Feasibility and Effectiveness of Norepinephrine Outside the Intensive Care Setting for Treatment of Hepatorenal Syndrome

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Vasoconstrictors are the treatment of choice for hepatorenal syndrome (HRS). We evaluate the real-life effectiveness of a sequential vasoconstrictor regimen of midodrine–octreotide followed by norepinephrine in a nonintensive care unit (non-ICU) setting in the United States, where terlipressin is not available. The diagnosis of HRS and definitions of response to therapy were based on 2015 guidelines from the International Club of Ascites. In adult patients with HRS without partial or full response to oral midodrine and subcutaneous octreotide, norepinephrine was administered at a starting dose of 5 mcg/minute, with a goal to achieve a mean arterial pressure (MAP) of 10 mm Hg above baseline. We assessed predictors of response and treatment outcomes. A total of 61 patients were administered midodrine and octreotide for the treatment of HRS, with a 28% response rate. The median MELD-Na (Model for End-Stage Liver Disease–sodium) score was 30 (interquartile range [IQR] 24-35). Responders were more likely to have alcohol-related liver disease and lower Acute-on-Chronic Liver Failure (ACLF) grade. Of the nonresponders, 20 were then administered norepinephrine, of whom 45% achieved full or partial response. Achieving an MAP increase of ≥10 mm Hg was associated with a greater probability of response. Patients who responded to norepinephrine experienced improved transplant-free survival at 90 days (88% versus 27%; $P = 0.02$); 5 of 20 patients experienced norepinephrine treatment–related adverse events, namely arrhythmias. Norepinephrine can be effectively used in a non-ICU setting as rescue therapy in patients who have not responded to midodrine and octreotide. Based on these data, we propose a practical stepwise algorithm for vasoconstrictor therapy to manage HRS in situations where terlipressin is not an option.

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Hepatorenal syndrome (HRS) occurs in patients with advanced, end-stage liver disease and is associated with high mortality and cost.[1] The pathogenesis has been conventionally attributed to systemic circulatory dysfunction and failure of renal perfusion at the level of the renal vasculature, although more recently, involvement of other mediators such as endotoxins and bile acids have been proposed.[2]

Medical therapies have been explored with varying efficacy, and liver transplantation remains the most definitive treatment. Goal-directed hemodynamic therapy using vasoconstrictors has been the cornerstone of treatment and is often deployed as a bridge to liver transplantation. The combination of midodrine, octreotide, and albumin has been shown to improve survival, although not consistently.[3] More recently, terlipressin has been shown to be more effective than octreotide and midodrine; however, terlipressin is yet to be approved by the US Food and Drug

Abbreviations: ACLF, Acute-on-Chronic Liver Failure; AKI, acute kidney injury; BP, blood pressure; CLIF-C OF, Chronic Liver Failure Consortium Organ Failure; CTP, Child-Turcotte-Pugh; CVC, central venous catheter; HRS, hepatorenal syndrome; ICA, International Club of Ascites; IQR, interquartile range; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease–sodium; PICC, peripherally inserted central catheter.

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Administration.[4] Several randomized controlled studies, albeit small, have suggested that norepinephrine is similar in efficacy to terlipressin for the treatment of HRS.[5-9] As a result, existing recommendations support the use of norepinephrine or terlipressin, when available.[10] While norepinephrine may be more cost-effective and readily available than terlipressin particularly in the United States, it is underutilized because in most settings, infusion of norepinephrine requires admission to an intensive care unit (ICU).[5]

At our institution, we implemented a norepinephrine protocol for patients with HRS outside of the ICU. In this study, we evaluate the real-life efficacy of vasoconstrictor therapy for HRS in a cohort of patients with end-stage liver disease and identify predictors of response. We then describe the results of norepinephrine infusion used as rescue therapy in patients who failed midodrine and octreotide treatment.

Patients and Methods

NOREPINEPHRINE PROTOCOL

A multidisciplinary team developed the protocol to administer norepinephrine on the inpatient floor in a nonintensive care setting, based on prior studies on the use of norepinephrine for the treatment of HRS (Fig. 1). The protocol was restricted to a single inpatient unit which specializes in patients with advanced liver disease and is designated as an acuity adaptable unit that can provide intermediate ICU level of care at a 3:1 patient-to-nurse ratio. We worked with nursing leadership to revise the protocol and train nurses through in-service education prior to formal implementation. If patients did not already have central access, they underwent peripherally inserted central venous catheter placement. Norepinephrine infusion began at a dose of 5 mcg/minute, which was adjusted by the hepatologist every 4 hours to achieve a goal mean arterial pressure (MAP) of 10 mm Hg above baseline. The maximum permitted dose of norepinephrine was 10 mcg/minute. All patients received continuous cardiac monitoring, with vital signs monitored every 15 minutes for the first hour after the initiation of norepinephrine. The infusion would be discontinued once the serum creatinine was ≤1.5 mg/dL, or if there was no apparent efficacy, that is, no reduction in serum creatinine after at least 48 hours. The creatinine endpoint was different from the International Club of Ascites (ICA) definitions for full and partial response, to allow for a more straightforward interpretation by providers.

