Diuretic Responsiveness and Its Prognostic Significance in Children With Heart Failure

JACK F. PRICE, MD,[1] SAMUEL YOUNAN, BS,[2] ANTONIO G. CABRERA, MD,[1] SUSAN W. DENFIELD, MD,[1] HARI TUNUGUNTLA, MD,[1] SWATI CHOUDHRY, MD,[1] WILLIAM J. DREYER, MD,[1] AND AYSE AKCAN-ARIKAN, MD[3]

Houston, and Dallas, Texas

ABSTRACT

Background: Loop diuretics are considered first-line therapy for congestion in children with heart failure, although some patients remain volume overloaded during treatment. We sought to characterize loop diuretic responsiveness (DR) in children hospitalized with acute decompensated failure and to determine whether a decreased response was associated with worse outcomes.

Methods and Results: DR was calculated for 108 consecutive children <21 years of age who were hospitalized with acute decompensated heart failure. DR was defined as net fluid (mL) output per 1 mg of furosemide equivalents during the first 72 hours of treatment with a loop diuretic. The primary outcome was the composite end point of inpatient death or use of mechanical circulatory support. The median DR was 6.0 mL/mg (interquartile range -2.4 to 15.7 mL/mg). Thirty-two percent of patients remained in a positive fluid balance after 72 hours of treatment with a loop diuretic. Death or use of mechanical circulatory support occurred in 29 patients (27%). Low DR was associated with the composite end point, even after adjusting for net urine output and loop diuretic dose indexed to weight (odds ratio 5.3; $P = .003$). Patients with low DR also experienced longer length of hospital stay than patients with greater DR (median 33 days vs 11 days; $P = .002$).

Conclusion: In children hospitalized with acute decompensated heart failure, early diminished loop DR during decongestion therapy is common and portends a poor prognosis. (*J Cardiac Fail 2019;25:941–947*)

Key Words: Pediatric, child, acute heart failure, diuretics.

Fluid overload, manifesting as high cardiac filling pressures, venous congestion, and sodium retention, is a common feature of advanced heart failure (HF), aggravating its progression and causing worsening symptoms. Loop diuretics are recommended as first-line therapy for decongestion of symptomatic patients, but diuretic efficacy is variable and some patients may develop diminished responsiveness to subsequent doses despite remaining in a positive fluid balance.[1] This refractory response to diuretics is frequently labeled diuretic "resistance" and is associated with increased risk of cardiovascular death and rehospitalization in patients with HF.[2–6]

Definitions of diuretic resistance are vague and rely on subjective assessments such as "persistent congestion" and "adequate diuretic dosing." Hence, objective measures of diuretic responsiveness (DR) are necessary and have recently been proposed in adults. Testani et al[7] defined diuretic "efficiency" as net fluid output produced per 40 mg furosemide equivalent, and Valente et al[8] referred to DR as the change in weight per 40 mg furosemide. Both of these simple metrics of diuretic efficacy emphasize the importance of measuring fluid removal in the context of diuretic dose without relying solely on urine output (or change in weight). Risk factors for diminished DR in adults include lower systolic blood pressure, renal dysfunction, and degree of volume overload.[9]

In contrast with adults, our understanding of DR in children with HF remains limited. There is no agreed upon definition of diuretic resistance in children, no standardized measure of diuretic efficiency, and no evidence that a change in weight or fluid balance offers a meaningful quantification of decongestion, especially in the youngest patients. Early identification of children at risk of poor diuretic response may result in modifications in

From the [1]Department of Pediatrics, Lillie Frank Abercrombie Section of Pediatric Cardiology, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas; [2]University of Texas Southwestern Medical School, Dallas, Texas and [3]Department of Pediatrics, Sections of Nephrology and Critical Care Medicine, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas.

Manuscript received November 16, 2018; revised manuscript received March 27, 2019; revised manuscript accepted March 30, 2019.

