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Clinical criteria for the definition of refractory septic shock: a joint Delphi consensus from the Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM)

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Abstract

Objective: A definition of refractory septic shock is necessary to guide diagnosis, management, prognostication, research, and future guidelines for this most severe form of the disease. We sought to achieve consensus on clinical criteria that would be used to define refractory septic shock.

Design: Review of literature, expert panel position statements, and Delphi rounds with an international expert group.

Setting: Consensus was defined as having at least 75% of panellists in agreement or disagreement on the three highest or lowest levels of a 7-point Likert scale or based on responses to single- or multiple-choice questions, respectively.

Subjects: A panel of multinational, multiprofessional, and multidisciplinary critical care experts assembled by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine (57 invitations and 56 participants).

Measurements and main results: A five-round Delphi process was conducted for consensus and stability. The steering committee proposed 34 statements, and five of them were rejected by panel experts after round 2. Among 29 statements selected from eight domains, consensus was reached for 13. The panel agreed on the need for a comprehensive consensus set of clinical criteria for refractory septic shock. Markers of organ dysfunction (75%, 2 rounds), tissue perfusion (91.1%, 2 rounds) including lactate (94.6%, 2 rounds) and capillary refill time (76.8%, 2 rounds), assessment of fluid responsiveness after initial resuscitation (92.9%, 5 rounds), and use of vasoactive drugs at norepinephrine equivalents greater than 0.5 µg/kg/min (75.0%, 3 rounds) were selected as clinical criteria of refractory septic shock. The use of critical care ultrasound (CCUS) (92.9%, 3 rounds) was the single diagnostic modality that reached a consensus-based agreement.

Conclusions: A consensus for 13 criteria to frame the definition of refractory septic shock was reached. Refractory septic shock is characterised by persistently elevated lactate concentrations and or prolonged capillary refill time in patients with septic shock who are fluid unresponsive, require a norepinephrine base equivalent dose greater than 0.5 µg per kilogram per minute, and undergo CCUS assessment when mixed shock is suspected.

Keywords: Refractory, Sepsis, Septic shock, Concept, Definition, Criteria

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1–3]. In the continuum of sepsis, progression to refractory septic shock poses significant challenges in clinical management and research. The term r*efractory septic shock*, which reflects a subset of septic shock, is used widely without a clear consensus on criteria or how to operationalise its application. A systematic review of literature identified a marked variability in the usage of the term refractory sepsis. This systematic review included different cut-off levels of important characteristics, including hypotension, hyperlactatemia, and norepinephrine equivalent doses (Table 1) [4].

Conceptualising refractory septic shock provides an opportunity to identify patients with the most severe cases and the poorest outcomes. A set of consensus-based criteria would help to frame refractory septic shock as the most advanced stage of the syndrome of sepsis. Another goal was to have a more uniform clinical phenotype for randomised controlled trials, since the definition of refractory is directly related to the intervention and outcomes being studied (Table 1) [5–18]. Furthermore, this would identify refractory septic shock in a timely manner based on standardised criteria, leading to targeted, prompt, consistent and specific therapeutic interventions.

An approach relying on the agreement of experts in the field seemed promising to increase adherence to this set of clinical criteria. Once a consensus is reached, this would aid in the identification of subgroups for research purposes, individual patient prognosis, and communication between clinicians and patients, their surrogates, and other stakeholders [19, 20]. In addition, some therapeutic interventions that show no benefit in all-comers with septic shock may have a role for those with refractory septic shock (Fig. 1) [21].

The European Society of Intensive Care Medicine (ESICM) and Society of Critical Care Medicine (SCCM) recognised these needs and brought together a diverse international group of experts in sepsis and septic shock to work on a Delphi process with the aim of achieving a consensus on the clinical criteria for a definition of refractory septic shock. Our goal was to generate consensus amongst expert panellists to formulate clinical criteria from statements to define refractory septic shock. The scope of the project was developed through qualitative

Table 1 Definitions available in the literature to frame refractory septic shock

Authors	Year	Description
Albanese et al. (16148457)	2005	Septic shock with haemodynamic instability and two or more organ dysfunctions (Maximal norepinephrine dosage: 1.7 ± 0.9 µg/kg/min)
Auchet et al. (28425079)	2017	Septic shock with the need for norepinephrine dosage ≥ 1 µg/kg/min for ≥ 1 h (Maximal norepinephrine dosage: 3.28 ± 2.41 µg/kg/min)
Dargent et al. (40019329)	2025	Septic shock (Sepsis-3 definition) and norepinephrine requirement ≥ 0.25 µg/kg/min (0.5 µg/kg/min of norepinephrine tartrate) with persistent circulatory failure (defined by lactate > 2 mmol/L, oliguria, or skin mottling) (Maximal norepinephrine dosage: 1.84 ± 1.07)
Dünser et al. (12732600)	2003	Vasodilatory shock with and without sepsis with MAP < 70 mmHg and norepinephrine infusions exceeding 0.5 µg/kg/min (Mean norepinephrine dosage: 0.84 ± 0.41 µg/kg/min)
Friesecke et al. (28589286)	2017	Progressive shock despite full standard therapy and meeting the following criteria were met; lactate (> 2.9 mmol/l) without localised cause and increasing compared to baseline or a high norepinephrine (NA) requirement (> 0.3 µg/kg/min) which had increased over the preceding 2 h
Jarcak et al. (36075200)	2023	Need for norepinephrine ≥ 0.2 µg/kg/min to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
Leone et al. (15377885)	2004	Septic shock with MAP < 55 not responding to high-dose norepinephrine (> 2.0 µg/kg/min) and adequate fluid resuscitation within 60–90 min of maximised therapy (Maximum norepinephrine dosage: 3.8 ± 1.3 µg/kg/min)
Martin et al. (26125087)	2015	Sepsis with the need for vasopressor administration (Norepinephrine dosage at 0.79 ± 1.03 µg/kg/min)
Micek et al. (17437364)	2007	Vasodilatory volume-refractory shock necessitating administration of norepinephrine or norepinephrine plus vasopressin for a minimum of six hours to maintain a minimum target MAP > 55 mm Hg
O'Brien et al. (11955542)	2002	Septic shock and high cardiac output with hypotension (MAP 50–55) un-responsive to fluid-loading and high-dose norepinephrine infusion or methylene blue and dexamethasone (Mean norepinephrine dosage: 0.59 µg/kg/min)
Thompson et al. (39675155)	2025	Vasopressor dose ≥ 0.5 µg/kg/min norepinephrine-equivalents in the first 24 h of septic shock (Maximal norepinephrine dosage: 0.65 (0.53, 0.90))
Tsuneyoshi et al. (39675155)	2001	Septic shock and persistent hypotension, with the need for norepinephrine with or without infusions of other catecholamines (maximum norepinephrine dosage: 0.3 µg/kg/min)
Yang et al. (23673091)	2013	Refractory septic shock was defined as the requirement of dopamine > 15 µg/kg/min or norepinephrine/epinephrine > 0.25 µg/kg/min to maintain mean blood pressure above 65 mmHg (80 mmHg if the patient had previous hypertension)