Because the efficacy of norepinephrine for the treatment of HRS is well-established, we developed this as a quality improvement protocol, to define standardized management of norepinephrine which had not been previously used outside of the ICU at our facility. The protocol was presented to the hospital's Pharmacy and Therapeutics committee by the multidisciplinary team (A.K., P.Y.K., and U.W.) and approved in February 2018. Approval from the Institutional Review Board and informed consent were not required for the administration of norepinephrine. The retrospective review of patient outcomes was approved by the Institutional Review Board at Stanford University.

COHORT DEFINITION

For the retrospective review, adults with HRS were identified using the Cohort Discovery Tool available through the Stanford Research Repository, based on age, diagnostic code of HRS (ICD-10 K76.7), and medication administration records. The cohort included qualifying patients who were administered vasoconstrictor therapy between May 2018 and December 2019, a period that was selected based on the implementation of the protocol to administer norepinephrine in a nonintensive care setting in May 2018. We verified that patients met the diagnosis of HRS-acute kidney injury (AKI) based on the 2015 guidelines from the ICA, which included (1) a diagnosis of cirrhosis and ascites, (2) a diagnosis of AKI according to ICA-AKI criteria, (3) no response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g/kg of body weight, (4)

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Paul Y. Kwo consults for Mallinckrodt and Ferring. Uerica Wang is on the speakers' bureau for Veloxis Pharmaceuticals.

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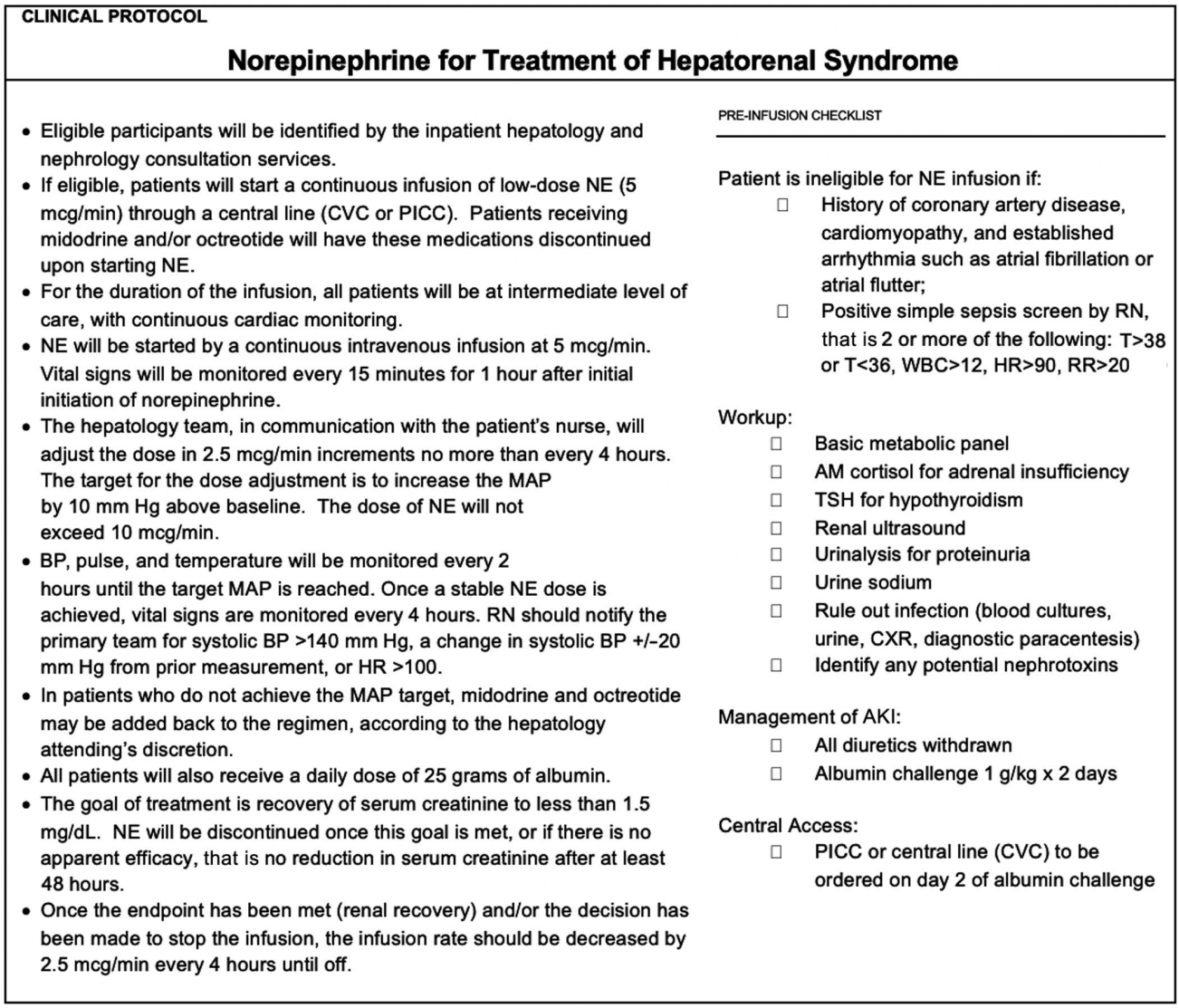

