Recommendations for hemodynamic Monitoring for Critically Ill Children – Expert Consensus Statement issued by the Cardiovascular Dynamics Section of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC)

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Abstract

Background

Cardiovascular instability is common in critically-ill children. There is scarcity of published high-quality studies to develop meaningful evidence-based hemodynamic monitoring guidelines and hence, with the exception of management of shock, currently there are no published guidelines for hemodynamic monitoring in children. The European Society of Paediatric and Neonatal Intensive Care (ESPNIC) Cardiovascular Dynamics section aimed to provide expert consensus recommendations on hemodynamic monitoring in critically ill children.

Methods

Creation of a panel of experts in cardiovascular hemodynamic assessment and hemodynamic monitoring and review of relevant literature - a literature search was performed, and recommendations were developed through discussions managed following a Quaker-based consensus technique and evaluating appropriateness using a modified blind RAND/UCLA voting method. The AGREE statement was followed to prepare this document.

Results

Of 100 suggested recommendations across 12 subgroups concerning hemodynamic monitoring in critically ill children, 72 reached “strong agreement”, 20 “weak agreement” and 2 had “no agreement”. Six statements were considered as redundant after rephrasing of statements following first round of voting. Due to lack of published evidence to develop evidence-based guidelines, most of the recommendations are based upon expert consensus.

Conclusions

These expert consensus-based recommendation may be used to guide clinical practice for hemodynamic monitoring in critically-ill children and they may serve as a basis for highlighting gaps in the knowledge base to guide further research in hemodynamic monitoring.

Introduction

Circulatory shock is defined as a “life threatening generalized maldistribution of blood flow resulting in failure to deliver and / or utilize adequate amount of oxygen, leading to tissue dysoxia” [1]. Cardiovascular instability with or without shock is common in children admitted to pediatric intensive care units. Over half of the children with hemodynamic instability in intensive care units have multiple-organ dysfunction and sepsis remains the leading cause [2]. Similarly, a multi-center international study

(Sepsis Prevalence, Outcomes, and Therapies; SPROUT) reported that over two-thirds of children with sepsis had multiorgan dysfunction, which was associated with a very high mortality. These data are similar to what has been described in the adult population [3]. However, there remains paucity of data regarding the epidemiology of circulatory derangement in children and how best hemodynamic status can be evaluated or monitored in the pediatric intensive care units.

Multiple studies have established that early recognition and treatment of pediatric circulatory insufficiency or shock is crucial to improve survival. However, the optimal way to resuscitate children with circulatory failure is controversial. The exact order and quantity of fluids or vasoactive drug administration in the critically-ill child with shock is supported by little evidence, although there are several consensus statements[4, 5]

Overzealous fluid resuscitation is detrimental to some children [6, 7]. There is some consensus regarding the first-line treatment in patients with shock or significant hemodynamic instability, but debate remains concerning how much fluid should be administered, which type of vasoactive drug should be used, how to assess the hemodynamic changes and ultimately what hemodynamic clinical goal should be targeted to guide optimal treatment. Ideal hemodynamic monitoring should accurately determine the severity of circulatory derangement and illustrate the underlying pathophysiologic mechanism to enable the clinician to choose the most appropriate treatment and to guide the therapy [7, 8].

Currently there is a wide range of devices and techniques available to evaluate the hemodynamic status. However, there are still no published evidence-based guidelines or even consensus specifically for hemodynamic monitoring (HD) in children. In the annual meeting of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) in October 2016, members of the Cardiovascular Dynamics Section were tasked to develop evidence-based guidelines if at all possible, or an expert consensus statement on the hemodynamic monitoring specifically for use in children.

Methods

A steering committee (SC) of three lead authors, one pediatric intensivist / anesthesiologist (JL), one neonatologist / pediatric cardiologist (YS) and one pediatric intensivist (JU), identified nine expert panel members who significantly contributed with publications in hemodynamic monitoring or cardiovascular status assessment in children in the last ten years, similarly to what had been done with previous ESPNIC guidelines [10–12]. Further, the three selection criteria for inclusion as panel member were: 1) must be clinicians working in a pediatric or neonatal intensive care; 2) needed to have experience with some form of HD monitoring; and 3) should have published in peer reviewed journals concerning the topic. Panelists' selection was performed prior to the literature search and for logistic reasons the number of participants was limited to a maximum of 12. All invited experts agreed to participate.

The working group had a face-to-face meetings during the ESPNIC conference in Lisbon 2017 and the European Academy of Paediatric Societies (EAPS) conference in Paris in 2018 and unanimously agreed to provide recommendations from full term infants over 37 weeks of gestation and over four weeks of

postnatal age (lower limit) to 18 years old (upper limit), in order not to overlap with preterm-neonatal and adult guidelines. The panel subdivided hemodynamic monitoring into 12 subgroups: arterial blood pressure, central venous pressure, pulmonary artery catheter, cardiac output, transpulmonary thermodilution, central venous oxygen saturation measurement, lactate levels, clinical signs, near-infrared spectroscopy, fluid responsiveness, microcirculation and role of ultrasonography. Panel members were assigned in pairs to one of the subgroups, and each subgroup was coordinated by one of the steering committee members. The tasks of each subgroups consisted of: performing a thorough review of the literature, writing a short description of the parameter/method, the technical background and physiological basis, writing a short overview of the reliability of the method if applicable, establishing, when possible, normal or target values, estimating the clinical value of the method or parameter in relation to the patient categories mentioned. Because of the hemodynamic knowledgeable background of the panel members, these documents served as an overview to provide the entire panel with recent collective knowledge. The documents were not intended as a structured systemic review of the specific technology or method. Also, given that there is only low-quality data available in many aspects of hemodynamic monitoring in children, and that the focus of this work was to reach consensus within the panel of experts, the working group decided not to use the GRADE system to evaluate the literature [13]. Finally, 3 types of recommendations were formulated: 1) recommendations considering the reliability of methods, but only if applicable; 2) recommendations considering normal or target values, but only if applicable; 3) recommendations considering clinical use in relation to specific patient groups.

