



ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Fluid and electrolytes

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1. Methods

The aim of the current revision is to update the previous chapter [1] on basis of the scientific evidence published since 2004. The work of the authors who wrote the previous version of this chapter is gratefully acknowledged and forms the basis of this updated guideline.

The literature search was conducted using the Medline and Cochrane syst. Database covering the period from 2004 until

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Table: Recommendations on fluid and electrolytes

Neonates during the transition phase (phase I)	
R 6.1	In term neonates, postnatal weight loss generally occurs during the first 2–5 days of life and should not usually exceed 10% of birth weight (LoE 2++, RG 0, conditional recommendation)
R 6.2	In ELBW and VLBW infants, 7–10% weight loss seems to be adequate taking into account their higher body water content and the adverse complications associated with fluid overload (LoE 2++, RG B, strong recommendation)
R 6.3	A gradual increase of fluid intake is recommended in preterm and term neonates after birth (LoE 3, RG B, strong recommendation)
R 6.4	Electrolytes (Na, Cl and K) should be supplied starting during phase I/contraction of ECF compartment/initial loss of body weight (LoE 3, RG 0, strong recommendation)
R 6.5	Cl intake should be slightly lower than the sum of Na and K intakes ($\text{Na} + \text{K-Cl} = 1\text{--}2 \text{ mmol/kg/d}$) to avoid excessive Cl intakes and risk of iatrogenic metabolic acidosis (LoE 3, RG 0, strong recommendation)
R 6.6	In ELBW and VLBW infants, Na and K may be recommended from the first day of life when giving the recommended high amino acids and energy supply, providing that urine output is ascertained, and taking into account the potential for the development of nonoliguric hyperkaemia (LoE 2+, RG 0, conditional recommendation)
R 6.7	It should be recognized that the needs of individual patients may deviate markedly from the ranges of generally recommended intakes depending on clinical circumstances such as fluid retention, dehydration or excessive water losses, or others (GPP, strong recommendation)
Neonates during intermediate phase (phase II)	
R 6.8	After initial postnatal weight loss, birth weight should usually be regained by 7–10 days of life (GPP, conditional recommendation)
Neonates during the phase of stable growth (phase III)	
R 6.9	Fluid and electrolyte homeostasis should be maintained while the infant is gaining appropriate weight during the phase of stable growth (LoE 3, RG B, strong recommendation)
Children and infants beyond the neonatal period	
R 6.10	Requirements for fluid and electrolytes for infants and children (beyond the neonatal period) on PN are mainly based on empirical evidence and recommendations are presented in Table 5 (LoE 4, RG 0, strong recommendation)
R 6.11	The Holliday and Segar formula for calculating the maintenance water needs in children by determining caloric/water needs from weight (see Table 4) is still regarded appropriate in the clinical setting (GPP, strong recommendation)
R 6.12	Generally, an isotonic fluid should be used as intravenous fluid for “maintenance hydration” in sick children especially during the first 24 h. However, this should not delay the initiation of PN if PN is indicated (LoE 1+, RG A, strong recommendation)
R 6.13	It should be recognized that the needs of individual patients may deviate markedly from the ranges of recommended fluid intakes depending on clinical circumstances such as fluid retention, dehydration or excessive water losses (GPP, conditional recommendation)

December 2014. The systematic literature review was performed by the Hungarian Branch of the German Cochrane Centre/Nutritional Research Unit; Department of Paediatrics, University of Pécs (by Szimonetta Lohner and her team). The search strategy was developed on basis of the strategy and the keywords of the 2005 Guidelines [1]. The language restriction used at the search 2004 (publication in English or German language) was discontinued. Search items used were “neonate”, “preterm infants”, “infants”, “children”, “fluids”, “sodium”, “potassium”, and “chloride” as well as some of their boolean combinations. Further literature on “fluid and electrolytes” not covered by the search were included in the updated version if it came to attention of the authors.

2. Introduction

Most published studies on the adaptation processes of water and electrolyte metabolism relate to the preterm neonate who may develop important and deleterious fluid and electrolytes anomalies during the first week of life. Studies on water and electrolyte metabolism in older paediatric patients are limited. Therefore, recommendations for children are often based on extrapolation from data in neonates and adults.

3. Fluid

Water is the major component of the human body at any age and is an essential carrier for nutrients and metabolites. Water and electrolyte requirements are usually proportional to growth rate. Needs per unit body mass are very high in neonates and decrease with age until adulthood [2]. Total body water is divided into two compartments: intracellular fluid (ICF) and extracellular fluid (ECF). The total volume of ICF increases with the number and size of body cells during body growth. ECF is subdivided into intravascular and extravascular components as well as a “third space” which characterises free fluid in preformed body compartments under physiological (urine, cerebral spinal fluid, etc) and pathological conditions (ascites, pleural effusions, etc).

