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REVIEW

Fluid management in the critically ill child

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Abstract Fluid management has a major impact on the duration, severity and outcome of critical illness. The overall strategy for the acutely ill child should be biphasic. Aggressive volume expansion to support tissue oxygen delivery as part of early goal-directed resuscitation algorithms for shock—especially septic shock—has been associated with dramatic improvements in outcome. Recent data suggest that the cost-benefit of aggressive fluid resuscitation may be more complex than previously thought, and may depend on case-mix and the availability of intensive care. After the resuscitation phase, critically ill children tend to retain free water while having reduced insensible losses. Fluid regimens that limit or avoid positive fluid balance are associated with a reduced length of hospital stay and fewer complications. Identifying the point at which patients change from the '*early shock*' pattern to the later '*chronic critical illness*' pattern remains a major challenge. Very little data are available on the choice of fluids, and most of the information that is available arises from studies of critically ill adults. There is therefore an urgent need for high-quality trials of both resuscitation and maintenance fluid regimens in critically ill children.

Keywords Fluids · Children · Intensive care

Introduction

Intensive care units (ICUs) came into existence in response to a variety of needs, such as respiratory support (initially in polio epidemics), treatment of shock (e.g. meningococcal disease) and care following increasing complex surgery [1, 2]. Intravenous fluid therapy has been a key element of the more intensive care provided to each of these groups of patients. There are important differences between the optimal fluid therapies in each of these scenarios and, perhaps more importantly, within the same patient at different stages in the natural history of his/her critical illness.

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Basic principles of fluid management

Total body fluid (TBF) consists of approximately one-third extracellular fluid (ECF) and two-thirds intracellular fluid (ICF). The ECF consists of both interstitial and intravascular fluid [3–7]. The relative size of the intravascular volume changes as the child grows. A term neonate has a circulating volume of around 80 ml/kg; this has been reduced to 60–70 ml/kg by adulthood [8].

Role of the circulating fluid volume

Intensive care doctors think in simple terms. For example, we view the primary role of the circulating intravascular volume to be the transport of oxygen from the lung to the tissues and the return of carbon dioxide from the tissues to the lungs [9]. Any threat to the size of the effective intravascular volume (haemorrhage or capillary leak) threatens this primary role of oxygen delivery. When oxygen delivery is insufficient, sophisticated compensatory mechanisms, such as increases in the heart rate and/or stroke volume, are activated to increase the flow rate (cardiac output) [10]. Further adaption is provided by selective redistribution of blood flow to the most vital organs (heart and brain). This occurs at the cost of further reductions in blood flow to other organs, especially skin, gut and kidneys [11].

Systemic inflammation and increased micro-vascular permeability

Critical illness is typically accompanied by the systemic inflammatory response syndrome (SIRS). This clinical syndrome

of pyrexia, tachycardia, tachypneoa and leucocytosis is present in around 75 % of unselected critically ill children [12]. SIRS is common even in the absence of infection, especially following major surgery or trauma [13]. A crucial consequence of SIRS is an alteration in endothelial permeability [14]. This has important implications for fluid therapy administered in the ICU.

In 1896, Ernest Starling from University College London proposed the famous model of capillaries as semi-permeable membranes, with fluid shifts reflecting the resultant of osmotic and hydrostatic pressures [15]. During SIRS or sepsis, capillary permeability increases with a resultant net loss of fluid from the circulation to the tissues [16, 17].

The molecular basis of this 'capillary leak' is now being understood. VE-cadherin is a major protein complex in cell junctions. In the normal state, this protein complex interacts with the p120-catenin receptor and stabilises tight cell junctions—thereby impeding capillary leak. However, during SIRS/sepsis, circulating cytokines induce endothelial activation and dysfunction. The endothelium loses its ability to induce vasoconstriction; it becomes less able to resist local coagulation factor activation and expresses numerous molecules that encourage leukocyte adhesion. Endothelial activation is also associated with the loss of cell surface VE-cadherin, causing the opening of inter-cellular gaps and capillary leak. Recent work has demonstrated that the Slit and ROBO-4 proteins combine to provide a stabilising effect on the VE-cadherin system. This raises the possibility of therapeutic manipulation of the degree of capillary leak with synthetic proteins [17, 18] (Fig. 1).

Bolus fluid resuscitation in shock

Intravenous administration of extra fluid to '*top-up*' the circulation increases cardiac output by the Frank–Starling relationship. Again, Ernest Starling described the key physiology we still use today at every bed space based on observations of isolated perfused dog hearts. He described the increase in stroke volume seen with increased left ventricular stretch [19, 20]. The result is that fluid administration increases cardiac output, tissue blood flow and oxygen delivery to vital organs (unless the heart is already failing). These core observations are translated into the current recommendations for haemodynamic support in septic shock in children. Consensus guidance recommends administering bolus aliquots of 20 ml/kg very rapidly (up to 60 ml/kg in ≤15 min). The volume given is titrated to observable indicators of adequate organ perfusion. These include capillary refill time, conscious level and urine output [21].

Although the evidence base behind this guidance is not robust, it is the most widely accepted reference for management of the critically ill child. An update of this guideline is currently under review and is due for publication in 2013 (Fig. 2).

