



## Angiotensin II (Giapreza™) Protocol

### Background

Sepsis and septic shock are medical emergencies that affect millions of people each year and killing as many as 1 in 4.<sup>1</sup> The cornerstones of therapy are fluid resuscitation, early appropriate antibiotics, source control if needed and vasopressors. A small portion of patients fail to respond to these therapies and develop refractory shock. The definition of refractory septic shock varies in the literature but is generally considered to be hypotension, with end-organ dysfunction, requiring high-dose vasopressor support.<sup>2</sup> The associated mortality of refractory septic shock is up to 60% and as high as 80-90% in patients requiring more than 1 mcg/kg/min of norepinephrine.<sup>2,3</sup> Patients who develop refractory septic shock comprise a very small portion of the population in large randomized controlled trials therefore limited data is available regarding outcomes and management.

**Indications:** Angiotensin II (Ang II) is a vasoconstrictor used to increase blood pressure in adults with septic or other distributive shock.

**Administration:** Starting dose of 5 (*nanograms*) ng/kg/min intravenously via central line only.

**Titration:** Every 5 minutes by increments of 5 ng/kg/min as needed. Maximum dose should not exceed 80 ng/kg/min (During the first 3 hours of administration); after the first 3 hours the maintenance (maximum) dose is 40 ng/kg/min.

**Monitoring:** Critical care setting only with telemetry, arterial blood pressure, and continuous SpO2 monitoring. *DVT Prophylaxis should be started (unless contraindicated) in all patients receiving Angiotensin II.*

## Literature Review

Population	Design and Population	Intervention	Outcomes
ATHOS-3 <sup>4</sup>	<p>Randomized, double-blind, placebo-controlled trial</p> <p><b>Inclusion:</b></p> <p>Age ≥ 18 years with catecholamine resistant hypotension defined as norepinephrine &gt;0.2 mcg/kg/min</p> <ul style="list-style-type: none"> <li>Vasodilatory shock despite volume resuscitation of ≥ 25 mL/kg in previous 24 hours</li> <li>Vasodilatory shock <ul style="list-style-type: none"> <li>Cardiac index (CI) &gt; 2.3 L/min/m<sup>2</sup></li> <li>ScvO<sub>2</sub> &gt;70% with CVP &gt;8 mmHg and MAP 55-70 mmHg</li> </ul> </li> </ul> <p><b>Exclusion:</b></p> <ul style="list-style-type: none"> <li>CV sofa ≤ 3</li> <li>Acute MI</li> <li>VA ECMO or ECMO &lt; 12 hours</li> <li>Liver failure with a MELD of ≥ 30</li> <li>Asthma or current bronchospasm; not mechanically ventilated</li> <li>Acute mesenteric ischemia</li> <li>Aortic dissection or abdominal aortic aneurysm</li> <li>Requirement for &gt; 500 mg hydrocortisone daily</li> <li>Raynaud's phenomenon, systemic sclerosis, or vasospastic disease</li> <li>Life expectancy &lt; 12 hours</li> <li>Active bleed and Hg &lt;7 g/dL or need for &gt;4 units of PRBCs</li> <li>ANC &lt; 1000 cells/mm<sup>3</sup></li> </ul>	<p><b>Angiotensin II (N=163):</b></p> <ul style="list-style-type: none"> <li>Initiated at 20 ng/kg/min and titrated to achieve a MAP ≥ 75 mmHg in first 3 hours</li> <li>Max rate during first 3 hours – 200 ng/kg/min</li> <li>Titration of other vasopressors not allowed except as necessary for safety</li> <li>Max rate between 3 and 48 hours 40 ng/kg/min</li> <li>Titrated to maintain MAP 65-75 mmHg</li> </ul> <p><b>Saline placebo (N=158)</b></p>	<p><b>Primary:</b></p> <p>MAP of ≥ 75mmHg or increase in MAP of ≥ 10 mmHg from baseline</p> <ul style="list-style-type: none"> <li>Ang II 69.9% vs 23.4% placebo (P &lt;0.001)</li> </ul> <p><b>Secondary:</b></p> <p>Change in CV SOFA</p> <ul style="list-style-type: none"> <li>Ang II -1.75 vs -1.28 placebo (P=0.01)</li> </ul> <p>Change in SOFA at 48 hours</p> <ul style="list-style-type: none"> <li>Ang II 1.05 vs 1.04 placebo (P=0.49)</li> </ul> <p><b>Safety:</b></p> <p>Adverse events</p> <ul style="list-style-type: none"> <li>Ang II 87.1% vs 91.8% placebo (NS)</li> <li>No statistically significant difference in individual adverse events except: <ul style="list-style-type: none"> <li>Infections: Ang II 30.1% vs 19% placebo (P=0.029)</li> <li>Delirium: Ang II 5.5% vs 0.6% (P=0.036)</li> <li>Thromboembolic events: Ang II 12.9% vs 5.1% placebo</li> </ul> </li> </ul> <p>Adverse event related drug discontinuation</p> <ul style="list-style-type: none"> <li>Ang II 14.1% vs 21.5% placebo (NS)</li> </ul> <p>7 day mortality: Ang II 29% vs 35% placebo (NS)</p> <p>28 day mortality: Ang II 46% vs 54% placebo (NS)</p>
Tumlin et al <sup>5</sup>	<p>Post hoc analysis of patients treated with renal replacement (RRT) therapy at the time of Ang II initiation</p> <p><b>Exclusion:</b></p> <ul style="list-style-type: none"> <li>End stage renal disease</li> </ul>	<p>As above</p> <p><b>Angiotensin II (N=45)</b></p> <p><b>Saline placebo (N=60)</b></p>	<p><b>Primary:</b></p> <p>28 day survival:</p> <ul style="list-style-type: none"> <li>Ang II 53% vs 30% placebo (HR: 0.52) (P=0.012)</li> </ul> <p><b>Secondary:</b></p> <p>Day 7 alive and free from RRT</p> <ul style="list-style-type: none"> <li>Ang II 38% vs 15% placebo (HR: 2.9) (P=0.007)</li> </ul> <p>Day 7 alive and free from vasopressor</p> <ul style="list-style-type: none"> <li>Ang II 55.6% vs 38.3% placebo (HR: 1.58) (P=0.113)</li> </ul> <p>Day 7 alive and free from ventilator</p> <ul style="list-style-type: none"> <li>Ang II 30.2% vs 10.7% placebo (HR 3.14) (P=0.015)</li> </ul>

