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Regional differences in the treatment of refractory vasodilatory shock using Angiotensin II in High Output Shock (ATHOS-3) data

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ABSTRACT

Introduction: Despite international guidelines, regional differences in treatment of vasodilatory shock remain. We characterized these differences using data from Angiotensin II in High Output Shock (ATHOS-3) trial.
Methods: The 321 patients treated in the ATHOS-3 trial were included. Baseline and hour-48 data were analyzed for differences in demographics, clinical characteristics, and treatment patterns, and grouped into four geographical areas: United States, Canada, Europe, and Australasia. Differences were analyzed by Kruskal-Wallis tests for continuous, and chi-square tests for categorical data. Temporal analysis compared changes in the treatment of shock during the treatment period.
Results: Differences in baseline characteristics across geographic areas were noted in BMI, albumin, CVP, MELD score, APACHE II score, and total SOFA score. Baseline norepinephrine and norepinephrine equivalent doses (NED) were higher ($p < .0001$ and $p = .0494$, respectively), and vasopressin use was lower ($p < .0001$) in Europe. Baseline steroids were utilized more in the US and Canada ($p = .0011$).
Conclusions: Management of vasodilatory shock differs globally with respect to utilization of steroids and vasopressors. This practice heterogeneity may influence shock trials interpretation and patient outcomes, though more definitive evidence would require larger prospective intervention data.

1. Introduction

Vasodilatory shock constitutes 66% or more of all shock subtypes. Septic shock is by far the most common type of vasodilatory shock and is defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone [1]. Nearly 6% of critically ill patients will develop refractory shock and will require high-dose vasopressors to maintain adequate mean arterial pressure (MAP) [2]. Norepinephrine is the recommended initial choice of pressor but there is ambiguity regarding second- and third-line agents [1,3-8]. In addition, there appears to be no demonstrable survival advantage for the use of any vasopressor over another [4,9,10]. Early protocolized administration of antibiotics, fluids, and vasopressors, along with necessary source control are the other main components of modern sepsis treatment. The bundling of these interventions may be the main reason why sepsis mortality has fallen over the past 20 years [1,11]. Current international sepsis guidelines like the Surviving Sepsis Campaign (SCC) have incorporated these practices and recommended a standardized approach to treating shock. However, a recent large meta-analysis has shown that protocolized early goal directed therapy (EGDT) had no better outcomes than usual care in three contemporary studies of sepsis [12]. This has led some clinicians to question the definition of usual care and whether this is the same around the world [13]. There is a paucity of data directly comparing regional differences in the care and treatment of septic shock [14]. This may be because a widely accepted definition of refractory septic shock has not been universally embraced and patient and disease-specific factors may affect local treatment patterns [15-17].

We endeavored to utilize data from the ATHOS-3 trial to examine a cohort of refractory septic shock patients from around the globe. The primary objective of ATHOS-3 was to determine whether the addition of angiotensin II to background vasopressors would improve blood pressure in patients with catecholamine-resistant vasodilatory shock [18]. Our primary objective was to characterize regional differences in

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treatment of refractory vasodilatory shock including vasopressor and steroid therapy utilizing data from the ATHOS-3 cohort. We also sought to characterize patient characteristics including clinical and treatment characteristics in the same patient population.

2. Methods

2.1. Study design

We categorized baseline patient demographic and clinical characteristics according to region of clinical site. Therapeutic data were examined at two time periods: at baseline (randomization or prior to study drug), and at 48 h after initiating study drug. Four geographic regions were identified a priori: United States, Canada, Europe, and Australasia. Therapeutic data consisted of utilization and doses of norepinephrine, vasopressin, norepinephrine equivalent doses (NED) and stress-dose steroids. We included 48-h therapeutic data for patients in the placebo group only, so as not to introduce the clinical influence of angiotensin II. All patients randomized in ATHOS-3 were required to have refractory vasodilatory shock defined as a cumulative utilization of vasopressors of >0.2 μg/kg/min of NED for a minimum of 6 h and a maximum of 48 h to maintain a MAP of 55–70 mmHg. NED were calculated using standard conversion measures. For example, an initial cardiovascular SOFA score of 4, and vasopressin (not included in SOFA) at a dose of 0.04 U/min was converted to a norepinephrine equivalent dose (NED) of 0.1 μg/kg/min. (See Fig. 1) [19]. Aside from this requirement, clinicians were free to choose any pressor combination or dose in order to achieve a globally accepted MAP of >65 mmHg. Per study design the MAP target was 75 mmHg up to 3 h, and 65 to 70 mmHg from 3 to 48 h. Norepinephrine, vasopressin, and steroid utilization rates were presented as a percentage based on the total number of patients analyzed at baseline and at 48 h.

