


CONFERENCE REPORTS AND EXPERT PANEL



ESICM guidelines on circulatory shock and hemodynamic monitoring 2025

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Abstract

Objective: These European Society of Intensive Care Medicine (ESICM) guidelines provide recommendations for the diagnosis of shock and hemodynamic monitoring for adult critically ill patients.

Methods: An international panel of experts formulated PICO-formatted questions, and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was applied to assess evidence and formulate recommendations. In the absence of strong evidence, panelists issued ungraded good practice statements (UGPS).

Results: Panelists issued 50 statements. Among others, skin perfusion should be monitored using the assessment of capillary refill time, and this may be complemented by the assessment of skin temperature and mottling (UGPS). In patients with a central venous catheter, serial measurements of (central) venous oxygen saturation and of the veno-arterial difference in carbon dioxide partial pressure should be performed (UGPS). In patients with persistent shock after initial fluid resuscitation, fluid responsiveness should be assessed before continuing fluid resuscitation (UGPS). It is recommended to use dynamic variables over static markers of preload for predicting fluid responsiveness, when applicable (graded statement). Cardiac output (CO) and/or stroke volume should be monitored in patients who do not respond to initial therapy (UGPS). Arterial pressure should be monitored with an arterial catheter in shock that is not responsive to initial therapy and/or requiring vasopressor infusion (UGPS), and central venous pressure should be measured in patients who have a central venous catheter (UGPS). Panelists suggest using echocardiography as the first-line imaging modality to assess the type of shock (graded statement). Echocardiographically defined phenotypes of left and right ventricular dysfunction may be of prognostic significance (UGPS).

Conclusions: The panel made 50 recommendations on shock diagnosis and hemodynamic monitoring.

Keywords: Acute circulatory failure, Lactate, Capillary refill time, Microcirculation, Venous oxygenation, Fluid therapy, Fluid responsiveness, Vasopressors, Arterial pressure, Intra-abdominal pressure, Central venous pressure, Cardiac output, Echocardiography, Practice guidelines

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Introduction

Shock is a state of acute circulatory failure that can be broadly attributed to four basic mechanisms: hypovolemic, cardiogenic, obstructive, or distributive, or a combination of these [1]. The unifying pathological process is altered tissue perfusion, resulting in decreased oxygen supply to the tissues and cellular oxygen uptake, which is associated with increased lactate levels and organ dysfunction [2]. In septic shock, microcirculatory abnormalities may further impair tissue perfusion.

Short-term mortality rates of patients with shock range from 20 to 50% [3]. Shock management requires a timely and comprehensive evaluation of several variables to recognize the presence of shock, assess its mechanism(s) and cause(s), plan treatment and interventions that improve organ perfusion and oxygenation, and may limit further organ dysfunction. These interventions essentially include fluid resuscitation, vasopressors, inotropic drugs, and/or mechanical circulatory support. Their indications and targets vary, depending on the mechanism(s) of shock and the patient's condition.

These guidelines update the previous consensus guidelines convened by the European Society of Intensive Care Medicine (ESICM) in 2014 [4], incorporating findings from relevant literature published thereafter (Table 1). The guidelines provide recommendations and suggestions based on evidence from scientific literature regarding the efficacy of different interventions on patient outcomes, complemented by expert opinions.

The scope of these guidelines is limited to adult patients covering diagnosis and monitoring of shock but not pharmacological treatments. Fluid therapy is only addressed through indices assessing and monitoring fluid responsiveness, while other aspects of the fluid prescription (choice of resuscitation fluids, or volume of resuscitation fluids) have been addressed in other recommendations of ESICM [5, 6]. Vasopressors are addressed only in the context of the effect on arterial pressure.

Methods

Topics and composition of the panel of panelists

These guidelines were developed under the aegis of the ESICM executive committee. It designated a chair (XM) and a co-chair (MCh). Twenty other panelists were chosen among the members of ESICM considering their expertise in the field (measured by the number of scientific publications in peer-reviewed journals in the different fields covered by the guidelines) and considering gender balance [7]. Two members of the

ESICM NEXT group (OH and TK) were also part of the panel. There were therefore 24 panelists in total. The ESICM methodology group appointed a methodologist (MG) assisted by two colleagues (MSa and GC). Four domains of acute circulatory failure were selected: definition of shock, fluid therapy, hemodynamic monitoring, and echocardiography. Each domain was assigned to a group of panelists coordinated by a chairperson (JB, AMes, XM, and MCh, respectively). Before the start of the process, panelists had to declare and compile a conflict-of-interest statement which was mandated by the chairs.

Selection of research questions and literature search

Except for Domain 1 (definitions), questions were formulated for each domain in accordance with the Population-Intervention-Comparator-Outcome (PICO) format. Each PICO question was discussed by the guideline's chairs and the methodologist, then reviewed, modified, and approved by all panelists. For each PICO question, a literature search was carried out using PubMed looking for articles published from January 1993 to April 2023 (see the Supplementary material). For Domain 1, a literature review was also carried out without performing a formal grading. For this area, we preferred a narrative approach.

The methodologist and two colleagues (MSa and GC) reviewed articles at the title and abstract level. Additional articles identified by snowballing methods were added. Pertinent full-text articles were selected according to PICO questions and shared with panelists. The final list of full-text studies for each PICO question was approved by the methodologist and panelists in the relevant field. The methodologist performed data extraction, synthesis, and risk of bias assessment for individual studies. Details of the search and selection procedures are provided in the Supplementary material.

Formulation of recommendations and consensus methodology

Following the literature review, panelists assessed the individual papers and the level of available evidence. The detailed methodology can be found in the Supplementary material. For each PICO question, panelists in the relevant domain formulated recommendations based on three key criteria: (i) certainty of the evidence (as provided by the methodologist), (ii) Grading of Recommendation Assessment, Development and Evaluation (GRADE) methodology [8], and (iii) expert opinions. Statements that describe the concept of shock or one of its key components were categorized as definitions. Regarding randomized controlled trials (RCTs) or observational studies focused on clinical outcomes, comprehensive methodological analysis and

Table 1 Comparative table between ESICM shock consensus 2014 and 2025

| Topic | Cecconi et al. 2014 | Monnet et al. 2025 |
|--|---|---|
| How should one define shock? | Shock is defined as a life-threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by the cells | Shock is a life-threatening acute circulatory failure characterized by decreased tissue perfusion, leading to inadequate oxygen delivery and/or oxygen utilization to meet cellular metabolic demands |
| What markers of the regional circulation and tissue oxygenation in shock should be used? | <p>We recommend serial assessment of tissue perfusion to follow shock evolution and help assess the underlying pattern and adequacy of cardiac output (CO) and vascular function</p> <p>We recommend monitoring skin perfusion using capillary refill time (CRT) and suggest complementing this with the assessment of skin temperature and mottling</p> <p>In patients with a central venous catheter, we recommend serial measurements of (central) venous oxygen saturation (ScvO₂)</p> <p>In patients with a central venous catheter and an arterial catheter, we recommend serial measurement of the veno-arterial difference in carbon dioxide partial pressure (Pv-aCO₂)</p> | <p>Serial assessment of tissue perfusion should be performed to follow shock evolution and to help assess the underlying pattern and the adequacy of CO and vascular function</p> <p>Monitoring skin perfusion should be performed using the assessment of CRT and this could be complemented with the assessment of skin temperature and mottling</p> <p>In patients with a central venous catheter, serial measurements of (central) venous oxygen saturation (ScvO₂) should be performed. In patients with a central venous catheter and an arterial catheter, serial measurement of the veno-arterial difference in carbon dioxide partial pressure (Pv-aCO₂) should be performed. In patients with a central venous catheter and an arterial catheter, one may consider performing serial measurements of the ratio of Pv-aCO₂ over the arterio-venous difference in oxygen content (Pv-aCO₂/Ca-vO₂)</p> |
| What is the target of arterial pressure in shock? | We recommend individualizing the target blood pressure. We suggest initially targeting a MAP of at least 65 mmHg | <p>The target blood pressure should be individualized during resuscitation of patients with shock.</p> <p>An initial MAP of 65-70 mmHg should be targeted in patients with septic shock</p> <p>A higher MAP target may be considered in patients with septic shock and a history of chronic arterial hypertension who show clinical improvement with higher blood pressure</p> <p>A higher MAP target may be considered in patients with septic shock with high CVP values who show clinical improvement with higher blood pressure. Lower MAP targets may be considered in patients with traumatic hemorrhagic shock and uncontrolled bleeding in the absence of traumatic brain injury. In the initial phase following trauma, a target systolic arterial pressure of 80–90 mmHg (MAP 50–60 mmHg) should be used until major bleeding has been stopped when there is no clinical evidence of traumatic brain injury and coma (Glasgow Coma Score ≤ 8). In traumatic brain injury (Glasgow Coma Score ≤ 8), we recommend targeting an initial mean arterial pressure ≥ 80 mmHg. Targeting an initial MAP of ≥ 65 mmHg may be considered in patients with cardiogenic shock</p> |
| When and how should one monitor arterial pressure in shock? | We recommend continuous monitoring of arterial pressure in patients with shock | Arterial pressure should be monitored in patients with shock. Arterial pressure should be monitored with an arterial catheter in shock that is not responsive to initial therapy and/or requiring vasopressor infusion |
| When should one monitor intra-abdominal pressure in shock? | We suggest serial monitoring of intra-abdominal pressure (IAP) in patients with shock and established risk factors for intra-abdominal hypertension | Serial monitoring of intra-abdominal pressure (IAP) may be considered in patients with shock and established risk factors for intra-abdominal hypertension |

Table 1 (continued)

| Topic | Cecconi et al. 2014 | Monnet et al. 2025 |
|--|---|--|
| When and how should one assess fluid responsiveness in shock? | We recommend using dynamic over static variables to predict fluid responsiveness. Perform a fluid challenge unless in cases of obvious hypovolemia | In patients with persistent shock after initial fluid resuscitation, fluid responsiveness should be assessed before continuing fluid resuscitation We recommend using dynamic variables over static markers of preload for predicting fluid responsiveness, when applicable. We recommend the passive leg raising (PLR) test to assess fluid responsiveness in mechanically ventilated patients in shock, with and without spontaneous breathing activity |
| When and how should one monitor cardiac output in shock? | We recommend additional hemodynamic assessment when clinical examination does not provide a clear diagnosis. We suggest echocardiography as the preferred modality for initial evaluation | Cardiac output and/or stroke volume should be monitored in patients who do not respond to initial therapy to assess the type of shock, evaluate hemodynamic status, and determine therapeutic response Frequent reevaluation of cardiac output may be considered When CO is monitored, its adequacy should be interpreted by evaluating organ function, tissue oxygenation, metabolism, and perfusion Transpulmonary thermodilution or pulmonary artery dilution with the PAC may be considered in patients for whom CO monitoring is required. Transpulmonary thermodilution or the PAC in patients with shock and moderate-to-severe ARDS may be considered be used for guiding fluid therapy. We suggest using echocardiography as the first line imaging modality to assess the type of shock and hemodynamic status. Serial echocardiographic evaluations should be performed to provide additional information on cardiac function, even when CO is monitored |
| When should one monitor central venous pressure in shock? | We recommend measuring CVP in patients with shock who have a central venous catheter | Central venous pressure should be measured in patients with shock who have a central venous catheter |
| What is the place of microcirculation assessment in shock? | Not explicitly addressed | When feasible, the assessment of microcirculation may be considered as an adjunct to comprehensive hemodynamic evaluation |
| Which markers should be monitored to evaluate the risk of fluid administration in shock? | We emphasize the need for careful fluid management even in fluid-responsive patients, especially in the presence of high filling pressures or increased extravascular lung water | The risk of harm from fluid administration could be assessed using markers such as intravascular filling pressures, intra-abdominal pressure, extravascular lung water (EVLW), pulmonary vascular permeability index (PVPI), venous excess ultrasound (VEXUS) grading, the ratio of the arterial oxygen partial pressure over the inspired oxygen fraction (PaO2/FiO2) ratio, or lung ultrasound score |
| Critical care echocardiography | In patients with circulatory shock, we recommend performing one or more echocardiograms | In patients with shock, echocardiographically defined phenotypes of left and right ventricular systolic function may be of prognostic significance In patients with circulatory shock, echocardiography leads to changes in management and supports therapeutic impact |

the GRADE approach were primarily applied to survival and mortality outcomes. In the evidence synthesis of diagnostic test studies, the certainty of evidence was determined by multiple factors, including the area under the curve receiver operating characteristic (ROC) curve (AUROC) analysis. A pooled AUROC of at least 85% indicated high certainty in diagnostic performance, while a moderate certainty was assigned for a pooled AUROC between 70 and 85%. Low certainty was designated when data were insufficient, the number of studies was limited, or substantial heterogeneity and inconsistency prevented a reliable pooled analysis.

Panelists issued ungraded good practice statements for recommendations which did not fulfill formal GRADE criteria for quality of evidence but were supported by substantial indirect evidence of benefit [9]. According to GRADE [9], panelists explicitly addressed the following issues before formulating ungraded good practice statements: (i) is the message really necessary in regard to actual health care practice?, (ii) after consideration of all relevant outcomes and potential downstream consequences, will implementing the good practice statement result in large net positive consequences?, (iii) is collecting and summarizing the evidence a poor use of a guideline panel's limited time and energy (opportunity cost is large)?, and (iv) is there a well-documented clear and explicit rationale connecting the indirect evidence? [9].

The panelists issued two levels of recommendations. Strong recommendations ("we recommend" for the graded recommendations and "one should do this" for the ungraded good practice statements) mean that the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects. This can be both in favor of an intervention and against it. Weak recommendations ("we suggest" for the graded recommendations and "one could do this" or "it may be considered to do this" for the ungraded good practice statements) mean that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is not confident about these trade-offs.

The recommendations were initially discussed within each domain during 17 online meetings and one in-person meeting (between dates June 16, 2022, and September 3, 2024). Members who could not attend had the opportunity to comment on the draft recommendations, and their feedback was incorporated. Once each group finalized its recommendations, they were reviewed and revised in online meetings with the entire panel. The finalized recommendations were then sent to all panelists for anonymous online voting.

The 24 panelists were required to vote on every statement. Each statement was rated on a scale of 1 (strongly disagree) to 9 (strongly agree). Statements that received a score of ≥ 7 from ≥ 19 (80%) of the participants were accepted and were classified as having "strong agreement". Statements with scores of ≥ 7 in < 14 (58%) of panelists or scores < 7 for any proportion of panelists were rejected, did not proceed to the next round of voting, and were classified as "no agreement". For statements with a score of ≥ 7 from 14 (58%) to 18 (75%) of panelists, a new version of the text was prepared based on the comments left by the experts during the first round. In the absence of comments, the statement was classified as receiving a "weak agreement". If a new version was suggested by the panelists' comments, a second round of voting was held for this revised version. The same rules as in the first round were applied. Again, for statements with a score of ≥ 7 from 14 (58%) to 18 (75%) of panelists, a revised version of the text of statements could be formulated from the panelists' comments and proposed in a third round of voting. The same rules were applied as for the two previous rounds, except that statements with a score of ≥ 7 from 14 (58%) to 18 (75%) of panelists were definitively classified as receiving a "weak agreement". The results of the vote are presented in the Supplementary material.

Domain 1: definition of shock (Fig. 1)

Question 1.1. How should one define shock?