CLINICAL PROTOCOL

Norepinephrine for Treatment of Hepatorenal Syndrome

- Eligible participants will be identified by the inpatient hepatology and nephrology consultation services.
- If eligible, patients will start a continuous infusion of low-dose NE (5 mcg/min) through a central line (CVC or PICC). Patients receiving midodrine and/or octreotide will have these medications discontinued upon starting NE.
- For the duration of the infusion, all patients will be at intermediate level of care, with continuous cardiac monitoring.
- NE will be started by a continuous intravenous infusion at 5 mcg/min. Vital signs will be monitored every 15 minutes for 1 hour after initial initiation of norepinephrine.
- The hepatology team, in communication with the patient's nurse, will adjust the dose in 2.5 mcg/min increments no more than every 4 hours. The target for the dose adjustment is to increase the MAP by 10 mm Hg above baseline. The dose of NE will not exceed 10 mcg/min.
- BP, pulse, and temperature will be monitored every 2 hours until the target MAP is reached. Once a stable NE dose is achieved, vital signs are monitored every 4 hours. RN should notify the primary team for systolic BP >140 mm Hg, a change in systolic BP +/–20 mm Hg from prior measurement, or HR >100.
- In patients who do not achieve the MAP target, midodrine and octreotide may be added back to the regimen, according to the hepatology attending's discretion.
- All patients will also receive a daily dose of 25 grams of albumin.
- The goal of treatment is recovery of serum creatinine to less than 1.5 mg/dL. NE will be discontinued once this goal is met, or if there is no apparent efficacy, that is no reduction in serum creatinine after at least 48 hours.
- Once the endpoint has been met (renal recovery) and/or the decision has been made to stop the infusion, the infusion rate should be decreased by 2.5 mcg/min every 4 hours until off.

PRE-INFUSION CHECKLIST

Patient is ineligible for NE infusion if:

- ☐ History of coronary artery disease, cardiomyopathy, and established arrhythmia such as atrial fibrillation or atrial flutter;
- ☐ Positive simple sepsis screen by RN, that is 2 or more of the following: T>38 or T<36, WBC>12, HR>90, RR>20

Workup:

- ☐ Basic metabolic panel
- ☐ AM cortisol for adrenal insufficiency
- ☐ TSH for hypothyroidism
- ☐ Renal ultrasound
- ☐ Urinalysis for proteinuria
- ☐ Urine sodium
- ☐ Rule out infection (blood cultures, urine, CXR, diagnostic paracentesis)
- ☐ Identify any potential nephrotoxins

Management of AKI:

- ☐ All diuretics withdrawn
- ☐ Albumin challenge 1 g/kg x 2 days

Central Access:

- ☐ PICC or central line (CVC) to be ordered on day 2 of albumin challenge

FIG. 1. Norepinephrine protocol. AM, ante meridiem; CXR, chest X-ray; HR, heart rate; RN, nurse; RR, respiratory rate; T, temperature; TSH, thyroid stimulating hormone.

absence of shock, (5) no current or recent use of nephrotoxins, and (6) no macroscopic signs of structural kidney injury; otherwise, they were excluded.[11] Consistent with the ICA-AKI criteria, the baseline creatinine was the closest value within 3 months of the admission or, where no previous creatinine value was available, the admission value. The definition of AKI was an increase in serum creatinine ≥0.3 mg/dL within 48 hours or >50% from baseline presumed to occur within the prior 7 days. Stage 1 AKI was an increase in serum creatinine ≥0.3 mg/dL or 1.5-2-fold from baseline, stage 2 AKI was an increase 2- to 3-fold from baseline, and stage 3 AKI was an increase >3-fold from baseline or serum creatinine >4.0 mg/dL with an acute increase >0.3 mg/dL or initiation of renal replacement therapy. Proteinuria was permitted although not exceeding the threshold of 500 mg/day. Patients who were administered vasopressors for treatment of shock or who were previously prescribed midodrine for hypotension were excluded.

VASOCONSTRICTOR TREATMENT

All patients were administered midodrine, titrated for a goal increase in MAP of 10 mm Hg above baseline with a maximum dose of 15 mg 3 times daily, and octreotide

100 mcg every 8 hours, administered subcutaneously. Patients with persistent renal failure despite midodrine and octreotide therapy were considered for the norepinephrine protocol. There was no specific time point to determine persistent renal failure or nonresponse; this was determined by the hepatologist. Exclusion criteria for the norepinephrine protocol were coronary artery disease, cardiomyopathy, an established arrhythmia, a positive sepsis screen, or enrollment in a clinical trial for terlipressin (n = 1). As this was a real-life use setting, the decision to administer either norepinephrine or midodrine and octreotide was also influenced by provider preference and familiarity with the protocol and logistic considerations including patient location and ability to place central venous access. Terlipressin was not available for use at our center outside of clinical trial.

DATA DEFINITIONS

Response to Vasoconstrictor Therapy

Progression was defined as an increase to a higher stage of AKI or a need for renal replacement therapy, while regression was a decrease to a lower stage. No regression of AKI was considered as no response to treatment. A partial response was regression of AKI stage with reduction in serum creatinine to ≥0.3 mg/dL above baseline, whereas a full response was regression of AKI stage with return to a value within 0.3 mg/dL of baseline.

