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Synthetic Human Angiotensin II in Pediatric Patients With Vasodilatory Shock: A Report on Two Patients

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Background: Severe sepsis and septic shock continue to be an important problem in children, with hospital mortality rates for pediatric severe sepsis as high as 25%.

Case Summary: Two pediatric patients with septic shock requiring high dose vasopressors, who were treated with angiotensin II as part of an open-label study. Both patients had a significant increase in mean arterial pressure shortly after initiation of angiotensin II, with a reduction of the dose of catecholamines and vasopressin infusions. Serious adverse events reported were not attributable to angiotensin II by investigators. One patient survived, and one died related to progressive cerebral edema.

Conclusions: Angiotensin II may represent another therapeutic option for pediatric patients who remain hypotensive despite receiving fluids and standard vasopressor therapy and deserves further study.

Key Words: angiotensin II; hypotension; pediatric shock; sepsis; septic shock; vasopressor

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Despite major advances in vaccines in the past 2 decades, severe sepsis and septic shock continue to be an important problem in children, with a prevalence of 8% (1). Although the outcomes for pediatric patients who remain hypotensive despite receiving fluid therapy and vasopressor therapy are not specifically described, the hospital mortality rate for pediatric severe sepsis has been shown to be as high as 25% (1–3).

The treatment of septic shock in children involves a progression of interventions, beginning with establishing source control and administering fluids and antibiotics urgently (4). Hydrocortisone may be administered if adrenal insufficiency is suspected but evidence for efficacy and safety is lacking in this population. If patients do not respond to fluids, vasoactive support is used. Commonly, catecholamine infusions, such as epinephrine, norepinephrine, or dopamine, are first-line agents used in children with septic shock (4). In the Sepsis Prevalence, Outcomes, and Therapies (SPROUT) study (1), vasoactive infusions were used in 55% of pediatric patients with severe sepsis, with epinephrine and norepinephrine being the most commonly used medications, at 43% and 42% of patients treated with vasoactive medications, respectively.

There is no robust evidence, however, supporting the use of one agent over the other in children with septic shock. The use of high dose catecholamines, such as epinephrine and norepinephrine, in adult patients with severe hypotension is associated with poor outcomes. Vasopressin is considered as rescue therapy in patients in vasodilatory shock who do not respond to high doses of norepinephrine or other sympathomimetics. The only placebo-controlled study of arginine vasopressin in children showed that children receiving vasopressin had an increase in mean arterial pressure (MAP) from baseline after 1 hour; however, there was no survival benefit. In that study, survival was worse for children receiving vasopressin, though this result was not statistically significant (5). Angiotensin II is also recommended as potential second-/third-line therapy in the American College of Critical Care Medicine pediatric shock guidelines (4). This recommendation is based on a case report utilizing the bovine angiotensin II formulation (6). A synthetic human angiotensin II was approved by

the U.S. Food and Drug Administration in 2017, and here we describe the use of angiotensin II infusion in two pediatric patients with septic shock requiring high dose vasopressors who were treated as part of an open-label study (NCT03431077).

CASE A

A previously healthy 8-year-old male presented to the emergency department secondary to listlessness, tachypnea, and chest pain. By history, the patient complained of malaise, cough, and myalgias, and was noted to have a fever of 101.8°F (38.8°C) 4 days prior to admission. The following day he presented to his pediatrician with similar symptoms and a fever of 104.1°F (40.1°C). He was diagnosed with influenza and recommended supportive care at home. Following presentation to the emergency department, he was admitted to the pediatric ward for noninvasive pulmonary support, where he was found to have a right basilar consolidation consistent with pneumonia on chest radiograph (CXR) (Fig. 1). Initial vital signs demonstrated a temperature of 103.2°F (39.6°C), heart rate of 148, respiratory rate of 46, oxygen saturation of 90% on room air, and blood pressure (BP) of 114/70 mm Hg. Laboratory evaluation revealed a white blood cell (WBC) count of 5,200/ μ L with a normal differential, hemoglobin level of 13.9 g/dL, platelet count of 139, $10^3/\mu$ L, and an unremarkable electrolyte panel. Ceftriaxone, clindamycin, oseltamivir, and IV fluids were administered. Oxygen saturations were 88–92% on 6 L/min of high flow nasal cannula (HFNC) on 0.4 F_{IO_2} . Over the subsequent 24 hours, the patient remained tachypneic requiring an increase of HFNC to 20L and 0.55 F_{IO_2} . He was transferred to the PICU and transitioned to bilevel positive airway pressure support of 15/7 on 1.0 F_{IO_2} , given his increased work of breathing and hypoxia. Repeat CXR revealed

