Which inotrope and when in neonatal and paediatric intensive care?

Mark A Turner,1 Paul Baines2

INTRODUCTION

Inotropes are medicines that increase the force of cardiac muscle contraction. Inotropes are used to improve cardiac output and so increase oxygen delivery to tissues. There are very few pure inotropes. Most have other effects, which can help or hinder therapy.

Deciding which inotrope to use, and when, is complicated for several reasons.

The evidence base for these medicines is patchy, particularly with respect to how development affects the targets for the medicines and how the body handles the medicines at different ages. The clinical signs and biomarkers we use to guide treatment have not been validated (can we measure them reliably? nor qualified (do the markers predict important outcomes?). The short-term clinical outcomes and biomarkers we can measure readily may not be the aspects that matter. For example, blood pressure (BP) is readily measured, but what may matter more is blood flow to key organs, which is more difficult to measure.

All are in agreement that it is essential to treat extremely low BP with evidence of poor circulation. However, there is uncertainty about which thresholds should be used to direct management of BP, or any other biomarker, if adverse outcomes such as death are to be minimised.

Nevertheless, these medicines are used widely and a range of professionals need to understand how and when to deploy these medicines.

In all cases where a child is critically ill, or could be critically ill, the standard of care is that an adequately experienced clinician follows a standardised care pathway. In the UK, the Advanced Paediatric Life Support scheme provides a good model.1 With respect to circulation, experienced clinicians need to (1) assess the circulation; (2) actively consider fluid resuscitation and then (3) start an inotrope if they judge the circulation to be insufficient after appropriate fluid resuscitation has been started. Inotropes are less effective and some may lower BP, if the intravascular volume is insufficient or if circulating levels of calcium or magnesium are too low.

The aim of this review is to present therapeutic strategies that include inotropes to trainees before or during their first attachment to paediatric/neonatal intensive care. We do not attempt to consider anaesthesia and postoperative care, thermal injury and cardiac intensive care as these are specialist areas in their own right. An overview of medicines used as inotropes is given in tables 1 and 2. We will cover the management on the paediatric intensive care unit first, followed by the neonatal intensive care unit. While the discussion includes initial stabilisation, it is important to recognise that similar principles should be applied at any time during a critical illness, if circulatory failure is suspected.

PAEDIATRIC INTENSIVE CARE UNIT

Different forms of shock (hypovolaemic, anaphylactic, septic, cardiac) may cause cardiovascular dysfunction and different forms of shock may respond differently to therapies. In particular, there are specific guidelines for anaphylactic shock.5 As well as this, adequate fluid resuscitation seems to be important in improving outcome from sepsis but less important in trauma – indeed fluid resuscitation may be harmful in some types of trauma.6 Here, we focus on the initial management of sepsis.

One important study used invasive monitoring to assess haemodynamic status longitudinally in critically ill children with septic shock that did not respond to fluids.4 Two thirds presented with low cardiac output needing inotropes (this can be described as ‘cold shock’). One fifth had vasodilation and a high cardiac output (this can be described as ‘warm shock’), and one fifth had low cardiac output and vasodilation. These patterns changed in some individuals from day to day.7 While this type of monitoring is not feasible in routine practice, it does illustrate the patterns that clinicians will encounter.

Other forms of assessment have been suggested. Functional echocardiography may have a role.5,6,7 The training requirements and clinical impact of functional echocardiography have not been described in children.

Other ways to measure the cardiac output have been suggested, but none are in widespread use because they have not been validated or qualified.8 Interestingly, in adult critical care, randomised controlled trials (RCTs) demonstrate that Swan-Ganz catheter-guided (and so cardiac output-guided) approaches to treatment do not reduce mortality. Other ways in which circulation may be assessed is by base deficit, or more specifically lactate, or superior vena cava (SVC) oxygenation.9 At present, the BP is most commonly used to assess the circulation, although there is a
Table 1  Summary of targets for inotropes

<table>
<thead>
<tr>
<th>Target</th>
<th>Important locations</th>
<th>Main actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α1</td>
<td>Arterioles</td>
<td>Constriction</td>
</tr>
<tr>
<td>α2</td>
<td>Arterioles: mainly coronary and renal</td>
<td>Constriction</td>
</tr>
<tr>
<td>β1</td>
<td>Conducting system of heart</td>
<td>Increase in heart rate</td>
</tr>
<tr>
<td></td>
<td>Atrial and ventricular muscle</td>
<td>Increase in contractility</td>
</tr>
<tr>
<td>β2</td>
<td>Conducting system of heart</td>
<td>Increase in heart rate</td>
</tr>
<tr>
<td></td>
<td>Atrial and ventricular muscle</td>
<td>Increase in contractility</td>
</tr>
<tr>
<td>D1</td>
<td>Postsynaptic receptor in peripheral vasculature</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td>D2</td>
<td>Presynaptic receptor in peripheral vasculature</td>
<td>Vasodilatation</td>
</tr>
</tbody>
</table>