The setup and some proposed recommendations were discussed in a face-to-face meeting during the European Academy of Pediatric Societies (EAPS) in Paris, France (October 2018). In May 2019 an anonymous electronic voting system (Survey Monkey®, San Mateo, USA) was used to vote on all recommendations by each panel member including the SC. Each panel member was given access to all the work from other subgroups with text, results and full text publications in order to vote with all available evidence. Panel members scored all the recommendations individually from 1 (complete disagreement) to 9 (complete agreement). Median score was calculated after eliminating one lowest and one highest value. Recommendations were labelled “strong agreement” (median 7–9 and with no individual score < 7), “equipoise” (median 4–6) or “disagreement” (median 1–3).

Recommendations without “strong agreement” were discussed and rephrased in the panel meeting during the ESPNIC conference in Salzburg, Austria (June 2019). The revised recommendations retaining “strong agreement” after the second electronic voting were labelled as “weak agreement” and where no consensus was reached they were classified as “no agreement”. Guidelines have been prepared according to the international Appraisal of Guidelines, Research and Evaluation (AGREE) [14].

Results

One hundred recommendations were drafted and voted by the panel for level of agreement. Seventy-two recommendations reached “strong agreement” after the first round. The remaining 28 recommendations, where no “strong agreement” was reached, were discussed in a face-to-face panel meeting during the

ESPNIC conference in Salzburg, Austria (June 2019): 21 were rephrased for 2nd round of voting, one was designated as “no agreement”, and panel proposed deleting 6 recommendations as they were thought to be redundant after discussing all other recommendations. (“Additional file 1 - Fig. 1”)

Finally, of the total 94 recommendations, 72 reached “strong agreement”, 20 “weak agreement”, and on 2 proposed recommendations “no agreement” was reached as summarized in “additional file 2 - Table 1”.

Table 1
Summary of expert consensus recommendations for hemodynamic monitoring in critically ill children

Sr No	Recommendation	Level of agreement
1. Clinical signs		
CS1	We recommend to perform a clinical assessment as the initial evaluation in all patients for the detection of hemodynamic alterations and thereupon decide on the subsequent monitoring, diagnostic tests and initial treatment	Strong agreement
CS2	There is no single clinical parameter that allows to evaluate the global hemodynamic status in children and, therefore, we recommend to analyze several parameters and make frequent assessments	Strong agreement
CS3	We recommend to interpret heart rate and respiratory rate with respect to the age or height of patient, sex, temperature and other influencing factors	Strong agreement
CS4	We recommend to measure thermal gradient and capillary refill time to evaluate peripheral perfusion	Strong agreement
CS5	In unstable patients we recommend to evaluate clinical signs periodically together with hemodynamic monitoring parameters	Strong agreement
CS6	We do not recommend to titrate hemodynamic therapy based upon clinical signs alone in unstable patients	Strong agreement
CS7	We do not recommend fluid loading solely based upon clinical signs with exception of the initial resuscitation phase	Strong agreement
CS8	We do not recommend fluid loading solely based upon a reduced urinary output	Strong agreement
2. Arterial blood Pressure		
BP1	We recommend the use of intra-arterial blood pressure (IBP) over oscillometric blood pressure (OBP) measurement when a reliable blood pressure (BP) measurement is of importance	Strong agreement
BP2	We recommend the use of IBP over OBP when fast and accurate changes in blood pressure need to be detected	Strong agreement
BP3	In children under 12 years of age we recommend a target blood pressure (preferably mean arterial pressure (MAP)) during shock and after return of spontaneous circulation from cardiac arrest higher than P5 for the age and sex, and if possible, around the P50, unless uncontrolled hemorrhage due to trauma is present. We advise to take blood flow parameters into account and avoid the overuse of vasoconstrictors when guiding hemodynamic therapy using BP	Weak agreement
BP4	In children under 12 years of age we do not recommend a target MAP > 65 mmHg unless under very specific conditions (e.g. intracranial hypertension)	Strong agreement
BP5	In children over 12 years of age we recommend a target blood pressure of > = 65 mmHg MAP (according to adults surviving sepsis guidelines) unless in children known to have prior hypertension	Strong agreement

Sr No	Recommendation	Level of agreement
BP6	We recommend not to use BP as the only therapeutic target in unstable children. The hemodynamic state should be evaluated integrating several clinical and hemodynamic parameters	Strong agreement
BP7	We recommend to measure IBP in children after major surgery that could produce hemodynamic, respiratory or neurologic alterations or risk of bleeding	Strong agreement
BP8	We recommend IBP monitoring in children in shock not responsive to initial fluid therapy or requiring vasopressor treatment	Strong agreement
BP9	We recommend to use IBP in malignant hypertension or other hypertensive emergencies to control the effect of continuous invasive hypotensive drugs. Oral or intermittent intravenous drugs can be monitored using OBP	Strong agreement
BP10	We recommend to use IBP in patients with intracranial hypertension to measure cerebral perfusion pressure and control the effects of the therapy	Strong agreement
BP11	We recommend to use IBP in patients on extracorporeal membrane oxygenation (ECMO)	Strong agreement
3. Serum lactate measurement		
LAC1	We recommend prompt point of care measurement of lactate or analysis in the laboratory according to local laboratory instructions	Strong agreement
LAC2	We recommend to obtain a repeat blood sample from a reliable site (central venous, arterial or peripheral venous with a time of tourniquet use shorter than 60 secs) when the lactate value of a capillary sample is higher than 3.0 mmol/L	Strong agreement
LAC3	We recommend to closely follow up patients with increased lactate levels until lactate values at least drop below 3.0 mmol/L, especially if other signs of tissue hypoxia are present	Strong agreement
LAC4	We recommend to interpret lactate levels always in conjunction with clinical indicators of poor systemic perfusion and monitoring parameters	Strong agreement
LAC5	We recommend to closely follow up and eventually intensify medical treatment in unstable patients with concerns regarding tissue hypoxia and lactate levels (> 3.0 mmol/L)	Strong agreement
LAC6	We recommend to use goal-directed medical therapy in patients admitted after open heart surgery based on serial blood lactate values obtained in short periods of time (4 hours in children, contemplate 1 hour in neonates), considering 5 mmol/L as a cut-off value	No agreement
LAC7	In children with septic shock and persistently high levels of lactate we recommend to intensify medical treatment (when possible)	Weak agreement
LAC8	In children treated with extracorporeal life support with persistently high levels of lactate, we recommend to intensify medical or mechanical treatment	Weak agreement
4. Central venous pressure		

