise approach to refractory oedema

Step 2: Combination oral diuretic therapy

When an adequate response to loop diuretics is not obtained, concurrent administration of a thiazide-like or thiazide-type diuretic to block distal sodium chloride reabsorption should be employed

Thiazides can produce a substantial additional diuresis when added to loop diuretics, even if kidney function is impaired

Drugs can be administered at the same time if given by the same route (IV or oral). If a thiazide is given orally in patients treated with an IV furosemide, the thiazide should precede the loop diuretic by 2-5 hours, since the peak effect of the thiazide is 4-6 hours after ingestion



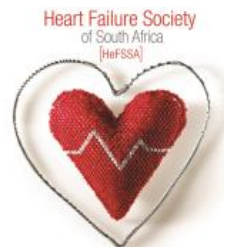
Stepwise approach to refractory oedema

Step 2: Combination oral diuretic therapy

Combination diuretic therapy can lead to a marked diuresis in which daily sodium and potassium losses can be greater than 300 mmol and 200 mmol: need careful monitoring of fluid and electrolyte balance

In hypokalaemic patients, consider adding a potassium-sparing diuretic first (e.g. amiloride or spironolactone)

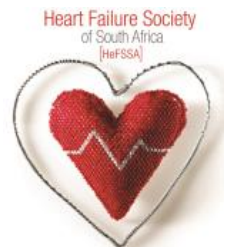
Mineralocorticoid receptor antagonist should be avoided in renal dysfunction



Stepwise approach to refractory oedema

Step 2: Combination oral diuretic therapy

Triple nephron blocking (loop diuretic + thiazide diuretic + potassium-sparing diuretic) should be considered in patients with refractory oedema and normal renal function



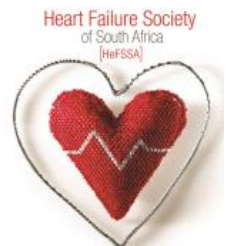
Stepwise approach to refractory oedema

Step 3: Intravenous loop diuretic bolus therapy

Patients with acute decompensated HF and hospitalised patients with refractory edema are typically treated with IV loop diuretics

The initial dose of IV loop diuretic should be approximately 2 or 2.5 times the patient's total maintenance daily oral

If there is little or no response to the initial dose, the dose should be doubled at two-hour intervals, as needed, up to the maximum recommended doses



Stepwise approach to refractory oedema

Step 3: Intravenous loop diuretic bolus therapy

Doses higher than the "maximum effective dose" often produce further diuresis, albeit with less sodium excretion per milligram of diuretic administered

Patients who do not have an adequate response to a maximal dose of one IV loop diuretic are unlikely to respond to another loop diuretic since their mechanisms of action are similar

In patients who fail to respond to maximal IV bolus doses of a loop diuretic, a thiazide diuretic can be coadministered

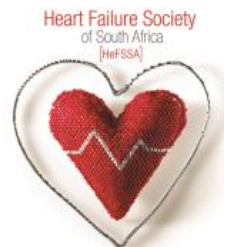


Stepwise approach to refractory oedema

Step 3: Intravenous loop diuretic bolus therapy

Resistance to oral diuretics is frequently reversible, and therefore, oral diuretic therapy may become more effective following removal of some of the oedema fluid with IV diuretics

Therefore, patients who are treated with an IV diuretic following failure of oral therapy can be given a repeat trial of oral diuretics once the hypervolemia has improved



Stepwise approach to refractory oedema

Step 4: Continuous IV infusion in patients who respond to bolus therapy

Patients with refractory oedema who respond to an IV bolus of a loop diuretic but need ongoing diuresis, may benefit from continuous loop diuretic infusion

Continuous diuretic therapy may be less ototoxic than bolus therapy and maintains a sustained effective rate of diuretic excretion



Stepwise approach to refractory oedema

Step 4: Continuous IV infusion in patients who respond to bolus therapy

A continuous infusion should **only** be used in patients who are first responsive to bolus loop diuretic therapy

The physiologic rationale for a continuous IV infusion compared with bolus therapy is related to maintenance of an effective rate of drug excretion and, therefore, inhibition of sodium chloride reabsorption in the loop of Henle over time

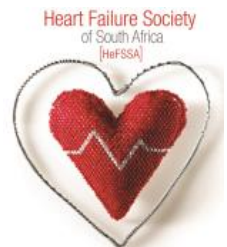


Stepwise approach to refractory oedema

Step 5: Patients unresponsive to IV diuretics

Ultrafiltration

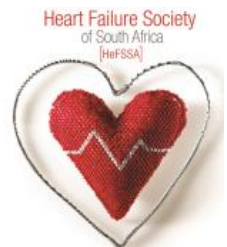
Dialysis



Benefit from a supine posture

Diuretic responsiveness can be influenced by posture, although the effects of posture have not been specifically studied in patients with refractory oedema (better outcomes, improved renal perfusion and presumably urinary diuretic delivery with supine position)

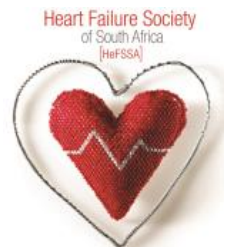
Supine position associated with improved creatinine clearance, diuretic response and lower plasma norepinephrine, renin, and aldosterone



Harmful/non-efficacious strategies

Renal dose dopamine increases incidence of arrhythmias

Albumin infusion for hypoalbuminaemia: no evidence of benefit



Conclusion

