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Eden Bitton [a], Shmuel Zimmerman [a], Luciano Cesar Pontes Azevedo [b], Dan Benhamou [c], Maurizio Cecconi [d,k], Jan J. De Waele [e], Jeffrey Lipman [f,l,m,n], Ignacio Martin-Loeches [g], Romain Pirracchio [h], Thomas W.L. Scheeren [i], Marc Leone [j,*], Sharon Einav [a]

[a] Intensive Care Unit of the Shaare Zedek Medical Center and the Hebrew University Faculty of Medicine, Jerusalem, Israel
[b] Emergency Medicine Department, University of São Paulo, School of Medicine, São Paulo, Brazil
[c] Département d'Anesthésie-Réanimation, Hôpital de Bicêtre, Université Paris-Saclay, Le Kremlin Bicêtre Cedex, France
[d] Department of Biomedical Sciences, Humanitas University Pieve Emanuele, Milan, Italy
[e] Department of Critical Care Medicine, Ghent University Hospital, Ghent, Belgium
[f] Intensive Care Services, Royal Brisbane and Women's Hospital, Brisbane, Australia
[g] Department of Clinical Medicine, Multidisciplinary Intensive Care Research Organization (MICRO), St James's Hospital & Trinity Centre for Health Sciences, Dublin, Ireland
[h] Department of Anaesthesia and Perioperative Medicine, Zuckerberg San Francisco General Hospital and Trauma Centre, University of California San Francisco, San Francisco, California, United States
[i] Department of Anaesthesiology, University Medical Centre Groningen, Groningen, The Netherlands
[j] Aix Marseille University, Hôpitaux Universitaires de Marseille, Department of Anesthesiology and Intensive Care, Hospital Nord, Marseille, France
[k] IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy
[l] The University of Queensland, Saint Lucia, Australia
[m] Jamieson Trauma Institute, Saint Lucia, Australia
[n] Nimes University Hospital, University of Montpellier, Montpellier, France

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ABSTRACT

Background: Our survey aimed to evaluate adherence to Surviving Sepsis Campaign (SSC) Guidelines 2016 among intensive care practitioners and to identify issues that remain controversial or lack clarity.
Methods: Members of the European Society of Intensive Care Medicine (ESICM) were surveyed using an anonymous web-based survey written by an international group of experts. The primary outcome measure was the rate of adherence to specific recommendations. Secondary outcomes were to describe areas of controversy and lack of data and to associate specific practices with clinician characteristics.
Results: Overall 820 questionnaires were completed. The SCC recommendations 2016 most adhered to were the choice of norepinephrine as first-line vasoactive drug (96.5%), vasopressor prescription based on therapeutic goal rather than dose (83.4%), targeting a specific mean arterial blood pressure during vasopressor use (77.9%), monitoring of blood pressure invasively (62.8%) and adding vasopressin or epinephrine as a second vasoactive agent (83.4%). We identified an internal conflict with regards to parallel versus sequential administration of fluids and vasoactive drugs and regional differences in practice that may be related to drug availabilities.
Conclusion: The use of vasopressors and fluid use in septic shock is largely compliant with current guidelines but several controversies should be addressed in future guideline iterations.

1. Introduction

The prevalence of sepsis and the mortality rates of patients with severe sepsis and septic shock have led to an international effort to improve the outcomes of these patients. This effort culminated in 2002 in the launching of the Surviving Sepsis Campaign (SSC) – a collaborative initiative of the European Society of Intensive Care Medicine (ESICM), the International Sepsis Forum and the Society of Critical

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* Corresponding author at: Service d'anesthésie et de réanimation, Hôpital Nord, Chemin des Bourrely, 13015 Marseille, France.
E-mail address: marc.leone@ap-hm.fr (M. Leone).

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Care Medicine (SCCM). The SSC and its accompanying recommendations have undergone several iterations and are currently viewed by most practicing intensivists as guidance for the treatment of patients with sepsis or septic shock [1].

However, recently questions have arisen regarding the value of SCC recommendations. This polemic stems mainly from the low quality of evidence underlying many of the recommendations [2]. Among other controversial issues are the dose and type of fluids to be used during the initial stages of shock resuscitation, the ideal timing for initiation of treatment with vasopressors in relation to fluid administration, the use of vasopressor combinations, the criteria for adding a positive inotrope and the definition of refractory shock [2].

In support of those clinicians who have hesitated to embrace the SCC recommendations regarding fluid administration are two meta-analyses performed in patients with severe sepsis and septic shock. These compared fluid resuscitation based on early goal-directed therapy with "usual care" and found no evidence of survival benefit when recommendations were followed [3,4]. An additional meta-analysis reported mortality benefit with early goal directed therapy but could not attribute this advantage specifically to fluid resuscitation [5].

As contentions regarding the clinical value of the SSC recommendations remain, real-life practice remains unclear [2]. We therefore aimed to assess physicians' self-reported adherence with SSC guidelines 2016. The hypothesis was that the rate of adherence to international recommendations regarding fluid resuscitation and vasoactive drug administration is low. We also aimed to identify areas of ambiguity in clinical practice, particularly in topics that are being criticized as gaps in the guidelines. We hypothesized that uncertainty regarding treatment effectiveness will manifest as diverse care. Finally, we aimed to identify specific professional characteristics that may be associated with deviation from the existing recommendations (e.g. country of practice, type of workplace).

2. Methods

The current report follows the Checklist for Reporting Results of Internet *E*-Surveys (CHERRIES) [6] and Consensus-Based Checklist for Reporting of Survey Studies (CROSS) [7].

2.1. Study design

The study was an internet-based survey of self-reported practice conducted via the ESICM (European Society of Intensive Care Medicine) website. The survey was made accessible online for three months from March 6, 2019 on the ESICM website.

2.2. Survey preparation (study tool)

The survey was written by an international group of experts in intensive care.