Sr No	Recommendation	Level of agreement
CVP1	We recommend to place the tip of a central venous catheter at the junction of the superior caval vein (SCV) and the right atrium to obtain an optimal central venous pressure (CVP) measurement	Strong agreement
CVP2	We recommend the use of a short catheter with a semi-rigid wall connected with a transducer and electronic monitor to record CVP continuously	Strong agreement
CVP3	We recommend to measure CVP in all unstable patients refractory to initial hemodynamic treatment	Strong agreement
CVP4	We recommend against the use of CVP to predict fluid responsiveness. Therefore, fluid loading should not be started solely based upon a low CVP	Strong agreement
CVP5	An abrupt elevation in CVP upon fluid administration should raise suspicion of significant cardiac dysfunction	Strong agreement
CVP6	An isolated CVP measurement is of limited value in clinical practice. However, trends in CVP may provide important information regarding changes in cardiovascular pathophysiology such as evolving right heart failure	Strong agreement
CVP7	CVP is not a reliable parameter to assess right ventricular function	Weak agreement
5. Central venous oxygen saturation measurement		
$ScvO_2$ 1	We recommend to measure central venous oxygen saturation ($ScvO_2$) in unstable patients not responding to the initial treatment	Strong agreement
$ScvO_2$ 2	$ScvO_2$ > 65%* (and arterial to venous difference less than 30%) is acceptable in children, and a sustained drop in $ScvO_2$ (or increase in arterio-venous difference) may reflect inability of the cardiovascular system to respond to an increased demand or decreased supply	Weak agreement
$ScvO_2$ 3	$ScvO_2$ values may differ depending upon the site of catheter tip: we recommend placing the central catheter tip at the junction of SVC and right atrium	Strong agreement
$ScvO_2$ 4	$ScvO_2$ is not an adequate marker of cardiac index (CI)	Strong agreement
$ScvO_2$ 5	When $ScvO_2$ is < 65% there is a possible hemodynamic alteration. However, in sepsis a normal or high $ScvO_2$ may reflect mitochondrial dysfunction and mask hemodynamic alterations	Strong agreement
$ScvO_2$ 6	We recommend against targeting hemodynamic therapy solely based upon $ScvO_2$	Strong agreement
6. Echocardiography / Ultrasonography		

**This only applies for normal arterial saturation*

Sr No	Recommendation	Level of agreement
US1	We recommend against using cardiac ultrasound for routine hemodynamic monitoring in intensive care setting but in infants and children with hemodynamic instability it should be used as an adjunct to gain additional information required for making accurate clinical decisions	Strong agreement
US2	Cardiac ultrasound can be reliably used in neonates and children with cardiac tamponade	Strong agreement
US3	Cardiac ultrasound can help in diagnosing pulmonary hypertension and assessing severity of pulmonary hypertension	Strong agreement
US4	Cardiac ultrasound may help in identifying underlying pathophysiology of shock and choosing the right intervention based upon deranged hemodynamic physiology (preload, afterload or cardiac function)	Strong agreement
US5	Cardiac ultrasound performed by adequately trained intensivists can help in assessing global cardiac function qualitatively on visual inspection and also semi-quantitatively	Weak agreement
US6	Cardiac ultrasound may help in assessing fluid responsiveness: we recommend using velocity time integral (VTI) across aortic valve for assessing fluid responsiveness rather than inferior vena cava collapsibility in mechanically ventilated infants and children	Strong agreement
US7	We recommend serial longitudinal assessment to assess response to therapy in patients with significant hemodynamic instability	Strong agreement
7. Cardiac output measurement and transpulmonary thermodilution		
CO1	We recommend against the use of PAC for measuring CO in children as the first-choice method	Strong agreement
CO2	In patients with a refractory shock when an accurate measurement of CO is needed, we recommend to use transpulmonary thermodilution (TPTD) or semi-invasive transpulmonary ultrasound dilution (TPUD)	Weak agreement
CO3	We recommend to use ultrasound/doppler based methods of estimating CO if TPTD or TPUD are not available or do not match the conditions to be used	Strong agreement
CO4	We recommend to use ultrasound/doppler based methods of estimating CO for the initial assessment of unstable patients, to decide if a more invasive method is needed or in stable patients	Strong agreement
CO5	We cannot give any recommendations regarding other non-invasive methods due to the limited experiences in critically-ill children	Strong agreement
CO6	We recommend that cardiac index (CI) should be maintained above 3.5 L/min/m^2, otherwise titrated to ensure adequate end organ support	Strong agreement
CO7	In young children the use of uncalibrated continuous arterial pressure-based CO monitoring is not recommended	Strong agreement

