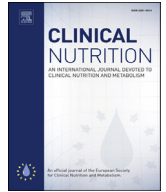




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ESPGHAN/ESPEN/ESPR guidelines on pediatric parenteral nutrition: Fluid and electrolytes

F. Jochum^{a,*}, S.J. Moltu^b, T. Senterre^c, A. Nomayo^a, O. Goulet^d, S. Iacobelli^e, the ESPGHAN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition¹

^a Ev. Waldkrankenhaus Spandau, Department of Pediatrics, Berlin, Germany

^b Department of Neonatal Intensive Care, Oslo University Hospital, Oslo, Norway

^c Service Universitaire de Néonatalogie, Centre Hospitalier Régional (CHR) de la Citadelle, Centre Hospitalier Universitaire (CHU) de Liège, Liege University, Liège, Belgium

^d Department of Pediatric Gastroenterology, Hepatology and Nutrition, Intestinal Failure Rehabilitation Centre, National Reference Centre for Rare Digestive Diseases, APHP Necker-Enfants Malades Hospital, Paris-Descartes University, Paris, France

^e Réanimation Néonatale et Pédiatrique, Néonatalogie CHU La Réunion, Site Sud-Saint Pierre and Centre d'Études Périnatales de l'Océan Indien, CHU La Réunion, Site Sud, Saint Pierre, France

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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

* Corresponding author. Department of Pediatrics, Ev. Waldkrankenhaus Spandau, Stadtrandstr. 555, D-13589 Berlin, Germany. Fax: +49 (0) 30/3702 2380.

E-mail address: frank.jochum@pgdiakonie.de (F. Jochum).