During intrauterine life, particularly during the third trimester of gestation [2–4], body water content decreases along with the relative increase in fat mass. Extremely low birth weight (ELBW, <1000 g) and very low birth weight (VLBW, <1500 g) infants have low body fat content and a higher percentage of lean body mass and body water than older infants, which is related to high water turnover. In premature infants, a daily weight gain of 15 g/kg results in a net storage of about 12 ml of water (~80% of weight gain). Water contributes almost 90% of body weight in the 24 week old foetus, nearly 75% in term infants, and around 50% in adults [2,3]. The proportion of ECF (intra- and extravascular) also decreases during infancy up to adulthood. Blood volume in neonates is 85–100 ml/kg body weight compared to 60–70 ml blood volume/kg body weight in adolescents and adults [5].

Water turnover is high in neonates and decreases with increasing age and the concomitant decrease of metabolic rate and growth velocity [6]. Water turnover, like energy turnover, is related to lean body mass and has no close relationship to body fat mass. In the assessment of fluid balance, metabolic water production may be of particular importance in paediatric patients because of their high metabolic rates. Endogenous water production equals 0.6, 1.0, and 0.4 ml water per gram of carbohydrates, fat and protein oxidised respectively [7]. Evaporation of water from upper respiratory passages accounts for approximately one third of net insensible water loss [8] and reaches the level of 0.8–0.9 ml/kg per hour in premature infants, 0.5 ml/kg per hour in term neonates [9], 0.4 ml/kg per hour in older children and 0.3 ml/kg per hour in adolescents [10].

Many of the regulatory processes involved in fluid and electrolyte balance have limitations in paediatric patients because of immaturity or limited efficacy [11]. The renal glomerular surface area available for filtration is small in preterm and term neonates compared to that in older infants and adults [12]. In neonates, glomerular filtration rate increases significantly during the first week of life [13] and continues to rise over the first two years of life [14]. The velocity of this increase is slower in premature infants and needs to be considered when estimating fluid and electrolyte physiology in these infants [15].

Immaturity of the distal nephron with an anatomically shortened loop of Henle leads to reduced ability to concentrate urine [16]. Maximum urinary concentrations are up to 550 mosm/l in preterm infants, and 700 mosm/l in term infants, compared to 1200 mosm/l in adults [17]. Neonates may be placed at risk for volume depletion when a high renal solute load cannot be compensated for by the ability to produce concentrated urine. Although hormonal factors i.e. the renin-angiotensin-aldosterone system, and the arginine-vasopressin-axis are mature early in gestation, the effects are limited by renal immaturity [18]. Thus, in VLBW infants urine output may frequently increase above 5 ml/kg/h. In preterm infants a lower plasma oncotic pressure and higher permeability of the capillary wall [19] also enhance the shift of water from the intravascular to the interstitial compartment. This puts preterm infants at an increased risk of oedema, especially under pathologic conditions such as sepsis [20].

4. Electrolytes

Sodium (Na) is the principal cation of the ECF and Na concentrations influence intravascular and interstitial volumes. Na excretion occurs primarily through urine, but also through sweat and faeces. Chloride (Cl) is the major anion of the ECF. The exchangeable Cl remains relatively constant per unit of body weight at different ages. Even if chloride balance usually parallels that of sodium, and so it is strictly correlated to the extracellular volume balance, chloride losses and excretion can also occur independently from sodium, mainly in equilibrium with bicarbonate status [21]. The daily turnover of Cl is high. Renal conservation occurs with tubular reabsorption of 60–70% of the filtrated Cl. In addition, Cl is involved in maintaining osmotic pressure, hydration, and ionic neutrality. Na and Cl are also the major ions influencing the ‘strong ion difference’ (SID), one of the 4 systems acting on blood pH. According to the Stewart’s approach, the concept of SID is used to help explain “metabolic” acid base abnormalities associated with changes in chloride concentration [22]. A decrease in the SID will result in an acidifying effect on plasma. The SID is calculated as the charge difference between the sum of measured strong cations (Na^+ , K^+ , Ca^{2+} , and Mg^{2+}) and measured strong anions (Cl^- , lactate) [23]. As both Na^+ and Cl^- are the major strong ions in plasma, the SID calculated as the simply difference between sodium and chloride represents one independent variable determining the hydrogen ion and the bicarbonate ion concentrations; so, an increase in the plasma Cl^- relative to Na^+ decreases the plasma SID and lowers the pH [24].

Potassium (K) is the major intracellular cation and the K pool correlates well with the lean body mass. The intracellular K concentration is dependent on Na/K-ATPase activity which can be impaired if there are insufficient supplies of oxygen and energy [25]. Ten percent of the K body pools are not exchangeable (bone, connective tissue, cartilage). Extracellular K concentration is not always related to intracellular concentration. In addition, intra- to extracellular K shifts can occur, e.g. in acidotic states through exchange with H ions.

Incidental gastrointestinal and skin electrolyte losses are very low. In neonates Na gastrointestinal losses represent 0.1–0.2 mmol/kg/d in premature infants and around 0.01–0.02 mmol/kg/d in term infants [26]. Electrolyte losses may be increased under pathological conditions like bowel obstruction, ileostomy, pleural effusions, peritoneal drainage, and external cerebrospinal fluid drainage. Under these circumstances the electrolyte losses due to lost fluids can only be estimated and continuous monitoring of serum electrolytes is recommended (see section monitoring below).

