Consensus recommendations for pediatric fluid resuscitation in Belgium

Milou Blits [a], Tom Schepens [b], Bart De Breuker [c], Elisabeth LIM Duval [b] on behalf of the Be-PIV-group

[a] Department of Pediatrics
[b] Department of Pediatric Critical Care Medicine
[c] Department of Critical Care Medicine, Antwerp University Hospital.

els.duval@uza.be

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Abstract

Fluid resuscitation is an important part of pediatric critical care therapy and shock treatment. To date, there are no Belgian guidelines on this topic. As children's (patho) physiology differs from adults, existing recommendations for adults should not be carelessly adapted. Although no superiority has been found for a specific type of fluid, strong recommendations against dextrose-containing fluids, hypotonic fluids and starch-based colloids have been uniformly accepted due to their safety profile and/or cost. There is also considerable debate about rate and volume of fluid boluses needed during resuscitation where a distinction is often made based on access to pediatric critical care units. As these are widely accessible in Belgium, we do not make this distinction but advocate early contact or transfer.

If a child requires fluid resuscitation, we recommend using boluses of 10 ml/kg balanced crystalloids with careful reassessment after each bolus to assess fluid responsiveness as well as signs of fluid overload. The choice should be tailored to the child´s underlying illness since specific situations may necessitate specific treatment, as is shown in the proposed algorithm.

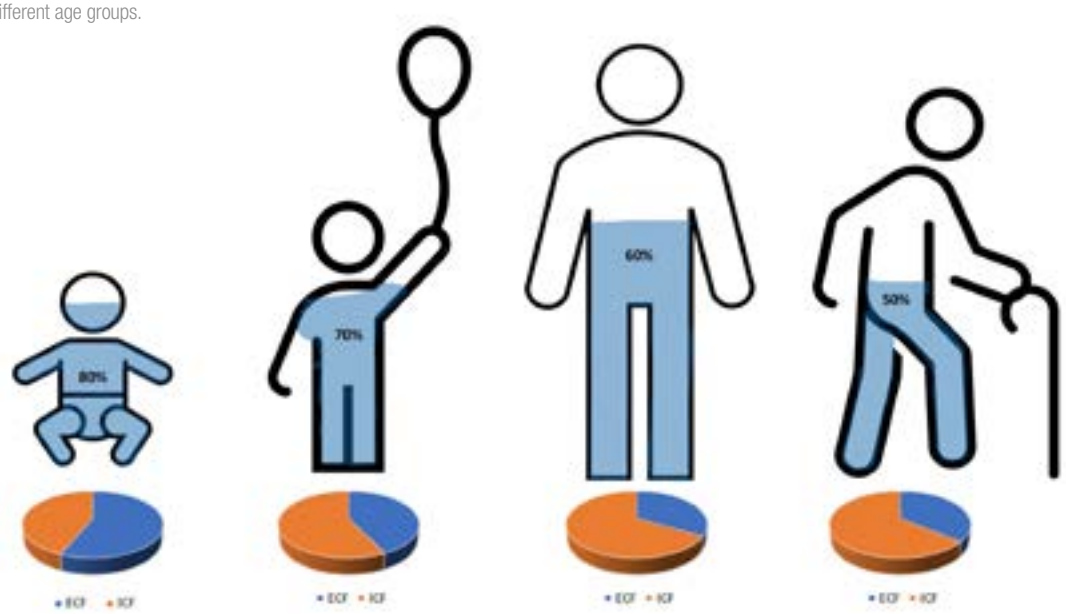
Introduction

Resuscitation is described as supporting or taking over the vital functions in a critically ill patient. One of the most important examples in the acute medical management of critically ill children is fluid resuscitation. Fluid deficit may be elicited by excessive fluid loss, insufficient fluid intake, a combination of both, or fluid redistribution. The most common cause in children is hypovolemia due to gastro-enteritis, but also sepsis, where shock can be multifactorial in etiology. Quick fluid resuscitation remains a key component in both children and adults although the pediatric recommendations were attenuated after publication of the FEAST trial reporting increased mortality (1, 2).

For fluid resuscitation three types of fluids can be used: crystalloids, colloids or blood products. Besides in the setting of trauma, there is no conclusive evidence on superiority of one type of fluid, although there seems to be increasing data in favor of using balanced crystalloids (3). A lot of ambiguity remains regarding the desired quantity or speed of infusion as well.

