Int J Heart Fail. 2026 Jan;8(1):91-94
https://doi.org/10.36628/ijhf.2025.0088
pISSN 2636-154X·eISSN 2636-1558

International Journal of Heart Failure
IJHF

Letter

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# Salvaging Diuretic-Resistant Advanced Heart Failure With Acetazolamide: A Bridge-to-Transplant Case

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OPEN ACCESS

**Received:** Oct 19, 2025
**Revised:** Nov 9, 2025
**Accepted:** Nov 30, 2025
**Published online:** Jan 12, 2026

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## INTRODUCTION

Residual congestion is a key determinant of worsening heart failure (HF).[1] Intravenous loop diuretics remain the mainstay of decongestive therapy in HF. However, their efficacy declines with chronic diuretic exposure, neurohormonal activation, and tubular adaptation, leading to diuretic resistance. Adjunctive thiazides or sodium-glucose cotransporter 2 (SGLT2) inhibitors may transiently augment natriuresis but are often limited by renal dysfunction or electrolyte imbalance.[2]

Acetazolamide, a carbonic anhydrase inhibitor acting on the proximal tubule, enhances distal sodium delivery and bicarbonate excretion, thereby improving loop diuretic efficacy.[1] In the ADVOR trial, adjunctive intravenous acetazolamide in combination with standardized loop therapy accelerated complete decongestion within 72 hours and shortened hospital stay without an increase in renal adverse events.[3] However, evidence in advanced, inotrope-dependent HF remains limited.

We report a case in which acetazolamide effectively reversed diuretic resistance and achieved sustained decongestion in an INTERMACS 3 patient awaiting heart transplantation, demonstrating the feasibility of acetazolamide use as adjunctive therapy in advanced HF.

## CASE

A 67-year-old cachectic woman (body mass index [BMI] 21.3kg/m$^2$, blood type B Rh+) presented with progressive dyspnea (New York Heart Association [NYHA] class IV) refractory to optimized guideline-directed medical therapy, including 4-pillar therapy, with vericiguat as adjunctive treatment. Her renal function was moderately reduced (estimated glomerular filtration rate$_{\text{Chronic Kidney Disease Epidemiology Collaboration}}$ [eGFR$_{\text{CKD-EPI}}$] 44 mL/min/1.73 m$^2$) at presentation. She had idiopathic dilated cardiomyopathy diagnosed in 2021 and was repeatedly hospitalized for worsening HF despite high-dose loop diuretics (oral furosemide 80 mg/day with intermittent intravenous bolus as needed). Given her clinical course, she was referred for heart transplant candidacy.

Chest radiography showed cardiomegaly, pulmonary edema with bilateral pleural effusions (**Figure 1A**). Echocardiography revealed a markedly dilated left ventricle (left ventricular end-diastolic diameter/end-systolic diameter 72/63 mm), severe global hypokinesia with a left ventricular ejection fraction of 32%, and severe secondary mitral regurgitation.