2.2. Statistical analysis

Regional differences were compared by non-parametric tests Kruskal-Wallis tests for continuous data and chi-square tests for categorical data. No adjustments for multiple comparisons were incorporated.

3. Results

3.1. Demographic characteristics of the study group

A total of 321 patients were randomized and initiated study drug as part of the ATHOS-3 trial. Two hundred participants were from 34 sites in the United States, 52 from 17 sites in Australasia, 33 from 15 sites in Europe, and 36 from 7 sites in Canada. Demographic characteristics are presented in Table 1. (See supplemental table 1 for comprehensive demographics data.) The median patient age was 64 years of age. 60.7% were male, and 19.9% were described as non-white. Median BMI was 29.1 kg/m^2, though 49.2% of patients from the United States and 50.0% of patients from Canada had BMI >30 kg/m^2, compared to only 33.3% and 28.0% for Europe and Australasia (p-value = .076). There were no statistically significant differences in age, gender, and race across geographic region.

Table 1
Baseline demographics for the ATHOS-3 cohort.

Variables	USA	CAN	Europe	AUS/NZL	Total
Number of Patients (N)	200	36	33	52	321[a]
Age (Years)					
Mean (SD)	62.2 (15.36)	63.9 (14.15)	59.0 (16.45)	63.9 (15.50)	62.3 (15.36)
Median	63.5	64	60	67	64
Range	22–89	26–88	22–88	25–89	22–89
p-value[c]=0.4737					
Gender					
N	200	36	33	52	321
Female	75 (37.5%)	14 (38.9%)	12 (36.4%)	25 (48.1%)	126 (39.3%)
Male	125 (62.5%)	22 (61.1%)	21 (63.6%)	27 (51.9%)	195 (60.7%)
p-value[d]=0.5573					
Ethnicity					
N	200	36	33	52	321
Hispanic or Latino	16 (8.0%)	0 (0%)	1 (3.0%)	0 (0%)	17 (5.3%)
Not Hispanic or Latino	184 (92.0%)	36 (100%)	32 (97.0%)	52 (100%)	304 (94.7%)
p-value[d]=0.0425					
Race					
N	200	36	33	52	321
White	155 (77.5)	27 (75.0%)	28 (84.8%)	47 (90.4%)	257 (80.1%)
Non-White	45 (22.5%)	9 (25%)	5 (15.2%)	5 (9.6%)	64 (19.9%)
White vs Non-white p-value[d]=0.1482					
Baseline Weight (kg)					
N	200	36	33	52	321
Mean (SD)	91.2 (29.17)	92.4 (28.20)	80.1 (25.04)	76.8 (17.53)	87.9 (27.63)
Median	87.5	90.2	73	75	84.5
Range	32.2–228.4	50.0–181.8	50–152.0	45.0–116.0	32.2–228.4
p-value[c] =0.0009					
Baseline Height (cm)					
N	199	34	33	50	316
Mean (SD)	170.6 (11.23)	170.4 (11.43)	169.4 (11.64)	168.4 (9.31)	170.1 (10.99)
Median	170	173.5	170	168.5	170
Range	127–193	147.3–193	150–193	150–188	127–193
p-value[c]=0.3608					
Baseline BMI[b]					
N	199	34	33	50	316
Mean (SD)	31.3 (9.50)	31.4 (8.29)	27.6 (6.76)	27.4 (6.18)	30.3 (8.80)
Median	29.9	29.3	26	26.4	29.1
Range	12.1–66.7	21.6–59.4	17.3–43.1	15.6–47.1	12.1–66.7
p-value[c]=0.0076					

Abbreviation: USA = United States of America, CAN = Canada, AUS/NZL = Australasia, BMI = Body Mass Index, SD = standard deviation.
[a] Modified intention-to-treat population which represents all patients who underwent randomization and began to receive angiotensin II or placebo.
[b] BMI is the weight in kilograms divided by the square of the height in meters.
[c] Wilcoxon rank sum of angiotensin II compared to Placebo.
[d] Fisher's Exact Test for binary outcomes, Chi-square Test for other categorical outcomes of angiotensin II compared to Placebo.