No guidelines exist on this topic in Belgium. In this narrative review, we give an overview of existing literature and guide the Belgian pediatrician through the plethora of fluids by means of a simple algorithm. We aim to harmonize the quality of fluid resuscitation in children in accordance with the current state of the art.

Figure 1: Percentage of total body water (number) changes with development. The pie charts at the bottom show the variation in extracellular fluid (ECF) and intracellular fluid (ICF) in different age groups.



Background

Essential physiological concepts

Children are not just small adults, a mantra that is also reflected when it comes to fluids. On average, water represents >80% of the body mass in newborns. It decreases during the first two years of life and at a slower rate during childhood to reach an adult level of 60-65% by the age of puberty (figure 1). In adults up to 70% of total body water (TBW) is intracellular fluid (ICF), the remaining being extracellular fluid (ECF), composed of interstitial fluid and plasma. In children these percentages vary with age, e.g., newborns have relatively more ECF (45% of their weight) which has implications in the dosage of water-soluble drugs.

Body water balance is defined as the equilibrium between body water gains and body water losses. In normal conditions, water is mostly lost through urine at a rate of at least 2 ml/kg/hr in neonates and 1-2 ml/kg/hr in children, as opposed to 0.5-1 ml/kg/hr in adults. Water is excreted through other routes as well, such as the skin, respiratory tract and stool. These losses, difficult to quantify, are bundled under the name insensible losses (ISL). Children's ISL are higher than those of adults since their respiratory rate is higher as is their body surface area to body mass ratio. In children up to 2 years of age, ISL can even be twice as high.

Thirst and hormonal mechanisms are both responsible for maintaining a proper water balance, where kidneys play a pivotal role in regulating both volume and composition of the ECF. To achieve this function, they are influenced by several hormones, especially anti-diuretic hormone (ADH), but also aldosterone and natriuretic factor. In normal circumstances, a water deficit increases plasma osmolality which stimulates the osmo-receptors in the hypothalamus. Drinking is stimulated and release of ADH increases, promoting water-reabsorption at the distal part of the nephron, leading to smaller volumes of concentrated urine. In the event of a water excess, the opposite effect will result in a decrease in intake and the production of larger volumes of diluted urine.

Fluid dysregulation during illness

Young children are more susceptible to dehydration due to a relatively larger TBW, renal immaturity, and inability to meet their needs independently. As dehydration progresses, hypovolemia ensues. If not corrected in a timely fashion, inadequate tissue perfusion and ischemic end-organ damage, the hallmark of shock, follow.

Shock can generally be defined as an acute dysfunction in which the circulatory system fails to provide adequate oxygen and nutrients to meet the metabolic demands of vital organs. Shock can and does exist without hypotension, especially in children. Although all types of shock encompass some degree of absolute or relative hypovolemia, they can be classified according to their underlying pathophysiological mechanism (Table 1). Nevertheless, the cause of shock can be multifactorial, e.g., in septic shock, hypovolemia, cardiac dysfunction and abnormal vascular tone frequently occur simultaneously. The most common cause of shock in children remains hypovolemia.

Table 1: Types and causes of shock.

Categories	Aetiology	Cause
Hypovolaemic	Loss of fluid	Haemorrhage, gastroenteritis, volvulus, burns, peritonitis, diabetic ketoacidosis
Distributive	Vessel abnormality	Septicaemia, anaphylaxis, vasodilating drugs, spinal cord injury
Cardiogenic	Pump failure	Arrhythmias, cardiomyopathy, myocarditis, valvular disease, myocardial contusion
Obstructive	Flow restriction	Tension-pneumothorax, cardiac tamponade, pulmonary embolism

Without prompt intervention, shock inevitably leads to multi-organ failure and ultimately death, making early recognition and appropriate therapy vital. A developing shock can clinically present with altered mental status, tachypnea, tachycardia, delayed capillary refill time (CRT), cool or sometimes warm extremities and clammy mottled skin. The variety and combination of symptoms, or the lack thereof, can be misleading and a high level of suspicion should be maintained during assessment. The World Health Organization defines pediatric shock when the following criteria are met: cold extremities with CRT greater than 3 seconds and weak, fast pulse (4).