Vasopressin ADH-R  Phosphodiesterase type III  All over  Inhibition of PDE III causes vasodilatation and increased contractility

This is a focused list. See standard textbooks for a comprehensive approach. ADH-R, antidiuretic hormone receptor; PDE, phosphodiesterase. NB, most of these data are from adult sources, so not necessarily relevant to babies and children.

pressing need to conduct research that will allow other parameters to be used. Irrespective of how a child is assessed, the general principles of treatment are to identify the underlying physiological state as well as possible and tailor treatments accordingly. Always seek a specific diagnosis, for example, anaphylaxis, and treat appropriately. Clear goals are important and should be used to guide management. If the child does not improve with specific treatment, reconsider whether the original diagnosis was correct.

While it is important to bear in mind that the diagnosis may be correct and the child has severe illness, it is important to consider that one way to fail to respond to treatment is to receive the wrong treatment. This is why discussion with senior colleagues is valuable and repeated as necessary.

MANIPULATION OF CIRCULATION

The circulation depends on peripheral resistance, cardiac output and intravascular volume. Cardiac output depends on filling (preload), rhythm, contractility and rate. Afterload also affects the efficiency of the heart. Excessive afterload (systemic vasoconstriction) can arise in sepsis, but is more usually a feature of primary cardiac disease such as cardiomyopathy and will reduce the cardiac output.

Systemic vasodilatation will mean reduced BP, though flow in major vessels may well be maintained or increased. One concern is that the channels through which flow occurs in vasodilatory shock may be abnormal non-nutritive blood vessels (‘shunts’) and so although blood flow is increased, tissue oxygen delivery is reduced. This can lead to reduced oxygen extraction, which may be reflected in a high venous oxygenation.

Endothelial responses to inflammation cause the capillary leak seen in many septic children, which may demand large volume fluid resuscitation. Therefore, inotropes are only one aspect of this problem. Fluid resuscitation is important, particularly in sepsis.

Catecholamines are the time-honoured approach to increasing BP in a hypotensive child (in parallel with the adjunctive measures described above). Epinephrine and norepinephrine are long established. Both may produce significant tachycardia (which reduces the time available for cardiac filling, thus reducing preload, reduces the time for perfusion of the coronary arteries and increases myocardial oxygen demand). Dopamine and dobutamine can also be used.

OVERALL APPROACH TO RESUSCITATION

Figure 1 gives a graphical summary of this discussion. The American College of Critical Care Medicine have published guidelines for the treatment of shock in sepsis, which are often used as a starting point for treatment in the UK. The reader is directed to these guidelines for more information. The initial management of shock is fluids and central venous pressure (CVP) placement. Fluids should be used liberally, if sepsis is likely; children can require up to 200 ml/kg during initial stabilisation of sepsis. In cases of suspected sepsis, fluid infusion should be repeated until clinical parameters, such as heart rate and peripheral perfusion, have normalised. In paediatric intensive care unit, it is essential to place a central venous line to allow reliable delivery of inotrope and to measure adequacy of fluid resuscitation by adequate volume resuscitation. In the absence of a central line, the titration of fluid resuscitation may be very difficult (some children with meningococcal disease will receive more than 200 ml/kg of fluid). Most children will need to be sedated, intubated and ventilated for safe and reliable placement of a central venous line.

For shock refractory to fluid, the first-line inotrope in the American guidelines is dopamine. Dopamine combines inotropic action with an increase in systemic resistance – a useful combination in sepsis: sepsis often leads to vasodilatation. Dobutamine would be suggested in cases of shock refractory to first-line inotrope. Dobutamine may lower BP in those without adequate volume resuscitation. In the absence of a central line, the titration of fluid resuscitation may be very difficult (some children with meningococcal disease will receive more than 200 ml/kg of fluid). Most children will need to be sedated, intubated and ventilated for safe and reliable placement of a central venous line.

For shock refractory to fluid, the first-line inotrope in the American practice parameters suggest a clinical classification to guide treatment. Cold shock (presumably due to low cardiac output) should be treated with epinephrine. Warm shock (presumably high cardiac output with low systemic vascular resistance (SVR)) should be treated with norepinephrine. As noted in table 2, norepinephrine acts primarily through α receptors,
which will increase the SVR and allow blood to be diverted away from the peripheral circulation towards important organs.

