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Refractory edema with congestive heart failure stepwise approaches nephrology perspectives

Abstract

Generalized edema occurs secondary to many clinical disorders; the usual management of edema is the using of diuretics. Diuretic resistance means failure to decrease the extracellular fluid volume despite the using of diuretics. Many factors are involved in the development of refractory edema, and the decreased response to the usual diuretic regimen, during management of diuretic resistance all these factors must be in consideration. Some pre-diuresis precautions, lab and imaging procedures are mandatory to ensure good effect of management. To use intermittent Intravenous Bolus versus Continuous IV Infusion Diuretic Therapy, which is better, which is safest? What is Single IV Effective Dose of Loop Diuretics What is Maximum IV Effective Dose of Loop Diuretics? If IV Furosemide is Ineffective, Can I Switch to Equivalent IV Dose of Bumetanide or Torsemide? When to Add Thiazide Diuretic? When to Add Spironolactone? IV High-Dose Furosemide and Hypertonic Saline Solutions, The new ERA. How to Monitor Response and Side Effects of IV Diuretic Therapy? All these questions are answered in the review article.

Keywords: refractory edema, congestive heart failure, furosemide-albumin infusion

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Abbreviations: CHF, congestive heart failure; HFSA, heart failure society of America; ADHF, acute decompensated heart failure; IV, intravenous; eGFR, estimated glomerular filtration rate; ACC/AHA, american college of cardiology/american heart association; HSS, hypertonic saline solution; BNP, brain natriuretic peptide; BUN, blood urea nitrogen

Introduction

Generalized edema occurs secondary to many clinical disorders, as heart failure, liver cirrhosis, nephrotic syndrome, and renal failure. The usual management of edema is the using of diuretics with other lines of precautions and steps of treatment specific for each clinical disorder. Diuretic resistance means failure to decrease the extracellular fluid volume despite the using of diuretics. The scope of this article is to discuss the cause of refractory edema to usual management with diuretics in patients with chronic congestive heart failure (CHF) and how to deal with it. Mechanism of actions, side effects of diuretics and other drug used in this approach is out of the scope of the article and will not discussed.

Mechanism of development of refractory edema

Many factors are involved in the development of refractory edema, and the decreased response to the usual diuretic regimen.

I. First factor is high salt intake which prevents net fluid loss even with adequate therapeutic doses of diuretics.[1]

II. Second factor that may contribute to refractory edema is decreased loop diuretic secretion. An important step in the mechanism of action of loop diuretics is that they enter the tubular lumen by secretion in the proximal tubule, not by glomerular filtration. After that loop diuretics inhibit the Na-K-2Cl carrier in the luminal membrane of the thick ascending limb of the loop of Henle, which will reduce NaCl reabsorption. Diuretic efficacy is mainly related to urinary excretion rates of the drug, rather than to its plasma concentrations.[2] In case of CHF, renal perfusion and tubular blood supply is decreased due to decreased cardiac output, which decrease the delivery of diuretics to their site of action causing insignificant effect. It is also well known that loop diuretics are highly (≥95 percent) protein bound, which keeps the diuretic within the intravascular space, which will ensure good delivery of the diuretic to the kidney. Hypoalbuminemia may occur in CHF if albumin is filtered in the urine secondary to high venous pressure. Secondary to this hypoalbuminemia; the degree of diuretic - protein binding is reduced, which will result in a larger extravascular space of distribution of the diuretic with a slower rate of delivery to the kidney, and then reduced diuresis. In addition, the filtered albumin in the urine secondary to high venous pressure may bind loop diuretics in the tubular lumen and interfere with its action.[3]

III. The third and one of the important causes of diuretic resistance is the use of nonsteroidal anti-inflammatory drugs, which reduce the synthesis of prostaglandins, which will affect diuretic responsiveness.[4]