¹ ESPGHAN/ESPEN/ESPR/CSPEN working group on Pediatric Parenteral Nutrition: BRAEGGER Christian, University Children's Hospital, Zurich, Switzerland; BRONSKY Jiri, University Hospital Motol, Prague, Czech Republic; CAI Wei, Shanghai Jiao Tong University, Shanghai, China; CAMPOY Cristina, Department of Paediatrics, School of Medicine, University of Granada, Granada, Spain; CARNIELLI Virgilio, Polytechnic University of Marche, Ancona, Italy; DARMAUN Dominique, Université de Nantes, Nantes, France; DECSI Tamás, Department of Pediatrics, University of Pécs, Pécs, Hungary; DOMELLÖF Magnus, Department of Clinical Sciences, Pediatrics, Umeå University, Sweden; EMBLETON Nicholas, Newcastle University, Newcastle upon Tyne, The United Kingdom; FEWTRELL Mary, UCL Great Ormond Street Institute of Child Health, London, UK; FIDLER MIS Nataša, University Medical Centre Ljubljana, Ljubljana, Slovenia; FRANZ Axel, University Children's Hospital, Tuebingen, Germany; GOULET Olivier, University Sordonne-Paris-Cité; Paris-Descartes Medical School, Paris, France; HARTMAN Corina, Schneider Children's Medical Center of Israel, Petach Tikva, Israel and Carmel Medical Center, Haifa Israel; HILL Susan, Great Ormond Street Hospital for Children, NHS Foundation Trust and UCL Institute of Child Health, London, United Kingdom; HOJSK Iva, Children's Hospital Zagreb, University of Zagreb School of Medicine, University of J. J. Strossmayer School of Medicine Osijek, Croatia; IACOBELLI Silvia, CHU La Réunion, Saint Pierre, France; JOCHUM Frank, Ev. Waldkrankenhaus Spandau, Berlin, Germany; JOOSTEN, Koen, Department of Pediatrics and Pediatric Surgery, Intensive Care, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; KOLACEK Sanja, Children's Hospital, University of Zagreb School of Medicine, Zagreb, Croatia; KOLETZKO Berthold, k LMU – Ludwig-Maximilians-Universität Munich, Dr. von Hauner Children's Hospital, Munich, Germany; KSIAZYK Janusz, Department of Pediatrics, Nutrition and Metabolic Diseases, The Children's Memorial Health Institute, Warsaw; LAPILLONNE Alexandre, Paris-Descartes University, Paris, France; LOHNER Szimonetta, Department of Pediatrics, University of Pécs, Pécs, Hungary; MESOTTEN Dieter, KU Leuven, Leuven, Belgium; MIHÁLYI Krisztina, Department of Pediatrics, University of Pécs, Pécs, Hungary; MIHATSCH Walter A., Ulm University, Ulm, and Helios Hospital, Pforzheim, Germany; MIMOUNI Francis, Department of Pediatrics, Division of Neonatology, The Wilf Children's Hospital, the Shaare Zedek Medical Center, Jerusalem, and the Tel Aviv University, Tel Aviv, Israel; MØLGAARD Christian, Department of Nutrition, Exercise and Sports, University of Copenhagen, and Paediatric Nutrition Unit, Rigshospitalet, Copenhagen, Denmark; MOLTU Sissel J., Oslo University Hospital, Oslo, Norway; NOMAYO Antonia, Ev. Waldkrankenhaus Spandau, Berlin, Germany; PICAUD Jean Charles, Laboratoire CarMEN, Claude Bernard University Lyon 1, Hôpital croix rouge, Lyon, France; PRELL Christine, LMU – Ludwig-Maximilians-Universität Munich, Dr. von Hauner Children's Hospital, Munich, Germany; PUNTIS John, The General Infirmary at Leeds, Leeds, UK; RISKIN Arie, Bnai Zion Medical Center, Rappaport Faculty of Medicine, Technion, Haifa, Israel; SAENZ DE PIPAON Miguel, Department of Neonatology, La Paz University Hospital, Red de Salud Materno Infantil y Desarrollo – SAMID, Universidad Autónoma de Madrid, Madrid, Spain; SENTERRE Thibault, CHU de Liège, CHR de la Citadelle, Université de Liège, Belgium; SHAMIR Raanan, Schneider Children's Medical Center of Israel, Petach Tikva, Israel; Tel Aviv University, Tel Aviv, Israel; SIMCHOWITZ Venetia, Great Ormond Street NHS Trust, London, The United Kingdom; SZITANYI Peter, General University Hospital, First Faculty of Medicine, Charles University in Prague, Czech Republic; TABBERS Merit M., Emma Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands; VAN DEN AKKER Chris H.B., Emma Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands; VAN GOUDOEVER Johannes B., Emma Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands; VAN KEMPEN Anne, OLVG, Amsterdam, the Netherlands; VERBRUGGEN Sascha, Department of Pediatrics and Pediatric Surgery, Intensive Care, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; WU Jiang, Xin Hua Hospital, Shanghai, China; YAN Weihui, Department of Gastroenterology and Nutrition, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China.

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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 ($\text{Na} + \text{K-Cl} = 1-2 \text{ mmol/kg/d}$) 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 homeostasis 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 homeostasis 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 homeostasis).
- provide enough extra water and electrolytes to reach an adequate rate of growth with adequate fluid and electrolyte homeostasis

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).^a

	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 2
Recommended 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 3
Recommended 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 growth 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.