The survey included 27 multiple choice questions. Part one (16 questions) was used to assess adherence to SSC guidelines 2016 and focused on clinician use of fluids and vasoactive drugs in patients with septic shock (see Appendix 1). Half of the questions in this section (1, 2, 3, 6, 9, 12, 14, and 16) cited a treatment option recommended in SSC guidelines 2016 as one of the response options. These questions were used to assess adherence. The rest of the questions in this section were intended to examine practice and knowledge on topics not addressed in the guidelines.

The second part of the survey included 11 questions on the participating physician's demographics, training, clinical experience, and workplace. These questions were intended for identifying associations between practice and specific physician/center characteristics.

The survey underwent face validity testing by content experts and post-hoc internal consistency testing.

2.3. Survey distribution

The survey was published online on the ESICM website as "the survey of the month" in the English language. Requests to participate in the survey were sent three times through the ESICM member newsletter to all members of the society. The link to the online survey was also circulated twice to members of the Society of Critical Care Medicine in order to capture practice in North America. No identifying data were requested and the researchers were blinded to the IP addresses of the respondents.

2.4. Study population

Clinically active physicians working in intensive care worldwide, that elected to respond to the calls to participate in the online survey. In the introduction to the survey potential respondents were requested to complete the survey only if they are responsible for treatment decisions in their ICU. The survey was completed electively by those who felt they filled this inclusion criterion.

2.5. Variables

The main outcome measure (the dependent variable) was defined as the rate of adherence to SSC guidelines 2016. This was expressed as the proportion of respondents selecting the answers citing SCC guidelines where such existed. The secondary outcome measure relating to areas of ambiguity was mainly descriptive and for the secondary outcome measure relating to the associations between specific physician characteristics and selection of specific practice choices (e.g. drug selection, parallel versus sequential vasopressor and drug administration) we studied country of practice, type of professional training, position and number of years since certification, workplace general characteristics (*e.g.* public or private, academic or not) and ICU characteristics (type, number of beds, patient:nurse ratio).

2.6. Sample size calculation

The sample size was calculated using the estimating approach. Based on the assumption that the percent of respondents who adhere to the guidelines would be 50%, in order to construct a 95% confidence interval (CI) with a 10% width (between 45%–55%), a sample size of at least 385 responders would be required. In order to ensure construction of a CI with no more than 10% width for each percentage between 30%–70% of adherence to the guidelines, a sample size of 403 would be required. The survey was kept online in order to double this number (>800 responses) since we aimed for a narrow CI and assumed that some questionnaires would be incomplete.

2.7. Statistical methods

The percent of adherence was calculated with a CI of 95%. The variables in this study were all categorical. Therefore in order to examine the association between two unrelated categorical variables we used the X^2 test and in order to determine whether differences exist in a dichotomous dependent variable between two related groups we used the McNemar's test.

3. Results

Overall 820 physicians from 75 countries responded to the survey. Brazil (16.6%, $n = 136$), France (11%, $n = 90$) and the United States (9.3%, $n = 76$) were the countries with the highest representation. The characteristics of the respondents are summarized in Table 1.

Table 1
The characteristics of the respondents.

Features	*n*	%	Missing data *n* (%)
Geographical areas*			35 (4.3)
Africa	43	5.2	
Asia	54	6.6	
Eastern Europe	43	5.2	
Western Europe	363	44.3	
North America	78	9.5	
South America	167	20.4	
Oceania	37	4.5	
Professional training**			30 (3.7)
Intensive care medicine	657	80.1	
Anesthesiology	377	46	
Internal medicine	140	17.1	
Surgery	22	2.7	
Other	85	10.4	
Number of years of practice since certification			30 (3.7)
0–5	232	28.3	
6–10	179	21.8	
11–15	130	15.9	
15–20	101	12.3	
>20	148	18	
Position			41 (5.0)
Attending physician	339	41.3	
Chair	145	17.7	
Consultant	205	25	
Trainee	90	11	
Type of hospital			32 (3.9)
Public	620	75.6	
Private	168	20.5	
			32 (3.9)
Academic	586	71.5	
Non-academic	202	24.6	
Type of ICU			29 (3.5)
Mixed surgical and medical	564	68.8	
Surgical	98	12	
Medical	62	7.6	
Cardiac	36	4.4	
Trauma	16	2.0	
Neuro	9	1.1	
Burn	6	0.7	
Number of ICU beds			30 (3.7)
< 10	168	20.5	
10–15	225	27.4	
16–20	150	18.3	
21–30	135	16.5	
>30	112	13.7	
Number of hospital beds			31 (3.8)
< 200	109	13.3	
200–499	249	30.4	
500–999	276	33.7	
1000–2000	125	15.2	
>2000	30	3.7	
Ratio patient:nurse			29 (3.5)
1/1	133	16.2	
2/1	338	41.2	
3/1	188	22.9	
More than 3/1	132	16.1	
Number of patient/year treated by norepinephrine			32 (3.9)
<20	16	2.0	
20–49	47	5.7	
50–79	97	11.8	
80–109	113	13.8	
>109	515	62.8	

ICU: intensive care unit.
*Geographical distribution categories:
Africa (7) – Morocco, Egypt, Algeria, Sudan, Tunisia, Angola, South Africa.
Asia (20) – Bangladesh, China, India, Indonesia, Japan, Jordan, South Korea, Lebanon, Pakistan, Qatar, Saudi Arabia, Singapore, Sri Lanka, Syria, Taiwan, Thailand, The Philippines, Turkey, United Arab Emirates, Vietnam.
Eastern Europe (14) – Belarus, Croatia, Czech Republic, Estonia, Georgia, Hungary, Moldova, Montenegro, Poland, Romania, Russia, Serbia, Slovakia, Slovenia.
Western Europe (18) – Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Norway, Portugal, Spain, Sweden, Switzerland, The Netherlands, United Kingdom.
North America (2) – Canada, United states of America.
North America (12) – Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Honduras, Mexico, Paraguay, Peru, Venezuela.
Oceania (2) – Australia, New Zealand.
** More than one answer possible.