IV. The fourth factor is that some patients with diuretic resistance have decreased natriuresis, despite adequate urinary delivery of the diuretic. This problem is often due to increased tubular sodium reabsorption in nephron segments other than the loop of Henle with the chronic use of diuretics (the diuretic braking phenomenon).[1,5] Increased tubular sodium reabsorption associated with the diuretic braking phenomenon may occur at different segments of the nephron:

a) In the proximal tubule, secondary to the activation of angiotensin II and Norepinephrine. The neurohumoral activation occurs secondary to the heart failure itself and also may occur as a consequence of diuretic-induced water and salt loss.[6]

b) In the distal tubule, a flow-dependent hypertrophy can occur with chronic loop diuretic therapy, which increases sodium reab-

sorption secondary to the increased activity of the sodium chloride cotransporter in the luminal membrane of the distal tubule cells and its hypertrophy.[7,8]

c) In the collecting tubules, due to increased mineral ocorticoid activity that occurs also secondary to neurohumoral activation as that affect sodium reabsorption in PCT.[4]

V. The fifth factor causing refractory edema is inadequate diuretic dose or frequency, and the non compliance of the patient for his prescribed doses.[3]

VI. The final and one of the most important factors is that in patients with CHF there may be decreased intestinal perfusion, reduced intestinal motility, and also intestinal mucosal edema, which will reduce the diuretic absorption, and hence diuretic delivery to the kidney and diuretic excretion rate.[9]

All these factors must be excluded during the stepwise approach of management of refractory edema in patients with CHF.

Stepwise approaches for management of refractory edema with CHF

Stepwise approaches for management of refractory edema with CHF are summarized in (Figure 1-3). It is important to know that these approaches are based on our clinical experience. No available enough data about target fluid loss or monitoring of overloaded resistant patients. Any physician can change any of the steps in our approach according the clinical situation and the need of the patient. The following approach is just only a skeleton that we will go around.

Pre-diuresis precautions (Figure 1)

It is important to ensure dietary sodium restriction, as increased sodium intake will cause refractory edema (refer to mechanism of development of refractory edema above). To estimate salt intake in CHF patients with refractory edema, a 24-hour urine should be collected. A value above 100mEq per day indicates that noncompliance with sodium restriction.[1] The 2010 Heart Failure Society of America (HFSA) guidelines on acute decompensated HF (ADHF) recommend a sodium intake of less than 2g/day. They even recommend greater sodium restriction in patients with recurrent or refractory volume overload. Water restriction may also be important.[10] Also stop all nonsteroidal anti-inflammatory drugs the patient uses, as they are of the important factors causing refractory edema (refer to mechanism of development of refractory edema above).[4] An important precaution is to exclude concomitant amino glycosides use, as this may increase the incidence of ototoxicity with the high doses of loop diuretics use[11] (refer to monitoring side effects (Table 1) and toxicity – ototoxicity below).

Pre-diuresis lab and imaging (Figure 1)

Pre-diuresis lab: Serum Albumin, urea/BUN, creatinine, Na, K, Ca, mg, uric acid, Hb, Ht%, and other lab investigations (as indicated).

Pre-diuresis imaging: Chest X-ray, ultrasound abdomen and pelvis, ECHO. The idea behind the pre-diuresis investigations is to have a baseline for all the parameters of the patient assessment that will be needed later to follow the response or to detect the side effects of the diuretics.

Posture during diuresis (Figure 2 & 3)

Patients with CHF cannot increase cardiac output in upright position; subsequently renal perfusion and urinary diuretic delivery will decrease. In addition, renal salt and water reabsorption increase. The efficacy of assuming a supine position was evaluated in a randomized trial. The supine position was associated with significantly higher mean creatinine clearance and diuretic response. The upright position was associated with significant increases in plasma norepinephrine, renin, and aldosterone; which is theoretically reasonable.[12]

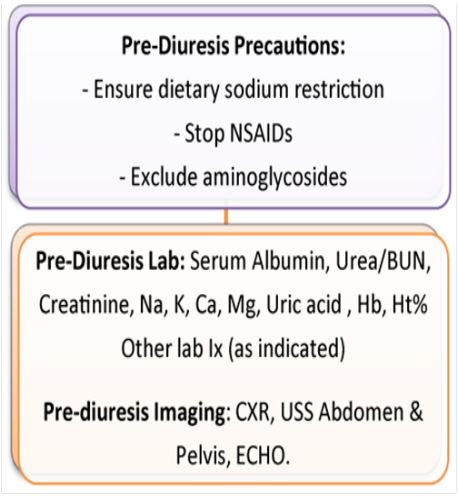

Figure 1 Pre-diuresis precautions, Lab & imaging investigations (refer to the paragraph for details).