Conversion to Norepinephrine Equivalent

Drug	Dose	Norepinephrine Equivalent
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	1.0 mcg/kg/min	0.1 mcg/kg/min
Vasopressin	0.04 U/min	0.1 mcg/kg/min

Fig. 1.

Table 2
Baseline clinical variables for the ATHOS-3 cohort.

Variables	USA	CAN	Europe	AUS/NZL	Total
Number of Patients (N)	200	36	33	52	321
Baseline Albumin					
N	194	34	31	51	310
Mean (SD)	2.2 (0.61)	2.1 (0.65)	2.3 (0.56)	2.6 (0.52)	2.3 (0.61)
Median	2.2	2.1	2.4	2.8	2.3
Range	1.1–4.7	1.0–4.0	1.4–3.3	1.4–3.5	1.0–4.7
p-value[a]<0.0001					
Baseline $ScVO_2$ (%)					
N	138	33	22	44	237
Mean (SD)	77.5 (9.51)	79.3 (7.55)	76.3% (6.84)	76.2 (7.86)	77.4 (8.75)
Median	76.6	77	78.6	76.1	77
Range	35–99	61.0–99	58–88	50.7–92.2	35.0–99
p-value[a]=0.5107					
Baseline Mean Arterial Pressure					
Mean (SD)	65.7 (5.67)	66.6 (5.76)	65.2 (5.04)	66.6 (4.37)	65.9 (5.42)
Median	66.3	66.5	65.3	67.3	66.3
Range	43.3–92.3	53.3–80.3	52.3–77.3	56–80	43.3–92.3
p-value[a]=0. 5455					
Baseline APACHE II Score [d]					
Mean (SD)	29.1 (8.49)	27.6 (6.76)	23.8 (7.65)	26.7 (8.54)	28 (8.37)
Median	29	26.5	24	26	28
Range	9–54	15–43	10–35	11–51	9–54
p-value[a]=0.0076					
Baseline SOFA Score					
N	197	35	33	51	316
Mean (SD)	12.70 (3.034)	11.49 (2.874)	10.39 (3.391)	12.22 (2.935)	12.24 (3.115)
Median	13.00	11.00	10.00	12.00	12.00
Range	5–21	7–16	5–18	5–19	5–21
p-value[a]=0.0007					
Exposure to ACE Inhibitors					
N	200	36	33	52	321
Yes	18 (9.0%)	2 (5.6%)	1 (3.0%)	9 (17.3%)	30 (9.3%)
p-value [b] = 0.1076					
Medical History of ARDS					
N	200	36	33	52	321
Yes	48 (24%)	5 (13.9%)	5 (15.2%)	2 (3.8%)	60 (18.7%)
p-value[b] = 0.0072					
Medical History of Sepsis					
N	200	36	33	52	321
Yes	173 (86.5%)	31 (86.1%)	19 (57.6%)	36 (69.2%)	259 (80.7%)
p-value[b] = 0.0001					
Cause of Distributive Shock					
N	200	36	33	52	321
Sepsis	173 (85.5%)	31 (86.1%)	19 (57.6%)	36 (69.2%)	259 (80.7%)
Other-Potentially Sepsis	9 (4.5%)	3 (8.3%)	12 (36.4%)	7 (13.5%)	31 (9.7%)
Vasoplegia	9 (4.5%)	0 (0.0%)	2 (6.1%)	8 (15.4%)	19 (5.9%)
Other	8 (4%)	2 (5.6%)	0 (0%)	0 (0%)	10 (3.1%)
Pancreatitis	1 (0.5%)	0 (0.0%)	0 (0%)	1 (1.9%)	2 (0.6%)
Baseline Angiotensin II					
N	173	34	31	46	284
Mean (SD)	226.32 (441.218)	383.18 (639.442)	324.95 (446.859)	350 (541.32)	275.93 (487.653)
Median	58	59.9	116	165.5	83.75
Range	10.5–3340	10.5–2640	10.5–1930	10.5–2740	10.5–3340
p-value[a]=0.0142					