evidence synthesis from a focussed search of the published literature on septic shock [4] to define criteria for refractory septic shock.

This work is intended to be aligned with the current definition of septic shock [1] and Surviving Sepsis Campaign guidelines [22] and to be a clinical tool to allow for uniformity in the diagnosis and management of refractory septic shock.

Methods

Composition of Steering Committee and Expert Panellists

A global multidisciplinary steering committee (SD, AKK, ML, SNM, LR, and PMW) with professional expertise in sepsis management was convened and approved by the SCCM and ESICM leadership. Members from the ESICM and the SCCM were selected by the steering committee and approved by the society leadership as expert panellists to participate in the Delphi process. This was based on objective and predefined criteria encompassing clinical and research expertise in shock, with a strong focus on geographical, professional, and gender diversity. The study protocol was registered on the websites of the SCCM and ESICM, https://sccm.org/survivingsepsiscampaign/sccm-esicm-joint-projects. The funding of this consensus was supported by the two organising societies and did not influence the results.

A series of steering committee e-meetings from August 2024 to April 2025 formulated a plan, reviewed literature, and discussed the need for these clinical criteria based on a Delphi consensus. The literature search strategy and subsequent PRISMA flowchart describing the studies included for qualitative evidence synthesis is provided in Appendix 1, https://sccm.org/survivingsepsiscampaign/sccm-esicm-joint-projects.

The steering committee that drafted the Delphi questionnaires and an independent group in charge of methodology did not participate in voting. Conflicts of interest were disclosed, collected, and adjudicated by the organising societies at the outset of the consensus. There were no restrictions on participation.

Delphi process

We used Delphi survey methodology to generate expert consensus for criteria that would be included in a definition of *refractory septic shock*. Survey rounds were conducted based on previously published Delphi survey studies and reported based on the Accurate Consensus Reporting Document (ACCORD) guideline [23].

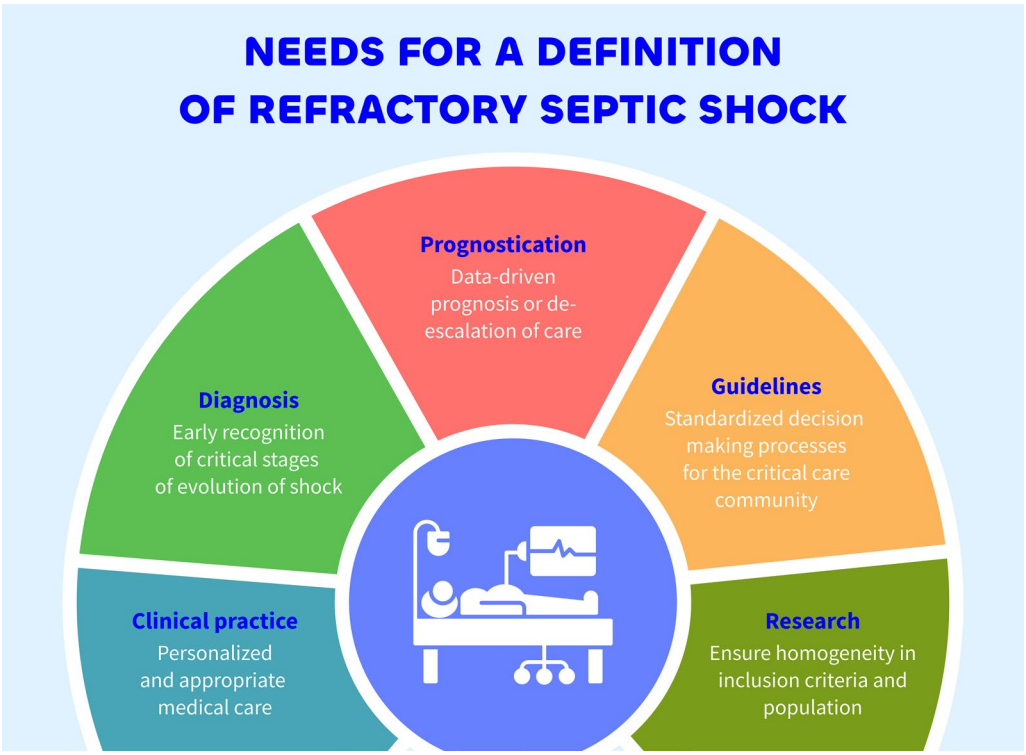

Fig. 1 The need for a definition of refractory septic shock

The ACCORD Checklist is provided in Appendix 2. The domains and statements used in the Delphi questionnaires were built based on results from the literature review, followed by detailed discussion within the steering committee. The survey was created and distributed electronically using SurveyLet (SurveyLet, Calibrum Inc., Utah, USA). The identity of the panellists was concealed by design until the end of the Delphi process. To ensure confidentiality, the panellists were blind carbon-copied in each email announcing the opening of each new round. The survey was built and shared using the English language only.

