New Drug Review

Angiotensin II: A New Vasopressor for the Treatment of Distributive Shock

John M. Allen, PharmD, BCPS, BCCCP, FCCM[1,3]; and
Brian W. Gilbert, PharmD, BCPS, BCCCP[2]

[1]Department of Pharmacotherapy and Translational Research, University of Florida College of Pharmacy, Orlando, FL, USA; [2]Department of Pharmacy, Wesley Medical Center, Wichita, KS, USA; and [3]Department of Internal Medicine, University of Central Florida College of Medicine, Orlando, FL, USA

ABSTRACT

Purpose: Angiotensin II (ATII) is a potent endogenous vasoconstrictor that has recently garnered regulatory approval for the treatment of distributive shock, including septic shock. Traditional vasoactive substances used in the management of distributive shock include norepinephrine, epinephrine, phenylephrine, and vasopressin. However, their use can be associated with deleterious adverse drug effects, such as splanchnic vasoconstriction and associated hypoperfusion. The purpose of this review is to describe ATII, including its pharmacologic mechanisms, pharmacokinetic profile, evidence of efficacy and tolerability, and potential role in contemporary critical care practice.

Methods: Peer-reviewed clinical trials and relevant treatment guidelines published from 1966 to September 14, 2019, were identified from Medline/PubMed using the following search terms: *angiotensin II* OR *angiotensin 2* AND *shock* OR *septic shock* OR *vasodilatory shock*. Pertinent review articles were reviewed for additional studies for inclusion and discussion. The final decision on the inclusion of studies in the current review was based on the expert opinion of the authors.

Findings: On the basis of the available evidence, ATII is effective at elevating blood pressure in patients with distributive shock and appears to reduce the dose of concurrent vasopressors to maintain adequate blood pressure. ATII has been investigated for other causes of shock; however, robust evidence of off-label indications is lacking and is much needed. Clinical and cost benefits compared with traditional vasopressors have yet to be established.

Implications: ATII represents a welcome addition to the armamentarium of critical care clinicians. Enthusiasm for the use of ATII should be balanced with the current gaps in our understanding of ATII in patients with shock. Until further evidence provides more clinically meaningful benefits, as well as cost-effectiveness compared with currently available vasopressors, critical care clinicians should reserve ATII for salvage therapy in patients with septic shock. (*Clin Ther*. 2019;41:2594–2610)

Key words: angiotensin II, distributive shock, septic shock, vasopressors.

INTRODUCTION

Circulatory shock is a medical emergency in which blood flow to tissues and organs is compromised by circulatory system dysfunction. The nature of circulatory shock can be varied and may be hypovolemic, cardiogenic, obstructive, or distributive. Furthermore, patients with circulatory shock can present with mixed etiologic factors. Vasodilatory shock is a subset of distributive shock in which profound, unregulated vasodilation occurs, and there is concurrent vascular hyporesponsiveness to endogenous vasoconstrictors. These factors combine to produce the hypotension associated with vasodilatory shock.

Accepted for publication September 24, 2019
https://doi.org/10.1016/j.clinthera.2019.09.014
0149-2918/$ - see front matter

The most common causes of shock are distributive (eg, septic shock, anaphylactic shock) or cardiogenic, with septic shock accounting for most cases. Historically, goals of therapy focus on restoration of blood flow to tissues and organs and prevention of complications, such as multiorgan failure. Management cornerstones of vasodilatory shock are aggressive fluid resuscitation and vasopressors in fluid nonresponders. Among vasopressors used for vasodilatory shock, norepinephrine and epinephrine are the usually preferred initial agents.[1] Secondary agents include vasopressin, phenylephrine, and dopamine.

Vasopressors are not without limitations, including adverse drug events, such as bowel ischemia, and excessive peripheral vasoconstriction. In addition, when administered peripherally, tissue necrosis can occur, principally when used at high doses or for an extended timeframe.[2] Despite the availability of multiple vasopressors, the mortality rate for various types of shock remains unacceptably high, with up to 50% mortality reported.[3] Alternative therapies, such as corticosteroids, methylene blue, and ascorbic acid, have yielded conflicting or underwhelming results. These factors combine to illustrate the rationale for the search for new vasopressors and methods to treat distributive shock. This review focuses on synthetic human angiotensin II (ATII), a new vasoconstrictor that was approved for use in the United States in December 2017 and in the European Union in August 2019 for the management of distributive shock. The discussion focuses on describing ATII, including its pharmacologic mechanisms, pharmacokinetic profile, evidence of efficacy and tolerability, and potential role in contemporary critical care practice.

METHODS

Peer-reviewed clinical trials in humans, case reports, and relevant treatment guidelines published from 1966 to September 14, 2019, were identified from Medline/PubMed using the following search terms: *angiotensin* OR *angiotensin II* OR *angiotensin 2* AND *shock* OR *septic shock* OR *vasodilatory shock* OR *distributive shock*. Pertinent review articles were reviewed for additional studies for article inclusion and discussion. The final decision on the inclusion of studies in the current review was based on the expert opinion of the authors.

RESULTS

Study Inclusion

The initial search yielded 1094 articles. After review of titles and abstracts for relevance, 16 studies were included in the final analysis.[4–19] Most of the studies were published in the past 2 years (n = 12), with most of the published literature limited to case reports or series (n = 13). Table I summarizes the included studies and case reports that used ATII for the treatment of shock.

Clinical Pharmacologic Mechanisms

Endogenous ATII exerts its multimodal effects via the renin-angiotensin-aldosterone system (RAAS), causing vasoconstriction, vasopressin secretion, aldosterone, and norepinephrine release via multiple G protein–coupled receptors.[20] Angiotensin II receptor type I (AGTR1) activation accounts for the main therapeutic effects of ATII. More specifically, ATII causes direct vasoconstriction via calcium- or calmodulin-dependent phosphorylation of myosin and vasoconstriction in the efferent arterioles of the kidneys. In addition, vasopressin is released via AGTR1 found in the hypothalamus, causing further vasoconstriction.[21] Conversely, activation of the angiotensin type II receptor type II (AGTR2) causes vasodilation at the afferent arteriole in the kidney. ATII lacks any direct chronotropic or ionotropic effects; however, synergetic effects with norepinephrine to augment cardiac output have been proposed.[5]

Even during circulatory compromise and increased endogenous ATII release, tachyphylaxis to the effects of ATII has been reported.[22] In addition to its effects on the circulatory system, ATII also produces a proinflammatory-mediated response and an increased production of plasminogen activator inhibitor 1, causing decreased fibrinolysis.[23] In addition to the antifibrinolytic activity, ATII activation on platelets causes increased aggregation. Conversely, activation of the AGTR2 causes decreased clot formation and increased expression of anti-inflammatory modulators.[24] No differences have been identified between endogenous and synthetic human ATII; thus, the actions of synthetic human AT would be expected to be identical to endogenous ATII. Figure 1 provides a schematic of the RAAS and the actions of ATII.