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**Guidelines for considering the use of Ang II:**

1. Patient must have clinical features of distributive shock in setting of adequate volume resuscitation and cardiac output (i.e. avoid use in patients with pure low output shock or pure cardiogenic shock)
2. Ang II should NOT be first-line treatment for vasodilatory shock
  - Ang II may be considered as a third-line vasopressor after initiation of Vasopressin
  - Ang II may be considered after initiation of stress dose steroids
  - Ang II may be considered when norepinephrine (NE) equivalents reach  $\geq 0.5$  mcg/kg/min in conjunction with vasopressin and stress dose steroids
3. Ang II should not be used as a rescue therapy for moribund patients

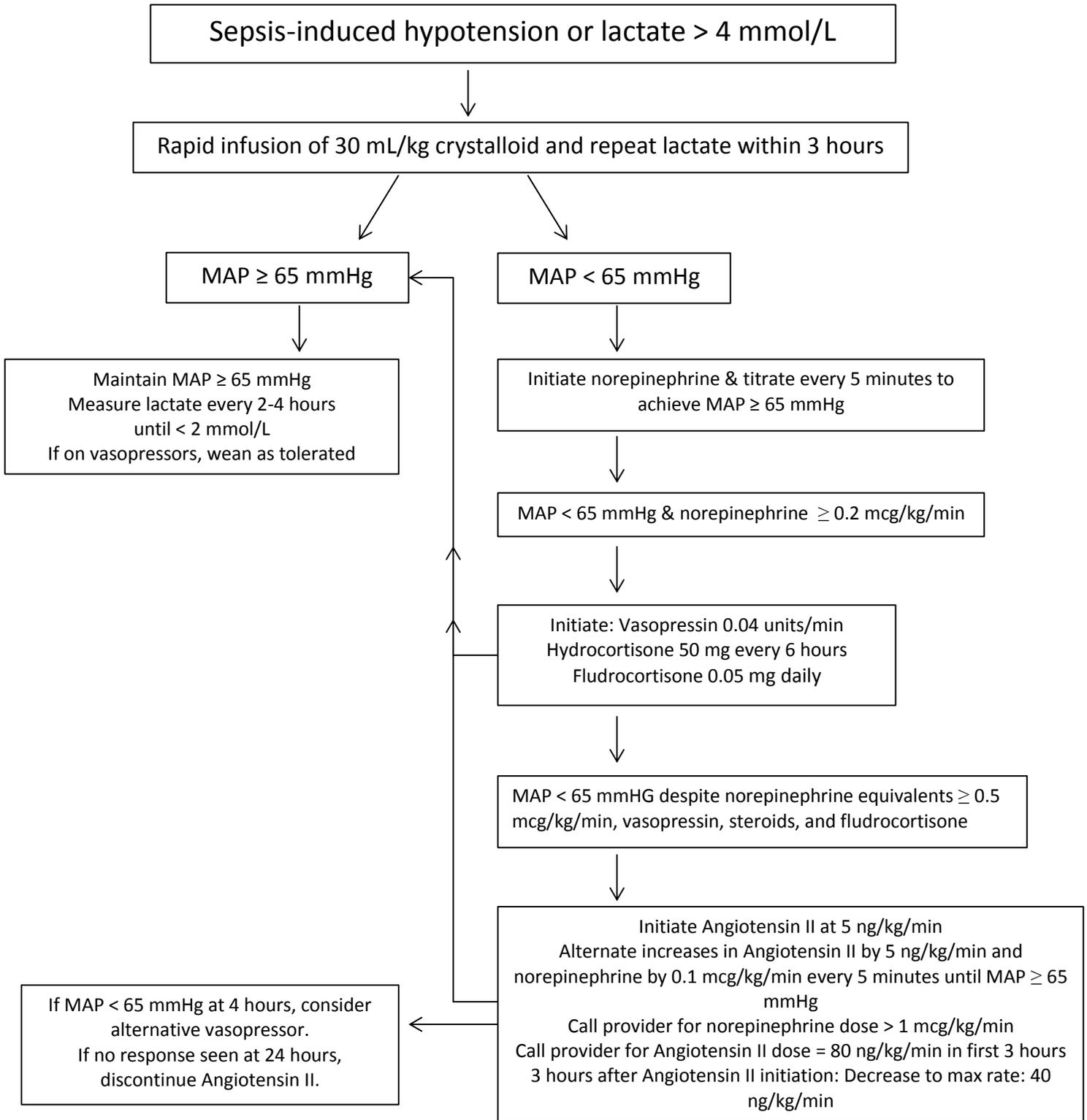
**Guidelines for use of Ang II:**

1. Patient must be in an ICU setting or the ED with intensivist consultation
2. Norepinephrine should be considered as first-line therapy (per guidelines)
3. Goal MAP  $\geq 65$  mmHg, unless otherwise specified by treating physician(s)
4. With worsening shock and increasing vasopressor requirements (NE  $\geq 0.1$  mcg/kg/min), addition of a second vasopressor should be considered (i.e. Vasopressin 0.03 Units/min to 0.04 Units/min)
5. Multimodal use of vasopressors with different mechanisms of action should be considered, including epinephrine, dopamine, phenylephrine, vasopressin and Ang II
6. Administer Ang II via central line only
7. Dosage of Ang II should use Actual Body Weight
