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Management of Neonatal Hypotension and Shock

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ABSTRACT

The current standard approach to manage circulatory insufficiency is inappropriately simple and clear: respond to low blood pressure to achieve higher values. However, the evidence for this is limited affecting all steps within the process: assessment, decision making, therapeutic options, and treatment effects. We have to overcome the 'one size fits all' approach and respect the dynamic physiologic transition from fetal to neonatal life in the context of complex underlying conditions. Caregivers need to individualize their approaches to individual circumstances. This paper will review various clinical scenarios, including managing transitional low blood pressure, to circulatory impairment involving different pathologies such as hypoxia-ischemia and sepsis. We will highlight the current evidence and set potential goals for future development in these areas. We hope to encourage caregivers to question the current standards and to support urgently needed research in this overlooked but crucial field of neonatal intensive care.

1. Introduction

Over preceding years there has been a growing realization that our current approach to the management of babies with cardiovascular instability is limited: limited in our assessment, limited in our understanding of the pathophysiology, and limited in our choice of therapeutic interventions. The current 'standard approach' to circulatory impairment continues to lack any supporting evidence base: intervention with volume followed by dopamine (DA), and observation of the response in mean blood pressure (BP_{mean}) values [1]. This prescriptive approach provides the clinician with great clarity: intervene below a certain BP value, titrate inotropic support to achieve certain BP values, and achieve that value safe in the knowledge that one has addressed the problem. However, while in many situations this approach may result in a positive outcome for the infant, it often fails to address the complexity of the underlying problem, and, in some circumstances may result in undue harm [2].

Deciding on when it is necessary to intervene, or not, is the crucial first step in the management pathway. Enhanced recognition of the underlying condition should allow improved choice of therapeutic strategies, which may range from careful ongoing observation to immediate intervention with volume and/or inotrope. Clinical evaluation, notwithstanding its limitations, in conjunction with readily available continuous bedside monitoring parameters such as heart rate (HR) and BP, intermittent measures such as urine output and point of care lactate values, should provide greater understanding of the underlying circulatory status. Recent objective assessment tools (discussed in other chapters of this series) including echocardiography, near infrared spectroscopy, and non-invasive cardiac output (CO) monitoring may provide an enhanced picture of the underlying pathophysiology. It is important that clinicians understand the specific limitations of each of these assessment tools. Application and utilization of these devices in the most immature infants present their own unique technical challenges. With an increased number of monitoring devices providing increased markers of circulatory status, decision-making becomes more complex but offers the hope that a much more informed rational decision can be made.

One of the major challenges in cardiovascular management is deciding when a numerically low BP value (hypotension) is something that warrants intervention and/or whether an infant with or without low BP is in a clinical state of hypoperfusion (shock). In this chapter, we set out to differentiate between hypotension and shock in the newborn infant and address the various therapeutic options available for the more commonly encountered causes of circulatory insufficiency.

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Abbreviations

BAPM	British Association Perinatal Medicine
CrCP	Critical Closing Pressure
DA	Dopamine
DOB	Dobutamine
EPI	Epinephrine
GNN	German Neonatal Network
LCOS	Low cardiac output syndrome
LEV	Levosimendan
LOS	Late onset Sepsis
MIL	Milrinone
NE	Norepinephrine
ni/i	non-invasive/invasive
TH	Therapeutic Hypothermia
PVR	Pulmonary Vascular Resistance
RDS	Respiratory Distress Syndrome
SVR	Systemic Vascular Resisitance

2. Definitions

2.1. Normal blood pressure and hypotension

Determining normality in a relatively heterogeneous population is challenging. Numerous normative reference ranges exist, which is a relatively unique phenomenon compared to other areas of neonatal care. The method of assessment is critical, especially for the most immature preterm infant where non-invasive (NI) measurements often overestimate the true invasive (I) BP_{mean} value. Lower gestational age (GA), postnatal age, birthweight, and gender all impact BP – thus a "one size fits all" approach defining certain absolute BP intervention values is rather limited. BP progressively increases in both term and preterm populations, especially during the first hours and days of life [3–5]. These dynamic changes are often neglected, especially in the most commonly used definitions of low BP.