Table I. ATII trial and case report summary.

Study	Indication for Use	Population and Case Description	Baseline Severity of Illness	ATII Dose Range	Major Efficacy Outcomes	Major Safety Outcomes
Chawla et al,[4] 2014 (ATHOS) (n = 20)	Vasodilatory, high-output shock	Mean (SD) age, 62.9 (15.9) years No./total No. (%) male, 15/20 (75)	APACHE II score, mean (SD) ATII: 27 (9.7) Placebo: 34 (6.8) Baseline NE dose, mean (SD) ATII: 19.8 (11.7) μg/min Placebo: 30.3 (20.4) μg/min	5–20 ng/kg/min	NE dose requirements at hour 2, mean (SD), mg/min ATII: 7.3 (11.9) Placebo: 28.6 (30.2) $P = 0.06$	Metabolic alkalosis, No./total No. (%) ATII: 4/10 (40) Placebo: 0/10
Khanna et al,[5] 2017 (ATHOS-3) (n = 321)	Vasodilatory shock	Median (IQR) age, 64 (52–75) years No./total No. (%) male, 195/321 (60.7)	APACHE II score, median (IQR) ATII: 27 (22–33) Placebo: 29 (22–34) Baseline vasopressor dose, median (IQR) ATII: 0.33 (0.23–0.56) μg/kg/min Placebo: 0.34 (0.23–0.56) μg/kg/min	20–200 ng/kg/min	3-Hour MAP response, No./total No. (%) ATII: 114/163 (69.9)* Placebo: 37/158 (23.4) $P < 0.001$ 28-Day mortality, No./total No. (%) ATII: 75/163 (46) Placebo: 85/158 (54) $P = 0.12$	Adverse event leading to discontinuation, No./total No. (%) ATII: 23/163 (14.1) Placebo: 34/158 (21.5)
Tumlin et al,[6] 2018 (ATHOS-3 post hoc RRT outcomes) (n = 105)	Vasodilatory shock	Median (IQR) age, 62 (51–73) years No./total No. (%) male, 62/105 (59)	APACHE II score, median (IQR) ATII: 32 (26–38) Placebo: 31.5 (27–38) Baseline vasopressor dose, median (IQR) ATII: 0.36 (0.23–0.49) μg/kg/min Placebo: 0.46 (0.32–0.78) μg/kg/min*	20–200 ng/kg/min	3-Hour MAP response, No./total No. (%) ATII: 24/45 (53.3)* Placebo: 13/60 (21.7) $P = 0.001$ 28-Day mortality, No./total No. (%) ATII: 21/45 (47)* Placebo: 42/60 (70) $P = 0.012$	NR

Wong et al,[7] 2019 (n = 16)	Distributive shock	Median (IQR) age, 59.5 (50–67.8) years Median No. (IQR) of vasopressors/ inotropes before initiation of angiotensin use, 4 (3.0–4.0)	APACHE II score, median (IQR) 40 (31.3–42.3) Median SOFA score at time of ATII initiation, 16.5 (15.8–20.0)	Maximum dose (IQR), 38.7 (20.0–40.1) ng/kg/min	Response at 3 h, No./total No. (%) 8/16 (50) Shock reversal 6/16 (37.5) Death due to refractory shock 10/16 (62.5)	Thrombotic complications 0/16 Fungal infection 0/16
Ostermann et al,[8] 2018 (n = 7)	Refractory shock requiring ECMO	Median (IQR) age, 38 (31.5–44.5) years No. (%) male, 4 (57) No./total No. (%) by type of ECMO: VA ECMO: 5/7 (71) and VV ECMO: 2/7 (29)	MAP at initiation of ATII, median (IQR) 61 (59–68) Vasopressor requirements before ATII, median (IQR) NE: 0.50 (0.25–0.90) μg/ kg/min AVP: 0.06 (0.04–0.07) U/ min Epinephrine: 0.07 (0.05 –0.18) μg/kg/min	20–40 ng/kg/min	Time to vasopressor discontinuation, median (IQR), h 96 (40–156)	NR
Ahmed et al,[9] 2018 (n = 1)	Multisystem trauma	56-year-old male pedestrian struck by a car at high speed. Injuries sustained include unstable pelvic fracture and retroperitoneal bleeding. Hospital course complicated by septic shock, cardiogenic shock, acute renal failure	Vasopressor requirements before ATII High-dose norepinephrine, vasopressin, and epinephrine (specific doses not provided)	5–15 ng/kg/min	Goal MAP achieved by hour 3 Weaned from vasopressor within 3 days	No adverse effects

(*continued on next page*)

Table I. (*Continued*)

Study	Indication for Use	Population and Case Description	Baseline Severity of Illness	ATII Dose Range	Major Efficacy Outcomes	Major Safety Outcomes
Chow et al,[10] 2018 (n = 1)	Septic shock	73-year-old man with a medical history of stage 4 colon cancer undergoing neoadjuvant chemotherapy Originally underwent an ileostomy for a large-bowel obstruction secondary to a colonic mass Three days postoperatively, the patient was found to have a bowel perforation and developed septic shock	Serum lactate before ATII, 5.4 mmol/L Vasopressor and adjunctive requirements before ATII NE: 0.28 μg/kg/min AVP: 0.04 U/min Hydrocortisone: 50 mg q6h Methylene blue Hydroxycobalamin: 5 g Crystalloids: 13.6 L	5–20 ng/kg/min	Hour 2 MAP 72 mm Hg Hour 2 NE requirement 0.05 μg/kg/min	NR
Bailey et al,[11] 2019 (n = 2)	Pediatric septic shock	Case 1: 8-year-old previously healthy boy diagnosed with pneumonia and subsequent septic shock. Case 2: 2-year-old previously healthy girl preliminarily diagnosed with meningitis complicated by septic shock	MAP at ATII initiation Case 1: 38 mm Hg Case 2: 57 mm Hg Serum lactate at ATII initiation Case 1: 3.35 mmol/L Case 2: 8.5 mmol/L Vasopressor requirements at ATII initiation Case 1: 0.05 μg/kg/min of NE 15 μg/kg/min of dopamine Case 2: 0.15 μg/kg/min of NE 0.1 μg/kg/min of epinephrine 1.5 nU/kg/min of AVP	1.25–39 ng/kg/min	Hour 3 MAP Case 1: 76 mm Hg Case 2: 55 mm Hg	No serious adverse events were attributable to ATII
Yunge and Petros,[12] 2000 (n = 2)	Pediatric septic shock	Case 1: 4-year-old previously healthy boy diagnosed with septic shock secondary to meningococcal infection Case 2: 4-year-old boy with chronic renal failure was receiving peritoneal	Vasopressor requirements before ATII Case 1: 1 μg/kg/min of NE 20 μg/kg/min of dopamine Case 2: 2 μg/kg/min of NE 1 μg/kg/min of epinephrine 20 μg/kg/min of dopamine	0.1–0.80 μg/kg/min	Case 2 immediate vasopressor requirements NE- ↓ to 0.7 μg/kg/min Epinephrine ↓ to 0.2 μg/kg/min	NR