Bolus administration of fluids has been assessed as a core element of newer resuscitation algorithms. These '*early goal-directed*' algorithms include tight feedback loops of searching for evidence of residual perfusion defects and pursuing rapid correction of abnormal values. These protocols have been associated with dramatic reductions in mortality from septic shock in adults and children [22, 23]. Detailed studies of serial pro-inflammatory cytokine profiles in shock patients demonstrate that aggressive resuscitation attenuates the subsequent inflammatory response, with reduced coagulation activation and a lesser degree of endothelial injury [24]. In short, good, early resuscitation is anti-inflammatory [25].

Impact of increased interstitial fluid

Our enthusiasm for rapid volume expansion in shock states must be tempered by knowledge of its potential downside. Excessive interstitial fluid reduces the efficacy of gas exchange at alveolar and tissue levels [26].

Oxygen diffusion efficiency is closely related to the thickness of the alveolar–arterial membrane. Interstitial oedema compromises oxygen delivery from the outside world to the mitochondrion at two main sites—across the alveolar membrane, where the diffusion of gases in hindered, and in tissues, where oxygen extraction from capillaries and carbon dioxide clearance are impaired [27] (Fig. 3).

Microcirculatory dysfunction in sepsis

Sepsis disrupts much of the fine local control of blood flow by mediators, including induced nitric oxide [28, 29]. This 'microcirculatory dysfunction' results in heterogeneous perfusion that is uncoupled from local tissue oxygen demands [30, 31]. It is believed that regional tissue hypoperfusion together with mitochondrial dysfunction result in tissue '*dysoxia*' [32–34]. Microvascular dysfunction compounds the detrimental effect of interstitial oedema on the flow of oxygen across the alveolar–arterial membrane and into tissues [27] (Fig. 3).

Several therapies to improve microvascular dysfunction have been investigated in trials. Interventions that boost early systemic haemodynamics hold promise [34]. The results of clinical studies suggest that early fluid expansion (<24 h) in sepsis can increase the proportion of perfused small vessels, whereas later fluid administration does not have this effect [35].

Dubin et al. used vasopressors to achieve a range of mean arterial pressure targets in septic patients. The cardiac index and other haemodynamic parameters increased, but no significant changes in the sub-lingual micro-vascular flow index were seen. Significant inter-individual variations were observed, again possibly reflecting variability occurring during the natural history of sepsis [36].

As yet, no interventions that target microcirculatory dysfunction are in clinical practice, but the available