These practice parameters also suggest guiding treatment according to goals. Protocols and goals are likely to improve outcome. One specific goal suggested by the American guidelines is to target continuously measured mixed venous saturations in the SVC. While this target has not been definitively validated and qualified, it has some support from a clinical trial. The group allocated to treatment targeted to mixed venous saturations in the SVC was given more fluid in the first 6 h and children were more likely to get blood transfusions and receive inotropes. The differences in treatment were more marked earlier on. The mortality reduction may have resulted from early aggressive fluid resuscitation of children rather than the use of the monitoring strategy.

OTHER MEDICINES THAT CAN BE USED
Phosphodiesterase inhibitors
Phosphodiesterase inhibitors are called inodilators, because they are thought to improve both contractility and cause vasodilation. Both of these effects may be useful in some septic children. Specific phosphodiesterase inhibitors, such as milrinone and amrinone, improve cardiac output without troublesome hypotension in short trials of septic children. As well as these effects, the phosphodiesterase inhibitors may improve ventricular relaxation – a lusitropic effect – which can improve ventricular filling and so cardiac output. Diastolic dysfunction is increasingly recognised to be important.

Steroids
There is a longstanding dispute over the role of steroids in septic shock, with only a limited evidence base. Steroid supplementation seems important for maintaining sensitivity to catecholamines. It is not clear how much difference steroids make. However, in a child who is deteriorating or is on escalating doses of inotrope, it is sensible to add hydrocortisone. Recent NICE guideline on bacterial meningitis and septicaemia suggests that in children and young people with shock that is unresponsive to vasoactive agents, steroid replacement therapy using low-dose corticosteroids (hydrocortisone 25 mg/m² four times daily) can be used, but only when directed by a paediatric intensivist.

Vasopressin
This is a pure vasoconstrictor that acts via a receptor to platelet-derived growth factor. Vasopressin (and its analogues) are used in sepsis in adults, where low blood concentrations of vasopressin are found. An RCT of vasopressin in shocked children showed no improvement in outcome and a higher (albeit insignificant) mortality in the treatment group. Vasopressin is used in selected children by some experienced clinicians.

Calcium
Ionised calcium is an important component and may be significantly different from total calcium concentrations (given abnormalities in pH or serum albumin). Calcium may improve contractility and increases vascular tone. Treating a low ionised calcium may be of benefit, especially in younger children with sepsis. Children with meningococcal sepsis may have particularly low concentrations of calcium.

PRACTICAL ADVICE
If inotropes are considered, it is important to have central venous access.
Table 2  Inotropes and other medicines mentioned in the text (see BNFC/Northern Neonatal Formulary/Summary of Product Characteristics for more details)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Pharmacology</th>
<th>Physiological effects*</th>
<th>Dosage†</th>
<th>Practical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>D1, D2, β1, β2 agonist</td>
<td>Increases contractility and vascular resistance. At lower doses, dopamine is claimed to be a vasodilator (acting on dopaminergic and then β-receptors), but at higher doses it has a greater effect on vasoconstriction.</td>
<td>Neonates: 5–20 µg/kg/min PICU starting dose: 3–5 µg/kg/min, maximum dose 20 µg/kg/min May have an effect at 1 µg/kg/min in healthy children</td>
<td>Associated with vasoconstriction so requires a long line or central line</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Predominant β1 agonist</td>
<td>Affects contractility without increasing vascular resistance. Dobutamine has a greater action on β-receptors, producing vasodilatation, tachycardia and chronotropy.</td>
<td>Neonates: 5–20 µg/kg/min PICU starting dose: 3–5 µg/kg/min, maximum dose 20 µg/kg/min</td>
<td>Can be infused via peripheral line</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>α1, α2, β1, β2 agonist</td>
<td>Increases contractility (with increased vascular resistance at higher doses). Theoretically, epinephrine acts more on the β-receptors than on the α-receptors and so should increase BP by increasing cardiac rate and contractility. Dopamine and dobutamine are less potent and have less peak effect than epinephrine or norepinephrine. All may produce tachycardia. Higher doses lead to receptor desensitisation but can be used sometimes.</td>
<td>Neonates: 100–300 ng/kg/min Others: 0.1 titrated up to 1.5 µg/kg</td>
<td>Associated with vasoconstriction so requires a long line or central line</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>α1, α2, β1 agonist</td>
<td>Norepinephrine has a proportionally greater action on the α-receptors and so increases BP by vasoconstriction.</td>
<td>Neonates: 20–100 ng/kg/min initially, up to 1.0 µg/kg/min as base. Others: 20–100 ng/kg/min initially, up to 1.0 µg/kg/min as base. Higher doses lead to receptor desensitisation</td>
<td>Associated with vasoconstriction so requires a long line or central line</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>ADH agonist in arterioles</td>
<td>May replace basal vasopressin levels in cases of severe hypotension.</td>
<td>0.018–0.12 units/kg/h May be used as rescue treatment</td>
<td>Uncertainty about role as rescue or primary treatment</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td></td>
<td></td>
<td>In neonates: 2.5 mg/kg 6 hourly Others: 1 mg/kg 6 hourly</td>
<td></td>
</tr>
<tr>
<td>Milrinone etc</td>
<td>PDE III inhibitor</td>
<td></td>
<td>0.5–0.75 µg/kg/min</td>
<td></td>
</tr>
</tbody>
</table>

