Interest of early combination of fluids and

vasopressors in septic shock

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Conflicts of interest

Member of the Medical Advisory Board of Getinge/Pulsion

Fluid infusion

↗ Mean systemic pressure

Intensive Care Med (2013) 39:1487–1488	EDITORIAL	
Jean-Louis Teboul	Mean systemic pressure: we can now estimate it, but for what?	

Venous return = (Pms – RAP) / Resistance to venous return



Effects of passive leg raising and volume expansion on mean systemic pressure and venous return in shock in humans

Laurent Guérin^{1,2}, Jean-Louis Teboul^{1,2}, Romain Persichini^{1,2}, Martin Dres^{1,2}, Christian Richard^{1,2} and Xavier Monnet^{1,2*}

Critical Care (2015) 19:411



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Fluid infusion

↗ Mean systemic pressure

✓ Venous Return and CO in preload responsive pts

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Critical Care (2015) 19:411

Mean systemic pressure was estimated by end-expiratory and end-inspiratoy occlusion manœuvres





Intensive Care Med (2015) 41:12 Manuel Ignacio Monge García Pedro Guijo González Manuel Gracia Romero Anselmo Gil Cano Chris Oscier Andrew Rhodes Robert Michael Grounds Maurizio Cecconi	ORIGINAL Effects of fluid administ in septic shock patients	tration on arterial load
SVR, dyn s cm ⁻⁵	Before volume expansion	After volume expansion
Preload responders	1058 (672–1475)	951 (652–1418)***
Preload non-responders	949 (614–1456)	928 (656–1650)
FI	uid infusion decreased when CO increased	SVR





Norepinephrine exerts an inotropic effect during the early phase of human septic shock

O. Hamzaoui^{1,*}, M. Jozwiak², T. Geffriaud², B. Sztrymf¹, D. Prat¹, F. Jacobs¹, X. Monnet², P. Trouiller¹, C. Richard² and J.L. Teboul²

British Journal of Anaesthesia, 120 (3): 517–524 (2018)







Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension

Olfa Hamzaoui, Jean-François Georger, Xavier Monnet, Hatem Ksouri, Julien Maizel, Christian Richard, Jean-Louis Teboul^{*}

Critical Care 2010, 14:R142





Olfa Hamzaoui, Jean-François Georger, Xavier Monnet, Hatem Ksouri, Julien Maizel, Christian Richard, Jean-Louis Teboul

Critical Care 2010, **14**:R142

Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients*

... as **fluid** infusion does

Xavier Monnet, MD, PhD; Julien Jabot, MD; Julien Maizel, MD; Christian Richard, MD; Jean-Louis Teboul, MD, PhD

Crit Care Med 2011; 39:689-694

Messages of these two studies

- NE increases cardiac preload
- NE increases CO in preload-dependent patients
- NE reduces the degree of preload-dependency

How does **NE impact** the **venous circulation**?

by blood **redistribution** from **unstressed** to **stressed** volume? Effects of norepinephrine on mean systemic pressure and venous return in human septic shock*

Romain Persichini, MD; Serena Silva, MD; Jean-Louis Teboul, MD, PhD; Mathieu Jozwiak, MD; Denis Chemla, MD, PhD; Christian Richard, MD; Xavier Monnet, MD, PhD

Crit Care Med 2012; 40:3146–3153



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Crit Care Med 2012; 40:3146-3153

In spite of an increase in venous resistance, venous return increases with NE through an increase in Mean Systemic Pressure related to blood redistribution from unstressed to stressed volume





Norepinephrine potentiates the efficacy of volume expansion on mean systemic pressure in septic shock

Imane Adda^{*}, Christopher Lai, Jean-Louis Teboul, Laurent Guerin, Francesco Gavelli and Xavier Monnet

Crit Care (2021) 25:302



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Sepsis in European intensive care units: Results of the SOAP study*

Jean-Louis Vincent, MD, PhD, FCCM; Yasser Sakr, MB, BCh, MSc; Charles L. Sprung, MD; V. Marco Ranieri, MD; Konrad Reinhart, MD, PhD; Herwig Gerlach, MD, PhD; Rui Moreno, MD, PhD; Jean Carlet, MD, PhD; Jean-Roger Le Gall, MD; Didier Payen, MD; on behalf of the Sepsis Occurrence in Acutely III Patients Investigators

Crit Care Med 2006; 34:344–353

44

Table 7. Multivariate, forward stepwise logistic regression analysis in sepsis patients (n = 1177), with intensive care unit mortality as the dependent factor