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| Recommendations 1.1 |
| 1. Shock is defined as a life-threatening acute circulatory failure characterized by decreased tissue perfusion, leading to inadequate oxygen delivery and/or oxygen utilization to meet cellular metabolic demands. |
| Ungraded definition/Ungraded evidence/Strong agreement |
| 2. The typical features are hypotension, tachycardia, and signs of hypoperfusion, such as abnormal skin perfusion, decreased urine output, and altered mental status. Although hypotension is commonly present, it is not required to define shock. |
| Ungraded good practice statement/Ungraded evidence/Strong agreement |
| 3. Lactate levels are typically increased (> 2 mmol/L) in shock states |
| Ungraded good practice statement/Ungraded evidence/Strong agreement |

Background
Shock is a clinical state in which cellular oxygen availability is insufficient to meet the tissues' demands. This subsequently results in organ dysfunction associated with increased mortality. Hypovolemic, cardiogenic, and obstructive patterns are characterized by low cardiac

| SHOCK | | SUMMARY OF CLINICAL QUESTIONS AND RECOMMENDATIONS FOR DEFINITION | | | | | | | | | |
|-------------------------|--|--|--|----------------------------------|--|----------------------------------|--|------|--|----------|--|
| RECOMMENDATION STRENGTH | | SUGGEST AGAINST | | WEAK RECOMMENDATION | | STRONG RECOMMENDATION | | | | | |
| CERTAINTY OF EVIDENCE | | UNGRADED DEFINITION | | UNGRADED GOOD PRACTICE STATEMENT | | UNABLE TO PROVIDE RECOMMENDATION | | | | | |
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Fig. 1 Summary of recommendations, certainties of evidence and agreement strengths for Domain 1: definition of shock. The corresponding 2014 recommendations are given for comparison

output (CO) and compensatory vasoconstriction. Conversely, distributive shock, in the context of an underlying inflammatory response, is frequently associated with high CO and peripheral vasodilation, particularly after initial fluid resuscitation. Even though these broad mechanisms are well defined and their treatment seems intuitive, the outcome is also related to the reversibility of the underlying cause, comorbidities, and the duration of shock. Therefore, prompt resolution of the cause and restoration of perfusion are critical elements of treatment. Several compensatory mechanisms maintain tissue perfusion that translate into clinical, hemodynamic, and laboratory characteristics.

Consensus on science

The main clinical element of shock, tissue hypoperfusion, in combination with compensatory vasoconstriction in regional and peripheral circulations, results in clinical symptoms of decreased urine output, altered mental state, and abnormal skin perfusion. They represent the “three windows” through which the clinician can explore the patient in shock in order to establish the diagnosis and assess its severity [10].

There is limited evidence for the clinical definition and presenting symptoms of shock, where such symptoms also depend on the type of shock. In a systematic review of the clinical signs characterizing shock, reduced peripheral perfusion/temperature, prolonged capillary refill time (CRT), skin mottling, and a shock index (ratio of systolic arterial pressure over heart rate) ≥ 0.7 – 0.8 were identified as valid clinical indicators of shock [11]. The critical element of our recommendation is not to rely on only one variable to diagnose shock but to use a multimodal assessment. This is underscored by the finding that combining several tissue perfusion variables may better relate to patient outcomes [12]. Many of the clinical characteristics of shock are related to morbidity and mortality [1]. However, that does not necessarily imply that outcomes will improve using these as a goal of therapy, as limited interventional studies are available [13, 14].

The two characteristics of shock outside of the “three windows” [10] are hypotension and increased blood lactate levels. Although the activated sympathetic nervous system in shock states may prevent an initial drop in blood pressure [15, 16], hypotension is associated with significantly abnormal markers of tissue perfusion and oxygenation [17]. The definition of hypotension in clinical practice varies, but a threshold of 65 mmHg for mean arterial pressure (MAP) or of 90 mmHg for systolic arterial pressure is most frequently used [18]. A MAP < 65 mmHg is associated with increased morbidity and mortality [19], but the presence or absence of markers

of tissue hypoperfusion affects this association [20]. All values of arterial pressure have physiological meaning. Diastolic arterial pressure depends mainly on arterial tone and heart rate, and pulse pressure is physiologically related to stroke volume and arterial compliance. Both have been associated with prognosis in critically ill patients [21].

Elevated lactate levels are typical for clinical shock. Lactate and lactate clearance are associated with outcomes in various forms of shock [22]. Even small increases above the 2.0 mmol/L upper normal limit are associated with increasing mortality [23]. In addition, the prognostic significance of lactate seems to be superior to blood pressure [13]. Although other mechanisms than tissue hypoxia may contribute to blood lactate levels and their changes over time [24], hyperlactatemia expressed as the absolute level, the time to reach normal levels, and as the area under the curve of the level–time relationship, is associated with increased organ failure and mortality [25]. A recent systematic review shows that decreases in lactate levels following treatment or using lactate levels to guide resuscitation are associated with improved outcomes of patients with septic shock [26]. A RCT targeting reductions in lactate levels compared to standard care in all types of shock with a baseline lactate level above 3.0 mmol/L showed no significant difference in mortality but a significantly lower hazard ratio for less organ failure in the protocol group [27].

Expert opinion

The definition of shock is based on the presence of multiple markers of altered tissue perfusion, ultimately leading to a life-threatening condition. Arterial pressure plays a central role, as a decrease in systolic arterial pressure and MAP is a typical feature of shock. Once shock has been diagnosed, diastolic arterial pressure and pulse pressure should be used to characterize the shock profile: typical shock in combination with systemic vasodilation is usually associated with a low diastolic arterial pressure and preserved pulse pressure. In cardiogenic and hypovolemic profiles, pulse pressure is usually low and diastolic arterial pressure is typically high. The main elements of treatment rely on determining the underlying cause and restoring adequate tissue perfusion. For this, serial measurements of these markers are essential. Importantly, while hypotension is common in shock, its absence does not rule out severe tissue hypoperfusion. We recommend a multimodal approach to accurately identify and assess patients with shock.

Question 1.2. What markers of the regional circulation and tissue oxygenation in shock should be used?

Recommendations 1.2

4. Serial assessment of tissue perfusion should be performed to follow shock evolution and to help assess the underlying pattern and the adequacy of CO and vascular function.

Ungraded good practice statement/Ungraded evidence/Strong agreement

5. Monitoring skin perfusion should be performed using the assessment of CRT and this could be complemented this with the assessment of skin temperature and mottling.

Ungraded good practice statement/Ungraded evidence/Strong agreement

6. In patients with a central venous catheter, serial measurements of (central) venous oxygen saturation ($S(c)vO_2$) should be performed.

Ungraded good practice statement/Ungraded evidence/Strong agreement

7. In patients with a central venous catheter and an arterial catheter, serial measurement of the veno-arterial difference in carbon dioxide partial pressure ($P_{v-a}CO_2$) should be performed.

Ungraded good practice statement/Ungraded evidence/Strong agreement

8. In patients with a central venous catheter and an arterial catheter, one may consider performing serial measurements of the ratio of $P_{v-a}CO_2$ over the arterio-venous difference in oxygen partial content ($P_{v-a}CO_2/C_{a-v}O_2$).

Ungraded good practice statement/Ungraded evidence/Strong agreement

Background

Clinical examination is key to assessing the critically ill patient with suspected circulatory failure. Although many clinical symptoms relate to global blood flow, they are not sensitive nor specific to assess the adequacy of CO [28]. In addition, improvements in macrocirculatory variables (such as arterial pressure and CO) may not necessarily translate into improvement in regional (or tissue) perfusion. Therefore, treatment of shock should also be guided by markers of peripheral/microcirculatory hypoperfusion. In experimental settings, numerous markers of tissue hypoperfusion and subsequent tissue hypoxia have been identified. However, their use in clinical practice is limited, either due to the requirement of specific monitoring devices (e.g., microdialysis) or specific measurements (e.g., lactate to pyruvate ratio).

Consensus on science

The skin may serve as an easy, early, and fast indicator of global tissue perfusion. CRT [29, 30] and skin mottling at first assessment have been related to outcome [31, 32]. Some studies have shown an association between markers of skin (peripheral) perfusion and perfusion of intra-abdominal organs [33] and sublingual microcirculation [34]. However, these markers are influenced by multiple

factors. Contrary to what has been observed in human models of shock [15], in critically ill patients, CRT and skin temperature are not reliable indicators of low CO [28] and do not follow CO changes [35].

Markers of peripheral perfusion may respond to various clinical interventions such as fluid resuscitation, inotrope, vasodilator, as well as vasopressor treatment [31, 36–39]. However, when compared to regular clinical practice, the ultimate efficacy of normalizing peripheral perfusion variables using these interventions is not yet fully established [14]. Current clinical practice consists of serial monitoring and assessing whether interventions normalize these markers, as the persistence of abnormality is associated with increased morbidity and mortality in septic shock [40]. In septic shock, these markers may serve for adapting the blood pressure target, for instance, using a vasopressor test to assess whether an abnormal peripheral perfusion would improve with higher blood pressure [41]. In an RCT in septic shock patients, the use of peripheral perfusion as a target of resuscitation was more beneficial than using lactate to guide resuscitation [14, 42]. In addition, continued resuscitation to decrease or normalize lactate levels in patients with normal peripheral perfusion was associated with increased mortality when compared to no further hemodynamic treatment [43]. A recent systematic review concluded that, compared to usual care, resuscitation guided by lactate or CRT was likely to improve outcomes [26].

In experimental conditions, a progressive decrease in oxygen delivery is followed by a decrease in SvO_2 . In contrast, $P_{v-a}CO_2$ mainly increases when the involved mechanism is decreased blood flow [44, 45]. The changes in $S(c)vO_2$ and $P_{v-a}CO_2$ do not reflect tissue oxygenation as such but reflect the balance between oxygen delivery and consumption. Therefore, they serve as an easy marker of tissue perfusion. Although the correlation between SvO_2 and $ScvO_2$ is limited [46] and may be affected by regional O_2 desaturation [47, 48], the trending between these parameters seems adequate for using $ScvO_2$ in clinical practice. Low and especially persistently low SvO_2 [49] and $ScvO_2$ [50] are associated with poor outcomes. Of note, high $S(c)vO_2$ values also are associated with a poor outcome [51, 52], highlighting that metabolism, microvascular perfusion, and mitochondrial function also influence $S(c)vO_2$ levels. Accordingly, interpreting and targeting $S(c)vO_2$ may be complex. The landmark study of Rivers et al. [53] showed improved outcome when incorporating $ScvO_2$ as a treatment target in septic shock patients. Although the subsequent early goal-directed therapy studies did not show benefit from this approach [54–56], this needs to be contextualized as the publication of the landmark study [53] changed clinical practice

significantly so that low ScvO₂ levels became rare [57]. Nevertheless, studies have suggested the benefit of targeting ScvO₂ in patients with sepsis [58].

In some studies, the P_{v-a}CO₂ was related to CO, ScvO₂, and tissue perfusion, suggesting this marker also functions as a flow-related variable in clinical practice [59]. In patients, improvements in global blood flow, by different interventions, are associated with decreases in P_{v-a}CO₂, increases in ScvO₂, and decreases in lactate levels, suggesting an improvement in tissue perfusion [60]. Of note, changes in metabolism may make the interpretation of changes in P_{v-a}CO₂ more complex. When excessive doses of inotropes are used, aerobic production of CO₂ increases more than the increase in flow, causing P_{v-a}CO₂ to increase [61]. Persistent abnormal P_{v-a}CO₂ is associated with increased mortality even in the context of normal S(c)vO₂ [62]. A P_{v-a}CO₂ >6 mmHg suggests a persistent shock state that may be responsive to fluid and/or inotrope administration.

The ratio of P_{v-a}CO₂ over C_{a-v}O₂ has been introduced as a marker of anaerobic metabolism [63]. It has been shown to be associated with increased mortality within certain patient subgroups [64], including in patients with a high ScvO₂ [65]. During resuscitation, patients who improve oxygen consumption after fluid resuscitation, suggesting improved tissue oxygen delivery, had a significant decrease in P_{v-a}CO₂/C_{a-v}O₂ from baseline, in contrast to patients in whom oxygen consumption did not change [66]. The improvement in oxygen consumption and the P_{v-a}CO₂/C_{a-v}O₂ ratio were present in patients with a normal to high baseline ScvO₂. This suggests adding the P_{v-a}CO₂/C_{a-v}O₂ to ScvO₂ and P_{v-a}CO₂ might optimize resuscitation. To date, only one study used the P_{v-a}CO₂/C_{a-v}O₂ as a goal of treatment, compared to SvO₂, reporting no difference in outcome between the two groups [67].

The clinical use of both the P_{v-a}CO₂ and the P_{v-a}CO₂/C_{a-v}O₂ requires careful interpretation as other factors (CO₂ production, and its dissociation from hemoglobin, body temperature, acidosis, and tissue perfusion [68, 69]) may play a role. Therefore, in clinical practice, none of the markers discussed in this section should be used in isolation.

Expert opinion

In experimental and clinical conditions, markers of peripheral perfusion and tissue perfusion may respond to improvements in blood flow and are related to clinical outcomes. Given the limited evidence of currently available RCTs in the presence of sound physiological studies and controversies, we do not recommend using these markers in isolation. On the contrary, we suggest measuring and interpreting them simultaneously. In practice,

the measurement of CRT, more or less associated with the assessment of skin temperature and mottling, should be coupled with the biological indices. Their meaning is different, and the information they provide is complementary. Indices of skin perfusion can be used as surrogates of global tissue perfusion, reflecting tissue blood flow and microcirculation reactivity. S(c)vO₂ directly reflects the adequacy between global oxygen supply and demand. The P_{v-a}CO₂ gradient is mainly determined by CO, and the P_{v-a}CO₂/C_{a-v}O₂ ratio is a marker of anaerobic metabolism.

These variables should be measured along with macrohemodynamic indices detailed in further statements, in particular arterial pressure and CO in patients in whom it is justified. In addition, these markers rapidly respond to improvements in tissue perfusion where changes in lactate levels are slow and may be unrelated to changes in tissue perfusion already after initial resuscitation. Therefore, normalization of lactate levels should not be used as a target but viewed as a consequence of the adequacy of overall treatment.

There is no evidence in the literature to specify the frequency with which tissue perfusion assessment should be performed. This assessment should at least occur when hemodynamic variables such as blood pressure deteriorate, and following therapeutic interventions aimed to modify regional perfusion in order to measure their effectiveness.

Question 1.3. What is the place of microcirculation assessment in shock?

Recommendation 1.3

9. When feasible, the assessment of microcirculation may be considered as an adjunct to comprehensive hemodynamic evaluation.

Ungraded good practice statement/Ungraded evidence/Strong agreement

Background

Ultimately, the macrocirculatory perfusion problem in shock translates to impaired oxygen delivery and the impaired removal of waste products from the microcirculation [10]. In human models of shock, a decrease in global blood flow is associated with impaired microcirculatory perfusion where restoration of blood flow results in the restoration of microcirculatory perfusion [17]. However, due to progressive endothelial and microcirculatory dysfunction, particularly in distributive shock, convection and diffusion of oxygen to the tissues may be further compromised. In experimental endotoxic shock, the microcirculatory perfusion is affected more profoundly, limiting the efficacy of resuscitation efforts [45, 70]. In severe cases, abnormal microcirculatory perfusion

may not be responsive to macrohemodynamic improvements [71]. Persistent abnormal microcirculatory perfusion is associated with morbidity and mortality, as shown in different forms of circulatory failure [40, 72–75] and in a mixed population of critically ill patients [76].

In clinical practice, several devices are available to visualize the microcirculation, where the sublingual area is most frequently used to assess its characteristics [77, 78]. Although a fast visualization at the bedside might be illustrative, a thorough assessment requires adequate methods [78] and multiple variables [79].

Consensus on science

Many clinical studies have shown that frequently used interventions in the resuscitation of patients with acute circulatory failure, such as fluid resuscitation, vasopressors, vasodilators, and blood transfusion, may improve microcirculatory perfusion [80]. However, a systematic review could not identify a single therapeutic agent to improve microcirculatory perfusion nor a benefit of one agent over another [80]. A failure to improve the microcirculation despite macrocirculatory optimization has been related to a worse organ failure and outcome in cardiogenic shock [81].

Very few studies have assessed the impact of using the microcirculation to guide resuscitation on outcome. In a trial including patients with mixed causes of circulatory failure, integrating parameters of sublingual microcirculatory failure into the treatment protocol on admission and after 24 h of starting treatment was not associated with improved outcomes [82]. This protocol has been criticized, as it did not represent an adjustment of therapeutic interventions based on changes in microcirculatory perfusion. Adjustment of treatment following the result of the microcirculatory assessment was not implemented in two-thirds of the patients. A study, in a homogeneous sepsis population, aimed at improving abnormal sublingual microcirculatory perfusion showed a reduced organ failure score at 24 h [83]. These data underscore the relevance of timely and adequate restoration of tissue perfusion using multiple variables.