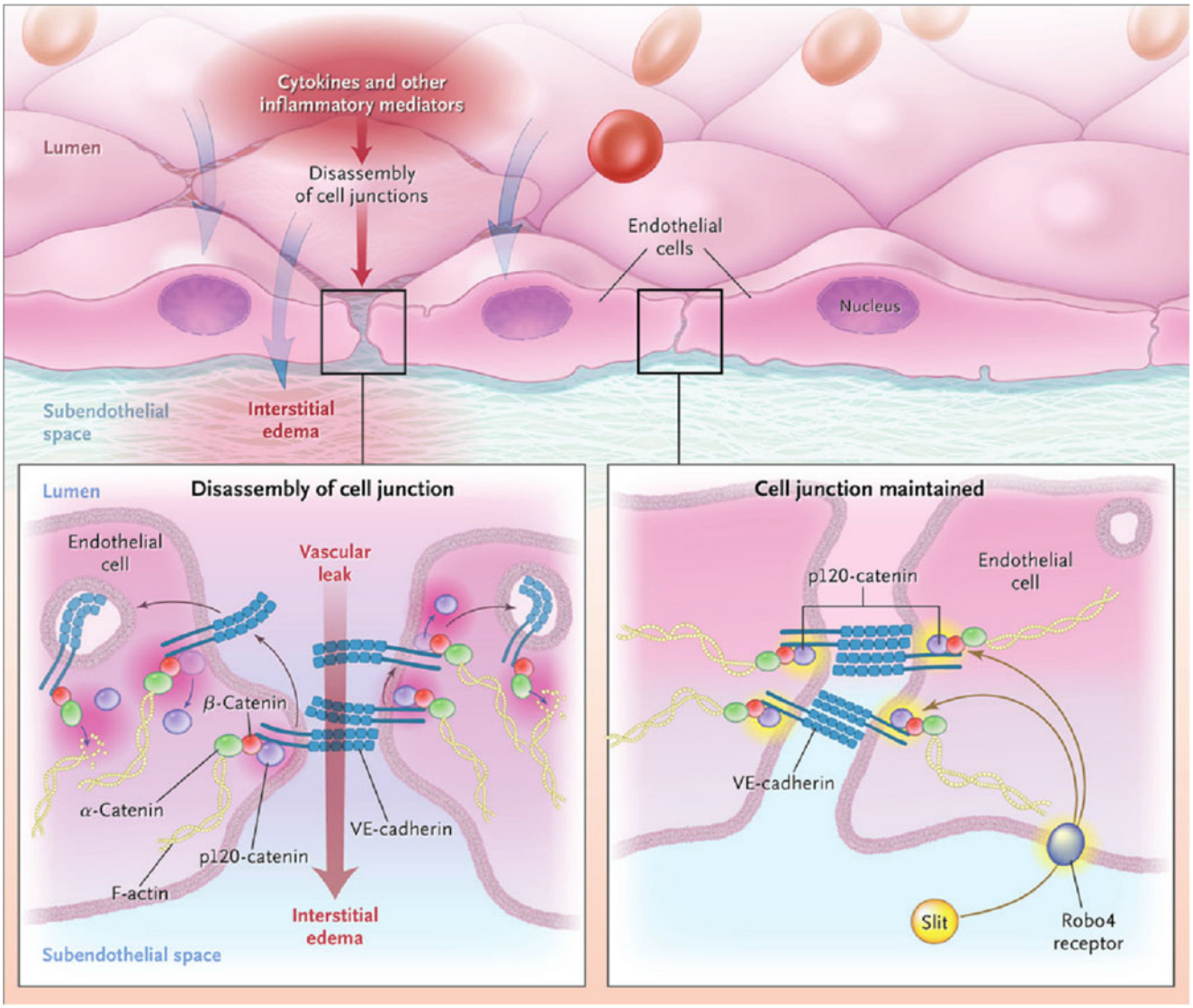

Fig. 1 Cytokines and other inflammatory mediators induce gaps between endothelial cells by causing the disassembly of intracellular junctions and/or alterations in the cellular cytoskeletal structure or by directly damaging the cell monolayer. This creation of gaps can result in microvascular leak and tissue edema. By binding the Robo4 receptor, the slit protein prevents the dissociation of p120-catenin from the VE-cadherin in response to inflammatory mediators, with the result that VE-cadherin remains on the plasma membrane. Thus, the disassembly of intercellular junctions is prevented, and barrier integrity is maintained. Figure is provided by courtesy of Warren Lee et al. [17] and used with permission

data are consistent with a biphasic response which is in line with published results on early goal-directed therapy (EGDT) [34].

The balance between effective resuscitation and the risk of fluid overload

The challenge is clear. In shock states, we have to re-establish tissue perfusion rapidly without overdosing into potentially harmful states of increased interstitial fluid. There is no definitive way of determining this balance, but timing, case-mix and the choice of fluids and resources available for respiratory support all influence the efficacy and safety of fluid resuscitation.

Recent history of goal-directed resuscitation

The last 40 years has seen numerous attempts to improve the efficacy and reduce the risks of resuscitation. A serious and systematic attempt to optimise resuscitation was undertaken by Shoemaker's group in the 1970s who used pulmonary artery catheters to measure cardiac output and identified detailed haemodynamic patterns associated with survival from critical illness. These patterns were then proposed as targets in resuscitation algorithms for the management of