		dialysis at home after an unsuccessful renal transplant and developed septic shock secondary to candida peritonitis				
Busse et al,[13] 2017 (n = 18)	Cardiac arrest	NR	NA	NR	SBP increase, mean (range), mm Hg +107.3 (0−250) Patients with ROSC, No./total No. (%) 11/18 (61)	NR
Wieruszewski et al,[14] 2018 (n = 4)	Postcardiopulmonary bypass vasoplegic syndrome	Case 1: 47-year-old man with postorthotopic heart transplant Case 2: 57-year-old man with aortic valve replacement Case 3: 37-year-old man with postbilateral orthotopic lung transplant Case 4: 64-year-old man with post-LVAD implantation	NE requirements before ATII Case 1: 0.18 μg/kg/min Case 2: 0.15 μg/kg/min Case 3: 0.25 μg/kg/min Case 4: 0.15 μg/kg/min	10−50 ng/kg/min	NA	NR
Evans et al,[15] 2019 (n = 1)	Post cardiopulmonary bypass vasoplegic syndrome	81-year-old man with multiple comorbidities presenting with an NSTEMI and EF of 16% Subsequent management included a 4-vessel coronary artery bypass graft after continued hypotension with norepinephrine, milrinone, epinephrine, vasopressin, and methylene blue	Baseline MAP 42 mm Hg NE requirements before ATII 0.41 μg/kg/min	20−40 ng/kg/min	Change in NE background dose from baseline by hour 1 −33.3% Change in NE background dose from baseline by hour 2 −88.9% MAP increase by hour 2 +10%	NR
Wieruszewski et al,[16] 2019 (n = 1)	Vasoplegic syndrome	34-year-old woman with complex congenital heart disease and cardiac cirrhosis who underwent combined orthotopic	Baseline vasopressor requirements 0.12 μg/kg/min of NE 0.04 U/min of AVP 15 mg PO q8h of midodrine	20 ng/kg/min	NE was downtitrated to 0.07 μg/kg/min and MAP >65 mm Hg	NR

(*continued on next page*)

Table I. (*Continued*)

Study	Indication for Use	Population and Case Description	Baseline Severity of Illness	ATII Dose Range	Major Efficacy Outcomes	Major Safety Outcomes
		heart and liver transplantation who developed worsening vasoplegia 2 weeks after transplantation				
Carpenter et al,[17] 2019 (n = 2)	Antihypertensive overdose	Case 1: 24-year-old woman with medical history of dilated cardiomyopathy after intentional overdose with multiple antihypertensives, including lisinopril, and amlodipine Case 2: 65-year-old man with medical history of hypertension and congestive heart failure after intentional overdose with multiple antihypertensives, including lisinopril, amlodipine, and carvedilol	MAP before ATII initiation Case 1: 55 mm Hg Case 2: 59 mm Hg Vasopressor requirements before ATII Case 1: 30 μg/min of NE 0.04 U/min of AVP 10 μg/min of epinephrine Case 2: 40 μg/min of NE 11 μg/min of epinephrine	10 ng/kg/min	MAP response Case 1: MAP 1 h after ATII initiation of 69 mm Hg Case 2: MAP 30 min after ATII initiation of 66 mm Hg	NR
Jackson et al,[18] 1993 (n = 1)	ACEi overdose	0600: 44-year-old patient presenting with enalapril overdose (600 mg), baseline BP: 75/40 mm Hg 1410: After unsuccessful treatment with intravenous fluids, dopamine, and norepinephrine, angiotensin infusion started at 3 μg/min, increased to 18 μg/min 1900: Angiotensin infusion successfully discontinued	Baseline NE requirement before ATII 0.02 μg/kg/min	3–18 mcg/min	NA	NA

Newby et al,[19] 1995 (n = 1)	ACEi overdose	46-year old patient presenting with enalapril overdose (140−200 mg), baseline BP unrecordable, HR of 50−60/min After unsuccessful treatment with intravenous fluids, dopamine, and norepinephrine, angiotensin infusion initiated at 202 ng/kg/min Improvement in BP to 110/70 mm Hg Angiotensin infusion successfully discontinued after 30 h	NA	11−22 ng/kg/min	NA	NA

ACEi = angiotensin-converting enzyme inhibitor; APACHE II = Acute Physiology and Chronic Health Evaluation II; ATII = angiotensin II; ATHOS-3 = Angiotensin II for the Treatment of High-Output Shock 3; BP = blood pressure; AVP = vasopressin; EF = ejection fraction; ECMO = extracorporeal membrane oxygenation; HR = heart rate; IQR = interquartile range; NA = not applicable; NE = norepinephrine; NR = not reported; NSTEMI = non−ST-elevation myocardial infarction; SBP = systolic blood pressure; SOFA = Sequential Organ Failure Assessment; MAP = mean arterial pressure; ROSC = return of spontaneous circulation; RRT = renal replacement therapy; VA = veno-arterial; VV = veno-venous.
*$P < 0.05$.