On the other hand it may be of importance that considerable amounts of Na and K may be supplied along with drugs (e.g. benzylpenicillin) and minerals that are prepared as Na or K salts (e.g. phosphates). Similarly, sources of Cl are numerous while on

parenteral nutrition (PN), e.g. normal saline, amino acid and calcium solutions.

5. The neonatal period

Immediate adaptation processes after birth affect the metabolism of water and electrolytes as a result of discontinuation of placental exchange with a relative immaturity of physiological processes. Birth also implies the onset of thermoregulation and sometimes considerable insensible water losses. Subsequent adaptation includes the onset of autonomic renal regulation of fluids and electrolytes, and intake of fluids and other nutrients.

The time course of adaptation may be divided into three major phases [10]:

- **Phase I: transition.** The immediate postnatal phase is characterised by an initial relative oliguria [27] lasting hours to days, and considerable insensible water losses via the immature skin. It is followed by a diuretic phase lasting some days, and progressive diminished insensible water losses along with increasing cornification of the epidermis. During this transitional phase, body fluid compartments are rearranged by isotonic or hypertonic (i.e. hypernatremic and hyperchloremic) contraction of the ECF compartment. Continuing natriuresis (as present during foetal life) also occurs during this phase of transition [28]. Phase I usually ends when maximum weight loss has occurred.
- **Phase II: the intermediate phase** corresponds to the period between minimal weight (maximal weight loss) and return to birth weight. In premature neonates – especially in ELBW and VLBW infants – urine output might still be high with high Na excretion during this phase. The duration of the intermediate phase varies in length, but birth weight is usually regained by 7–10 days of life in normal breastfed term infants.
- **Phase III: stable growth** is characterized by continuous weight gain with a positive net balance for water and electrolytes.

5.1. Phase I/transition

R 6.1	In term neonates, postnatal weight loss generally occurs during the first 2–5 days of life and should not usually exceed 10% of birth weight (LoE 2 ⁺⁺ , RG 0, conditional recommendation, strong consensus)
R 6.2	In ELBW and VLBW infants, 7–10% weight loss seems to be adequate taking into account their higher body water content and the adverse complications associated with fluid overload (LoE 2 ⁺⁺ , RG B, strong recommendation, strong consensus)
R 6.3	A gradual increase of fluid intake is recommended in preterm and term neonates after birth (LoE 3, RG B, strong recommendation, strong consensus)
R 6.4	Electrolytes (Na, Cl and K) should be supplied starting during phase I/contraction of ECF compartment/initial loss of body weight (LoE 3, RG 0, strong recommendation, consensus)
R 6.5	Cl intake should be slightly lower than the sum of Na and K intakes ($\text{Na} + \text{K} - \text{Cl} = 1 - 2 \text{ mmol/kg/d}$) to avoid excessive Cl intakes and risk of iatrogenic metabolic acidosis (LoE 3, RG 0, strong recommendation, strong consensus)
R 6.6	In ELBW and VLBW infants, Na and K may be recommended from the first day of life when giving the recommended high amino acids and energy supply, providing that urine output is ascertained, and taking into account the potential for the development of nonoliguric hyperkalaemia (LoE 2 ⁺ , RG 0, conditional recommendation, strong consensus)
R 6.7	It should be recognized that the needs of individual patients may deviate markedly from the ranges of generally recommended intakes depending on clinical circumstances such as fluid retention, dehydration or excessive water losses, or others (GPP, strong recommendation, strong consensus)

The goals for fluid and electrolyte administration during this phase are to [11]:

- allow contraction of ECF with negative water and Na balance but without compromising intravascular fluid volume and cardiovascular function and while maintaining normal serum electrolyte concentrations;
- secure a sufficient urinary output without oliguria (<0.5–1.0 ml/kg per hour) for longer than 12 h;
- ensure regulation of body temperature by providing enough fluid for transepidermal evaporation.

During the postnatal transition phase, body fluid compartments are rearranged by isotonic or hypertonic contraction. Normally the phase occurs without oliguria (<0.5–1 ml/kg/h within 12 h), electrolyte disturbances, and/or acidosis. Expected postnatal weight loss depends on hydration status at birth, e.g. intrauterine growth-restricted neonates typically lose less weight than eutrophic neonates. Environmental factors and nutritional intakes also significantly influence postnatal weight loss. Double wall incubators reduce insensible water loss in VLBW neonates by about 30% when a humidity of 90% is used at thermo-neutral temperature. After postnatal maturation of the epidermal barrier and cornification during the first 5 days of life, ambient humidity can be reduced step by step [29]. The use of waterproof coverings (such as plastic films, plastic blankets, and bubble blankets) in addition to treatment in a double wall incubator leads to further reduction of insensible water loss by 30–60% [30]. Endotracheal intubation and mechanical ventilation using warmed and humidified air significantly reduce insensible respiratory water loss [31] and fluid requirements are reduced by 20 ml/kg/d. The use of emollient ointments decreases insensible water loss of up to 50% in open care conditions [32,33] but may also increase infection rates [34,35]. Radiant warmers and single wall incubators significantly increase water loss and impair thermoregulation in VLBW infants [36]. Phototherapy also increases insensible water loss.