Tonicity and balance

Tonicity details the concentration of non-penetrating solutes as compared to plasma and describes the effect intravenous (IV) fluids have on the osmolality of the ECF (table 2). Administration of hypotonic fluids decreases it, causing an influx of water into the cells. Hypertonic fluids such as NaCl 3%, force water out of the cells. Isotonic fluids will cause no osmotic driving force, cells will neither shrink nor swell. Although Dextrose 5% is an iso-osmolar solution, once infused its sugar breaks down and is transported intracellularly, leading to an in vivo hypotonic solution.

Table 2: Tonicity and its effect on extracellular fluid (ECF).

Type of fluid	Effect on extracellular fluid
Hypotonic · Dextrose 5-10% · Glucion 5-10%® · Glu 2,5%/ NaCl 0,45% (1/2-1/2) · Glu 3.3%/ NaCl 0,3% (2/3-1/3)	Decreases osmolality and ECF
Isotonic · NaCl 0,9% · Plasma-Lyte® · Hartmann's solution®	No effect
Hypertonic · NaCl 3% · NaCl 5%	Increases osmolality and ECF

Different fluids have different therapeutic targets.

- Isotonic fluids are typically employed both for *fluid resuscitation* (to correct an acute intravascular fluid deficit), and for *fluid replacement* of extracellular losses which cannot be compensated by oral fluid intake alone.
- Hypotonic fluids were historically used as *maintenance fluids* since they generate an osmotic driving force allowing water to move intracellularly, intended to replace water and electrolyte needs due to ISL and diuresis. Their use recently became the topic of intense debate.
- Hypertonic fluids are specifically used to decrease intracranial pressure (ICP) in children with impending herniation, or to correct severe hyponatremia.

Balanced solutions are isotonic fluids with an electrolyte composition which closely mimics plasma levels. Consequently, they maintain electrical neutrality with a total amount of free dissolved cations equal to that of free dissolved anions (figure 2). Most available fluids achieve electrical neutrality through added organic anions such as acetate or lactate (which rapidly metabolize to the anion bicarbonate) (table 3). In contrast, NaCl 0.9% contains a supra-physiological concentration of Cl^-, leading to a strong ion difference (SID or the difference between the cations (mainly Na^+) and anions (mainly Cl^-)) of zero, far beyond normal values (25-35 mEq/L). Addition of NaCl 0.9% to plasma will decrease plasma SID and therefore directly and independently decrease plasma pH leading to a hyperchloremic metabolic acidosis. In addition to acidosis, hyperchloremia alone is linked to renal injury: it reduces renal blood flow, causes renal vasoconstriction and reduces the glomerular filtration rate. Although other mechanisms may exist, most studies suggest the use of chloride-rich fluids is related to worse renal outcomes (3, 5).

Crystalloid versus colloid, a dying debate?

Both crystalloids and colloids are plasma volume expanders aiming at re-

Table 3: Content of fluids used in resuscitation.

	Plasma (ECF)	Isotonic non-balanced crystalloid	Isotonic Balanced crystalloid		Colloid				
		NaCl 0.9%	**Hartmann's solution®**	**Plasma-Lyte®**	**Albumin 5%**	**Gelofusine®**	**Geloplasma®**	**Voluven®**	**Volulyte 6%®**
Osmolarity (mOsm/l)	291	308	273	296	255	308		308	286
Na^+ (mmol/l)	135-145	154	130-131	140	130-160	154	150	154	137
K^+ (mmol/l)	4-5	0	4-5	5	< 2	0	5	0/0	4
Cl^-(mmol/l)	94-111	154	109	98	105-137	120	100	154	110
Ca^{++}(mmol/l)	2.2-2.6	0	1.5	0					
Bicarbonate (mmol/l)	23-27	0	0	0	0	0	0	0	0
Lactate (mmol/l)	1-2	0	28-29	0	0	0	30	0	34
Acetate (mmol/l)	0	0	0	27	0	0	0	0	0
Gluconate (mmol/l)	0	0	0	23	0	0	0	0	0
Octanoate (mmol/l)	0	0	0	0	32	0	0	0	0
Na^+-caprylate (mmol/g alb)					0.08	0	0	0	0
SID	± 35	0	±22	±42	Variable	±34	±54	0	±34