Abbreviation: $ScVO_2$ = Central Venous Oxygen Saturation. MELD = Model of End-stage Liver Disease. APACHE = Acute Physiology And Chronic Health Evaluation. SOFA = Sequential Organ Failure Assessment. ACE = Angiotensin Converting Enzyme. ARB = Angiotensin II Receptor Blocker. ARDS = Acute Respiratory Distress Syndrome.
[a] Wilcoxon rank sum of angiotensin II compared to Placebo.
[b] Fisher's Exact Test for binary outcomes, Chi-square Test for other categorical outcomes of angiotensin II compared to Placebo.

3.2. Clinical characteristics of the study group

Clinical characteristics are presented in Table 2. (See supplemental table 2 for comprehensive clinical data.) At randomization 18.7% of patients were noted to have ARDS at and 90.4% had a diagnosis of sepsis or potential sepsis. For the total cohort, patient medians included an albumin level of 2.3 g/dL, central venous oxygen saturation (ScVO2) of 77%, central venous pressure (CVP) of 12 mmHg, cardiac index of 3.1 L/min/m^2, MELD score of 22, MAP of 66.3 mmHg, and an APACHE II score of 28. Albumin levels, CVP, APACHE II, SOFA, and MELD scores were different among regions. Albumin levels below 2.5 g/dL were more common in the United States (68%) and Canada (79.4%),

compared to Europe (51.6%) and Australasia (33.3%), (p-value <.0001). MELD scores were higher for the Canadian cohort (24.1) compared to the United States (21.1), Europe (19.1) or Australasia (20.2), (p-value = .0191). APACHE II was lower in Europe (23.8) than in the United States (29.1), Canada (27.6), or Australasia (26.7), (p-value = .0076). SOFA scores exhibited a similar pattern (p-value = .0007). ARDS was more commonly cited as a diagnosis in the United States (24%) compared to Canada (13.9%), Europe (15.2%), and Australasia (3.8%), (p-value = .0072). Known septic causes of vasodilatory shock were significantly less common in Europe and Australasia (57.6% and 69.2%) compared to the United States and Canada (86.5% and 86.1%), (p-value = .0001). There were no statistically significant differences across regions in the baseline ScVO2, cardiac index, or MAP.

3.3. Characteristics of therapeutic intervention

Details regarding baseline therapeutic interventions by region are presented in Table 3. For the total cohort, median norepinephrine and NED at baseline were 0.36 μg/kg/min and 0.46 μg/kg/min, respectively. 67.0% of all patients were receiving vasopressin. Overwhelmingly, norepinephrine was used in all regions as a first-line agent, but the use of other vasopressors as second-line agents varied considerably. While 13.1% of the total cohort received epinephrine at baseline, in the United States and Canada, 15.5% and 16.7% of patients received epinephrine, versus 3.0% and 7.7% in Europe and Australasia, respectively. Patients in Canada received more phenylephrine (44.4%) than those in the United States (16.5%), versus none of the patients in Europe or Australasia. Dopamine was used for 2.0% of the patients in the United States and 3.8% of patients in Australasia. Vasopressin use varied widely by region as well. In the United States and Canada, vasopressin was used extensively, in 77.0% and 83.3% of patients, respectively. 48.1% of Australasian patients received vasopressin, while in Europe, only 18.2% received vasopressin ($p < .0001$). 58.3% of all patients at baseline received stress-dose steroids, which were used extensively in the United States (63.0%) and Canada (72.2%), but less so in Europe (48.5%), and Australasia (36.5%), ($p = .0011$).