Proteinuria was defined by greater than trace protein on urinalysis or >0.3 mg/g on urine protein-to-creatinine ratio. Acute-on-chronic liver failure was defined by the Chronic Liver Failure Consortium Organ Failure (CLIF-C OF) classification, which is a modification of the CLIF-C sequential organ failure assessment (SOFA) score and graded using previously proposed classification.[12]

STATISTICAL ANALYSIS

For the initial descriptive analysis, patients with partial and full response were compared with patients with no response. Logistic regression analyses were performed with the primary outcome of any response to treatment, partial or full. Patients who were administered norepinephrine, all of whom were previously administered midodrine and octreotide and had not responded, were compared with nonresponders to midodrine and octreotide who were not administered norepinephrine. Treatment outcomes included transplant-free survival at 90 days and adverse events.

Statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). For all analyses, a P value of <0.05 was considered significant, and all tests were 2-tailed.

Results

During the study period, 61 patients with cirrhosis were administered midodrine and octreotide for the treatment of HRS-AKI (Table 1). The most common etiology of liver disease was alcohol-associated liver disease (52.5%), followed by nonalcoholic steatohepatitis (23.0%). The prevalence of risk factors for chronic kidney disease including hypertension and diabetes was 32.8% and 21.3%, respectively, while proteinuria was observed in 30% of patients. The median MELD-Na (Model for End-Stage Liver Disease–sodium) was 30 (interquartile range [IQR] 25-35), with a CLIF-OF score of 9 (IQR 8-10). Overall, the median MAP at the start of treatment was 73 (IQR 67-79) mm Hg.

Of the 61 patients administered midodrine and octreotide, 17 (28%) responded, including 5 partial responders. Figure 2A displays creatinine trends among non, partial, and full responders to midodrine and octreotide therapy. Compared with nonresponders, patients who achieved partial or full response to midodrine and octreotide were more likely to have alcohol-associated liver disease and lower Acute-on-Chronic Liver Failure (ACLF) grade (Table 1).

Of the 44 nonresponders to midodrine and octreotide, 20 (45%) were administered norepinephrine through the standardized protocol. Between patients who were administered norepinephrine and those who were not, no statistically significant difference was noted, not unexpectedly given the small sample size (Supporting Table 1). Norepinephrine was administered for a median of 2 days (IQR 2-6). To achieve the MAP goal (≥10 mm Hg from baseline), 8 of 20 (40%) patients required increase beyond the starting dose of 5 mcg/minute; 5 of whom reached the maximum allowable dose of 10 mcg/minute. The majority (95%) of patients were administered norepinephrine via a peripherally inserted central catheter specifically inserted by the hospital's vascular access team for this purpose, in consultation with the nephrology team. In 1 patient, norepinephrine was administered via a right internal jugular central venous catheter, which had

TABLE 1. Baseline Characteristics for All Patients Stratified by Response to Midodrine and Octreotide

	Total	Nonresponders	Responders	
	n = 61	n = 44	n = 17	*P*
Median (IQR) age (years)	61 (54-68)	62 (54-68)	59 (53-65)	0.77
Sex, male, n (%)	38 (62.3)	27 (61.4)	11 (64.7)	>0.99
Race, n (%)				0.77
White	38 (62.3)	26 (59.1)	12 (70.6)	
Hispanic/Latino	15 (24.6)	11 (25.0)	4 (23.5)	
Asian	4 (6.6)	3 (6.8)	1 (5.9)	
Black	2 (3.3)	2 (4.5)	0 (0.0)	
Other	2 (3.3)	2 (4.5)	0 (0.0)	
Etiology of liver disease, n (%)				0.03
Alcohol	32 (52.5)	18 (40.9)	14 (82.4)	
Nonalcoholic fatty liver disease	14 (23.0)	13 (29.5)	1 (5.9)	
Viral (hepatitis B/C virus)	5 (8.2)	4 (9.1)	1 (5.9)	
Other	10 (16.4)	9 (20.5)	1 (5.9)	
History of hypertension, n (%)	20 (32.8)	16 (36.4)	4 (23.5)	0.51
History of diabetes mellitus, n (%)	13 (21.3)	9 (20.5)	4 (23.5)	>0.99
Proteinuria, n (%)	18 (29.5)	15 (34.1)	3 (17.6)	0.34
Median MELD (IQR)	30 (24-35)	32 (25-35)	27 (21-30)	0.11
Median MELD-Na (IQR)	32 (29-37)	33 (29-37)	32 (27-33)	0.42
Median initial bilirubin, mg/dL (IQR)	6.1 (1.8-17.0)	6.8 (2.2-18.2)	5.4 (1.3-14.3)	0.30
Median initial international normalized ratio (IQR)	2.0 (1.6-2.4)	2.1 (1.6-2.4)	1.7 (1.5-2.4)	0.27
Median initial sodium, mmol/L (IQR)	131 (126-134)	131 (126-135)	128 (125-134)	0.24
Median initial creatinine, mg/dL (IQR)	2.6 (2.0-3.2)	2.6 (2.2-3.2)	2.3 (1.8-2.8)	0.27
Initial AKI stage, n (%)				0.41
1	26 (42.6)	19 (43.2)	7 (41.2)	
2	22 (36.1)	14 (31.8)	8 (47.1)	
3	13 (21.3)	11 (25.0)	2 (11.8)	
CTP class, n (%)				0.27
A	1 (1.6)	0 (0.0)	1 (5.9)	
B	22 (36.1)	16 (36.4)	6 (35.3)	
C	38 (62.3)	28 (63.6)	10 (58.8)	
CLIF-C OF score (IQR)	9 (8-10)	9.5 (8-11)	8 (7-10)	0.07
ACLF grade, n (%)				0.04
0	7 (11.5)	2 (4.5)	5 (29.4)	
1	30 (49.2)	22 (50.0)	8 (47.1)	
2	18 (29.5)	15 (34.1)	3 (17.6)	
3	6 (9.8)	5 (11.4)	1 (5.9)	
Median baseline MAP (IQR)	73 (67-79)	73.5 (69-78)	69 (66-80)	0.43
Achieved MAP goal, n (%)*	17 (27.9)	10 (22.7)	7 (41.2)	0.26
Median days on treatment (IQR)	3 (2-5)	3 (2-5)	3 (3-6)	0.41
Response, n (%)				
Full	12 (19.7)	0 (0.0)	12 (70.6)	
Partial	5 (8.2)	0 (0.0)	5 (29.4)	
None	44 (72.1)	44 (100.0)	0 (0.0)	