Table 1 Monitoring Response and Side Effects of IV Diuretic Therapy

Lab	Na, K (daily)
	Urea/BUN, Creatinine (daily)
	Hb, Ht% (daily)
	ABG (daily)
	Ca, Mg
	Uric Acid
	Serum Albumin
	Other lab Ix (as indicated)
Radiology (as needed)	CXR
	USS Abdomen & Pelvis
	ECHO
Clinical	**Weight measurement**
	Should be performed at the same time each day, usually in the morning, prior to eating and after voiding
	Signs of hypovolemia (not less than 4 times/day)
	Weakness
	Hypotension
	orthostatic hypotension
	cool extremities
	+ elevated serum creatinine
	+ rapidly elevated Ht%
	Signs of ototoxicity (not less than 4 times/day)
	decreased hearing
	tinnitus
	deafness: transient (most lasting 30minutes to 24hours) or permanent deafness

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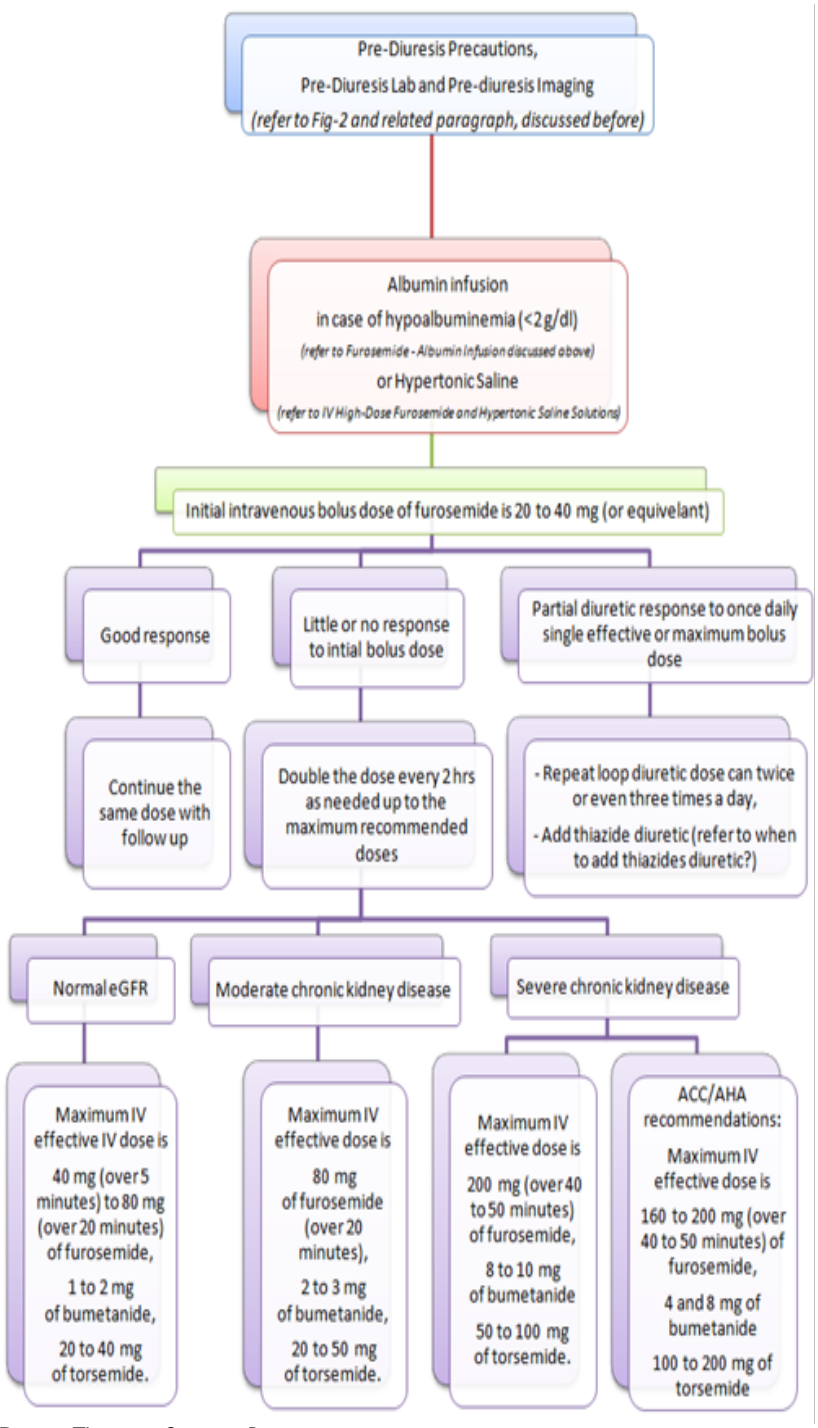