References

- [1] Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R, Parenteral Nutrition Guidelines Working Group; European Society for Clinical Nutrition and Metabolism; European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN); European Society of Paediatric RESEARCH (ESPR). Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr* 2005 Nov;41(Suppl. 2):S1–87.
- [2] Friis-Hansen B. Body water compartments in children: changes during growth and related changes in body composition. *Pediatrics* 1961;28:169–81.
- [3] Fomon SJ, Haschke F, Ziegler EE, Nelson SE. Body composition of reference children from birth to age 10 years. *Am J Clin Nutr* 1982;35:1169–75.
- [4] Fusch C, Slotboom J, Fuehrer U, Schumacher R, Keisker A, Zimmermann W, et al. Neonatal body composition: dual energy X-ray absorptiometry, magnetic resonance imaging, and three dimensional chemical shift imaging versus chemical analysis in piglets. *Pediatr Res* 1999;46:465–73.
- [5] Nicholson J, Pesce M. Laboratory testing and reference values in infants and children. In: Nelson W, Behrman R, Kliegman R, Jenson HB, editors. *Textbook of Pediatrics*. Saunders WB: Philadelphia; 2002. p. 2031–84.
- [6] Fusch C, Hungerland E, Scharer B, Moeller H. Water turnover of healthy children measured by deuterated water elimination. *Eur J Pediatr* 1993;152:110–4.
- [7] Martin D. Wasser und anorganische Elemente. In: Harpner H, Martin D, Mayes P, Rodwell V, editors. *Medizinische Biochemie*. Berlin: Springer Verlag; 1983. p. 657–71.
- [8] Winters R. Maintenance fluid therapy. *The body fluids in pediatrics*. Boston: Little Brown; 1973.
- [9] Sinclair JC. Metabolic rate and temperature control. In: Smith CA, Nelson N, editors. *The physiology of the newborn infant*. Springfield: Charles Thomas; 1976. p. 354–415.
- [10] Fusch C, Jochum F. Water, sodium, potassium, and chloride. In: Tsang RC, Lucas A, Uauy R, Zlotkin S, editors. *Nutritional needs of the preterm infant*. Baltimore: Williams and Wilkins; 2004.
- [11] Fusch C, Jochum F. Water, sodium, potassium and chloride. In: Koletzko B, Poindexter B, Uauy R, editors. *Nutritional care of preterm infants: scientific basis and practical guidelines*, vol. 110. Basel, Karger: World Rev Nutr Diet; 2014. p. 99–120. <https://doi.org/10.1159/000358461>. Epub 2014 Apr 11.
- [12] Knutson DW, Chieu F, Bennett CM, Glascock RJ. Estimation of relative glomerular capillary surface area in normal and hypertrophic rat kidneys. *Kidney Int* 1978;14:437–43.
- [13] Fawer CL, Torrado A, Guignard JP. Maturation of renal function in full-term and premature neonates. *Helv Paediatr Acta* 1979;34:11–2.
- [14] Spitzer A. Renal physiology and function development. In: Edelmann CM, editor. *The kidney and urinary tract*. Boston: Little Brown; 1978. p. 125–8.
- [15] Guignard JP, Gouyon JB. Glomerular filtration rate in neonates. In: Oh W, Guignard JP, Baumgart S, editors. *Nephrology and fluid/electrolyte physiology. Neonatology questions and controversies*. Philadelphia: Saunders WB; 2012. p. 117–35.
- [16] Speller AM, Moffat DB. Tubulo-vascular relationships in the developing kidney. *J Anat* 1977;123:487–500.
- [17] Chevalier RL. Developmental renal physiology of the low birthweight preterm newborn. *J Urol* 1996;156:714–9.
- [18] Haycock GB, Aperia A. Salt and the newborn kidney. *Pediatr Nephrol* 1991;5:65–70.
- [19] Friis-Hansen B. Water – the major nutrient. *Acta Paediatr Scand Suppl* 1982;299:11–6.
- [20] Jobe A, Jacobs H, Ikegami M, Ikegami M, Jacobs H. Lung protein leaks in ventilated lambs: effects of gestational age. *J Appl Physiol* 1985;58:1246–51.
- [21] Senterre T, Abu Zahirah I, Pieltain C, de Halleux V, Rigo J. Electrolyte and mineral homeostasis after optimizing early macronutrient intakes in VLBW infants on parenteral nutrition. *J Pediatr Gastroenterol Nutr* 2015;61(4):491–8.
- [22] Worthley LI. Strong ion difference: a new paradigm or new clothes for the Acid-base emperor. *Crit Care Resuscit* 1999;1(2):214.
- [23] Stewart PA. Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol* 1983;61:1444–61.
- [24] Skellert S, Mayer A, Durward A, Tibby SM, Murdoch IA. Chasing the base deficit: hyperchloraemic acidosis following 0.9% saline fluid resuscitation. *Arch Dis Child* 2000;83:514–6.
- [25] Linshaw MA. Selected aspects of cell volume control in renal cortical and medullary tissue. *Pediatr Nephrol* 1991;5:653–65.
- [26] Bower TR, Pringle KC, Soper RT. Sodium deficit causing decreased weight gain and metabolic acidosis in infants with ileostomy. *J Pediatr Surg* 1988;23:567–72.
- [27] Modi N. Development of renal function. *Br Med Bull* 1988;44:935–56.
- [28] Modi N, Hutton JL. The influence of postnatal respiratory adaptation on sodium handling in preterm neonates. *Early Hum Dev* 1990;21:11–20.
- [29] Hammarlund K, Sedin G, Stromberg B. Transepidermal water loss in newborn infants. VIII. Relation to gestational age and post-natal age in appropriate and small for gestational age infants. *Acta Paediatr Scand* 1983;72:721–8.