Sr No	Recommendation	Level of agreement
CO8	We recommend to use invasive (and if possible continuous) CO monitoring in unstable post-operative patients after major (cardiothoracic) surgery, multiple trauma injuries or burns or patients with complex cardiopulmonary interactions	Strong agreement
CO9	We recommend to use invasive and or calibrated continuous CO monitoring in patients with high intrathoracic pressure that “threatens” the hemodynamic status (like severe PARDS) for titrating hemodynamic and ventilatory therapy	Weak agreement
TPD1	We recommend against the routine use of transpulmonary dilution (TPD) in children	Strong agreement
TPD2	Blood volumes measured with TPD reflect volume status in children, however we recommend against targeting fluid therapy based upon these parameters	Strong agreement
TPD3	Lung water measurement may provide a physiological insight into the amount of pulmonary edema in critically ill children. However, we recommend against targeting hemodynamic therapy based upon this parameter	Strong agreement
TPD4	TPD methods can be useful for indicating cardiac or non-cardiac shunts	Weak agreement
TPD5	TPD methods are the most accurate methods available at the bedside for measuring CO in children	Weak agreement
TPD6	When reliable absolute measurements of CO are deemed necessary TPD is the method of first choice	Strong agreement
TPD7	Because of their intermittent measurement technique, TPD methods are not suitable for the detection of fast changes in CO unless used in conjunction with continuous trend monitoring using pulse contour analysis, calibrated by transpulmonary indicator dilution technology	Strong agreement
TPD8	In unstable children TPD measurements may be advantageous. However, the risk of femoral arterial access when using transpulmonary thermodilution (TPTD) method and complicated measurements must be weighed against the potential benefit	Strong agreement
8. Pulmonary artery pressure		
PAC1	Transthoracic echocardiography is reliable enough to estimate systolic pulmonary artery pressure (SPAP) at the bedside in most patients when tricuspid valve regurgitation is present and in absence of severe right ventricle (RV) failure	Weak agreement
PAC2	We recommend using pulmonary artery catheters (PAC) for measurement of (gold standard) pulmonary arterial pressure (PAP) only during cardiac catheterization or, in selected cardiac surgery patients, using surgically inserted catheters	Strong agreement
PAC3	We do not recommend to use a PAC for the measurement of cardiac output (CO)	Strong agreement

Sr No	Recommendation	Level of agreement
PAC4	We do not recommend to use a PAC for the measurement of pulmonary artery wedge pressure	Strong agreement
PAC5	We recommend the monitoring of left atrial pressure only in selected cardiac surgery patients or patients after lung transplant using a surgically inserted catheter	Strong agreement
PAC6	We do not recommend non-invasive techniques using cardiac ultrasound to estimate left atrial pressure	Strong agreement
PAC7	We recommend monitoring of PAP using ultrasound in young patients with refractory shock states to exclude pulmonary hypertension	Strong agreement
PAC8	Transthoracic echocardiography can be a useful tool to estimate SPAP in patients on VV or VA ECMO	Weak agreement
9. Volume resuscitation and fluid responsiveness		
FR1	We recommend to observe the patient's clinical situation, physical exam and various perfusion indicators suggesting an inadequate CO (or oxygen transport) caused by hypovolemia before considering fluid loading	Strong agreement
FR2	We recommend, when possible or available, to confirm fluid responsiveness before commencing fluid loading when hypovolemia is suspected	Strong agreement
FR3	In delivering a bolus of fluid we recommend to administer a small bolus of fluid in a short time period while tracking changes in cardiac output, blood pressure and CVP	Strong agreement
FR4	We recommend alternative therapeutic strategies for hypotension management in fluid non-responders**	Strong agreement
FR5	We recommend against delivering a fluid bolus based on static measures, particularly CVP	Strong agreement
FR6	We recommend to withhold fluid therapy in patients with an increasing CVP and no significant increase in blood pressure or cardiac output as a result of previous fluid therapy	Strong agreement
FR7	We recommend fluid therapy (with boluses 5–10 ml/kg) as part of early resuscitation in unstable patients guided by the effect on blood pressure and / or cardiac output	Strong agreement
FR8	No specific recommendations regarding estimating fluid responsiveness can be made in patients with raised intracranial pressure or extracorporeal life support (ECLS)	Weak agreement
***Non-responders defined cases who had no rise in cardiac output (or stroke volume) as a result of volume resuscitation.*		
8. Near infrared spectroscopy		

Sr No	Recommendation	Level of agreement
NIRS1	The mean baseline cerebral capillary-venous hemoglobin saturation (rSO_2) is > 70% in healthy children and those with an acyanotic heart disease (similar to the adult population). Infants and children with cyanotic heart disease have a mean cerebral rSO_2 between 46–57%*	Weak agreement
NIRS2	Cerebral rSO_2 less than 40% or a significant drop from the baseline may be associated with hypoxic-ischemic neural injury	No agreement
NIRS3	It is recommended that the cerebral probe should be placed on the right and or left side of the forehead	Weak agreement
NIRS4	Near infrared spectroscopy (NIRS) can be useful during the peri-operative period after surgery for congenital heart defects	Weak agreement
NIRS5	We recommend against the routine use of NIRS during non-cardiac surgery	Weak agreement
NIRS6	We cannot make recommendations regarding the use of NIRS while treating children in shock, post-cardiac arrest, post traumatic brain injury and infants with hypoxic-ischemic encephalopathy	Weak agreement
NIRS7	Trend in NIRS values may provide valuable physiological information in children with hemodynamic instability but routine use in all children with hemodynamic instability is not recommended	Strong agreement
**Normal range described is while using INVOS NIRS monitor and practitioners should be mindful that different devices and sensors provide different values – we recommend checking normal values for the device being used in clinical practice*		
11. Microcirculation		
MICRO1	In addition to monitoring blood pressure and cardiac output assessment of microcirculation should be considered in children with shock	Weak agreement
MICRO2	Many routinely used parameters like capillary refill, peripheral temperature, lactate, NIRS etc. reflect aspects of the hemodynamic condition but do not adequately reflect the microcirculation and cannot be used as such	Strong agreement
MICRO3	We recommend against routine microcirculation evaluation by video microscopy in stable children except those in clinical studies	Strong agreement
MICRO4	We recommend to evaluate the microcirculation by video microscopy in various types of patients with hemodynamic compromise or complicated clinical course only for research purposes	Strong agreement
MICRO5	We recommend the use of microcirculation measurement technologies such as sidestream dark field (SDF) or incident dark field (IDF) in sublingual area in critically ill children that are deeply sedated to evaluate microcirculation	Strong agreement
MICRO6	We recommend to use the recommendations of 2017 adult consensus to the acquisition and analysis of video microscopy (SDF or IDF cameras)	Strong agreement