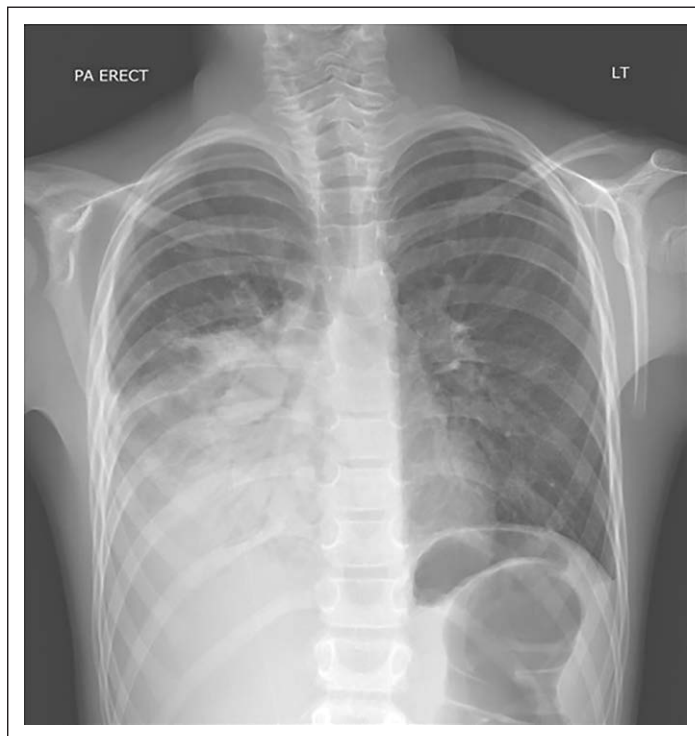


Figure 1. Chest radiograph of case A with right basilar consolidation consistent with pneumonia. LT = left side, PA = posteroanterior.

significant interval worsening of right-sided lung infiltrate and development of a left basilar consolidation (Fig. 2). Repeat labs in the PICU demonstrated a reduction in WBC to 2.8 and platelet count of 126. Further pulmonary decompensation with refractory hypoxemia and hypercarbia (pH 7.21, P_{aCO_2} 66 mm Hg, P_{aO_2} 49, oxygen saturation 79%) led to intubation, conventional mechanical ventilation (CMV), and a rapid progression to high-frequency oscillatory ventilation (HFOV) of MAP 28, amplitude 85, Hz 6.5, 1.0 F_{IO_2} . A transthoracic echocardiogram was completed revealing normal cardiac anatomy, chamber sizes and biventricular function with a left ventricular ejection fraction of 67%, a small to moderate circumferential pericardial effusion without evidence of tamponade physiology, and bilateral large pleural effusions. The patient subsequently developed vasodilatory septic shock requiring initiation of dopamine and norepinephrine infusions. Despite ongoing titration of the vasopressor therapy regimen, he remained hypotensive with evidence of inadequate end-organ perfusion, including decreased urine output (UOP) and rising serum lactate. Having exceeded the norepinephrine equivalent dosing threshold established by the study of 0.1 μ g/kg/min (the patient's norepinephrine equivalents were 0.15 μ g/kg/min at the current regimen) and ongoing demonstration of refractory vasodilatory shock, the patient was subsequently consented for and enrolled in an open-label study of the investigational drug LJPC-501 (angiotensin II), a synthetic human angiotensin II for vasodilatory shock requiring high dose vasopressors. At the time of initiation of angiotensin II, his inotropic support consisted of norepinephrine 0.05 μ g/kg/min and dopamine 15 μ g/kg/min with clinical demonstration of continued vasodilatory shock physiology despite this therapy. He was started on an angiotensin II infusion at 1.25 ng/kg/min, per the study protocol, and titrated per clinical examination, physiology, and target hemodynamic variables. At 2 hours post-initiation of