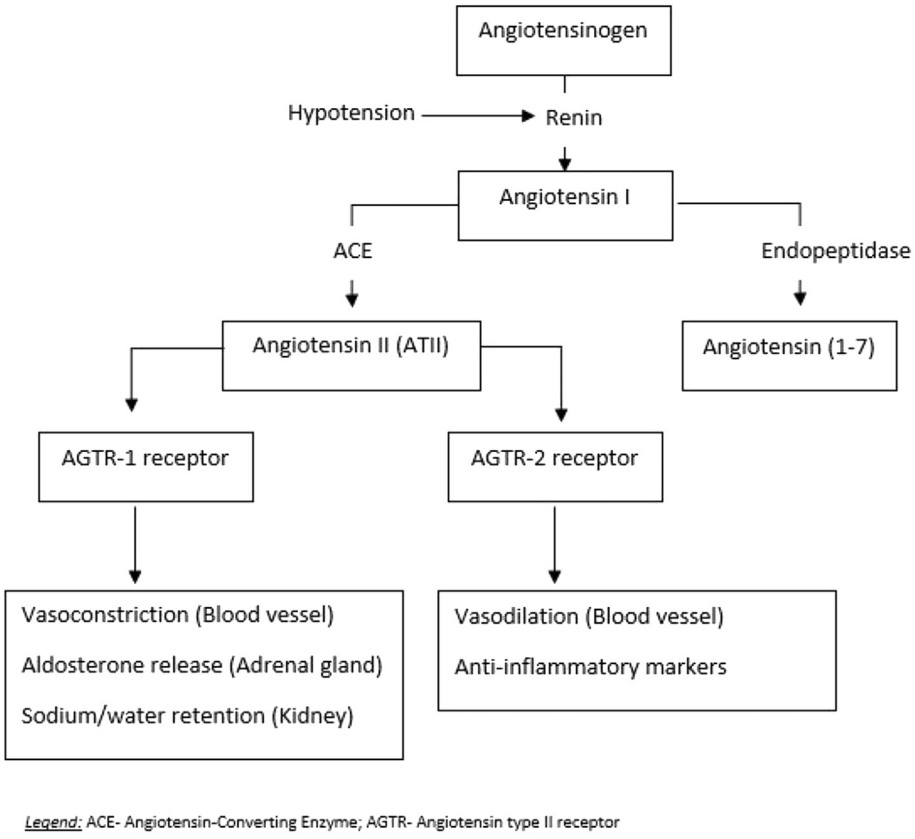

Figure 1. Renin- Angiotensin- Aldosterone System.

Pharmacokinetic Profile

ATII is administered intravenously and undergoes ultrarapid metabolism by aminopeptidase A and angiotensin-converting enzyme (ACE) 2 to angiotensin III and angiotensin (1−7). This conversion occurs primarily in the plasma, erythrocytes, and other major organs.[25] Among the ATII metabolites, the contribution of angiotensin III to the overall therapeutic effects of ATII is significant because angiotensin III accounts for approximately 40% of all AGTR1-mediated activity. Angiotensin (1−7) counteract the activities of ATII and angiotensin III, causing peripheral vasodilation.[22] Renal and hepatic function does not affect ATII metabolism, thus eliminating the need for dose adjustments in patients with renal or hepatic impairment.

In addition, ATII metabolism is not affected by cytochrome P450 isoenzymes or various types of drug transporters. ATII serum concentrations are similar between baseline and after 3 h of exogenous ATII administration. However, after 3 h, the serum concentrations of endogenous angiotensin I (precursor to ATII) are decreased by approximately 40%, suggesting that tachyphylaxis may occur with prolonged ATII administration. This tachyphylaxis is presumably attributable to compensatory mechanisms in the RAAS. Table I provides a comparison between ATII and other vasopressors commonly used in distributive shock.

Efficacy of Clinical Trials

Reports of using bovine ATII in shock were initially described in the 1960s.[26,27] However, fascination from researchers and clinicians for alternatives to catecholamine-based vasopressors has renewed interest in the clinical utility of synthetic human ATII.

The largest trial to date of human ATII in patients with vasodilatory shock is the Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3) trial, which was designed as a Phase III, multinational, randomized, double-blind, placebo-controlled trial to determine whether the addition of ATII to background vasopressors would improve blood pressure in patients with catecholamine-resistant vasodilatory shock.[5] Vasodilatory shock was defined as a cardiac index of >2.3 L/min/m^2 or as central venous oxygen saturation of >70% coupled with central venous pressure of >8 mm Hg, with a mean arterial pressure (MAP) between 55 and 70 mm Hg. All enrolled patients had refractory hypotension with receipt of at least 25 mL/kg of crystalloid fluid resuscitation in the prior 24 h before study enrollment. In addition, all patients were taking high-dose vasopressors to maintain a MAP between 55 and 70 mm Hg for 6−48 h before study enrollment. High-dose vasopressors were defined as ≥0.2 μg/kg/min of norepinephrine equivalents. The primary end point was MAP response at 3 h after enrollment without an increase in background vasopressors. MAP response was defined as absolute MAP ≥75 mm Hg or MAP increase by ≥10 mm Hg from baseline. Secondary end points included changes in the cardiovascular Sequential Organ Failure Assessment (SOFA) score, total SOFA score between baseline measurement and hour 48 after study enrollment, change in norepinephrine dose from baseline to 3 h after enrollment, and all-cause mortality (days 7 and 28).

In the final analysis, ATHOS-3 included 321 patients, with 259 (80%) having sepsis identified as the reason for vasodilatory shock. Baseline MAP was similar between the treatment groups, with a median baseline MAP of 66 mm Hg among all study patients (interquartile range [IQR], 63.7−68.7 mm Hg). Baseline Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were also similar between the treatment groups, with a median score for all study patients of 28 (IQR, 22−33), which is representative of a study cohort with high severity of illness. Baseline vasopressor use was similar between the study groups, with a median norepinephrine-equivalent dose of 0.34 μg/kg/min (IQR, 0.23−0.56 μg/kg/min) for all study patients. ATII achieved the primary end point of MAP response at 3 h after enrollment more frequently than the placebo group (odds ratio [OR] = 7.95; 95% CI, 4.76−13.3; $P < 0.001$).