Delphi rounds

Panellists responded to iterative rounds to prioritise consensus on topics for inclusion and were able to provide comments in the first two rounds. In the first round, panellists were given the opportunity to comment on the questions and their general scope, to provide guidance on the domains and statements, and advise changes or suggest additional elements to be included in the survey. Of note, no comments were allowed after round 2. All comments were screened, and any potential identifying information was removed prior to consolidating the round report. Based on the feedback obtained in each round, the steering committee and the methodological group refined the questions, which were then presented back to the expert panellists in the subsequent round as a consolidated report. The methodological group oversaw summarising the data from each of the Delphi rounds (statistical analysis, distribution, level of agreements, reporting, and summarisation of comments). All raw data was anonymised. Participation of all expert panellists was expected at each round. Repeated email reminders were sent to complete the Delphi surveys between rounds. Figure 2 summarises the Delphi rounds and reported response rates.

The Delphi survey included eight domains: A: Need for a definition and major domains, B: Blood pressure targets, C: Markers of tissue perfusion, D: Fluid resuscitation, E: Vasoactive therapy, F: Adjunct therapies, G: Source control, H: Type of Shock. The survey questionnaire included multiple-choice questions (including single-answer and multiple-answer questions) and 7-point Likert scale statements.

Consensus, stability, and statistics

Consensus was considered to have been achieved if 75% or more of panellists voted for a particular option in multiple-choice questions or on an ordinal 7-point Likert scale for agreement (score of 5–7) or disagreement (score of

1–3). Median and interquartile range (IQR) were used to describe the central tendency and dispersion of responses in Likert-scale statements. The choice of 75% as a consensus threshold is justified as it represents the median of the observed values in published literature [24].

A question was continued in the Delphi process until stability, which was assessed between two consecutive rounds, starting from round two onwards, using the non-parametric Chi-square (χ^2) test, with $p < 0.05$ considered a significant variation (instability) between the considered rounds. A question was removed from the subsequent rounds once it achieved stability, regardless of whether consensus was achieved (Table 2). All comments from each applicable round were reviewed by the steering committee. The comments were then aggregated into the following categories to ensure that all content matter was addressed: (i) agreement; (ii) disagreement; (iii) wording changes; and (iv) identified themes. Subsequently, these comments were used to either add more questions or modify existing ones for the next Delphi round. The data analysis and report generation was performed using R software (R Core Team—2024. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. R version 4.4.0—2024-04-24).

Clinical criteria for the definition of refractory septic shock

The steering committee drafted clinical practice statements from the proposals that generated consensus and stability during the Delphi process. The results of the Delphi process and the draft manuscript were circulated amongst the panellists for comments and approval prior to submission for publication.

Participants

Five separate Delphi rounds from 13 May 2025 to 06 September 2025 were required. A total of 57 expert panellists were proposed by the steering committee members and validated by the executive committees of ESICM and SCCM, and 56 of them accepted the invitation. All 56 panellists participated in each round except for round 1 (55 panellists). The panellists practiced in 22 countries across five continents (Supplemental Table S1). This expert panel was composed of 1 PhD scientist, 6

Fig. 2 Method description

Table 2 Consensus and stability

Round	Respondents (%)	Number of questions (*n*)	Consensus[a] (%)	Stable[b] (*n*)	Comments (*n*)	Questions (*n*)		
						Modified	Added	Deleted
Round 1	55 (98)	34 (16 Likert, 13 MCQ, 5 MCMA)	9/34 (27)	Not applicable	641	–	–	–
Round 2	56 (100)	34 (16 Likert, 13 MCQ, 5 MCMA)	13/34 (38)	19	753	3	–	5
Round 3	56 (100)	13 (4 Likert, 7 MCQ, 2 MCMA)	6/13 (46)	11	14	–	–	2
Round 4	56 (100)	3 (3 Likert, 0 MCQ, 0 MCMA)	1/3 (33)	0	Not permitted	–	–	–
Round 5	56 (100)	3 (3 Likert, 0 MCQ, 0 MCMA)	1/3 (33)	3	Not permitted	–	–	–
		Overall Agreement	13/29 (45)					

MCQ multiple-choice question (single answer), *MCMA* multiple choice, multiple answers

[a] Consensus was achieved if 75% or more of panellists voted for a particular option in multiple-choice questions or on an ordinal 7-point Likert scale for agreement (score of 5–7) or disagreement (score of 1–3)

[b] Computation of stability requires two consecutive rounds. It can thus be computed only from Round 2 onward

pharmacists, 3 nurses, and 46 intensivists, who had training in intensive care medicine ($n=11$) alone or combined with anaesthesiology ($n=11$). Other intensivists also trained in internal medicine ($n=11$), pulmonology ($n=5$), cardiology ($n=4$), infectious diseases ($n=2$), emergency medicine ($n=2$).

Delphi rounds

The steering committee drafted 34 statements or proposals, and the panellists excluded five statements after round 2 (Supplemental Table S2). Consensus was reached for 13 proposals (Table 2). Of note, panellists sent 641 and 753 comments after the first and second rounds, respectively, which the steering committee and methodological group assessed in detail to inform changes to the following round. Details of votes according to consensus and stability are presented in Table 2. Details of the evolution of proposals across rounds are presented in Supplemental Table S3.

Summary of findings

A consensus was reached for 13 proposals. Six proposals were validated (consensus and stability achieved) in the second round, six in the third round, and one in the fifth round. Twelve proposals reached stability without consensus in the second round, 2 in the third round, and 2 in the fifth round. Panellists agreed on the inclusion of the following clinical criteria for defining refractory septic shock: markers of tissue perfusion (91.1%) [lactate (94.6%) and capillary refill time (CRT) (76.8%)], assessment of fluid responsiveness after initial resuscitation (92.9%), and use of vasoactive drugs at norepinephrine equivalents greater than 0.5 µg/kg/min (75.0%). Critical care ultrasonography (CCUS) was the single diagnostic modality that reached a consensus-based agreement (92.9%) (Table 3). In addition, consensus and stability were reached to exclude the need for a cut-off value for central oxygen venous saturation (ScvO2), the volume of urine output, and any mention of a specific blood pressure component or a mean arterial pressure threshold from the criteria.