8. Ang II can be considered for third-line therapy with refractory shock requiring NE equivalents  $\geq 0.5$  mcg/kg/min, Vasopressin and stress dose steroids
9. Weaning should be done in a stepwise approach
10. Ang II should be down-titrated every 5 minutes by increments of 5 ng/kg/min
11. Auto-stop at 48 hours: reassess continued use

**Exclusion Criteria:**

- Life expectancy < 48 hours
- Platelets < 20 K/mcL
- Current venous thromboembolism with contraindication to anticoagulation

Algorithm for Use<sup>1,7</sup>



## References

1. Rhodes A, Evas LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock. *Critical Care Medicine*. 2017;45(3):1-67.
2. Nandhabalan P, Loannou N, Meadows C, et al. Refractory septic shock: our pragmatic approach. *Critical Care*. 2018;22:215.
3. Brown SM, Lanspa MJ, Jones JP, et al. Survival after shock requiring high-dose vasopressor therapy. *CHEST*. 2013;143(3):664-671.
4. Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. *N Eng J Med*. 2017;377(5):419-430.
5. Tumlin JA, Murugan R, Deane AM, et al. Outcomes in patients with vasodilatory shock and renal replacement therapy treated with intravenous angiotensin II. *Critical Care Medicine*. 2018.
6. Dellinger RP, Schorr CA, Levy MM. A users' guide to the 2016 surviving sepsis guidelines. *Critical Care Medicine*. 2017

# Angiotensin II

## Norepinephrine Equivalents

### Norepinephrine Equivalent (NE)

<b>Drug</b>	<b>Dose</b>	<b>NE</b>
Epinephrine	0.1 mcg/kg/min	0.1 mcg/kg/min
Norepinephrine	0.1 mcg/kg/min	0.1 mcg/kg/min
Dopamine	15 mcg/kg/min	0.1 mcg/kg/min
Phenylephrine	1 mcg/kg/min	0.1 mcg/kg/min
Vasopressin	0.04 Units/min	0.1 mcg/kg/min