3.1. Adherence to SCC recommendations

The SCC recommendations 2016 most adhered to were the choice of norepinephrine as first-line vasoactive drug (96.5%, $n = 791$), vasopressor prescription based on therapeutic goal rather than dose (83.4%, $n = 684$), targeting a specific mean arterial blood pressure during vasopressor use (77.9%, $n = 639$), monitoring of blood pressure invasively and adding vasopressin or epinephrine as a second vasoactive agent. With regards to second line vasoactive drugs, vasopressin (67.2%, $n = 551$) and terlipressin (52.4%, $n = 430$) were most commonly selected (Table 2).

3.2. Controversial and unresolved issues

Intravenous access – The guidelines do not address the use of a specific venous access. When queried regarding their choice of practice, most respondents stated they administer norepinephrine through a peripheral line for fewer than 6 h and for rates lower than 0.2 $\mu g.kg^{-1}.min^{-1}$ if required (68.5%, $n = 562$) (Table 2).

Vasopressor compound and preparation – Half of the respondents stated they do not know which specific norepinephrine compound is used in their ICU (50.0%, $n = 410$). They were almost equally divided between dose description as $mg.h^{-1}$ (51.8%, $n = 425$) and $ml.h^{-1}$ (44.6%, $n = 366$). Drug dilution was mostly reported to be based on local protocol (57.1%, $n = 468$) and one quarter of respondents reported the use of several dilutions (26.0%, $n = 213$).

Additional treatment after administration of norepinephrine – Most clinicians stated they initiate treatment with steroids (Fig. 2) or a second vasopressor (Fig. 3) only after the dose of norepinephrine was 0.5 $\mu g.kg^{-1}.min^{-1}$ or above. Most respondents tend to initiate a second vasopressor (82.2%, $n = 668$) rather than steroids (63.7%, $n = 519$) when the dose of norepinephrine increased (Fig. 4). Lacking a recommendation on the topic, the respondents also selected varying doses of norepinephrine as the point at which they introduce the second-line drug ranging between 0.2 (13%, $n = 107$), 0.5 (32.3%, $n = 265$) and 1 $\mu g.kg^{-1}.min^{-1}$ (49.1% $n = 403$) (Table 2).

Regarding the addition of an inotrope, participants reported several options: a low cardiac output as assessed by echocardiography (37%, $n = 303$), thermodilution (19%, $n = 154$) or clinical evidence of sustained hypoperfusion (18%, $n = 150$).

Finally, the respondents reported that they administer low-dose steroids when the dose of norepinephrine exceeds different thresholds: 0.2 ($n = 141$, 17.3%), 0.5 ($n = 314$, 38.5%) or 1 $\mu g.kg^{-1}.min^{-1}$ ($n = 205$, 25.2%). Some respondents (7.9%, $n = 65$) reported they introduce steroids simultaneously with initiating norepinephrine infusion. One in 10 respondents (11%, $n = 90$) stated they never use steroids (Table 2).

3.3. Association between physician characteristics and response selection

Sequential versus *parallel fluid and vasopressor administration* – We identified an internal conflict with regards to parallel versus sequential administration of fluids and vasoactive drugs. Two thirds of the respondents (67.4% $n = 553$) stated they start fluid resuscitation of 30 $ml.kg^{-1}$ before initiating infusion of norepinephrine. However, when they were asked specifically regarding their strategy of administration (i.e.

Table 2
Survey questions and rates of adherence.

Question number	Question	Categories	Respondents		Overall *n* (%) reporting adherence to the specific SSC guidelines (strength of guideline recommendation, level of evidence)	Missing data *n* (%)
			n	**%**		
1	**Your patient has a plasma lactate concentration above 2 mmol.L^{-1}, mean arterial pressure below 65 mmHg and diastolic arterial pressure above 45 mmHg. You have started fluid resuscitation. Before initiating the infusion of norepinephrine, do you infuse 30 ml.kg^{-1} of fluid in your septic patient as recommended by the Surviving Sepsis Campaign?**	Yes (correct response) No	553 257	67.4% 31.3%	553 (67.4%) (strong recommendation, low quality of evidence)	10 (1.2%)
2	**In the majority of your patients with septic shock, do you use a sequential (fluid first and then vasopressor) or a parallel strategy (fluid and vasopressor in the same time)?**	Sequential (correct response) Parallel	371 444	45.2% 54.1%	371 (45.2%) (strong recommendation, low quality of evidence)	5 (0.6%)
3	**What vasopressor do you normally choose to administer as the first line continuous infusion?**	Norepinephrine (correct response) Dopamine (correct response) Vasopressin or analog Phenylephrine Epinephrine I don't use continuous first, but a bolus of any of above drugs	791 3 4 4 10 3	96.5% 0.4% 0.5% 0.5% 1.2% 0.4%	791(96.5%) (strong recommendation, moderate quality of evidence)	5 (0.6%)
4	**Do you administer norepinephrine (continuous infusion) in peripheral line, even for a short duration?**	No, never Yes, only for few hours (< 6 h) or low dosages (< 0.2 μg.kg^{-1}.min^{-1}) Yes, whatever the duration or dosage	229 562 23	27.9% 68.5% 2.8%	2008 guidelines –through a central catheter (GRADE 1C) 2012 guidelines only for children can begin with peripheral support (GRADE 2C) 2016 guidelines no recommendation	6 (0.7%)
5	**Do you administer phenylephrine (continuous infusion) in peripheral line, even for a short duration?**	No, never Yes, only for few hours (< 6 h) Yes, frequently	509 218 85	62.1% 26.6% 10.4%	509 (62.1%) Not mentioned as either a first- or second-line drug in the guidelines	8 (1%)
6	**Do you always monitor invasively the blood pressure in patients treated with norepinephrine?**	Yes, always No, never Yes, above 0.1 μg.kg^{-1}.min^{-1}	515 41 255	62.8% 5% 31.1%	515 (62.8%) (weak recommendation, very low quality of evidence)	9 (1.1%)
7	**In your unit, which type of norepinephrine do you use?**	Base Tartrate I do not know	117 287 410	14.3% 35% 50%	Not in the guidelines	6 (0.7%)
8	**How do you express the dosage of norepinephrine (or catecholamine)?**	μg.kg^{-1}.min^{-1} mg.h^{-1} ml.h^{-1}	0 425 366	0 51.8% 44.6%	Not in the guidelines	29 (3.5%)
9	**How do you prescribe the vasopressor?**	As dosage, as shown above in question 8 As therapeutic goal, for instance mean arterial pressure target	129 684	15.7% 83.4%	684 (83.4%) (strong recommendation, moderate quality of evidence)	7 (0.9%)
10	***How do you dilute norepinephrine?**	Decision of the physician in charge Decision of the nurse in charge Based on local protocols A single dilution is used in the unit Several dilutions are used in the unit	117 44 468 259 213	14.3% 5.4% 57.1% 31.6% 26%	Not in the guidelines	
11	**At which dosage of norepinephrine do you introduce low-dose steroids?**	Never As soon as I start the norepinephrine administration At 0.2 μg/kg/min At 0.5 μg/kg/min	90 65 141 314	11% 7.9% 17.2% 38.3%	Not in the guidelines	5 (0.6%)