One of the most commonly used definitions is a BP_{mean} < GA in weeks - the so called British Association Perinatal Medicine (BAPM) rule [6]. While there is little evidence to support this definition, it seems to be embedded in clinical practice. This definition is somewhat similar numerically to a recent large German Neonatal Network (GNN) cohort study [7]. The GNN data suggest that the BAPM rule may be an overestimate in extremely low gestational age newborns (ELGANs) on the first day. Infants born < 29 weeks were found to have at least one median minimal BP_{mean} 1–2 mmHg below their equivalent GA in completed weeks [7] on the first day of life. Alternative single BP_{mean} values have been suggested. Vesoulis identified iBP_{mean} of approximately 33 mmHg at birth to be "normal" in 35 preterm infants < 28 weeks' GA [8]. However, they excluded high risk infants: those who received inotropic support, those who died within first 14 days, or those who developed severe intraventricular hemorrhage (IVH grade III/IV). The BP_{mean} < 30 mm Hg is based on physiologic aspects regarding cerebral perfusion and impaired autoregulation in low BP states – the so called cerebral critical closing pressure (CrCP). An older study by Miall-Allen identified an increased incidence of significant IVH, ischemic lesions, or death in 33 preterm newborns (GA ranged from 26 to 30 weeks) whose BP_{mean} was less than 30 mmHg for at least 1 h on the first day of life [9]. No severe lesions developed with a BP_{mean} greater than or equal to 30 mmHg. However, this study was conducted some 30 years ago and a number of confounders including pethidine use and inotrope administration were not factored into the analysis. It seems physiologically unlikely that a single BP_{mean} value should exist for a relatively wide gestational age cohort. Recently published measured and calculated cerebral CrCP in ELGANs (GA range 23–26 weeks) indicate lower median (interquartile range) values: measured 20 mmHg (18–25 mmHg) and calculated 19 mmHg (17–22 mmHg) [10].

Some of these definitions have been associated with adverse outcome, but in many instances no association was identified. Much of this variability probably relates to differing definitions, differing assessment methods, different populations, different statistical methods, and the inability to account for potential known (or unknown) confounders. We believe we have to accept the current limitations in definitions and stop searching for simple solutions to more complex issues. Big data analysis may provide an enhanced approach to better define low BP but will also be challenged with associations instead of clear causality [11]. Thus, we need definitions that at least consider the method of assessment, and