- [30] Baumgart S. Reduction of oxygen consumption, insensible water loss, and radiant heat demand with use of a plastic blanket for low-birth weight infants under radiant warmers. *Pediatrics* 1984;74:1022–8.
- [31] Sosulski R, Polin RA, Baumgart S. Respiratory water loss and heat balance in intubated infants receiving humidified air. *J Pediatr* 1983;103:307–10.
- [32] Lane AT, Drost SS. Effects of repeated application of emollient cream to premature neonates' skin. *Pediatrics* 1993;92:415–9.
- [33] Nopper AJ, Horii KA, Sookdeo-Drost S, Wang TH, Mancini AJ, Lane AT. Topical ointment therapy benefits premature infants. *J Pediatr* 1996;128:660–9.
- [34] Conner JM, Soll RF, Edwards WH. Topical ointment for preventing infection in preterm infants. *Cochrane Database Syst Rev* 2004;(1):CD001150.
- [35] Edwards WH, Conner JM, Soll RF, Vermont Oxford Network Neonatal Skin Care Study Group. The effect of prophylactic ointment therapy on nosocomial sepsis rates and skin integrity in infants with birth weights of 501 to 1000 g. *Pediatrics* 2004 May;113(5):1195–203.
- [36] Meyer MP, Payton MJ, Salmon A, Hutchinson C, de Klerk A. A clinical comparison of radiant warmer and incubator care for preterm infants from birth to 1800 grams. *Pediatrics* 2001;108:395–401.
- [37] Neville MC, Keller R, Seacat J, Lutes V, Neifert M, Casey C, et al. Studies in human lactation: milk volumes in lactating women during onset of lactation and full lactation. *Am J Clin Nutr* 1988;48:1375–86.
- [38] Neville MC, Allen JC, Archer PC, Casey CE, Seacat J, Keller RP, et al. Studies in human lactation: milk volume and nutrient composition during weaning and lactogenesis. *Am J Clin Nutr* 1991;54:81–92.
- [39] Macdonald PD, Ross SR, Grant L, Young D. Neonatal weight loss in breast and formula fed infants. *Arch Dis Child Fetal Neonatal* 2003;88(6):472–6.
- [40] Wright CM, Parkinson KN. Postnatal weight loss in term infants: what is "normal" and do growth charts allow for it? *Arch Dis Child Fetal Neonatal* 2004;89:254–7.
- [41] Adamkin DH. Issues in the nutritional support of the ventilated baby *Clin Perinatol* 1998;25:79–96.
- [42] Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants (Cochrane Review). In: *The Cochrane library*. Chichester, UK: John Wiley & Sons, Ltd.; 2004. Issue 1.
- [43] Moltu SJ, Blakstad EW, Strømmen K, Almaas AN, Nakstad B, Rønnestad A, et al. Enhanced feeding and diminished postnatal growth failure in very-low-birth-weight infants. *J Pediatr Gastroenterol Nutr* 2014 Mar;58(3):344–51.
- [44] Senterre T, Rigo J. Reduction in postnatal cumulative nutritional deficit and improvement of growth in extremely preterm infants. *Acta Paediatr* 2012 Feb;101(2):e64–70.
- [45] Moltu SJ, Strømmen K, Blakstad EW, Almaas AN, Westerberg AC, Brække K, et al. Enhanced feeding in very-low-birth-weight infants may cause electrolyte disturbances and septicemia – a randomized, controlled trial. *Clin Nutr* 2013 Apr;32(2):207–12. <https://doi.org/10.1016/j.clnu.2012.09.004>. Epub 2012 Sep 21.
- [46] Senterre T, Rigo J. Optimizing early nutritional support based on recent recommendations in VLBW infants and postnatal growth restriction. *J Pediatr Gastroenterol Nutr* 2011 Nov;53(5):536–42.
- [47] Christmann V, Visser R, Engelkes M, de Grauw AM, van Goudoever JB, van Heijst AF. Yes, we can – achieve adequate early postnatal growth in preterm infants. *Acta Paediatr* 2013 Dec;102(12):e530.
- [48] Maggio L, Cota F, Gallini F, Lauriola V, Zecca C, Romagnoli C. Effects of high versus standard early protein intake on growth of extremely low birth weight infants. *J Pediatr Gastroenterol Nutr* 2007;44:124–9.