*Increase by ≥10 mm Hg from baseline MAP.

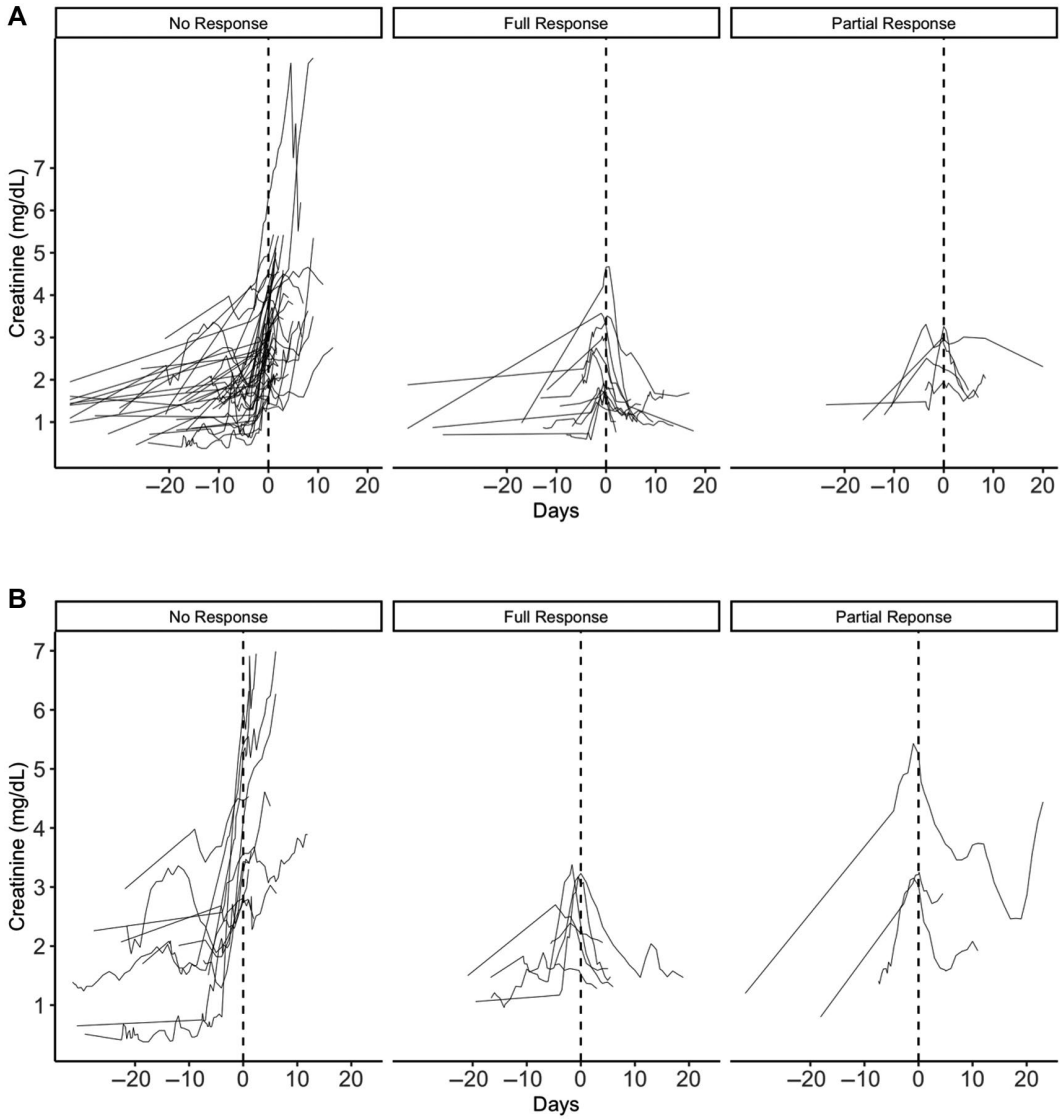

FIG. 2. Creatinine trajectories for the entire cohort, day 0 being start of vasoconstrictor therapy. Censored at initiation of norepinephrine, dialysis, transplant, or death. (A) Midodrine and octreotide. (B) Midodrine nonresponders who were administered norepinephrine. Midodrine and octreotide were prescribed for a median of 3 days (IQR 2-5) prior to norepinephrine administration.