	OR (95% CI)	p Value
SAPS II score ^a (per point increase)	1.0(1.0-1.1)	<.001
Cumulative fluid balance ^{b} (per liter increase)	1.1(1.0-1.1)	.001
Age (per vear increase)	1.0 (1.0–1.0)	.001
Init		02
Blo Desitive supplicative	fluid halanca	04
Ciri POSILIVE Cumulative	e nuid balance	08
Pse		17
Med is an independent factor as	sociated with morta	lity 49

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RESEARCH

Open Access

Early versus delayed administration of norepinephrine in patients with septic shock

Xiaowu Bai, Wenkui Yu^{*}, Wu Ji, Zhiliang Lin, Shanjun Tan, Kaipeng Duan, Yi Dong, Lin Xu and Ning Li^{*}

Critical Care 2014, 18:532

Characteristic	<2 hours (number = 86)	\geq 2 hours (number = 127)	P value
24-hour norepinephrine administration (mg)	29.4 ± 9.7	32.8 ± 10.0	0.013
Time to initial antimicrobial treatment (h)	1.6 ± 1.4	1.7 ± 1.5	0.126
Volume of intravenous fluids within 6 h (L)	3.1 ± 0.9	3.3 ± 0.8	0.092
Volume of intravenous fluids within 24 h (L)	6.2 ± 0.6	6.9 ± 0.7	< 0.001
Effective antimicrobial therapy, number (%)	55 (64.0)	87 (68.5)	0.489
Corticosteroid treatment, number (%)	54 (62.8)	74 (58.3)	0.508
Norepinephrine duration (days)	2.6 ± 0.6	2.9 ± 1.0	0.001
Hypotension duration (h)	4.6 ± 1.2	6.1 ± 1.0	< 0.001
ICU duration (days)	10.7 ± 6.0	11.2 ± 5.2	0.520

The volume of fluids was lower when norepinephrine was given early

Effects of very early start of norepinephrine in patients with septic shock: a propensity score-based analysis

Gustavo A. Ospina-Tascón^{1,2*}, Glenn Hernandez³, Ingrid Alvarez¹, Luis E. Calderón-Tapia¹, Ramiro Manzano-Nunez¹, Alvaro I. Sánchez-Ortiz¹, Egardo Quiñones¹, Juan E. Ruiz-Yucuma¹, José L. Aldana^{1,2}, Jean-Louis Teboul⁴, Alexandre Biasi Cavalcanti⁵, Daniel De Backer⁶ and Jan Bakker^{3,7,8,9}

Critical Care (2020) 24:52





Serior shield Serior connector	Intensive Care Med (2010) 36:1882–1889 Jean-François Georger Olfa Hamzaoui Anis Chaari Julien Maizel Christian Richard Jean-Louis Teboul	ORIGINAL Restoring arterial with norepinephrin oxygenation asses spectroscopy in se patients	pressure ne improves m sed by near-in everely hypoter	uscle tissue frared nsive septic
MAP mmHg 54 ± 8 StO _{2 of}	77±9	MAP mmHg	54 ± 8	77±9
90 85 Correcting	hypotension	and increa	sing car	diac
⁸⁰ 75 Output	with NE resu	lted in <mark>rec</mark> i	ruitment	t in the second s
65 of microve	essels and bet	ter tissue o	oxygena	tion
55- before NE	with NE			



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Critical Care (20





Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER) A Randomized Trial

Chairat Permpikul¹, Surat Tongyoo¹, Tanuwong Viarasilpa¹, Thavinee Trainarongsakul¹, Tipa Chakorn², and Suthipol Udompanturak³

Am J Respir Crit Care Med 2019; 199: 1097-1105



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Early NE group: **lower incidence** of:

- cardiogenic pulmonary edema

- new onset of cardiac arrhythmia

Cardiogenic pulmonary edema	22 (14.4)	43 (27.7)	0.70 (0.56–0.87)	0.004
Acute respiratory distress syndrome	17 (11)	14 (9)	1.12 (0.75–1.68)	0.56
New-onset cardiac arrhythmia	17 (11)	31 (20)	0.74 (0.56–0.94)	0.03
Hospital-acquired infection	22 (14.5)	21 (13.7)	1.03 (0.74–1.43)	0.85
Upper gastrointestinal hemorrhage	6 (3.9)	5 (3.2)	1.12 (0.58–2.15)	0.73
Acute limb and/or intestinal ischemia	5 (3.2)	3 (1.9)	1.35 (0.55–3.32)	0.47
Skin necrosis	1 (0.6)	1 (0.6)	1.0 (0.25-4.02)	1.0

Timing of norepinephrine initiation in patients with septic shock: a systematic review and meta-analysis