- [49] Heimler R, Bamberger JM, Sasidharan P. The effects of early parenteral amino acids on sick premature infants. *Indian J Pediatr* 2010 Dec;77(12):1395–9.
- [50] Hartnoll G, Betremieux P, Modi N. Randomised controlled trial of postnatal sodium supplementation on body composition in 25 to 30 week gestational age infants. *Arch Dis Child Fetal Neonatal* 2000;82:F24–8.
- [51] Al-Dahhan J, Haycock GB, Nichol B, Chantler C, Stimmler L. Sodium homeostasis in term and preterm neonates. III. Effect of salt supplementation. *Arch Dis Child* 1984;59:945–50.
- [52] Baraton L, Ancel PY, Flamant C, Orsonneau JL, Darmaun D, Rozé JC. Impact of changes in serum sodium levels on 2-year neurologic outcomes for very preterm neonates. *Pediatrics* 2009;124(4).
- [53] Christmann V, de Grauw AM, Visser R, Matthijse RP, van Goudoever JB, van Heijst AF. Early postnatal calcium and phosphorus metabolism in preterm infants. *J Pediatr Gastroenterol Nutr* 2014 Apr;58(4):398–403.
- [54] Ichikawa G, Watabe Y, Suzumura H, Sairenchi T, Muto T, Arisaka O. Hypophosphatemia in small for gestational age extremely low birth weight infants receiving parenteral nutrition in the first week after birth. *J Pediatr Endocrinol Metab* 2012;25(3–4):317–21.
- [55] Bonsante F, Iacobelli S, Latorre G, Rigo J, De Felice C, Robillard PY, et al. Initial amino acid intake influences phosphorus and calcium homeostasis in preterm infants – it is time to change the composition of the early parenteral nutrition. *PLoS One* 2013 Aug 15;8(8):e72880. <https://doi.org/10.1371/journal.pone.0072880>. eCollection 2013.
- [56] Bonsante F, Iacobelli S, Chantegret C, Martin D, Gouyon JB. The effect of parenteral nitrogen and energy intake on electrolyte balance in the preterm infant. *Eur J Clin Nutr* 2011 Oct;65(10):1088–93.
- [57] Elstgeest LE, Martens SE, Lopriore E, Walther FJ, te Pas AB. Does parenteral nutrition influence electrolyte and fluid balance in preterm infants in the first days after birth? *PLoS One* 2010 Feb 3;5(2):e9033. <https://doi.org/10.1371/journal.pone.0009033>.
- [58] Jamin A, D'Inca R, Le Floc'h N, Kuster A, Orsonneau JL, Darmaun D, et al. Fatal effects of a neonatal high-protein diet in low-birth-weight piglets used as a model of intrauterine growth restriction. *Neonatology* 2010 Jun;97(4):321–8.
- [59] Cooke RWI. Factors associated with periventricular haemorrhage in very low birth weight infants. *Arch Dis Child* 1981;56:425–31.
- [60] Jadhav P, Parimi PS, Kalhan SC. Parenteral amino acid and metabolic acidosis in premature infants. *J Parenter Enteral Nutr* 2007 Jul–Aug;31(4):278–83.
- [61] Kermorvant-Duchemin E, Iacobelli S, Eleni-Dit-Trolli S, Bonsante F, Kermorvant C, Sarfati G, et al. Early chloride intake does not parallel that of sodium in extremely-low-birth-weight infants and may impair neonatal outcomes. *J Pediatr Gastroenterol Nutr* 2012 May;54(5):613–9.
- [62] Peters O, Ryan S, Matthew L, Cheng K, Lunn J. Randomised controlled trial of acetate in preterm neonates receiving parenteral nutrition. *Arch Dis Child Fetal Neonatal* 1997 Jul;77(1):F12–5.
- [63] Iacobelli S, Kermorvant-Duchemin S, Bonsante F, Lapillonne A, Gouyon JB. Chloride balance in preterm infants during the first week of life. *Int J Pediatr* 2012;931597. <https://doi.org/10.1155/2012/931597>.
- [64] Engelke SC, Shah BL, Vasan U, Raye JR. Sodium balance in very low birth-weight infants. *J Pediatr* 1978;93:837–41.
- [65] Asano H, Taki M, Igarashi Y. Sodium homeostasis in premature infants during the early postnatal period: results of relative low volume of fluid and sodium intake. *Pediatr Nephrol* 1987;1:C38.
- [66] Costarino AT, Gruskal JA, Corcoran L, Polin RA, Baumgart S. Sodium restriction versus daily maintenance replacement in very low birth weight premature neonates: a randomized, blind therapeutic trial. *J Pediatr* 1992;120:99–106.