Expert opinion

Visualization of the sublingual microcirculation may reveal persistent abnormal perfusion after initial macrocirculatory targeted resuscitation. This technique can reveal important information that may help diagnose circulatory failure and optimize treatment. There is no strong evidence in current literature that exploring microcirculation in shock patients improves outcome. However, when available, assessing microvascular perfusion in a multimodal model with the other tissue

perfusion variables may help to optimize global, regional, and microcirculatory perfusion in patients with shock.

Domain 2: fluid therapy (Figs. 2, 3)

Question 2.1. Should one assess fluid responsiveness in shock?

Recommendation 2.1

10. In patients with persistent shock after initial fluid resuscitation, fluid responsiveness should be assessed before continuing fluid resuscitation.

Ungraded good practice statement/Ungraded evidence/Strong agreement

11. The potential benefit of fluid administration, predicted by the assessment of fluid responsiveness, should be weighed against the potential risk of fluid administration.

Ungraded good practice statement/Ungraded evidence/Strong agreement

Background

Fluid administration is aimed at increasing the stressed blood volume, mean systemic filling pressure, the pressure gradient of venous return, and therefore CO. Fluid accumulation is harmful to critically ill patients [84]. In addition, fluid administration in non-responders may result in hemodilution and—without a corresponding increase in CO—reduced oxygen delivery, contrary to the goal of hemodynamic resuscitation. Finally, restricting fluid administration in non-responders helps minimize overall fluid balance, although it is important to note that fluid resuscitation constitutes only a portion of the total fluid volume received during an ICU stay [85].

The proportion of fluid responders varies in the different studies from about 50% (as described in studies enrolling ICU patients with hemodynamic instability and receiving continuous hemodynamic monitoring [86]) to much less, as described in already resuscitated septic shock patients (i.e., 20% of patients 4 h after an initial resuscitation) [87]. Moreover, in a smaller previous study, only half of fluid responders were still responders 30 min after the fluid bolus infusion [88].

These studies highlight the importance of promptly assessing fluid responsiveness after initial resuscitation. Since hemodynamic instability may reoccur over time, re-assessment is essential whenever during shock management.

Consensus on science

The literature search identified seven RCTs investigating fluid responsiveness assessment in patients during the acute phase of shock [89–95] and only one study was classified as having a low risk of bias [92] (Supplementary material). The sample size ranged between 50 and 150

































| FLUID THERAPY | | | | | | | | | | SUMMARY OF CLINICAL QUESTIONS AND RECOMMENDATIONS FOR DEFINITION | | | | | |
|---|--|---|--|--|--|--|--|---|--|---|---|---|--|--|--|
| RECOMMENDATION STRENGTH | |  SUGGEST AGAINST |  WEAK RECOMMENDATION |  STRONG RECOMMENDATION | | | | | | Recommendation strength | Certainty of evidence | Certainty of evidence | | | |
| | |  UNGRADED DEFINITION |  UNGRADED GOOD PRACTICE STATEMENT |  UNABLE TO PROVIDE RECOMMENDATION | | | | | | | | | | | |
| CERTAINTY OF EVIDENCE | |  VERY LOW |  LOW |  MODERATE |  HIGH |  UNGRADED | AGREEMENT STRENGTH | | | | | | | | |
| | | | | | | |  WEAK |  MODERATE |  STRONG | | | | | | |
| [2014] STATEMENT OF RECOMMENDATION | | UNGRADED, BEST PRACTICE STATEMENT | | | | | UNGRADED, STATEMENT OF FACT | | | | | | | | |
| [2014] CERTAINTY OF EVIDENCE | | LEVEL 1, QOE B | | LEVEL 1, QOE C | | LEVEL 2, QOE B | | LEVEL 2, QOE C | | | | | | | |
| SHOULD ONE ASSESS FLUID RESPONSIVENESS IN SHOCK? | | | | | | | | | | | | | | | |
| ➔ In patients with persistent shock after initial fluid resuscitation, fluid responsiveness should be assessed before continuing fluid resuscitation. | | | | | | | | | |  |  |  | | | |
| 2014 | We recommend to assess volume status and volume responsiveness. [UNGRADED, BEST PRACTICE STATEMENT] | | | | | | | | | | | | | | |
| | When the decision for fluid administration is made we recommend to perform a fluid challenge, unless in cases of obvious hypovolemia (such as overt bleeding in a ruptured aneurysm). [LEVEL 1, QoE C] | | | | | | | | | | | | | | |
| ➔ The potential benefit of fluid administration, predicted by the assessment of fluid responsiveness, should be weighed against the potential risk of fluid administration. | | | | | | | | | |  |  |  | | | |
| 2014 | We recommend that even in the context of fluid-responsive patients, fluid management should be titrated carefully, especially in the presence of elevated intravascular filling pressures or extravascular lung water. [UNGRADED, BEST PRACTICE STATEMENT] | | | | | | | | | | | | | | |
| | We recommend early treatment, including hemodynamic stabilization (with fluids and vasopressors if needed) and treatment of the shock etiology, with frequent reassessment of response. [UNGRADED, BEST PRACTICE STATEMENT] | | | | | | | | | | | | | | |
| WHICH MARKERS SHOULD BE MONITORED TO EVALUATE THE RISK OF FLUID INFUSION IN SHOCK? | | | | | | | | | | | | | | | |
| ➔ The risk of harm from fluid administration could be assessed using markers such as intravascular filling pressures, intra-abdominal pressure, extravascular lung water (EVLW), pulmonary vascular permeability index (PVPI), venous excess ultrasound (VExUS) grading, the ratio of the arterial oxygen partial pressure over the inspired oxygen fraction (PaO ₂ /FiO ₂) ratio, or lung ultrasound score (LUS). | | | | | | | | | |  |  |  | | | |
| HOW SHOULD ONE ASSESS THE EFFECTIVENESS OF A FLUID BOLUS? | | | | | | | | | | | | | | | |
| ➔ A fluid challenge is defined as a bolus of 200 to 500 mL given over 5-10 minutes while evaluating its effects. | | | | | | | | | |  |  |  | | | |
| ➔ One may consider assessing the effects of a fluid bolus on CO and, when not available, on pulse pressure rather than MAP. | | | | | | | | | |  |  |  | | | |
| ➔ The effectiveness of a fluid bolus in improving tissue perfusion should be evaluated by considering changes in variables such as CRT, skin mottling, S _{(c)v} O ₂ , carbon dioxide partial pressure (pCO ₂)-derived variables, and lactate. | | | | | | | | | |  |  |  | | | |
| 2014 | We recommend that fluid resuscitation should be guided by more than one single hemodynamic variable. [UNGRADED, BEST PRACTICE STATEMENT] | | | | | | | | | | | | | | |

Fig. 2 Summary of recommendations, certainties of evidence and agreement strengths for Domain 2: fluid therapy (part 1). The corresponding 2014 recommendations are given for comparison

Fig. 2 Summary of recommendations, certainties of evidence and agreement strengths for Domain 2: fluid therapy (part 1). The corresponding 2014 recommendations are given for comparison

patients, except for one trial that included 700 patients [92]. Of the six RCTs, three were terminated early [90, 94, 95] and only three trials were multicentric [90, 92, 94].

In all trials, mortality was analyzed as a secondary outcome, but none were adequately powered for this endpoint, limiting the precision of the estimates. Instead, these trials were designed with statistical power based on

surrogate markers of clinical improvement or fluid balance. Nevertheless, pooled data from three trials demonstrated no impact on 28-day or in-hospital mortality.

Expert opinion

No study has demonstrated a mortality benefit using the assessment of fluid responsiveness in the management

FLUID THERAPY



SUMMARY OF CLINICAL QUESTIONS AND RECOMMENDATIONS FOR DEFINITION
















































| RECOMMENDATION STRENGTH | |  SUGGEST AGAINST |  WEAK RECOMMENDATION |  STRONG RECOMMENDATION | | | | | | |
|--|---|---|--|--|--|--|--------------------|--|--|--|
| | |  UNGRADED DEFINITION |  UNGRADED GOOD PRACTICE STATEMENT |  UNABLE TO PROVIDE RECOMMENDATION | | | | | | |
| CERTAINTY OF EVIDENCE | |  VERY LOW |  LOW |  MODERATE |  HIGH |  UNGRADED | AGREEMENT STRENGTH |  WEAK |  MODERATE |  STRONG |
| [2014] STATEMENT OF RECOMMENDATION | | UNGRADED, BEST PRACTICE STATEMENT | | | UNGRADED, STATEMENT OF FACT | | | | | |
| [2014] CERTAINTY OF EVIDENCE | | LEVEL 1, QoE B | | LEVEL 1, QoE C | | LEVEL 2, QoE B | | LEVEL 2, QoE C | | |
| HOW SHOULD ONE ASSESS FLUID RESPONSIVENESS IN SHOCK? | | | | | | | | | | |
| → We recommend using dynamic variables over static markers of preload for predicting fluid responsiveness, when applicable. | | | | | | | |  |  |  |
| 2014 | We recommend using dynamic over static variables to predict fluid responsiveness, when applicable. [LEVEL 1, QoE B] | | | | | | | | | |
| | We recommend that commonly used preload measures (such as CVP or PAOP or end diastolic area or global end diastolic volume) alone should not be used to guide fluid resuscitation. [LEVEL 1, QoE B] | | | | | | | | | |
| → We recommend the passive leg raising (PLR) test to assess fluid responsiveness in mechanically ventilated patients in shock, with and without spontaneous breathing activity. | | | | | | | |  |  |  |
| → We recommend the end-expiratory occlusion test as an alternative to PLR test in mechanically ventilated patients in shock without spontaneous breathing activity. | | | | | | | |  |  |  |
| → We are unable to provide recommendations regarding the use of the tidal volume challenge as alternative to PLR test in mechanically ventilated patients in shock, due to paucity and/or heterogeneity of available data. | | | | | | | |  |  |  |
| → We recommend pulse pressure variation (PPV) to assess fluid responsiveness in mechanically ventilated patients in shock without spontaneous breathing activity and a tidal volume ≥ 8 mL/kg. | | | | | | | |  |  |  |
| → We suggest against the use of PPV alone to assess fluid responsiveness in mechanically ventilated patients in shock with spontaneous breathing activity and a tidal volume < 8 ml/kg. | | | | | | | |  |  |  |
| → We suggest using stroke volume variation (SVV) to assess fluid responsiveness in mechanically ventilated patients in shock without spontaneous breathing activity and a tidal volume ≥ 8 ml/kg. | | | | | | | |  |  |  |
| → We are unable to provide recommendations regarding the use of PPV to assess fluid responsiveness in mechanically ventilated patients in shock with spontaneous breathing activity. | | | | | | | |  |  |  |
| → We are unable to provide recommendations regarding the use of SVV to assess fluid responsiveness in mechanically ventilated patients in shock with spontaneous breathing activity. | | | | | | | |  |  |  |
| → We are unable to provide recommendations regarding the use of the mini fluid challenge test in patients with shock, due to paucity and/or heterogeneity of available data. | | | | | | | |  |  |  |
| → We suggest against the use of changes in IVC diameter alone in critically ill patients to assess fluid responsiveness. | | | | | | | |  |  |  |

Fig. 3 Summary of recommendations, certainties of evidence and agreement strengths for Domain 2: fluid therapy (part 2). The corresponding 2014 recommendations are given for comparison

of patients, as none has been sufficiently powered to test this hypothesis. Therefore, we provide an ungraded expert opinion.

Some RCTs in septic patients have shown reductions in the cumulative fluid balance when using such a strategy [89–91, 93]. This may have clinical benefit as an increasingly positive fluid balance has been associated with a

worse outcome [84]. Using fluid responsiveness has also been shown to decrease the need for ventilation and for renal replacement therapy in septic shock [90]. The clinical benefit should be even more obvious if the potential benefit of fluid resuscitation in terms of CO and tissue perfusion is weighed against its inherent risk.

Moreover, given the tools available, assessing fluid responsiveness is feasible and applicable in many patients. It requires at least invasive arterial blood pressure monitoring and/or minimally invasive or invasive hemodynamic tools, although these may not always be readily available in the early phase of shock. Nonetheless, in the ANDROMEDA SHOCK trial [14], the assessment of fluid responsiveness was incorporated into the decision-making process during early septic shock resuscitation and turned out to be feasible at baseline (within 4 h of septic shock diagnosis) in 82% of the enrolled patients [87].

Physiologically, fluid responsiveness is inherently present in hypovolemic shock, at least in its initial phase, making formal testing redundant in this context. Similarly, in the early stages of septic shock, hypovolemia—whether absolute (fluid losses) or relative (vasodilation)—is common, often justifying initial fluid resuscitation without prior assessment of responsiveness. Fluid responsiveness should be assessed as soon as possible after initial resuscitation. Repeated evaluation is crucial to guide fluid resuscitation while avoiding fluid accumulation.

Question 2.2. Which markers should be monitored to evaluate the risk of fluid administration in shock?

Recommendation 2.2

12. The risk of harm from fluid administration could be assessed using markers such as intravascular filling pressures, intra-abdominal pressure, extravascular lung water (EVLW), pulmonary vascular permeability index (PVPI), venous excess ultrasound (VExUS) grading, the ratio of the arterial oxygen partial pressure over the inspired oxygen fraction (P_aO_2/F_iO_2) ratio, or lung ultrasound score.

Ungraded good practice statement/Ungraded evidence/Strong agreement

Background

Given the fact that fluid resuscitation may contribute to the fluid accumulation syndrome and its associated harms, the decision to administer a fluid bolus should consider the likelihood of therapeutic benefit vs. the potential for harm. The presence of fluid responsiveness indicates that fluid administration may be effective, but is not in itself an indication for infusion. Certain markers can support a more comprehensive assessment of fluid accumulation and help assess the risk/benefit balance when considering fluid therapy.

Consensus on science

This question was defined a priori as expert opinion, as primarily addressing conceptual aspects and definition rather than available good-quality clinical evidence. A

systematic review of 9 studies enrolling patients with septic shock suggested that the use of transpulmonary thermodilution devices for at least 72 h after admission may be associated with a lower positive fluid balance when compared to CVP-guided management. In addition, both the static and dynamic parameters provided by transpulmonary thermodilution were superior in reducing a positive fluid balance when compared to using measurements of CVP and early goal-directed therapy [96]. There is no strong evidence supporting the integration of these markers of fluid accumulation listed above in the decision process of fluid resuscitation. Large RCTs implementing these indices in the decision process of fluid administration are currently missing.

Expert opinion

Even though RCTs with mortality as a primary endpoint investigating the integration of markers of fluid accumulation in the decision process of fluid resuscitation are missing, the panel suggests using these, when available, to limit the negative effects of fluid therapy. The deleterious effects of fluid overload have been clearly established. There are now several valid indices for detecting fluid overload, and many are easily implemented. Therefore, the assessment of the risks of fluid therapy pre-administration, especially in critically ill patients whose physiological condition is fragile, seems logical.

The choice between the different indices of harm due to fluid infusion depends on the availability of the monitoring techniques and their familiarity to the user. The value of high CVP values suggesting the presence of venous congestion is detailed below (Question 3.6), based on the demonstrated relationship between high CVP values and the incidence of acute kidney injury (AKI) [97].

Lung ultrasound has been suggested as a semi-quantitative approach requiring the assessment of several regions for the presence of specific artifacts caused by increased EVLW and/or loss of aeration. Nevertheless, the simple scores based on the number of B-lines, reflecting interstitial lung edema, do not perfectly correlate well with EVLW values [98] or pulmonary capillary wedge pressure [99].

VExUS is an integrated 4-point ultrasound assessment of the splanchnic venous system, assessing the inferior vena cava (IVC), hepatic, portal, and renal veins and providing an overall “grade” of venous congestion [100]. VExUS has been developed in a post-cardiac surgery context, and, except for IVC assessment, venous Doppler assessments are not considered to be basic ultrasound skills for intensivists [101]. In a recent observational study among 145 ICU patients, early assessment of systemic venous congestion was not

associated with the development of AKI or with 28-day mortality [102]. Another study showed that signs of venous congestion were equally prevalent in fluid responders and non-responders and were not associated with fluid balance [103]. Moreover, issues regarding intra- and interobserver reproducibility, the time required to complete the examination, and its overall clinical applicability raise concerns about VExUS for routine bedside assessment.