(continued on next page)

Table 2 (*continued*)

Question number	Question	Categories	Respondents		Overall *n* (%) reporting adherence to the specific SSC guidelines (strength of guideline recommendation, level of evidence)	Missing data *n* (%)
			n	**%**		
		> 1 μg.kg^{-1}.min^{-1}	205	25%		
12	**Which is your main goal of resuscitation in your patients treated with norepinephrine?**	Specific mean arterial pressure	639	77.9%	639 (77.9%) (strong recommendation, moderate quality of evidence)	4 (0.5%)
		Specific systolic arterial pressure	25	3%		
		Specific diastolic arterial pressure	7	0.9%		
		Specific urine output	34	4.1%		
		Plasma lactate concentration reduction	97	11.8%		
		Specific cardiac index	14	1.7%		
13	***In your routine practice, do you have access to?**	Angiotensin 2	40	4.9%		
		Vasopressin	551	67.2%		
		Terlipressin	430	52.4%		
		Methylene blue	361	44%		
		Metamarinol	115	14%		
14	**If you need to add a second vasopressor after norepinephrine, which would you usually add for the same patient who is in septic shock?**	Epinephrine	234	28.5%	437 (53.3%) (weak recommendation, moderate quality of evidence) 234 (28.5%) (weak recommendation, low quality of evidence) Total 671 (83.4%)	15 (1.8%)
		Vasopressin	437	53.3%		
		Terlipressin	114	13.9%		
		Angiotensin 2	2	0.2%		
		Phenylephrine	18	2.2%		
15	**At which dosage of norepinephrine do you introduce a second vasopressor?**	Never	35	4.3%	Not in the guidelines	7 (0.9%)
		As soon as I start the norepinephrine administration	3	0.4%		
		At 0.2 μg.kg^{-1}.min^{-1}	107	13%		
		At 0.5 μg.kg^{-1}.min^{-1}	265	32.3%		
		> 1 μg.kg^{-1}.min^{-1}	403	49.1%		
16	**What is your usual indication for adding a positive inotrope in septic shock?**	Low central venous oxygen saturation	115	14%	303 + 154 = 457 (56.2%) (weak recommendation, low quality of evidence)	7 (0.9%)
		Low cardiac output using a thermodilution based monitor	154	18.8%		
		Low cardiac output on cardiac ultrasound	303	37%		
		Sustained hypoperfusion evidenced by mottling and oliguria	150	18.3%		
		Increasing plasma lactate concentration despite a level of mean arterial pressure above 65 mmHg	91	11.1%		

Of the 16 questions, half have explicit recommendations in recent SCC guidelines. The rest of the questions had either been addressed in older guideline iterations had never been addressed.

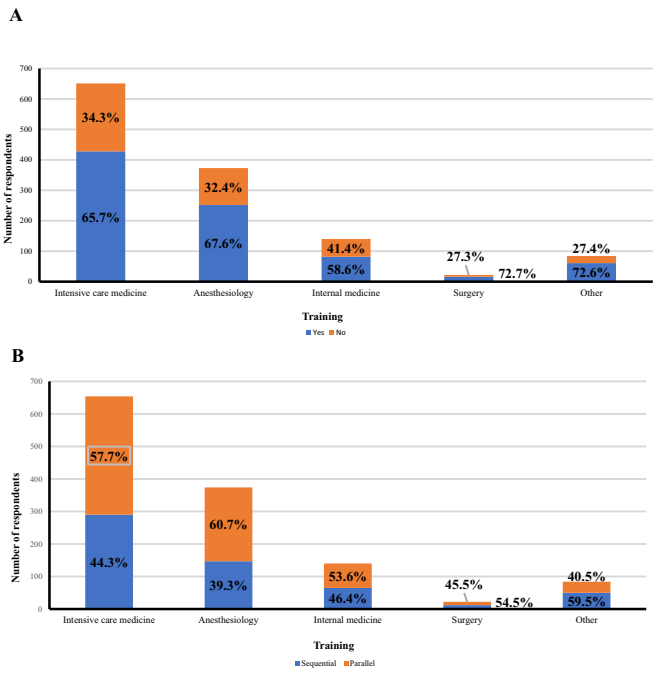

Fig. 1. Comparison between responders who reported sequential versus parallel via indirect question (Q1, Fig. 1A.) and theoretical, direct question (Q2, Fig. 1B) per professional training (Q18).
Comparison between the response to a general question addressing sequential vs. parallel administration of fluids and vasopressors in a patient with septic shock and a specific real-life vignette describing this situation. More respondents selected sequential administration in the vignette (indirect question Q1, Fig. 1A) than in the theoretical question (direct question, Q2, Fig. 1B). The data are shown per respondent professional training (Q18).

sequential or parallel), over half (54.1%, $n = 444$) reported parallel administration while the rest of the respondents (45.2%, $n = 371$) stated sequential, as suggested in the SSC guidelines 2016. Fig. 1a and b show the difference in response with regards to the general question addressing sequential versus parallel administration of fluids and vasopressors in a patient with septic shock and the specific real-life vignette describing this situation. Fewer respondents selected sequential administration in the theoretical question than in the vignette. Clinicians who administer fluids in parallel to vasopressors had a greater tendency to administer norepinephrine via a peripheral line and initiate steroids earlier (Table 3).