Figure 2 Intermittent IV Bolus Diuretic Therapy – Stepwise Regimen.

Furosemide-albumin infusion

As mentioned some patients with hypoalbuminemia may be resistant to the usual diuretic therapy (refer to mechanism of development of refractory edema above). Theoretically, infusion of the furosemide-albumin complex can increase diuretic delivery to the kidney by keeping furosemide within the vascular space.[13] However, subsequent studies found that the use of mixture of loop diuretic and albumin in hypoalbuminemic patients (secondary to cirrhosis or nephrotic syndrome), with mean plasma albumin 3.0g/dL, produced only a modest increase in sodium excretion compared with furosemide alone without an increase in the rate of furosemide excretion.[14,15] But the significance of infusion of loop diuretic plus albumin may appear in patients with refractory edema and severe hypoalbuminemia (plasma albumin less than 2.0g/dL). However, the evidence supporting this is weak as this has not been studied yet. It is important to know that there are different preparations of albumin; the most recommended in our case is the salt low salt albumin.

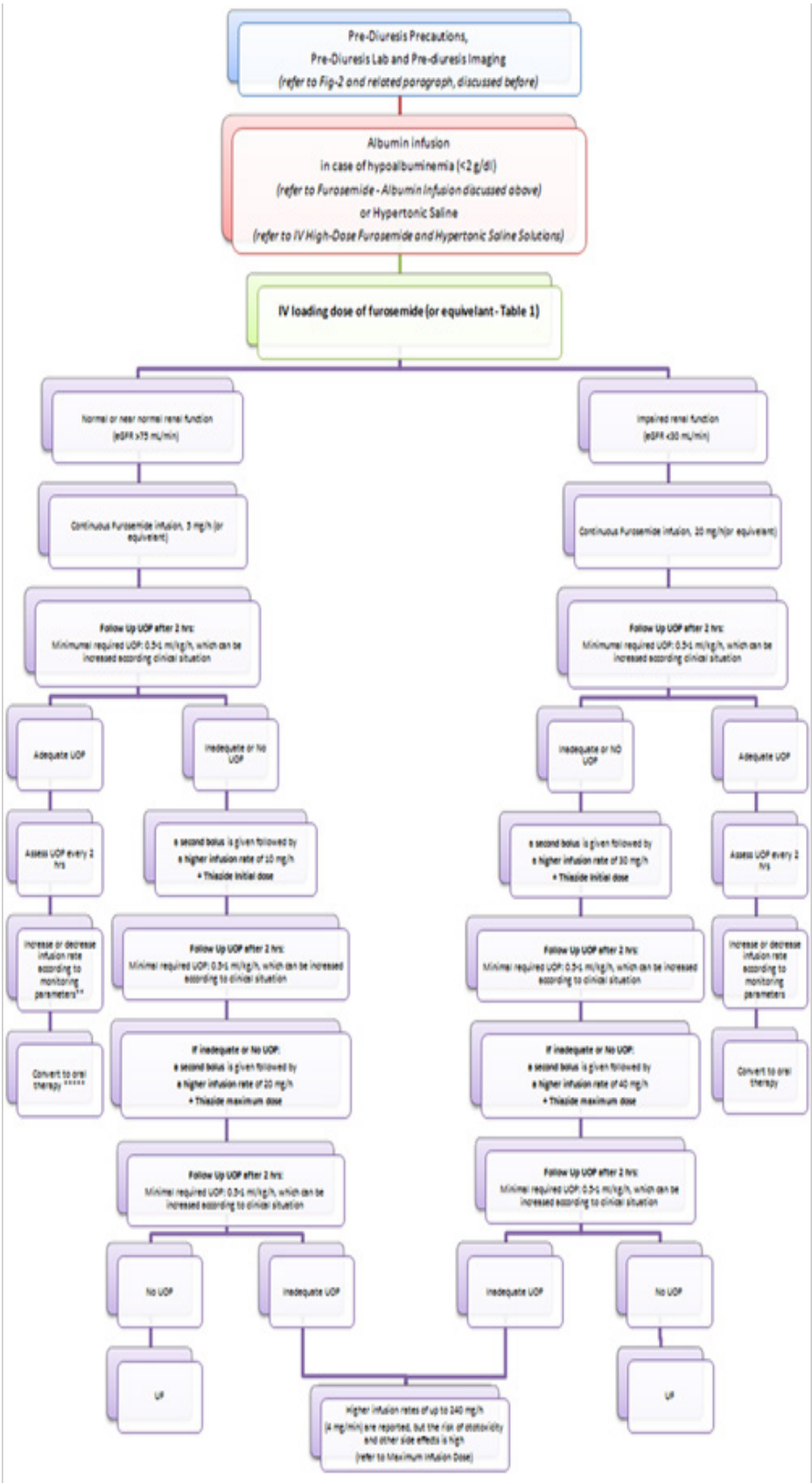

Figure 3 Continuous IV Infusion Diuretic Therapy – Stepwise Regimen.

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Intermittent intravenous (IV) bolus versus continuous IV infusion diuretic therapy

The efficacy of a continuous IV infusion compared with intermittent IV bolus therapy has been evaluated in randomized trials, and they appear to have similar efficacy. But a continuous intravenous infusion is safer, less ototoxicity (tinnitus and hearing loss) than bolus injections of loop diuretics (refer to monitoring side effects (Table 1) and toxicity–ototoxicity below).[16–18] Also continuous IV infusion is able to maintain an effective stable rate of drug excretion and therefore a maintained inhibition of sodium chloride reabsorption in the loop of Henle through the duration of therapy. In contrast, intermittent IV bolus therapy will lead to initially higher rate of diuretic excretion, followed thereafter by lower rates; as a result, sodium excretion is at maximal levels for the first two hours but then gradually falls.[18]

Single and maximum effective IV dose of loop diuretics: Before discussing the stepwise bolus and continuous infusion approaches, we have to know first the concepts of single and maximum IV effective dose of loop diuretics.