Transpulmonary thermodilution provides an estimation of EVLW and PVPI. EVLW reflects the interstitial and alveolar fluid in perfused areas. It correlates well with mortality [104, 105] and post-mortem weight of normal and injured lungs in various clinical conditions [104]. The normal EVLW value is below 7 mL/kg, whereas a value > 10 mL/kg represents an optimal discrimination threshold for defining pulmonary edema, and > 15 mL/kg has a 99% positive predictive value for detecting diffuse alveolar damage [106]. EVLW may be considered a clinically relevant safety limit to titrate fluid therapy during the optimization phase of fluid management of septic shock, reflecting the risk of worsening pulmonary function.

The PVPI is calculated as the ratio between EVLW and the pulmonary blood volume. It estimates the degree of the pulmonary permeability due to inflammation and differentiates between hydrostatic and inflammatory pulmonary edema [107]. In addition to providing mechanistic etiology, the PVPI may be used to indicate the risk of aggravating lung edema with fluid resuscitation.

Question 2.3. How should one assess the effectiveness of a fluid bolus?

Recommendations 2.3

13. A fluid challenge is defined as a bolus of 200 to 500 mL given over 5–10 min while evaluating its effects

Ungraded definition/Low certainty of evidence/Strong agreement.

14. One may consider assessing the effects of a fluid bolus on CO and, when not available, on pulse pressure rather than MAP.

Ungraded good practice statement/Ungraded evidence/Strong agreement

15. The effectiveness of a fluid bolus in improving tissue perfusion should be evaluated by considering changes in variables such as CRT, skin mottling, S_{tO_2} , carbon dioxide partial pressure (pCO_2)-derived variables, and lactate.

Ungraded good practice statement/Ungraded evidence/Strong agreement

Background

During fluid resuscitation, fluid is administered by intravenous boluses which must have a sufficient volume to “challenge” the cardiovascular system. Their efficacy may also be influenced by the duration of the fluid infusion.

The effectiveness of a fluid bolus is initially determined by a significant increase in CO. Subsequently, it is expected to enhance tissue perfusion and finally improve organ function. Fluid responsiveness is defined by a bolus’s ability to increase CO or its surrogates beyond a predefined threshold. Patients are usually and arbitrarily classified as “non-responders” and “responders” by considering a specific threshold of fluid-induced increase in CO (e.g., > 10% or 15% from baseline), while fluid responsiveness is in fact not dichotomous. The efficacy of a fluid bolus should not be considered equivalent to clinical effectiveness. The latter is assessed by considering its systemic impact, particularly improvements in tissue perfusion. Ultimately, the true benefit of fluid administration is determined by its ability to enhance oxygen delivery and metabolic homeostasis rather than an increase in CO.

Consensus on science

This question was defined a priori as expert opinion, as primarily addressing conceptual aspects and definitions rather than available good-quality clinical evidence.

Volume and rate of infusion of a fluid bolus

To be effective, a fluid challenge must first be sufficient to increase the stressed blood volume. Based on the currently available literature and consensus within the working group, the smallest volume of intravenous fluid that increases the mean systemic filling pressure above its smallest detectable change is 4 mL/kg [108]. This volume is close to the 250 mL required to detect a meaningful increase in stroke volume [109]. However, most studies investigating fluid responsiveness in ICU patients adopted an average volume of 500 mL [110].

The rate of the administration of a fluid challenge has changed over time from on average 30 min in the past to currently on average 15 min [110]. The rate of the infusion is unlikely to impact clinical outcomes. In an unblinded RCT in 10,520 critically ill patients, the 90-day mortality was similar in patients receiving the fluid bolus at 333 mL/h or 999 mL/h [111]. A faster rate of infusion is likely associated with an increased prevalence of fluid responsiveness [112].

Assessment of the effectiveness of a fluid bolus

In the absence of continuous CO monitoring, the effectiveness of a fluid infusion is usually assessed by considering changes in clinical signs (such as blood pressure, skin perfusion, urine output, and lactate). However, these are not necessarily and/or entirely correlated to the changes in CO following the fluid challenge. The physiological relationship between changes in stroke volume and changes in arterial pulse pressure is not straightforward

and depends on vascular tone. Observational studies in critically ill patients have shown that the changes in arterial pulse pressure are poorly [113, 114] or not at all [115] correlated with fluid-induced changes in CO. In particular, the absence of pulse pressure changes after a fluid bolus does not exclude an increase in CO [113].

The literature search did not identify studies investigating whether assessing the effects of a fluid bolus improved clinical outcomes compared to a strategy that did not assess it.

The ultimate goal of a fluid bolus is to improve organ perfusion (by increasing CO and possible organ perfusion pressure), and tissue oxygen delivery, and thus decrease anaerobic metabolism. However, even if CO increases significantly, oxygen consumption may not improve [66], either because the oxygen consumption is independent of oxygen delivery, or as frequently seen during sepsis, because of abnormalities in the microcirculation limiting tissue oxygen delivery.

Expert opinion regarding the assessment of the effects of a fluid bolus

In the absence of evidence based on mortality regarding this issue, the expert opinion is based on the following arguments. First, the effect of a fluid bolus is to restore tissue perfusion by increasing CO, but this efficacy is not constant. The effect of a fluid bolus on CO is inconsistent. In addition, even when CO increases, the improvement in organ perfusion, tissue oxygenation, and, ultimately, oxygen consumption may be absent. Second, detecting the efficacy of a fluid bolus may have an important impact. Given the well-demonstrated side effects of fluid overload, the infusion of a fluid bolus should not be repeated in the case of ineffectiveness. This response may change over time, which justifies repeating this assessment.

Detecting an increase in CO of 10–15% after a fluid bolus is widely accepted as a reasonable physiological effect of fluid administration that may have an effect on tissue perfusion. Due to the poor correlation between fluid-induced changes in pulse pressure and in CO, the effects of a fluid bolus should be at best directly assessed through changes in CO, stroke volume, or some of their surrogates. Estimating the effectiveness of fluid resuscitation should also include evaluating changes in tissue perfusion, the oxygen supply/demand balance, and markers of anaerobic metabolism. The significance, advantages, and disadvantages of these indices have been explained above.

Question 2.4. How should one assess fluid responsiveness in shock?

Recommendations 2.4

16. We recommend using dynamic variables over static markers of preload for predicting fluid responsiveness, when applicable.

Strong recommendation/High certainty of evidence/Strong agreement

17. We recommend the passive leg raising (PLR) test to assess fluid responsiveness in mechanically ventilated patients in shock, with and without spontaneous breathing activity.

Strong recommendation/High certainty of evidence/Strong agreement

18. We recommend the end-expiratory occlusion test as an alternative to PLR test in mechanically ventilated patients in shock without spontaneous breathing activity.

Strong recommendation/Moderate certainty of evidence/Strong agreement

19. We are unable to provide recommendations regarding the use of the tidal volume challenge as alternative to PLR test in mechanically ventilated patients in shock, due to paucity and/or heterogeneity of available data.

No recommendation/Low certainty of evidence/Strong agreement

20. We recommend pulse pressure variation (PPV) to assess fluid responsiveness in mechanically ventilated patients in shock without spontaneous breathing activity and a tidal volume ≥ 8 mL/kg.

Strong recommendation/High certainty of evidence/Strong agreement

21. We suggest against the use of PPV alone to assess fluid responsiveness in mechanically ventilated patients in shock with spontaneous breathing activity and a tidal volume < 8 mL/kg.

Suggest against/Moderate certainty of evidence/Strong agreement

22. We suggest using stroke volume variation (SVV) to assess fluid responsiveness in mechanically ventilated patients in shock without spontaneous breathing activity and a tidal volume ≥ 8 mL/kg.

Weak recommendation/Moderate certainty of evidence/Strong agreement

23. We are unable to provide recommendations regarding the use of PPV to assess fluid responsiveness in mechanically ventilated patients in shock with spontaneous breathing activity.

No recommendation/Low certainty of evidence/Strong agreement

24. We are unable to provide recommendations regarding the use of SVV to assess fluid responsiveness in mechanically ventilated patients in shock with spontaneous breathing activity.

No recommendation/Low certainty of evidence/Strong agreement

25. We are unable to provide recommendations regarding the use of the mini-fluid challenge test in patients with shock, due to paucity and/or heterogeneity of available data.

No recommendation/Low certainty of evidence/Strong agreement

26. We suggest against the use of changes in IVC diameter alone in critically ill patients to assess fluid responsiveness.

Suggest against/Moderate certainty of evidence/Weak agreement

Background

Fluid responsiveness depends on the interaction between cardiac function and the cardiovascular response. It reflects preload responsiveness, which is physiologically related to end-diastolic pressure, volume, and

ventricular contractility. Due to the inconsistent relationship between cardiac preload and stroke volume, single values of markers of cardiac preload do not indicate preload responsiveness, except at extreme values. In contrast, a dynamic approach involves observing the effects of spontaneous or induced changes in cardiac preload on CO, or its surrogates [116].

A functional hemodynamic test involves a change in cardiac preload provoked by mimicking a fluid challenge or using heart–lung interactions, with the resulting hemodynamic response varying between fluid responders and non-responders [116].

Consensus on science

For answering this PICO question, the literature was searched for studies determining the diagnostic performance of the methods used to predict fluid responsiveness. A comprehensive review of the functional dynamic tests and indices of fluid responsiveness can be found elsewhere [116]. The literature search results specifically focused on studies conducted in patients with shock (Supplementary material). It can be summarized as follows.

Pulse pressure variation and stroke volume variation

In mechanically ventilated patients, PPV and SVV are based on the cyclic changes in alveolar pressure which influence the right ventricular (RV) preload and afterload, the left ventricular (LV) afterload, and, consequently, stroke volume. PPV was first used, followed by the SVV, the latter requiring continuous CO monitoring with pulse wave analysis.

Historically, controlled mechanical ventilation with high tidal volumes of 10–12 mL/kg of predicted body weight without spontaneous effort was routinely used in critically ill patients. It allowed for complete control over the patient's ventilatory parameters and stable heart–lung interactions. Under these circumstances, PPV and SVV are highly predictive of fluid responsiveness. Our meta-analysis found a pooled PPV AUROC of 0.94 [95% CI 0.88–0.99] in patients with shock who were ventilated with high tidal volume and had no spontaneous breathing activity (Supplementary material).

The essential limitation of PPV and SVV is that they cannot be used in many clinical circumstances that create false positives (spontaneous ventilation, cardiac arrhythmia, and perhaps RV failure) and false negatives (low tidal volume, low lung compliance, very high respiratory rate) [117]. In patients with shock, when the two main validity criteria of PPV (high tidal volume and the absence of spontaneous breathing activity) are respected, the pooled AUROC is comparable to the pooled AUROC for PLR [118, 119]. In patients with tidal volume < 8 mL/

kg, our meta-analysis revealed a pooled AUROC of 0.74 [95% CI 0.67–0.81] (Supplementary material). Therefore, PPV should be used with caution as a standalone variable for assessing fluid responsiveness. High PPV values may still reliably predict fluid responsiveness, whereas lower values are likely to be less reliable. Notably, using a low PPV to confirm fluid unresponsiveness, this may potentially also act as a safety parameter during fluid removal. In the presence of increased intrathoracic pressures (e.g., intra-abdominal hypertension), the thresholds for fluid responsiveness may be increased.

A recent and promising advance in this field is the use of PPV changes after applying a functional hemodynamic test. This approach overcomes the classic limitations of the single pre-fluid challenge values of PPV, considering its decrease (during a PLR) or increase (during a tidal volume challenge) as indicative of fluid responsiveness. Importantly, no CO monitoring is required, making it attractive in limited-resource settings.

Passive leg raising test

PLR is a functional hemodynamic test mimicking a fluid challenge, by reproducing the hemodynamic effects of approximately 300 mL of fluid load, while being reversible [116]. From the pooled AUROC of 0.94 [0.92–0.97] retrieved from 4 studies [120–123] and the results of previous meta-analyses [124, 125], the following can be concluded: the PLR is the functional test of choice for assessing fluid responsiveness in ICU patients with shock and may be applied to spontaneously breathing patients as well as patients on invasive mechanical ventilation with or without spontaneous breathing activity. In the presence of intra-abdominal hypertension, the PLR test can be falsely negative [126].

End-expiratory occlusion test

The end-expiratory occlusion test (EEOT) consists of transiently interrupting mechanical ventilation and measuring the CO response [127]. The test can be considered as a valid alternative to the PLR in patients with no significant spontaneous breathing activity [121, 128–132]. However, heterogeneity exists in underlying studies enrolling patients with low tidal volume [127]. Nevertheless, the threshold of CO changes to indicate fluid responsiveness is consistent among studies.

Threshold values for CO changes to indicate fluid responsiveness (i.e., 5%) are close to the smallest change detectable by many CO measurement techniques. For this reason, the EEOT has been mostly validated using pulse wave analysis [130]. When echocardiography is used, the diagnostic cut-off is close to the smallest detectable change in velocity time integral of the left ventricular (LV) outflow tract [133]. Therefore, one study suggested

considering the effect of both end-expiratory and end-inspiratory occlusion [134].

The mini-fluid challenge and tidal volume challenge

The mini-fluid challenge assesses the stroke volume response to a fast infusion of a small volume of fluids (from 100 to 150 mL) [135, 136]. The mini-fluid challenge's use is limited by the reliability of the hemodynamic tool used to detect the small changes in stroke volume to discriminate fluid responsiveness (around 5%). These changes may also be masked by the changes caused by spontaneous or mechanical ventilation. The mini-fluid challenge reliably predicts fluid responsiveness in surgical patients [137, 138]. The studies included in the literature search (Supplementary material) showed an overall pooled sensitivity and specificity of 0.73 (95% CI 0.51, 0.90) and 0.90 (95% CI 0.78, 0.97), respectively, but with a high degree of heterogeneity (>75%).

The tidal volume challenge overcomes the limitations of PPV when low tidal volume is used and can be useful and reliable in patients with an intraarterial blood pressure monitoring without CO measurements [139, 140]. The studies included in the literature search (Supplementary material) showed an overall pooled sensitivity and specificity of 0.93 (95% CI 0.79, 0.99) and 0.83 (95% CI 0.58, 0.98), respectively, but with a high heterogeneity (>75%).

Respiratory variations in vena cava diameter

Respiratory variations in superior and IVC diameters can be estimated by transesophageal (for superior vena cava) or transthoracic echocardiography (for the IVC) [141]. Initially described in non-shocked fully mechanically ventilated patients with good results [142], IVC variations were subsequently applied in spontaneously breathing patients with conflicting results, resulting in higher diagnostic cut-offs than traditionally assumed [143–146]. The predictive value of respiratory variations of superior vena cava seems superior to that of IVC [141], but requires transesophageal echocardiography. In addition, no study was found in patients with shock. Of note, in the largest study conducted in this field, enrolling 540 patients with acute circulatory failure, the overall AUROC for the IVC variations was 0.63, decreasing to 0.60 for patients with hypotension and high lactate [141].

General comment

One important limitation regarding the reliability of functional hemodynamic tests in predicting fluid responsiveness is the precision of measurements, since the changes induced are relatively small (5–10% for stroke volume or CO). Accordingly, more precise techniques,

such as pulse wave analysis, might be more suitable. The best cut-off for predicting fluid responsiveness is the one showing the overall best sensitivity and specificity, as assessed by ROC methodology. However, an overlap exists between responders and non-responders creating a 'gray zone' of predictive uncertainty. Some studies report a low cut-off value that excludes fluid responsiveness in 90% of patients (favoring negative predictive value), whereas a high cut-off value predicts fluid responsiveness in 90% of cases (favoring positive predictive value) [147].

Finally, despite the large number of studies assessing the performance of dynamic indices and functional hemodynamic tests, the substantial variability in cut-offs, type of fluid challenge test, ICU setting, and measuring system makes retrieving consistent information difficult. For this reason, the Cardiovascular Dynamics section of the ESICM has recently produced a document to improve the consistency of data reporting in studies on fluid responsiveness [85].