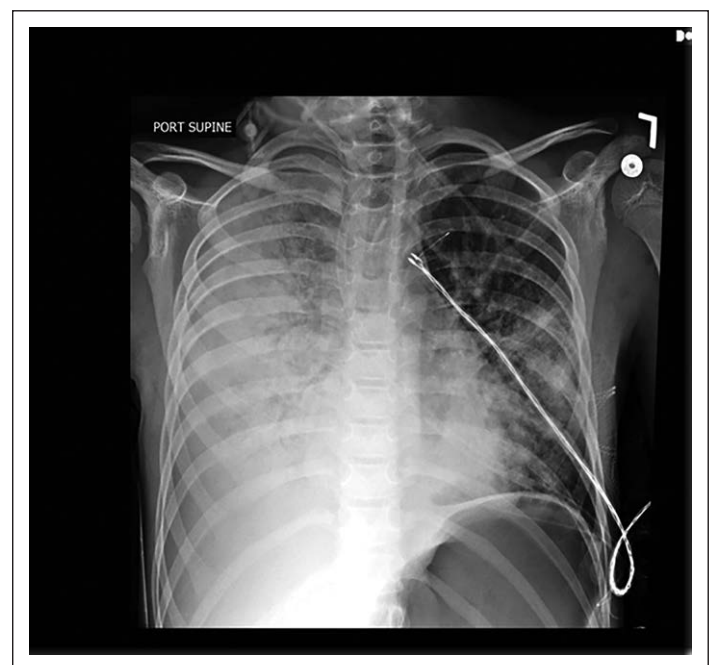


Figure 2. Repeat chest radiograph of case A with significant interval worsening of right-sided lung infiltrate and development of a left basilar consolidation.

angiotensin II, at a dose of 15 ng/kg/min, the norepinephrine infusion was discontinued, and the dopamine was decreased to 5 µg/kg/min. At 3 hours of treatment, all traditional vasopressor therapy was successfully discontinued while meeting goal hemodynamic variables with clinical improvement in vasodilatory physiology and improved biochemical surrogates for systemic oxygen delivery as demonstrated by a trend toward normalization of serum lactate, improved UOP, and improved patient vital signs. Despite this trend toward improved systemic perfusion, the treatment team kept the patient on the angiotensin II infusion for a total duration of 80 hours, titrated to effect per hemodynamic and biochemical goals, through the conversion from HFOV to CMV. The patient experienced six treatment-emergent adverse events (TEAEs), none of which were considered related to the study drug (Table 1). The patient was subsequently transitioned to CMV, eventually extubated, and ultimately achieved a complete recovery, being discharged from the hospital 14 days from his admission date.

CASE B

A previously healthy, unimmunized 2-year-old white female presented to the emergency department at an outlying hospital for being unresponsive, limp, and drooling after a nap. Her history was notable for 2–3 days of abdominal pain and feeling warm with intermittent fussiness. On presentation, she was noted to be unresponsive with eye deviation and jerking, and was febrile (107°F), tachycardic (170 beats/min), hypoxemic (87% oxygen saturation on room air), and hypotensive. Due to a concern of ongoing seizure activity, she was given IV benzodiazepines and emergently intubated. Initial laboratory studies were notable for hypoglycemia (glucose 40 mg/dL), elevated creatinine (1.3 mg/

dL), elevated lactate (4.5 mmol/L), and urine analysis with small leukocyte esterase, 10–20 WBCs, and 1+ bacteria. She was administered a normal saline bolus for hypotension, dextrose, and ceftriaxone and transferred to the PICU for ongoing care of status epilepticus, respiratory failure, and septic shock.

On presentation to the PICU, she was in shock with a capillary blood gas showing severe metabolic acidosis with an elevated lactate (7.2 mmol/L). An echocardiogram showed normal ventricular function and electroencephalogram (EEG) revealed ongoing seizure activity. Head CT scan showed no abnormalities. She was given additional fluid boluses and started on an epinephrine infusion for distributive shock due to sepsis. Broad-spectrum antimicrobial coverage with ceftriaxone, vancomycin, and acyclovir was started. She was given dexamethasone and started on a midazolam infusion in addition to fosphenytoin for ongoing status epilepticus. Additional laboratory values suggested she was in disseminated intravascular coagulation with thrombocytopenia and an elevated international normalized ratio. Given this, a lumbar puncture to assess spinal fluid was deferred. Given her history and presentation, her preliminary diagnosis was intracranial infection (meningitis/encephalitis) complicated by septic shock.