Despite some controversies, normal term breastfed neonates usually serve as a reference for all neonates when considering postnatal nutrition, adaptation, and growth. Fluid intakes may significantly vary in normal term breastfed neonates [10]. On average, milk production and infant intakes increase rapidly from less than 100 ml per day on the first day of life to 500–600 ml per day after 4–5 days, then increase more slowly to reach 600–800 ml per day after 1 month and 700–900 ml per day after 6 months [37,38]. On average, the postnatal weight nadir usually occurs after 2–3 days and represents a weight loss of 6–7% in breastfed infants [39]. In formula fed term infants, the timing of loss is similar but weight loss is lower, between 3 and 4% of birth weight. This implies that mean time to regain birth weight is also quicker in formula fed (6–7 days) than in breastfed neonates (8–9 days) [39]. Even though postnatal weight loss exceeding 10% is frequently not wished in term neonates, it is not always linked to an underlying pathology [40]. Because of higher insensible water losses and immature kidneys, premature neonates, especially ELBW infants, require more fluids than term infants during the first week of life [41]. A review of four randomized clinical studies with different levels of fluid intake during the first week of life concluded that fluid restriction reduces the risk of patent ductus arteriosus, necrotising enterocolitis, and death. Fluid restriction also tends to reduce the risk of bronchopulmonary dysplasia but to increase the risk of dehydration [42]. However, tight goals for fluid restriction may interfere with the feasibility of providing sufficient a nutrient supply. Recent investigations regarding enhanced early

nutritional support for very preterm infants point to a postnatal weight loss of 7–10% of birth weight in ELBW and VLBW infants receiving higher nutritional supplies starting from birth [43–48]. Loss of body weight higher than generally expected may indicate inadequate fluid, Na, protein and/or energy intakes besides other pathology, and should lead to further investigations. Thus, during the body water contraction of phase I, close clinical monitoring should be performed to avoid inadequate intakes, oliguria (diuresis <1 ml/kg/h for longer than 12 h), electrolytes disturbances and acidosis.

Electrolyte homeostasis during the first week of life also depends on maturity, birth weight, energy and amino acid intakes [45,49]. In term breastfed neonates, human milk Na content usually decreases from around 40 mmol/L on day 1, to 10–15 mmol/L after day 3. The evolution of Cl content is quite similar to Na content but with 10–20% higher concentrations. Conversely, K content increases from 12 to 16 mmol/L during the first two days of life to 16–20 mmol/L after day 3 [37,38].

In preterm neonates, restricted Na intake has positive effects on oxygen requirements and the risk of later bronchopulmonary dysplasia [50]. However, there is also evidence that Na restriction gives rise to a higher risk of hyponatremia [21,51]. Furthermore, large variations in serum Na concentration may impair later neurocognitive outcome in preterm infants [52]. In addition, restricted supply of Na and K may also affect phosphorus supply if Na- or K-phosphate salts are used.

A restriction of Na intake during the period of ECF contraction should be performed cautiously allowing for a negative net balance for Na of about 2–3 mmol/kg per day during the first 2–3 postnatal days while closely controlling serum concentrations until a weight loss of approximately 5–10% has occurred. Along with the contraction of ECF, Na serum concentrations generally increase during the first 2–5 days, but should remain within the high normal range (<150 mmol/l). Na concentrations <140 mmol/L in combination with significant weight loss around 10% may indicate Na depletion and should always instigate clinical assessment.

Recent studies have demonstrated an increased incidence of hypokalaemia, hypophosphatemia and hypercalcaemia while optimising protein and energy intakes according to current recommendations in VLBW infants [21,43,45,53–58]. It corresponds to a refeeding-like syndrome. In infants with adequate protein and energy intake, especially in growth restricted and ELBW premature infants who have low mineral stores and high requirements, K supplementation may be initiated from the first day of life to reduce the risk of hypokalaemia and to enable the provision of adequate phosphorus supply. However, especially during the oliguric phase and in infants with high risk for nonoliguric hyperkalaemia (i.e. ELBW infants) close monitoring is necessary to ensure normal K serum concentrations. A deferment of K supply might be required in some of these infants to avoid hyperkalaemia. However Na and K supply should start latest before serum concentration of these electrolytes drop below recommended values [21].

A high Cl intake may induce hyperchloraemic metabolic acidosis in VLBW infants and should be avoided. Indeed, these are a causative factor for intraventricular haemorrhage and other morbidities in preterm babies [59].

The use of “Cl-free” Na and K solutions should be considered in preterm infants on PN in order to reduce the risk of metabolic acidosis [21,60–63]. Table 1 shows the recommended parenteral fluid and electrolyte intake of neonates during the first days of life (Phase I of adaptation).

