Hyponatremia and hypernatremia in the newborn: *in medio stat virtus*

Maria Antonietta Marcialis[1], Angelica Dessi[1], Maria Cristina Pintus[1], Viviana Marinelli[1], Vassilios Fanos[1]

[1]*Department of Pediatrics, Section of Neonatal Intensive Care Unit, University of Cagliari, Italy*

TABLE OF CONTENTS

1. ABSTRACT

Hyponatremia and hypernatremia are complex clinical problems that occur frequently in full term newborns and in preterm infants admitted to the Neonatal Intensive Care Unit (NICU) although their real frequency and etiology are incompletely known. Pathogenetic mechanisms and clinical timing of hypo-hypernatremia are well known in adult people whereas in the newborn is less clear how and when hypo-hypernatremia could alter cerebral osmotic equilibrium and after how long time brain cells adapt themselves to the new hypo-hypertonic environment. Aim of this review is to present a practical approach and management of hypo-hypernatremia in newborns, especially in preterms.

2. INTRODUCTION

Sodium, an element essential to growth, is contained in bone, cartilage and connective tissue and is indispensible for the development and operation of the central nervous system.During intrauterine life the foetus lives in a warm, watery environment where it receives a constant supply of water and electrolytes from the mother. On the contrary, following birth the neonate must adapt to a relatively cold, dry environment with much wider fluctuations than those experienced in the uterus (1-2).Variations in the hydro-electrolytic balance in the preterm neonate of very low weight are extreme due to the immaturity of the different organs. The immature kidney in particular leads to high toxicity caused by fluids: in excess
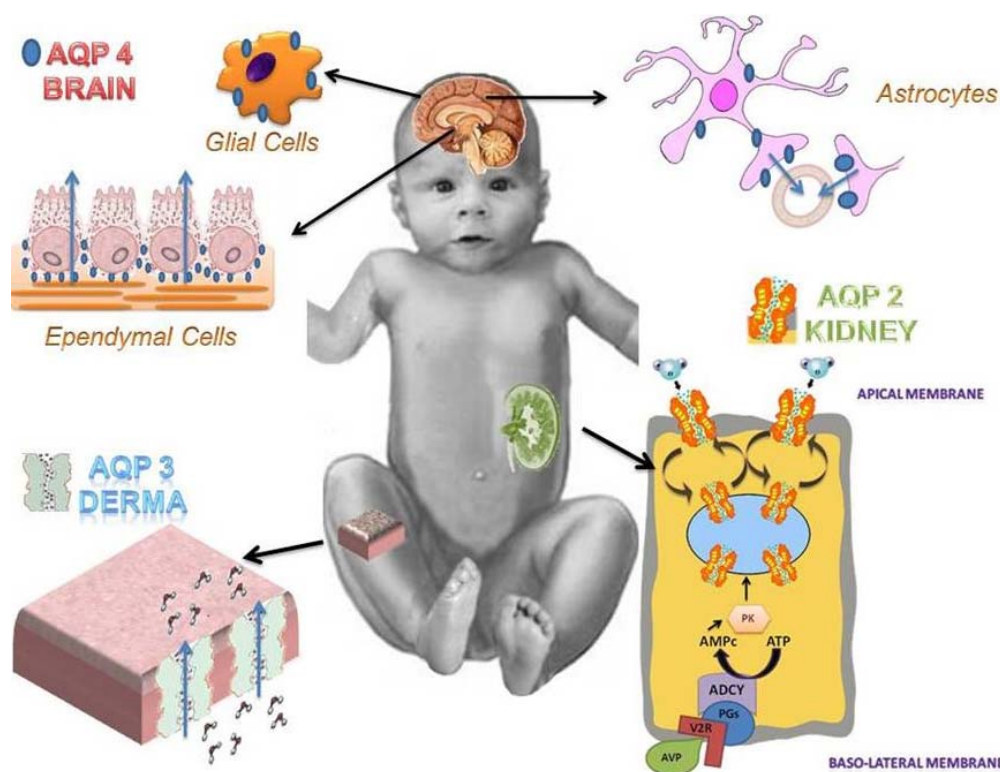
Figure 1. The brain-kidney-skin connection in preterm neonate aquaporins (AQP).