In addition, mean (SD) norepinephrine dose requirements during the initial 3 h after enrollment were significantly lower in the ATII group (ATII: −0.03 [0.10] μg/kg/min; placebo: +0.03 [0.23] μg/kg/min; $P < 0.001$). ATII was associated with an improvement in mean (SD) cardiovascular SOFA score at 48 h after enrollment compared with placebo (ATII: −1.75 [1.77]; placebo: −1.28 [1.65]; $P = 0.01$). However, no difference was observed in total mean (SD) SOFA score at 48 h after enrollment (ATII: 1.05 [5.50]; placebo: 1.04 [5.34]; $P = 0.49$). No significant differences in mortality at day 7 (hazard ratio [HR] = 0.78; 95% CI, 0.53−1.16; $P = 0.22$) or day 28 (HR = 0.78; 95% CI, 0.57−1.07; $P = 0.12$) were observed. The study results suggest that ATII is effective at increasing blood pressure during the first 3 h of use while concurrently allowing for a decrease in the dosage of other vasopressors. The results from ATHOS-3 were used to garner regulatory approval in the United States in 2017, with the European Medicines Agency Human Medicines Committee recommending granting marketing authorization in June 2019; however, final European Medicines Agency approval is pending.[28]

In a separately reported post hoc analysis of ATHOS-3, the efficacy of ATII was evaluated in 105 patients who required continuous renal replacement therapy (CRRT).[6] The primary efficacy outcome was 28-day all-cause mortality. Secondary efficacy outcomes include time to discontinuation of CRRT, vasopressor(s), and ventilator support through day 7 and MAP response at 3 h after enrollment. Baseline characteristics were similar for most characteristics, including median APACHE II scores and median MAP. However, baseline median norepinephrine equivalent doses were higher in the placebo group, compared with the ATII group (ATII: 0.36 μg/kg/min; placebo: 0.46 μg/kg/min; $P = 0.019$), indicating a potential imbalance in the severity of illness between the patients included in the post hoc analysis. Regarding the primary outcome, when adjusted using multivariate analysis to account for potential baseline imbalances, ATII was associated with better survival to day 28 compared with placebo (HR = 0.44; 95% CI, 0.24−0.80; $P = 0.007$). Similar to the full ATHOS-3 trial, MAP response at 3 h after enrollment was higher in the ATII group

compared with placebo (OR = 4.31; 95% CI, 1.77−10.5; $P = 0.001$). At day 7, compared with placebo, ATII use was associated with a higher likelihood of discontinuing CRRT (HR = 2.90; 95% CI, 1.29−6.52; $P = 0.007$), and ventilator support (HR = 3.14; 95% CI, 1.19−8.26; $P = 0.015$). Conversely, there were no observed differences in discontinuation of vasopressor use at day 7 between the treatment groups (HR = 1.58; 95% CI, 0.89−2.78; $P = 0.113$). The findings suggest in a subset of patients requiring CRRT that ATII may have a mortality benefit. However, because the results were driven from a post hoc analysis, they should be viewed as merely hypothesis-generating rather than being definitive.

Safety Outcomes of Clinical Trials

The aforementioned ATHOS-3 trial provides most of the data related to safety outcomes in patients treated with ATII.[5] Among the enrolled patients, adverse events of any grade were reported at similar rates (ATII: 142 of 163 [87.1%]; placebo: 145 of 158 [91.8%]). Rates of serious adverse events were similar between groups (ATII: 60.7%; placebo: 67.1%). Overall, the most common adverse events reported in patients with ATII include multiorgan failure (15.3%), atrial fibrillation (13.5%), and hypotension (10.4%); however, these adverse events occurred in similar rates compared with patients taking placebo. Delirium occurred more frequently in the ATII group (ATII: 5.5%; placebo: 0.6%; $P = 0.036$). Adverse events leading to discontinuation of treatment occurred in 23 of all 163 patients (14.1%) in the ATII group compared with 34 of the 158 patients (21.5%) in the placebo group. The most common adverse events leading to drug use discontinuation include septic shock, multiorgan failure, and cardiogenic shock. One prominent adverse event that was observed more in the ATII group compared with placebo was deep vein thrombosis (ATII: 3 of 163 [1.8%]; placebo: 0%). Other adverse events were similar between the 2 groups. Table II provides an overview of clinical trials and case reports that used ATII.

Special Populations

Investigation of the use of ATII in special populations is limited. A total of 154 of 321 patients (48%) evaluated in the ATHOS-3 trial were 65 years or older, with 83 patients (25%) 75 years or older.[5] Decreased systemic perfusion attributable to age-related atherosclerosis and increased peripheral vascular resistance is further magnified during sepsis.[29] Given its primary effects as a vasoconstrictor, one could hypothesize that older patients may need higher ATII doses compared with younger patients; however, this was not reported in ATHOS-3. Further investigation into potential age-related differences in the efficacy of ATII is warranted.

The clinical use of ATII in pediatric patients with shock is an area with a paucity of data. A recently completed Phase II clinical trial (NCT03431077) evaluated ATII in patients 2−17 years of age and assessed effects on MAP, norepinephrine requirements, and the safety profile of ATII in the pediatric population.[30] No study results have yet been reported. However, an ongoing Phase III trial (NCT03623529) that is expected to be completed in 2023 may help to explore the potential benefits and harms associated with the use of ATII in pediatric patients with refractory shock.[31] In one of the earliest case reports evaluating ATII in the pediatric septic shock population, ATII achieved MAP response, even in patients with high inotropic and vasopressor support.[12] When considering that a significant subset of shock management in pediatrics is dedicated to cardiac output optimization via inotropic or chronotropic therapy, it remains to be seen whether ATII displays any added benefit in this patient population compared with more conventional vasopressors and inotropes.[32] Currently, there is a paucity of data to support the routine use of ATII in the pediatric population.

Data on safety and tolerability outcomes are limited in those receiving ATII during pregnancy. In 2 different cohort studies, ATII was infused at 10 ng/kg/min up to 64 ng/kg/min with no adverse events noted. However, these studies were not in patients with septic shock and had a relatively low sample size.[33,34] There is also no evidence to date to evaluate the safety profile of ATII during lactation. Given the lack of compelling evidence of efficacy and tolerability, routine use of ATII in pregnancy or lactation must be weighed against the use of more traditional options for the management of vasodilatory shock.

Table II. Comparison of ATII and select vasopressors used in distributive shock.