solving a depleted circulating volume. *Crystalloids* contain water-soluble electrolytes and non-electrolytes (e.g., dextrose), and lack proteins and insoluble molecules. They are classified by tonicity and whether they are balanced or not. Examples of crystalloids often used during resuscitation are NaCl 0.9%, Plasma-Lyte® and Lactated Ringer's® or Hartmann's solution®. Ringer's original saline solution was invented in the early 1880's by Sydney Ringer. In the 1930's, Hartmann added lactate for the purpose of treating acidosis, since lactate mitigates changes in pH by acting as a buffer for acid: Ringer's lactate® or Hartmann's solution® was born. *Colloids* are heterogeneous mixtures where the dispersed particles are intermediate in size between those of a solution (very small particles) and a suspension (large non-dissolving particles). Examples of colloids are 5-20% Albumin, gelatin-based fluids (Gelofuscine®, Geloplasma®), dextran or hydroxyethyl starch-based fluids (Volulyte®, Voluven® or HAES-steril®).

Since crystalloids contain small particles, they diffuse more readily into the interstitial space, thus greater volumes might be needed to expand the vascular space with a risk of edema. The bigger molecules of colloids remain in the intravascular space longer, which could theoretically favor fluid reabsorption into the plasma, reducing the risk of volume overload. Also, colloids could hypothetically account for less pulmonary edema by keeping a higher plasma oncotic pressure through creating less dilutional hyponatremia. Extensive research has been done to support this theoretical advantage of colloids during resuscitation, but literature remains inconclusive. Notably, a Cochrane review in 2018 showed no difference in survival or hospitalization (6). When using higher volumes of colloids (>15 ml/kg) in patients with severe sepsis, mortality was even increased. Also the renewed model of the endothelial glycocalyx has provided us with a better understanding of endothelial permeability, disproving the theoretical advantage of colloids (7).

In addition, colloids are more expensive, have a risk of anaphylaxis and some are unsuitable for vegetarian patients. Crystalloids are inexpensive and non-allergenic.

Fluid resuscitation 2.0

What?

A general advice advocating isotonic crystalloids was issued by the National Institute for Health and Care Excellence (NICE), the American Academy of Pediatrics (AAP) and the European Resuscitation Council (ERC) (3, 8, 9). We follow their advice.

Shock is not one entity but the end stage of many different pathologies. Hence, treatment should be based on the underlying etiology, pathophysiology, age, context, comorbidities and available resources. Nevertheless, some general remarks and a practical approach regarding fluid resuscitation can be advocated (Figure 3).

Figure 2: Plasma electro-neutrality with strong anions left and strong cations right. (SID = Strong ion difference, composed of weaker anions, meanly bicarbonate, albumin and phosphates).