Reprint requests: Jack F. Price, MD, Associate Professor of Pediatrics (Cardiology and Critical Care Medicine), Baylor College of Medicine, Co-Director, Advanced Heart Failure Unit, Texas Children's Hospital, 6651 Main Street, Legacy Tower MC-E.1920, Houston, TX 77030. Phone: 832-826-5048. E-mail: jprice@bcm.tmc.edu

Supported with assistance of the Cardiovascular Clinical Research Core at Texas Children's Hospital.

1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2019.03.019

management that lead to improved outcomes. Thus, we sought to characterize DR in children hospitalized with acute decompensated HF (ADHF), identify risk factors for low DR, and determine whether a decreased response was associated with worse outcomes. We hypothesized that patients with low DR would be at greater risk of death or use of mechanical circulatory support (MCS) during hospitalization.

Materials and Methods

Patient Selection

We reviewed the electronic medical records of all patients <21 years of age hospitalized at a single institution (Texas Children's Hospital) with a primary diagnosis of ADHF between January 2011 and June 2015. Patients were identified from the institution's acute HF database. Clinical information from the database was collected as an observational cohort analysis. ADHF was defined as the gradual or rapid deterioration of HF signs or symptoms resulting in the need for hospitalization and urgent therapy. A pediatric HF cardiologist reviewed each patient's medical record to determine whether the purpose for the admission was for the primary treatment of ADHF. When patients were hospitalized more than once during the study period, only data from the first hospitalization were included for analysis. For inclusion in the study, we required that patients must have been treated with a loop diuretic for ≥72 consecutive hours and that the therapy must have been initiated within 72 hours of admission. We excluded patients whose HF was not attributable to ventricular dysfunction, those with large left-to-right intracardiac shunts, and those with obstruction or narrowing of the ventricular outflow tract or aortic arch. We also excluded patients with preexisting chronic kidney disease, any patient who was transferred to our institution from another hospital, and patients who died or required MCS within 72 hours of admission.

Study Protocol

We defined DR as net fluid output produced per milligram of loop diuretic received (expressed as milliliters of net fluid output per 1 mg furosemide equivalent). This definition is similar to that used in adult studies and is akin to the equation using change in weight in place of net fluid loss.[3,4,7,9] The relationship between net fluid output and loop diuretic dose was nonlinear, and DR could not be analyzed reliably as a continuous variable. Therefore, loop DR was divided into high and low DR based on values greater than and less than the median, respectively. Loop diuretic doses were converted to furosemide equivalents: 1 mg intravenous bumetanide = 40 mg intravenous furosemide, and 1 mg intravenous furosemide = 2 mg oral furosemide, as per previous studies.[7−11] Detailed measurements of urine output and total fluid intake were obtained during the first 72 hours of treatment. All patients had orders for the strict collection of volume taken in and urine output eliminated during hospitalization. For infants and toddlers whose urine was collected in a diaper, measurements were recorded by the nurse after determining the difference in weight between a soiled diaper and a clean diaper. Diapers that contained stool were not included for analysis. Supplemental intravenous fluids were defined as intravenous fluids comprising ≥40% of total fluid intake. The estimated glomerular filtration rate (eGFR) was calculated using the modified Schwartz equation.[12] Worsening renal function was defined as a decrease in the estimated eGFR by ≥25% from baseline to day 4 of treatment with a loop diuretic. The composite end point was death or use of MCS (either extracorporeal membrane oxygenation or ventricular assist device) during hospitalization. At our institution, the decision to support the circulation mechanically is generally made based on inotropic dependence and worsening symptoms or evidence of deteriorating cardiac output. We also provide short-term circulatory support for patients with cardiogenic shock or impending shock. This study was approved by the Baylor College of Medicine Institutional Review Board and procedures were followed in accordance with institutional guidelines. The protocol received a waiver of patient and parent consent.