First and second choice of vasoactive agent – The vast majority of physicians, regardless of geographical location, use norepinephrine as the drug of first choice (Fig. 5). However, 2.4% of responders from Africa and Eastern Europe stated they use dopamine first. More than 75% of respondents chose vasopressin as the second vasopressor in North America, South America and Oceania. In Africa and Western Europe epinephrine was preferred by more practitioners than was vasopressin (51.4%, 35.6%, respectively) (Fig. 6). Although not guideline recommended, terlipressin was the second choice of quite a few responders from Western Europe (28%), Eastern Europe (9.3%) and Africa (5.7%).

4. Discussion

Our study revealed several findings. Of eight questions suggesting a treatment option based on SSC guidelines 2016 most physicians adhered to five. These included the use of norepinephrine as the first-line vasoactive drug, of vasopressin and epinephrine as the second vasoactive drug, titration of norepinephrine to achieve a therapeutic goal, targeting a specific mean arterial blood pressure and the need for invasive blood pressure monitoring. The recommendations most adhered to usually had strong recommendations with at least moderate quality of evidence (Appendix 2). The exception to this rule was invasive monitoring of blood pressure.

The recommendation for norepinephrine as an optional drug of first choice appeared in the SCC guidelines 2008 [8]. It is also well supported by evidence [9,10]. Titration of treatment to a therapeutic goal and targeting MAP have been mainstays of intensive care treatment for decades [11].

We also identified several areas of ambiguity. A major issue is the lack of common terminology and precision in recommendations. Most respondents were unaware of the norepinephrine compound they commonly administer. Differences between norepinephrine compounds are probably similarly unknown. When recommending drug treatment, ideally the drug compounds should be described and an initial standard dose should be recommended. A second issue is the safety profile for vasopressor administration via peripheral intravenous catheters. The guidelines 2008 recommended administration of vasopressors only via a central line [8] based on concerns regarding complications such as tissue necrosis and limb ischemia [12].

Additional areas of ambiguity are the timing of introduction of vasopressors in relation to fluid administration. The lack of differentiation between fluid preloading and fluid co-loading is surprising given that in other populations (e.g. obstetric anaesthesia) this discussion has been ongoing for almost a decade [13]. It takes at least 26 min to administer the 2 l of fluid recommended for a 70 kg patient in septic shock (30 $ml.kg^{-1}$) via a standard adult 18G intravenous catheter. Given the importance attributed to MAP and the concerns raised regarding the safety of vasopressor administration via a peripheral line, vasopressor administration may be further delayed by the time required to achieve beat-to-beat blood pressure monitoring and central venous catheterization. In the interim, the clinician faces a patient with a MAP far below the ideal for end-organ perfusion. This probably explains the differences in the responses with regards the timing and mode of vasopressor administration, highlighting an area that should be addressed in future research. The differences in opinion with regards to parallel versus sequential administration of fluids and vasoactive drugs may also reflect the challenge of guidelines interpretation at the bedside. Indeed, at first glance, the reading of the guidelines leads to using a sequential approach. However, in real life such as described in the clinical vignette, both fluid resuscitation and vasopressors are used in parallel, probably to achieve a rapid effect.

Finally, with regards to the indication for a second drug and low-dose steroids, clarification is required on when and how to assess the "response" to fluids and drugs. Prioritization of physiological targets based on the existing evidence, and a discussion of measurement tool pros-and-cons would also probably generate greater treatment consensus. This ambiguity resulted in a great deal of variation in reported clinical practice which may explain the paucity of findings in studies of the effect of the SCC guidelines on patients' outcomes [14].

The main strength of this study is its global reach, resulting in a multinational survey. Guidelines must be implementable; a minority of clinicians, mostly from Africa and Eastern Europe, stated they use as dopamine first-line vasopressor. This raises the questions regarding norepinephrine availability and/or education. The platform we used ensured that the information was provided by a relevant target population. The large number of respondents enabled achievement of the study aim. The anonymity guaranteed to the respondents promoted honest reporting. Finally, our findings validate the results of a survey conducted by Scheeren et al. two years earlier [15,16]. The authors surveyed 839 clinicians using the same ESICM platform to evaluate practice and therapeutic goals regarding vasopressor use in septic shock. Where overlap occurs between the two questionnaires used, our findings are

Table 3
Comparison between responders who reported sequential versus parallel fluid and vasopressor administration (Q2) with respect to other questions.