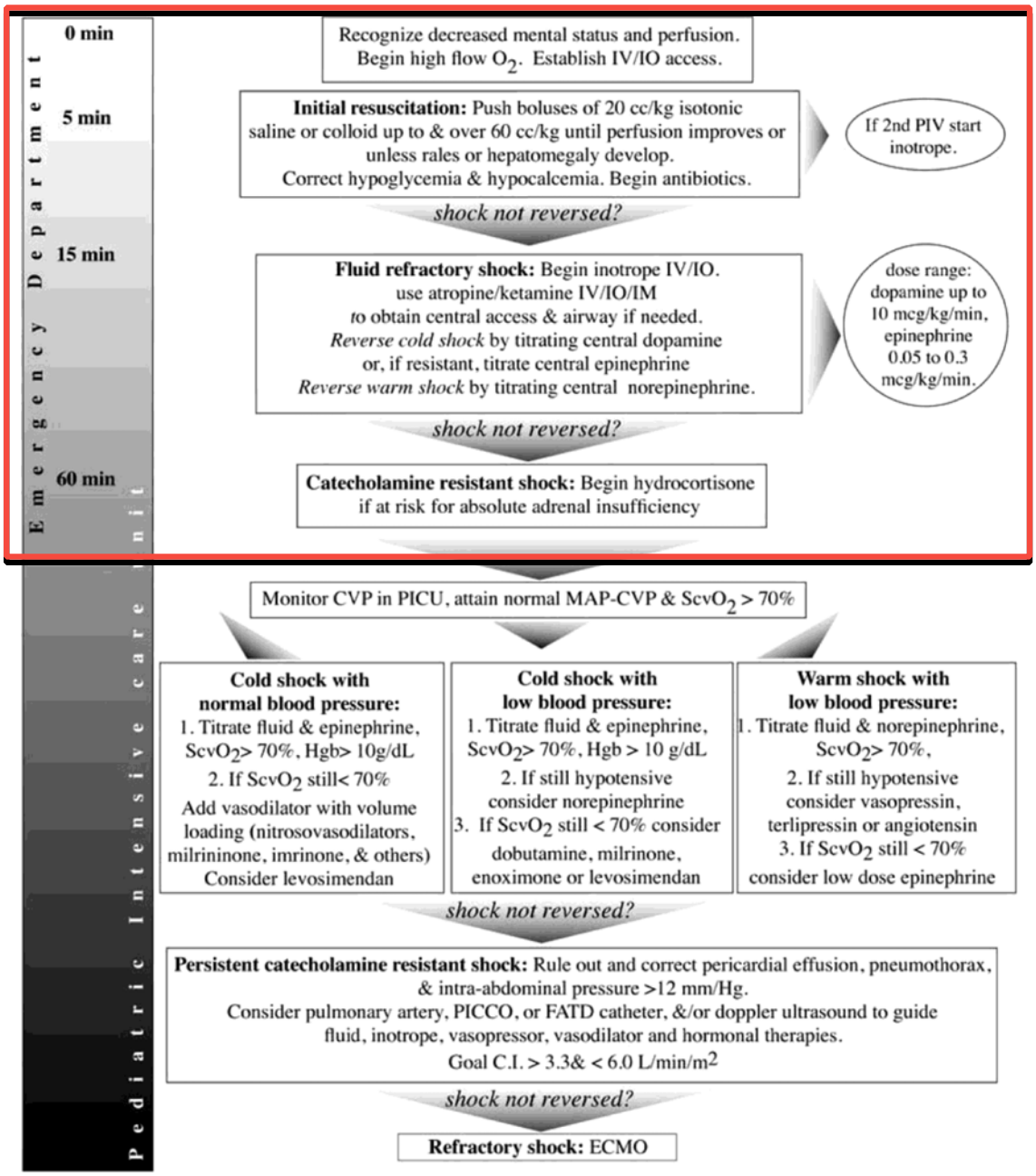

Fig. 2 American College of Critical Care Medicine (ACCM) guidance algorithm 2007 for time-sensitive, goal-directed, stepwise management of haemodynamic support in infants and children. The physician proceeds to the next step if shock persists. First-hour goals: restore and maintain heart rate thresholds and achieve capillary refill of ≤2 s and a normal blood pressure in the first hour/emergency department. Support oxygenation and ventilation as appropriate. Subsequent intensive care unit goals: if shock is not reversed, intervene to restore and maintain normal perfusion pressure [mean arterial pressure (*MAP*)–central venous pressure (*CVP*)] for age, central venous O_2 saturation of >70 % and cardiac index (CI) of>3.3 and <6.0 l/min/m^2 in pediatric intensive care unit (*PICU*). *Hgb* Hemoglobin, *PICCO* pulse contour cardiac output, *FATD* femoral arterial thermodilution, *ECMO* extracorporeal membrane oxygenation, *CRRT* continuous renal replacement therapy, *IV* intravenous, *IO* interosseous, *IM* intramuscular, $ScvO_2$ superior caval vein oxygen saturation, *PIV* peripheral *IV*. Figure is provided courtesy of Brierley et al. [21] and used with permission

septic patients in the emergency department in the early 1980s. Initially, observational studies suggested shorter resuscitation times and fewer shock-related complications [37–39].

The early promise of this approach was subsequently challenged by three factors. Firstly, high rates of complications of pulmonary artery catheters were reported [40]. Secondly, the extent of potential harm of increased extravascular lung water