Over the course of the first 12 hours in the PICU, her clinical condition deteriorated with worsening seizure activity, which required escalation of midazolam infusion and initiation of pentobarbital infusion, resulting in seizure control. Concomitantly, her shock state worsened with worsening lactic acidosis; infusions with norepinephrine and vasopressin were initiated. On hospital day 2, repeat head CT showed worsening with concern for diffuse cerebral edema. She was transitioned off pentobarbital to a ketamine infusion for status epilepticus given her elevated lactate, and she was kept on continuous EEG monitoring. Given her nonresponse

TABLE 1. Treatment-Emergent Adverse Events

Case	Preferred Term	Severity ^a	Serious Adverse Event ^b	Outcome (Study Day)
Case A	Hypokalemia	3	No	Resolved (day 6)
	Pericardial effusion ^c	2	No	Resolved (day 7)
	Pleural effusion ^c	3	No	Resolved (day 7)
	Metabolic alkalosis	3	No	Resolved (day 7)
	Sedation complication	2	No	Resolved (day 9)
	Nausea	1	No	Resolved (day 7)
Case B	Cerebral infarction	4	Yes	Not resolved
	Hepatic failure	4	Yes	Not resolved
	Hypokalemia ^c	4	Yes	Resolved (day 3)
	Activated partial thromboplastin time prolonged ^c	2	No	Not resolved
	Hypophosphatemia	3	No	Not resolved
	Hypernatremia ^c	3	No	Not resolved
	Brain edema ^c	5	Yes	Fatal (day 4)

^aGrade 1 = mild; grade 2 = moderate; grade 3 = severe; grade 4 = life-threatening; grade 5 = death.

^bSerious adverse events reported were not attributable to angiotensin II by investigators.

^cWorsening/progression in verbatim description.

to multiple vasoactive infusions, she was consented and enrolled in an open-label study with investigational drug LJPC-501 (angiotensin II). Angiotensin II administration was started at a rate of 1.25 ng/kg/min and increased to 39.1 ng/kg/min at 42 minutes. At the time of initiation of angiotensin II, she was receiving infusions of epinephrine 0.1 µg/kg/min, norepinephrine 0.2 µg/kg/min, and vasopressin 2 mU/kg/min. Within 90 minutes of initiation of angiotensin II, the patient was able to come off norepinephrine and vasopressin infusions. A third head CT scan, approximately 2 hours after initiating treatment with angiotensin II, showed further worsening with increase in cerebral edema with effacement of cisterns and cerebral sulci and cerebral infarction in the right temporal and occipital lobes. Given these findings, an intracranial parenchymal pressure monitor was placed. Increased transaminases (alanine aminotransferase 515 U/L, aspartate aminotransferase 1,378 U/L)

indicated worsening liver injury consistent with shock liver. Her blood cultures were reported as negative and urine culture was positive for *Escherichia coli*. On hospital day 3, she remained on angiotensin II and low dose epinephrine infusion to maintain her BP. Despite improved hemodynamics, she continued to have persistently elevated lactate. Her EEG continued to show significant suppression while on midazolam and ketamine infusions. She was taken off fosphenytoin, given her ongoing liver injury, and started on brivaracetam. She began to have intermittent spikes in intracranial pressure (ICP) needing hyperosmolar therapy. A repeat head CT scan showed worsening diffuse cerebral edema with further decreased attenuation consistent with a cerebral infarct with no acute intracranial hemorrhage or midline shift. On hospital day 4, the patient's primary team determined the patient to have a non-survivable illness. As a result, she was weaned off angiotensin II