when the supply of water is abundant and scanty when the supply of water is insufficient (3).An abundant supply of fluids is the cause of generalized oedemas and insufficient lung activity brought about by the increase in interstitial liquid directly or indirectly through maintenance of a patent Botallo duct (4). On the contrary, the insufficient administration of fluids may lead to hypovolemia, hyperosmolarity, metabolic anomalies and kidney insufficiency (5).Since the concentration of sodium in the serum is the main indicator of the water balance in the preterm infant, this group of patients presents a particular frequency of hyponatremia and hypernatremia (6).Recently, serious sequels associated with hyponatremia and variations in sodium concentration in preterm infants have been reported (6-7). Hyponatremia is most frequently caused by an excessive supply of water rather than by a reduced sodium intake, while hypernatremia is most frequently secondary to a reduced supply of water or increased losses of water rather than by a excessive supply of sodium (8).The questions and controversies in neonatology concern the supply of liquids in the first days of life and the amount of the sodium supplement.

3. HYPO- AND HYPERNATREMIA IN THE PRETERM INFANT: DEFINITION AND FREQUENCY

Hyponatremia is defined as a serum concentration of sodium of < 133-135 mEq/L, although the several case histories give a natremia of < 125mEq/L as clinically significant.We speak of hypernatremia when the serum sodium concentration is > 150mEq/L, even though it would be better not to exceed 145 mEq/L.In clinical practice the neonatologist must make great efforts to ensure that the very low weight preterm neonate maintains an optimal natremia between 135 and 145 mEq/l. Sodium variations are in fact often iatrogenic and can be avoided (5). Hyponatremia affects about two thirds of the Very Low Birth Weight infants (VLBW) while hypernatremia presents with a frequency that varies, depending on case histories, between 4 and 30%[4] of VLBW neonates and of low gestation age (<27 weeks) (3,8).

4. THE BRAIN-KIDNEY-SKIN CONNECTION IN PRETERM NEONATE AQUAPORINS (AQP)

Aquaporins are tetramers that perform extremely important functions in maintaining the water balance of the organism. At least thirteen varieties of them have been discovered. Each monomer has a hydrophile foramen through which water passes following a local osmotic gradient. Some (AQP3-AQP7, AQP9) also transport glycerol and other small polar molecules. In preterm neonates the most important are AQP4, AQP3 and AQP2 (Figure 1). AQP4 is the aquaporin most expressed in the brain; it is situated in the cells of the blood-brain or blood-cerebrospinal fluid interfaces, settling in the cytoplasmatic extensions of the glial cells, in the ependymal cells and in the supraoptic and suprachiasmatic cells of the hypothalamic nuclei. The expression of AQP4 is reduced in the immature brain. This protein plays an important role in hyponatremic cerebral oedema, hydrocephalus, stroke and

infections of the nervous system (9-10). Its scanty expression probably represents a defence mechanism against cerebral oedema.AQP2s are normally located inside the cytoplasm of the cells of the kidney collector ducts. They move until they reach the apical plasmatic membrane of the collector duct, thus favouring the reabsorption of water in response to vasopressin (AVP). AQP2 is the primary target in water regulation by vasopressin (11). In the neonate there is a reduced sensitivity to AVP, not connected with the reduction of V2 receptors, located at the level of the baso-lateral membranes of the collector tubules, already expressed during foetal life, but in connection with the immaturity of the structures designated to respond to the AVP-receptor ligand with the consequent reduction of the expression of AQP2 at the level of the apical plasmatic membrane of the kidney collector duct. This explains the reduced capacity of the immature kidney to concentrate urine.The most important hormones in kidney maturation are the glucocorticoids. Besides favouring the maturation of sodium transporters, they also favour the postnatal maturation of kidney aquaporins (12).Finally, AQP3s allow the passage of water from the derma to the basal layer of the epidermis and are abundantly expressed in the cutis of the premature, thus favouring the loss of water by evaporation (2).