been placed in the ICU; no patients were administered norepinephrine peripherally. One patient experienced positional arrhythmia that resolved with central venous catheter repositioning; no other access-related complication was noted. Figure 2B displays creatinine trends among non, partial, and full responders to norepinephrine therapy. The median creatinine level at the start of therapy was 3.1 mg/dL (IQR 2.8-4.2 mg/dL). There was 1 patient for whom the stopping criteria for norepinephrine according to the protocol (serum creatinine ≤1.5 mg/dL) did not meet ICA criteria for response; for this patient, norepinephrine was continued until full response was achieved (serum creatinine to within 0.3 mg/dL of baseline).

Of the 20 patients administered norepinephrine, 6 (30%) achieved full response with an additional 3 (15%) meeting the partial response criteria (Table 2). Patients who responded to norepinephrine had a higher baseline MAP (78 versus 70 mm Hg; $P = 0.03$), but they otherwise were similar to those who did not respond. Patients who had achieved an increase in MAP by ≥10 mm Hg from baseline were more likely to respond

TABLE 2. Characteristics of Responders Versus Nonresponders to Norepinephrine Therapy

	Total	Nonresponders	Responders	
	n = 20	n = 11	n = 9	*P*
Median (IQR) age (years)	64 (55-67)	63 (53-67)	65 (61-67)	0.62
Sex, male, n (%)	14 (70.0)	8 (72.7)	6 (66.7)	>0.99
Race, n (%)				0.53
White	10 (50.0)	6 (54.5)	4 (44.4)	
Hispanic/Latino	6 (30.0)	2 (18.2)	4 (44.4)	
Asian	3 (15.0)	2 (18.2)	1 (11.1)	
Other	1 (5.0)	1 (9.1)	0 (0.0)	
Etiology of liver disease, n (%)				0.20
Alcohol	7 (35.0)	3 (27.3)	4 (44.4)	
Nonalcoholic fatty liver disease	6 (30.0)	2 (18.2)	4 (44.4)	
Viral (hepatitis B/C virus)	3 (15.0)	3 (27.3)	1 (11.1)	
Other	4 (20.0)	3 (27.3)	0 (0.0)	
History of hypertension, n (%)	7 (35.0)	4 (36.4)	3 (33.3)	>0.99
History of diabetes mellitus, n (%)	5 (25.0)	3 (27.3)	2 (22.2)	>0.99
Proteinuria, n (%)	5 (25.0)	3 (27.3)	2 (22.2)	>0.99
Median MELD (IQR)	31 (25-35)	33 (27-39)	29 (24-33)	0.29
Median MELD-Na (IQR)	32 (28-36)	34 (30-39)	31 (27-34)	0.24
Median initial bilirubin (IQR)	4.0 (1.7-12.4)	4.4 (2.6-14.5)	2.2 (1.5-5.1)	0.32
Median initial international normalized ratio (IQR)	2.0 (1.6-2.5)	2.2 (1.7-2.7)	1.9 (1.5-2.3)	0.47
Median initial sodium (IQR)	132 (128-133)	130 (128-133)	133 (131-134)	0.29
Median initial creatinine (IQR)	3.1 (2.8-4.2)	3.4 (2.8-4.8)	3.1 (2.3-3.2)	0.31
Putative trigger for HRS-AKI, n (%)				0.68
Postparacentesis circulatory dysfunction	5 (25.0)	2 (18.2)	3 (33.3)	
Infection	8 (40.0)	5 (45.5)	3 (33.3)	
Diuretics/nephrotoxin	1 (5.0)	1 (9.1)	0 (0.0)	
Other/unknown	6 (30.0)	3 (27.3)	3 (33.3)	
AKI stage at start of norepinephrine, n (%)				0.38
1	7 (35.0)	4 (36.4)	3 (33.3)	
2	4 (20.0)	1 (9.1)	3 (33.3)	
3	9 (45.0)	6 (54.5)	3 (33.3)	
CTP class, n (%)				0.41
B	8 (40.0)	3 (27.3)	5 (55.6)	
C	12 (60.0)	8 (72.7)	4 (44.4)	
CLIF-C OF score (IQR)	9 (8-10)	9 (8-11)	8 (8-9)	0.20
ACLF grade, n (%)				0.70
0	1 (5.0)	0 (0.0)	1 (11.1)	
1	11 (55.0)	6 (54.5)	5 (55.6)	
2	5 (25.0)	3 (27.3)	2 (22.2)	
3	3 (15.0)	2 (18.2)	1 (11.1)	
Median baseline MAP (IQR)	74 (69-78)	70 (68-74)	78 (77-82)	0.03
Achieved MAP goal (%)	12 (60.0)	4 (36.4)	8 (88.9)	0.05
Median days on treatment (IQR)	2 (2-6)	2 (2-4)	5 (2-7)	0.31
Response, n (%)				
Full	6 (30.0)	0 (0.0)	6 (66.7)	
Partial	3 (15.0)	0 (0.0)	3 (33.3)	
None	11 (55.0)	11 (100.0)	0 (0.0)	

to norepinephrine with borderline statistical significance (88.9% versus 36.4%; $P = 0.05$). Transplant-free survival at 90 days was 89% among those who responded to norepinephrine compared with 27% among nonresponders ($P = 0.02$). In a multivariable Cox regression analysis adjusted for MELD components, achieving response to norepinephrine was associated with reduced probability of death or transplant at 90 days (hazard ratio, 0.07; 95% confidence interval, 0.01-0.77). Although the protocol allowed for providers to add back midodrine and octreotide if the target MAP was not achieved with norepinephrine, this did not occur in our cohort.