Agent	Hemodynamic Effect	Dosing	Adverse Event Profile	Estimated Daily Cost, $*
Norepinephrine	↑HR, ↑ MAP, Ø CO	0.05–1 μg/kg/min	Arrhythmias, immune dysfunction, ischemia	50
Epinephrine	↑HR, ↑ MAP, ↑ CO	0.05–1 μg/kg/min	Lactate acidosis, tachycardia, myocardial events	100
Vasopressin	Ø HR, ↑ MAP, Ø CO	0.04 U/min	Bradycardia, hyponatremia, ischemia	350
Angiotensin II	Ø HR, ↑ MAP, ~↑CO	1.25–200 ng/kg/min	Thrombotic events, infection, hypertension, ischemia	1785
Dopamine	↑HR, ↑ MAP, ↑ CO	1–20 μg/kg/min	Arrhythmias, ischemia, pituitary gland suppression, impaired thyroid function	125
Phenylephrine	Ø HR, ↑ MAP, ↓CO	0.2–1.8 μg/kg/min	Arrhythmias, ischemia, bradycardia, headache	75

CO = cardiac output; HR = heart rate; MAP = mean arterial pressure.
* Daily cost based on 70-kg patient and norepinephrine equivalents of 0.3 μg/kg/min.

Other Potential Uses

Although the exact role of ATII use in vasodilatory shock has yet to be determined, other possible roles for ATII could be explored. There have been 18 documented cases of patients in cardiac arrest who have achieved a return of spontaneous circulation after ATII administration.[13] Given the ability of ATII to increase afterload via the RAAS, its use in this realm seems intriguing, particularly in those with prior ACE inhibitor (ACEi) exposure. However, noting the ambiguity on the use of vasopressor support and lack of positive outcomes-associated data in cardiac arrest, it is difficult to ascertain any real benefit of ATII in this patient population.

Another area of active interest in the use of ATII is in the cardiothoracic surgery population. Alternative therapies for post–cardiopulmonary bypass vasoplegic syndrome after cardiothoracic surgery is limited. Noncatecholamine therapies, such as methylene blue, ascorbic acid, and hydroxocobalamin, have tolerability or efficacy concerns. ATII may potentially have a role as an alternative agent.[14,15] Wieruszewski et al[14] recently reported the use of ATII in 4 patients with catecholamine refractory high-output shock after a cardiothoracic procedure, with AT doses ranging from 10 to 50 ng/kg/min. After administration of ATII, vasopressor requirements decreased with improved hemodynamic parameters. No adverse events were noted after ATII administration. A well-designed randomized controlled trial would be needed to validate the use of ATII in the cardiothoracic population with refractory vasoplegic high-output shock, and given the increased associated cost of ATII compared with other noncatecholamine-based therapies, cost-effectiveness should also be evaluated.

After acquired brain injury, especially atraumatic subarachnoid hemorrhage, cerebral salt wasting is common, causing excess sodium and fluid losses at the distal renal tubules.[35] Typical treatment of cerebral salt wasting consists of fluid repletion and fludrocortisone, which causes increased aldosterone release, sodium, and water retention. Activation of AGTR1 by ATII causes increased aldosterone release and theoretically could serve a role for those who are unable to tolerate fludrocortisone or aggressive fluid replacement. However, in clinical practice, this population may be limited.

There may also be a role for ATII in the management of ACEi overdose. However, there remains a paucity of data that have examined ATII role in this scenario. The use of ATII in this setting is limited to adjunctive therapy to more traditional management strategies, such as fluid resuscitation, gastrointestinal decontamination, and vasopressor support.[18,19] Although limited evidence exists, it would appear to be reasonable to consider ATII in ACEi overdose if traditional management strategies are ineffective.

Lastly, ongoing animal model data have revealed promising neuroprotective effects of ATII in middle cerebral artery occlusion murine models.[36] In animal models, systemic and topical ATII reduces infarct size and improves neurologic scores. Although much data are needed before routine implementation of ATII in acute ischemic stroke care, animal models suggest early ATII use in large vessel stroke may have benefits. It remains to be seen whether angiotensin metabolites have systemic effects beyond their proven role in hemodynamics.

Dosing and Administration

Most of our understanding of ATII dosing and administration comes from the Phase III ATHOS-3 trial. ATII was administered at an initial dose of 20 ng/kg/min and titrated in increments of 15 ng/kg/min every 5 min until the target MAP of 65–75 mm Hg was achieved. Dose titration of concomitant vasopressors was not allowed in the first 3 h of study enrollment.[5] The dosing range within the first 3 h of the study was 1.25–200 ng/kg/min, although the mean ATII dose used within the initial study period was <40 ng/kg/min. After study hour 3, the allowed dosing range was 1.25–40 ng/kg/min, with titration every 5–15 min to maintain a goal MAP of 65–75 mm Hg. The mean dose of ATII during this period was approximately 20 ng/kg/min. According to the manufacturer, the maximum recommended AT dosing during the initial 3-h period is 80 ng/kg/min and 40 ng/kg/min after that. ATII infusion was discontinued at 48 h after enrollment per a predefined tapering process. The US Food and Drug Administration–approved labeling recommends that once blood pressure control is achieved, ATII can be down-titrated every 5–15 min by increments of up to 15 ng/kg/min based on blood pressure.[25] ATII is

recommended to be administered via a central catheter. One additional dosing consideration is exposure to ACEis and angiotensin II receptor blockers. Approximately 15% of the entire ATHOS-3 study population had exposure to an ACEi. On the basis of the mechanism of ATII, it would be expected that these patients may need an increased dose compared with patients without exposure to either agent. However, this has not been fully elucidated, and further research is needed to confirm this hypothesis.

DISCUSSION

ATII represents a new therapeutic option in the treatment of shock that effectively and rapidly elevates MAP after initiation. However, despite the rationale for the need for new vasopressors and methods to treat vasodilatory shock, a distinct role for ATII remains yet to be elucidated. The proposed benefits of ATII in vasodilatory shock include reduced background vasopressor requirements and rapid increase in MAP. However, these benefits appear to be short term, with similar vasopressor requirements noted after 24−36 h of ATII compared with the placebo group. In addition, the primary efficacy end point of MAP response at hour 3 of study drug use has not been used as an end point in clinical trials or routine practice in the management of septic shock and has not been evaluated as a predictor of positive outcomes. In addition, although not adequately powered to evaluate more clinically relevant outcomes, such as survival, the lack of survival benefit observed leaves clinicians to wonder if an observed increase in MAP with ATII ultimately will lead to an improvement in clinical outcomes compared with more traditional vasopressors. These issues notwithstanding, the results of ATHOS-3 were sufficient to garner regulatory approval in the United States.