Yuting Li, Hongxiang Li and Dong Zhang*

Critical Care (2020) 24:488

	Early g	roup	Late gr	oup		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
1.1.1 RCTs							
Elbouhy 2019	16	57	24	44	15.0%	0.33 [0.14, 0.74]	_
Permpikul 2019	24	155	34	155	22.1%	0.65 [0.37, 1.16]	
Subtotal (95% CI)		212		199	37.0%	0.52 [0.32, 0.83]	\bullet
Total events	40		58				
Heterogeneity: Chi ² = 1	I.82, df = 1	(P = 0.	18); l² = 4	5%			
Test for overall effect: 2	Z = 2.72 (P	9 = 0.00	7)				
1.1.2 Cohort studies							
Bai 2014	25	86	55	127	24.2%	0.54 [0.30, 0.96]	
Colon Hidalgo 2020	19	76	22	43	16.2%	0.32 [0.14, 0.70]	
Ospina-Tascón 2020	17	93	36	93	22.6%	0.35 [0.18, 0.69]	_ _
Subtotal (95% CI)		255		263	63.0%	0.41 [0.28, 0.61]	◆
Total events	61		113				
Heterogeneity: Chi ² = 1	1.39, df = 2	(P = 0.	50); l² = 0	%			
Test for overall effect: 2	Z = 4.48 (P	< 0.00	001)				
Total (95% CI)		467		462	100.0%	0.45 [0.34, 0.61]	
Total events	101		171				
Heterogeneity: Chi ² = 3	3.74. df = 4	(P = 0.	44): $ ^2 = 0$	%			
Test for overall effect: 2	Z = 5.20 (P	< 0.000	001)				0.01 0.1 1 10 100
Test for subgroup diffe	rences: Ch	i ² = 0.53	3, df = 1 (P = 0.4	7), l² = 0%		Favours [Early group] Favours [Late group]
in 2 Forest plot for sh	ort-term n	oortality	,				
	on termin	nontanty					

Current use of vasopressors in septic shock

Thomas W. L. Scheeren^{1*}, Jan Bakker^{2,3,4,5}, Daniel De Backer⁶, Djillali Annane⁷, Pierre Asfar⁸, E. Christiaan Boerma⁹, Maurizio Cecconi¹⁰, Arnaldo Dubin¹¹, Martin W. Dünser¹², Jacques Duranteau¹³, Anthony C. Gordon¹⁴, Olfa Hamzaoui¹⁵, Glenn Hernández¹⁶, Marc Leone¹⁷, Bruno Levy¹⁸, Claude Martin¹⁷, Alexandre Mebazaa¹⁹, Xavier Monnet^{20,21}, Andrea Morelli²², Didier Payen²³, Rupert Pearse²⁴, Michael R. Pinsky²⁵, Peter Radermacher²⁶, Daniel Reuter²⁷, Bernd Saugel²⁸, Yasser Sakr²⁹, Mervyn Singer³⁰, Pierre Squara³¹, Antoine Vieillard-Baron^{32,33}, Philippe Vignon³⁴, Simon T. Vistisen³⁵, Iwan C. C. van der Horst³⁶, Jean-Louis Vincent³⁷ and Jean-Louis Teboul³⁸

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Table 4 Summary of the expert's recommendations and its degree of consensus and grade of recommendation

Statement	Degree of consensus	Grade of recommendation
Blood pressure monitoring		
1. In patients with shock, arterial blood pressure should be monitored invasively and continuously via a arterial catheter	n Perfect	Strong
Ideal moment to start vasopressor therapy in treating circulatory shock		
2. Vasopressors should be started early, before (complete) completion of fluid resuscitation	Reasonable	Conditional
Vasopressors should be started early R	easonable	consensus
before completion of fluid resuscitation (2)	70-80% ехре	erts agreed)
Treatment options in refractory hypotension		
7 Adding a second vasopressor in case of refractory hypotension	Good	Strong
8. Using vasopressin or terlipressin as second vasopressor	Good	Strong
Reason to stop vasopressor treatment	0000	5
9. Vasopressor treatment should be reduced/stopped when the patient improves clinically, when side effects occur, or in case of ineffectiveness	Perfect	Strong
Use of steroids to reach target		
10. Steroids should be considered in septic shock	Good	Strong

Conclusion

Fluid + NE combination

- 1) Increases the mean systemic pressure more than fluid alone (better CO)
- 2) Corrects hypotension better than fluid alone
- 3) Limits fluid overload
- 4) May improve tissue oxygenation
- 5) May improve outcome

Valuable in **shock** with **hypovolemic + vasodilatory** components

... such as **septic** shock and **hemorrhagic** shock