Subsequently, we proposed clinical criteria for defining refractory septic shock as the presence of persistently high lactate concentrations and/or prolonged CRT in a patient with septic shock who is fluid unresponsive, receiving at least a norepinephrine (base) equivalent dose > 0.5 µg/kg/min and with confirmation by critical care ultrasound (CCUS) in case of mixed shock (Fig. 3).

Table 3 Recommended statements that achieved consensus (> 75% agreement) and stability during the Delphi process

No	Statement	Percent agreement	Stability after
1	A comprehensive consensus definition for refractory septic shock is needed	52 (92.9%)	2 rounds
2	Markers of tissue perfusion should be part of a definition for refractory septic shock	51 (91.1%)	2 rounds
3	Markers of organ dysfunction should be part of a definition for refractory septic shock	42 (75.0%)	2 rounds
4	Optimal fluid resuscitation and adequate intravascular volume should be part of a definition for refractory septic shock	44 (78.6%)	2 rounds
5	Use of vasoactive drugs should be part of a definition for refractory septic shock	54 (96.4%)	2 rounds
6	The duration of the clinical condition/therapies applied should be included in definition	46 (82.1%)	2 rounds
7	The dosage of the therapeutic agent/s should be included in definition	49 (87.5%)	2 rounds
8	Serum lactate concentration is a marker of tissue perfusion that should be considered in the definition of refractory septic shock	53 (94.6%)	2 rounds
9	Capillary refill time is a marker of tissue perfusion that should be considered in the definition of refractory septic shock	43 (76.8%)	2 rounds
10	Following initial fluid resuscitation, additional fluid should be considered based on fluid responsiveness status prior to defining refractory septic shock	52 (92.9%)	5 rounds
11	The method most appropriate to quantify vasopressor exposure when defining refractory septic shock is norepinephrine equivalent dose (NEE)	47 (83.9%)	2 rounds
12	The threshold dosage of norepinephrine (base) equivalent (NEE) should be $\geq$ 0.5 µg/kg/min for the definition of refractory septic shock	42 (75.0%)	3 rounds
13	Critical care ultrasonography (CCUS) should be used to assess for alternative causes of shock (e.g. obstructive or cardiogenic) before confirming the diagnosis of refractory septic shock	52 (92.9%)	3 rounds
14	Level of $S_{cv}O_2$ should not be part of the definition of refractory shock	43 (76.8%)	3 rounds
15	Urine output should not be part of the definition of refractory shock	44 (78.6%)	3 rounds

Clinical statements and rationale

Need for consensus-based clinical criteria to frame a definition

Criteria 1. A comprehensive consensus definition for refractory septic shock is needed

Criteria 2. A consensus definition for refractory septic shock is needed for the following reasons:

1. **Patients receive appropriate and standardised clinical care**
2. **Research data can be consistently compared and aggregated**
3. **Health professionals communicate effectively about patient conditions**
4. **Guidelines can be accurately developed and implemented**

Rationale for a consensus on clinical statements

As underlined by the panellists, the inconsistencies in the use of the term *refractory septic shock* may affect the ability to screen, enrol and study these patients in research, the ability to communicate about these patients between healthcare providers, and obscures evidence synthesis that is critical for the development of clinical practice guidelines addressing the care of these patients.

Domains of the proposed clinical statements

Criteria 3. The following broad domain components should be part of a definition for refractory septic shock:

1. **Markers of tissue perfusion**
2. **Markers of organ dysfunction**
3. **Optimal fluid resuscitation and adequate intravascular volume**
4. **Use of vasoactive drugs**

Criteria 4. Markers of tissue perfusion to be included in the definition of refractory septic shock:

1. **Serum lactate concentration**
2. **Capillary refill time**

Rationale for domains of the clinical statements

The panellists selected markers of tissue perfusion, organ dysfunction, optimal fluid resuscitation, adequate intravascular volume, and use of vasoactive drugs as broad domain components to be included in the clinical statements for refractory septic shock. These choices reflect the clinical criteria used in the Sepsis 3.0 definition [1].

Organ dysfunction is part of the definition of sepsis 3.0. Non-resolution of organ dysfunction despite first-line resuscitation, i.e. an initial fluid bolus of around 30 mL/kg depending on patient characteristics, was considered by panellists as a criterion of refractory septic shock. However, no consensus was reached for details on the type of organ dysfunction. In addition, with respect to organ dysfunction, no specific organ was retained in the Delphi rounds. Two crucial components related to patient management, the volume of intravenous fluids and dosages of vasopressors, probably best reflect the severity of illness and could be considered surrogates for inadequate haemodynamic control, vasoplegia, and extravascular fluid leakage. Blood pressure targets were excluded by panellists, probably because all these patients had to meet the criteria of septic shock (which includes a mean arterial pressure target) and because these patients are likely to be on vasopressors before they could be considered to have refractory shock. In addition, this may also stem from observed variability in thresholds used, unknown effect of using different thresholds, the effect of relative changes from a pre-morbid threshold and that blood pressure is often normalised in patients with septic shock by vasopressors.

Tissue perfusion can be impaired despite meeting resuscitation goals in terms of blood pressure, cardiac index and urine output, described as haemodynamic coherence [25]. Serum lactate, a key component of the Sepsis 3.0 septic shock definition [1], is a surrogate marker of tissue perfusion. A randomised controlled trial of septic shock resuscitation guided by serum lactate resulted in improved adjusted survival as compared to controls [26]. This lends support to including serum lactate and persistently elevated serum lactate despite adequate fluid resuscitation as part of the criteria for describing refractory septic shock. Of note, elevated serum lactate can be due to impaired tissue perfusion, but other causes of persistent elevation should not be omitted (including but not limited to seizures, mitochondrial dysfunction, malignancy, thiamine deficiency, liver dysfunction, and drug or toxin-related causes) [27]. In

addition, a specific cut-off value of persistently elevated serum lactate did not achieve consensus because panellists were divided between 2 and 4 mmol/L. Finally, the concept of lactate clearance was not retained by the expert panel as one of the criteria of refractory septic shock.