However, questions persist regarding the potential advantages of ATII, particularly when considering the applicability of the ATHOS-3 trial to all patients. One notable population that was excluded from the ATHOS-3 trial was patients with low cardiac output, leaving unanswered questions regarding whether the proposed benefits of ATII are also seen in this population. In addition, the ATHOS-3 trial was not designed as a head-to-head comparison with other available vasopressors, making a comparison of the efficacy of ATII with other available vasopressors difficult. Moreover, approximately two-thirds of patients in the ATHOS-3 trial were taking multiple vasopressors at baseline, suggesting ATII is at best a third-line treatment option for most patients.

The rate of deep vein thrombosis is also cause for concern, particularly in patients at the highest risk of developing thromboembolic events. The exact reason for the observed result has yet to be elucidated; however, one potential mechanism is the effect of angiotensin on platelet aggregation. Compared with other historical landmark sepsis trials, the rate of deep vein thrombosis reported in the ATII group was higher (1 of 778 [0.12%] in the Vasopressin and Septic Shock Trial or 0% in the Sepsis Occurrence in Acutely Ill Patients 2 trial), suggesting the potential therapeutic benefits of ATII must be weighed against the possible risk of thrombosis in high-risk patients with venous thromboembolism.[37−39]

Figure 2 represents a possible algorithm for ATII use in patients with distributive shock. Off-label use of ATII has garnered attention, particularly in patients with vasoplegic syndrome, which is a frequently encountered complication in post−cardiothoracic surgery patients. In this population, maintaining adequate perfusion while also avoiding an increase in myocardial oxygen demand often noted with other vasopressors are desired. ATII represents an attractive treatment option and may be considered in patients refractory to other first-line options; however, current evidence of use in this population is severely lacking and warrants further investigation to assess the risk vs benefit of ATII vs other vasopressors traditionally used in this setting.

Lastly, the significant financial burden associated with ATII compared with currently available treatment options has caused many institutions to consider whether the relatively minor clinical benefits of ATII compared with other more cost-effective options, such as alternate vasopressors or adjunctive corticosteroids, justify the increase in drug costs. Estimated daily costs for ATII are significantly more than traditional vasopressors used in the management of vasodilatory shock (Table II). In the United States, the manufacturer has introduced several programs to facilitate the use of ATII, including a limited

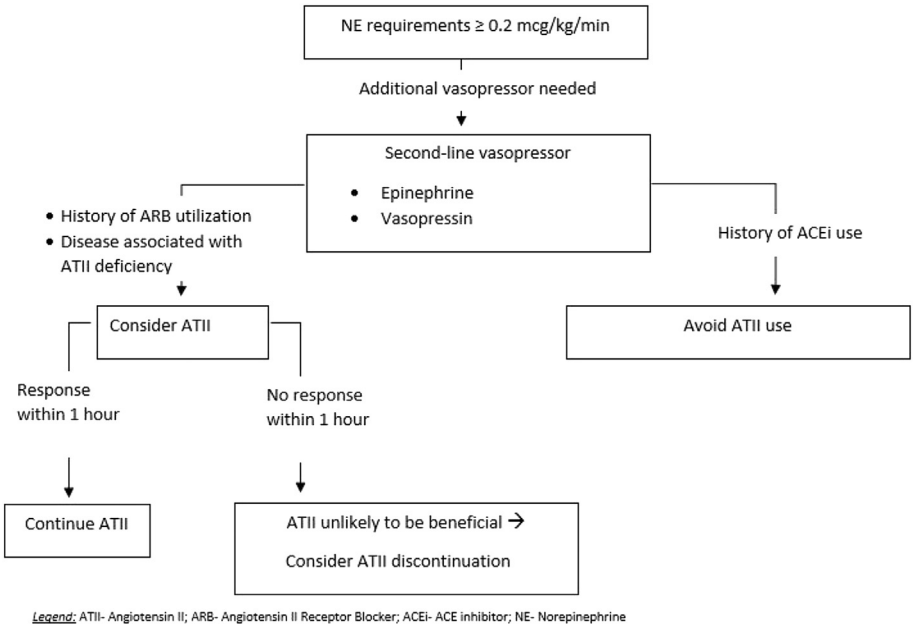

Figure 2. Proposed ATII algorithm for use in distributive shock.

warranty program. In addition, in the United States, the Centers for & and Medicaid Services has granted a new technology add-on payment for ATII, which provides additional reimbursement beyond the routine Medicare Severity Diagnosis-Related Group reimbursement for new products that meet strict criteria.[40,41] For institutions considering adding ATII to the formulary, these programs may be useful. Future investigation into the cost-effectiveness of ATII compared with other vasopressors commonly used in shock is needed.

CONCLUSION

ATII represents a welcome addition to the armamentarium of critical care clinicians. ATII is effective at increasing blood pressure in patients and appears to have a catecholamine-sparing effect. However, the availability of other more widely studied options that produce similar effects (ie, corticosteroids) may limit the broad applicability of ATII. Enthusiasm for the use of ATII should be balanced with the current gaps in our understanding of ATII in patients with shock. Concerns with potential thromboembolic events and delirium associated with ATII warrant further evaluation. Until further evidence provides more clinically meaningful benefits and cost-effectiveness compared with currently available vasopressors, critical care clinicians should reserve ATII for salvage therapy in patients with distributive shock.

DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

REFERENCES

1. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45:486–552.
2. Allen JM. Understanding vasoactive medications: focus on pharmacology and effective titration. *J Infus Nurs*. 2014;37:82–86.
3. Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of global incidence and mortality of hospital-treated sepsis. current estimates and limitations. *Am J Respir Crit Care Med*. 2015;193:259–272.