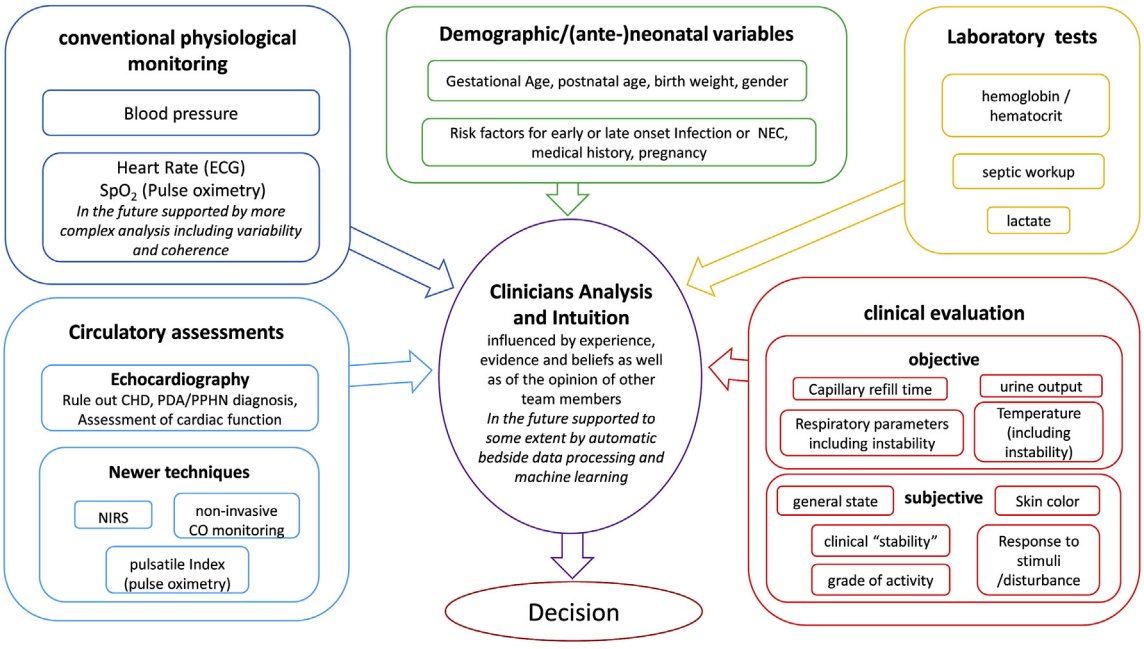


Fig. 1. Complexity of Decision making in Circulatory Management.

both the gestational and postnatal age, to guide us. Perhaps the best way to think of BP during transition is to think of an *evaluation pressure* and a *trigger pressure*. The initial evaluation pressure should be based around gestational age equivalent values on day one. The trigger pressure is the value upon which one decides to intervene and is more complicated. This should not be a single value alone, but rather considered as an important value in the setting of other equally important elements, whether they be clinical, biochemical, or other objective assessment criteria.

2.2. Shock

Shock can be summarized descriptively as circulatory impairment leading to a state of impaired oxygen delivery to tissues. Normal cellular or tissue oxygenation depends on blood flow, oxygen saturation, transport capacity of the blood, and tissue oxygen demand. If this deficiency is for a short time period, cellular metabolism could be impaired but reversible; however, if prolonged, it may become irreversible. Currently, there is no single direct bedside measure of shock. Various technical and clinical surrogates or biomarkers are used to estimate tissue oxygenation and perfusion in neonates and are discussed elsewhere in more detail in this issue. The challenge is that in the early stages of newborn shock many subtle compensatory mechanisms occur that may mask the degree of circulatory impairment. It may be difficult to appreciate these subtle changes, such that by the time shock becomes clinically obvious, the infant is often in an uncompensated state. Relying solely on BP to determine whether or not an infant is in shock is problematic: when the BP is genuinely low, the patient may be in the uncompensated or even irreversible state, but a normal BP does not necessarily imply a normal flow state, and equally, a low BP can be present in the absence of shock. Each of these factors makes management such a complicated area. Fig. 1 provides a schematic overview of the complexity in this decision-making process.

3. Individual scenarios

Low BP and shock can occur in many settings in the neonatal period. It is often helpful to consider the timing of such events, as they provide an insight into the underlying pathophysiology: early, within the first few days of life, and late, beyond this time period. It is equally important to acknowledge the structural, metabolic, and developmental aspects of the cardiovascular system and the changes that occur over the first weeks of life. Table 1 provides a summary of different factors potentially affecting the circulatory status. This may aid with the choice and dose of therapeutic interventions used. Also, it needs to factor in the natural postnatal increase in blood pressure over this time period.