Statistical Analysis

For continuous variables, the *t* test or Wilcoxon rank-sum test were used for data with normal or non-normal distributions, respectively. The χ^2 test was used for binary variables. Variables analyzed in the regression model for association with the composite end point included age, gender, preexisting HF, use of furosemide before admission, ejection fraction, serum sodium, B-type natriuretic peptide, estimated eGFR, mechanical ventilation, inotropes, cumulative loop diuretic dose, cumulative loop diuretic dose/weight, cumulative urine output, cumulative urine output/weight, net fluid output, net fluid output/weight, and DR and DR/weight. Multivariable logistic regression models were created using backward elimination where all covariates with a *P* value of <.2 were retained to determine independent associations with low DR and with the composite end point. LASSO analysis was performed to ensure stability of the odds ratios (ORs) and minimize prediction error. Software used was SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

During the study period, 197 consecutive hospitalizations were reviewed. One hundred eight patients met the study criteria and were included in this analysis. Baseline patient clinical characteristics at admission are listed by high or low DR in Table 1. Overall, the median age of the cohort was 6.5 years (interquartile range [IQR] 1.3−12.5 years) and the sex distribution was evenly divided. Just over 54% of patients had a preexisting history of HF and 35% were receiving a loop diuretic before admission. Kidney function was relatively preserved in the cohort with only 12 patients

Table 1. Baseline Characteristics of Patients Based on DR

Characteristic	High DR (n = 54)	Low DR (n = 54)	*P* value
Demographics			
Mean age (y)	8.2 ± 2.7	3.7 ± 0.9	<.001
Male sex	61%	39%	.021
Weight (kg)	33.1	15.9	<.001
Medical history			
Preexisting HF	57%	50%	.439
Dilated cardiomyopathy	67%	67%	.841
Congenital heart disease	17%	15%	.765
Suspected myocarditis	9%	7%	.791
Restrictive cardiomyopathy	2%	11%	.060
Hypertrophic cardiomyopathy	2%	0%	—
Ischemic cardiomyopathy	2%	0%	—
Findings on chest radiograph			
Cardiomegaly	80%	85%	.450
Pleural effusion	43%	22%	.024
Pulmonary vascular congestion	46%	44%	.841
Physical examination findings			
Hepatomegaly	41%	39%	.841
Gallop rhythm	43%	46%	.699
Peripheral edema	39%	11%	.001
Rales	11%	11%	.764
Laboratory at admission			
Serum sodium, mmol/L	136 ± 3.8	137 ± 4.6	.274
Chloride, mmol/L	102 ± 5.0	100 ± 5.9	.249
Potassium, mmol/L	4.3 ± 0.8	4.1 ± 0.8	.540
Serum creatinine, mg/dL	0.6 ± 0.3	0.5 ± 0.3	.003
Blood urea nitrogen, mg/dL	19 ± 11	10 ± 15	.618
eGFR, mL·min·1.73 m^2	84 ± 21	95 ± 29	.032
Hemoglobin, g/dL	12.4 ± 2.6	11.6 ± 2.0	.075
B-type natriuretic peptide, pg/mL	3419 ± 4049	3777 ± 3715	.647
Cardiac function			
Ejection fraction, %	29 ± 15	28 ± 17	.842
LVEDD z-score	4.6 ± 4.2	5.2 ± 4.4	.537
Home medication use			
Loop diuretic	35%	35%	.841
Thiazide diuretic	4%	10%	.437
Spironolactone	24%	24%	.806
ACE inhibitor or ARB	44%	39%	.559
Beta-blocker	43%	29%	.160
Digoxin	11%	9%	.752

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DR, diuretic responsiveness; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEDD, left ventricular end-diastolic dimension.

(11%) having an estimated eGFR of <60 mL·min·1.73 m^2 at admission.