A total of 5/20 patients (25%) experienced norepinephrine treatment–related adverse events. Two withdrew from the protocol when they developed sustained tachycardia (heart rate >100 beats/minute), which resolved with discontinuation of norepinephrine. One patient had intermittent supraventricular tachycardia, whereas another had dose limitations due to nonsustained ventricular tachycardia and demand ischemia, although neither required protocol discontinuation. The fifth patient, described previously, experienced catheter-related arrhythmia. Of the 41 patients who were only administered midodrine and octreotide, 1 (2%) required discontinuation due to bradycardia.

Discussion

In this study, we highlight the feasibility of administering norepinephrine as a continuous infusion in a nonintensive care setting in a cohort of patients with end-stage liver disease, HRS-AKI, and high MELD score. Out of the entire cohort of 61 patients administered our vasoconstrictor regimen, 26 (43%) achieved full or partial response, that is, regression of their AKI stage. Of these 26 responders, 17 (65%) responded to midodrine and octreotide alone, and an additional 9 (35%) responded to norepinephrine. Norepinephrine, when deployed as a rescue therapy, was associated with full or partial response in 45% of patients who failed midodrine and octreotide, particularly if the MAP goal (increase in MAP by ≥10 mm Hg) was achieved. Achieving response to norepinephrine in this setting was associated with improved transplant-free survival at 90 days.

Terlipressin has been available for several years in Europe, Australia, and other countries, but is not yet available in North America. Norepinephrine, whose efficacy has been previously shown in randomized trials and meta-analyses, may be used as an alternative to terlipressin. Here, we provide a blueprint for administering norepinephrine with close monitoring but without the need for intensive care, similar to what terlipressin therapy would require.[13] In our study, adverse effects of norepinephrine were mostly related to its arrhythmogenic property, in contrast to terlipressin, for which vasoconstrictive and ischemic adverse effects were more pronounced. We do note that 5 of 20 (25%) of patients administered norepinephrine experienced treatment-related adverse events, although these were minor and only 2 had to withdraw from the protocol as a result of these events. Certainly, administration of this medication requires close monitoring, particularly during the initiation phase. Our protocol entailed strict dosing parameters, increased vital sign and telemetry monitoring, and specific training of nurses in a specialized unit. Prior to implementation of this protocol, our patients had few options for treatment of HRS that did not respond to midodrine and octreotide—access to ICU beds solely for the purpose of norepinephrine was severely limited, and the only alternatives were renal replacement therapy or liver transplantation. Such protocols can serve to optimize health care resource utilization, particularly in the context of escalating health care costs, potentially restricted ICU-level care, and the unavailability of terlipressin.

Successful implementation of this protocol required close collaboration with our pharmacy and nursing staff to provide adequate support and training. In addition, interdisciplinary communication was critical, as there were many providers involved in each patient's care, including residents, fellows, advanced practice providers on the internal medicine, hepatology, and nephrology services. Operationally, it was important to designate a point person familiar with the protocol (in our case, the gastroenterology or hepatology fellow). In addition, we developed a template in the electronic medical record outlining the steps of the protocol, which was placed in the patient's chart upon the decision to start norepinephrine. The protocol and outcomes were reviewed on an ongoing basis. Importantly, we have had to emphasize that this protocol should not delay the initiation of renal replacement therapy or escalation of care when indicated and should not be used for the treatment of hypotension or shock.

As with previous studies, we demonstrated that achieving the MAP goal is key to achieving vasoconstrictor treatment response. This is consistent with previous observations of terlipressin, where sustained rise in MAP is required to observe HRS reversal.[14]