5. HYPO- AND HYPERNATREMIA AND THE WATER BALANCE

Premature birth requires a sudden adaptation to a gaseous environment with low humidity, and in the first week of life the premature infant presents a physiologically negative sodium and water balance caused by the contraction of extracellular liquid. The neonatologist has several ways in which to help or hinder this transition phase. Establishing the daily water quotient in very low weight premature infants is a dynamic rather than a static process. Thus the amount of liquids in the first, second, third and subsequent days of life cannot be established beforehand (13). Although in intensive therapy units the protocols ensure a certain internal coherence, the amount of water must be decided case by case and must take into account the gestational age, environmental humidity and clinical conditions (14). The water balance in the immediate neonatal period is influenced by the gestational age and intrauterine growth) the lower the gestational age, the greater will be the post-natal weight loss.The youngest in gestational age, even when they present more mature skin, lose more weight than appropriate since they present a higher water content and little fat (15).The premature infant loses a very large amount of water through the cutis: The cutaneous surface of very low weight premature infants is ample with respect to their weight (4). The premature infant's cutis is not completely developed. AQP3s, are abundantly expressed in the cutis of the premature infant (2). The premature neonate has a transparent and gelatinous skin containing only two or three strata of epidermic cells with absence or scarce development of the corneal layer. The cutis of the very immature neonate is thus more permeable and its water content is higher.Prenatal steroids reduce imperceptible losses since they favour maturation of the cutis and improve kidney perfusion, thus causing an

increase in diuresis (16).Cutaneous maturation is accelerated by delivery: the air induces cutaneous maturation in very low weight neonates in normal environmental humidity conditions (following birth there is an exponential loss of water at the cutis level and the cutis reaches a level of maturation similar to that of term infants after two to three weeks (17). The water balance is also influenced by intrauterine growth and gestational age.

In the premature infant of very low gestational age, the daily insensible water losses through the respiratory tract (30-40%) and cutis (60-70%) are quite high and may reach 1.5 times the haematic volume in the preterm infant (150 ml/kg/day) (3).Insensible losses through the cutis vary also as a function of the vapour pressure of environmental water (13). Indeed, high environmental humidity (80-100%) during the first week of life contrasts the loss of water through the cutis and is effective in reducing the risk of dehydration and hypernatremia, but may represent a greater risk of hospital infections caused by *Pseudomonas* (18). Strong condensation (with the "rain-out" effect, as if it had just stopped raining on the inside walls of the incubator) represents the ideal "pabulum" for this kind of germ (19).In 2009, Baumgart recommended a prudential maintenance of humidity between 60 and 80% (20).It is thus auspicious to have an environment with high humidity in the first and second weeks of life, but the times and ways of reducing environmental humidification are still the subject of studies (3). Plastic polyurethane sheets, some of which containing antibacterial substances, have proved to be effective in reducing water loss through the cutis and in bringing about a reduction in the incidence of hypernatremia and mortality in very immature infants (21-22). However, problems of skin maceration and hyperthermia have been reported. These possible side effects can be avoided only by means of proper nursing assistance: nurses must perform additional axillary and rectal temperature measurements. It is also indispensible to avoid such sheets coming into contact with the neonate's skin, possibly by using rolls of cotton placed around the infant so that a thin layer of air separates the soft and delicate skin of the neonate from the plastic film (20).Emollients, used in the past to reduce transepidermic water loss in extremely low weight preterms, are today not advisable since they favour bacterial sepsis (23) and candidiasis (24).