The median net fluid output during the first 72 hours of treatment with a loop diuretic was 513 mL (IQR -182 to 1523 mL). The median net fluid output per kilogram was 26.6 mL/kg (IQR -13.4 to 44.1 mL/kg). The median cumulative loop diuretic dose was 85 mg (IQR 40−144 mg) or 4.0 mg/kg (IQR 2.0−6.7 mg/kg).

Associations With DR

The median DR was 6.0 mL net fluid output per milligram of loop diuretic (IQR -2.4 to 15.7 mL/mg). The distribution of DR values are shown in Fig. 1. Baseline clinical characteristics at admission associated with high DR included older age, male sex, greater weight, lower eGFR, the presence of edema on examination, and pleural effusion on chest radiographs (Table 1). On multivariable analysis, all variables but gender remained associated with high DR (Table 2).

Table 2. Multivariable Associations of Baseline Characteristics With Low Diuretic Responsiveness

Variable	OR (95% CI)	*P* value
Patient age	0.92 (0.85−0.99)	.025
Presence of edema	0.17 (0.05−0.61)	.006
Pleural effusion on chest radiograph	0.33 (0.11−0.95)	.040
eGFR	1.02 (1.00−1.04)	.018

CI, confidence interval; OR, odds ratio; other abbreviation as in Table 1.

Table 3 shows the in-hospital variables of the cohort grouped by high and low DR. There was no difference in the change of eGFR at 72 hours or 7 days for the 2 groups. Patients in the low DR group were more likely to be treated with inotropes (81% vs 57%; *P* = .007) and more likely to receive thiazide diuretics after the first 72 hours of treatment with a loop diuretic (22% vs 6%; *P* = .045). They also had a longer median length of hospital stay (11 days vs 33 days; *P* = .002).

Other Treatments

On day 4, 32% of the cohort had reached a positive fluid balance while being treated with a loop diuretic. Supplemental intravenous fluids comprising ≥40% of total fluid intake were administered in combination with loop diuretics in 39% of the cohort. During that time, worsening renal function developed more frequently in the low DR than in the high DR group (18% vs 2%; *P* = .018, Table 3). After the first 72 hours of treatment with a loop diuretic, the low DR group was more likely to receive continuous renal replacement therapy and mechanical ventilation than the high DR group (31% vs 9%; *P* = .008, Table 3).

Associations With the Composite End Point

The composite end point of inpatient death or use of MCS occurred in 29 patients (27%). MCS was deployed as extracorporeal membrane oxygenation in 4 patients, a left ventricular assist device in 14 patients, and a total artificial heart in 1 patient. Consistent with findings in adults with HF, low DR in our cohort was associated with poor outcome by multivariable analysis (OR 5.3, 95% confidence interval [CI] 1.7−16.3; *P* = .003, Table 4). When DR was indexed to patient weight, it remained associated with the combined end point (OR 2.99, 95% CI 1.11−8.10; *P* = .031). Neither net fluid output nor loop diuretic dose remained associated with this end point, even when indexed to patient weight. None of the clinical features of congestion were associated with the combined end point: cardiomegaly (OR 3.70, 95% CI 0.79−17.15; *P* = .092), increased pulmonary vascular markings (OR 2.08, 95% CI 0.88−4.94; *P* = .127), hepatomegaly (OR 1.95, 0.82−4.60; *P* = .185), edema (OR 0.36, 95% CI 0.11−1.16; *P* = .087), pleural effusion (OR 1.14, 95% 0.46−2.80, CI *P* = .819),