Usual concentrations in use at Alder Hey PICU: Epinephrine and norepinephrine – 0.1 µg/kg/min as a starting dose increased to up to 1.5 µg/kg/min. 0.3 mg per kg body weight (ie, 3 mg for a 10 kg child) made up to 50 ml and then run at 1 ml/h will give 0.1 µg/kg/min. Dopamine and dobutamine – 3–5 µg/kg/min increasing to 15–20 µg/kg/min. 15 mg/kg body weight made up to 50 ml and run at 1 ml/h will give 5 µg/kg/min. Vasopressin 1 unit/kg made up to 50 ml run at 1–3 ml/h will get 0.02–0.06 units/kg/h. NB norepinephrine doses here expressed as base. 1 mg norepinephrine acid tartrate = 500 µg base.

*Not all these effects have been validated in neonates or some older age groups.

†Short half-lives due to breakdown.

There are several reasons for this recommendation. First, it is important to ensure that the heart is adequately filled with blood, but not overfilled. One measure of this is the CVP. Second, in conditions where inotropes are needed, peripheral perfusion is poor with sluggish peripheral venous return. Inotrope return to the central circulation will be unreliable. Third, tissue drips and extravasation may be a problem. If inotropes are delivered peripherally (while a central line is being sited), then it is sensible to use more dilute concentrations so that they may run with higher infusion rates of 5–10 ml/h. If the facilities to gain central access are not available when the child presents, then it is essential to discuss transfer to an appropriate centre with experienced colleagues. In the meantime, intraosseous access can be invaluable.

When considering management beyond initial stabilisation, all aspects of the circulation should be considered (including circulating volume, preload, myocardial contractility and afterload).

NEONATES

Cardiovascular management of neonates needs to consider whether or not the baby is in a transitional circulation or not. A transitional circulation includes the ductus arteriosus. The haemodynamics change once the duct is closed. Other factors influencing choice are developmental stage (contractility, regulation) and disease (infection, often associated with vasodilatation, or hypoxia).

Echocardiographic assessment can help. However, functional echocardiography in neonates requires a high level of skill with continuous supervision by paediatric cardiologists. It has not yet been shown to improve outcomes in clinical practice.

TRANSITIONAL CIRCULATION

The main complication of the transitional circulation is that shunts between the pulmonary and systemic circulation in the heart and lungs or
through the duct lead to a dissociation between systemic blood flow and brain blood flow. If the aim of treatment is to maintain oxygen delivery to the brain and, if measures of peripheral circulation are the only form of assessment, then this dissociation can make assessment difficult.16 On the other hand, measurements of brain circulation are technically demanding, have not been validated or qualified and cannot be recommended outside the research setting.

Consider fluid status but bear in mind that most brand new babies are not fluid depleted (babies likely to have fluid depletion include those with obvious blood loss, eg, from vasa praevia). Excessive fluid and sodium intake in the first few days after preterm birth are associated with prolonged oxygen dependency.17 Neonates with hypoxia often have renal failure and may require fluid restriction.

See figure 2 for a summary of this discussion. Two strategies have been suggested to treat circulatory insufficiency in the hours after birth:

**Strategy 1: target postductal, systemic circulation**

This is based on the assessment of BP and systemic signs. Some units use age-appropriate thresholds for BP. Others make an assessment that includes BP and systemic signs (perfusion, lactate and urine output). BP is objective but may not be related to long-term outcomes.

Systemic signs are not well validated or clearly related to outcomes. If invasive BP measurement is not possible, systemic signs can be used to guide therapy. Dopamine has more effect on BP than dobutamine,18 and is the first-line medicine in many units. Dobutamine is an important medicine in this context, if there are concerns that vasoconstriction will add to the problems faced by an immature myocardium. Epinephrine has similar effects to dopamine on BP and brain blood flow.19 Thresholds for starting epinephrine and other inotropes vary in the absence of studies about how thresholds for treatment relate to outcomes.