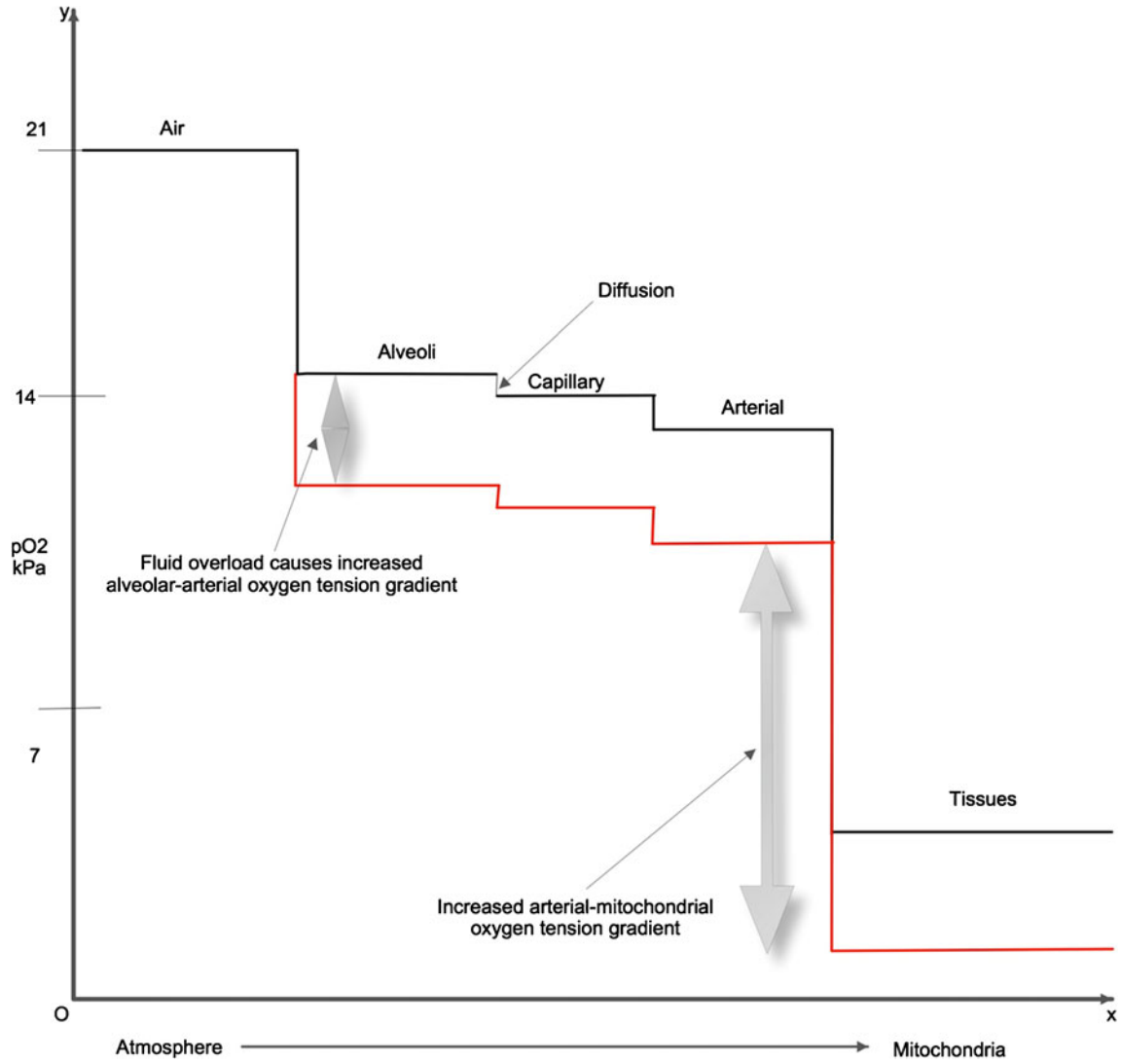

Fig. 3 Impact of fluid overload on oxygen cascade. Partial pressure of oxygen decreases at the level of alveoli, capillary, arteries and tissues. *Black line* Normal gradation in partial pressure of oxygen, *red line* impact of fluid overload at the level of alveoli and tissues

in the subset of patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) was recognised [41]. Consequently, the benefits of this approach were not demonstrable in high-risk surgical patients [42]. The situation was further complicated by studies that suggested that the benefits of reaching oxygen delivery targets depended on how much treatment was required to achieve these targets [43, 44].

A meta-analysis of 21 randomised controlled trials of resuscitation algorithms in critical illness highlights that efficacy is restricted to interventions *before* established organ failures in *high-risk patients* [45]. There is an inherent risk to low-risk patients or to those in established organ failure from early-targeted resuscitation, such as fluid overload and increased complications [46].

Both these elements—*early* and *targeted* interventions to the highest risk patients—have been explored in recent studies in severe sepsis. The landmark study by Rivers et al. [22] demonstrated the efficacy of adding a target of superior caval vein oxygen saturation ($ScvO_2$>70 %) to standard measures in the first 6 h of resuscitation from septic shock in adults. $ScvO_2$ is a measure of the global adequacy of oxygen delivery measured through a standard central line rather than a pulmonary artery catheter. Values above 70 % provide evidence that oxygen delivery is exceeding tissue consumption. The 16 % absolute risk reduction for death in this study remains the largest impact on sepsis mortality of any intervention yet reported [22]. Similar results were reproduced in paediatric sepsis from a team in San Paulo, Brazil: 28-day mortality was 11.8 % in the $ScvO_2$ goal-directed algorithm group compared to 39.2 % in the standard American College of Critical Care Medicine (ACCM) algorithm control group (p<0.002) [23].

The results of these studies are consistent with *early* aggressive resuscitation *targeted* at those cases, with evidence of inadequate oxygen delivery being effective. The very high control group mortalities in both of these breakthrough studies have meant that the relevance of these results to lower risk populations must be considered carefully while mega-trial results are awaited [47]. These studies are on-going [21, 48–50]. In the meantime, it seems that the presence of a feedback loop to keep reviewing the adequacy of resuscitation may be the key feature of this approach—and the effect may not be specific to $ScvO_2$. For example, recent work suggests that resuscitation targeted at reducing raised serum lactate levels is equivalent to targeting $ScvO_2$> 70 %. This would have clear practical advantages in view of the difficulty of obtaining $ScvO_2$ estimations in children [51–54].

A recent audit by the UK Paediatric Intensive Care Society Study Group showed that nearly 60 % of children diagnosed with sepsis are not being resuscitated according to the 2002 ACCM guideline. It may be that clinical improvement methodology represents the most effective next step in shock resuscitation rather than more complex goal-directed algorithms [50, 55].

FEAST

A recent large study (n=3,141) of three different fluid resuscitation regimens (no bolus fluid vs.0.9 % saline bolus vs. 4.5 % albumin bolus of 20–40 ml/kg) in children with fever and evidence of poor perfusion superficially seems to contradict our confidence in fluid resuscitation. Control group mortality was 7.3 % whereas that of the saline or albumin groups was 10.5–10.6 %. There are many potential explanations for this dramatic result (including the lack of availability of positive pressure ventilation), but one of these might simply be another version of the message we learned in the early 1990s—that aggressive resuscitation only benefits those at high risk (not a control group mortality of 7 %) when it is started early. Extended pre-hospital times might well have contributed to the lack of efficacy of this study [56].

Impact of fluid resuscitation on the renal function

Glomerular filtration is dependent on renal perfusion pressure [57]. Bolus fluid augments both mean arterial blood pressure and renal perfusion pressure. However, in a rat model of haemorrhagic shock Legrand et al. demonstrated that fluid resuscitation does not improve direct measures of renal oxygenation [58]. These observations have been reproduced in a sheep model wherein bolus fluid infusion augmented cardiac output, but did not influence renal blood flow and oxygenation [59].