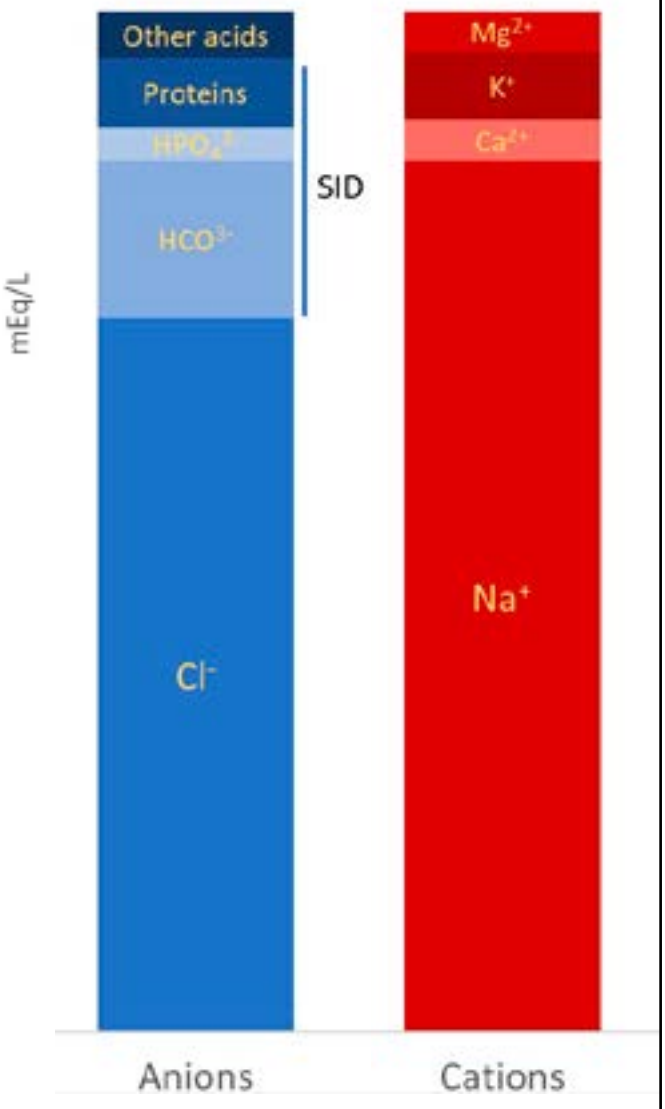
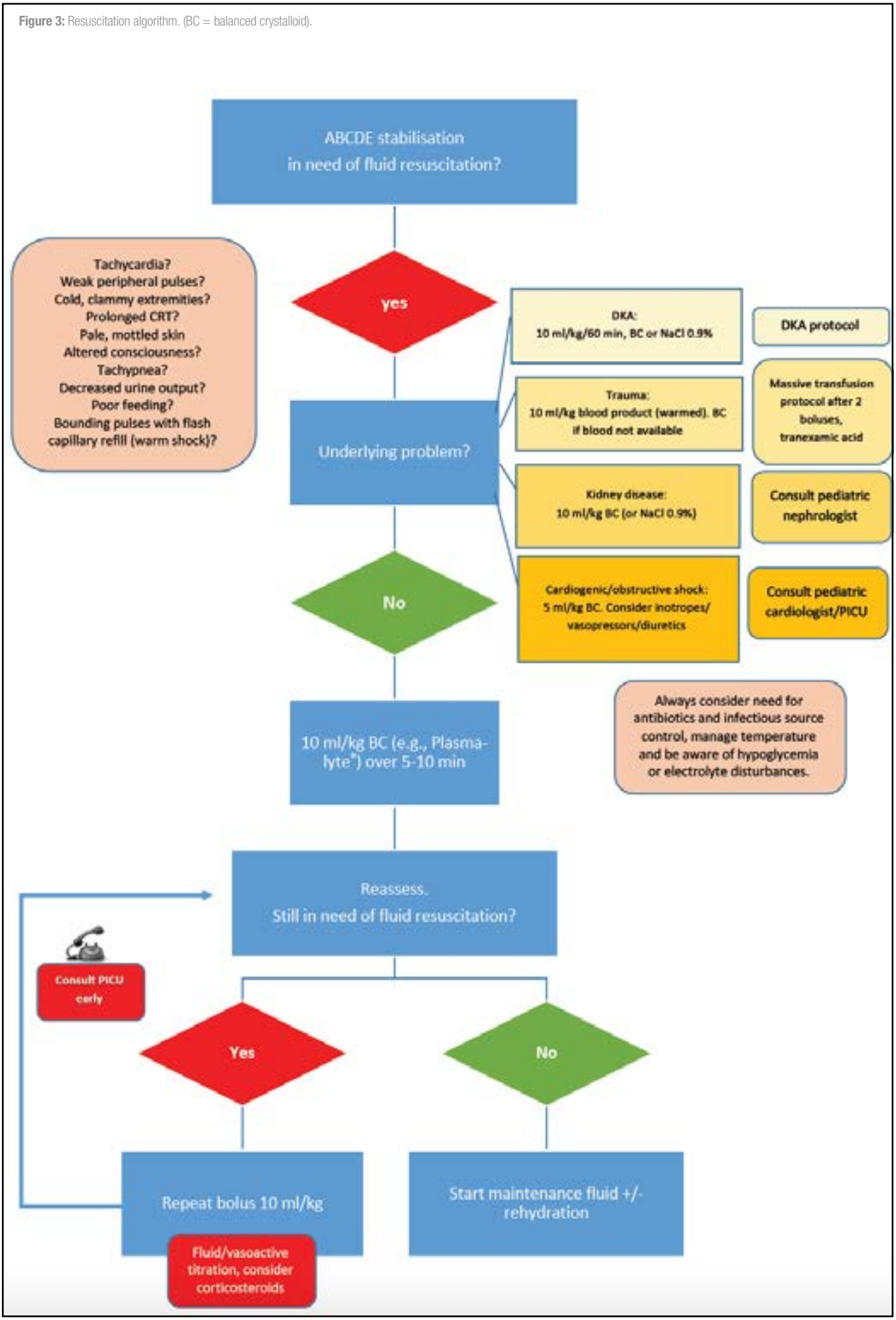


Figure 3: Resuscitation algorithm. (BC = balanced crystalloid).