5.2. Phase II: the intermediate phase

R 6.8 After initial postnatal weight loss, birth weight should usually be regained by 7–10 days of life (GPP, conditional recommendation, strong consensus)

The goals for fluid and electrolyte management during this intermediate phase are to [11]:

- replete the body for electrolyte losses and replace actual water and electrolytes;
- maintain proper fluid and electrolyte homoeostasis while the infant is regaining birth weight;

The recommended fluid intakes in phase II are based on studies suggesting that a daily fluid intake equal to or higher than 170 ml/kg body weight per day is accompanied by high urinary Na excretion with negative Na balance, even if Na intake is as high as 10 mmol/kg body weight per day [64]. Fluid therapy in ELBW infants in excess of 200 ml/kg/d does not maintain Na balance, regardless of the amount of NaCl provided. There is evidence that fluid intake lower than 140 ml/kg body weight per day, together with Na intake of about 1 mmol/kg body weight per day, is adequate to maintain Na balance in ELBW neonates [65–70].

However, in preterm infants of less than 35 weeks of gestation Na supplementation of 4–5 mmol/kg/day during the first 2 weeks of life led to better neurocognitive performance at the age of 10–13 years compared to a control group of infants with Na intake of only 1–1.5 mmol/kg/d under the study conditions [71]. It seems sensible to increase Na and fluid supply in order to replace electrolyte and fluid losses during the intermediate phase (see Table 2).

Common recommendations suggest an average time to regain birth weight by about 7–10 days after birth. This is supported by evidence from epidemiological studies. Observations from population-based cohorts of healthy neonates point to a median time to recover birth weight in healthy neonates around 8.3 and 6.5 days (in breast-fed and formula-fed infants, respectively), but also suggest a considerable proportion of infants have not regained their birth weight before 12–14 days [39,40]. In those neonates pathology needs to be carefully excluded and the feeding regime checked.

5.3. Phase III: stable growth

R 6.9 Fluid and electrolyte homoeostasis should be maintained while the infant is gaining appropriate weight during the phase of stable growth (LoE3, RG B, strong recommendation, strong consensus)

The goals for fluid and electrolyte management during stable growth (phase III) are to

- replace losses of water and electrolytes (maintain water and electrolyte homoeostasis).
- provide enough extra water and electrolytes to reach an adequate rate of growth with adequate fluid and electrolyte homoeostasis

Fluid requirements during stable growth are related to the expected weight gain. Water loss from stool is negligible in early life prior to establishing enteral feeding in premature infants. When full enteral feeding is achieved, faecal losses of 5–10 ml/kg per day are usually assumed to balance metabolic water production [72].

Accretion of body mass during growth periods requires an adequate supply of electrolytes. It has been shown that restricted administration of Na impairs longitudinal growth and weight gain [26]. Plasma Na concentrations were normal in VLBW infants with Na intake of 1.5–2.6 mmol/kg/d and fluid intakes of 140–170 ml/kg/d [73,74]. With more “aggressive” feeding regimes and increased growth rates, additional Na supply in relation to growth rate might be necessary.

Breast-fed term infants need as little as 0.35–0.7 mmol/kg body weight per day of Na during the first 4 months of life to achieve adequate growth [75]. In preterm infants, a higher growth rate explains a higher Na requirement.

The amount of K usually recommended is similar to the amount provided in human milk, about 2–3 mmol/kg per day [76].

Preterm infants also retain about 1.0–1.5 mmol/kg body weight per day of K, which is about the same as foetal accretion [77].

Table 3 shows the recommended parenteral fluid and electrolytes for neonates during the first month of life (phase III/stable growth).

Table 1

Recommended parenteral fluid and electrolyte intake during the first days of life in neonates (Phase I of adaptation).^e

	Days after birth				
	Day 1	Day 2	Day 3	Day 4	Day 5
Fluid intake ^a (ml/kg/d)					
Term neonate	40–60	50–70	60–80	60–100	100–140
Preterm neonate >1500 g	60–80	80–100	100–120	120–140	140–160
Preterm neonate 1000–1500 g	70–90	90–110	110–130	130–150	160–180
Preterm neonate <1000 g	80–100	100–120	120–140	140–160	160–180
Na ^{b,d} (mmol/kg/d)					
Term neonate	0–2	0–2	0–2	1–3	1–3
Preterm neonate >1500 g	0–2 (3)	0–2 (3)	0–3	2–5	2–5
Preterm neonate <1500 g	0–2 (3)	0–2 (3)	0–5 (7)	2–5 (7)	2–5 (7)
K ^{c,d} (mmol/kg/d)	0–3	0–3	0–3	2–3	2–3
Cl (mmol/kg/d)	0–3	0–3	0–3	2–5	2–5

^a Postnatal fluid requirements are highly dependent on treatment conditions and environmental factors. Certain clinical conditions may afford modifications of daily fluid intakes, e.g. phototherapy (add volume ca. 10–20%), infants with asphyxia/respiratory distress syndrome/mechanical ventilation with humidified respiratory gases (reduce volume by ca. 10–20%).

^b Careful adjustment of water and electrolyte administration is needed in ELBW infants at onset of diuresis and in polyuric patients. In cases of high urinary Na losses the need for Na supply may exceed 5 mmol/kg/d, especially in neonates <1500 g at the end of phase I.