Domain 3: Hemodynamic monitoring (Figs. 4, 5)

Question 3.1. When should one monitor cardiac output in shock?

Recommendations 3.1

27. CO and/or stroke volume should be monitored in patients who do not respond to initial therapy to assess the type of shock, evaluate hemodynamic status, and determine therapeutic response.

Ungraded good practice statement/Ungraded evidence/Strong agreement

28. Frequent reevaluation of CO may be considered.

Ungraded good practice statement/Ungraded evidence/Strong agreement

29. When CO is monitored, its adequacy should be interpreted by evaluating organ function, tissue oxygenation, metabolism, and perfusion.

Ungraded good practice statement/Ungraded evidence/Strong agreement

Background

Knowing CO may be beneficial for (i) diagnosing the type of shock, (ii) selecting therapeutic interventions, and (iii) following their effects and the course of shock. CO is typically low in cardiogenic and hypovolemic shock and typically elevated during the initial phase of septic shock especially after fluid resuscitation. CO is a major determinant of oxygen delivery, i.e., the flow of oxygen carried toward the organs and tissue. Fluids and inotropes infusions are administered to increase CO, so that changes in CO may be used as a direct evaluation of their therapeutic effect. Many fluid responsiveness tests also require CO measurement [116]. Fluid bolus-induced changes in

| HAEMODYNAMIC MONITORING | | | | | | | | | | SUMMARY OF CLINICAL QUESTIONS AND RECOMMENDATIONS | | |
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| RECOMMENDATION STRENGTH | | SUGGEST AGAINST | | WEAK RECOMMENDATION | | STRONG RECOMMENDATION | | UNABLE TO PROVIDE RECOMMENDATION | | Recommendation strength | Certainty of evidence | Agreement strength |
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HAEMODYNAMIC MONITORING



SUMMARY OF CLINICAL QUESTIONS AND RECOMMENDATIONS

| RECOMMENDATION STRENGTH | | | | | | Recommendation strength | Certainty of evidence | Agreement strength |
|---|---|---|---|--|--|--|--|--------------------|
|  SUGGEST AGAINST |  UNGRADED DEFINITION |  WEAK RECOMMENDATION |  STRONG RECOMMENDATION |  UNABLE TO PROVIDE RECOMMENDATION | | | | |
| CERTAINTY OF EVIDENCE | |  VERY LOW |  LOW |  MODERATE |  HIGH |  UNGRADED | AGREEMENT STRENGTH | |
| | | | | |  WEAK |  MODERATE |  STRONG | |
| [2014] STATEMENT OF RECOMMENDATION | | UNGRADED, BEST PRACTICE STATEMENT | | | UNGRADED, STATEMENT OF FACT | | | |
| [2014] CERTAINTY OF EVIDENCE | | LEVEL 1, QOE B | | | LEVEL 1, QOE C | LEVEL 2, QOE B | LEVEL 2, QOE C | |

| WHEN AND HOW SHOULD ONE MONITOR ARTERIAL PRESSURE IN SHOCK? | | | | | | |
|---|---|--|--|---|---|---|
| → Arterial pressure should be monitored in patients with shock. | | | |  |  |  |
| → Arterial pressure should be monitored with an arterial catheter in shock that is not responsive to initial therapy and/or requiring vasopressor infusion. | | | |  |  |  |
| 2014 | We recommend arterial and central venous catheter insertion in shock not responsive to initial therapy and/or requiring vasopressor infusion. [UNGRADED, BEST PRACTICE STATEMENT] | | | | | |

| WHAT IS THE TARGET OF ARTERIAL PRESSURE IN SHOCK? | | | | | | |
|---|---|--|--|---|---|---|
| → The target blood pressure should be individualized during resuscitation of patients with shock. | | | |  |  |  |
| 2014 | We recommend individualizing the target blood pressure during shock resuscitation. [LEVEL 1, QoE B] | | | | | |
| → An initial MAP of 65-70 mmHg should be targeted in patients with septic shock. | | | |  |  |  |
| 2014 | We recommend to initially target a MAP of ≥65 mmHg. [LEVEL 1, QoE C] | | | | | |
| → A higher MAP target may be considered in patients with septic shock and a history of chronic arterial hypertension who show clinical improvement with higher blood pressure. | | | |  |  |  |
| → A higher MAP target may be considered in patients with septic shock with high CVP values who show clinical improvement with higher blood pressure. | | | |  |  |  |
| 2014 | We suggest a higher MAP in septic patients with history of hypertension and in patients that show clinical improvement with higher blood pressure. [LEVEL 2, QoE B] | | | | | |
| → Lower MAP targets may be considered in patients with traumatic hemorrhagic shock and uncontrolled bleeding in the absence of traumatic brain injury. | | | |  |  |  |
| 2014 | We suggest to tolerate a lower level of blood pressure in patients with uncontrolled bleeding (i.e. in patients with trauma) without severe head injury. [LEVEL 1, QoE C] | | | | | |
| → In the initial phase following trauma, a target systolic arterial pressure of 80–90 mmHg (MAP 50–60 mmHg) should be used until major bleeding has been stopped when there is no clinical evidence of traumatic brain injury and coma (Glasgow Coma Score ≤ 8). In traumatic brain injury (Glasgow Coma Score ≤ 8), we recommend targeting an initial mean arterial pressure ≥80 mmHg. | | | |  |  |  |
| → Targeting an initial MAP of ≥ 65 mmHg may be considered in patients with cardiogenic shock. | | | |  |  |  |

| WHEN SHOULD ONE MONITOR INTRA-ABDOMINAL PRESSURE IN SHOCK? | | | | | | |
|---|--|--|--|---|---|---|
| → Serial monitoring of intra-abdominal pressure (IAP) may be considered in patients with shock and established risk factors for intra-abdominal hypertension. | | | |  |  |  |

| WHEN SHOULD ONE MONITOR CENTRAL VENOUS PRESSURE IN SHOCK? | | | | | | |
|---|--|--|--|---|---|---|
| → Central venous pressure should be measured in patients with shock who have a central venous catheter. | | | |  |  |  |
| → A pre-specified CVP value should not be targeted during the resuscitation of patients with shock. | | | |  |  |  |

Fig. 5 Summary of recommendations, certainties of evidence and agreement strengths for Domain 3: Hemodynamic monitoring (part 2). The corresponding 2014 recommendations are given for comparison

pulse pressure are poorly [113, 114] or not [148] correlated with changes in CO.

Consensus on science

The literature search was limited to the past 30 years and provided 5 RCTs [149–153] and 2 observational trials [154, 155] (Supplementary material).

We included 5 RCTs, analyzing the effect of CO monitoring in patient in shock in different settings. The study by Velmahos et al. focused on 75 trauma patients with hemorrhagic shock, randomized to CO monitoring vs. no CO monitoring [150]. The study by Yuanbo et al. randomized 302 thoracic trauma patients with ARDS to PiCCO monitoring vs. CVP monitoring [153].

Septic patients with hypotension were evaluated in two studies [149, 152]. The former randomized 80 patients between uncalibrated CO monitoring and no CO monitoring. The latter focused on 350 septic shock/ARDS patients randomized to CO monitoring using a calibrated device, vs. CVP monitoring. The last study involved 71 patients with cardiogenic shock, randomized to calibrated pulse contour monitoring vs. no monitoring [151]. There was a slight tendency toward reduction of days on vasopressor in the population of cases. The five included studies showed variability in protocol, setting, technique of CO monitoring, and secondary outcomes (Supplementary material).

The two observational studies examined the effect of CO monitoring in severe sepsis/septic shock patients [154, 155]. Latham et al. performed a case-control study with matching involving 191 patients suffering from severe sepsis or septic shock. It explored the efficacy of stroke volume-guided resuscitation using non-invasive CO monitoring compared to usual care [154]. Lu et al. included 105 patients with septic shock. It assessed the effectiveness of a therapy based on PiCCO-guided bundle vs. standard therapy on hospital mortality [155]. Both studies reported no statistically significant differences in hospital mortality with the use of advanced hemodynamic monitoring techniques compared to standard care in septic shock patients.

Three RCTs [149, 152, 153] were considered sufficiently homogeneous to be included in the pooled analysis (Supplementary material). A single outcome of ICU or 28-day mortality was considered in this analysis. The pooled analysis did not demonstrate an advantage in using CO monitoring in patients in shock. The two observational studies were not combined in a pooled analysis due to their heterogeneity and the likely result in biased estimates (Supplementary material). In our final grading system, there is neither evidence supporting nor opposing the use of CO monitoring in patients in shock when

considering mortality as an outcome, with an overall low quality of available evidence (Supplementary material).

We could not identify RCTs comparing a strategy using repeated evaluations of CO vs. no repeated evaluations; also, no RCT comparing a strategy using CO measurements and assessment of organ function, tissue oxygenation, metabolism, and perfusion vs. CO measurements without these assessments was found. Finally, we found no study comparing CO monitoring with or without additional echocardiography.

Expert opinion

The panel assessed that the retrieved literature did not allow a graded recommendation. The available studies on the effects on mortality of using different monitoring systems are highly heterogeneous regarding the types of shock, using treatment protocols [150–152, 155–157] or no use of treatment protocols [149, 158, 159], and the targeted variables and values. Moreover, in patients with acute circulatory failure, mortality might not be the ideal primary outcome for RCTs evaluating the value of hemodynamic monitoring. As mortality in these patients is influenced by numerous factors, it is unlikely that modifying a single aspect of management—such as monitoring—would result in a measurable reduction in mortality [160]. In addition, CO monitoring can only influence outcome if it leads to a more effective therapy. Building decision algorithms linking hemodynamic monitoring, including CO, to therapeutic interventions is challenging, as numerous factors influence treatment decisions [161]. CO monitoring-based decision algorithms proposed in studies are sometimes oversimplistic and have therefore been criticized [150, 151, 155–157, 162] because they ignore a large amount of data that the clinician may consider when making a therapeutic decision.

Therefore, panelists decided to provide an expert opinion based on three arguments. First, knowing CO may help to understand the hemodynamic status, evaluate oxygen delivery, and follow the effects of two main treatments used in shock, fluid resuscitation and inotropes. The goal of augmenting CO is to increase tissue perfusion and thus oxygenation, thereby reducing anaerobic metabolism, and improving organ function. Therefore, the adequacy of CO should be evaluated within this context. Second, a simple measurement of changes in arterial pressure does not accurately estimate CO changes [113, 114, 148]. Third, no RCT retrieved by the literature search demonstrated a worse outcome with CO monitoring. However, large retrospective studies of pulmonary artery catheter (PAC)-guided management suggest improved outcomes in patients with cardiogenic shock [163, 164].

The suggestion to reserve CO monitoring for patients who do not improve following initial treatment is based on two major considerations. First, in this subgroup, the potential benefits of knowing CO are more likely to outweigh the costs and invasiveness of the monitoring devices, as well as the risks associated with erroneous measurements. Second, no response to initial treatment often reflects a more complex clinical scenario, in which CO data—and other hemodynamic variables provided by advanced monitoring—are especially valuable for guiding further management.

The literature does not provide precise criteria for defining shock that persists despite initial treatment. The latter typically consists of initial fluid resuscitation [6], performed before fluid responsiveness needs to be estimated, and the use of low-dose vasopressors. Persistence of shock after this treatment will typically be detected by the absence of stabilization of blood pressure above the chosen target, and/or by the persistence of the signs of hypoperfusion described above. Such criteria should be adapted to many other indices that cannot all be listed. The premonitory condition, the source of sepsis and/or cause of shock, the number of failing organs, the initial severity of hypotension and tissue hypoperfusion, and the intensity of treatment to be provided also typically come into play.

Changes in CO are more informative than absolute values. However, there is no precise indication for how often CO should be reassessed. Typically, re-assessment is required after implementing therapeutic interventions intended to increase it (e.g., fluid boluses, inotropes). In addition, re-assessment is indicated/required when the hemodynamic status deteriorates, as indicated, for example, by hypotension, new or worsening signs of tissue hypoperfusion, stable high or increasing lactate levels, or a decrease in urine output.

Echocardiography is a useful adjunct to CO monitoring because it additionally helps to determine the cause of hemodynamic instability. It provides information regarding structural and functional cardiac abnormalities, and information beyond CO (e.g., filling status, contractility, and right-sided pressures). Using mortality as an end-point may not reflect echocardiography's utility (or lack thereof), and other outcomes should be explored. Nevertheless, given its widespread availability, minimally invasive nature, and ability to provide incremental diagnostic information, the panel recommends the continued use of echocardiography to support diagnosis, guide and monitor treatment, and assess prognosis in patients with shock.

Question 3.2. How should one monitor cardiac output in shock?

Recommendations 3.2

30. Transpulmonary thermodilution or pulmonary artery dilution with the PAC may be considered in patients for whom CO monitoring is required.

Ungraded good practice statement/Ungraded evidence/Strong agreement

31. Transpulmonary thermodilution or the PAC in patients with shock and moderate-to-severe ARDS may be considered be used for guiding fluid therapy.

Remark: In patients without RV failure, transpulmonary thermodilution is preferred because it measures EVLW.

Remark: In patients with RV failure, the PAC is preferred because it measures the pulmonary artery pressure.

Ungraded good practice statement/Ungraded evidence/Strong agreement

32. The PAC may be considered in patients with persistent shock and RV failure after cardiac surgery in addition to serial echocardiography

Ungraded good practice statement/Ungraded evidence/Strong agreement

33. Less invasive CO monitoring devices could be used, if these have been proven to provide accurate estimation of CO for this specific context, over more invasive ones like the PAC or transpulmonary thermodilution in patients with shock.

Ungraded good practice statement/Ungraded evidence/Strong agreement

34. We suggest using echocardiography as the first-line imaging modality to assess the type of shock and hemodynamic status.

Weak recommendation/Low certainty of evidence/Strong agreement

35. Serial echocardiographic evaluations should be performed to provide additional information on cardiac function, even when CO is monitored.

Ungraded good practice statement/Ungraded evidence/Strong agreement

Background

Commercially available CO monitoring systems can be categorized into invasive (PAC, transpulmonary thermodilution in combination with externally calibrated pulse wave analysis), less invasive (esophageal Doppler, internally calibrated and uncalibrated pulse wave analysis), and non-invasive (finger cuff systems using internally calibrated pulse wave analysis, bioreactance, bioimpedance) methods. These methods differ in costs, invasiveness, amount of information they provide, and performance for measuring CO in critically ill patients.

Intermittent pulmonary artery or transpulmonary thermodilution is considered the clinical reference method for CO measurement, although both have limitations. In addition, transpulmonary thermodilution provides real-time, continuous estimation of CO through calibrated pulse wave analysis. The newest

version of the PAC provides real-time CO monitoring through pulse wave analysis of the RV pressure curve [165], but validation of this new technique is lacking.

The reliability of CO measurement by esophageal Doppler was established by older studies, which often did not use the metrological methodology that is the reference today [166]. Invasive internally calibrated and uncalibrated pulse wave analysis use various algorithms to estimate CO based on different pathophysiological assumptions [167, 168]. The reliability of the CO measurement they provide has been questioned in the context of changing arterial tone, spontaneously or during treatment with vasoactive agents. The majority of validation studies have been conducted in the perioperative context. Internally calibrated pulse wave analysis is also possible in a fully non-invasive way using a finger cuff method. A meta-analysis (9/16 studies conducted in the ICU, either in critically ill or in post-operative patients) found a percentage of error > 30% (unacceptable value) in 79% of the studies and > 45% in 47% of the studies [169]. Another meta-analysis showed that the reliability of CO measurement was lower in patients with a MAP < 65 mmHg and receiving vasopressors [170]. However, most studies were conducted with older versions of the algorithm. Newer versions of the algorithm are more reliable, including in vasoplegic states [171]. The same concerns were raised regarding bioimpedance and bio-reactance. A meta-analysis of 10 studies with bioimpedance revealed a percentage error of 47% [172]. In the only study performed in critically ill patients with the latest version of a bio-reactance system, the percentage error was 48% when compared to transpulmonary thermodilution [173].