Table 4 presents data from the 129 patients from ATHOS-3 placebo group who were alive at 48 h. Norepinephrine and NED for the entire cohort were 0.25 μg/kg/min for the 72 patients receiving norepinephrine and 0.18 μg/kg/min for all patients, respectively. Norepinephrine remained the pressor of choice in all regions, used in 55.8% of all patients, though in 84.6% of patients in Europe, 77.8% in Canada, but in only 50.0% in Australasia and 50.6% in the United States. Second-line pressor choices still varied. Vasopressin was used in 25.6% of all patients but in only 7.7% of patients in Europe and 15.0% in Australasia compared to 26.4% and 66.7% in the United States and Canada ($p < .0001$). At 48 h, epinephrine was utilized only in the United States (6.9%). Phenylephrine was used most commonly in Canada (22.2%) and less so in the United States (5.7%). Dopamine was used only in Australasia (5.0%). Stress-dose steroids were still used heavily by the entire cohort (42.6% of all patients), most commonly in the United States (48.3%) and least commonly in Australasia (20.0%). There was no statistically significant difference among regions for the use of steroids at 48-h ($p = .1268$).

3.4. Temporal analysis

Temporal analysis illustrating changes in therapeutic interventions (dose and frequency of vasopressors and steroids) from baseline to hour-48 is presented in Table 5. In all regions, mean norepinephrine and NED fell, suggesting some degree of resolution of shock in the surviving patients. Correspondingly, the use of vasopressin and steroids also fell. Mean norepinephrine doses regionally bore little relationship to the percentage of patients on steroids. The United States, Europe, and Australasia all continued steroids at higher rates than commensurate with the decline in NED. In the United States and Australasia, despite NED that fell by 64.4% and 70.7% respectively, steroid utilization only fell by 23.4% and 45.3%. By comparison, in Europe, despite NED that fell by 35.4%, steroid utilization only fell by 4.8%. The outlier was Canada, which discontinued stress-dose steroids at about the same rate as NED. In Canada, norepinephrine dosing fell 48.8% and steroid use fell 53.4%.

4. Discussion

This retrospective cohort analysis of regional variation in practices from the ATHOS-3 trial highlights global similarities and differences in demographics, clinical characteristics, and therapeutic interventions with regards to septic and other vasodilatory shock. Patient acuity was high (as reflected in SOFA and APACHE II scores), but some important differences could potentially have health implications, including BMI (higher in the western hemisphere), markers of liver dysfunction (higher in Canada), and the diagnosis of ARDS (higher in the United States and lower in Australasia). Consistent with current international guidelines, norepinephrine was the primary vasopressor in all four regions across all comparison time points. Dopamine use was minimal, likely reflecting a preference to avoid this agent due to known higher risk of arrhythmia and no added benefit over norepinephrine [4]. Vasopressin appears to be the most common second-line agent globally but was relied on much less heavily in Europe, which translated into a higher reliance on catecholamines. Additionally, steroid utilization differed markedly across regions. Steroids were relied on extensively in the western hemisphere, but much less so in Europe and Australasia. Though the expected practice would deem the utilization of steroids necessary with hemodynamic instability despite increasing dose of catecholamines and or vasopressin, our cohort did not show a clear relationship of steroid use and norepinephrine equivalent doses. In fact, in those patients that were started on steroids, in all regions except Canada, the rate of de-escalation of steroids did not keep pace with the rate of decline of norepinephrine equivalents of vasopressors. The use of steroids in septic shock has conflicting evidence [20,21]. The Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial investigators noted a faster resolution of shock with a continuous infusion of hydrocortisone but no overall mortality benefit [22]. Annane et al. in a separate analysis have shown a survival benefit with the use of low dose combination steroids [23]. An updated recent meta-analysis of >10,000 patients showed a very small reduction in mortality at the cost of increase in neuromuscular weakness [24].

In Europe, there was a tendency for increased dependence on catecholamines, and rate of vasopressin utilization at baseline and at 48 h was minimal as compared with the United States and Canada. These observations have important implications for the understanding of practice habits and highlighted the current heterogeneity in management practices of refractory shock. SSC guidelines recommend the addition of either epinephrine or vasopressin when an escalating dose of norepinephrine cannot maintain a MAP >65 mmHg [1]. However, current guidelines stop short of recommending a specific dose, or a timing of initiation in relationship to dose combination. Some evidence suggests that initiation of vasopressin 12–48 h after catecholamine initiation may provide the best response [25]. Catecholamine agents may also contribute to morbidity and mortality at excessive doses [26,27]. Adjunctive agents like vasopressin may have a role in catecholamine-resistant hypotension by virtue of their catecholamine-sparing effect, but this has not consistently translated into a mortality benefit [28-32]. This lack of consistent mortality benefit, we hypothesize, is the major reason that global critical care societies have refrained from strong recommendation for the use of non-catecholamine vasopressor support.