Sr No	Recommendation	Level of agreement
MICRO7	Although central venous to arterial CO_2 difference could provide additional insight into the microcirculatory condition, we recommend against its use to guide resuscitation in critically ill children	Strong agreement

Discussion And Evidence For The Recommendations

The details of technique, methods, reliability, search for published evidence and references are provided in the online supplement (**ESM supplement; website link…please insert when ready**). The commonly used parameters for hemodynamic monitoring in critically-ill children are measurements of: blood pressure, central venous pressure (CVP), central venous oxygen saturation, cardiac output, serum lactate, pulmonary artery catheter, transpulmonary dilution, clinical signs, near-infrared spectroscopy, fluid responsiveness, microcirculation and role of ultrasonography A brief summary of the evidence related to each sub-section has been summarized below.

1. Clinical signs

Paediatric resuscitation courses teach initial assessment of the shocked child well (ETAT WHO, APLS). Most caregivers will be familiar with the clinical signs and symptoms that help assess the hemodynamic status in children, including heart rate (HR); blood pressure; respiratory rate (RR); state of consciousness; diuresis; core and peripheral temperature; capillary refill time and peripheral perfusion. Some of these parameters are age-dependent and some can be altered by ambient temperature, pain, anxiety and many other factors. The role of the primary resuscitation team is to identify the shocked child in need for urgent intervention and treatment, usually with fluids and then inotropes or vasopressors in some combination.

All recommendations reached a high level of agreement, both in identifying children in need for treatment and in the limited value of clinical signs to guide hemodynamic treatment. There is a significant variability in clinicians' abilities to assess hemodynamic clinical parameters at the bedside. Early signs of hemodynamic decompensation may be subtle and can be easily missed by the clinicians [15]. For these reasons, the frequent and trend evaluation of clinical signs are more important than a single specific determination. A combination of vital signs can be more useful to evaluate hemodynamic state than individual parameters [16].

Disappointingly, there is no good correlation between clinical assessment and invasive hemodynamic parameters, which only indicates that clinical parameters and invasive parameters do not measure the same compartment [17]. Hence, in hemodynamically unstable patients apart from frequent meticulous assessment, monitoring trends of several measurable clinical, biochemical and monitoring parameters should be used to guide the therapy timely and accurately.

2. Arterial blood pressure

Blood pressure (BP) measurement is one of the most commonly used hemodynamic parameters for diagnostic and therapeutic decisions in critically-ill children, not least due to ease of utilization and, if invasive, the additional benefit of arterial blood sampling, as well as continuous data sampling. Both a low and a high BP on admission are related to an increased mortality [18]. Accurate measurement of BP is considered essential for the diagnosis and treatment of hypertension as well as of hypotension, including various categories of hemodynamic shock [19, 20]. BP can be measured invasively but also by using several less reliable non-invasive methods [21].

The committee strongly agreed on the use of intra-arterial blood pressure (IBP) over oscillometric blood pressure (OBP) measurement when there is a need for reliable BP measurement in children with shock not responding to initial fluid therapy or requiring inotropes or vasoactive medication; in patients with intracranial hypertension to measure cerebral perfusion pressure; during major surgery and in children with malignant hypertension or other hypertensive emergencies and to monitor the effect of continuous intravenous vasoactive medications or inotropes. However, the clinical value of BP in guiding hemodynamic therapy was not appreciated equally among the panel members. Nevertheless, there was strong agreement that BP should not be used as the only therapeutic target in unstable children, so the hemodynamic state should be evaluated integrating BP with several clinical and additional hemodynamic parameters [22].

Optimal values for BP in healthy and critically-ill children, including therapeutic thresholds, should be determined with regard to the clinical condition, age, sex and body size [21–26]. There was only weak agreement concerning BP values in children under 12 years of age. In children over 12 years of age generally we strongly recommend a target mean arterial pressure (MAP) of > = 65 mmHg, although in specific situations the targeted BP may be higher such as when managing raised intracranial pressure.

3. Lactate measurement

Determination of blood lactate concentration is a cheap, fast and easy bedside parameter that has demonstrated utility to predict the outcome or to trigger the need to intensify medical treatment [27]. Ideally, it should be analyzed with a point-of-care measurement, which allows frequent timely measurement and rapid assessment of resuscitation, rather than in the laboratory. The committee showed some variation in their approach to the use of lactate in children since 5 out of 10 recommendations needed a revision.

In critically-ill patients or children with shock, early and serial lactate blood sampling from a reliable site such as a central venous or arterial indwelling catheter is recommended, though peripheral venous sampling with tourniquet time < 60 secs is possible [28]. This is specifically recommended when the initial capillary lactate value is > 3.0 mmol/L [28–30]. Studies report an association between failure to normalize lactate levels to a certain threshold (3.0 ± 1.0 mmol/L) during the first 12 to 24hours of ICU admission, and adverse outcomes regardless of the reason for ICU admission [31, 32]. Experts could not agree on the use of lactate as part of a goal = directed approach and only weakly agreed on the approach to a persistent high lactate level. In the latter, lactate levels should always be used in conjunction with

other clinical indicators of poor systemic perfusion and monitoring parameters. Persistently elevated lactate levels may reflect other mechanisms rather than those derived from poor tissue perfusion in shock, and instead reflect aerobic glycolytic mechanisms including catecholamine administration or endogenous release [33].