Table 3. In-Hospital Characteristics by DR

Variable	High DR	Low DR	*P* value
DR, median (IQR), mL net urine output/mg loop	15.7 (10.0 to 22.2)	-2.2 (-20.4 to 2.2)	—
Fluid output, median (IQR)			
Cumulative fluid output at 72 hours, mL	4470 (3356 to 6206)	2397 (1534 to 3224)	.001
Cumulative fluid output per weight at 72 hours, mL/kg	151 (86 to 257)	177 (126 to 236)	.694
Net fluid output at 72 hours, mL	1521 (749 to 2479)	-174 (-730 to 186)	.001
Net fluid output per weight at 72 hours, mL/kg	44 (33 to 78)	-13 (-68 to 10)	.001
Loop diuretic dose, median (IQR)			
Cumulative loop diuretic dose, mg	103 (50 to 180)	80 (28 to 121)	.019
Cumulative loop diuretic dose per weight, mg/kg	3.3 (1.7 to 5.5)	5.2 (2.9 to 7.6)	.003
Kidney function, median (IQR)			
Change in eGFR at 72 hours, mL·min·1.73 m^2	8 (-2 to 24)	4 (-8 to 22)	.325
Change in eGFR at 7 days or discharge, mL·min·1.73 m^2	8 (-3 to 29)	8 (-11 to 24)	.137
Median change in weight at 72 hours, kg (n = 76)	-1.3 (-2.4 to -0.4)	-0.3 (-1.1 to 0.03)	.009
Treatment			
Inotropes	57%	81%	.007
Continuous infusion of loop diuretic	15%	15%	.791
Thiazide added after 72 hours of loop diuretic	2%	9%	.205
Loop diuretic at discharge	41/51 (80%)	29/36 (81%)	.791
Thiazide diuretic at discharge	3/51 (6%)	8/36 (22%)	.045
Received ≥40% of total fluid intravenously	37%	54%	.121
Mechanical ventilation during the 72 hours of diuretic	17%	31%	.072
Mechanical ventilation or CRRT after 72 hours of diuretic	9%	31%	.008
Worsening renal function at day 4	2%	18%	.019
Length of stay, median (IQR)	11 (7 to 27)	33 (11 to 102)	.002

CRRT, continuous renal replacement therapy; IQR, interquartile range; other abbreviations as in Table 1.

gallop rhythm (OR 1.81, 0.77−4.27; $P = .195$), or crackles (OR 1.42, 95% CI 0.39−5.13; $P = .730$).

Discussion

In the present study, we found that lower DR early in the treatment of ADHF was strongly associated with in-patient death or the use of MCS. Net fluid output, total urine output, and loop diuretic dose, however, were not associated with the composite end point, even when indexed to weight. Clinical characteristics at admission that predicted higher DR included the presence of edema on examination, pleural effusion on chest radiographs, lower eGFR, and greater weight. Additionally, failure to decongest early in the hospitalization was common, with more than 1 in 3 patients having a net positive fluid balance after 72 hours of treatment with a loop diuretic.

A standardized and quantifiable definition of diuretic resistance does not exist; therefore, the exact frequency with which it occurs in HF is not known. Diuretic resistance has frequently been conceptualized in descriptive terms as inadequate urine output occurring or persisting in an edematous state despite high or escalating doses of diuretics and before therapeutic goals of decongestion are achieved.[13−15] More recently, simple measures of diuretic response have been proposed, focusing on the efficiency with which the kidney produces urine after a given dose of diuretic rather than on urine output, change in weight, or diuretic dose alone.[7,8] Calculations of DR have been expressed as net fluid output per 40 mg furosemide or change in weight per 40 mg furosemide and, when tested, are strongly and independently associated with mortality, hospital readmission, and incomplete symptom relief in adults with HF.[3,7−9,16] The current study confirms these findings and shows that the measurement of DR also applies to children. In fact, this analysis was more stringent than previous adult studies by its exclusion of any patients with chronic kidney disease as well as those who were treated with thiazide diuretics during the study period, potential influencers of urine output and confounders of the relationship between DR and outcome. Furthermore, a pediatric cohort free from the common comorbidities found in adults with HF (atherosclerosis, atrial fibrillation, chronic kidney disease, diabetes, etc) may be a group more suited to study the kidney's response to diuretics.