	Response options	Total in response option ($n_1 + n_2$, %)	Response category		*P*-value
			Sequential (n_1, %)	Parallel (n_2, %)	
Q4: Do you administer norepinephrine (continuous infusion) in peripheral line, even for a short duration?	Yes, only for few hours (< 6 h) or low dosages (< 0.2 μg.kg^{-1}.min^{-1})	561 69.0%	239/370 64.6%	322/443 72.7%	**0.020**
	Yes, whatever the duration or dosage	23 2.8%	9/370 2.4%	14/443 3.2%	
	No, never	229 28.2%	122/370 33%	107/443 24.1%	
	Total	813 (100%)	370/813 45.5%	443/813 54.5%	
Q6: Do you always monitor invasively the blood pressure in patients treated with norepinephrine?	Yes, always	514 63.5%	230/370 62.1%	284/440 64.5%	0.233
	Yes, above 0.1 μg.kg^{-1}.min^{-1}	255 31.4%	116/370 31.4%	139/440 31.6%	
	No, never	41 5.1%	24/370 6.5%	17/440 3.9%	
	Total	810 (100%)	370/810 45.7%	440/810 54.3%	
Q11: At which dosage of norepinephrine do you introduce low-dose steroids?	Never	90 11.1%	49/371 13.2%	41/443 9.3%	**0.099**
	As soon as I start the norepinephrine administration	65 8.0%	29/371 7.8%	36/443 8.1%	
	At 0.2 μg.kg^{-1}.min^{-1}	141 17.3%	52/371 14.0%	89/443 20.1%	
	At 0.5 μg.kg^{-1}.min^{-1}	313 38.4%	142/371 38.3%	171/443 38.6%	
	Above 1 μg.kg^{-1}.min^{-1}	205 25.2%	99/371 26.7%	106/443 23.9%	
	Total	814 (100%)	371/814 45.6%	443/814 54.4%	
Q12: Which is your main goal of resuscitation in your patients treated with norepinephrine?	Specific mean arterial pressure	638 78.3%	294/371 79.2%	344/443 77.7%	0.562*
	Specific systolic arterial pressure	25 3.1%	14/371 3.8%	11/443 2.5%	
	Specific diastolic arterial pressure	7 0.9%	4/371 1.1%	3/443 0.7%	
	Specific urine output	33 4.1%	16/371 4.3%	17/443 3.8%	
	Plasma lactate concentration reduction	97 11.9%	37/371 10.0%	60/443 31.6%	
	Specific cardiac index	14 1.7%	6/371 1.6%	8/443 1.8%	
	Total	814 (100%)	371/814 45.6%	443/814 54.4%	
Q15: At which dosage of norepinephrine do you introduce a second vasopressor?	Never	35 4.3%	16/370 4.3%	19/441 4.3%	*0.159
	As soon as I start the norepinephrine administration	3 0.4%	2/370 0.5%	1/441 0.2%	
	At 0.2 μg.kg^{-1}.min^{-1}	107 13.2%	45/370 12.2%	62/441 14.1%	
	At 0.5 μg.kg^{-1}.min^{-1}	263 32.4%	107/370 28.9%	156/441 35.4%	
	Above 1 μg.kg^{-1}.min^{-1}	403 49.7%	200/370 54.1%	203/441 46.0%	
	Total	811(100%)	370/811 45.6%	441/811 54.4%	
Q26: Ratio patient: nurse	1/1	133 16.9%	59/356 16.6%	74/431 17.2%	0.925
	2/1	336 42.7%	152/356 42.7%	184/431 42.7%	
	3/1	186 23.6%	82/356 23.0%	104/431 24.1%	
	More than 3/1	132 16.8%	63/356 17.7%	69/431 16.0%	
	Total	787 (100%)	356/787 45.2%	431/787 54.8%	
****Q4: Do you administer norepinephrine (continuous infusion) in peripheral line, even for a short duration? (2 categories)**	No, Never	229 28.2%	122/370 33.0%	107/443 24.2%	**0.005**
	Yes ((Yes, only for few hours (< 6 h) or low dosages (< 0.2 μg.kg^{-1}.min^{-1}) + Yes, whatever the duration or dosage))	584 71.8%	248/370 67.0%	336/443 75.8%	
	Total	813 (100%)	370/813 45.5%	443/813 54.5%	

Table 3 (*continued*)

	Response options	Total in response option ($n_1 + n_2$, %)	Response category		*P*-value
			Sequential (n_1, %)	Parallel (n_2, %)	
****Q11: At which dosage of norepinephrine do you introduce low-dose steroids? (3 categories)**	Never	90 11.1%	49/371 13.2%	41/443 9.3%	**0.043**
	As soon as I start the norepinephrine administration +At 0.2 μg.kg^{-1}.min^{-1}	206 25.3%	81/371 21.8%	125/443 28.2%	
	At 0.5 μg.kg^{-1}.min^{-1} + Above 1 μg.kg^{-1}.min^{-1}	518 63.6%	241/371 65.0%	277/443 62.5%	
	Total	814 (100%)	371/814 45.6%	443/814 54.4%	
****Q12: Which is your main goal of resuscitation in your patients treated with norepinephrine? (2 categories)**	Blood pressure goals (Specific mean arterial pressure + Specific systolic arterial pressure + Specific diastolic arterial pressure)	670 82.3%	312/371 84.1%	358/443 80.8%	0.221
	Non-blood pressure goals (Specific urine output + Plasma lactate concentration reduction + Specific cardiac index)	144 17.7%	59/371 15.9%	85/443 19.2%	
	Total	814 (100%)	371/814 45.6%	443/814 54.4%	

Responders who reported parallel fluid and vasopressor administration had a greater tendency to administer norepinephrine in a peripheral line (Q4) and initiate steroids earlier (Q11). No difference was observed in their responses to other questions.
*Fisher's exact test.
**Response categories pooled.

mostly in line with their results. However, these authors did not report percent adherence to specific guidelines. The wording and content of most of our questions was somewhat different which served to strengthen those findings, which were similar. These authors also did not address drug compounds, but they did identify the same conundrum related to delays in vasopressor treatment and conducted a Delphi process on this issue. This resulted in a recommendation not to delay vasopressor treatment until fluid resuscitation is completed but rather to start with norepinephrine early in order to achieve a target MAP ≥65 mmHg.

This study has several limitations. First, the study population was limited to members of either ESICM or SCCM and was self-selected. These are clinicians who pay membership dues to their society, have access to the internet and have sufficient interest in the topic to complete the survey. Selection bias is therefore very probable. Although we cannot ascertain how many clinicians received the mail blasts, the two societies together have approximately 8000 members. Thus, our response rate approximated 10%, which is relatively low even for a web-based survey [17,18]. Local protocols and drug availabilities may have affected the responses. In such circumstances, patient management is determined by necessity, confounding any finding with regards to adherence. In addition, the case mix of patients with septic shock may differ across locations. As none of the questions related to specific patients, this heterogeneity might have affected the responses. Finally, the survey did not