Single IV effective dose of loop diuretics: Diuretics have a dose-response curve, as there will be no natriuresis seen until a threshold rate of drug excretion in urine is attained. For example, if a patient does not respond, i.e. no diuresis, to 40mg of furosemide, the dose may not have exceeded the threshold of the single effective dose, so this single dose (40mg) should be increased to 60 or 80mg, rather than giving it twice a day. Once a single effective dose has been determined, i.e. there is a response of diuresis; it should be administered multiple times per day, with a frequency which is individualized according to the diuretic needs of the patient.[18–20] So simply, single effective dose is the least dose that will cause response i.e. diuresis.

Maximum IV effective dose of loop diuretics: The maximum IV effective dose is the dose at which loop sodium chloride transport is completely inhibited. So administering higher doses will produce little or no further diuresis, a plateau is reached, but it may increase the risk of toxicity and side effects. Maximum IV effective dose differs according the cause of edema and renal function of the patient. In CHF patients with normal or near normal estimated glomerular filtration rate (eGFR), the maximum effective IV dose is 40 to 80mg of furosemide, 1 to 2mg of bumetanide, and 20 to 40mg of torsemide.[3] In chronic kidney disease, the maximum IV effective dose varies with the severity of the kidney disease (eGFR). In moderate chronic kidney disease; maximum IV effective dose is 80mg of furosemide, 2 to 3mg of bumetanide, and 20 to 50mg of torsemide. In severe chronic kidney disease; it is 200mg of furosemide, 8 to 10mg of bumetanide, and 50 to 100mg of torsemide.[20] The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline on heart failure recommended maximum IV effective dose of furosemide (160 to 200mg), bumetanide (4 and 8mg), and torsemide (100 to 200mg) for patients with severe heart failure and a substantially reduced GFR. This recommendation differs in the dose of bumetanide and torsemide than other literature.[21] The rate of IV bolus administration is important to be slow to decrease the incidence of side effects. A bolus dose of about 20 to 40mg of furosemide is better to administered over 5minutes, while a bolus dose of 60 to 120mg is better to administered over 20minutes, and finally a bolus dose of 160 to 200mg of furosemide is better to be given over 40 to 50minutes.