For the neonatologist, the hydroelectrolytic balance is a real challenge: the clinical situation must necessarily be evaluated hour after hour, shift after shift, especially in the first week of life. It is often necessary to readjust the volumes two or three times a day with evaluation of hydroelectrolytic gains and losses. The role of the nurse is indispensible and consists of controlling temperature, environmental humidity and that of the gases in the ventilator circuit, of keeping to a minimum the time required for changing diapers and of any treatment that may be required. The nurse must also be sure that the infant's skin does not present excoriations, must report any signs of dehydration (such as depressed fontanelles with imbricate sutures) or excess water (oedemas) (25). When diuresis is evaluated through diaper weight, in the very

small it must be recalled that a part of the urine may evaporate if the incubator is not well humidified.In the first days following birth, all neonates present natriuresis favoured by different mechanisms such as the increase in haematic concentration of the atrial natriuretic factor produced by the myocardial cells following secondary stretching with the increase in the left atrial venous return caused by reabsorption of pulmonary liquid and the fall of resistance in the pulmonary vascular pressure (26). The neonatal kidney is not a reduced version of the adult kidney (12). The mechanism of tubular transport of sodium is functional in the neonate, but reaches a less mature stage (27). Preterms have a reduced number of sodium transporters, a smaller reabsorption surface and inadequate hormonal control (28). In the uterus the foetus produces urine rich in sodium. The fractioned excretion of sodium (FENa), that is, the amount of sodium eliminated in the urine compared to the filtered part, is inversely correlated with gestational age (29).FENa is higher in preterms (up to 12.5%) compared to term births (3.4% in the first hours of life, 1.5% afterwards) and adults (1%).The loss of sodium is the cause of the negative sodium balance and the weight loss in the first days of life. Very Low Birth Weight infants have a longer period of negative sodium balance. In preterms having a gestational age of < 32 weeks, the higher natriuresis is caused by a defect in reabsorption at the level of the proximal tubule with a subsequent higher load at the level of the distal convoluted tubules (30).

In the neonate there are high levels of aldosterone (the hormone that controls the expression and activity of different sodium, potassium and water transporting proteins such as Na-K ATPasi and AQP2), but the is also a partial physiological resistance (31). In the preterm the reabsorbtion of sodium at the intestinal level is also reduced (29).In the preterm there is a poor response to the antidiuretic hormone (ADH) in the secondary distal convoluted tubule due both to deficient secretion and reduced tubular sensitivity. The low osmotic pressure present in the extremely low weight premature infant may also hinder the secretion of ADH and contribute to the very high diuresis that is often observed in the third and fourth day of life (3).Losses of water and sodium that take place in the first week of life are probably part of an adaptive process from aquatic intrauterine life where the reabsorption of sodium is unnecessary to the extrauterine environment where sodium reabsorption becomes essential (31). The liquids administered to very low weight preterms should correspond to amounts strictly necessary to avoid both dehydration and hyperhydration.An initial rational amount of water in preterms weighing <1000g, suggested by Modi, may be represented by the sum of urinary losses and estimated losses through the cutis equivalent to approximately 100ml/Kg/day in an environment with a humidity of 70% (14).

Lorenz recommends an initial, more customized amount of water that varies with gestational age and in an environment with 50% humidity (Table 1).Subsequently the supply of liquids and sodium will depend on the post-natal phase. During the prediuretic phase(from birth to two or three days), diuresis is scanty: there may be