In general, *crystalloids* are often preferred because they are effective, safer, cheaper and widely available. However, a few exceptions exist: dengue or cerebral malaria might benefit from early use of albumin as a resuscitation fluid, and albumin can be used as a second line option following crystalloids during pediatric shock (8, 10). Other *colloids* no longer have a place in resuscitation due to their safety profile and cost (6).

Dextrose-containing crystalloids are also not to be used during resuscitation, as they greatly worsen the neurologic outcome due to hyperglycemia (11). The dangers of *hypotonic fluids* in resuscitation are as well known, although unfortunately resuscitation with these fluids still occurs (12). A rapid fall in serum sodium level reduces plasma osmolality which causes water to shift intracellularly in the brain parenchyma leading to edema and hyponatremic encephalopathy associated with a mortality of 34% (13). Children are at higher risk than adults as they develop hyponatremic encephalopathy on higher plasma sodium levels. Moreover, due to a high brain/skull ratio and because children's brains contain more water, there is a greater risk of brain herniation. Hypotonic solutions should thus be avoided. Current data on *hypertonic solutions* in resuscitation are limited but they could cause pontine demyelination due to a risk of rapid increase in plasma osmolality (6, 14).

The next question that needs to be addressed is whether to use *balanced* or *unbalanced* solutions. The differences between balanced isotonic fluids and NaCl 0.9% are widely investigated, although mainly in adult patients. Historically, NaCl 0.9% is used the most, it is also the cheapest product. Some studies in adults reported an increased mortality and need for renal replacement therapy, or an increased incidence of persistent renal dysfunction with the use of NaCl 0.9% (5). This was most noticeable in very ill patients resuscitated with large volumes of fluids, or in sepsis with shock. A meta-analysis however, found no evidence that the risk of death or acute kidney injury among critically ill adults in the ICU was lower with the use of balanced fluids than with saline (15). In children, evidence is limited and no more than a trend towards better outcome is observed in reviews (16, 17).

Balanced fluids do not cause hyperchloremia or acidosis. Another theoretical benefit is the buffering effect of the added anions: e.g., Ringer's lactate® alkalinizes via its consumption in the citric acid cycle in the liver to bicarbonate. Some use Ringer's acetate, which has similar properties but no lactate. This was thought to be helpful when analyzing blood-lactate in shock. Later, it was shown that lactate is metabolized much faster than infused, so Ringer's lactate® does not cause hyperlactatemia except possibly in severe liver-failure (18).

Although the superiority of balanced isotonic fluids to NaCl 0.9% is still debated, many physiologic advantages hence exist. Considering the limited extra cost and potential benefits, we recommend their use in children, as do others (3, 8, 9, 19). Effects will be most profound when substantial volumes are needed — the choice of fluid in those receiving a one-time bolus is unlikely to matter.

NaCl 0.9% is still a good choice in patients who developed hypovolemia with a chloride responsive metabolic alkalosis (e.g., from vomiting). It can be advantageous when administering blood or certain medications (e.g., ceftriaxone) because it does not contain calcium, but neither does Plasma-Lyte®.

How fast and how much?

Until recently, early aggressive fluid resuscitation was recommended in children with septic shock, but the FEAST-trial challenged this (2). Most protocols however still recommend multiple boluses during the first hour to reverse shock although cautiously and with continuous assessment after each bolus (1, 3, 9, 14). The recently updated ERC-guidelines advocate 10 ml/kg boluses, up to 40-60 ml/kg might be needed in the first hour (8). The Society of Critical Care Medicine follows the same approach for sepsis when there is (pediatric) intensive care (PICU) availability (1). If not, fluid boluses are still advised but only in the case of hypotension and with a maximum of 40 ml/kg in the first hour. For children with septic shock without hypotension in low-resource settings, they recommend against bolus fluid administration while starting maintenance fluids (2). This restrictive approach seems to be at least as effective and reduces the incidence of mainly respiratory side effects necessitating PICU.