Intermittent IV bolus diuretic therapy – stepwise regimen (Figure 2)

Start IV bolus loop diuretic targeting to reach the single effective dose (mentioned above). The usual initial intravenous bolus dose of furosemide is 20 to 40mg. Next action depends on the response of the patient:

If good diuretic response continues the same dose with follow up (refer to monitoring side effects – (Table 1) and toxicity – ototoxicity below). If little or no response to the initial bolus dose, the dose should be doubled at two-hour intervals as needed up to the maximum recommended doses (discussed above).[18,19,21] If partial diuretic response to once daily single effective or maximum bolus dose, different strategies can be done to increase the response, for example the loop diuretic dose can be repeated twice or even three times a day,[7] and also adding a thiazide diuretic can add a lot of benefit (refer to when to add thiazides below).

Continuous IV infusion diuretic therapy – stepwise regimen (Figure 3)

Loading bolus dose: Use of a continuous IV infusion requires the patient to be responsive to loop diuretics. Thus, a continuous IV infusion should not be tried in CHF patients who have not responded to repeated bolus doses up to the maximum bolus doses (discussed above). IV bolus therapy will lead to initially higher rate of diuretic excretion, which will lead to high initial rates of urinary diuretic and sodium excretion.[22]

Continues IV infusion therapy: If there is a good response to the initial loading bolus dose, then it must be followed by the continuous IV infusion, which dose is dependent on the renal function of the patient. A start of continues infusion dose of approximately 5mg/h is reasonable in patients with normal or near normal renal function (eGFR>75mL/min) and of approximately 20mg/h in patients with impaired kidney function (estimated GFR<30mL/min).[23]

Maximum infusion dose: Higher infusion rates of up to 240mg/h (4mg/min) are reported, but the risk of ototoxicity and other side effects is high and the use of this high infusion rate must be weighed against alternative strategies such as the addition of a thiazide diuretic or fluid removal via ultrafiltration. This high infusion rate is not recommended.[3,11] Acute and Chronic kidney diseases also increase the risk of ototoxicity. Permanent deafness has been reported in patients with acute kidney injury receiving furosemide continuous IV infusion dose of 80 to 160mg/h.[24] (Refer to monitoring side effects (Table 1) and toxicity – ototoxicity below).

If IV Furosemide is Ineffective, Can I Switch to Equivalent IV Dose of Bumetanide or Torsemide? (Table 2)

Table 2 Equivalent doses of other loop diuretics to furosemide dose

Furosemide IV	Torsemide IV / PO	Bumetanide IV / PO
20 mg	10 mg	1 mg
40 mg	20 mg	2 mg

If the patient is resistant to IV furosemide, it is not likely to respond to an equivalent intravenous dose of any other loop diuretic as bumetanide or torsemide.[3]

When to add thiazide diuretic?: Sequential nephron blockade is a way to overcome the pathophysiology of diuretic resistance. Sequential nephron blockade means a parallel use of different diuretics acting at different segments of the nephron; therefore producing an additive or synergistic diuretic response.[25] As mentioned above, long term administration of a loop diuretic will increase the distal

sodium delivery, a flow-dependent hypertrophy in distal convoluted tubule can, which increases sodium reabsorption secondary to the increased activity of the sodium chloride cotransporter in the luminal membrane of the distal tubule cells and its hypertrophy.[7,8] Therefore adding thiazide diuretic (in patient with known long term use of loop diuretics) will block the distal reabsorption of sodium, leading to a better diuretic effect. Also thiazides will add benefit if added to cases with partial diuretic response to the single effective/maximum bolus dose, or cases with partial diuretic response to continuous IV infusion diuretic therapy.[26] The timing of combination therapy depends upon the route by which the diuretics are given. Loop and thiazides diuretics can be administered at the same time if given by the same route i.e. intravenous or oral. If, however, a thiazide diuretic is given orally, so the thiazide diuretic should precede the loop diuretic by 2-5hours, since the peak effect of the thiazide is 4-6hours after ingestion.[27]