^c K administration should regard initial phase of oliguria and the risk of non-oliguric hyperkalemia in VLBW infants. A deferment of parenteral K supply might be required to avoid hyperkalemia.

^d Parenteral Na and K supply should start latest before serum concentrations drop below recommended values.

^e The recommendations of Table 1 are based on clinical experience, expert opinion, and extrapolated data from different studies in animals and humans.

Table 2Recommended parenteral fluid and electrolyte intake for neonates during the intermediate phase (phase II) – prior to the establishment of stable growth.^a

	Fluid (ml/kg/d)	Na (mmol/kg/d)	K (mmol/kg/d)	Cl (mmol/kg/d)
Term neonate	140–170	2–3	1–3	2–3
Preterm neonate >1500 g	140–160	2–5	1–3	2–5
Preterm neonate <1500 g	140–160	2–5 (7)	1–3	2–5

^a The recommendations of Table 2 are based on clinical experience, expert opinions, and extrapolated data from different studies on animal and men.

6. Children and infants beyond the neonatal period

R 6.10	Requirements for fluid and electrolytes for infants and children (beyond the neonatal period) on PN are mainly based on empirical evidence and recommendations are presented in Table 5 (LoE 4, RG 0, strong recommendation, strong consensus)
R 6.11	The Holliday and Segar formula for calculating the maintenance water needs in children by determining caloric/water needs from weight (see Table 4) is still regarded appropriate in the clinical setting (GPP, strong recommendation, strong consensus)
R 6.12	Generally, an isotonic fluid should be used as intravenous fluid for “maintenance hydration” in sick children especially during the first 24 h. However, this should not delay the initiation of PN if PN is indicated (LoE 1+, RG A, strong recommendation, strong consensus)
R 6.13	It should be recognized that the needs of individual patients may deviate markedly from the ranges of recommended fluid intakes depending on clinical circumstances such as fluid retention, dehydration or excessive water losses (GPP, conditional recommendation, strong consensus)

6.1. Fluid

Total water requirements in children and infants beyond the neonatal period mainly consist of maintenance needs, replacement of ongoing losses (urinary and stool losses) and replacement of deficits. Insensible water loss from the skin and lungs is an energy costly process that consumes a quarter of the overall caloric expenditure, 0.5 kcal per 1 ml of water lost.

Urine osmotic load results from protein catabolism and electrolyte excretion, but is little affected by carbohydrate and fat metabolism which produce metabolic water and CO₂. Electrolytes, urea and other substances constitute urine osmotic load. High nitrogen and energy supply with PN require sufficient water supply as the vehicle for nutrient delivery.

Generally, water requirements parallel energy needs with 1 kcal per 1 ml water [78]. With increasing age and decreasing metabolic activity, maintenance water and energy requirements fall. In 1957, Holliday and Segar provided a simple-to-use formula for calculating the maintenance water needs in children by determining caloric/water needs from weight alone. Fluid requirements can be fulfilled by infusing 100 ml/kg/d (4 ml/kg/h) for every kilogram of body weight < 10 kg plus 50 ml/kg/d (2 ml/kg/h) per kg body weight between 10 and 20 kg plus 25 ml/kg/d

(1 ml/kg/h) per kg body weight above 20 kg [79,80]; (see Table 4).

However, it is important to emphasize that there will be clinical situations with altered water and energy needs. Water requirements increase with fever, hyperventilation, hypermetabolism and gastrointestinal losses and decrease in renal failure and congestive heart failure. Water and energy requirements are also decreased during critical illness, mechanical ventilation and in temperature-controlled environments. It is beyond the scope of this guideline to cover individual diseases, but it is obvious that parenteral water management should be adjusted according to disease state.

6.2. Electrolytes

Electrolyte requirements for infants and children beyond the neonatal period are mainly based on empirical evidence and are set at the level of 1–3 mmol for Na and 1–3 mmol of K required per intake of 100 kcal [1,78,79,81–86]. This is close to the electrolyte composition of human breast milk or cow milk and is probably appropriate in “healthy”, well hydrated children with physiological growth (i.e. patients on parenteral nutritional support).

6.3. Maintenance of hydration

Fluid and electrolyte management is an essential part of supportive care in the acutely ill child and in children in the operative setting. Traditionally, maintenance parenteral fluids have been administered as hypotonic saline (Na 35–77 mmol/L in 5% dextrose in water), but a number of publications have addressed the risk of hospital-acquired hyponatremia (<135 mmol/L) and potentially fatal hyponatremic encephalopathy with this fluid and electrolyte regimen if the free water intake is not adapted to individual needs [87,88].

In postoperative and critically ill children a large meta-analysis documented an increased risk of hyponatremia with the administration of hypotonic “maintenance fluids” compared to the use of isotonic (Na 140 mmol/L) fluids [89,90]. This was further underlined in the randomized, double-blind, controlled trial by McNab et al. [91] confirming a lower risk of hyponatremia with the use of isotonic fluid (Na 140 mmol/L) as compared with a hypotonic fluid (Na 77 mmol/L) in a large heterogeneous population of hospitalized children [91]. There is substantial evidence supporting the use of isotonic fluid as intravenous fluid for maintenance hydration in hospitalized children in addition to PN if needed.