TABLE 2. Patient Variables Over Time

Timepoint	Baseline	Hour 0	Hour 0.5	Hour 1	Hour 1.5	Hour 2	Hour 3	Hour 6	Hour 12	Hour 24	Hour 30
Case A											
Dopamine (µg/kg/min)	0	15	15	13	10	5	0	0	0	0	0
Norepinephrine (µg/kg/min)	0	0.05	0.05	0.03	0	0	0	0	0	0	0
Angiotensin II (ng/kg/min)	0	0	2.5	10	12.5	15	17.5	12.5	15	12.5	10
EF (%) 2D echocardiogram	67	NA	NA	65	NA	NA	69	65	63	64	NA
Heart rate (beats/min)	148	137	129	132	126	112	110	116	110	108	111
MAP (mm Hg)	40	38	54	72	76	79	76	81	74	70	82
Lactate (mmol/L)	4.58	3.35	4.21	1.98	2.08	1.31	1.92	1.27	0.94	0.76	0.68
UOP (mL/kg/hr)	0	0	<0.1	0	0.3	0	<0.1	<0.1	0.2	0.8	0.9
CVP (mm Hg)	17	16	15	15	12	13	12	11	12	9	10
Oxygen saturation (%)	79	89	92	87	88	86	91	90	93	92	94
FiO ₂	1	1	0.9	0.75	0.55	0.6	0.55	0.55	0.4	0.45	0.4
Case B											
Dopamine (µg/kg/min)	0	0	NA	0	NA	0	0	0	0	0	0
Norepinephrine (µg/kg/min)	0.2	0.15	NA	0	NA	0	0	0	0	0	0
Epinephrine (µg/kg/min)	0.05	0.1	NA	0.1	NA	0.1	0.1	0.1	0.1	0.06	0.07
Vasopressin (mU/kg/min)	2	1.5	NA	0.5	NA	0	0	0	0	0	0
Angiotensin II (ng/kg/min)	0	1.25	NA	39.06	NA	39.06	39.06	39.06	20	20	15
EF (%) 2D echocardiogram	56.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Heart rate (beats/min)	100	98	NA	110	NA	105	109	132	111	112	106
MAP (mm Hg)	70	57	NA	62	NA	62	55	70	77	79	72
Lactate (mmol/L)	9.5 ^a	8.5 ^a	NA	NA	NA	8.3 ^a	NA	7.9 ^b	8.1 ^b	7.1 ^b	7.5 ^b
UOP (mL/kg/hr)	13.4	14.4	NA	8.7	NA	16	14.2	9.7	2.4	2	1
CVP (mm Hg)	17	17	NA	17	NA	13	8	9	15	12	16
Oxygen saturation (%)	97	98	NA	96	NA	94	97	93	99	99	97
FiO ₂	0.3	0.3	NA	0.3	NA	0.3	0.3	0.3	0.4	0.4	0.4

CVP = central venous pressure, EF = ejection fraction, MAP = mean arterial pressure, NA = not available, UOP = urine output.

^aPoint-of-care lactate.

^bLactic acid level.

after a total of 40 hours 29 minutes and maintained on other vasopressors to optimize cerebral perfusion pressure. Vasopressin continued for another ~25 hours and epinephrine for another ~27.5 hours after discontinuing angiotensin II. Her liver failure worsened with further increase in liver enzymes. She developed worsening intracranial hypertension despite maximal osmotherapy in addition to being on high dose sedation. Her EEG continued to be significantly suppressed. On hospital day 5, she developed refractory intracranial hypertension (ICP peaked at 88 mm Hg) despite maximal therapy and suppression on EEG. Given her worsening neurologic conditions, care was withdrawn, and the patient passed away. The patient experienced seven TEAEs, none of which were considered by the investigator to be related to the study drug (Table 1). An autopsy revealed severe and diffuse cerebral edema associated with tonsillar herniation. Vascular congestion and edema of the lungs without evidence of significant pneumonia were noted. The liver showed extensive areas of lobular necrosis consistent with ischemic necrosis. Preliminary cultures obtained at autopsy including blood and lung cultures, showed no evidence of any bacterial growth.

DISCUSSION

The renin-angiotensin-aldosterone system (RAAS), along with the arginine-vasopressin system, and the sympathetic nervous system make up the three major mechanisms to regulate BP (7). Angiotensin II is a naturally occurring peptide hormone that is the major bioactive component of the RAAS and regulates BP through activation of the angiotensin II type 1 receptor in smooth muscle vascular cells (8). Endogenous angiotensin II induces peripheral vasoconstriction, increases sodium and water retention, aldosterone release, and vasopressin release leading to increase in BP (9, 10). A synthetic human angiotensin II has been developed for the treatment of catecholamine-resistant hypotension, and in numerous published clinical studies, angiotensin II has demonstrated significant effects on systemic and renal blood flow and has been shown to be safe in adults (11). A large phase 3 clinical trial in adults with vasodilatory shock demonstrated a significant increase in BP in patients who did not respond to fluids and high dose conventional vasopressors (Angiotensin II for the Treatment of High-Output Shock 3 [ATHOS-3]) (12). Given this, angiotensin II is now approved in the United States to increase BP in adults with septic or other distributive shock.