The concept of turning to adjunctive agents, such as steroids when catecholamines become ineffective is often referred to as catecholamine resistance. As with the case of combination vasopressors, the guidelines remain unclear on timing of steroid initiation, in relation to vasopressor dosing. Part of this issue is the lack of clarity on what constitutes catecholamine-resistant hypotension [2,28,33-35]. The ATHOS-3 trial

Table 3
Baseline therapeutic interventions across regions for the ATHOS-3 cohort.

Interventions	USA	CAN	Europe	AUS/NZL	Total
Number of Patients	200	36	33	52	321
Baseline Norepinephrine dose*					
N	193	34	33	51	311
% of Total N	96.5%	94.4%	100.0%	98.1%	96.9%
Mean (SD)	0.32 (0.317)	0.28 (0.224)	0.63 (0.520)	0.37 (0.319)	0.36 (0.348)
Median	0.23	0.23	0.48	0.25	0.25
Range	0.02–2.58	0.04–1	0.16–2.68	0.07–1.64	0.02–2.68
p-value[a] < 0.0001					
Baseline Norepinephrine Equivalent Dose (NED)*					
N	200	36	33	52	321
Mean (SD)	0.45 (0.4111)	0.43 (0.245)	0.65 (0.526)	0.41 (0.328)	0.46 (0.400)
Median	0.34	0.37	0.48	0.29	0.34
Range	0.05–3.8	0.10–1.10	0.16–2.68	0.10–1.72	0.05–3.8
p-value [a] = 0.0494					
Baseline NED*					
N	200	36	33	52	321
<0.2	22 (11%)	4 (11.1%)	1 (3.0%)	8 (15.4%)	35 (10.9%)
0.2–0.35	85 (42.5%)	11 (30.6%)	10 (30.3%)	25 (48.1%)	131 (40.8%)
≥ 0.35 - < 0.5	38 (19%)	10 (27.8%)	7 (21.2%)	6 (11.5%)	61 (19.0%)
≥ 0.5	55 (27.5%)	11 (30.6%)	15 (45.5%)	13 (25%)	94 (29.3%)
p-value[b] = 0.2106					
Baseline Epinephrine Dose*					
N	31	6	1	4	42
% of Total N	15.5%	16.7%	3.0%	7.7%	13.1%
Mean (SD)	0.2 (0.313)	0.06 (0.016)	0.1 (NA)	0.12 (0.169)	0.17 (0.277)
Median	0.08	0.06	0.1	0.05	0.08
Range	0.00–1.50	0.05–0.08	0.1–0.1	0.00–0.37	0.00–1.50
Baseline Phenylephrine Dose*					
N	33	16	0	0	49
% of Total N	16.5%	44.4%	0.0%	0.0%	15.3%
Mean (SD)	2.13 (1.568)	1.49 (1.086)	NA	NA	1.92 (1.450)
Median	1.57	1.44			1.52
Range	0.47–7.41	0.28–4.64			0.28–7.41
Baseline Dopamine dose*					
N	4	0	0	2	6
% of Total N	2.0%	0.0%	0.0%	3.8%	1.9%
Mean (SD)	8.38 (8.138)	NA	NA	7.50 (3.536)	8.08 (65.15)
Median	5.5			7.5	6.5
Range	2.5–20.00			5.00–10.00	2.50–20.00
Mean (SD)	0.45 (0.411)	0.43 (0.245)	0.65 (0.526)	0.41 (0.328)	0.46 (0.400)
Median	0.34	0.37	0.48	0.29	0.34
Range	0.05–3.80	0.1–1.1	0.16–2.68	0.10–1.72	0.05–3.8
p-value [a] = 0.494					
Baseline Vasopressin Use					
Yes	154 (77.0%)	30 (83.3%)	6 (18.2%)	25 (48.1%)	215 (67.0%)
p-value [b] < 0.0001					
Baseline Stress-Dose Steroids Use					
Yes	126 (63.0%)	26 (72.2%)	16 (48.5%)	19 (36.5%)	187 (58.3%)
p-value [b] = 0.0011					
Baseline vasopressin analogues use					
Yes	0 (0%)	0 (0%)	1 (3%)	1 (1.9%)	2 (0.6%)
p-value [b] = 0.1122					
Baseline methylene blue use					
Yes	5 (2.5%)	1 (2.8%)	0 (0%)	1 (1.9%)	7 (2.2%)
p-value [b] = 0.8236					
Baseline vasopressin dose (U/min)					
% of Total N	77.0%	83.3%	18.2%	48.1%	67.0%
Mean (SD)	0.04 (0.012)	0.04 (0.011)	0.03 (0.009)	0.04 (0.017)	0.04 (0.013)
Median	0.04	0.04	0.04	0.04	0.04
Range	0.00–0.10	0.03–0.08	0.02–0.04	0.00–0.08	0.00–0.1