Although these studies suggest no benefit of fluid resuscitation on renal oxygenation, the paediatric EGDT study describes a lower incidence of new onset renal failure in the intervention group when compared to controls (6.7 vs. 26.7 %, p<0.02) [23].

Rivers et al. did not specifically report on renal dysfunction. However, the intervention group had reduced severity of multi-organ dysfunction scores (MODS) when compared to controls (mean ± standard deviation 5.1±3.9 vs. 6.4±4.0; p<0.001) [22]. These studies imply a further mechanism is at work during EGDT that might enhance organ function independent of the effects on tissue oxygenation [24].

Later fluid management

Restrictive maintenance fluid strategy in the ICU

Insensible fluid losses are greatly reduced in patients admitted to ICUs because inspired gas is warmed and humidified, pyrexia is typically avoided and movements are greatly reduced by anaesthesia often with neuromuscular blockade. In addition, a critically ill child has a reduced capacity to excrete free water [60].

Decreased free water clearance is also described as the syndrome of inappropriate antidiuresis (SIAD). SIAD is manifest secondary to the unregulated secretion of argenine–vasopression (AVP), the elevated basal secretion of AVP despite normal regulation of osmolality or the suppression of AVP secretion or undetectable levels of AVP with a reset of the serum sodium level to lower than normal. Common causes of SIAD include central nervous system and malignant disorders and pulmonary disease [61].

SIAD and decreased insensible losses mean that hyponatremia occurs readily in critically ill children. Cerebral oedema and hyponatremic encephalopathy are less well tolerated in young children than adults due to the larger brain to intracranial volume of the former. Deaths from hyponatremia after routine surgery have been well documented. Isotonic solutions mitigate the risk of hyponatremia [62].

The National Patient Safety Agency in 2007 warned: "*The use of intravenous hypotonic solutions puts children at a greater risk of developing life-threatening hyponatraemia than other types of fluid and should be prescribed with caution. All children are at risk. Wherever possible, carefully managed oral fluids are preferable to intravenous fluid therapy*" [63].

As a result hypo-osmolar maintenance fluids, such as 0.18 % sodium chloride with 4 % glucose, have disappeared from routine use [64].

The extent to which excessive free water may cause harm has been considered in two recent large studies. Neither of these studies randomised between fluid strategies, but a

positive fluid balance was observed to be an independent predictor of worse outcome in both the Vasopressin in Septic Shock Trial (n=778) and the Sepsis in European Intensive Care Units study (n=3,147) [65, 66]. Importantly this effect remained after case-mix adjustment—reducing the probability of a 'para-phenomenon effect'.

In the Fluid and Catheter Treatment Trial (FACTT) 1,000 adults with ARDS were randomised to a strictly protocolised conservative or liberal fluid management strategy . The conservative group had improved gas exchange and higher ventilator-free and ICU-free days (p=0.001). Interestingly, this result did not equate to a statistical difference in survival rates at 60 days—perhaps reflecting the impact of underlying disease on mortality [67].

Murphy et al. [68] studied 212 patients with ALI following septic shock. Patients who received adequate initial fluid resuscitation had lower mortality than those who did not [32.2 vs. 60.6 %; odds ratio (OR) 0.20, 95 % confidence interval (CI)0.08–0.48, p<0.001)] Those who received conservative late fluid management had lower mortality than those who received more liberal later fluid (24.8 vs. 62.6 %; OR 0.16, 95 % CI0.07–0.36, p<0.001). Lowest hospital mortality was noted in those who achieved both adequate early and conservative late regimens (18.3 %) [68] (Fig. 4).

In the last decade, paediatric ICUs (PICUs) have used these adult studies to incorporate restrictive fluid strategy into practice. Arikan et al. reported on 80 critically ill children in whom the peak fluid overload percentage was independently associated with higher oxygenation index (p=0.009), longer duration of ventilation (p=0.004) and longer length of PICU (p=0.008) and hospital stay (p=0.02) [69]. Valentine et al. [70], on behalf of the Paediatric Acute Lung Injury and Sepsis Investigators (PALISI) network, have assessed net fluid balance in children with ALI against the groups in the FACTT. Among the 168 children reviewed, increasing fluid balance on day 3 was noted to be inversely proportional to ventilator-free days (p=0.02). The fluid balance pattern was similar to that of the liberal arm of the FACTT [70].

Relationship of fluid overload to acute kidney injury and mortality

The incidence of acute kidney injury (AKI) in children admitted to the ICU can be as high as 60 % [71]. These cases are more likely to remain in a positive fluid balance. This relationship has been demonstrated in several large cohort studies. In the large Sepsis Occurrence in Acutely Ill Patients study (SOAP; n=3,147), 36 % of patients had acute renal failure at some point in their ICU stay; of these, 30.2 % died compared to 12.1 % of the non-acute renal failure group (p<0.01) [72]. Positive fluid balance was an independent predictor of death. Similarly, in the Programme to Improve Care in Acute Renal Disease (PICKARD) study, 618 critically ill patients with AKI were examined. The mean percentage fluid accumulation was lower in survivors than in non-survivors (8.8 vs. 14.2 %; p<0.001). The odds ratio for death for patients with fluid overload compared to those without fluid overload was 2.07 (95% CI1.3–3.4) [73]. Hence, renal failure appears to increase ICU mortality, at least in part, as a result of fluid retention.