3.1. Early hypotension/circulatory insufficiency

3.1.1. Permissive hypotension

Much has been written about the management of low BP in the extremely preterm infant during the first days of life, but unfortunately there is very little evidence to support or refute these various approaches. We previously described an approach termed 'permissive hypotension' that advocated a global assessment of the infant including various clinical and biochemical parameters in addition to BP values prior to intervening, and not based solely on BP_{mean} values [12]. More recent data from the Epipage 2 nested matched-control cohort study showed a higher incidence of significant brain injury in the low BP group who **did not** receive any antihypotensive treatment (fluid bolus, inotropes, or corticosteroids) compared to those who did for treatment of isolated hypotension defined by BAPM rule [13]. This suggests a worse short-term outcome when an approach of limiting inotropic therapy was advocated. Interestingly, in the subgroup of infants with a minimal $BP_{mean} \leq$ GA-5, survival without severe morbidity was higher for the treated group (Odds Ratio, 3.15; 95% Confidence Interval 1.28 to 7.74). However, there were a number of potential confounders not factored into this analysis. A recent prospective randomized trial attempted to address the problem of intervening or not when the mean BP falls below a certain numeric threshold (BAPM rule). The HIP trial compared a restrictive versus a more conventional approach (volume and DA when $BP_{mean} <$ GA) in preterm infants < 28 weeks' gestation. Recruitment stopped after only 58 patients were included, primarily because of the challenges with enrolment. Approximately one in four infants < 28 weeks had a BP_{mean} less than their GA in the first three days of life which lasted for at least a 15 min period, and this occurred predominantly on day 1. There was no difference in the primary outcome of survival free of significant brain injury at 36 weeks' corrected gestational age in the restrictive compared to the conventional approach (69% versus 62%). This would suggest that a 'wait and see approach' is not unreasonable in this group of extreme preterm infants. The overall incidence of gastrointestinal complications was approximately 20%, suggesting that low BP may be associated with later gastrointestinal complications. However, it should be acknowledged that the sample size was very small, and no long-term outcome data are available. The inclusion of echocardiography as an assessment tool may help better classify patients with low BP who may benefit from targeted intervention. However, trials of low flow states identified on echocardiography have not shown any difference between DA and dobutamine (DOB) use [14], and the only trial aimed at reducing the incidence of low blood flow utilized milrinone (MIL) and found no improvement in outcome [15]. Targeting end organ blood flow, as is occurring with the SafeBoosC-III trial, may provide an alternative physiology-based approach. This trial represents a paradigm shift in the care of preterm infants in the first few days of life. It focuses on maintaining cerebral oxygenation above a certain threshold value. If it falls below this threshold, an assessment occurs, which incorporates cardiovascular, respiratory, and metabolic variables prior to deciding to intervene. Low BP values and/or the presence of a patent ductus arteriosus represent potential cardiovascular factors that may warrant therapy. This trial is currently ongoing (ClinicalTrials.gov NCT03770741).

Table 1
Factors contributing to early cardiovascular insufficiency.

Problem	Potential Hemodynamic Disturbances
Immature Myocardium	Reduced contractility, altered filling, reduced cardiac output, reduced effect of endogenous and exogenous catecholamine
Immature Vasomotor Tone	Decreased SVR, Increased SVR, altered effect of catecholamine
Patent ductus arteriosus	Shunting direction, dependent on SVR and PVR, Altered cardiac output
Sepsis (Inflammation)	Affects SVR and PVR, impaired contractility, reduced intravascular volume due to capillary leak
Hypoxia	Altered SVR, PVR, impaired contractility
Therapeutic Hypothermia	Increased SVR, reduced heart rate and cardiac output
Respiratory Conditions eg RDS, PPHN	High PVR, Right to left shunt, hypoxia
Mechanical Ventilation/Pneumothorax	Impact on cardiac filling and cardiac output
Blood Loss/early cord clamping	Reduced blood volume and oxygen transport capacity, decreased cardiac output

3.1.2. Hypoxia- ischemia

Circulatory impairment in hypoxic-ischemic encephalopathy is common and its pathophysiologic background and specific treatment options were recently summarized [16]. Whereas the initial period following injury is often characterized by a global multiorgan insult, prolonged circulatory insufficiency can lead to further organ dysfunction. Despite the introduction of therapeutic hypothermia (TH) and its documented benefits, there remains a significant risk for mortality and long-term neuro-disability. When circulatory compromise exceeds the limited cerebral autoregulatory capacity, further brain injury may occur [17]. Thus, hemodynamic management provides the clinician with an opportunity to potentially improve short- and long-term outcomes [18]. The severity of right ventricular dysfunction is associated with adverse outcome [19]. Pulmonary hypertension often exacerbates the degree of circulatory compromise, and its presence is associated with abnormal brain imaging on MRI [20]. Management involves primarily reducing pulmonary vascular resistance with a view to enhancing right ventricular performance and ultimately biventricular performance.