Predictors of DR

In our cohort, baseline clinical characteristics of the high DR and low DR groups were strikingly similar, with comparable left ventricular size and function, neurohormonal activation, etiology of HF, and use of diuretics before admission. Patients in the high DR group were significantly older and male, but after adjusting for clinical variables, gender did not remain a predictor of DR. Clinical features of fluid overload such as edema and pleural effusions predicted high DR, suggesting that patients who are most congested have the most fluid to give. This observation has also been made in adults.[3,9] In a post hoc analysis of the ASCEND-AHF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial, adults with diminished DR had fewer signs of congestion (edema) on examination.[3] The authors speculated that acute HF in those patients may have been due to fluid redistribution

Table 4. Univariable and Multivariable Associations With the Combined End Point of Death or Use of Mechanical Support

Variable	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	0.96 (0.90−1.03)	.286	1.07 (0.32−2.50)	.164
Male gender	0.62 (0.26−1.47)	.280	—	—
eGFR at admission	1.0 (1.0−1.03)	.130	1.02 (1.00−1.04)	.065
Mechanical ventilation during first 72 hours	4.12 (1.61−10.59)	.003	3.05 (0.98−9.47)	.054
Inotropes	8.72 (1.93−39.29)	.005	5.43 (1.07−27.4)	.041
Cumulative urine output/weight	0.91 (0.39−2.13)	.828	—	—
Net fluid output/weight	2.94 (1.19−7.26)	.019	—	—
Cumulative loop diuretic dose/weight	1.95 (0.82−4.67)	.132	—	—
DR (dichotomous variable)	5.93 (2.17−16.22)	<.001	5.31 (1.73−16.3)	.003
DR, per 1 unit increase (continuous variable)	0.96 (0.94−0.97)	.002	0.97 (0.95−0.99)	.023

Abbreviations as in Tables 1 and 2.

The ORs were calculated for urine output/weight below the median, for net fluid output/weight below the median, for loop diuretic dose/weight above the median, and for DR below the median.

rather than fluid accumulation and, therefore, was less likely to respond to diuretics. Furthermore, in a hemodynamic model of diuretic response in adults, high intracardiac filling pressure, but not cardiac index, was predictive of better urine output.[9]

Another predictor of better DR in our cohort was a lower eGFR at admission. This finding contrasts with adults in whom a positive correlation (if any) exists between the eGFR and DR. At first glance it might seem counterintuitive that kidneys with decreased glomerular filtration would have a more robust response to diuretics. However, the main hemodynamic driver of diminished eGFR in HF patients is elevated right atrial pressure (ie, venous congestion) and as noted previously, higher filling pressures are associated with a more robust DR.[17−20] We speculate that a lower eGFR may be more of a surrogate marker of fluid overload than intrinsic kidney injury in this cohort without chronic kidney disease. This finding further supports the argument that the most congested patients are those most likely to respond favorably to diuretics. Furthermore, adults with a low eGFR and poor DR also have elevated cystatin C levels, implying some degree of intrinsic kidney disease in addition to fluid overload.[16] Studies in adults are also more likely to include patients with a much lower baseline eGFR at admission.

Association of DR With Death and MCS

This study also shows that children hospitalized with HF who have a low DR are at increased risk of worse outcomes. A low DR was strongly and independently associated with the composite end point of death or use of MCS. Although the net fluid output correlated with DR, it did not remain associated with DR after controlling for other variables, including loop diuretic dose and weight. These findings are consistent with studies in adults and confirm that a quantifiable measure of DR has prognostic importance in children as well.