The most invasive systems provide several other hemodynamic variables in addition to CO. In particular, the PAC is unique for estimating pulmonary vascular resistance and direct measurement of left atrial and pulmonary arterial pressures [174]. Transpulmonary thermodilution allows easy quantification of EVLW at the bedside, which is associated with outcome [105]. It also estimates PVPI, which is related to the degree of diffuse alveolar damage in ARDS [106].

Consensus on science

The literature search provided one RCT [175] and one prospective observational study [176]. The RCT by Trof et al. was limited by the small sample size of 120 patients, stratified into 72 septic and 48 non-septic patients, randomized between PAC-guided and transpulmonary thermodilution-guided management [175]. There was no difference between groups regarding ventilator-free days, length of stay, organ failures, and mortality. The use of a transpulmonary thermodilution algorithm resulted

in more days of mechanical ventilation and ICU length of stay compared with the PAC algorithm in non-septic shock but not in septic shock [175]. However, the algorithm used for transpulmonary thermodilution has been criticized [177]. The study also raised concerns in terms of randomization and allocation concealment, as well as protocol adherence, and was classified as high risk of bias (Supplementary material).

The retrospective study by Ni et al. included 72 patients with traumatic shock [176]. There was no difference between patients treated with PAC and patients treated with PiCCO. The study did not employ propensity score matching or any defined matching and did not employ multivariable models to adjust for confounders. Consequently, the study was considered at critical risk of bias (Supplementary material).

The level of identified evidence is low. As reported in the Supplementary material, after evaluation of available evidence provided by the systematic research query, there is no evidence supporting or opposing the use of a specific monitoring system against another system in septic patients, when considering mortality as an outcome.

Expert opinion

In the absence of robust evidence on how the choice of any hemodynamic monitoring device affects mortality, the expert opinion was based on three arguments. First, for patients in whom monitoring of CO is considered, the choice of PAC or transpulmonary thermodilution devices over other techniques is justified by their superior reliability for measuring CO, despite existing limitations. Second, these systems provide a range of variables that help to better describe the hemodynamic state than less invasive devices: the PAC provides SvO₂ and PvCO₂, pulmonary artery pressures, and pulmonary artery occlusion pressure, while transpulmonary thermodilution estimates EVLW, PVPI, global ejection fraction, and global end-diastolic volume. Third, in critically ill patients, the potential benefit of PAC and transpulmonary thermodilution may counterbalance their costs and invasiveness.

The choice between PAC and transpulmonary thermodilution is often pragmatic. One should only use systems for which one has adequate expertise. As it estimates the pulmonary vascular resistance and directly measures pulmonary vascular pressures, the PAC may be particularly useful in RV failure in ARDS patients and patients with persistent shock after cardiac surgery. The estimation of EVLW and PVPI provided by transpulmonary thermodilution may guide the fluid strategy by estimating the risk of pulmonary fluid accumulation. Although unreliable for estimating the absolute value of CO when arterial tone changes [167, 168], uncalibrated or internally calibrated pulse wave analysis systems may

be used to estimate relative changes in CO during short interventions manipulating cardiac preload.

Finally, if CO monitoring tools are not available (limited resources or contraindication), alternatives allow estimation of relative changes in CO. Changes in end-tidal CO₂ (in intubated patients without spontaneous breathing) [122, 178, 179], changes in PPV (in ventilated patients without arrhythmia and spontaneous breathing) [180–182], and changes in the perfusion index of the plethysmography signal (in patients without cardiac arrhythmia) [183–185] are proportional to simultaneous changes in CO, induced, for example, by a fluid bolus or by a PLR test. If echocardiography is available, it can be an alternative, if repeated frequently, especially before and after each therapeutic intervention. These repeated measurements should preferably be performed by the same observer.

Question 3.3. When and how should one monitor arterial pressure in shock?

Recommendations 3.3

36. Arterial pressure should be monitored in patients with shock.

Ungraded good practice statement/Ungraded evidence/Strong agreement

37. Arterial pressure should be monitored with an arterial catheter in shock that is not responsive to initial therapy and/or requiring vasopressor infusion.

Ungraded good practice statement/Ungraded evidence/Strong agreement

Background

During shock, blood pressure is a critical hemodynamic variable [186]. It provides information on the characteristics of circulatory failure, guides therapeutic choices, and allows monitoring of the response to therapy. A retrospective analysis from an electronic ICU dataset with nearly 80,000 patients with septic shock showed that systolic, diastolic, and mean pressures were comparable in their strength of association with organ system injury and ICU mortality [21].

Blood pressure can be measured with automated oscillometry or directly with an arterial catheter inserted in the radial or femoral artery. Arterial cannulation is associated with iatrogenic risks, and its initiation may delay other urgent procedures. However, it may provide a more accurate estimation of arterial pressure, and its complications are rare [187].

Consensus on science

We identified no studies that explicitly associated the timing or method of arterial blood pressure monitoring

(whether continuous vs. non-continuous blood pressure monitoring or femoral vs. radial catheter sites) with critical outcomes such as mortality, organ dysfunction, or complications. Due to the lack of data regarding key clinical outcomes, we evaluated the concordance between various blood pressure measurement methods as a surrogate for clinically meaningful outcomes (i.e., clinically significant difference in MAP between different techniques could possibly influence patient outcomes).

The research query identified no studies assessing intermittent vs. continuous blood pressure measurement in patients in shock (Supplementary material). However, 10 studies comparing invasive vs. non-invasive techniques of monitoring or catheterization site were included.

All studies were observational. Eight studies compared non-invasive (mainly oscillatory) with invasive blood pressure measurements [188–195]. Four studies compared the radial vs. femoral site of arterial catheterization [196–199]. Apart from the study by Dorman et al. [197], all studies reported mean bias (mean difference) between different methods and were mainly based on Bland–Altman analysis. All studies reported MAP, except for Rebesco et al. [195] which used systolic blood pressure, and were thus excluded from the pooled analysis on MAP (Supplementary material). The study by Lakhal et al. [189] presented two different devices of non-invasive blood pressure measurement and two different nonoverlapping patient cohorts. It was considered separately in the pooled analysis.

When considering femoral vs. radial access site, the pooled analysis demonstrated a higher MAP for the femoral site, with a mean MAP difference of 4.13 [0.67–7.58] mmHg (Supplementary material). Due to the indirect nature of the outcome, the evidence for clinical recommendations targeting major clinical outcomes remains very low. When considering invasive vs. non-invasive techniques in patients in shock, there were small mean differences in terms of MAP (mean bias = 0.47 [95% CI –4.17; 5.11] mmHg) (Supplementary material), which are unlikely to be clinically significant.

Expert opinion

There is no evidence in the literature supporting nor opposing intermittent vs. continuous monitoring in patients in shock nor the preferred site of cannulation. The expert opinion is based on two arguments. First, in patients with shock, hemodynamic instability and its acute treatment justify continuous monitoring of systemic arterial pressure rather than intermittent monitoring with a brachial cuff. Second, arterial cannulation

allows for easy performance of the repeated blood sampling that is necessary in these patients.

Question 3.4. What is the target of arterial pressure in shock?

Recommendations 3.4

38. The target blood pressure should be individualized during resuscitation of patients with shock.

Ungraded good practice statement/Ungraded evidence/Strong agreement

39. An initial MAP of 65–70 mmHg should be targeted in patients with septic shock.

Ungraded good practice statement/Ungraded evidence/Strong agreement

40. A higher MAP target may be considered in patients with septic shock and a history of chronic arterial hypertension who show clinical improvement with higher blood pressure.

Ungraded good practice statement/Ungraded evidence/Strong agreement

41. A higher MAP target may be considered in patients with septic shock with high CVP values who show clinical improvement with higher blood pressure.

Ungraded good practice statement/Ungraded evidence/Strong agreement

42. Lower MAP targets may be considered in patients with traumatic hemorrhagic shock and uncontrolled bleeding in the absence of traumatic brain injury.

Ungraded good practice statement/Ungraded evidence/Strong agreement

43. In the initial phase following trauma, a target systolic arterial pressure of 80–90 mmHg (MAP 50–60 mmHg) should be used until major bleeding has been stopped when there is no clinical evidence of traumatic brain injury and coma (Glasgow Coma Score ≤ 8). In traumatic brain injury (Glasgow Coma Score ≤ 8), we recommend targeting an initial mean arterial pressure ≥ 80 mmHg.

Ungraded good practice statement/Ungraded evidence/Strong agreement

44. Targeting an initial MAP of ≥ 65 mmHg may be considered in patients with cardiogenic shock.

Ungraded good practice statement/Ungraded evidence/Strong agreement

Background

As MAP is an essential factor in the perfusion of all organs except the left ventricle, it is the target for vasopressor use. In a meta-analysis of 13 studies (34829 patients), hypotension during ICU stay was associated with increased mortality and AKI in most included studies, and poorer outcomes were observed with increasing hypotension severity [19]. In a retrospective observational study with 77328 septic patients, arterial pressure component association with ICU mortality was the strongest for mean followed by systolic, diastolic, and weakest for pulse pressure [21].

The concept of “permissive hypotension” has emerged in the context of uncontrolled hemorrhage in trauma

[200]. It consists of a trade-off between the lowest possible blood pressure to limit blood loss and maintaining adequate perfusion [201]. The concept has been extended to septic shock, to reduce the deleterious effects of vasopressors in older patients [202].

The target MAP may also differ depending on other conditions. As organ perfusion depends on the pressure difference between MAP upstream and CVP downstream, an elevation of CVP may decrease the organ perfusion pressure gradient and may impair organ function. This may justify targeting higher MAP levels when CVP is elevated, e.g., during cardiogenic shock. The same holds true for increased intra-abdominal pressure (IAP). However, organ perfusion does not solely depend on the difference between MAP and CVP or IAP.

As in chronic hypertension, the relationship between organ perfusion pressure and organ blood flow is shifted to the right; the same MAP may correspond to abnormal organ perfusion in hypertensive patients, while it would represent normal organ perfusion in others. This may also justify raising the MAP target in this subgroup of patients. In patients with trauma and hemorrhagic shock, rapidly reaching high levels of arterial pressure, particularly with fluids and vasopressors, could increase blood losses. This supports the concept of a damage control strategy with lower systolic arterial pressure targets.

Consensus on science

The literature search included articles up to 30 years ago and yielded a total of 11 RCTs [202–207, 210–213, 280] and 3 observational trials [209, 214, 215]. The trials span a range of conditions including septic shock, vasodilatory shock, out-of-hospital cardiac arrest (OHCA), hemorrhagic shock in trauma patients, and cardiogenic shock, each with specific experimental and control protocols (Supplementary material).

Septic and vasodilatory shock

We retrieved 4 RCTs conducted in septic or vasodilatory shock patients [202, 203, 212, 280]. Various high vs. low MAP management strategies were tested across these trials. Similarly, there is wide variation in the assessed outcomes. Mortality and other clinical outcomes such as renal replacement therapy needs and the duration of vasopressor use were commonly evaluated, with significant variation in results across different patient groups and intervention strategies.

After excluding one study on hepatorenal syndrome to maintain homogeneity [204], the studies were considered of high quality, with a low risk of bias and homogeneous outcomes related to 28-day or hospital mortality.

The pooled analysis on septic patients, including 3516 patients, did not demonstrate any advantage in

increasing MAP in septic shock patients (RR 1.06, 95% CI 0.97–1.15) (Supplementary material). Consequently, in the GRADE evaluation, there is no evidence supporting an increase in MAP in the overall population of septic shock patients.

Hemorrhagic shock

The search retrieved 3 RCTs in trauma patients with hemorrhagic shock [205–207]. Two RCTs were not included as the intervention was conducted mainly in the pre-hospital setting [200, 208]. The studies displayed a low quality of evidence, marked by serious risks of bias and moderate imprecision (Supplementary material). We incorporated the 3 RCTs evaluating the impact of permissive hypotension as an intra-hospital intervention on patients with trauma and hemorrhagic shock.

The trials included a total of 380 patients. The quality of evidence was low, with a serious risk of bias and moderate imprecision in the estimate (Supplementary material). The intervention was not associated with a reduction or an increase in 28-day mortality, with a relative risk of mortality of 1.16 [0.76–1.76]. According to the GRADE evaluation, the quality of evidence was low, and the topic is insufficiently studied to recommend interventions to reduce MAP in trauma patients with hemorrhagic shock.

The literature search retrieved one observational study in patients with hemorrhagic shock undergoing emergency laparotomy [209]. Edelman et al. compared three different populations of patients according to three different levels of systolic blood pressure (<89 mmHg, 90–109 mmHg, >110 mmHg). We considered only the 90–110 mmHg and the >110 mmHg strata [209]. The study reported an increase in mortality for reduced systolic arterial pressure. However, due to the study's limitations, we could not elaborate recommendations from it in this specific population.

OHCA

We initially included 4 studies to assess whether an intervention of increasing MAP compared to controls could be beneficial [210–213]. A study was subsequently excluded [210] as it reported only 180-day mortality, while the other studies reported hospital or 28-day mortality.

Three RCTs were then included for a total of 1070 patients [211–213]. The studies were homogeneous and evaluated as low-intermediate risk of bias, with small imprecision (Supplementary material). There was no significant effect on 28-day mortality from increasing MAP with a RR of 1.11 [0.93 to 1.33]. Regarding final GRADE evaluation, we found no evidence supporting or opposing an increase in MAP in OHCA patient (moderate quality of evidence).

Cardiogenic shock

Two non-randomized studies enrolled cardiogenic shock patients [214, 215]. The study by Burstain et al. reported three different groups according to MAP (<65 vs. 65–75 vs. >75 mmHg). It demonstrated an association between lower MAP levels and mortality [214]. Parlow et al. reported a secondary analysis of the DOREMI randomized trial, comparing milrinone and dobutamine in cardiogenic shock patients [215]. Patients achieving a MAP >70 mmHg were considered cases, while patients with MAP <70 mmHg were controls. A reduced MAP was associated with higher mortality [215]. However, these studies were unable to adequately adjust for confounders that might impact the relationship between arterial pressure and mortality, making the findings indicative of predictive associations rather than causal association.

Expert opinion

The suggestion of targeting a MAP of 65–70 mmHg rather than higher values in patients with septic shock is mainly based on the results of the SEPSISPAM and OVATION trials. However, the lowest targeted MAP values differed among studies (60–65 mmHg in OVATION, 65–70 mmHg in SEPSISPAM). Finally, the MAP values reached in practice in the “lower MAP” groups were higher than mandated by the protocol.

Individual data analysis of the SEPSISPAM and OVATION cohorts does not provide evidence for higher MAP targets for patients with pre-existing hypertension. However, the panelists considered that a higher MAP target in this population may be reasonable on pathophysiological grounds, especially when guided by markers of tissue perfusion.

The suggestion to target higher MAP levels in septic shock patients with high CVP values is also based on pathophysiological considerations. It is also supported by a retrospective study in 2118 critically ill patients, which demonstrated that the organ perfusion pressure gradient (MAP–CVP) better predicted renal function deterioration than MAP alone [216]. Facing a patient with high CVP values, the first attempt should be to decrease CVP by treating its cause. Moreover, one should not neglect that next to CVP other factors also influence the organ perfusion pressure, such as the waterfall phenomenon, the pre-capillary sphincter status, and the post-capillary venous pressure.

In cardiogenic shock, the available data encourage recommending a MAP target of ≥ 65 mmHg [214, 215]. RCTs are required to better define MAP targets in this population. Although it makes empirical sense to personalize targets based on patient characteristics, data are still unavailable. The effects of treatment on indices

of organ function, tissue metabolism, and perfusion must be considered.

A recent European guideline recommended a restricted volume replacement strategy in the initial phase following trauma, with a target systolic blood pressure of 80–90 mmHg (MAP of 50–60 mmHg) until major hemorrhage has been stopped without clinical signs of brain and/or spinal injury [217]. Our recommendations are in accordance with these previous ones. Accordingly, in patients with severe traumatic brain injury (coma Glasgow scale ≤ 8), a MAP ≥ 80 mmHg should be maintained [217].