TH may effect hemodynamic parameters such as BP, HR, HR variability, and CO [21]. Bradycardia is perhaps the most common feature, and is associated with decreased CO. However, studies evaluating the prognostic value of lower HR or low CO are controversial. As TH reduces tissue oxygen demand, high CO is potentially associated with reperfusion injury [22], and low HR seems to be an appropriate response to decreased oxygen demand [23]. Clinical features of shock, such as skin color, capillary refill time, or urine output, may be difficult to appreciate during hypothermia treatment [16]. This underlines the urgent need for objective assessment of cardiovascular stability in this patient group. Non-invasive CO monitoring and cerebral perfusion monitoring is feasible in the setting of neonatal encephalopathy [24], but further investigation is needed prior to its routine use at the bedside.

Joynt and Cheung recently summarized specific circulatory management options in neonatal encephalopathy [25]. Data from pre-cooling RCTs must be interpreted cautiously. Excessive use of fluid boluses risk overload, and may potentially exacerbate the risk of cerebral edema. DA, DOB, Epinephrine (EPI), Norepinephrine (NE), MIL, and vasopressin, as well as respiratory strategies [oxygen, nitric oxide (NO)] all may have an important role in this setting, especially with associated pulmonary hypertension [25]. The evidence relating the choice of agent is limited to predominantly pre-clinical studies, with the majority of clinical studies mainly observational in design and limited to small numbers. Individualization of therapy is required, as there may be different degrees of myocardial dysfunction, vasomotor dysfunction, and pulmonary hypertension present. Incorporation of echocardiography and non-invasive cardiac output monitoring may assist in individualizing the agent/s used. MIL was associated with greater BP_{mean} deviation below autoregulation-derived values, and this deviation was shown to be associated with brain injury [26]. Hydrocortisone may play a specific role in neonatal encephalopathy, as physiologic responses to stress may be impaired. A recent RCT compared effects of low dose hydrocortisone to placebo on BP in addition to DA in term infants undergoing TH with low BP (defined by BAPM rule) not responding to a fluid bolus [27]. They found increased BP within 2 h comparable to the effects of a DA dose of 15 μg/kg/min accompanied by decreased peak and cumulative dose and decreased duration of cardiovascular support. However, short-term clinically relevant outcomes were unaffected. For the neonate with severe circulatory compromise and persistent pulmonary hypertension (PPHN) resistant to standard treatment, additional options that may be considered including discontinuation of TH and/or the initiation of extracorporeal membrane oxygenation. If these options are to be considered they must be balanced against the realization that TH is thus far the only therapy proven to reduce brain injury in some patients.

Another important aspect to consider is the potential effect of TH on drug metabolism. At the moment, there is no evidence for adapted dosing strategy for cardiovascular active therapy during TH in neonates. However, TH is known to affect pharmacokinetics of certain drugs, including sedatives, which may have a negative impact on cardiovascular status [28]. Animal studies suggest that TH alters the efficacy of inotropic agents, with a decreasing efficacy as the temperature is lowered [29]. It should also be noted that the original insult often has multiorgan involvement with a degree of renal insufficiency which may affect drug clearance and this may need to be considered in treatment and dosing decisions, something particularly relevant for MIL use. Thus, there remains a paucity of data to guide therapy in the setting of therapeutic hypothermia and studies, including pharmacokinetic/pharmacodynamic studies, are urgently warranted in this area.