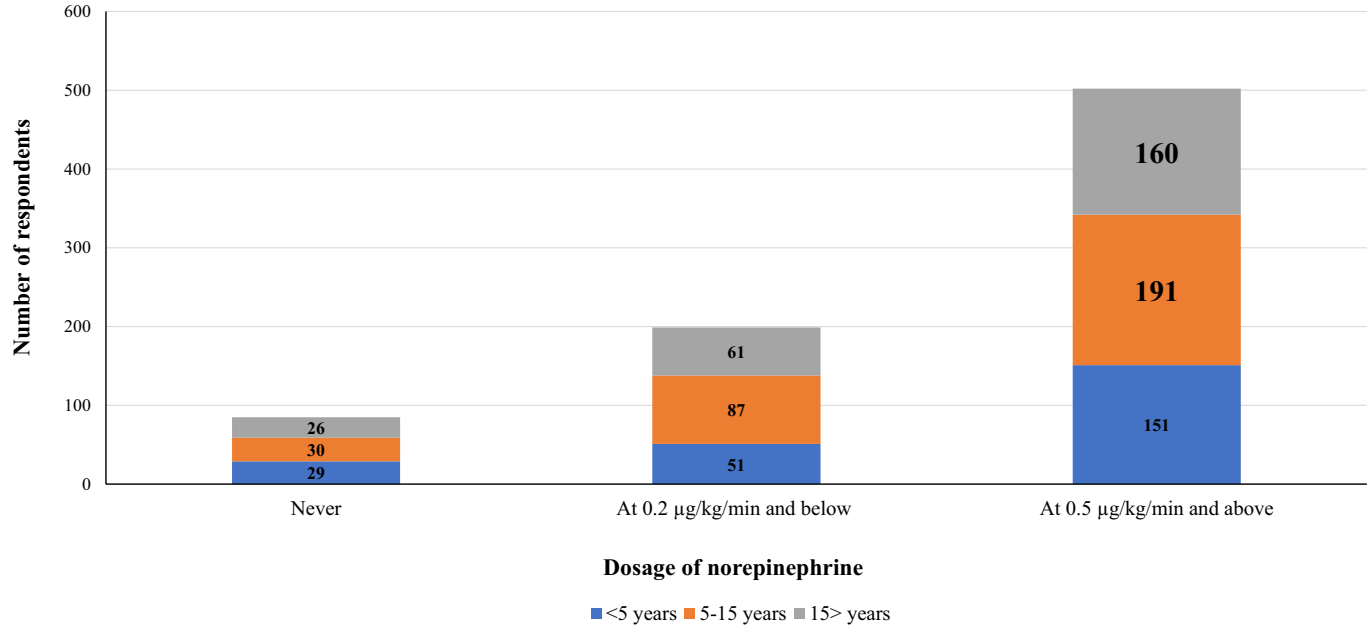

Fig. 2. Comparison between norepinephrine dosage before adding low dose steroids (Q11) and years of experience (Q19).
Comparison between norepinephrine dosage before adding low dose steroids and years of experience. Most respondents stated they introduce low dose steroids at higher doses of norepinephrine. The data are shown per years of training experience (Q18) although there is no correlation to it.

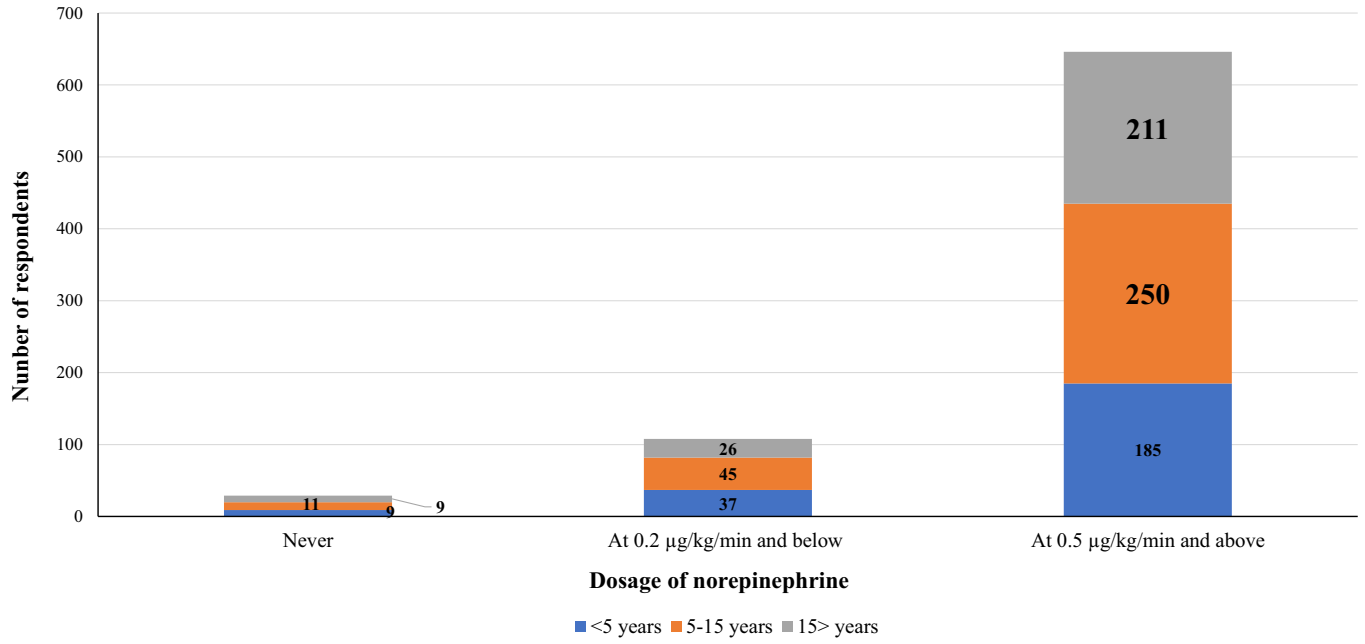

Fig. 3. Comparison between norepinephrine dosage before adding second vasopressor (Q15) and years of experience (Q19).
Comparison between norepinephrine dosage before adding second vasopressor and years of experience. Most respondents stated they add a second vasoactive agent at higher doses of norepinephrine. The data are shown per years of training experience (Q18) although there is no correlation to it.

vasopressor? (3 categories)

11: At which dosage of repinephrine do you ntroduce low-dose steroids? (3 categories)	Never	At 0.2 µg.kg^{-1}.min^{-1} and below	At 0.5 µg.kg^{-1}.min^{-1} and above	Total
Never	**7**	15	68	90
	0.9%	1.8%	8.4%	11.1%
At 0.2 µg.kg^{-1}.min^{-1} and below	7	**60**	137	204
	0.9%	**7.4%**	16.9%	25.2%
At 0.5 µg.kg^{-1}.min^{-1} and above	21	35	**461**	517
	2.6%	4.3%	**56.8%**	63.7%

Fig. 4. The association between the addition of a second vasopressor (Q15) and steroids (Q11) when a patient is already receiving norepinephrine (McNemar's test).
The main diagonal shows 65.1% agreement. In case of disagreement 27.1% of clinicians preferred to administer a second vasopressor rather than steroids and only 7.8% preferred to administer steroids at higher norepinephrine levels rather than steroids. In cases of disagreement clinicians tended to be more careful with the initiation of steroids rather than of a second vasoactive agent.