- [67] Ekblad H, Kero P, Takala J, Korvenranta H, Välimäki I. Water, sodium and acid-base balance in premature infants: therapeutical aspects. *Acta Paediatr Scand* 1987;76:47–53.
- [68] Engle WD, Magness R, Faucher DJ, Arant BS, Rosenfeld CR. Sodium balance in the growing preterm infant. *Infant Pediatr Res* 1985;19:376a.
- [69] Lorenz JM, Kleinman LI, Kotagal UR, Reller MD. Water balance in very low-birthweight infants: relationship to water and sodium intake and effect on outcome. *J Pediatr* 1982;101:423–32.
- [70] Shaffer SG, Meade VM. Sodium balance and extracellular volume regulation in very low birth weight infants. *J Pediatr* 1989;115:285–90.
- [71] Al-Dahhan J, Jannoun L, Haycock GB. Effect of salt supplementation of newborn premature infants on neurodevelopmental outcome at 10–13 years of age. *Arch Dis Child Fetal Neonatal* 2002;86:120–3.
- [72] Catzeflis C, Schutz Y, Micheli JL, Welsch C, Arnaud MJ, Jéquier E. Whole body protein synthesis and energy expenditure in very low birth weight infants. *Pediatr Res* 1985;19:679–87.
- [73] Day GM, Radde IC, Balfe JW, Chance GW. Electrolyte abnormalities in very low birthweight infants. *Pediatr Res* 1976;10:522–6.
- [74] Polberger SK, Axelsson IA, Raiha NC. Growth of very low birth weight infants on varying amounts of human milk protein. *Pediatr Res* 1989;25:414–9.
- [75] Ziegler EE, Fomon SJ. Major minerals. In: Fomon SJ, editor. *Infant nutrition*. Philadelphia: Saunders, WB; 1974. p. 267–97.
- [76] Gross SJ. Growth and biochemical response of preterm infants fed human milk or modified infant formula. *N Engl J Med* 1983;308:237–41.
- [77] Butterfield J, Lubchenco LO, Bergstedt J, O'Brien D. Patterns in electrolyte and nitrogen balance in the newborn premature infant. *Pediatrics* 1960;26:777–91.
- [78] Darrow DC, Pratt EL. Fluid therapy; relation to tissue composition and the expenditure of water and electrolyte. *J Am Med Assoc* 1950 May 27;143(4):365–73.
- [79] Chesney CR. The maintenance need for water in parenteral fluid therapy, by Malcolm A. Holliday, MD, and William E. Segar, MD. *Pediatrics*, 1957;19:823–832. *Pediatrics* 1998 Jul;102(1 Pt 2):229–30.
- [80] Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics* 1957 May;19(5):823–32.
- [81] Allison ME, Walker V. The sodium and potassium intake of 3 to 5 year olds. *Arch Dis Child* 1986;61:159–63.
- [82] Kanarek KS, Williams PR, Curran JS. Total parenteral nutrition in infants and children. *Adv Pediatr* 1982;29:151–81.
- [83] Liappis N, Reimnitz P. Reference values of sodium, potassium, calcium, chloride and inorganic phosphate excretion in 24-hour urine of healthy children. [Article in German]. *Klin Pediatr* 1984;196:367–9.
- [84] Jochum F, Krohn K, Kohl M, Loui A, Nomayo A, Koletzko B and the DGEM Steering Committee. Parenterale Ernährung in der Kinder- und Jugendmedizin S3-Guideline of the German Society for Nutritional Medicine (DGEM) in Cooperation with the GESKES, the AKE, the DGKJ and the GNPI. *Parenterale Nutrition in Paediatrics Aktuell Ernährungsmed* 2014;39:e99–147.
- [85] Jochum F, Krohn K, Kohl M, Loui A, Nomayo A, Koletzko B, and the DGEM Steering Committee. Parenterale Ernährung von Kindern und Jugendlichen: Empfehlungen und Experten-Statements. Essentials der S3-Leitlinie der Deutschen Gesellschaft für Ernährungsmedizin (DGEM) in Zusammenarbeit mit der Gesellschaft für Klinische Ernährung der Schweiz (GESKES), der Österreichischen Arbeitsgemeinschaft für Klinische Ernährung (AKE), der Deutschen Gesellschaft für Kinder- und Jugendmedizin (DGKJ), sowie der Gesellschaft für Neonatologie und