While hard to measure in many organ systems, especially at the bedside, several clinical tests may serve as surrogate markers of poor tissue perfusion. CRT was selected as part of this Delphi to reflect poor tissue perfusion. A trial randomised 424 patients with septic shock to a peripheral perfusion-targeted resuscitation strategy (using CRT) or a lactate normalisation-targeted strategy and found that resuscitation based on CRT was associated with less organ dysfunction compared to lactate normalisation [28]. A more recent randomised controlled trial confirmed that a personalised protocol based on CRT assessment as tissue perfusion surrogate resulted in improved outcomes as compared with the standard of care [29]. CRT is an inexpensive and easy-to-perform procedure that can be implemented in low-resource settings. Based on expert input, the lack of normalisation of CRT should be included in the clinical criteria of refractory septic shock. Other clinical surrogates for tissue perfusion, such as mottling, did not reach a consensus amongst the panel to be included in the clinical criteria of refractory septic shock.

Criteria 5. Central venous oxygen saturation should not be part of the definition of refractory septic shock

Rationale against central venous oxygen saturation to be part of the clinical criteria for refractory septic shock. The panellists did not retain ScvO2 in the criteria of refractory septic shock. Four parameters—cardiac output, serum haemoglobin, arterial oxygen saturation, and oxygen consumption—determine the level of ScvO2 [30]. Literature about its utility in septic shock is inconsistent [31–34], although ScvO2 measurement, with no predefined value, is recommended in recent ESICM guidelines on circulatory shock and haemodynamic monitoring [35]. In patients with septic shock, it has been shown that the association between ScvO2 levels and mortality is a U-shaped curve [36]. Another comparable marker of tissue perfusion, the central venous–arterial carbon dioxide difference (PCO2 gap), was not retained by the panel, although this biomarker could be useful to understand the cause of tissue hypoperfusion [37].

Criteria 6. Urine output should not be part of the definition of refractory septic shock

Rationale against urinary output Panellists voted against incorporating urine output into the clinical criteria for refractory septic shock. In addition, the impact of resuscitation on urine output may not be immediate [38]. There is a debate regarding 'normal' urine output, which has been arbitrarily fixed at 0.5 mL/kg/min or greater [39]. Lastly, urine output depends on several variables that are independent of tissue perfusion (osmolar excretion, sodium excretion, free water clearance, chronic kidney dysfunction, diuretic administration, exposure to nephrotoxic drugs, local inflammation, etc.).

Duration

Criteria 7. The duration of the clinical condition/therapies applied should be included in the definition of refractory septic shock

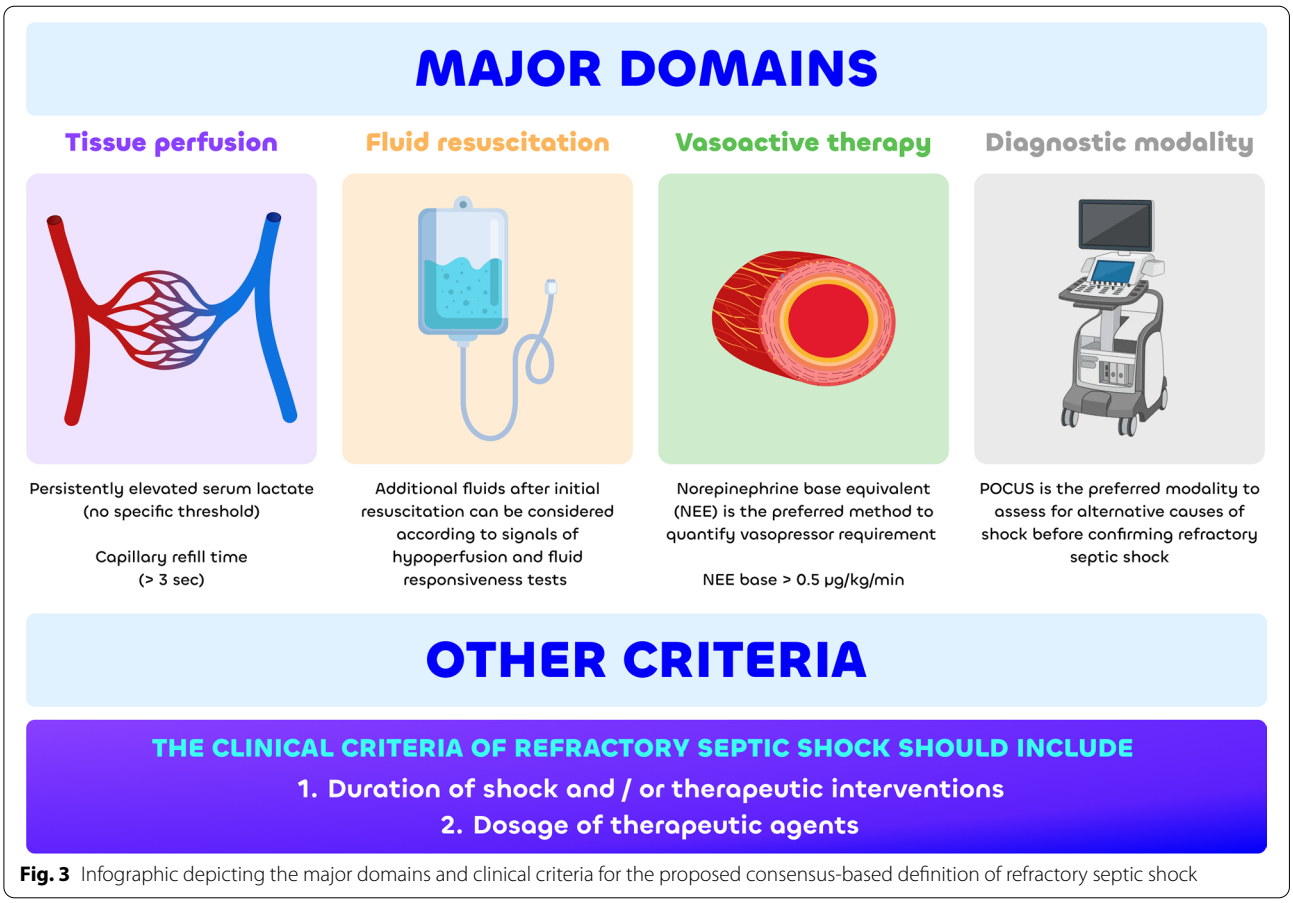

Fig. 3 Infographic depicting the major domains and clinical criteria for the proposed consensus-based definition of refractory septic shock

