Resistance to Loop Diuretics: How to Address it in the Current Scenario?

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Persistent congestion despite the use of loop diuretics (LD) is one of the most important challenges in the management of acute heart failure (HF) and is associated with a worse prognosis. One of the main reasons for this persistence in congestion is resistance to LD, which can be defined as a reduction in sensitivity to diuretics, with reduced natriuresis and diuresis and limitation of reaching euvolemia – LD can reach up to 1/3 of patients admitted for acute HF and independently increases the risk of death by 1.37 times.[1-3]

Regarding the mechanisms of LD, there are several factors possibly involved, such as bioavailability of the diuretic and delivery to its site of action, neurohormonal activation, compensatory tubular adaptation, and interaction with other drugs (Table 1). It is worth mentioning that, in patients with systemic congestion Importantly, it is possible that the occurrence of edema of intestinal loops, impairing the absorption of diuretics, may be one of the factors associated with less action of oral furosemide.[4] Furthermore, the presence of chronic kidney disease associated with HF leads to a lower glomerular filtration rate and, consequently, less effect of diuretics on the nephron. Hypoalbuminemia is also associated with greater resistance to LD, given the greater affinity of diuretics to albumin-bound molecules and a lesser effect of the diuretic on its site of action, which is the nephron.[5-8]

Resistance to diuretics may also occur due to greater absorption of sodium and chlorine in the proximal tubule, interfering with the sodium-potassium-chlorine cotransporter system in the distal nephron and minimizing the effect of the loop diuretic. Compensatory tubular readaptation is another mechanism that explains the lower response to the diuretic and occurs when there is an increase in sodium reabsorption in the proximal tubule. At the same time, chronic use of LD - which inhibit sodium uptake in the loop of Henle - leads to an increase in the amount of sodium in the distal tubule with compensatory hyperplasia and hypertrophy.[8-10]

Neurohormonal activation is directly linked to the renin-angiotensin-aldosterone system and LD can activate this system through a variety of mechanisms, leading to greater sodium reabsorption and sodium retention after diuretic use, as well as the drop in urinary volume after several doses of diuretic. Finally, interactions with other medications can also impair the effect of LD, such as the use of non-steroidal anti-inflammatory drugs.[8,9]

To overcome diuretic resistance, it is essential to understand the resistance mechanisms and look for the cause, which can be different depending on the particularities of each patient. Increasing the dose of the diuretic, opting for continuous infusion, performing sequential nephron blockade or even using hypertonic saline solution (HSS) are some options to manage cases in which resistance to LD is identified.[11]

In the CLOROTIC and ADVOR studies, the association of diuretics from other classes together with LD in patients with acute HF was associated with a better diuretic response.[11,12]

The CLOROTIC study included patients with decompensated HF and persistent congestion, and the association of oral hydrochlorothiazide with intravenous furosemide resulted in greater weight loss, greater urinary output, and decongestion, but there was worsening of renal function more frequently in

Table 1 - Mechanisms of resistance to loop diuretics[8,9]

Bioavailability of the diuretic and less effect on the nephron	Poor adherence to diuretics Very low doses Malabsorption (e.g. edema of intestinal loops) Hypoalbuminemia Nephrotic syndrome Hepatical cirrhosis Renal malperfusion
Neurohormonal activation	Activation of the RAAS Sympathetic nervous system activation
Compensatory tubular adaptation	Compensatory sodium retention after the effect of the diuretic Hypertrophy and hyperplasia of distal tubule cells Increased sodium absorption in the proximal and distal tubule
Interaction with other drugs	Ex: NSAIDs
Incorrect diagnosis	lymphatic edema Intravascular volume depletion and third space edema
Poor adherence to sodium and water restriction recommendations	
Chronic Renal Failure	

RAAS: renin-angiotensin-aldosterone system; NSAIDs: non-steroidal anti-inflammatory drugs.

Keywords

Diuretics; Resistance; Refractoriness.

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Manuscript received November 23, 2023, revised manuscript December 16, 2023, accepted December 16, 2023

DOI: https://doi.org/10.36660/abchf.20230090

patients who received thiazide diuretics, with no difference in mortality or risk of hyponatremia or hypokalemia.[11,12]

The ADVOR study evaluated whether the combination of acetazolamide, a carbonic anhydrase inhibitor that reduces sodium absorption in the proximal tubule, could improve the response to LD and lead to greater and faster decongestion in patients with acute HF and volume overload. In this study, the use of a loop diuretic with a carbonic anhydrase inhibitor resulted in greater urine output and natriuresis, findings consistent with greater diuretic efficacy, with no significant difference in worsening renal function, hypokalemia or hypotension.[13]

Furthermore, quantifying urinary sodium can also contribute to evaluating the response to diuretics, as demonstrated in the ADVOR study and the PUSH-AHF study. In this, the investigators evaluated the effectiveness of diuretic therapy guided by natriuresis and the early and repeated quantification of urinary sodium associated with subsequent adjustments of diuretic treatment led to a better diuretic response in the first 48 hours of treatment, with no impact on mortality or re-hospitalization.[13,14]