Diminished urine output was not the only factor related to low DR for a given diuretic dose. High total fluid intake also played an important role. In fact, after 72 hours of treatment with a loop diuretic, 34% of the cohort had taken in more fluid than they had made in urine output. In addition, close to one-half of the patients received both loop diuretics plus supplemental intravenous fluids, a treatment strategy that seems at odds with a goal of early symptomatic relief. Although the administration of intravenous fluids was not associated with DR in our cohort, it may have hindered effective decongestion in some patients. It may have also contributed to morbidity. According to data in adults, the coadministration of intravenous fluids and diuretics during hospitalization for HF exacerbation is associated with subsequent intensive care admission, mechanical ventilation, and continuous renal replacement therapy.[21]

Patients with low DR in this study were administered higher doses of loop diuretics per kilogram of body weight. This finding has also been observed in adults and may represent the caregiver responding to perceived diminished urine output, inadequate weight loss, or persistent congestion on examination. By day 4, more patients in the low DR had developed worsening renal function than in the high DR group (defined as a decrease in eGFR by 25%). The worsening renal failure may be explained by more aggressive use of diuretics, but could also be due to the fact that this group was less congested and therefore at greater risk of acute kidney injury from intravascular depletion.

These data shed new light on a frequently complex and demanding clinical problem—decongesting the fluid overloaded child who has HF. Attempting to determine cardiac filling pressures or the degree of fluid overload at a child's bedside is fraught with error and lacking in evidence. Relying solely on urine output (or even urine output per kilogram of weight), change in patient weight, or loop diuretic dose to determine the adequacy of diuretic therapy may be less informative than calculating the DR. The measurement of DR certainly has its limitations, but may be more instructive to important goals of therapy. These findings could serve as first steps toward a better understanding of the early impact of diminished diuretic efficacy on clinical outcome, as well as aid in the early identification of children that might be at risk of decreased response to diuretic therapies or might benefit from alternative therapies. Further validation of this simple measure of diuretic effectiveness may allow for clinical application at the bedside or use in research related to diuretic resistance beyond the HF population.

Limitations

This study has several important limitations that should be recognized. First, the retrospective design prevented us from determining causality. Prospective studies will be necessary to determine what, if any, impact diuretic resistance or responsiveness have on clinical outcome of patients with HF. Second, patient weights were frequently not documented, making it impossible to assess the role of change in weight in determining DR. Third, the reliability of urine output quantification was not consistent because approximately 25% of measurements came from diaper weights and, therefore, some urine output measurements may be inaccurate. Fourth, although all patients were treated with a loop diuretic for congestion, we did not have a reliable estimate of the degree of fluid overload (eg, central venous pressure monitoring or cardiac catheterization data). Fifth, although the standard and accepted conversion of intravenous furosemide to oral dosing is 1 mg IV = 2 mg oral, the bioavailability of furosemide is quite variable and may be further altered in patients with advanced HF.

Conclusions

In a cohort of children hospitalized with HF, a quantifiable assessment of loop diuretic response (net fluid output per 1 mg furosemide) was strongly and independently linked with worse clinical outcome, confirming that this metric is functional and has prognostic significance in a pediatric population as well as in adults. The clinical features of congestion such as edema, pleural effusion, and a lower eGFR predicted high DR. Prospective analyses of DR are necessary to determine its role in research and clinical care.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.03.019.

