requirements that the American Board of Internal Medicine (ABIM) introduced in January 2014 require more effort than previous iterations. Completing NEJM Knowledge+ modules allows clinicians to earn both AMA PRA (American Medical Association Physician's Recognition Award) Category 1 Credits and up 80 points toward the Self-Evaluation of Medical Knowledge requirement of the ABIM Maintenance of Certification (MOC) program; accumulated MOC points are automatically reported to the ABIM so that clinicians can focus on learning rather than on tracking their activities.

Each week, we will post a question from NEJM Knowledge+ to help *Journal* readers test their understanding and see some of what we've created. There's more information available at the program website, knowledgeplus.NEJM.org.

We know that for busy practitioners, time is the most precious commodity. The NEJM Knowledge+ learning system is designed to help clinicians identify what they really know and what they don't know and then to help fill in the gaps efficiently and effectively. We think this program will benefit physicians as a community of lifelong learners — and will ultimately benefit the patients who rely on us to make the right decision every time.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

DOI: 10.1056/NEJMe1401777

Is There a Good MAP for Septic Shock?

James A. Russell, M.D.

As fundamental as the issue is, there is no clear, high-level evidence to determine the most effective mean arterial pressure (MAP) for resuscitation of patients with septic shock. During hypotension, three salient aspects of cardiovascular physiology are important. First, the autoregulation of cerebral blood flow maintains an adequate level over a wide range of pressures until a critical pressure (about 50 mm Hg) is reached; below this level, as the pressure falls, so does cerebral blood flow. Second, chronic hypertension shifts the autoregulatory curve of the relationship between pressure and perfusion so that perfusion is decreased at a higher critical pressure; long-term antihypertensive treatment restores the autoregulatory curves toward normal. Third, there are differences among organs in the critical point for oxygen delivery: gut oxygen delivery decreases earlier in shock than oxygen delivery to other organs. The consequence of inadequate perfusion is ischemic injury to the kidney, gut, brain, and myocardium, followed by multiple organ dysfunction and death.

The goal of cardiovascular resuscitation of septic shock is to improve organ perfusion, often by increasing the MAP. Adequate fluid resuscitation is limited when the administration of fluids causes edema (e.g., acute lung injury). Vasopressors are added if fluid resuscitation does not restore adequate perfusion, but such therapy is limited by excessive vasoconstriction and organ ischemia. A common clinical problem is distinguishing between ischemia that is caused by inadequate resuscitation (e.g., as manifested by oliguria) and ischemia that is caused by excessive vasoconstriction.

Reviews[1,2] and sepsis guidelines[3] recommend a target MAP of more than 65 mm Hg in patients with septic shock. However, these recommendations are based on low-quality evidence. Accordingly, Asfar et al.[4] now report in the *Journal* the results of a large, randomized, controlled trial of targeting a low MAP (65 to 70 mm Hg) versus a high MAP (80 to 85 mm Hg) among patients with septic shock at 29 centers in France. By 28 days, there was no significant difference in mortality (the primary end point) between the low-target group and the high-target group. In the prospectively defined stratum of patients with chronic hypertension (more than 40% of the patients), those in the high-target group had less renal dysfunction and need for renal-replacement therapy than did those in the low-target group. However, there was a safety concern, since patients in the high-target group had an increased risk of new atrial fibrillation, which is

Table 1. Comparison of Norepinephrine Control Groups and Intervention Groups in Randomized, Controlled Trials of Vasoactive Agents in Shock.*

Trial	Mean Arterial Pressure (MAP)			Norepinephrine Infusion Rate			Fluid Balance			Renal-Replacement Therapy	Death at 28 Days
	Target	Actual, Day 0	Actual, Day 1	Day 0	Day 1	Day 2	Day 0	Day 1	Days 0 to 4		
	mm Hg			*μg/kg/min*			*ml*			%	
Asfar et al.[4]†											
Low-target group											
All patients	65 to 70	74	74	0.35	0.45	0.16	1603	1016	2,800	35.8	34
Patients with chronic hypertension	65 to 70									42.2	
High-target group											
All patients	80 to 85	74	84	0.40	0.58	0.38	1595	1106	2,400	33.5	36
Patients with chronic hypertension	80 to 85									31.7	
Annane et al.[6]‡	70	70	80	0.94	1.09	0.65	1586	172	–2,767	24.8	34
De Backer et al.[7]	MD	58	76	0.54	0.82	0.68	2100	1700	8,300	17.0§	48
Myburgh et al.[8]¶	MD	70	73	0.26	0.17	0.07	2232	1782	5,712	22.1	26
Rivers et al.[9]‖	65	76	81	NA	NA	NA	3500	NA	10,602**	NA	49
Russell et al.[10]	65 to 75	72	73	0.28	0.20	0.08	1500	2500	11,000	43.6	39