3.1.3. Septic shock

The clinical presentation of early onset sepsis in the newborn is variable. Typically, cold shock is characterized by peripheral vasoconstriction, cool peripheries, and tachycardia; hypotension is often a pre-terminal event. Warm shock is characterized by peripheral vasodilation and hypotension secondary to endotoxin release. These clinically different presentations may benefit from different therapeutic interventions. The most up to date recommendations for treatment in pediatric sepsis include volume expansion up to 40–60 mL/kg in boluses (10–20 mL/kg per bolus), titrated to clinical markers of CO, and EPI or NE, rather than DA as the first choice vasoactive agents, followed by vasopressin in non-responders [30]. All these recommendations were classified as “weak,“ based on low or very low quality evidence in pediatric studies.

In a recent retrospective study in older children, moderate fluid administration, compared to larger volumes, was found to be associated with improved survival [31]. The Fluid Expansion as Supportive Therapy (FEAST) study showed increased mortality in pediatric participants in receipt of 40 mL/kg of volume (either saline or albumin) compared to those who did not receive a bolus [32]. Another study compared the effects of more intravenous fluid intake (i.e., liberal fluid therapy, defined as 40 mL/kg of fluid over 15 min) versus less intravenous fluid intake (i.e., conservative fluid therapy defined as 20 mL/kg over 20 min) for children with septic shock. There was no difference identified between the two groups, other than increased hepatomegaly in the group in receipt of the larger bolus volume [33].

There is a paucity of data pertaining to volume resuscitation and inotrope administration in septic shock in the newborn infant. Rapid volume administration has been associated with an increased risk of coagulopathy in animal models. In the preterm neonate, volume has been associated with an increased risk of IVH and mortality [34]. Higher versus lower fluid intake regimens have been associated with an increased risk of patent ductus arteriosus (PDA) and chronic lung disease in preterm neonates. These data suggest that volume should be used judiciously, particularly in the preterm infant. There are no newborn trials that allow us to draw any firm conclusions about the agent, the amount, and rate of administration of volume in the setting of neonatal sepsis. However, given the current lack of evidence, it would seem reasonable to use normal saline rather than albumin as a general rule, but balanced/buffered crystalloids could be an alternative to saline based on very low quality evidence [30].

Data pertaining to inotrope use in neonatal sepsis are also limited because of a paucity of clinical trials. Unlike the pediatric and adult world, DA remains the first line agent used in neonatal care. Epidemiologic information from large databases confirms this finding. Most of the randomized trials of cardiovascular support in the newborn have included DA (18 of 21 studies) as the primary inotrope. DA will increase BP compared to volume, placebo, and DOB, and has similar efficacy to EPI and NE. However, its effect on CO is variable (inotrope/vasopressor imbalance) and there are little data suggesting improved clinically relevant endpoints. However, it continues to be used presumably because in a significant percentage of patients it increases BP_{mean}, clinicians are familiar with its use and there is no compelling

evidence to suggest an alternative agent. Baske et al. found comparable efficacy of EPI vs. DA in a randomized trial of neonatal septic shock fluid non-responders [35]. However, five neonates in the EPI group and no neonates in the DA group had reversal of shock after the initial 45 min, and the overall mortality was very high (70/80%) between both groups. EPI is thought to have variable effects depending on the dose administered, with predominantly beta-mediated effects at lower doses and alpha-mediated effects at higher doses. One potential adverse effect of EPI is an increase in serum lactate and metabolic acidosis. NE infusion might be beneficial, especially when there is loss of vascular tone as can occur in warm shock. Rizk et al. found improved BP, urine output, and oxygen dependency in a retrospective study of preterm infants treated with NE for septic shock [36]. It may be considered that a single inotrope may not as effective as a combination of agents. A recent meta-analysis of adult studies suggests that a combination of cardiovascular agents improves outcome [37]. It remains to be seen whether single therapeutic agents or a combination of agents improves outcome in neonates with early onset sepsis.

3.1.4. Cardiogenic shock secondary to congenital heart disease (CHD)

CHD is a rare cause of shock and/or hypotension. However, it is an important and specific contributor to neonatal mortality. Despite its rarity, CHD is the major underlying cause of cardiogenic shock in neonates [38]. Early recognition of cardiac defects results in an enhanced outcome for the infant, as delayed presentations often present with cardiogenic shock and impaired cerebral blood flow.