- Pädiatrische Intensivmedizin (GNPI). *Monatsschr Kinderheilkd* 2015;(2): 150–63.
- [86] Vakilova L, Sluncheva B, Jarukova N, Pramatarova T, Shishkova R, Emilova Z. Guidelines for parenteral nutrition in high risk newborn babies. *Akush Ginekol (Sofia)* 2010;49(2):61–4.
- [87] Moritz ML, Ayus JC. Intravenous fluid management for the acutely ill child. *Curr Opin Pediatr* 2011;23:186–93.
- [88] Moritz ML, Ayus JC. Prevention of hospital-acquired hyponatremia. *Pediatrics* 2003;111:227–30.
- [89] McNab S, Ware RS, Neville KA, Choong K, Coulthard MG, Duke T, et al. Isotonic versus hypotonic solutions for maintenance intravenous fluid administration in children. *Cochrane Database Syst Rev* 2014 Dec 18;12: CD009457. <https://doi.org/10.1002/14651858.CD009457.pub2>.
- [90] Foster BA, Tom D, Hill V. Hypotonic versus isotonic fluids in hospitalized children: a systematic review and meta-analysis. *J Pediatr* 2014 Jul;165(1): 163–169.e2. <https://doi.org/10.1016/j.jpeds.2014.01.040>. Epub 2014 Feb 28.
- [91] McNab S, Duke T, South M, Babl FE, Lee KJ, Arnup SJ, et al. 140 mmol/L of sodium versus 77 mmol/L of sodium in maintenance intravenous fluid therapy for children in hospital (PIMS): a randomised controlled double-blind trial. *Lancet* 2015 Mar 28;385(9974):1190–7. [https://doi.org/10.1016/S0140-6736\(14\)61459-8](https://doi.org/10.1016/S0140-6736(14)61459-8). Epub 2014 Dec 1.
- [92] D'Antiga L, Goulet O. Intestinal failure in children: the European view. *J Pediatr Gastroenterol Nutr* 2013;56:118–26.
- [93] Windsor CW, Fejfar J, Woodward DA. Gastric secretion after massive small bowel resection. *Gut* 1969;10:779–86.
- [94] Cortot A, Fleming CR, Malagelada JR. Improved nutrient absorption after cimetidine in short-bowel syndrome with gastric hypersecretion. *N Engl J Med* 1979;300(2):79–80.
- [95] Murphy JP, King DR, Dubois A. Treatment of gastric hypersecretion with cimetidine in the short-bowel syndrome. *N Engl J Med* 1979;300:80–1.
- [96] Williams NS, Evans P, King RF. Gastric acid secretion and gastrin production in the short bowel syndrome. *Gut* 1985;26:914–9.
- [97] Hyman PE, Everett SL, Harada T. Gastric acid hypersecretion in short bowel syndrome in infants: association with extent of resection and enteral feeding. *J Pediatr Gastroenterol Nutr* 1986;5:191–7.
- [98] Nightingale JM, Lennard-Jones JE, Walker ER, Farthing MJ. Jejunal efflux in short bowel syndrome. *Lancet (London, England)* 1990;336:765–8.