When to add spironolactone?: Utilization of spironolactone may be more effective when circulating aldosterone concentrations are increased (which is usually the case in more advanced CHF, such as New York Heart Association classes III and IV).[28] The associated reduction in collecting tubule sodium reabsorption and potassium secretion enhanced by spironolactone (Figure 1) can both increase the diuresis and minimize the degree of potassium wasting. Therefore, it may be highly suggested to start spironolactone in patients who have developed low or low-normal serum potassium with loop diuretic therapy alone. It is also reasonable to start a spironolactone before the addition of a thiazide diuretic, as combination therapy of loop diuretics and thiazides can lead to a marked diuresis and hypokalemia.[27]

IV high-dose furosemide and hypertonic saline solutions (Figure 2 & 3): Excessive diuresis induces hypovolemia and reduced cardiac output, which will diminish GFR.[29] So, theoretically it is reasonable that maintaining an adequate intravascular volume during high dose diuretic therapy will maintain good renal perfusion, which in turn will reduce the incidence and frequency of side effects. Different studies approved that this can be achieved by combining high dose furosemide with the administration of hypertonic saline solution (HSS). A study showed that the combination of high dose furosemide intravenous infusion (250-2,000mg/d) with the administration of small volume HSS (150mL of 1.4%-4.6% NaCl) twice a day for 6 to 12days improves clinical signs and symptoms of CHF; also it improves the severity of the illness (NYHA class).[30]

Another study compared 30-minute intravenous infusion of furosemide (500-1,000mg) plus HSS (150mL of 1.4%-4.6% NaCl) twice daily in one group of patients, versus an intravenous bolus infusion of furosemide alone in another group. Symptoms improved in both groups, but the severity of the illness (NYHA class) was greatly improvement in patients receiving HSS. Also urine output and sodium excretion were significantly of a greater degree in the group treated with HSS and furosemide than in those received furosemide alone. Serum creatinine level decreased in patients receiving HSS and furosemide.[31] Also it was proved that combined high furosemide IV dose and HSS has long-term benefits, regarding reducing mortality and hospital readmission rates.[32]

A randomized double blind study was done to detect the effect of the furosemide and HSS infusion on brain natriuretic peptide (BNP) plasma levels in patients with advanced CHF (NYHA functional class IV),[33] as it is well known that natriuretic peptides have a very powerful prognostic markers.[34] The results of the study showed that plasma levels of BNP were significantly lower in the HSS group at 6days and at 30days after treatment.[33] Also combined therapy reduces the plasma levels of markers of neurohormonal and inflammatory activation.[35] To conclude, studies examined the use of intravenous high dose furosemide in combination with small volume HSS in management of refractory edema with CHF; suggest that this combination therapy may be of high benefit as a step of management of these cases. In my own opinion, HSS may be of high value if the treated patient is already hyponatremic, or having a low border line blood pressure which may exacerbate the depletion of the intravascular effective circulating volume with the used aggressive diuresis.

Effect on renal function

I. The blood urea nitrogen (BUN) and serum creatinine often rise during diuretic treatment of HF and careful monitoring is recommended. Heart Failure Society of America2010 Comprehensive Heart Failure Practice Guidelines for management of patients with HF with elevated or rising BUN and/or serum creatinine include the following:

II. Other potential causes of kidney injury (e.g., use of nephrotoxic medications, urinary obstruction) should be evaluated and addressed.

III. Patients with severe symptoms or signs of congestion, particularly pulmonary edema, require continued fluid removal independent of changes in GFR. In the presence of elevated central venous pressure, renal function may improve with diuresis.

IV. If the BUN rises and the serum creatinine is stable or increases minimally, and the patient is still fluid overloaded, the diuresis can be continued to achieve the goal of eliminating clinical evidence of fluid retention with careful monitoring of renal function.