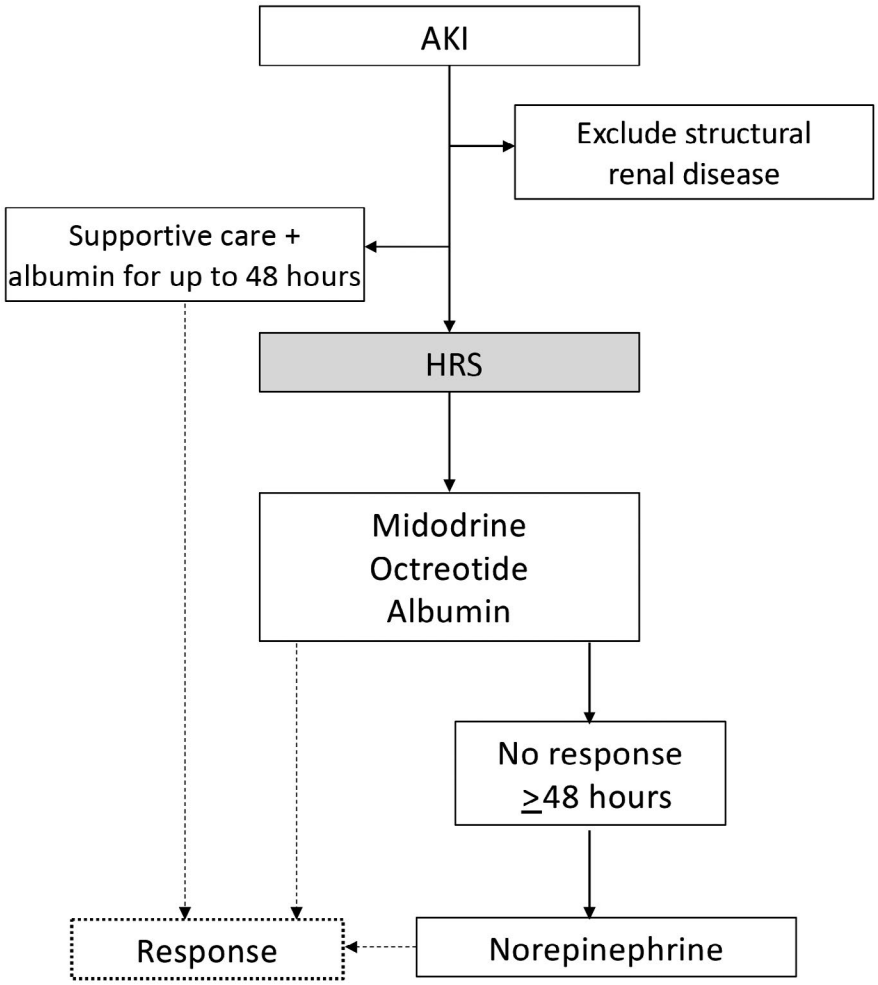

FIG. 3. Proposed algorithm to manage HRS, administering norepinephrine in a nonintensive care setting as rescue therapy in patients not achieving hemodynamic response to midodrine and octreotide.

Norepinephrine and terlipressin may facilitate achievement of the MAP goal in some patients for whom the hemodynamic response to midodrine and octreotide is inadequate. Our response rates to norepinephrine are comparable to those previously observed with terlipressin, which range from 24% to 46%.[15-18] Previous studies have noted that serum creatinine levels predict response to terlipressin, but we did not observe this in our experience with norepinephrine, although our study may have been underpowered.[18,19] This may be related to different definitions of response, as previous studies in terlipressin, including the recently published CONFIRM trial, defined reversal of HRS as 2 consecutive serum creatinine measurements of <1.5 mg/dL, rather than per 2015 ICA guidelines.[18] The higher rates of response observed in our cohort using norepinephrine may be related to the more liberal endpoints using the ICA guidelines. Unfortunately, in our cohort, still more than half of the patients remained nonresponders, highlighting that classes of therapy other than vasoconstrictors need to be developed and investigated, and that we need to better phenotype HRS-AKI based on their responsiveness to vasoconstrictor therapy. In addition, terlipressin if available may be preferable to norepinephrine in certain contexts, as it has been shown in ACLF to be superior in the terms of reversal of HRS, requirement of renal replacement therapy, and 28-day survival.[20] It must also be noted that the norepinephrine dose in our protocol did not exceed a rate of 10 mcg/minute because of safety and monitoring concerns with higher doses of norepinephrine outside of the ICU; a greater rate of

response may have been observed if higher doses had been administered, as in previous studies.[5,8,20]

Limitations of this study are its small sample size, leading to possible type II errors. In addition, many patients eventually underwent liver transplantation, the definitive therapy for end-stage liver disease and HRS. These patients were censored at the time of transplantation, which may have influenced our ability to assess treatment response. There may have also been selection bias and confounding by indication, where the decision to initiate norepinephrine was influenced by feasibility and/or the provider's perception of the patient's severity of illness and transplantability. The criteria for nonresponse to midodrine and octreotide, eligibility for the protocol, and decision to administer norepinephrine were ultimately determined by the treating hepatologist, which may have contributed to heterogeneity. Finally, to the extent that the standard criteria for HRS-AKI is an exclusion, we cannot eliminate the possibility of overlap and/or misclassifications related to other etiologies of kidney injury.

In summary, we describe the real-life feasibility and effectiveness of a stepwise vasoconstrictor therapy algorithm for HRS in a cohort of high-MELD patients with cirrhosis in the United States. In Fig. 3, we propose a practical algorithm to manage HRS using vasoconstrictors available in the United States. Thus, in patients with cirrhosis with an acute rise in creatinine without structural renal disease and who do not respond to supportive care and albumin infusion, midodrine and octreotide may be used as the initial therapy, with norepinephrine as rescue therapy in a non-ICU setting. Moreover, patients who are predicted to have no response to midodrine and octreotide (eg, ACLF grade 2 or 3) may benefit from proceeding directly to norepinephrine therapy. Norepinephrine as rescue therapy may have a role as a potential bridge to transplantation. We submit that the algorithm, subject to validation via larger, prospective studies, may be applied as an alternative approach to terlipressin, making it relevant at present and in the future.

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