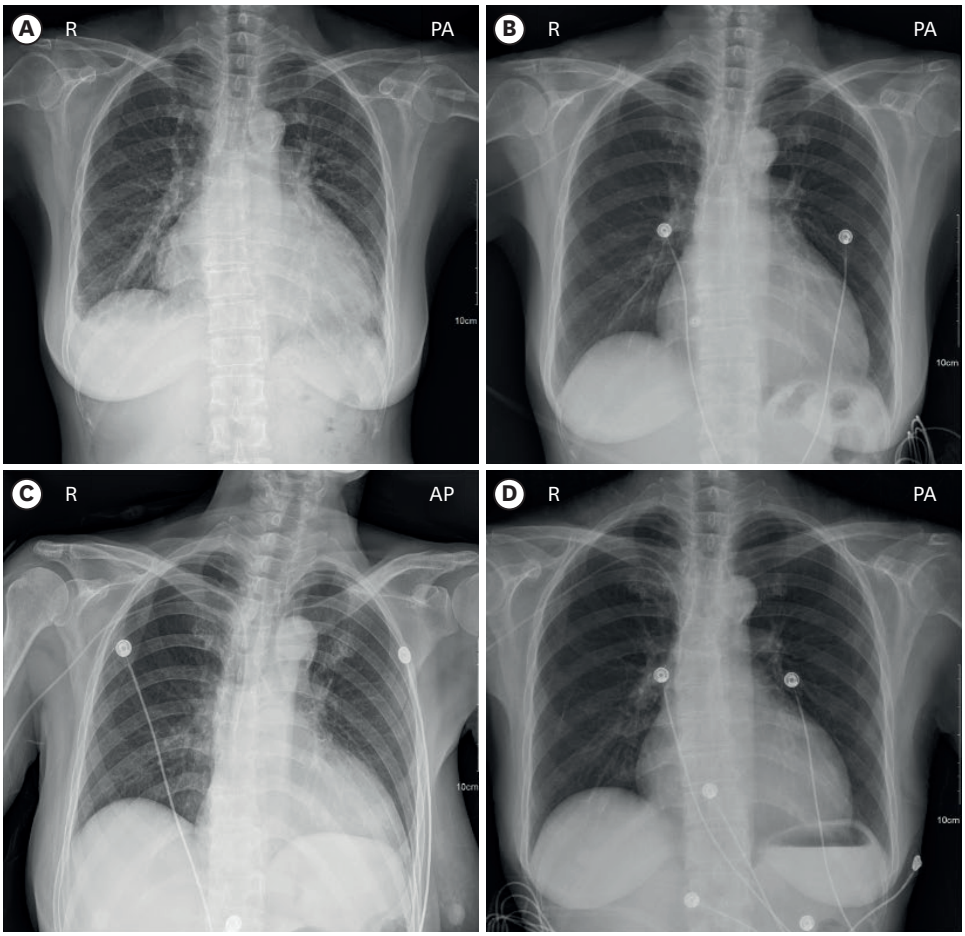


**Figure 1.** Change in chest radiography. (A) At the time of referral, (B) during initial decongestive response, (C) at the time of recurrent congestion, and (D) after acetazolamide initiation and achievement of clinical euvolemia before heart transplantation.
R = right; PA = posteroanterior view; AP = anteroposterior view.

While maintaining dapagliflozin and low-dose sacubitril/valsartan (25 mg daily), intensive decongestion therapy was initiated upon inpatient admission, with an escalation of loop diuretics. Initially, oral furosemide 80 mg/day was administered, but as the patient continued to exhibit signs of worsening HF and persistent congestion, treatment was adjusted. The loop diuretics was switched to torsemide 10 mg twice daily to improve bioavailability, and hydrochlorothiazide 12.5 mg twice daily was added to achieve a synergistic effect. Despite these adjustments, the patient continued to require daily intermittent intravenous bolus furosemide, and symptoms of orthopnea and dyspnea persisted. Given the patient's poor oral intake due to cachexia and ongoing volume overload, total parenteral nutrition was initiated to support nutrition, and low-dose dobutamine (2.8 μg/kg/min) was started.

Treatment initially appeared effective (**Figure 1B**). N-terminal pro-B-type natriuretic peptide (NT-proBNP) decreased from 20,427 to 4,432 pg/mL, but the effect waned within days, with NT-proBNP rebounded to 11,283 pg/mL. The patient maintained a low urine output of approximately 1.5 L per day, while congestion persisted (NYHA III–IV) with continued complaints of orthopnea and insomnia (**Figure 1C**). Additional intravenous continuous furosemide infusion (120 mg daily) concurrently with intermittent bolus was administered.

The patient consistently demonstrated signs of diuretic resistance, as evidenced by persistent fluid overload and difficulty in achieving optimal decongestion. Further dobutamine escalation was limited by dose dependent increases in non-sustained ventricular tachycardia. Considering the patient's low BMI and the ceiling effect of furosemide, alternative decongestive strategies were pursued rather than additional dose escalation. This prompted the introduction of intravenous acetazolamide 500 mg once daily, as supported by the ADVOR trial, with the patients' elevated serum bicarbonate levels (total $CO_2$ [$tCO_2$] 33 mmol/L) reflecting diuretic resistance. Within 48 hours, the patient's daily urine output exceeded 2.5 L, and NT-proBNP fell to 7,350 pg/mL. Symptoms markedly improved, corresponding to NYHA class