V. If increases in serum creatinine appear to reflect intravascular volume depletion, then reduction in or temporary discontinuation of diuretic and/or angiotensin converting enzyme (ACE) inhibitor/angiotensin II receptor blocker therapy should be considered. Adjunctive inotropic therapy may be required.[10]

VI. As stated in the American College of Cardiology/American Heart Association HF guideline, adverse effects must be monitored closely:

VII. Electrolyte imbalances (particularly hypokalemia, hypomagnesemia, and metabolic alkalosis) that develop during diuresis should be promptly treated while the diuresis is continued.

VIII. If hypotension or worsening renal function develops before the goals of treatment are achieved, the diuresis may be slowed. Diuresis should be maintained until fluid retention is eliminated even if this results in asymptomatic mild to moderate decreases in blood pressure or renal function. Excessive concern about hypotension and azotemia can lead to underutilization of diuretics and persistent volume overload. Persistent volume overload contributes to continued symptoms, may reduce the efficacy of drug therapy for HF, and, persistent volume overload may be associated with increased mortality.[23]

Ototoxicity

Monitory the evidence of toxicity during the therapy period is mandatory. Decreased hearing, tinnitus, or deafness transient (most lasting 30minutes to 24hours) or permanent deafness.[17] As mentioned above the mechanism of action of loop diuretics is mediated by a Na-K-2Cl cotransporter inhibition at the ascending loop of Henle. A secretory isoform of this cotransporter is present in the inner ear

and plays an important role in the composition of endolymph. It was approved that inactivation of this transporter in mouse led to reduced endolymph secretion, structural damage to the inner ear, and deafness.[36]

The following are the factors which may increase the risk of ototoxicity in CHF patients receiving loop diuretics:

i. Patients who are treated with high IV dose of bolus therapy are at high risk of developing ototoxicity. Bolus IV furosemide doses of 160 to 200mg (and the equivalent doses of bumetanide and torsemide) can cause transient tinnitus. This effect can be minimized by giving the dose more slowly as mentioned above in bolus IV therapy.[17]

ii. Although the risk of ototoxicity may be reduced by a continuous infusion rather than bolus therapy.[22,17] But continuous diuretic infusion can also cause ototoxicity especially with rates above 4mg/min.[3,11]

iii. Risk of ototoxicity is increased if the patient is already taking other ototoxins such as amino glycosides antibiotic.[11]

iv. Acute and Chronic kidney diseases also increase the risk of ototoxicity. Permanent deafness has been reported in patients with acute kidney injury receiving furosemide continuous IV infusion dose of 80 to 160mg/h.[24]

The decision of replacing IV diuretic therapy by the oral one (Table 3) depends on the clinical situation and the clinician sense. No special recommendations for when to switch from IV to oral loop diuretics. When converting to oral therapy, the dose should usually be doubled for oral furosemide, a twofold higher dose than the intravenous dose is a reasonable starting point as its mean bioavailability is only about 50%, with substantial inter patient and intra patient variability (range 10 to 100 percent).Further dose adjustments may be needed according to the patient response, the dose of diuretic should be adjusted once the patient's dry body weight is attained to the minimum dose required to maintain dry body weight. In contrast, the intravenous and oral doses are similar in patients treated with bumetanide or torsemide, which have higher rates of oral bioavailability (70 to 95 percent and 80 to 90 percent, respectively), but also with further dose adjustments may be needed according to the patient response.[3,23,37]

Table 3 Switching from IV to Oral Loop Diuretics

When to start?	It depends on the clinical decision of the treating physician.
Dosage	The oral dose of Furosemide is approximately twice the intravenous dose. The oral dose of Torsemide & Bumetanide is the same as the intravenous dose.
Important Considerations	In our mind it is important to try at least one to two days on oral therapy will the patient still in hospital. This facilitates the adjustment of the oral dose to avoid over or under diuresis. No special recommendations. But mainly the dose of diuretic should be adjusted once the patient's dry body weight is attained to the minimum dose required to maintain dry body weight.

Can we use dopamine to enhance diuresis?

There is no strong evidence conformation about the significant benefit and effect from intravenous dopamine (natriuretic and renal vasodilator activity), few data and reports are available on this subject.[38]

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None.

Conflict of interest

The author declares no conflict of interest.

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