* MD indicates clinician judgment, and NA not available.
† Listed are results for both the control (low-target) group and the intervention (high-target) group.
‡ In the study by Annane et al., fluid balance was reported for survivors only.
§ The percentage was 19.9% in the subgroup with septic shock.
¶ In the study by Myburgh et al., if no target MAP was ordered, the default target MAP was 70 mm Hg.
‖ In the study by Rivers et al., the control group received a combination treatment.
** Fluid balance was averaged over 3 days rather than 4.

independently associated with an increased risk of stroke.[5] Unfortunately, stroke was not evaluated by Asfar and colleagues.

The strengths of this trial are that the intervention was assigned by blinded randomization in a multicenter context in intensive care units; the two study groups were well balanced; the intervention was a pragmatic, real-world study; and the difference in ranges of MAP values between the two groups was significant. One limitation was that the interventions targeting a low or high MAP were not blinded.

How do these results align with those of other randomized, controlled trials of vasoactive interventions in shock? I compared intervention application and outcomes of this study with both published and unpublished data regarding the norepinephrine control groups of large, randomized, controlled trials of shock[6-10] (Table 1). As compared with the findings in the study by Asfar et al., the target and actual MAP on day 1 in trials in which vasoactive agents were used were similar to those in the low-target group and lower than those in the high-target group. Asfar and colleagues used less fluid and higher doses of norepinephrine than were used in some trials[8-10] but administered less norepinephrine and lower fluid levels than were used in another trial.[7] Thus, there is variability in how fluids and vasopressors are used to achieve target MAPs in randomized, controlled trials. Finally, rates of death in the trial by Asfar el al. were similar to those in two trials,[6,10] higher than those in one trial,[8] and lower than those in two other trials.[7,9] These mortality differences may arise from differences in the inclusion criteria used in these trials (septic shock,[4,6,10] severe sepsis,[9] and shock[7,8]) and trial location,[4,6-10] since mortality associated with

septic shock varies according to country,[11] making comparisons between countries and continents difficult.

The findings of Asfar et al. have at least three major clinical implications. First, they show that there is no indication for routinely targeting a high MAP in patients with septic shock, since there was no significant between-group difference in mortality, although patients in the high-target group had an increased rate of atrial fibrillation. Second, a high MAP target may decrease the risk of renal injury and the need for renal-replacement therapy (number needed to treat of 9.5 to prevent one patient from needing renal-replacement therapy) in patients with hypertension. I make this point because of the well-known risks and costs of renal-replacement therapy. Thus, there are several target MAPs for septic shock, depending on the circumstances of the patient. In some randomized, controlled trials (and in clinical practice), practitioners use more fluid (increasing the risk of acute lung injury), whereas others use more vasopressors (increasing the risk of renal injury). Indeed, methods for targeting a MAP among patients in septic shock are probably critical to the success of the strategy and deserving of greater investigation.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Center for Heart Lung Innovation and the Division of Critical Care Medicine, St. Paul's Hospital, University of British Columbia, Vancouver, Canada.

This article was published on March 18, 2014, at NEJM.org.

1. Vincent J-L, De Backer D. Circulatory shock. N Engl J Med 2013;369:1726-34.
2. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013;369:840-51. [Erratum, N Engl J Med 2013; 369:2069.]
3. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013;39:165-228.
4. Asfar P, Meziani F, Hamel J-F, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med 2014; 370:1583-93.
5. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. JAMA 2011;306:2248-54.
6. Annane D, Vignon P, Renault A, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet 2007;370:676-84. [Erratum, Lancet 2007;370:1034.]
7. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010;362:779-89.
8. Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, Santamaria J. A comparison of epinephrine and norepinephrine in critically ill patients. Intensive Care Med 2008;34:2226-34.
9. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.
10. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008;358:877-87.
11. Levy MM, Artigas A, Phillips GS, et al. Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study. Lancet Infect Dis 2012; 12:919-24.

DOI: 10.1056/NEJMe1402066