- [99] Jacobsen O, Ladefoged K, Stage JG, Jarnum S. Effects of cimetidine on jejunostomy effluents in patients with severe short-bowel syndrome. *Scand J Gastroenterol* 1986;21:824–8.
- [100] Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. *Gastroenterology* 2003;124: 1111–34.
- [101] Kett K, Aadland E, Berstad A. Inhibition of gastric secretion in man with a new H₂-receptor antagonist, ranitidine. *Scand J Gastroenterol* 1980;15: 249–51.
- [102] Dammann HG, Simon B. The new histamine H₂-receptor antagonist ranitidine. Duration of action. *Scand J Gastroenterol Suppl* 1981;69:39–43.
- [103] Holloway RH, Kuljian B, Eshelman F, McCallum RW. Effects of ranitidine and of cimetidine on pentagastrin-stimulated gastric acid secretion. *Clin Pharmacol Ther* 1984;35:203–7.
- [104] Thompson JC, Walker JP. Indications for the use of parenteral H₂-receptor antagonists. *Am J Med* 1984;77:111–5.
- [105] McFadden MA, DeLegge MH, Kirby DF. Medication delivery in the short-bowel syndrome. *J Parenter Enteral Nutr* 1993;17:180–6.
- [106] Hyman PE, Garvey TQ, Harada T. Effect of ranitidine on gastric acid hypersecretion in an infant with short bowel syndrome. *J Pediatr Gastroenterol Nutr* 1985;4:316–9.
- [107] Bullock L, Parks RB, Lampasona V, Mullins RE. Stability of ranitidine hydrochloride and amino acids in parenteral nutrient solutions. *Am J Hosp Pharm* 1985;42:2683–7.
- [108] Walker SE, Bayliff CD. Stability of ranitidine hydrochloride in total parenteral nutrient solution. *Am J Hosp Pharm* 1985;42:590–2.
- [109] Williams MF, Hak LJ, Dukes G. In vitro evaluation of the stability of ranitidine hydrochloride in total parenteral nutrient mixtures. *Am J Hosp Pharm* 1990;47:1574–9.
- [110] Baumgartner TG, Henderson GN, Fox J, Gondi U. Stability of ranitidine and thiamine in parenteral nutrition solutions. *Nutrition* 1997;13:547–53.
- [111] Allwood MC, Martin H. Stability of cocarboxylase in parenteral nutrition mixtures stored in multilayer bags. *Clin Nutr* 1998;17:231–4.
- [112] Baptista RJ. Cimetidine and parenteral nutrition in the ICU patient. *Clin Ther* 1986;8(Suppl. A):34–8.
- [113] Nightingale JM, Walker ER, Farthing MJ, Lennard-Jones JE. Effect of omeprazole on intestinal output in the short bowel syndrome. *Aliment Pharmacol Ther* 1991;5:405–12.
- [114] Jeppesen PB, Staun M, Tjellesen L, Mortensen PB. Effect of intravenous ranitidine and omeprazole on intestinal absorption of water, sodium, and macronutrients in patients with intestinal resection. *Gut* 1998;43:763–9.