Rationale for duration of septic shock and interventions used The expert panel acknowledged that a minimal duration was required to define refractory septic shock, but agreement could not be reached to determine a precise duration. It seems important to have a defined duration (1) to allow time for initial resuscitation, so if no response then only it can be declared refractory, (2) refractoriness to treatment implies that treatments are given, which needs some time, and (3) the duration needs to be standardised, so patients in this group will be on the same time point of the disease trajectory. Several randomised controlled trials suggested a window of six to eight hours of appropriate standardised clinical care [29, 34], but the panel did not achieve sufficient consensus on a specific time to define the clinical criteria for refractory septic shock. Fluid resuscitation may require time to translate into haemodynamic improvement due to time of administration [40]. In addition, antimicrobials require time to be efficient, and the haemodynamic response to fluid and vasopressors may differ after source control [41, 42]. However, no consensus was achieved on a given duration of resuscitation post, which one can be considered refractory.

Therapeutic agents

Criteria 8. Following initial fluid resuscitation, additional fluid challenge(s) should be considered based on fluid responsiveness status prior to defining refractory septic shock

Rationale for additional fluid challenge The Surviving Sepsis Campaign suggested a 30 mL/kg bolus of fluid resuscitation within three hours in patients with septic shock [22], while the experts of ESICM suggested administering up to 30 mL/kg of intravenous crystalloids in the initial phase, with adjustments based on clinical context and frequent reassessments [43]. Albeit debated [44, 45], this recommendation seems to reflect most clinical practices in the literature. Regarding refractory septic shock clinical criteria, the experts suggested that refractory septic shock could only be considered if no benefit could be expected from additional fluid infusion, that is, in cases of fluid unresponsiveness. Recent ESICM guidelines state that, in patients with persistent shock after initial fluid resuscitation, fluid responsiveness should be assessed before continuing fluid resuscitation and detail the dynamic tests that should be used for this purpose [35].

In a systematic review of literature [46], fluid challenge was considered positive in 52% of patients in whom it was performed (not only septic shock patients). This indirectly underlines the need to reassess this response during the resuscitation of patients with septic shock, as it may change over time, influenced by several factors, including the intensity of vasoplegia, cardiac performance, the degree of fluid loss, and the therapies designed to address those factors. In addition, different haemodynamic phenotypes should be considered. Thus, reassessing fluid responsiveness prior to defining refractory septic shock is a critical step in the management of patients with septic shock.

Rationale for vasopressor dosage A systematic review suggested that the vasopressor dose, notably norepinephrine dose, was the most cited component for refractory septic shock (Table 4) [4]. Indeed, vasopressor dose serves as a surrogate marker for blood pressure and, to a lesser extent, organ perfusion. While the general need for vasopressors was already included in the sepsis 3.0 criteria of septic shock [1], in the present clinical criteria for refractory septic shock, panellists emphasised the actual vasopressor dose. Some of the large variability in norepinephrine and norepinephrine base equivalent dose (NEE) reported from previous trials reflected the different ways of reporting norepinephrine dosages by clinicians (norepinephrine base, tartrate or other salts) [47]. In a previous position paper, experts from ESICM and SCCM suggested expressing norepinephrine doses as the norepinephrine base (pharmacologically active component) amount and ensuring transparency in reporting dose formulations for patient safety [48].

Norepinephrine has been recommended as the first-line vasopressor for septic shock by experts of the Surviving Sepsis Campaign [22]; however, other vasopressors alone or in combination may be used worldwide [49–51]. For this reason, it was suggested to use NEE, reflecting an equivalent dose of norepinephrine base, whatever vasopressor is used [52–55]. Panellists selected a threshold at 0.5 µg/kg/min in agreement with reported literature [4]. Receipt of this NEE dose was also identified as a risk marker for early mortality

Criteria 9. The dosage of the therapeutic agent/s should be included in the definition of refractory septic shock

Criteria 10. The method most appropriate to quantify vasopressor exposure when defining refractory septic shock is *Norepinephrine Base Equivalent Dose*

Criteria 11. A threshold dosage of norepinephrine base equivalent dose of > 0.5 µg/kg/min should be included in the definition of refractory septic shock