4. Central venous pressure (CVP)

The committee shared a strong common opinion regarding CVP. CVP should be measured as accurately as possible and be evaluated only as part of multi-modal hemodynamic monitoring to assess intravascular volume and cardiac function [34, 35]. Isolated CVP measurement is of limited value but trends of CVP, both the value and the wave morphology, or change in CVP in response to fluid or vasoactive therapy may provide useful information about overall hemodynamic status and cardiovascular physiology in critically-ill children. Specifically, a rise or high levels of CVP should be avoided [36].

We therefore recommend measuring CVP in all unstable patients refractory to initial hemodynamic treatment with an indwelling central venous catheter (CVC). However, studies have shown that the use of CVP to assess preload and fluid responsiveness is inaccurate [37]. Furthermore, even measurement of ventricular volumes failed to predict accurate fluid responsiveness [38–40]. Therefore, CVP should not be used as a sole parameter to guide fluid therapy. Its use in clinical practice needs good understanding of its limitations and pathophysiology of underlying disease process.

5. Central venous oxygen saturation measurement

Central venous oxygen saturation ($ScvO_2$) approximates but does not equal mixed oxygen saturation (SmvO2). The normal ranges for ScvO2 and SmvO2 are 70–80% and 60–70%, respectively, in the setting of a normal aortic saturation [41, 42]. Trends between ScvO2 and SmvO2 are often interchangeable, although SmvO2 values are generally around 7–10% lower than ScvO2. A low $ScvO_2$ typically indicates a mismatch between oxygen supply and utilization. Conversely, a normal, or high $ScvO_2$ value, does not necessarily signify supply-demand adequacy, as tissue dysoxia (which may occur in sepsis) may cause an artificial elevation (or normalization) of $ScvO_2$. Lastly, ScvO2 in isolation cannot be considered a surrogate of cardiac index / cardiac output [43]. However, there is some evidence that resuscitation in sepsis might be more beneficial when $ScvO_2$ is incorporated in the treatment strategy [44].

The committee agreed that $ScvO_2$ is important to measure in unstable patients not responding to first treatment and that its trend is helpful in hemodynamic management. However, we recommend that hemodynamic therapy should not be targeted solely based upon $ScvO_2$ levels.

6. Echocardiography / Ultrasonography

Cardiac ultrasound or functional echocardiography is non-invasive and easily available at the bedside in the intensive care setting, and it allows rapid evaluation of hemodynamic status in real time. It can be used to assess cardiac function and preload, to estimate cardiac output and fluid responsiveness, to

measure pulmonary artery systolic pressure and serial assessment allows to evaluate response to therapy [9, 11]. Hence, it can be used, as an adjunct to other parameters, in children with hemodynamic instability to gain additional information required for making accurate clinical decisions such as myocardial failure, pulmonary hypertension or cardiac tamponade [11]. It can help in understanding the pathophysiology of shock in children, and it can help in selecting timely, targeted specific and right intervention [11, 45, 46].

The committee was united in strongly recommending the use of cardiac ultrasound for hemodynamic evaluation of infants and children with hemodynamic instability. Since cardiac ultrasonography does not provide continuous measurements and is limited by a wide intra and inter-observer variability [9, 47] we strongly recommend using serial assessments. Furthermore, cardiac ultrasound is very helpful in patients requiring extra-corporeal membrane oxygenation (ECMO): it is invaluable in placing the ECMO catheter at the appropriate position, assessing cardiac function and evaluation of pericardial effusion [11, 47].

7. Cardiac output monitoring and transpulmonary thermodilution

Cardiac output (CO) is the product of heart rate and stroke volume. Stroke volume depends on preload, contractility and afterload. The physical examination and simple commonly used hemodynamic parameters are the surrogate markers of cardiovascular well-being but they do not provide direct assessment of the cardiovascular hemodynamic status of the patient and clinical estimation of cardiac output has showed to be mostly inaccurate. Hence, there seems to be a need of advanced hemodynamic monitoring to titrate therapies [48, 49]. In patients with refractory shock, when an effective and accurate measurement of CO is needed, the following methods may be used depending upon available resources and expertise: measurement of CO using transthoracic ultrasound (echocardiography), transpulmonary thermodilution (TPTD) or transpulmonary ultrasound dilution (TPUD) [48–50].

Ultrasonography is non-invasive, easily available and can provide a fairly accurate and serial estimation of cardiac output at the bedside to monitor the response to therapy [9, 51]. However, it requires specific skills and is operator-dependent.

Although they are the most reliable clinically available methods to measure cardiac output, TPTD or TPUD may be challenging to apply in the clinical practice because of resources, technical difficulties or lack of expertise. Transpulmonary dilution (TPD) is invasive and not suited to emergency resuscitation. Only two methods are available in children below 40 Kg: transpulmonary thermodilution (TPTD) by PiCCO (Pulsion Medical Systems, Germany) and transpulmonary ultrasound dilution (TPUD) by CO status (Transonic, USA) [48–50, 52]. Neither are in frequent use in ICU due to their intricate set-up, and particularly for PICCO the risk to children's vessels from relatively large bespoke arterial catheter required. Moreover, because of their intermittent measurement technique TPD methods are not suitable for the detection of rapid, frequent, changes in hemodynamic status, as required in critically-ill children. The committee could only reach a weak agreement on their use, except that TPD methods are recommended as the most accurate methods available at the bedside for measuring CO in children. TPD methods also

measure blood volumes and lung water but the committee recommended against using these parameters for targeting hemodynamic goals.

Cardiac output can also be estimated at the bedside using other non-invasive methods like bioimpedance and bioreactance, pulse contour and Doppler. Validation of these methods in critically-ill children is sparse and these methods are therefore not consensually viewed as accurate enough to estimate absolute values of CO in the intensive care setting in children [53]. However, they might provide a trend over time. In general, the committee strongly agreed that at the current time no recommendations regarding these methods can be given due to the limited experiences in critically-ill children.