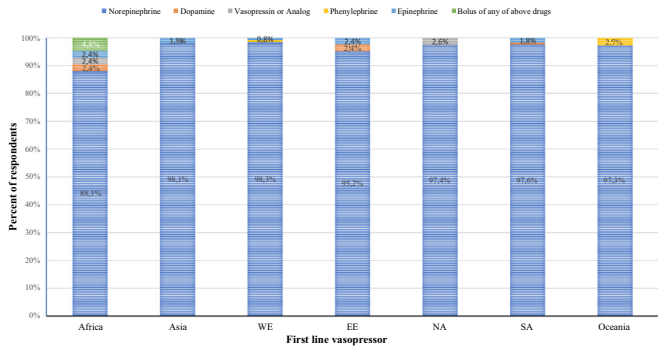

Fig. 5. First choice vasoactive agent (Q3) by geographical area (Q17).
The majority of respondents chose norepinephrine as first line agent for a patient in septic shock. Africa has the almost equal distribution between the other agents including Dopamine which is no longer in SCC guidelines. Dopamine is still used in Eastern Europe as well (2.4% per each).

investigate the practice of fluid management whereas this remains a controversial issue in retrospect. Of note, our findings remain pertinent since the problems we identified have not been addressed in the 2021 Surviving Sepsis Campaign guidelines [19].

5. Conclusion

Management of sepsis is a complicated clinical challenge requiring rapid diagnosis and monitoring, timely and correct decisions made with regards to treatment. Several controversies have remained with regards to SCC recommendations. These and new publications since the last iteration of the SSC recommendations have recently led the ESICM and SCCM to begin a process of recommendation updates. This study sheds light on several areas that require elucidation in the upcoming iteration of the guidelines and on gaps in research with regards to how best to treat patients with septic shock.

Declaration of Competing Interest

EB. No relevant conflicts of interest.
SZ. No relevant conflicts of interest.
LCPA received research grants from Ache Laboratorios farmaceuticos, consulting fees from Halex-Istar and lecture fees from Pfizer and Baxter, all outside the present work.
DB. No relevant conflicts of interest.
MC. No relevant conflicts of interest.
JDW received consulting fees from Pfizer and MSD (all outside the present work, and honoraria were paid to his institution).
JL. No relevant conflicts of interest.
IML received fees from MSD and Aspen for lectures and from Pfizer, Gilead and Ambu for consulting.
RP. No relevant conflicts of interest.
TWLS received research grants and honoraria from Edwards Lifesciences (Irvine, CA, USA) and Masimo Inc. (Irvine, CA, USA) for consulting and lecturing (all payments made to institution).
ML. Received fees from MSD and Aspen for lectures and from Amomed, Gilead and Ambu for consulting.
SE. No relevant conflicts of interest.

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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.2021.11.016.

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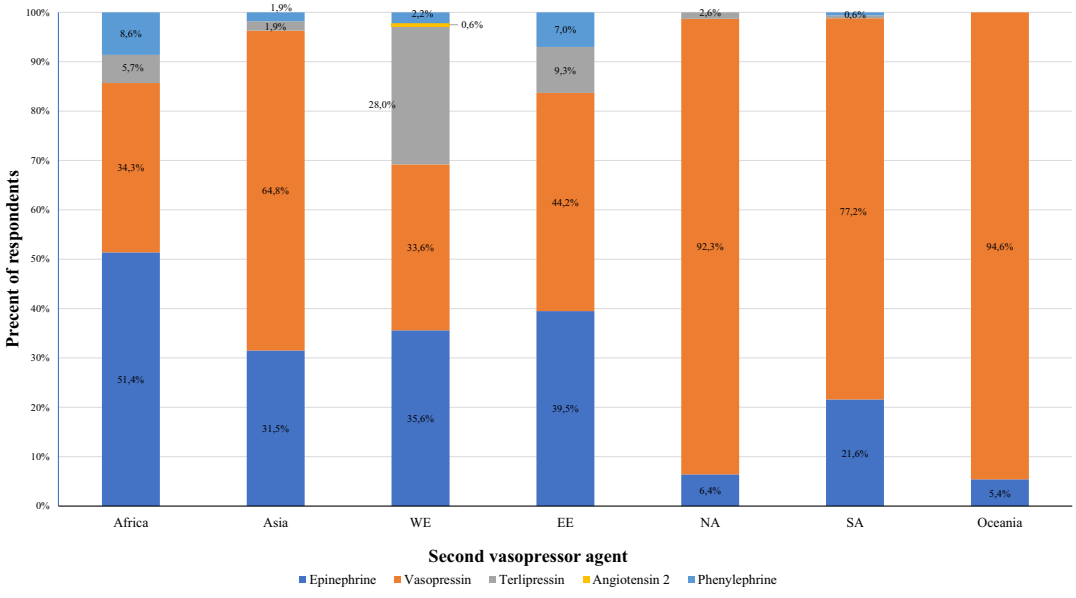

Fig. 6. Second choice vasoactive agent (Q14) by geographical area (Q17).
Vasopressin was commonly selected as the second agent in Oceania, South America North America and Asia. In Africa, epinephrine was selected more commonly. In Western and Eastern Europe vasopressin and epinephrine were almost equally selected. These two drugs are recommended in the guidelines. In Western Europe almost one third of the respondents selected terlipressin which was not commonly available at the time of guideline publication.

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