Table 3Recommended parenteral fluid and electrolytes intake for neonates during the first month of life with stable growth (phase III).^a

	Fluid (ml/kg/d)	Na (mmol/kg/d)	K (mmol/kg/d)	Cl (mmol/kg/d)
Term neonate	140–160	2–3	1.5–3	2–3
Preterm neonate >1500 g	140–160	3–5	1–3	3–5
Preterm neonate <1500 g	140–160	3–5 (7)	2–5	3–5

^a The recommendations of Table 3 are based on clinical experience, expert opinions, and extrapolated data from different studies on animal and men.

Table 4
Maintenance fluid requirements in children and infants beyond neonatal period (Holliday and Segar) [79,80].

Weight	ml/kg/d	ml/kg/h
A: the first 10 kg	100	4
B: weight between 10 and 20 kg	+50 ml/extra kg/d	+2 ml/extra kg/h
C: weight above 20 kg	+25 ml/extra kg/d	+1 ml/extra kg/h
Sum total requirements	A + B + C	A + B + C

Table 5
Recommended parenteral fluid and electrolyte intake for children and infant beyond neonatal period.^b

	<1 y ^a	1–2 y	3–5 y	6–12 y	13–18 y
Fluid (ml/kg/d)	120–150	80–120	80–100	60–80	50–70
Na (mmol/kg/d)	2–3	1–3	1–3	1–3	1–3
K (mmol/kg/d)	1–3	1–3	1–3	1–3	1–3
Cl (mmol/kg/d)	2–4	2–4	2–4	2–4	2–4

^a After 1 month of age.

^b The recommendations of Table 5 are based on clinical experience, expert opinions, and extrapolated data from different studies on animal and men.

Nevertheless, there have been some concerns about the non-physiological nature of normal saline solution as it contains equal concentrations of Na and Cl. The increased Cl load has been associated with hyperchloraemia and acidosis, and there is discussion about whether it would be more appropriate to use intravenous solutions with lower Cl than Na concentrations, so called balanced solutions. At present, there is not enough evidence to strictly recommend balanced solutions over the use of normal saline.

7. Monitoring of parenteral fluid and electrolyte treatment

Postnatal fluid and electrolyte homeostasis are highly dependent on postnatal environment (humidity, temperature, incubator or open radiant warmer, phototherapy). Premature neonates are vulnerable to both insufficient and excessive intakes, especially ELBW and VLBW infants. Thus in neonates, tight assessment of body water balance, prevention of high insensible water losses, and monitoring of serum electrolyte concentrations should be included in a protocol adapted to the individual condition and clinical presentation of the patient. Monitoring intervals depend on clinical status, underlying pathophysiology, medications and treatment modalities [10].

Indicators of changes of hydration and electrolyte status may include:

- clinical status of the patient
- body weight and estimation of body composition
- blood electrolyte concentrations and acid base status
- fluid and electrolyte balance (it implies the measurement of urine output, urine specific gravity or osmolarity and the measurement of urine electrolyte concentrations).
- haematocrit and blood urea nitrogen

In parenterally fed infants and children, serum electrolyte concentrations and weight are usually monitored daily for the first days of treatment; then the monitoring intervals are adapted depending on the clinical status and the stability of the patient's condition.

8. High fecal output and water/electrolyte losses

High fecal output with subsequent water/electrolyte losses are observed in patients with some types of intestinal failure on long-

term parenteral nutrition: i) Short bowel syndrome (SBS), ii) chronic intestinal pseudo-obstruction syndrome (CIPOS) and iii) total or sub-total intestinal aganglionosis (TIA). Both CIPOS and TIA are requiring, most often, an enterostomy [92].

For a safe long-term management, high water-electrolytes losses require sodium supplementation and tools for decreasing gastric hypersecretion and fecal output.

8.1. Sodium supplementation

As discussed above, replacing sodium losses only with sodium chloride solutions exposes to high cumulative Cl intake and risk of metabolic acidosis associated hyperchloraemia. These may lead to neurological morbidities, are a causative factor of growth faltering, and should be avoided not only in premature babies on a short term, but also in older children with high water-electrolyte losses on the long term [59].

In order to reduce the occurrence of these unwanted metabolic consequences, imbalance between electrolytes provided by the PN solution should be detected and corrected and part of sodium intake, in the form of sodium chloride solutions, should be replaced by, for instance, sodium lactate or sodium acetate [61,63].