**Strategy 2: target brain circulation**

Various approaches to monitoring brain circulation have been proposed. None have been validated for use outside research settings. Most studies that target brain circulation in clinical practice measure SVC flow. If SVC flow is targeted, then limited RCT data suggest using dobutamine first, then dopamine, and then epinephrine.20 Hydrocortisone may have indirect effects on contractility or rescue subclinical adrenal insufficiency. Many clinicians have found it to be a useful rescue medicine. There is some evidence to suggest that it may be a useful first-line inotrope,21 but safety concerns mean that many clinicians are at equipoise for this treatment at the time of writing.

**SPECIAL CONSIDERATIONS**

These include:

- Persistent fetal circulation/pulmonary hypertension (PHT). When pulmonary pressures are high, it is important to maintain systemic BP. Inotropes with effects on vascular resistance can affect pulmonary arteries as well as systemic circulation. So in a baby with PHT, the first choice might be dobutamine. However, these babies often require multiple inotropes to maintain adequate systemic BP. Management of PHT should also focus on avoiding and correcting acidosis, hypoglycaemia and hypothermia. Medication such as inhaled nitric oxide can be used as well. It is important to ensure the baby is transferred to a suitable centre if there is a significant risk of PHT.
- ‘Renal dopamine’. There is some evidence that dopamine affects renal artery blood flow but no evidence that this improves outcome.

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**Figure 2** Overview of approach to managing a premature neonate with circulatory failure. At each step, review progress and move onto the next step if clinical goals are not reached (eg, mean arterial pressure at an appropriate level for gestational age, lactate falling). Points to consider at each step are also shown. Assessments should be repeated frequently. If the treatment is not effective, discuss with a senior colleague and reconsider the diagnosis.
in neonates. A meta-analysis of 61 randomised trials, including 5 trials in neonates, found that urine output and serum creatinine improved in the 24 h after low-dose dopamine (≥ 5 μg/kg/min) was started but that low-dose dopamine had no effect on survival or need for renal replacement. The use of ‘renal dopamine’ is at the discretion of the attending physician.

- High frequency oscillatory ventilation (HFOV): high mean airway pressures can be associated with low BP (presumably due to poor intrathoracic venous return). Inotropes (following close attention to intravascular volume) are an important adjunct to HFOV, especially if there are underlying reasons for poor contractility.
- Patent ductus arteriosus (FDA) can be associated with shock in severe cases.
- Congenital heart disease. Low BP can be a feature of left-sided congenital heart disease that has not been identified antenatally. Check for hepatomegaly and poorly palpable femoral arteries.

POST-TRANSITIONAL CIRCULATION

Here, for example, during necrotizing enterocolitis (NEC) or fulminating late onset sepsis, the physiology is more straightforward. Intravascular volume may be depleted, mainly through third space losses so it is important to have a low threshold for fluid resuscitation. However, systemic vasodilatation is an important factor so that inotropes with vasconstriction are likely to be useful. Beware the older neonate with a duct that becomes clinically significant during sepsis. In the absence of a duct, two strategies can be used.

Strategy 1: target contractility
Dobutamine.

Strategy 2: broader target
Dopamine/dobutamine/epinephrine.

SPECIAL SITUATIONS

Heart failure due to a persistent duct. In this case, consider diuretics. Inotropic support may be required during sepsis or other intercurrent illness.

TOP TIPS IN ALL AGE GROUPS

Common deficits in care are

- lack of appropriate fluid supplementation;
- delay in starting inotropes despite clear evidence of poor circulation;
- lack of attention to other aspects (electrolytes).

Abnormalities of rhythm and afterload may cause shock and these may need to be manipulated to increase cardiac output. For example, it can be difficult to distinguish supraventricular tachycardia (SVT) from the sinus tachycardia of ill children. SVT has a sudden onset but this may be unrecognised if at home.

OVERVIEW

Despite the lack of evidence, or even age-appropriate physiological knowledge, the clinician has to make choices. The approaches outlined here are compatible with practice in many centres. As research proceeds, it will be important to investigate the balance between safety and efficacy for inotropes. For example, dopamine has effects on the immune system and the endocrine system. The relationships between these short-term effects and long-term outcomes have not been studied.

‘Aggressive’ inotrope therapy may save lives. Aggressive inotrope therapy does not mean use the highest doses possible as quickly as possible. It means assess the haemodynamic status of your patient carefully, intervene early, titrate judiciously and pay attention to other factors that affect cardiovascular function.

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REFERENCES


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