Cardiac output is influenced by patient size. Hence, it is useful to quantify it as cardiac index (CI) (CI = CO/Body surface area). This removes the influence of different body sizes and provides a consistent reference range for children of different sizes. Normal values of CI have been established between 3.5–5.5 L/min/m^2 [48, 49] and we recommend that cardiac index (CI) should ideally be maintained above 3.5 L/min/m^2, otherwise titrated to ensure adequate end organ support.

8. Pulmonary artery pressure (PAP)

The pulmonary artery catheter (PAC) can provide continuous measurement of right atrial, PAP, measurement of CO and pulmonary arterial occlusion pressure (wedge pressure). However, because of invasiveness and size it is not used or recommended in intensive care clinical practice in children [54]. Similarly, left atrial pressure can be measured using surgically inserted left atrial catheters (LAC) [55, 56]. Still, alternative less invasive techniques are being used in children to estimate left atrial pressure in unstable patients and LAC or PAC are rarely used in today's intensive care clinical practice [57, 58].

Because of the above, the committee recommends not to use a PAC in children to measure cardiac output or PAP in the ICU. Instead, transthoracic ultrasound echocardiography can be easily used to estimate PAP at the bedside non-invasively and it can provide serial assessment to monitor the response to therapy or disease process (as above). However, it should not be used to estimate PAP in patients with right ventricular (RV) failure [59]. For precise measurement of PAP, we recommend using the PAC only at the cardiac catheterization laboratory.

9. Volume resuscitation and fluid responsiveness

Volume resuscitation in hemodynamically unstable patients is one of the most commonly used therapeutic options. Nevertheless, excessive fluid administration may impair tissue perfusion even further by promoting edema and third-space fluid accumulation [6, 7, 60]. A rise in cardiac output (or stroke volume) as a result of volume resuscitation is called fluid responsiveness. To prevent unnecessary fluid administration, it could be beneficial to predict fluid responsiveness before the fluids are delivered. Unfortunately, there is no clear, simple and proven method to predict fluid responsiveness in children. Static measures, mostly CVP, are not appropriate to test fluid responsiveness [37, 39] and we therefore do not recommend fluid bolus or therapy based on these static measures. The published evidence suggests that respiratory variation in aortic blood flow peak velocity {(ΔVPeak / velocity time integral (VTI)} is the

most reliable indicator of fluid responsiveness, but only in ventilated children that fulfil various criteria [61]. Other dynamic methods, like passive leg raising test and liver pressure, have not been adequately assessed in children of all ages [62].

Due to the lack of simple bedside available methods to determine fluid responsiveness and the risk of fluid overload with aggressive approach, the committee recommended the following: recurrent smaller fluid boluses (maximal 5–10 ml/kg) in a short time interval in patients with hemodynamic instability while tracking changes in cardiac output, blood pressure and CVP to confirm or assess fluid responsiveness. Furthermore, we strongly agreed to recommend withholding fluid therapy in patients with an increasing CVP and no significant increase in blood pressure or cardiac output as a result of previous fluid therapy. No specific recommendations regarding estimating fluid responsiveness can be made in patients with raised intracranial pressure or extracorporeal life support (ECLS).

10. Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) is a non-invasive, bedside technique to estimate regional capillary-venous hemoglobin saturation (rSO2). The mean baseline cerebral rSO_2 is > 70% in healthy children. Infants and children with cyanotic heart disease may have a cerebral rSO_2 between 46–57% [63–67]. Moreover, practitioners should be mindful about a considerable variability in NIRS values between commercially available devices. It has been observed that values measured in both monitors INVOS 5100-C® (Medtronic; Boulder, CO, USA) and Foresight Elite® monitor (CAS Medical Systems; Branford, CN, USA) are not interchangeable [68]. Although NIRS is mainly used to measure rSO2 in the brain, there are also reports of its use on other organs. In a study by Dabal et al. [69], it appears that renal NIRS and inferior vena cava desaturations precede rScO2 changes in the prediction of serious cardiovascular adverse events in patients after stage 1 Norwood palliation. Trend in NIRS values may provide valuable physiological information in children with hemodynamic instability although clear (cut-off) values and evidence of benefit are lacking.

The committee strived to define recommendations with regard to this subject and 6 out of 7 recommendation had to be redefined. As a result, the only strong recommendation was to advise against routine use of NIRS in all children with hemodynamic instability. Moreover, the committee agreed not to make recommendations regarding the use of NIRS while treating children in shock, post-cardiac arrest, post traumatic brain injury and infants with hypoxic-ischemic encephalopathy. Lastly, there was no agreement on the clinical usefulness of a decline of cerebral rSO2 under 40–50% or a change in baseline of more than 20% [70].

11. Microcirculation

Microcirculatory assessment by videomicroscopy using side-stream or incident dark field is expensive, and not widely available. Currently it does not allow for assessment of rapid circulatory changes during resuscitation [71]. No studies have defined the normal values of microcirculation in children outside the neonatal period but do report that vascular density seems to decrease with age [72]. So far, published

studies have not defined target values of microcirculatory parameters in critically ill children [72–77]. At this point in time, the committee recommends its use only for research purposes.

The committee also states that many routinely used parameters like capillary refill, peripheral temperature, lactate, may reflect aspects of the hemodynamic condition but do not adequately reflect the microcirculation and cannot be used as such. Although central venous to arterial CO_2 difference could provide additional insight into the microcirculatory condition, we currently recommend against its use to guide resuscitation in critically ill children.

Limitations

We acknowledge the limitations of these recommendation: 1) The most important limitation is the lack of high-quality evidence. These recommendations are based upon expert consensus and review of the published literature including experts' opinions, which can involve subjective value judgments, 2) Both lower and upper limits of age, from term infant > 37 weeks and postnatal age > 4 weeks to 18 years, are artificial - to avoid overlapping with neonatal and adult population specific guidelines, and 3) some of these recommendations may not be appropriate for low-resources settings and may not be applicable in all settings requiring hemodynamic monitoring in children because of their limited availability or expertise.