A bolus of 10 ml/kg is thus given in a timeframe of 5-15 minutes, with the severity of shock determining the speed. The bolus should be repeated in case of insufficient improvement and if there are no signs of fluid overload (deterioration of respiratory distress, increasing oxygen need, gallop rhythm, hepatomegaly, bradycardia). Following every bolus, reassessment should occur to identify those who are fluid responsive. This can be very challenging: clinical signs (heart rhythm, breathing frequency, CRT, consciousness, diuresis) and laboratory values (lactate, pH) could be helpful when combined, since one good parameter can be misleading. If experienced, the use of echocardiography or Point-Of-Care Ultrasound to recognize myocardial dysfunction or persistent hypovolemia can guide fluid administration (8). If more than 3-4 boluses are needed rapidly and the child is still shocked, or shows signs of cardiac decompensation, vasoactive/inotropic drugs are needed. Since fluid resuscitation is only one part of a much broader treatment plan in shocked children, PICU must be involved early in these patients to give advice and retrieve the patient.

Comparable to other guidelines, we recommend rehydration of severely dehydrated children who are not shocked to be done more gradually and preferably enterally (1, 20).

Special circumstances

Trauma

In trauma, active bleeding must be looked for and stopped via direct pressure or damage control surgery to avoid or reverse shock. Hemorrhagic shock not only generates fluid loss but also loss of blood components, thus blood products should be given as soon as possible, and crystalloids kept to a minimum (8). In general, there seems to be a tendency to over-resuscitate in pediatric trauma with higher risk of complications such as ascites, pleural effusion, increased need of ventilation and prolonged ICU stay attributable to excess fluid (21, 22).

In adults, permissive hypotension (maintaining a blood pressure lower than physiological levels) during trauma is aimed at limiting blood loss and avoid overly aggressive fluid resuscitation until definitive surgical control of bleeding occurs. There is no evidence to support permissive hypotension in children (mean arterial pressure at 5th percentile for age). Most children with trauma have associated brain injury. In these cases, permissive hypotension will be detrimental for cerebral perfusion. Excessive fluid administration on the other hand, may worsen cerebral edema. Hence fluids should be given stepwise aiming at maintaining a normal circulation (8, 23). Permissive hypotension could only be considered in children with hemorrhagic shock due to torso injuries from gunshots or stab wounds, without any suspicion of head trauma.

Major hemorrhage following injury is uncommon in children. Concepts that became standard in adult trauma care, e.g., the use of tranexamic acid, the avoidance of hypothermia and balanced resuscitation with plasma, platelets and packed cells in optimal ratio, are hence poorly studied in children. Retrospective analyses are the best to support using at least as much plasma as red blood cells and considering platelets early in pediatric massive transfusion protocols (22, 24). Tranexamic acid should be used in all requiring transfusion within the first three hours after injury, and/or (suspected) significant hemorrhage (8).

In burn victims, shock generally does not occur acutely. If so, other causes should be actively looked for. Fluid formulas correct fluid losses immediately after the initial approach but are outside the scope of this article.

Cardiogenic shock

Cardiogenic shock is a state of circulatory failure due to impairment of myocardial contractility, a less common entity in children. Possible causes are congenital cardiopathy, cardiomyopathy, myocarditis and arrhythmia. Extra-cardiac comorbidities exist as well, e.g., sepsis, leading to increased mortality.

In general, fluid resuscitation should be avoided in cardiogenic shock to avoid further decompensation. Some children may still benefit from a ju-

dicious fluid bolus (5 ml/kg) to optimize preload, while others will benefit from diuretics, ventilation or inotropes. All patients with cardiogenic shock should be transferred to a PICU and urgent advice of a pediatric cardiologist should be sought for further diagnostics and tailored treatment (25).

Kidney failure and/or hyperkalemia

Historically, balanced crystalloids were avoided in patients with kidney failure due to the risk of hyperkalemia. However, recent data suggest it might be safe and even preferable. The serum potassium concentration in a hyperkalemic patient is often higher than the potassium concentration in most balanced crystalloids. Moreover, NaCl 0.9% causes a hyperchloremic metabolic acidosis, which shifts potassium out of cells, increasing the hyperkalemia. Potassium shifts have a greater effect on the serum potassium than the actual concentration of potassium in the infused solution. Studies in renal transplant patients reported indeed higher potassium levels when using NaCl 0.9% as compared to balanced fluids (26). For most patients (with or without hyperkalemia) the effect of the potassium present in balanced solutions is minimal. Their use might even be beneficial in patients with concomitant metabolic acidosis.