[a] Wilcoxon rank sum of angiotensin II compared to Placebo.
[b] Fisher's Exact Test for binary outcomes, Chi-square Test for other categorical outcomes of angiotensin II compared to Placebo.
* Doses at mcg/kg/min.

designated a NED of >0.2 μg/kg/min based on a calculated 50% mortality using SOFA scores, but other higher doses that cited nearly 80–100% mortality have been proposed as well [33,34,36].

Our study has numerous strengths and limitations. We devised a simple clinical question which allowed for optimal analysis given a limited data set. The a priori determination of regional boundaries were

Table 4
48-Hour Therapeutic Data for the ATHOS-3 placebo group.

Interventions	USA	CAN	Europe	AUS/NZL	Total
Number of Patients[a]	87	9	13	20	129
48-Hour Norepinephrine Dose*					
N	44	7	11	10	72
% of Total N	50.6%	77.8%	84.6%	50.0%	55.8%
Mean (SD)	0.22 (0.350)	0.18 (0.112)	0.44 (0.496)	0.20 (0.243)	0.25 (0.353)
Median	0.10	0.20	0.30	0.10	0.11
Range	0.01–2.13	0.02–0.31	0.03–1.51	0.01–0.78	0.01–2.13
p-value	0.4174				
Norepinephrine Equivalent dose* at 48-h					
N	86	9	12	20	127
Mean (SD)	0.16 (0.319)	0.22 (0.141)	0.42 (0.526)	0.12 (0.226)	0.18 (0.329)
Median	0.04	0.25	0.26	0.01	0.06
Range	0.00–2.50	0.00–0.39	0.00–1.68	0.00–0.88	0.00–2.50
p-value	0.0110				
48-Hour NED*					
N	52	8	11	11	82
<0.2	32 (61.5%)	2 (25%)	4 (36.4%)	7 (63.6%)	45 (54.9%)
≥ 0.2- < 0.35	8 (15.4%)	4 (50%)	3 (27.3%)	2 (18.2%)	17 (20.7%)
≥ 0.35 - < 0.5	6 (11.5%)	2 (25%)	0 (0%)	0 (0%)	8 (9.8%)
≥ 0.5	6 (11.5%)	0 (0%)	4 (36.4%)	2 (18.2%)	12 (14.6%)
48-Hour Epinephrine Dose*					
N	6	0	0	0	6
% of Total N	6.9%	0.0%	0.0%	0.0%	4.7%
Mean (SD)	0.07 (0.049)	NA	NA	NA	0.07 (0.049)
Median	0.05	NA	NA	NA	0.05
Range	0.03–0.16	NA	NA	NA	0.03–0.16
48-Hour Phenylephrine Dose*					
N	5	2	0	0	7
% of Total N	5.7%	22.2%	0.0%	0.0%	5.4%
Mean (SD)	2.36 (0.683)	1.01 (0.365)			1.98 (0.878)
Median	2.59	1.01			1.80
Range	1.53–3.18	0.75–1.27			0.75–3.18
48-Hour Dopamine dose*					
N	0	0	0	1	1
% of Total N	0.0%	0.0%	0.0%	5.0%	0.8%
Mean (SD)				10.00 (NA)	10.00 (NA)
Median				10.00	10.00
Range				10–10	10–10
48-h Vasopressin Use (U/min)					
N (Yes)	23 (26.4%)	6 (66.7%)	1 (7.7%)	3 (15.0%)	33 (25.6%)
Mean (SD)	0.04 (0.015)	0.04 (0.005)	0.07 (NA)	0.03 (0.013)	0.04 (0.014)
Median	0.04	0.04	0.07	0.04	0.04
Range	0.02–0.10	0.03–0.04	0.07–0.07	0.02–0.04	0.02–0.10
P-value	<0.0001				
48-Hour Stress-Dose Steroids Use					
N (Yes)	42 (48.3%)	3 (33.3%)	6 (46.2%)	4 (20.0%)	55 (42.6%)
P-value	0.1268				
SOFA Score[b] at 48 h					
N	87	9	13	20	129
Mean (SD)	11.72 (5.148)	12.44 (5.769)	10.85 (4.375)	10.25 (5.118)	11.46 (5.094)
Median	12.00	11.00	10.00	10.00	11.00
Range	3–22	1–19	3–18	2–19	1–22
P-value	0.5496				