Nevertheless, despite these limitations the committee members believe that these are consensual expert recommendations based upon literature review and rigorous standardized process of developing expert consensus – followed DELPHI approach, a well-established standardized approach (DELPHI approach) – to reach consensus in such circumstances of limited published evidence to develop evidence-based guidelines.

Future directions

The committee recognize that there is an important lack of knowledge and evidence concerning hemodynamic monitoring in children. There is a great need for: 1) studying the relationship between measured parameters and end-organ perfusion, and 2) evaluating the clinical efficiency and patient outcome when therapy is guided by specific monitoring technologies.

Conclusions

Cardiovascular instability is common in children admitted to pediatric intensive care. Multiple-organ dysfunction is commonly associated with cardiovascular derangements in patients with shock and carries high mortality. Effective hemodynamic monitoring can help in identifying cardiovascular instability early and choosing the appropriate targeted therapy timely. Currently, with the exception of management of shock there are no published HD monitoring guidelines for critically-ill children, and the published evidence remains scarce. These are therefore the first expert consensus recommendations for HD monitoring in critically-ill children with hemodynamic instability. These recommendations can help

clinicians in their clinical practice and may become the frame for future research aiming at providing strong data for evidence-based guidelines in this field.

Declarations

Ethical Approval and Consent to participate:

Not applicable. All authors participated by accepting the invitation.

Consent for publication:

Not applicable. All authors have reviewed and agreed on the final manuscript for publication.

Availability of supporting data:

Supplementary material provided and attached with manuscript submission. Supporting data on consensus development and voting available if required.

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JL, YS and JU conceptualized and designed the development of the whole project. JL took care of the whole methodology and supervised the whole project. YS and JU wrote the first manuscript draft. All authors performed literature search and analysis, interpreted the literature data with their specific expertise, participate in meetings discussions and voted on recommendations and manuscript preparation. Moreover, all authors critically reviewed the manuscript for important intellectual content, approved it in its final version and agreed to be accountable for all aspects of the work. The participation to the project did not entail any honorarium.

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Figures

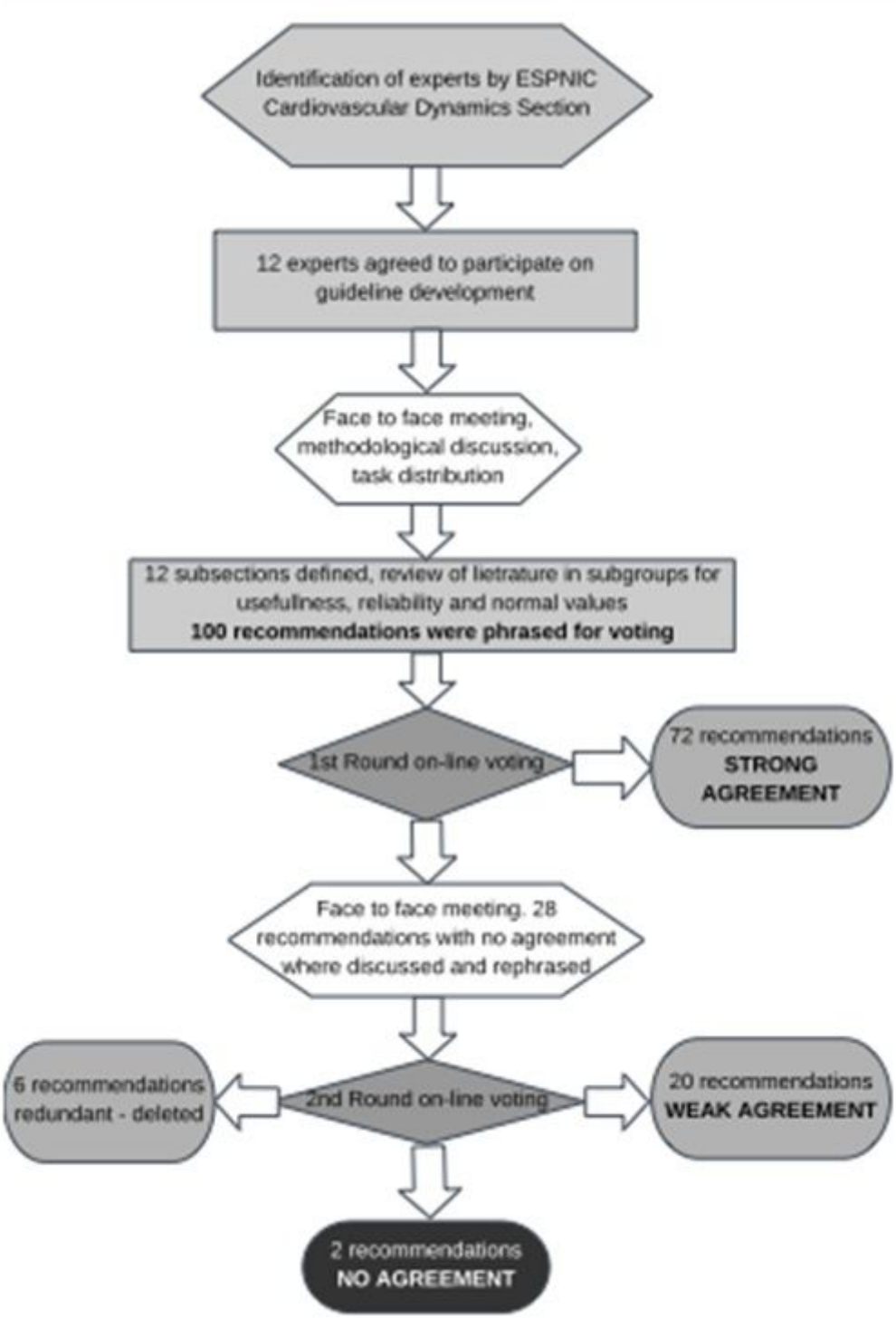

Figure 1

Flow chart of the methodology used in consensus development.

Supplementary Files

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- Additionalfile2Table1.pdf
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