Resuscitation strategies aimed at permissive hypotension are contraindicated in patients with traumatic brain and/or spinal injury to preserve brain perfusion pressure [217]. A retrospective analysis of cohorts of patients with traumatic brain injury showed that systolic arterial pressure < 90 mmHg significantly increased mortality [218, 219]. Furthermore, the concept of permissive hypotension during traumatic shock must be considered cautiously in elderly patients [220] or those suffering from chronic arterial hypertension. The expected duration of hypotension, determined by the time required to control the hemorrhage (surgical or radiology intervention), must also be considered.

Question 3.5. When should one monitor intra-abdominal pressure in shock?

Recommendation 3.5

45. Serial monitoring of IAP may be considered in patients with shock and established risk factors for intra-abdominal hypertension

Ungraded good practice statement/Ungraded evidence/Strong agreement

Background

Over the last 20 years, the pathophysiological consequences of intra-abdominal hypertension and abdominal compartment syndrome have been highlighted and widely studied. Intra-abdominal hypertension is defined as a sustained increase in IAP ≥ 12 mmHg, while abdominal compartment syndrome is defined as sustained IAP > 20 mmHg (with or without abdominal perfusion pressure < 60 mmHg, calculated as MAP minus IAP) associated with new organ dysfunction/failure [221]. Both intra-abdominal hypertension and abdominal compartment syndrome can be primary, associated with injury or disease of the abdominal pelvic region that frequently requires early therapeutic intervention, or secondary, mainly associated with overzealous crystalloid fluid resuscitation in patients with capillary leak (e.g., sepsis, burns, severe acute pancreatitis). In critically ill patients, administration of large volumes of intravenous

fluids can lead to abdominal compartment syndrome [222].

Elevation of IAP results in the compromise of multiple organ systems, including cardiovascular, respiratory, central nervous system, renal, and gastrointestinal ones. A poly-compartment syndrome is a condition in which two or more anatomical compartments have elevated pressures [223]. IAP is key to understanding hemodynamics in patients with shock. It impacts the interpretation of barometric filling pressures, functional hemodynamic tests (increased PPV and SVV, false negative PLR tests). Elevated IAP may also explain, as it decreases kidney perfusion.

Intra-abdominal hypertension occurs in about 25% on admission and almost half of all ICU patients during the first week of their stay and is twice as prevalent in mechanically ventilated patients as in spontaneously breathing patients [224]. This is associated with increased mortality, independently from other severity factors [224].

Consensus on science

A sensitive search strategy complemented by manual searches reference was employed, yielding 56 articles which were assessed in full text. After full-text evaluation, no article was found which was pertinent to the PICO (Supplementary material).

Expert opinion

No study has compared IAP monitoring in critically ill patients to no monitoring. The suggestion to measure IAP is based on three arguments. First, studies have shown an association between intra-abdominal hypertension and organ dysfunction and mortality [224]. Second, IAP is one of the variables that may contribute to the hemodynamic failure of the patient and may affect fluid accumulation. It is also one of the variables that may help assess fluid accumulation and the risk of additional fluid administration. Third, measuring IAP does not increase invasiveness as it uses an already present urinary catheter and can thus be set up with reasonable additional costs.

Question 3.6. When should one monitor central venous pressure in shock?

Recommendations 3.6

46. Central venous pressure (CVP) should be measured in patients with shock who have a central venous catheter.

Ungraded good practice statement/Ungraded evidence/Strong agreement

47. A pre-specified CVP value should not be targeted during the resuscitation of patients with shock.

Recommendations 3.6

Ungraded good practice statement/Ungraded evidence/Strong agreement

Background

CVP reflects the right atrial pressure. Transmural CVP (CVP–pleural pressure) is an indicator of RV preload. Many studies have shown that a static value of CVP cannot predict fluid responsiveness, except perhaps extreme values [225]. Several studies also have demonstrated an association between high CVP levels and poor outcomes in critically ill patients [97]. Although this association does not demonstrate a causal relationship, it is supported by studies showing that elevated CVP values are associated with organ dysfunction, especially of the liver and kidney [97]. Elevated CVP decreases the organ perfusion pressure gradient (MAP–CVP) and promotes tissue edema. A retrospective study of 2118 critically ill patients demonstrated that the organ perfusion pressure gradient better predicts renal function deterioration than MAP alone [216].

The concept of using CVP targets was initiated by Rivers et al., demonstrating reduced in-hospital mortality in septic shock patients assigned to early goal-directed therapy compared to routine care [53]. However, the CVP (8–12 mmHg) was similar in both arms, and the range of this CVP target in the intervention group was set arbitrarily. This was also the case in three large RCTs demonstrating no benefit of goal-directed therapy in patients with shock [54–56].

In the FACCT trial, patients with ARDS after initial hemodynamic stabilization were allocated to a “liberal” or a “conservative” fluid strategy, guided by targeting higher or lower values of CVP or pulmonary artery occlusion pressure [226]. Although 60-day mortality was similar between groups, the conservative strategy was associated with improved lung function, shorter duration of mechanical ventilation, and ICU stay without increasing non-pulmonary-organ failures [226]. This study also showed that the use of CVP was associated with fewer complications when compared to the use of pulmonary artery occlusion pressure requiring a PAC. In addition, in a secondary analysis, different sepsis phenotypes had opposite responses, one phenotype benefiting from lower CVP targets while another benefited from higher ones [227].

Consensus on science

We identified 3 RCTs [152, 153, 228] and one observational study [159] using CVP in patients in shock as a target for relevant clinical outcomes. Two RCTs were excluded as they are comparing CVP as a control group

measure to assess advanced CO monitoring as study treatment and are included in the relative PICO above [152, 153]. The retained RCT by Yu et al. included 71 patients with shock and chronic obstructive pulmonary disease. They compared a strategy guided by transpulmonary thermodilution-derived global end-diastolic index and another guided by CVP. The CVP-guided strategy was associated with lower administered fluid volumes, a higher norepinephrine dosage, a lower 24-h blood lactate clearance, and a longer ICU stay. The 90-day and ICU mortalities were similar between groups [228].

The observational study by Hata et al. compared outcomes associated with the use of PAC, central venous catheters, arterial pressure waveform analysis for CO monitoring and no “central” monitoring in patients with shock [159]. Study bias was deemed high, and the study was not included in recommendation. The final evaluation is that there is neither evidence supporting nor opposing the monitoring of CVP in patients in shock, and the quality of the evidence available is very low (Supplementary material).

Expert opinion

In the absence of evidence, the panelists decided to issue an ungraded good practice statement. The expert opinion is based on the following arguments. First, CVP is of pathophysiological value, which may help guide therapeutic choices. As the transmural CVP indicates right heart preload, it can help to assess the type of shock, where a very low CVP typically suggests a hypovolemic component, while a high CVP suggests cardiac involvement. A rise in CVP can signal the occurrence of right heart failure. In addition, CVP is the downstream pressure of venous return, and as such may help to understand the effects of a fluid bolus. Elevated CVP values are associated with tissue edema [229], hepatic [230], and renal [97] dysfunction, so they can be used as a safety index indicating a high risk from additional fluids. Considering the value of the organ perfusion pressure gradient (MAP–CVP) compared to MAP alone for predicting AKI [216], CVP should be interpreted together with MAP values. The second argument supporting this expert opinion is that measuring and monitoring CVP is simple and entails limited extra costs for patients with a central venous catheter already in place.

The panelists do not recommend targeting a specific CVP value when resuscitating patients with shock. First, the CVP values fluctuate according to the presence or absence of mechanical ventilation. Second, adjusting CVP to reach a predefined target in hemodynamically stable patients without tissue hypoperfusion, despite CVP values outside the 8–12 mmHg target, seems

unwarranted. A physiologically reasonable strategy is to aim for the lowest value of CVP associated with adequate CO and tissue perfusion. As stipulated in recommendation 2.2, CVP is also one of the variables that may help assess fluid accumulation syndrome and the risk of additional fluid administration.

Domain 4: Echocardiography (Fig. 6)

Question 4.1. In patients with shock, does performing echocardiography improve clinical outcomes?

Recommendation 4.1

48. We suggest performing one or more echocardiograms in patients with circulatory shock

Weak recommendation/Low certainty of evidence/Strong agreement

Background

The impact of echocardiography on clinical management of critically ill patients in shock is well documented, where it may be used as a diagnostic tool and as a hemodynamic monitor [231]. Multiple studies have described changes in clinical management due to echocardiography, and while echocardiography allows a more comprehensive hemodynamic evaluation in this population,

questions remain regarding its ability to improve clinical outcomes, whether specific echocardiographic features offer prognostic significance or if they provide any predictive value in shock.

Consensus on science

Only one single-center RCT was identified [232] (Supplementary material). In a mixed shock population (60% with primary cardiovascular cause), the use of continuous transesophageal echocardiography during the first 72 h shortened the time to resolution of hemodynamic instability at day 3 after ICU admission (SHR 1.26, 95% CI 1.02–1.55, $p=0.03$), whereas the effect could not be sustained through day 6 (SHR 1.20, 95% CI 0.98–1.46, $p=0.06$).

In a single-center pre- and post-intervention study in mechanically ventilated patients with undifferentiated circulatory shock, basic transthoracic echocardiography to guide fluid and inotrope therapy after initial resuscitation was associated with improved survival at 28 days (HR 0.64, 95% CI 0.41–0.98) and more days alive and free of renal support (28 [9.7–28] vs. 25 [5–28], $p=0.04$) [233].

In a retrospective, propensity-matched analysis of 3291 patients with septic shock from the MIMIC-3 database

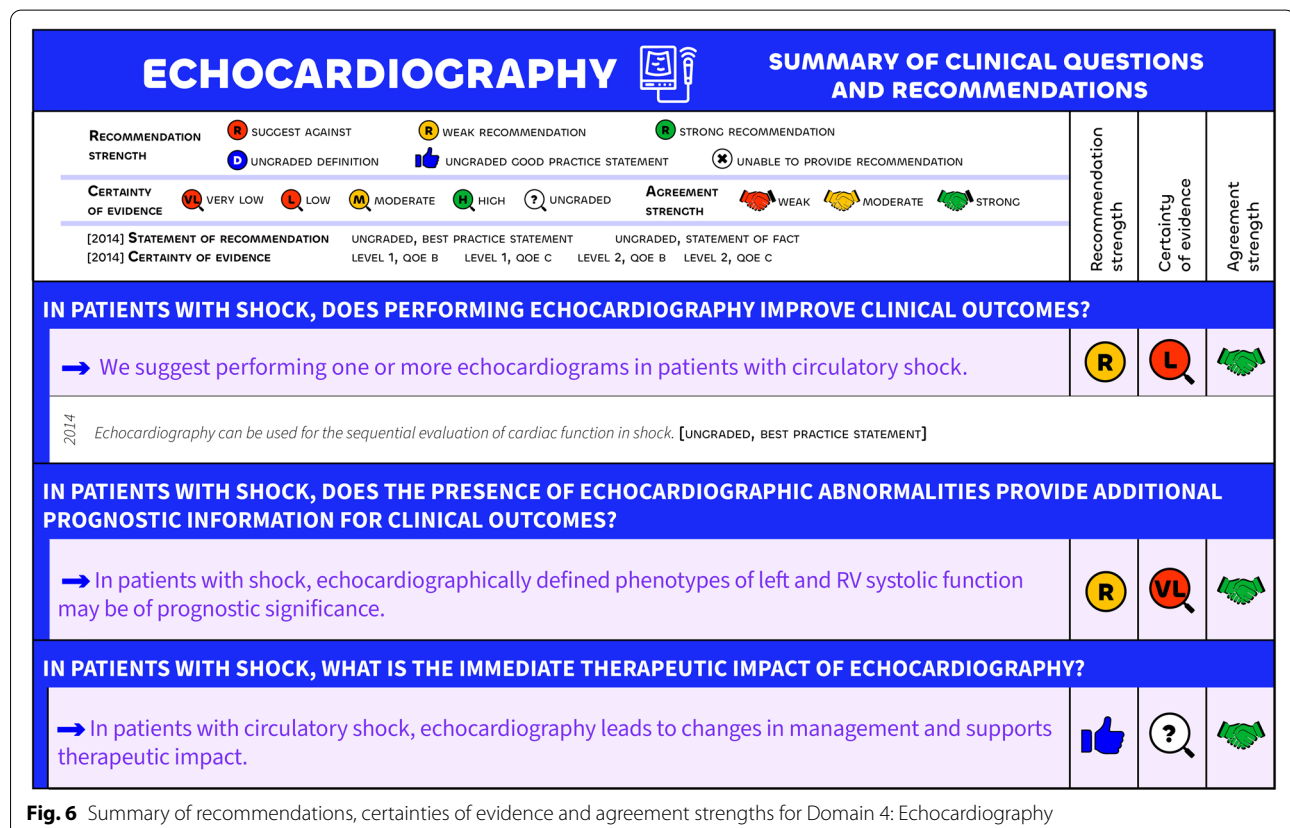


Fig. 6 Summary of recommendations, certainties of evidence and agreement strengths for Domain 4: Echocardiography

[234], echocardiography in patients with septic shock was associated with an increased use of inotropes (17.8% vs. 7.1%) and pulmonary artery catheterization (4.2% vs. 0.2%). Echocardiography within 24 h of septic shock occurrence was associated with a decreased 28-day mortality (OR 0.83, 95% CI 0.73–0.95, $p=0.005$). In another retrospective analysis of patients with septic shock from the MIMIC-3 database, early transthoracic echocardiography within 10 h of ICU admission was associated with reduced 28-day mortality (HR 0.74, 95% CI 0.60–0.91, $p<0.01$), possibly mediated by a lower fluid balance [235].

Echocardiography is an essential part of an integrative hemodynamic approach at all stages of shock. Minimum requirements for training have been established, including specified skill sets required to obtain vital information in shock [101, 236]. The minimally invasive nature of echocardiography and its frequently rapid availability in combination with its ability to comprehensively assess cardiovascular function and volemic status to provide a timely and appropriate working hypothesis and treatment plan at all stages of shock were considered when making this recommendation. Echocardiography also provides a means to evaluate hemodynamic consequences in therapeutic trials in patients with shock. Despite limited evidence demonstrating improved clinical outcomes due to echocardiography, there are many studies demonstrating the usefulness of echocardiography. The panelists considered that the benefit of echocardiography in shock outweighed its risks.

Question 4.2. In patients with shock, does the presence of echocardiographic abnormalities provide additional prognostic information for clinical outcomes?

Recommendation 4.2

49. In patients with shock, echocardiographically defined phenotypes of left and RV systolic function may be of prognostic significance.

Weak recommendation/Very low certainty of evidence/Strong agreement

Background

Although LV ejection fraction (LVEF) is a commonly measured echocardiographic variable in critical care, its prognostic value in shock is uncertain. Multiple studies suggest that LVEF may not be a sensitive marker of cardiac dysfunction in septic shock, and that longitudinal markers of contractility such as global longitudinal strain (GLS) and mitral annular plane systolic excursion (MAPSE) may be more sensitive markers of LV systolic function [237–240]. The contribution of previous cardiovascular disease to the prognostic effect of echocardiographic abnormalities is relevant and is poorly

investigated [241]. A spectrum of left- and right-sided, systolic and diastolic echocardiographic abnormalities has been observed in septic shock [242, 243], but the relative contributions of multiple abnormalities to clinical outcomes have seldom been studied. Whether specific echocardiographic features may be used to define sepsis-induced myocardial dysfunction in patients with shock is still unknown.

Consensus on science

Left ventricular systolic function

In septic shock, 6 studies were identified evaluating the association of LV systolic function variables with clinical outcomes [244–249] (Supplementary material). Increased MAPSE was independently associated with lower 28-day mortality [244]. In contrast, a higher myocardial velocity measured by tissue Doppler imaging (s') at the septal and lateral mitral valve annulus was associated with a higher 90-day mortality [245]. Another study identified that a hyperkinetic phenotype with increased LVEF in the presence of reduced afterload was associated with increased hospital mortality [246]. The presence of dynamic LV obstruction, a finding in hyperkinetic and hypovolemic ventricles, was identified in 22% of patients with septic shock and was a risk factor for 28-day mortality [247]. Conversely, a severely reduced LV systolic function was also associated with a higher in-hospital mortality [248]. A large retrospective cohort study in 1897 patients with septic shock found a U-shaped relationship between LVEF and in-hospital mortality, with higher mortality observed with both hypo- and hyperkinetic LV systolic function [249]. The relationship was observed among patients with extreme values of LVEF ($<25\%$ and $>70\%$) on high doses of noradrenaline ($>0.5 \mu\text{g/kg/min}$).