Historically, DA and EPI were the primary agents used. More recent trials have focused on the role of MIL and levosimendan (LEV), both peri- or post-operatively. Low cardiac output syndrome (LCOS) is a common condition occurring following coronary artery bypass in neonates and is multifactorial in origin. The PRIMACORP study found that high dose MIL resulted in a significant reduction in the incidence of LCOS in the 36 h following cardiac surgery [39]. MIL is now the most common agent used following cardiac surgery. LEV has recently been evaluated for its use post-cardiac surgery, but data on long term safety are lacking [40]. It might improve cerebral oxygenation and systemic perfusion [41] in post-surgical LCOS – comparable to MIL – without an incremental increase in myocardial oxygen demand [42]. However, in a recent double blind RCT by Wang et al. of 187 infants undergoing cardiac surgery, the primary outcome of LCOS did not differ significantly between prophylactic postoperative LEV and placebo (10.6% vs 19.4%). An alternate study by Lechner and colleagues compared the effect of prophylactically administered LEV and MIL on cardiac index in neonates and infants after corrective open-heart surgery [43]. They found no difference between the groups over time.

3.1.5. Rarer causes

Typically, acute shock from blood loss occurs in the delivery room secondary to a substantial fetal antepartum hemorrhage, vasa praevia, feto-maternal transfusion, or a subgaleal hemorrhage. The infant may present relatively well in appearance but pale, or may be significantly distressed, either bradycardic or tachycardic. The clinical situation will often determine the rate at which intervention is required. A well appearing infant may require a blood transfusion administered slowly in the neonatal unit, or the unwell infant may require volume and whole blood transfusion immediately in the delivery suite [44]. The potential role of delayed cord clamping for the depressed term infant is currently being evaluated. Obstructive shock in the setting of a tension pneumothorax is another rare cause of shock typically occurring in the first days of life. Initial management involves treating the air leak, either with needle aspiration or thoracostomy tube insertion, prior to dealing with any underlying cardiac compromise.

3.2. Late onset hypotension/circulatory insufficiency

3.2.1. PDA

A moderate to large PDA can negatively impact the overall circulatory status, and may result in reduced CO, hypotension, and decreased organ perfusion later in life, but also as early as the first days of life [45,46]. PDA-associated hypotension can be difficult to treat, with retrospective data demonstrating that hypotension may be resistant to both volume and inotropes [47]. Early treatment of PDA does result in a lower incidence of hypotension requiring inotropes within the first week [48]. Surgical treatment of PDA may result in severe hemodynamic effects in the immediate post-surgical time period [49]. This post-ligation cardiac syndrome is associated with increased morbidity [50] and potentially increased risk of long-term neuro-developmental impairment [51]. Therefore, close peri- and post-operative monitoring is mandatory [46]. Hydrocortisone might be particularly beneficial in catecholamine-resistant hypotension [52]. Echocardiography in the immediate post-operative period may help to identify infants who may benefit from targeted therapy. However, in a retrospective study of infants following PDA surgical closure, treatment with MIL was not associated with improved outcome, but prospective clinical trials are lacking [53].