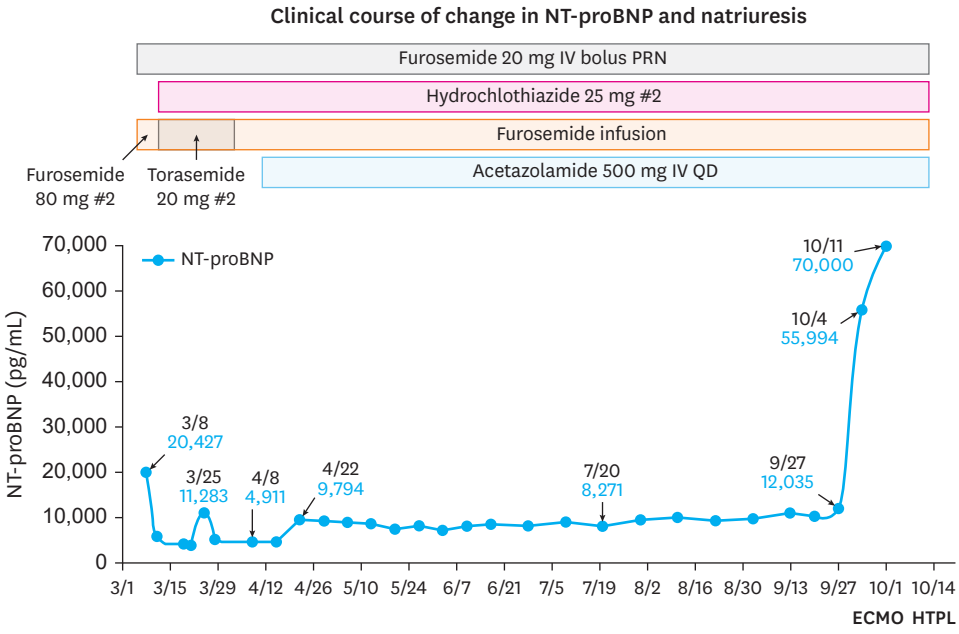


**Figure 2.** Clinical course and changes in NT-proBNP in relation to diuretic adjustments. Serial changes in NT-proBNP (blue) from March to October 2024.
NT-proBNP = N-terminal pro-B-type natriuretic peptide; PRN = as needed; IV = intravenous; QD = once daily; ECMO = extracorporeal membrane oxygenation; HTPL = heart transplantation.

I–II status at follow-up. Her renal function improved from 44 to 66 mL/min/1.73 $m^2$ while electrolytes remained stable throughout treatment.

After stabilization, attempts were made to gradually reduce dobutamine. However, even subtle reductions led to symptom progression, worsening kidney function, and decreased urine output, indicating insufficient systemic perfusion, thereby confirming persistent inotropic dependence. Classified as INTERMACS Profile 3 with end-stage HF highly dependent on inotropic support, she was maintained on dobutamine, continuous furosemide infusion, twice-daily intravenous boluses, and adjunctive acetazolamide infusion once daily during the pre-transplant period (**Figure 2**).

Clinical euvolemia was well maintained, follow-up imaging confirmed resolution of pleural effusions (**Figure 1D**). She remained hemodynamically stable for approximately 4 months under continuous inotropic support and adjunctive acetazolamide, which was administered daily without interruption throughout this time. Subsequently, abrupt pump failure developed and necessitating extracorporeal membrane oxygenation, at which point all diuretics were discontinued as adequate diuresis was achieved with effective left ventricular unloading. Serial monitoring confirmed stable acid-base status, electrolytes, and renal function, with no adverse events observed. Heart transplantation was successfully performed in he ultimately underwent successful heart transplantation in October 2024, followed by an uneventful postoperative recovery.

### Ethical approval statement

This case report complied with the principles of the Declaration of Helsinki, and written informed consent for publication was obtained from the patient. However, this has not been approved by an ethical board.

## DISCUSSION

This case illustrates the potential utility of acetazolamide in diuretic-resistant advanced HF, particularly in patients with loop diuretic-induced metabolic alkalosis and refractory congestion.

Under normal physiology, approximately two-thirds of glomerular-filtered sodium is reabsorbed in the proximal nephron.[4] However, in the neurohormonally activated state of HF, enhanced proximal tubular sodium reabsorption is mediated by angiotensin II–dependent NHE3 and $Na^+/HCO_3^-$ cotransport, leading to reduced distal sodium delivery and loop diuretic efficacy.[5] This mechanism was reflected in the ADVOR trial, in which the loop-diuretic-only group showed progressive bicarbonate elevation, a marker of persistent neurohormonal activation and enhanced proximal sodium reabsorption, that further attenuates the diuretic response despite intensified therapy.[3,5] Acetazolamide counteracts this process by inhibiting proximal carbonic anhydrases, thereby improving distal sodium delivery and enhancing loop responsiveness.[2] This effect is more evident in patients with elevated serum

bicarbonate, in whom acetazolamide increases natriuresis and facilitates decongestion.[5] Our patient exemplified this phenotype, presenting with an elevated $tCO_2$ of 33 mmol/L and refractory volume overload, and showed a prompt decline in NT-proBNP after acetazolamide initiation, with complete decongestion achieved without renal deterioration.

The concurrent use of dapagliflozin was also noted. Although both acetazolamide and SGLT2 inhibitors act on the proximal tubule, their mechanisms differ (carbonic anhydrase inhibition vs. SGLT blockade) providing complementary natriuretic and decongestive effects.[6,7] In the EMPULSE trial, early in-hospital initiation of SGLT2 inhibitors improved clinical status within 90 days in the acute HF setting,[8] consistent with the favorable response observed in our patient receiving combined therapy.

In contemporary practice, most patients with advanced HF receive loop diuretics and often develop elevated serum bicarbonate, which is frequently considered benign but may reflect compensatory proximal sodium retention. Thus, adjunctive acetazolamide offers a physiological strategy to overcome diuretic resistance and facilitate decongestion in this setting.

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**Conflict of Interest**

Chan Joo Lee serves as an associate editor of the *International Journal of Heart Failure*, but has no role in the decision to publish this article. Except for that, no potential conflict of interest relevant to this article was reported.

**Author Contributions**

Conceptualization: Lee J, Oh J; Data curation: Lee J, Oh J; Investigation: Lee J, Lee CJ, Kim M, Kang SM, Oh J; Supervision: Kang SM, Oh J; Visualization: Lee J, Oh J; Writing - original draft: Lee J, Oh J; Writing - review & editing: Lee J, Oh J.

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