Table 4 Details of studies describing patients with refractory septic shock

Authors	Study type	Aim and outcomes	N	Age (years)	Severity	Mortality
Albanese et al. 2005 (16148457)	RCT	Comparison of haemodynamic effects of NE and TP	20	Median (range) NE: 65 (24–76) TP: 66 (23–79)	APACHE II (Median (range) NE: 29 (24–31) TP: 28 (24–30)	NE:40% TP:50%
Auchet et al. 2017 (28425079)	Retrospective, observational, study	28-day mortality	106	Mean ± SD 62 ± 16	SOFA A (Mean ± SD): 12 ± 3	28-day: 60% 90-day: 65%
Dargent et al. 2025 (40019329)	RCT	Evaluate the effect of dexmedetomidine on the vasopressor response in patients with refractory septic shock	32	Mean ± SD: Intervention: 62.2 (± 16.1) Placebo: 67.1 (± 11.2)	SAPS II (Mean ± SD): Dexmedeto-midine: 75.3 (± 15.9) Placebo: 66.4 (± 13.3)	3-day (N (%)): Dexmedeto-midine: 8 (50) Placebo: 2 (13) ICU-mortality: Dexmedeto-midine: 10 (63) Placebo: 6 (38)
Dünser et al. 2003 (12732600)	RCT	Evaluate differences in haemodynamic response and organ functions between a combined infusion of AVP and NE or NE alone	48	Mean ± SD AVP/NE: 68 ± 9 NE: 68 ± 14	SAPS II (Mean ± SD): AVP/NE: 52 ± 17 NE: 50 ± 18	ICU: 71%
Friesecke et al. 2017 (28589286)	Prospective interventional single-centre	Effect of extracorporeal cytokine elimination on NE requirement in refractory septic shock	20	Mean ± SD: 60 ± 19	SAPS II score (Mean ± SD): 70 ± 11	28-d: 55%
Jarczak et al. 2023 (36075200)	RCT	Effect of hemadsorption therapy in patients with COVID-19 and refractory shock	24	Median (IQR 60 (56–63) vs. 69 (58–76)	SAPS II 75 (72–83) vs 79 (74–84) APACHE II 33 (29–41) vs 38 (36–41)	28-d: 63% (no difference between groups)
Leone et al. 2004 (15377885)	Prospective open-label study	Effects of TP on haemodynamics, biomarkers and renal function in catecholamine resistant septic shock	17	Mean SD 54 ± 12	APACHE II (Mean ± SD) 27 ± 4	Hospital: 47%
Martin et al. 2015 (26125087)	Retrospective, single-centre observational study	Association between NE dosage and mortality	324	Mean SD 62 ± 15	Median (IQR): SOFA 8 (6–10)	ICU: 44% Hospital: 48%
Micek et al. 2007 (17437364)	Prospective observational cohort study	Predictors of 28-day mortality in patients with refractory septic shock treated with NE with or without AVP	137	Mean ± SD: Survivors: 57 ± 16 Non-survivors 63 ± 15	APACHE II (Mean ± SD): 26 ± 6	28-d: 37%
O'Brien et al. 2002 (11955542)	Report, case series	Effects of TP in patients with norepinehrine-or methylene blue resistant septic shock	8 (unselected)	Mean (range) 60 (40–82)	APACHE II (Mean (range) 28 (25–37)	ICU: 50%
Thompson et al. 2025 (39675155)	Retrospective, observational, non-interventional	To assess the impact of the timing of maximal vasopressor dose on outcomes	702	Mean SD 63.7 ± 15.7	APACHE III (median-IQR): 140 (112–161) SOFA: 13 (11–16)	28-d: 58%
Tsuneyoshi et al. 2001 (11373409)	Prospective, case-controlled study	Cardiovascular and metabolic effects of low-dose intravenous AVP	16	Mean (range) 64 (16–80)	Mean (range) MOF score: 11 (7–15)	Hospital/ICU: 44%
Yang et al. 2013 (23673091)	RCT	The effect of active body temperature control on mortality in patients with refractory sepsis	65	Mean (range): 68 (22–88)	APACHE II (Mean ± SD): 22.0 ± 7.5 vs 23.8 ± 7.1	28-d: High-temp: 26%, Low-temp: 62%

APACHE Acute Physiology and Chronic Health Evaluation, *ARISE* Australasian Resuscitation in Sepsis Evaluation, *AVP* vasopressin, *d* day, *IQR* interquartile range, *MOF* multi-organ failure, *NE* norepinephrine, *RCT* randomised controlled trial, *SAPS* simplified acute physiology score, *SD* standard deviation, *SOFA* sequential organ failure assessment; temp, body temperature, *TP* terlipressin

in shock, including septic shock [56]. We acknowledge that this expert statement for a dose threshold is based on a weak level of evidence. Of note, 0.5 µg/kg/min is higher than that used in most trials to introduce a second-line vasopressor [57, 58]. Indeed, the Surviving Sepsis Campaign suggested introducing a second vasopressor for a threshold of NEE ranging from 0.25 to 0.5 µg/kg/min [22]. This reflects that refractory septic shock should be discriminated from the use of a second-line vasopressor.

The panellists disagreed on clinical criteria of refractory septic shock based merely on the addition of a second or third vasopressor, as the total amount of vasopressor seems more critical than the number of vasopressors. Heterogeneity of practices has been reported regarding the use of vasopressors [50, 51], with early introduction of a second agent being advocated by several groups [59–62]. Thus, the introduction of a second-line agent may simply reflect a multimodal strategy rather than indicating refractory septic shock [59, 63].

Diagnostic modalities

Criteria 12. Critical care ultrasonography (CCUS) should be used as a diagnostic modality to assess for alternative causes of shock (e.g., obstructive or cardiogenic) including mixed shock before confirming the diagnosis of refractory septic shock

Rationale for CCUS

Diagnostic modalities to exclude other causes of shock are probably not directly related to the current criteria. The use of invasive devices such as the pulmonary artery catheter has been excluded by most panellists, in line with a randomised controlled trial showing the lack of effect of this device on outcome in patients with septic shock [64]. A recent systematic review including 26 studies and 1323 patients suggested that most cardiac output monitors had poor agreement with reference methods in septic shock [65].

Imaging, including x-ray and computed tomography scan, has also been excluded. Indeed, it is useful to identify the source of infection [66]. It seems that imaging should be part of the standard of care, not related to refractory septic shock. Similarly, the panellists excluded the use of laboratory markers such as troponin and BNP, as no strong evidence showed the use of such markers in patients with severe septic shock to determine the presence or absence of other causes of shock. However, one should note that they can be good surrogate markers for myocardial dysfunction and outcome [67, 68]. In septic shock, several conditions may explain the increase in these biomarkers, making their specificity low.

Finally, the panellists selected critical care ultrasonography (CCUS) [69] as the preferred diagnostic modality to exclude other causes of shock [70]. This statement is in line with a recent SCCM consensus guideline and a recent ESICM consensus on haemodynamic monitoring to support the use of CCUS [35, 69]. The advantage of CCUS is bedside availability with no need for transferring a patient [71, 72]. The use of cardiac point-of-care ultrasonography (POCUS) has been debated, but most panellists considered that cardiac POCUS is part of CCUS [73, 74]. In addition, CCUS serves to exclude bleeding, to assess the lungs, to guide fluid resuscitation, and to identify the presence of vascular thrombosis [75–77]. The utility of CCUS is not confined only to the diagnosis of refractory septic shock, of course, but extends to all types of shock states.