Another alternative is the use of HSS associated with high-dose intravenous furosemide. Despite little evidence for its use, the rationale for its use is the osmotic effect, mobilizing extravascular fluid and correcting hyponatremia and hypochloremia which, as described in the resistance mechanisms previously, may be linked to diuretic resistance.[14]

Furthermore, SGLT2 inhibitors, despite not being a class of diuretics per se, among other mechanisms of action, inhibit the reabsorption of glucose in the proximal convoluted tubule, resulting in glycosuria. As shown in the DICTATE-AHF study, this class of medications may also contribute to diuretic efficacy by increasing natriuresis and diuresis for the same dose of loop diuretic, reducing the total dose and duration of loop diuretic use, as well as the length of hospitalization in acutely decompensated HF patients.[15,16]

In cases of refractory congestion, management can be used with a continuous infusion of furosemide at a dose of 40 to 150 mg/hour associated with sequential nephron blockade with a combination of spironolactone and hydrochlorothiazide. In cases of anasarca or refractory ascites and severe hyponatremia, paracentesis must be performed to reduce intra-abdominal pressure; Hypertonic sodium chloride solution is also suggested to increase the plasma filling rate by mobilizing fluid from the extracellular to the intracellular environment. When renal replacement therapy is indicated, ultrafiltration is associated with it; However, it is worth highlighting that the use of ultrafiltration has not been shown to be superior to diuretics in decongesting and progressing decompensated patients, in addition to having a greater potential for complications.[2,6,7]

A suggested flowchart covering this new recent evidence is found in figure 1.

Conclusion

Resistance to diuretics is a frequent reality in many patients with HF and is associated with a worse prognosis. Several recent studies have addressed this problem by seeking alternative treatments for LD, either with more frequent monitoring or using natriuresis to help when combining diuretics. It is always important to seek the treatment of congestion with adequate doses of LD, association with SGLT2 inhibitors and, in refractory cases, consider the association of other classes of diuretics such as acetazolamide or thiazides.

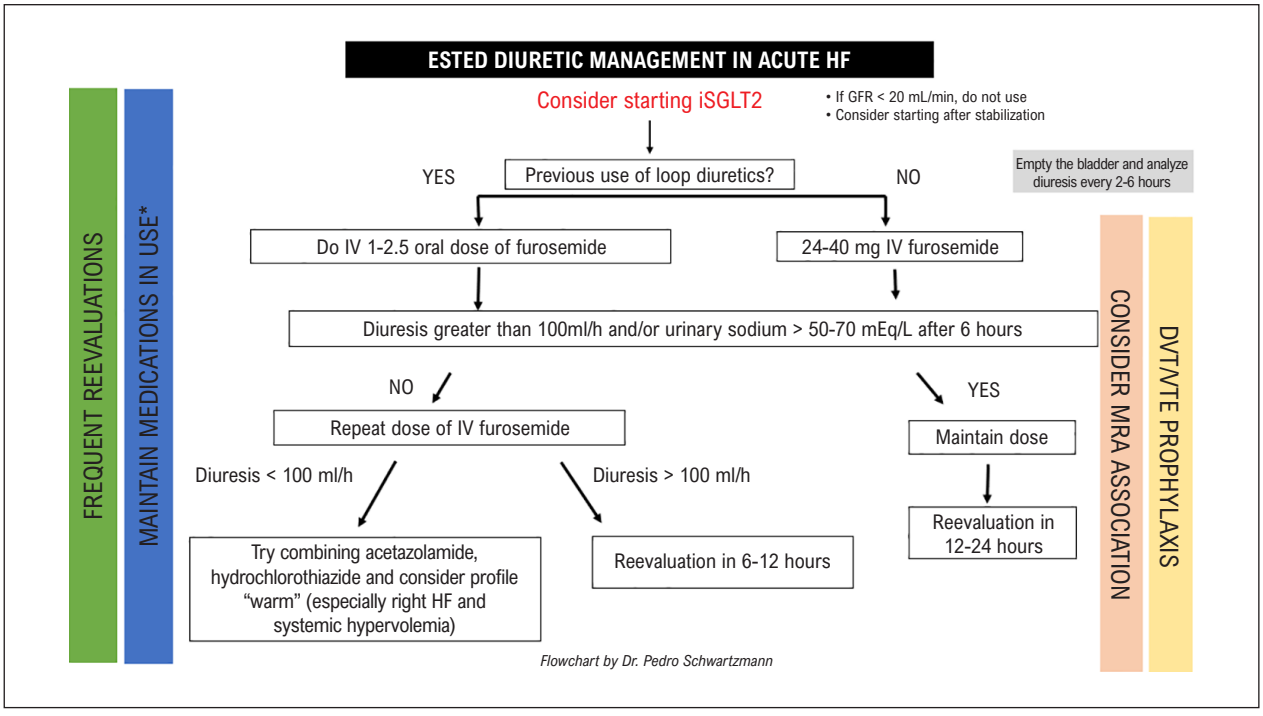

Figure 1 – *Diuretic therapy management in acute heart failure.*

Author Contributions

Writing of the manuscript and Critical revision of the manuscript for content: Savaris SL, Andrade FA, Schwartzmann PV.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

Sources of funding

There were no external funding sources for this study.

Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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