3.2.2. Late onset sepsis (LOS)

LOS occurs in up to 25% of extremely preterm infants and can result in significant short-term morbidity and adverse long-term neurodevelopmental outcomes. Abnormalities of heart rate characteristics have been associated with the development of sepsis and may play an important role in the early detection and management of the at-risk infant. However, circulatory instability may occur early and complex continuous analysis of vital signs might further improve diagnosis of both LOS and necrotizing enterocolitis (NEC) [54]. It must be remembered that reliance on BP values needs to take into consideration the significant postnatal changes that occur in BP over the first weeks of life. Also, in the majority of circumstances the BP values available will typically be non-invasive and may be falsely reassuring. In circumstances where there is uncertainty, placement of a peripheral arterial catheter should be considered. Postnatal age reference ranges may serve as a useful guide, but the evaluation pressure here is substantially higher than the GA-based rule. As an example, an infant delivered at 24 weeks who develops sepsis at 4 weeks of age, a BP_{mean} in the high 20's should be very concerning and certainly warrant intervention. This is on contrast to a day 1 BP_{mean} in a newborn delivered at 28 weeks. In a retrospective study of NE use in preterm infants less than 32 weeks, in almost two-thirds of cases the primary underlying diagnosis was sepsis. De Waal and Evans described the hemodynamic changes and their evolution over time in preterm infants with late onset clinical sepsis. The mean (SD) values for right ventricular, left ventricular CO, and Superior Vena Cava flow were high at 555 (133), 441 (164), and 104 (39) mL/kg/min, respectively, at the first assessment [55]. All infants received volume and inotrope(s). COs were found to decrease, and systemic vascular resistance increase in non-surviving infants, whereas there was no change in these parameters in the survivors. Echocardiography may have an important role in the individualization of care in this setting. The choice of optimal agent is guided somewhat by the clinical presentation, and in some circumstances may warrant a combination of agents such as NE and MIL, but again there is no evidence to support such therapeutic choices.

3.2.3. NEC

NEC is multifactorial in origin. Hypotension in the first days of life has been associated with NEC [56]. Hypovolemia and impaired cardiac contractility can occur in the setting of NEC. The first line intervention is typically volume replacement. Vasoconstrictive effects of catecholamine are mediated via alpha adrenergic receptors. In an animal model reduction of perfusion in newborn swine intestine enhanced efficacy of

NE via decreased NO production [57]. As vasopressin uses a different receptor to catecholamine, it might be preferable, but further investigations are needed. NEC itself might cause further hemodynamic changes: intestinal vascular resistance, and microcirculatory and increased abdominal pressure cause reduced inferior vena cava flow. The increased intraabdominal pressure often results in increased ventilatory support, which may have negative connotations on preload and resultant cardiac output. In an animal study myocardial dysfunction was found to be associated with endotoxin release mediated by decreased adrenergic responsiveness [58].

3.2.4. Other causes

Blood loss is a rare cause of hypovolemic shock but can be devastating when it occurs. A catastrophic hemorrhage can occur if an umbilical venous catheter is malpositioned and infiltrates a portal vein. The infant can present with signs of acute blood loss, and despite fluid, red blood cells, and additional blood products, the situation may not be retrievable. Early recognition and prompt intervention may result in an improved outcome. Likewise, an obstructive form of shock can occur in the setting of cardiac tamponade secondary to infiltration of a peripherally inserted catheter resulting in a large pericardial effusion. Prompt recognition and drainage can be lifesaving. In both situations meticulous central line management procedures should significantly reduce the risk of either of these events.

4. Conclusion

Each section above highlighs one consistent factor: limited data upon which to guide intervention. Conducting trials in this area of care has been challenging. This lack of evidence should not result in an inappropriate simplification that leads to an automatic response to low BP values. However, low BP should trigger evaluation of the infant's status, including a spectrum physiologic parameters, clinical status, and more objective assessments of the hemodynamic status. This brings complexity to the bedside decision-making process but should result in a more individualized approach. Despite the importance of hemodynamic management to further improve outcome, there have been no large randomized controlled trials evaluating particular inotropes for specific conditions. The opposite can be said for other trials of cardiovascular intervention such as PDA management. It is difficult to pinpoint exactly why this is the case, but a number of recent trials have highlighted a few important points: the incidence of some of the conditions has improved (e.g., PPHN, transitional low BP), the problem often occurs in the first hours of life, physician willingness to depart from firmly held (though unsupported) beliefs, and finally challenges with obtaining timely informed consent. We will continue to make strides in reducing the prevalence of each of the conditions listed above, but we need to work harder at convincing physicians of the importance of conducting trials in this area, and perhaps consider alternative consent pathways. Otherwise, we will continue to treat patients inappropriately, potentially subjecting them to more harm than good.

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Declaration of Competing Interest

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