Previous analyses further support the role of angiotensin II in the management of patients with vasodilatory shock. Tumlin et al (13) reported outcomes in patients with acute kidney injury requiring renal replacement therapy at baseline and showed that 28-day survival and MAP response were higher and the rates of renal replacement therapy liberation were greater in patients receiving angiotensin II plus standard care compared with patients receiving standard care plus placebo. In addition, a recent review on the use of angiotensin II in patients with vasodilatory shock (14) discussed the use of angiotensin II and its potential role in patients with increased severity of illness, acute respiratory distress syndrome, and in responders to minimal doses of therapy.

Despite adult data, there is a paucity of literature describing the usage of angiotensin II in children. A single article reports on two children with severe septic shock who were treated with a bovine

form of angiotensin II (6). One had meningococcal septicemia and the other *E coli* septicemia. In both cases, there was significant improvement in BP, resulting in a reduction in doses of other vasoactive agents, and both patients successfully survived their septic episodes. Our case series of two patients represents the first described use of synthetic human angiotensin II in children with septic shock. Both patients had a significant increase in MAP shortly after initiation of angiotensin II, with a reduction of the dose of catecholamines and vasopressin infusions (Table 2). Serious adverse events reported were not attributable to angiotensin II. One patient survived and one died related to progressive cerebral edema, which was felt to be unrelated to angiotensin II. Based on the safety evaluation from the ATHOS-3 study, a higher rate of arterial and venous thrombotic and thromboembolic events in adult patients who received angiotensin II compared with placebo was observed, leading to a warning and requirement for concomitant venous thromboembolism prophylaxis when administering angiotensin II. Further research is needed regarding this novel vasoactive drug with unique mechanisms of action in children who have septic or distributive shock.

REFERENCES

- Weiss SL, Fitzgerald JC, Pappachan J, et al; Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Global epidemiology of pediatric severe sepsis: The Sepsis Prevalence, Outcomes, and Therapies study. *Am J Respir Crit Care Med* 2015; 191:1147–1157
- Hartman ME, Linde-Zwirble WT, Angus DC, et al: Trends in the epidemiology of pediatric severe sepsis*. *Pediatr Crit Care Med* 2013; 14:686–693
- Ruth A, McCracken CE, Fortenberry JD, et al: Pediatric severe sepsis: Current trends and outcomes from the pediatric health information systems database. *Pediatr Crit Care Med* 2014; 15:828–838
- Davis AL, Carcillo JA, Aneja RK, et al: American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock. *Crit Care Med* 2017; 45:1061–1093
- Choong K, Bohn D, Fraser DD, et al; Canadian Critical Care Trials Group: Vasopressin in pediatric vasodilatory shock: A multicenter randomized controlled trial. *Am J Respir Crit Care Med* 2009; 180:632–639
- Yunge M, Petros A: Angiotensin for septic shock unresponsive to noradrenaline. *Arch Dis Child* 2000; 82:388–389
- Chopra S, Baby C, Jacob JJ: Neuro-endocrine regulation of blood pressure. *Indian J Endocrinol Metab* 2011; 15(Suppl 4):S281–S288
- Fyhrquist F, Metsärinne K, Tikkanen I: Role of angiotensin II in blood pressure regulation and in the pathophysiology of cardiovascular disorders. *J Hum Hypertens* 1995; 9(Suppl 5):S19–S24
- Harrison-Bernard LM: The renal renin-angiotensin system. *Adv Physiol Educ* 2009; 33:270–274
- Basso N, Terragno NA: History about the discovery of the renin-angiotensin system. *Hypertension* 2001; 38:1246–1249
- Busse LW, Wang XS, Chalikonda DM, et al: Clinical experience with IV angiotensin II administration: A systematic review of safety. *Crit Care Med* 2017; 45:1285–1294
- Khanna A, English SW, Wang XS, et al; ATHOS-3 Investigators: Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med* 2017; 377:419–430
- Tumlin JA, Murugan R, Deane AM, et al; Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3) Investigators: Outcomes in patients with vasodilatory shock and renal replacement therapy treated with intravenous angiotensin II. *Crit Care Med* 2018; 46:949–957
- Wakefield BJ, Busse LW, Khanna AK: Angiotensin II in vasodilatory shock. *Crit Care Clin* 2019; 35:229–245