Real-life practical use

Structured expert consensus processes, like Delphi, help to produce informed, defensible statements, notably when empirical evidence is weak or emerging. While randomised controlled trials would provide the highest level of evidence to support or contradict these statements, known methodological, ethical, and practical challenges make conducting such studies difficult [78, 79]. Big data study methodologies can address challenges related to heterogeneity and low power that have been described in the literature while testing these clinical statements in real-world populations [80]. Given the current absence of standardised criteria and the challenges of conducting randomised controlled trials in this population, observational studies would be valuable for testing these consensus clinical statements and further developing meaningful definitions related to refractory septic shock [4]. In addition, these clinical statements may have clear research implications, such as inclusion in septic shock trials or individual patient data meta-analyses.

Limitations

Our use of a Delphi method may be criticised because the need for a consensus-based on closed questions limited the possibility of responding to other key components of these clinical criteria. The panel was commissioned because of the lack of formal consensus-building efforts for identifying clinical statements of refractory septic shock in the literature and the lack of standardisation in clinical practice. The expert panel acknowledges that a minimal duration was required to define refractory septic shock, but no agreement was obtained to determine this duration. Our final consensus criteria should be interpreted with caution, and a validation period before bedside implementation is necessary. Some parts of the clinical statements, such as the use of CCUS, may be a matter of discussion, but the consensus was based on a large diversity of international physicians and healthcare professionals. Indeed, recent ESICM recommendations on circulatory shock and haemodynamic monitoring suggested a broad range of monitoring tools in patients with shock [35]. Although CCUS was the only modality for which consensus was reached, it is not necessarily available to all, particularly those in low-resource settings. Where CCUS is not available, the refractory nature of septic shock could be determined using other tools to confirm that hypovolemia has been adequately addressed.

Conclusion

The panellists agreed upon the need for a consensus on clinical criteria which could be used for a definition of refractory septic shock. Based on their responses, such a definition should include markers of tissue perfusion and surrogate markers for volume status and quantification of vasoactive drugs (Fig. 2). Organ dysfunction was part of the domains for defining refractory septic shock, but no consensus was reached on this outcome. Refractory septic shock is defined as the presence of persistently high lactate concentrations and/or prolonged capillary refill time (CRT) in a patient with septic shock who is fluid unresponsive, receiving at least a NEE dose > 0.5 µg/kg/min and with confirmation by critical care ultrasound (CCUS) in case of mixed shock. These clinical criteria, which frame a potential future definition of refractory septic shock, require external validation before clinical use or inclusion in guidelines.

Supplementary Information

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Data availability
Data are available on reasonable request to the to corresponding author.

Declarations

Conflicts of interest
Commercial Andre Holder: speaker for Baxter and consultant for Philips Medical. Ashish K Khanna: advisor or consultant for Edwards Lifesciences, GE Healthcare, Medtronic, Pharmazz Inc., Philips Research North America, Innoviva, Viatris, Bayer Corporation and AOP Clifford S. Deutschman: Consultant for Enlives. Daniel De Backer: Speaker for Viatris and AOP Healthcare and consultant for Pharmazz. Djillali Annane: Advisor for Regeneron and a speaker for Viatris Italia; Erin F. Barreto: Consultant for Wolters-Kluwer. Flavia Machado: PI on NOVA trial funded by Biolab; speaker for BioMérieux; Advisor on balanced solutions for Baxter. Greg S. Martin: Consultant for Abionic, CytoVale, Grifols, and Inclin Gretchen Lynn Sacha: Consultant for Wolters-Kluwer. Hallie Prescott: Consultant for Aurobac Therapeutics. Ignacio Martin-Loeches: Advisor or speaker for MSD, Mundipharma, Pfizer, Thermofisher, and Biomerieux. Ines Lakbar: Speaker for Viatris. Katia Donadello: Consultant for Viatris Giovanni Landoni: Speaker for AOP, Baxter, Medis, Paion, Viatris, and consultant for Pharmazz and Viatris. Marc Leone: Speaker for AOP Pharma, Edwards Life Sciences, Grifols, Pharmazz, Viatris, and advisor for Mindray, Previa and BioMérieux. Marlies Ostermann: Researcher for Baxter & BioMérieux (All funding goes to institutions). Matthieu Legrand: Consultant for Alexion, Radiometer, and Viatris. Maurizio Cecconi: Consultant for Edwards Lifesciences and GE Healthcare. Mervyn Singer: Speaker for AOP and BioMérieux; Advisor or consultant for Aptarion, Bayer, Deltex Medical, Matisse, Biotest, DeePull, Volition, and Radiometer; Consultant for Gentian, Pfizer, Sanofi, and Safeguard (these relationships are now ended). Michelle Chew: Speaker for Edwards Lifesciences, Laboratoire Agguetant, Philips Healthcare, and AOP Health. Michelle Ng Gong: Section editor for Wolters Kluwer. Naomi E. Hammond: Received IV fluid from Baxter for the PLUS trial; Researcher for Baxter Healthcare. Nicole Juffermans: Consultant for Bayer; Independent contractor for Octapharma; Researcher for Werfen. Patrick M. Wieruszewski: Consultant for UptoDate (on goingongoing) and for Viatris Inc (past). Ricard Ferrer Roca: Speaker for Pfizer and owns stocks for Grifols. Ryan C. Maves: Researcher; Funding from AiCuris, Biotest, Geovax, and Merck (to his institution); Consultant for Shionogi. Teresa A. Rincon: Advisor for Baxter health and Viven health; Consultant for blue cirrus consulting. Xavier Monnet: Speaker and consultant for Baxter, Getinge, AOP Health, and Becton-Dickinson. Yuki Kotani: Consultant for Viatris (past).
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