Importantly, among patients who receive renal replacement therapy (RRT), late initiation (>2 days after ICU admission) is associated with higher ICU mortality (late 61.5 % vs. early 39.4 %; p<0.01) [72].

Although it is generally agreed that there is a need to '*keep* '*em dry*', management strategies to achieve this have not been well researched. A recent systematic review reports that loop diuretics improve urine output and shorten the duration of RRT but that they do not have an effect on the eventual recovery of renal function or mortality of the patient [74]. The initiation of early RRT has been advocated [75].

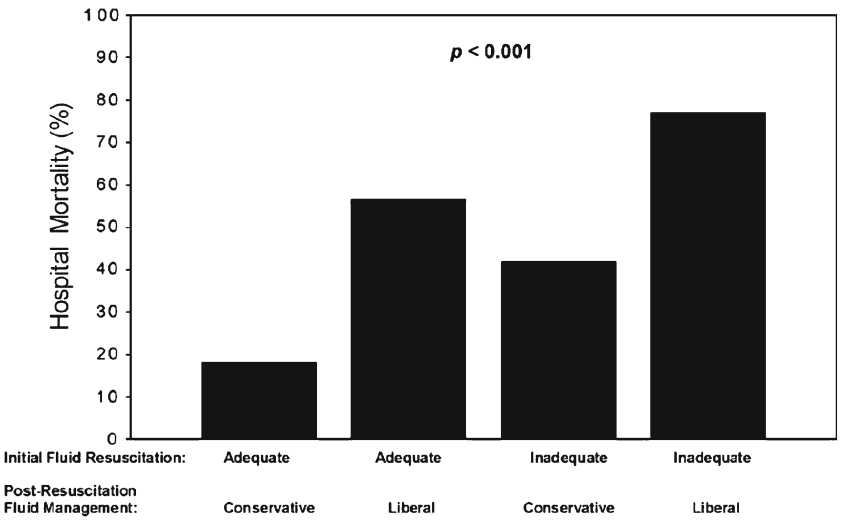

Fig. 4 Hospital mortality according to whether or not patients achieved adequate initial fluid resuscitation, conservative later fluid management, both, or neither. Figure is provided courtesy of Murphy et al. [68] and used with permission