4. Chawla LS, Busse L, Brasha-Mitchell E, et al. Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study. *Crit Care*. 2014;18:534.
5. Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med*. 2017;377:419–430.
6. Tumlin JA, Murugan R, Deane AM, et al. Outcomes in patients with vasodilatory shock and renal replacement therapy treated with intravenous angiotensin II. *Crit Care Med*. 2018;46:949–957.
7. Wong A, Alkazemi A, Eche IM, et al. A retrospective review of angiotensin II use in adult patients with refractory distributive shock. *J Intensive Care Med*. 2019 Sep 3 [Epub ahead of print] Pubmed ID: 31480886.
8. Ostermann M, Boldt DW, Haper MD, Lim GW, Gunnerson K. Angiotensin in ECMO patients with refractory shock. *Crit Care*. 2018;22:288.
9. Ahmed M, Habis S, Mahmoud A, Rutland C, Saeed R. Angiotensin II use in refractory multisystem shock: a case report. *Cureus*. 2018;10, e3665.
10. Chow JH, Galvagno Jr SM, Tanaka KA, et al. When all else fails: novel use of angiotensin II for vasodilatory shock: a case report. *AA Pract*. 2018;11:175–180.
11. Bailey DM, Chima RS, Tidmarsh GH, Williams MD. Synthetic human angiotensin II in pediatric patients with vasodilatory shock: a report on two patients. *Crit Care Explorations*. 2019;1, e0036.
12. Yunge M, Petros A. Angiotensin for septic shock unresponsive to noradrenaline. *Arch Dis Child*. 2000;82:388–389.
13. Busse LW, McCurdy MT, Ali O, et al. The effect of angiotensin II on blood pressure in patients with circulatory shock: a structured review of the literature. *Crit Care*. 2017;21:324.
14. Wieruszewski PM, Radosevich MA, Kashani KB, Daly RC, Wittwer ED. Synthetic human angiotensin II for postcardiopulmonary bypass vasoplegic shock. *J Cardiothorac Vasc Anesth*. 2019 Mar 8;33(11):3080–3084 [Epub ahead of print].
15. Evans A, McCurdy MT, Weiner M, Zaku B, Chow JH. Use of angiotensin II for post cardiopulmonary bypass vasoplegic syndrome. *Ann Thorac Surg*. 2018;108:e5–e7.
16. Wieruszewski PM, Sims CR, Daly RC, Taner T, Wittwer ED. Use of angiotensin II for vasoplegic shock in a combined heart and liver transplant recipient with systolic anterior motion physiology. *J Cardiothorac Vasc Anesth*. 2019;33:2366–2367.
17. Carpenter JE, Murray BP, Saghafi R, et al. Successful treatment of antihypertensive overdose using intravenous angiotensin II. *J Emerg Med*. 2019 Jul 3 [Epub ahead of print] Pubmed ID: 31279637.
18. Jackson T, Corke C, Agar J. Enalapril overdose treated with angiotensin infusion. *Lancet*. 1993;341:703.
19. Newby DE, Lee MR, Gray AJ, Boon NA. Enalapril overdose and the corrective effect of intravenous angiotensin II. *Br J Clin Pharmacol*. 1995;40:103–104.
20. Hall A, Busse LW, Ostermann M. Angiotensin in critical care. *Crit Care*. 2018;22:69.
21. Feener EP, Northrup JM, Aiello LP, King GL. Angiotensin II induces plasminogen activator inhibitor-1 and -2 expression in vascular endothelial and smooth muscle cells. *J Clin Invest*. 1995;95:1353–1362.
22. Bissell BD, Browder K, McKenzie M, Flannery AH. A blast from the past: revival of angiotensin II for vasodilatory shock. *Ann Pharmacother*. 2018;52:920–927.
23. Skurk T, Lee YM, Hauner H. Angiotensin II and its metabolites stimulate PAI-1 protein release from human adipocytes in primary culture. *Hypertension*. 2001;37:1336–1340.
24. Fyhrquist F, Saijonmaa O. Renin-angiotensin system revisited. *J Intern Med*. 2008;264:224–236.
25. *Giapreza (Angiotensin II) [package Insert]*. San Diego, CA: La Jolla Pharmaceutical Company; 2018.
26. Singh S, Malhotra RP. Comparative study of angiotensin and nor-adrenaline in hypotensive states (shock). *J Assoc Physicians India*. 1966;14:639–645.
27. Perroni G, Briguglio FS. [First clinical experiences on the use of beta-angiotensin II: treatment of a grave case of shock]. *Gazz Int Med Chir*. 1965;69:1557–1560.
28. European Medicines Agency website. Meeting Highlights from the Committee for Medicinal Products for Human Use (CHMP); 24-27 June 2019. https://www.ema.europa.eu/en/news/meeting-highlights-committeemedicinal-products-human-usechmp-24-27-june-2019. Accessed July 1, 2019.
29. Rowe TA, McKoy JM. Sepsis in older adults. *Infect Dis Clin North Am*. 2017;31:731–742.
30. A study of LJPC-501 in pediatric patients with hypotension. Available from: https://ClinicalTrials.gov/show/NCT03431077. Accessed July 1, 2019.
31. A study of LJPC-501 in paediatric patients with hypotension associated with distributive or vasodilatory shock. Available from: https://ClinicalTrials.gov/show/NCT03623529. Accessed July 1, 2019.
32. Martin K, Weiss SL. Initial resuscitation and management of pediatric septic shock. *Minerva Pediatr*. 2015;67:141–158.
33. Conti C, Tranquilli AL, Garzetti GG, Romanini C. Modulation of vascular reactivity after acute calcium antagonist administration in pregnant women moderately sensitive to angiotensin infusion. *Boll Soc Ital Biol Sper*. 1994;70:243–248.
34. Oney T, Kaulhausen H. The value of the angiotensin sensitivity test in the early diagnosis of hypertensive disorders in pregnancy. *Am J Obstet Gynecol*. 1982;142:17–20.

35. Yee AH, Burns JD, Wijdicks EF. Cerebral salt wasting: pathophysiology, diagnosis, and treatment. *Neurosurg Clin N Am*. 2010;21:339–352.
36. Min LJ, Mogi M, Tsukuda K, et al. Direct stimulation of angiotensin II type 2 receptor initiated after stroke ameliorates ischemic brain damage. *Am J Hypertens*. 2014;27:1036–1044.
37. Allen JM, Feild C, Shoulders BR, Voils SA. Recent updates in the pharmacological management of sepsis and septic shock: a systematic review focused on fluid resuscitation, vasopressors, and corticosteroids. *Ann Pharmacother*. 2019;53:385–395.
38. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358:877–887.
39. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362:779–789.
40. GIAPREZA. NTAP - GIAPREZA [online] Available at: https://www.giapreza.com/ntap/; 2019. Accessed July 1, 2019.
41. GIAPREZA. NTAP - GIAPREZA [online] Available at: https://www.giapreza.com/ntap/; 2019. Accessed July 1, 2019.

Address correspondence to: John M. Allen, PharmD, BCPS, BCCCP, FCCM, Department of Pharmacotherapy and Translational Research, University of Florida College of Pharmacy, 6550 Sanger Rd, Ste 420G, Orlando, FL, USA. E-mail: john.allen@cop.ufl.edu