Diabetic keto-acidosis (DKA)

Although most children with DKA are volume depleted, shock is rare (27). The range of ECF-deficit is usually in the range of 5-8% of bodyweight. Volume expansion starts with 10 mL/kg crystalloids infused over 60 minutes, although when signs of shock are present, this should be done faster. The remaining fluid deficit is corrected at a slower pace, usually over 48 hours. A second fluid bolus is rarely needed.

DKA often presents with acute kidney failure. Usually this resolves quickly with appropriate fluid therapy, confirming its prerenal etiology.

Mental status abnormalities occur in 4-15% of children treated for DKA; cerebral edema, rarely seen after adolescence, occurs in less than 1% but with a mortality rate of > 20%. It was initially attributed to rapid fluid administration causing abrupt changes in serum osmolality. More recently, an alternative hypothesis suggest intrinsic factors to DKA may be the cause of blood-brain-barrier disruption, which could be worsened during treatment. This is supported by the fact that cerebral edema correlates to the degree of initial hyperventilation and dehydration. No such link was found with the osmolality at presentation, nor with the osmotic changes caused by fluid resuscitation (27). Nevertheless, resuscitation in DKA must be monitored closely to avoid excessive fluid administration.

The Spink trial compared 0.9% saline with Plasma-Lyte® as initial fluid in pediatric DKA: Plasma-Lyte® was similar to 0.9% saline in time to resolution of DKA, need for renal replacement therapy, mortality, and length of PICU or hospital stay (28). Plasma-Lyte® does contain potassium, but studies suggest the serum potassium is unchanged or even higher with NaCl 0.9% because of the abovementioned shifts related to the metabolic acidosis caused by NaCl 0.9% (27). A recent meta-analysis showed that the use of NaCl 0.9% may be associated with longer time to DKA resolution, higher plasma chloride levels and lower plasma bicarbonate levels post resuscitation, and longer hospital stay (29). Although the International Society for Pediatric and Adolescent Diabetes recommends the use NaCl 0.9% the first hour, more and more data support the use of balanced crystalloids.

Conclusion

The most important in treating shock in children is to recognize the need for resuscitation in a timely fashion. The quest for the optimal resuscitation fluid is still ongoing, but there is growing evidence to recommend against using colloids, dextrose containing solutions and hypotonic fluids as a first choice. Even though NaCl 0.9% is historically the most widely used fluid during resuscitation, there is no physiologic reason we should still recommend it. Based on the available evidence and international guidelines, we recommend isotonic balanced crystalloids during fluid resuscitation in children in most cases. Therapy should start with a bolus of 10 ml/kg in 5-15 minutes depending on the clinical situation, with careful evaluation during and after each bolus.

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X. Beretta-Piccoli, Department of Intensive Care, Hôpital Universitaire des Enfants Reine Fabiola, Brussels, Belgium.

M. Blits, Department of Pediatrics, Antwerp University Hospital, Antwerp University Hospital, Antwerp, Belgium.

T. Boiy, Department of Pediatrics, Antwerp University Hospital, Antwerp, Belgium.

D. Bulckaert, Department of Emergency Medicine/Pediatric Care, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium.

S. Debulpaep, Department of Pediatrics, Ghent University Hospital, Ghent, Belgium.

T. Detaille, Department of Anesthesiology, Cliniques Universitaires St. Luc, Catholic University of Louvain Medical School, Brussels, Belgium.

E. Duval, Department of Pediatric Critical Care Medicine, Antwerp University Hospital, Antwerp, Belgium.

N. Godefroid, Pediatric nephrology, Cliniques Universitaires St. Luc, Catholic University of Louvain medical School, Brussels, Belgium.

K. Huysentruyt, Department of Pediatric Gastroenterology, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium.

A. Raes, Pediatric Nephrology and Rheumatology, Ghent University Hospital, Belgium.

T. Schepens, Department of Pediatric Critical Care Medicine, Antwerp University Hospital, Antwerp, Belgium.

D. Van Brusselen, Department of Paediatric Infectious Diseases, GZA Hospitals, Antwerp, Belgium.

K. Van Hoeck, Department of Pediatric Nephrology, Antwerp University Hospital, Antwerp, Belgium.

M. van Oort, Department of Pediatrics, Antwerp University Hospital, Antwerp, Belgium.

K. Vergaelen, Pediatric Intensive Care Unit, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium.

F. Vermeulen, Department of Pulmonology, University of Leuven, Leuven, Belgium.

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