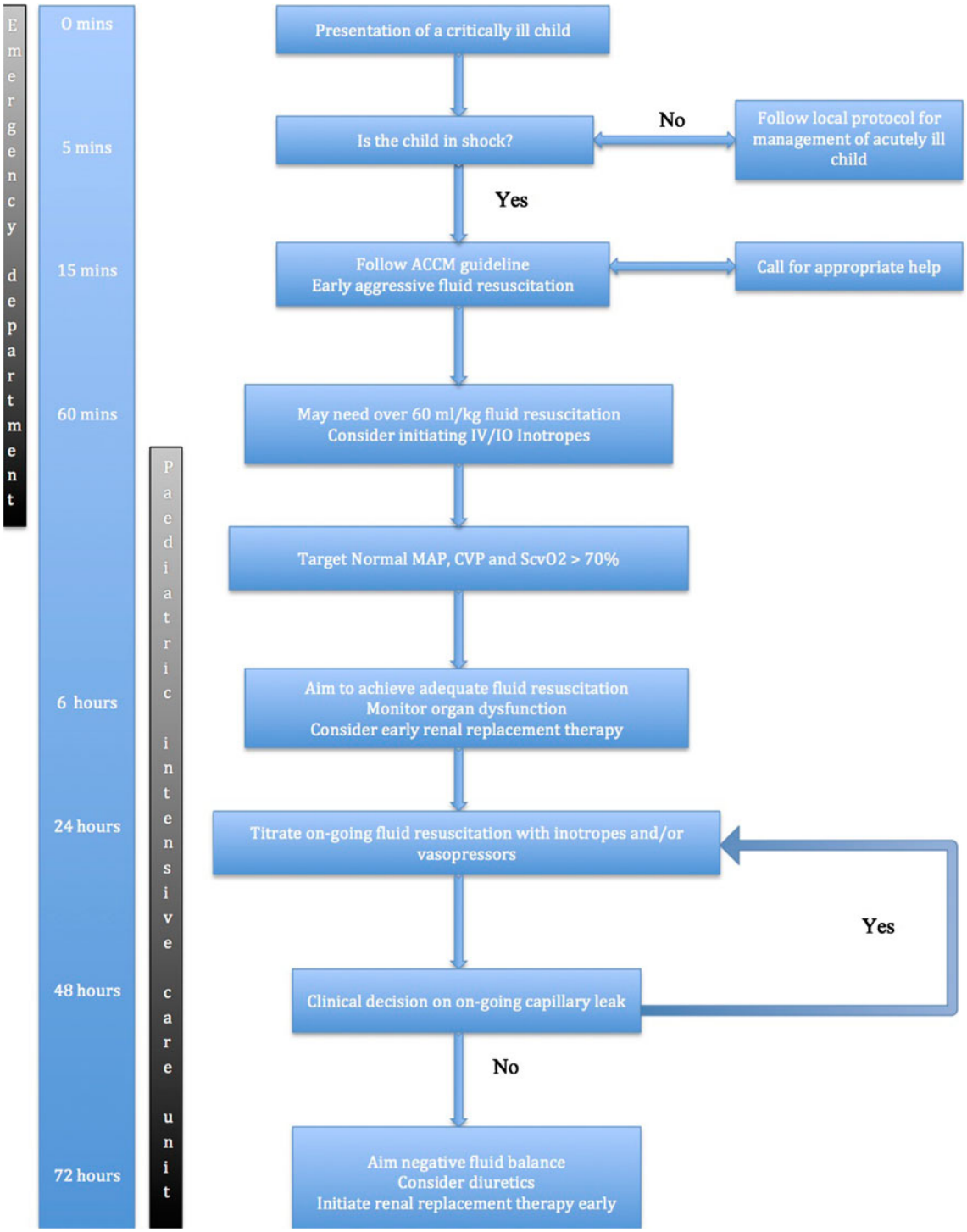

Fig. 5 Algorithm for management of fluid balance in the critically ill child

Choice of fluid for volume expansion

Numerous animal studies have supported either crystalloid or colloid as preferable for resuscitation in various species with various aetiologies of shock [76–78]. The Saline vs. Albumin for Fluid Evaluation (SAFE) multicentre randomised controlled mega-trial compared resuscitation with albumin and saline (n=6,997). The relative risk of death in 28 days for patients in the albumin group compared to the saline group was 0.99 (95 % CI 0.91–1.09). However, this did not end the debate as subgroup analyses revealed an advantage for severe sepsis managed with albumin. Case-mix adjusted odds ratio for death for albumin versus saline was 0.71 (95 % CI 0.52–0.97, p=0.03). The same group is now assessing this result in a further trial [79–81].

Interestingly, an opposite effect is observed in head trauma cases (relative risk of death by 24 months with albumin 1.63; 95 % CI 1.17–2.26, p=0.003) [82].

While the results of numerous studies of artificial colloids have suggested minor effects on the times to shock reversal in comparison to crystalloids, the effect are largely small and short-lived. There are indications of an increased risk of AKI, especially with hydroxyethyl starches (HES) [83]. The first large-scale study in 798 adults with severe sepsis recorded increased mortality with HES compared to ringer's lactate (relative risk 1.17, 95% CI 1.01–1.36, p=0.03) [84]

Myburgh et al. reported on 7,000 critically ill adult patients requiring fluid resuscitation randomised to HES or normal saline. No difference in the risk of death was noted (relative risk 1.06, (5 % CI0.96–1.18), however 7 % of the HES group needed RRT compared to 5.8 % in the saline group (p=0.04) [85].

To summarise these data—the choice between crystalloid and colloid in septic shock is still open with some data in favour of each [86, 87]. Starch-based solutions should probably be avoided. Our practice is to use a 4.5 % human albumin solution if immediately available in sepsis cases and normal saline in trauma cases [88, 89].

Choice of maintenance fluid

As early as 1932, Hartmann showed that normal saline causes acidosis in children [90]. Much later, Ringer's lactate was shown to cause a decrease in osmolality [91].

Although studies have looked at the most appropriate fluid for maintenance, no clear guidance is available in this regard other than the caution on hypotonic solutions [92]. At our hospital, we use isotonic solutions for maintenance with close monitoring of electrolyte parameters.

Potential value of hyperosmolar therapy

Cerebral oedema is a risk in the traumatic brain injury patient due to primary and secondary brain injury. Mannitol and hypertonic saline have been used in this group. The aim is to reduce cerebral edema by creating an osmotic gradient. Osmolar therapies are well established in the treatment of cerebral oedema although evidence for their efficacy is limited. Both therapies are used nearly equally in the paediatric intensive care settings as shown by a recent study [93].

Resuscitation of the major trauma patient

Doctors working in armed conflict zones were the first to recognise that victims of major trauma with uncontrolled haemorrhage had better outcomes when resuscitated with lower blood pressures. This has led to the principle of damage control resuscitation and integrates permissive hypotension, haemostatic resuscitation and damage control surgery [94].

The results of animal trails have been encouraging, with a systematic review by Mapstone et al. reporting a lower relative risk of death of 0.37 (95 % CI –0.27 to 0.52) with hypotensive resuscitation compared to normotensive resuscitation. (p< 0.00001) [95].

Data from large human trails are lacking. Preliminary results from a randomised control trial suggest that hypotensive resuscitation may be a safe and feasible option. Larger adult studies and paediatric studies are necessary before incorporation of this principle into paediatric practice [96].

Conclusion

Fluid management of the critically ill child still has facets that are contentious. We agree that bolus fluid resuscitation is crucial to a child in shock. However, current evidence suggests that *early goal-directed therapy* is only beneficial in the high-risk patient before the development to organ failure. Following resuscitation, restrictive fluid strategy garners widespread consensus.

We propose an algorithm for fluid management in the critically ill child drawn from current literature (Fig. 5).

Although there is no clear-cut guidance on the appropriate fluid to use for bolus fluid resuscitation, recent literature raises concerns on the usage of HES. Guidance on maintenance fluid prescriptions is clearer. We follow the National Patient Safety Agency guidance and avoid hypotonic solutions. The art is to deliver a biphasic fluid strategy: resuscitate early, resuscitate hard and then '*keep 'em dry*'.

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