Among patients post-cardiac arrest, a higher LVEF indicating a “distributive shock” phenotype was associated with fewer days without organ failure and higher mortality [250]. On the other hand, data from the FAST-MI registry demonstrated that LVEF $<40\%$ was independently predictive of poorer long-term survival among patients with cardiogenic shock due to acute myocardial infarction [251]. In a large retrospective study investigating patients with cardiogenic shock, a higher early mitral valve inflow velocity to early diastolic annular velocity (E/e') ratio and a lower stroke volume index but not a reduced LVEF were associated with increased in-hospital mortality, after adjustment for confounders [252]. Similarly, in a retrospective study in patients with cardiogenic shock and LVEF $<40\%$ due to acute myocardial infarction, neither LVEF nor velocity time integral at the LV outflow tract were associated with 28-day mortality [253]. Yet, another retrospective study demonstrated

contradictory findings—in cardiac ICU patients with cardiogenic shock, LVOT VTI and LVEF during the first day of admission were associated with in-hospital mortality [254].

In summary, the data suggest LV dysfunction may be of prognostic significance in various shock states. Among patients with septic shock, there may be a nonlinear relationship between some variables of LV systolic function and mortality. The importance of LV systolic dysfunction was further supported by a study showing that septic shock patients with an LV systolic dysfunction phenotype identified by 2-step clustering demonstrated higher ICU mortality than other phenotypes [242]. The panel acknowledged that in patients with pre-existing cardiac disease and sepsis (with and without shock), LV global longitudinal systolic strain may have the potential to identify patients at high risk for major adverse cardiovascular events [241]. The fact that severely reduced LV systolic function, as well as hyperkinetic LV systolic function, may be associated with worse clinical outcomes and may have implications for the clinical management of septic shock was considered when making this recommendation. For patients with cardiogenic shock, limited studies suggest a variable relationship between LV systolic function variables and clinical outcome. The International Society for Heart and Lung Transplantation Consensus Conference in Heart Failure Related Cardiogenic Shock recommended the measurement of the LVEF, velocity time integral at the LV outflow tract, and assessment of RV function for additional prognostic information among patients with heart failure-related cardiogenic shock [255].

Further research in populations with different types of shock is required to determine the prognostic value of LV echocardiographic abnormalities and phenotypes for clinical outcomes.

Right ventricular function

Abnormalities in RV function are variably defined in the literature and encompass RV dysfunction according to consensus-defined variables [256] and a ‘failure’ phenotype [257]. Two retrospective studies identified that impaired RV function was independently associated with in-hospital and 28-day mortalities in patients with septic shock [258, 259]. In the latter study, LVEF < 50% was also associated with in-hospital mortality. However, the size of the effect estimate was smaller than that for RV dysfunction [260]. Abnormalities in RV size and systolic and diastolic functions were common in a cohort of septic shock ICU patients examined within 24 h of admission. However, none were associated with decreased survival [257]. Supporting an expected physiological response, the demonstration of a “RV failure” phenotype, defined

as a dilated RV by echocardiography in combination with CVP > 8 mmHg, was less likely to be associated with fluid responsiveness in patients with septic shock [257]. A few studies, not identified by the literature search and/or that did not fulfill the inclusion criteria, have shown that RV impairment (defined variably) may have implications for short- and long-term mortality. For example, RV free wall strain and a RV failure phenotype may be associated with short and mid-term mortalities [242, 261]. Geri and co-workers identified a RV failure phenotype in 22.5% of 360 patients with septic shock, with the second highest ICU mortality among the 5 phenotypes identified [242]. Further, in a recent systematic review and meta-analysis including 1373 patients of whom 82% had septic shock, RV dysfunction was associated with short- and long-term mortalities [262]. Among patients with cardiogenic shock and LVEF < 40%, a retrospective study identified RV s' wave, but not TAPSE, velocity time integral at the LV outflow tract, or LVEF as an independent predictor of 28-day mortality [253].

Although publication bias may be a limitation and studies including only patients with shock are limited, the panel considered that the overall evidence suggests a significant prognostic role of RV dysfunction for clinical outcomes. Additional prospective studies among patients with different types of shock are required to determine the independent prognostic value of specific RV echocardiographic abnormalities and phenotypes for clinical outcome.

Left ventricular diastolic function

Numerous studies, including a meta-analysis among patients with severe sepsis and septic shock, suggest that diastolic dysfunction may be associated with mortality [263]. Data for patients with septic shock are less prolific and less clear. In patients with cancer developing septic shock, impaired diastolic function indicated by lateral $e' < 8$ cm/s was associated with higher ICU mortality [264]. In a limited study of patients with septic shock, an independent association between E/e' and hospital mortality was demonstrated, but no differences were observed between survivors and non-survivors for septal e' [265]. In patients with septic shock assessed with tissue Doppler imaging, Weng et al. observed no association between any diastolic function variable and 90-day mortality [245]. Finally, a recent single-center study showed that lateral e' of the mitral annulus < 10 cm/s was associated with ICU mortality but was not statistically significant after multivariable adjustment [266]. In the largest study to date, published after the literature search, Vignon et al. demonstrated that LV diastolic dysfunction evaluated according to consensus guidelines was present in a majority of patients with septic shock, with

44% having persisting defects at 28 days after ICU admission [267]. Diastolic dysfunction early during ICU admission did not have an impact on short-term mortality. In patients with cardiogenic shock, the presence of a restrictive filling pattern on echocardiography was associated with lower LVEF despite intra-aortic balloon pump support. Still, it was limited in power to detect a major prognostic effect of diastolic dysfunction [268].

The panel was unable to make a robust conclusion regarding the prognostic value of diastolic dysfunction in septic shock. Different definitions of diastolic dysfunction, other population characteristics, and a risk of bias may account for the imprecision and inconsistency of the findings of the literature review. Knowledge gaps include how to evaluate best/define diastolic dysfunction in this population, and whether or not diastolic function should be treated in the critical care setting. The panel could not issue recommendations regarding the prognostic value of diastolic dysfunction for other types of shock due to a lack of evidence.

Question 4.3. In patients with shock, what is the immediate therapeutic impact of echocardiography?

Recommendation 4.3

50. In patients with circulatory shock, echocardiography leads to changes in management and supports therapeutic impact.

Ungraded good practice statement/Ungraded evidence/Strong agreement

Background

Echocardiography is now recommended as the first-line imaging modality in all types of shock, in settings within and outside ICUs. Focused echocardiography is used to rapidly exclude reversible causes in the early phase of shock, and more advanced echocardiography may complement other hemodynamic monitoring methods to guide and monitor therapeutic decisions [269]. Since echocardiography is minimally invasive, widely available, and already recommended in many guidelines and local protocols for the investigation of shock, it would be difficult, if not impossible, to conduct RCTs on the impact of echocardiography vs. no echocardiography in this population. However, the immediate therapeutic impact of echocardiography may vary and is summarized in this section.

Consensus on science

We conducted a pragmatic search to identify studies documenting the therapeutic impact of echocardiography in shock (Supplementary material). In a review including more than 2500 transesophageal echocardiography

studies performed in critically ill patients, echocardiography was conducted in 39% of patients with hemodynamic instability [269]. LV systolic dysfunction was found in 27% of cases, RV dysfunction in 14%, and hypovolemia in 11%. The therapeutic impact, defined as a change in patient management, was considerable, occurring in 68.5% of cases. Surgical impact, defined as an indication for surgery, occurred in 5.6%. In 152 medical ICU patients, transesophageal echocardiography allowed physicians to diagnose acute cor pulmonale in 27% of cases, LV dysfunction in 23%, aortic endocarditis in 12%, and pericardial tamponade in 9% [270]. The transesophageal echocardiography findings resulted in a change in clinical management in 58 (38%) patients such as the start of inotropic agents, use of extracorporeal life support, the start of antibiotics for endocarditis, and adjustment of ventilator settings.

Echocardiography has an immediate impact on fluid management. By its ability to monitor LV stroke volume with the aortic velocity time integral, echocardiography allows assessment of the response to a PLR test or to fluid administration. Furthermore, considering the optimized sensitivity and specificity cut-offs of different variables, transthoracic and transesophageal echocardiography can be used to predict the response to fluids [141]. Measuring the end-expiratory diameter of the IVC may add some value for guiding fluid therapy and fluid resuscitation even if it should not be used alone for fluid prediction purposes [271]. In a single-center pre- and post-intervention study, basic transthoracic echocardiography in mechanically ventilated patients with circulatory shock led to less fluid administration during the first 24 h compared to the control group [233].

Echocardiography has an immediate impact on the use of inotropic and vasoactive agents. In critically ill patients with undifferentiated shock, a higher proportion of patients required dobutamine infusion if basic transthoracic echocardiography was used than if it was not (22% vs. 12%) [233]. Both restrictive fluids and increased dobutamine use were associated with a decrease in 28-day mortality. Among 46 patients admitted to ICU for septic shock, the agreement between an echocardiography approach and the Surviving Sepsis Campaign (SSC) guidelines was weak (kappa 0.23) for prescription of dobutamine [272]. In the echocardiography group, dobutamine infusion was expected in 30%, while in only 8.9% in the SSC group. How this impacts outcome remains to be definitively determined. Data from the MIMIC-3 database indicated that the use of echocardiography in patients with septic shock was associated with an increased use of inotropes (17.8% vs. 7.1%) and that echocardiography within 24 h of septic shock occurrence was associated with a decreased 28-day mortality [234].

It is also well known that echocardiography helps physicians detect pericardial effusion and diagnose cardiac tamponade, while this diagnosis is mainly clinical. Nevertheless, clinical signs may be masked in critically ill patients with increased LV filling pressure, aortic regurgitation, loculated effusions, or hypovolemia that may have reduced or absent respiratory variations. Added to clinical evaluation, echocardiography findings help guide the timing of pericardiocentesis [273].

By its ability to detect RV failure, echocardiography can also suggest modification in respiratory strategy, especially in ARDS patients [274]. In a cohort of 393 patients with sepsis and septic shock, RV systolic dysfunction diagnosed by echocardiography was independently associated with 28-day mortality [275]. Using the same echocardiographic criteria, a high prevalence of isolated RV dysfunction was observed in patients with sepsis and septic shock that was associated with 1-year but not short-term mortality [276]. In 282 mechanically ventilated patients with septic shock, Vieillard-Baron et al. reported that RV failure occurred in 42% of cases and was associated with a lower degree of fluid responsiveness [257].

Current guidelines recommend performing routine transthoracic or transesophageal echocardiography to manage cardiogenic shock. Indeed, echocardiography is an ideal tool for managing cardiogenic shock and allows visualization of the heart's functioning using hemodynamic indices ranging from simple ones like LVEF and CO to more complex variables such as ventricular strain. Echocardiography helps to provide a diagnosis or suggestion of etiologies such as endocarditis or myocardial infarction. It enables intermittent hemodynamic monitoring by providing estimates of filling pressures (although this variable is debatable), CO, and pulmonary pressures [277]. Nevertheless, the main limitation is the lack of studies validating the use of echocardiography as a tool for improving patient management in cardiogenic shock. In this regard, right heart catheterization [278] and measurements of tissue oxygenation variables such as lactate, SvO₂, and the arterio-venous PCO₂ gradient are complementary tools allowing for multimodal monitoring [279]. In addition, the use of echocardiography is limited by operator dependency and interobserver variability. In clinical practice, echocardiography should be performed initially to characterize cardiogenic shock, and any changes in the patient condition or therapeutic interventions should prompt a repeat echocardiogram. Echocardiography is also used to confirm the indication for veno-arterial extracorporeal membrane oxygenation, such as severely reduced ejection fraction, velocity time integral < 8 cm, or low CO, in conjunction with other variables (e.g., SCAI classification). During veno-arterial extracorporeal membrane oxygenation support,

echocardiography enables daily assessment of ventricular function recovery, aiding in the decision-making process for decannulation timing [280].

Expert opinion

Although no formal literature search was conducted, a vast body of evidence supports the immediate therapeutic impact of echocardiography for diagnosis, identification of the causes of shock, and guiding clinical management. It is difficult to tease out the contribution of echocardiography per se to therapeutic impact, since clinical decisions are made using a combination of patient history, clinical examination, laboratory, and imaging findings. Nevertheless, the panel considered the role of echocardiography important for its therapeutic impact.

Conclusion

This guideline presents 50 evidence-based and expert opinion-based recommendations regarding shock definition, fluid therapy, hemodynamic monitoring, and echocardiography for patients with shock. We updated and expanded on the recommendations formulated in 2014.

Supplementary Information

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Abbreviations

ARDS: Acute respiratory distress syndrome; AUROC: Area under the receiver operating characteristic curve; CO: Cardiac output; CVP: Central venous pressure; CRT: Capillary refill time; EVLW: Extravascular lung water; IAP: Intra-abdominal pressure; ICU: Intensive care unit; IVC: Inferior vena cava; LV: Left ventricular; LVEF: Left ventricular ejection fraction; MAP: Mean arterial pressure; PAC: Pulmonary artery catheter; P_aO₂/F_iO₂: Ratio of the arterial oxygen partial pressure over the inspired oxygen fraction; PCO₂: Partial pressure of carbon dioxide; PLR: Passive leg raising; PVPI: Pulmonary vascular permeability index; RCT: Randomized controlled trial; RV: Right ventricular; SVV: Stroke volume variation; SvO₂: Venous oxygen saturation; VA ECMO: Veno-arterial extracorporeal membrane oxygenation; VExUS: Venous excess by ultrasound score.

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Data availability

Not applicable.

Declarations

Conflicts of interest

XM received is a consultant for BD, Getinge, and Pulsion Medical Systems. XM received honoraria for giving lectures from AOP health, Baxter healthcare, BD, Edwards Lifesciences, Getinge, Masimo, and Philips healthcare. XM received an unrestricted research grant from Retia Medical, Masimo, and Edwards Lifesciences. XM is an associate editor of *Annals of Intensive Care*, a member of the editorial board of *Critical Care*, and the co-editor-in-chief of *Hemodynamics*. AMes received travel expenses and registration for meetings, congresses, courses, and lecture fees from Vygon and Edwards Lifesciences. MG has no conflict of interest. JB received honoraria for giving lectures from Abbott and Radiometer. JB is editor-in-chief of the *Journal of Critical Care*. JB is a member of the guideline committee for the Hemodynamic Monitoring in Adult Patients with Sepsis and Septic Shock of the CHEST organization and a member of the section Sepsis/Shock of the CHEST organization. NA has no conflict of interest. MCE received honoraria for giving lectures from Edwards Lifesciences, Directed Systems, and GE healthcare. GC has no conflict of interest. DDB received honoraria for consultancy for Viatris and Pharmazz. DDB received honoraria for giving lectures from AOP Health, Edwards Lifesciences, and Philips. VKE has no conflict of interest. LE is a co-investigator on an NIH-funded trial of sepsis bundle implementation and a co-investigator on an NIH-funded trial of sepsis bundle implementation. LE received honoraria from the American Board of Internal. LE received travel support for the Surviving Sepsis Campaign and from the American Board of Internal Medicine. GH has no conflict of interest. OH has no conflict of interest. CI is CSO of Active Medical BV, Leiden, The Netherlands, a company which provides devices, software, education, and services related to clinical microcirculation. TK has no conflict of interest. BL received grants for research from AOP health, BD, and Viatris. BL received honoraria for consultancy from AOP health, BD, and Viatris. BL received honoraria for giving lectures from AOP health, BD, and Viatris. BL received support for attending meetings and/or travel from AOP health, BD, and Viatris. BL received equipment, materials, drugs, medical writing, gifts, or other services from Viatris. MLNGM is co-founder, past-President, and current Treasurer of WSACS (The Abdominal Compartment Society, <http://www.wsacs.org>). He is a member of the medical advisory board of Pulsion Medical Systems (now fully part of the Getinge group), Sentinel Medical, and Baxter. He consults for BBraun, Becton Dickinson, Fresenius Kabi, Lexin, Spiegelberg,

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