Abbreviation: SOFA = Sequential Organ Failure Assessment.
* Doses in mcg/kg/min.
[a] Number of patients at hour-48 in the placebo arm only.
[b] Scores on the Model for End-Stage Liver Disease (MELD) range from 6 to 40, with higher scores indicating more advanced liver disease.

consistent with the possible likelihood of differences in geographical critical care practice habits. Additionally, the ATHOS-3 data represents a relatively large and timely patient cohort with refractory septic shock. That said, despite a large total number of participants, regional number of participants per geographic area were small in some regions, must notable Canada, and may not truly reflect practice patterns in that specific region. In addition, the demographic and clinical depiction of the refractory shock patient described herein may not reflect the prototypical patient, as certain populations were excluded, including patients with burn injuries, neutropenia, mixed shock, and certain concomitant conditions, like asthma, mesenteric ischemia, acute myocardial infarction or aortic aneurysm [18]. These conditions may represent a significant number of patients with refractory septic shock, and their demographics, clinical data and preferred therapeutic interventions may be different. Our analyses were not adjusted for multiple comparisons or multiple endpoints. Our results are also subject to survival bias, as the participants who died before 48 h were not included in the final analysis. Moreover, because this is a cross-sectional study, results do not reflect specific characteristics or interventions for any given patient. Our results serve as a descriptive review of management practices for refractory vasodilatory shock across the world, and differences in vasopressors and steroid use reported would best serve to be regarded as hypothesis-generating.

Table 5
Temporal analysis.

		Baseline	Hour 48
	Total on NE	96.5%	50.6%
United States	Mean NED*	0.45	0.16
	Total on Vasopressin	77.0%	26.4%
	Total on Steroids	63.0%	48.3%
	Total on NE	94.4%	77.8%
Canada	Mean NED*	0.43	0.22
	Total on Vasopressin	83.3%	66.7%
	Total on Steroids	72.2%	33.3%
	Total on NE	100.0%	84.6%
Europe	Mean NED*	0.65	0.42
	Total on Vasopressin	18.2%	7.7%
	Total on Steroids	48.5%	46.2%
	Total on NE	98.1%	50.0%
Australasia	Mean NED*	0.41	0.12
	Total on Vasopressin	48.1%	15.0%
	Total on Steroids	36.5%	20.0%

Abbreviation: NE = norepinephrine. NED = norepinephrine-equivalent dose.
* Dose in mcg/kg/min.

In conclusion, there is a significant inconsistency in treatment practices of refractory vasodilatory shock worldwide. This may reflect incomplete understanding of this syndrome, a lack of clear and concise recommendations or guidelines, along with insufficient high-quality data across varied geographical regions of clinical practice. Importantly, this may be an opportunity for improvement in the management of vasodilatory shock with a careful and thorough analysis of currently used vasopressor and steroid regimens and practice patterns in different parts of the world.

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Authors' contributions

All authors qualify for authorship under the ICMJE Recommendations (www.icmje.org), including: substantial contributions to the conception or design of the work (MKA, AKK,DH,LWB,CMN); drafting the article (MKA,AKK,LWB,CMN); critical revisions of the article (AKK, MKA,LWB); final approval of the version to be published (MKA,AKK, LWB,CMN,DH).

[a]Score from 6 to 24, with higher scores indicating higher mortality rate.

Conflict of interest

Dr. (s) Busse and Khanna consult for the La Jolla pharmaceutical Co.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.12.007.

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