References

1. Verbrugge FH, Mullens W, Tang WH. Management of cardiorenal syndrome and diuretic resistance. Curr Treat Options Cardiovasc Med 2016;18:11. https://doi.org/10.1007/s11936-015-0436-4.
2. Neuberg GW, Miller AB, O'Connor CM, Belkin RN, Carson PE. PRAISE Investigators. Prospective Randomized Amlodipine Survival Evaluation. Diuretic resistance predicts mortality in patients with advanced heart failure. Am Heart J 2002;144:31–8.
3. Voors AA, Davison BA, Teerlink JR, Felker GM, Cotter G, Fillipatos G. for the RELAX-AHF Investigators. Diuretic response in patients with acute decompensated heart failure: characteristics and clinical outcome—an analysis from RELAX-AHF. Eur J Heart Fail 2014;16:1230–40. https://doi.org/10.1002/ejhf.170.
4. Ter Maaten JM, Dunning AM, Valente MAE, Damman K, Ezekowitz JA, Califf RM, et al. Diuretic response in acute heart failure—an analysis from ASCEND-HF. Am Heart J 2015;170:313–21. https://doi.org/10.1016/j.ahj.2015.05.003.
5. Ter Maaten JM, Rao VS, Hanberg JS, Perry WF, Bellumkonda L, Assefa M, et al. Renal tubular resistance is the primary driver for loop diuretic resistance in acute heart failure. Eur J Heart Fail 2017;19:1014–22. https://doi.org/10.1002/ejhf.757.
6. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J 2014;35:455–69. https://doi.org/10.1093/eurheartj/eht386.
7. Testani JM, Brisco MA, Turner JM, Spatz ES, Bellumkonda L, Parikh CR, et al. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. Circ Heart Fail 2014;7:261–70. https://doi.org/10.1161/circheartfailure.113.000895.
8. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, et al. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. Eur Heart J 2014;35:1284–93. https://doi.org/10.1093/eurheartj/ehu065.
9. Aaronson D, Burger AJ. Diuretic response: clinical and hemodynamic predictors and relation to clinical outcome. J Cardiac Fail 2016;22:193–200. https://doi.org/10.1016/j.cardfail.2015.07.006.
10. Buckley LF, Carter DM, Matta L, Cheng JW, Stevens C, Belenkiy RM, et al. Intravenous diuretic therapy for the management of heart failure and volume overload in a multidisciplinary outpatient unit. JACC Heart Fail 2016;4:1–8. https://doi.org/10.1016/j.jchf.2015.06.017.
11. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR. NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797–805. https://doi.org/10.1056/NEJMoa1005419.
12. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate eGFR in children with CKD. J Am Soc Nephrol 2009;20:629–37. https://doi.org/10.1681/ASN.2008030287.
13. Kramer BK, Schweda F, Riegger GA. Diuretic treatment and diuretic resistance in heart failure. Am J Med 1999;106:90–6.
14. Horn EJ, Ellison DH. Diuretic resistance. Am J Kidney Dis 2016;69:136–42.
15. Ravnan SL, Ravnan MC, Deedwania PC. Pharmacotherapy in congestive heart failure: diuretic resistance and strategies to overcome resistance in patients with congestive heart failure. Congest Heart Fail 2002;8:80–5. https://doi.org/10.1053/j.ajkd.2016.08.027.
16. Kiernan MS, Stevens SR, Tang WH, Butler J, Anstrom KJ, Birati EY, et al. on behalf of the NHLBI Heart Failure Clinical Trials Network Investigators. Determinants of diuretic responsiveness and associated outcomes during acute heart failure hospitalization: an analysis from the NHLBI Heart Failure Network Clinical Trials. J Card Fail 2018;24:428–38. https://doi.org/10.1016/j.cardfail.2018.02.002.
17. Damman K, van Deursen, Gerjan Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol 2009;53:582–8. https://doi.org/10.1016/j.jacc.2008.08.080.
18. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009;53:589–96. https://doi.org/10.1016/j.jacc.2008.05.068.
19. Chen S, Dykes JC, McElhinney DB, Gajarski RJ, Shin AY, Hollander SA, et al. Haemodynamic profiles of children with end-stage heart failure. Eur Heart J 2017;38:2900–9. https://doi.org/10.1093/eurheartj/ehx456.

20. Tunuguntla H, Arikan A, Guffey D, Minard C, Cabrera A, Jeewa A, et al. Venous congestion is associated with renal impairment in children with cardiovascular disease. J Heart Lung Transpl 2016;35:S405–6. doi.org/10.1016/j.healun.2016.01.1171.

21. Bikdeli B, Strait KM, Dharmarajan K, Li SX, Mody P, Partovian C, et al. Intravenous fluids in acute decompensated heart failure. J Am Coll Cardiol HF 2015;3:127–33. https://doi.org/10.1016/j.jchf.2014.09.007.