8.2. Decreasing gastric hypersecretion and fecal output

Cimetidine and ranitidine are histamine H2-receptor antagonist (H2 blockers). Several studies have shown the beneficial effects of H2 blockers in decreasing gastric hypersecretion especially in the setting of SBS [92–100]. Ranitidine has a 7 times more powerful effect than cimetidine [101] and a longer duration of action [102,103]. Intravenous administration of ranitidine is efficient in reducing the water-electrolytes losses in SBS as well as in patients with enterostomy for CIPOS or TIA, and is indicated when enteral administration is impossible or inefficient [104,105]. Side effects are very rare in children [106]. Continuous ranitidine infusion at a lower dosage, is more efficient than intermittent infusion [112]. Stability of ranitidine in PN bags has been established at a dose of 10–15 mg/kg/d [107–111]. One might consider that proton-pump inhibitors (PPI) have the same effects and indications as ranitidine. However, PPIs have a different mechanism of action by decreasing acid secretion rather than gastric hypersecretion as a consequence of extensive small bowel resection. Two studies performed in adults, failed to show any difference between ranitidine and PPI [113,114]. Moreover, there is no data available about the stability of PPIs in PN bags.

9. Electrolyte disturbances

This paragraph summarizes the most frequent electrolyte disturbances which may occur in neonates on PN.

9.1. Hypernatraemia

Hypernatraemia (Na >145 mmol/L) is often 'iatrogenic'. Especially in VLBWI it mostly results from incorrect replacement of transepidermal water loss (TEWL), inadequate water intake, or excessive Na intake (which can be 'inadvertent') during the transition phase. Therapeutic measures should be based on the aetiology. This should be ascertained by assessment of the infant's intravascular volume and hydration status. In case of symptomatic hypovolaemia, plasma volume should be replaced. A rapid correction of hypernatremia may induce cerebral oedema, seizures and neurological injury. A reduction rate of 10–15 mmol/l/24 h is recommended.

9.2. Hyponatraemia

Hyponatraemic states ($\text{Na} < 135 \text{ mmol/L}$) reflect absolute or relative water overload with Na pool reduced, normal or increased. Diagnostic measures for hyponatremia rely on clinical and ECF assessment (intra- and extravascular component) and urinary Na ($_{\text{u}}\text{Na}$) measurement. ECF excess with inadequate postnatal weight loss or weight gain suggests water overload (acute renal failure should also be considered in case of oliguria and $_{\text{u}}\text{Na} > 20 \text{ mmol/l}$). ECF contraction with adequate weight loss or failure to grow suggests Na depletion: $_{\text{u}}\text{Na}$ is $< 20 \text{ mmol/l}$ and a clinical history of acute anaemia or postnatal dehydration are usual.

Finally, primary Na depletion is frequent in preterm infants born before 34 weeks gestation due to deficient proximal and distal tubule Na reabsorption (amplified due to drug side effects from e.g. caffeine, diuretics, or others), and should be anticipated.

Treatment of hyponatremia must be based on the underlying causes. Corrections of severe hyponatremia more rapid than 48–72 h have been associated with an increased risk of pontine myelinolysis.

9.3. Hyperkalemia

Hyperkalemia ($\text{K} > 6 \text{ mmol/L}$) may occur with or without impaired renal K excretion. Early hyperkalemia can develop in the absence of oliguria and potassium intake. Non-oliguric hyperkalemia (NOHK) should be checked for, after birth, in VLBWI at risk (lack of antenatal corticosteroids, systemic acidosis, birth asphyxia, massive haematomas, haemolysis, catabolic state, and other situations). In NOHK diuresis is usually within normal range and $\text{K}_{\text{u}} > 20 \text{ mmol/l}$. Oliguric hyperkalemia is mostly due to renal failure and exhibits $\text{K}_{\text{u}} < 20 \text{ mmol/l}$. Both conditions need to be identified, in order to avoid excessive K intake in PN. Severe hyperkaemia ($\text{K} > 7 \text{ mmol/l}$) requires prompt intervention.

9.4. Hypokalemia

Hypokalemia ($\text{K} < 3.5 \text{ mmol/L}$) may develop in cases of enhanced demand (immaturity), electrolyte depletion (growth restriction), inadequate supply (inappropriate parenteral or enteral supply) or due to increased renal losses (f.e. as side effect of medications like caffeine or diuretics, or renal pathology). Early enhanced PN increases endogenous insulin production and promotes the transfer of K (and phosphate) into the cells for protein synthesis. It has been shown that the supply of K (and phosphate) should parallel the supply of amino acids to avoid a refeeding-like syndrome. Thus, when providing early high amino acids and energy from birth according to the revised guidelines, sufficient K intake is also required.

9.5. Severe metabolic acidosis

Severe metabolic acidosis ($\text{pH} < 7.2$ with base deficit $> 10 \text{ mmol/L}$ or bicarbonates $< 12 \text{ mmol/L}$) during PN may be induced by high cumulative Cl intake [$> 10 \text{ mmol/kg}$ during the first 3 days (i.e. 3.3 mmol/kg/day on average) and $> 45 \text{ mmol/kg}$ during the first 10 days (i.e. 4.5 mmol/kg/day on average)]. This could be especially the case for infants at high risk (large PDA, weight loss $> 15\%$, ELBW). The use of “Cl-free” Na and K solutions should be considered in preterm infants on PN, in order to reduce the risk of hyperchloraemia and metabolic acidosis.

Conflict of interest

None declared.

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