hyponatremia caused by water retention (expansion of LEC) or hypernatremia caused by an excessive loss of insensible water. Sodium excretion is minimum. The diuretic phase (defined as a volume of urine exceeding more than 80% of the volume of liquids administered) (32) takes place between the first and the fifth day and is characterized by a sharp increase in diuresis (5-7 ml/Kg/day) and natriuresis. Natremia is often reduced. Clinically, it is revealed by a weight loss and follows the reabsorption of foetal pulmonary fluid with expansion of the LEC. Finally the homeostatic phase is characterized by normal diuresis (2-3 ml/Kg/day).The three phases do not take place at the same postnatal age in all neonates (4). The diuretic phase, for example, is delayed in the case of Respiratory Distress Syndrome (RDS) while the use of antenatal steroids causes a fairly marked diuresis starting from the first day (16). On the average, very low weight preterm infants lose 2% of their body weight per day up to a maximum of 15% in the first week. Fluids must be increased if the daily weight loss is above 2% or the cumulative loss exceeds 15% and when natremia exceeds 145mEq/L.On the contrary, fluids must be reduced if weight is decreasing less than 1% per day and if there is hyponatremia associated with a weight increase (13).Some Neonatal Intensive Cares Unit (NICU) adopt a sodium restriction and administration of routine large amounts of water as an expedient to avoid hypernatremia, but in the long run this may not prove to be useful, considering the risk of pathologies such as Patent Ductus Arteriosus (PDA), Chronic Lung Disease (CLD) and Bronchopulmonary Dysplasia (BPD) (4). Excessive hydration causes an increase in interstitial liquid with a subsequent alteration in ventilation, a reduced response to the administration of exogenus surfactant (33).The neonatologist's task is thus that of allowing a weight loss of 10 to 15%.Recently, Sung reported an improvement in growth in the first twenty-eight days, a better sodium balance and a lower incidence of severe bronchopulmonary dysplasia in 95 preterms weighing < 1000g kept in incubators (Giraffe Omni bed) with 70-80% humidity in the first week of life, 50-60% afterwards, with respect to controls (87 cases) kept in non-humidified incubators. The amount of water prescribed in the first day was 100-120ml/Kg/day with daily increases of 20 ml/Kg/day up to a maximum of 160-180ml/Kg/day at five days. The fluids administered varied so as to allow a weight loss of 10-15% and to maintain a natremia between 135 and 145 mEq/L.The frequency of hypernatremia (positively correlated with brain haemorrhage) as also the insensible loss of water, diuresis and consequently the daily water requirement were higher in controls (34).

6. HYPONATREMIA AND PATENT DUCTUS ARTERIOSUS

During the diuretic-natriuretic phase which starts between the second and third day of life, natremia begins to decrease. This is a crucial time for the very immature neonate because it is necessary to reduce fluid intake in order to prevent the overload which could promote a significant PDA during the next fourth or fifth day of life. The restricted fluid intake should be kept on during the

Table 1. Guidelines for initiating fluid therapy in newborns

Gestational age	Postnatal day 1
<25 wk	150ml/Kg
25 to 27 wk	120ml/Kg
28 to 30 wk	100ml/Kg
31 to 36 wk	80ml/kg

Table 2. Variations in natremia and outcome in low weight preterm infants

Baraton (2009) (6) Variations in natremia >8mEq/L	G.A: <33 weeks	Motor and/or cognitive outcomes
Gawloswski (2006) (8) Natremia>150mEq/L	G.A: 27 weeks	Mortality*, CLD*, IVH*, PDA*, NEC*
Bhatty (1997-2002) (51) Rapid correction of hyponatremia	ELBW	Spastic cerebral paralysis Hypotonia Neurosensorial hearing loss
Murphy (1997) (45) Natremia<125mEq/L	VLBW	Spastic cerebral paralysis
Leslie (1995) (55) Natremia<125mEq/L	ELBW	Neurosensorial hearing loss
Ertl, Sulyok (2001) (44) Natremia<125mEq/L	VLBW	Neurosensorial hearing loss

*more hypernatremic patients experienced such complications but this was not significant

treatment with indomethacin or ibuprofen as it is often complicated by hyponatremia, excessive gain of weigh and oliguria (20,32).

During this phase should be necessary to reduce fluid intake until 60-80 ml/Kg or until natremia is higher than 145-150 mEq/L. To optimize nutrition it is advisable to concentrate the infused solutions. Furosemide promotes the prostaglandin (PGE2) synthesis and reduces the ductal response to ibuprofen therefore appears to be contraindicated or not recommended (35-38).

7. HYPO- AND HYPERNATREMIA: PRATICAL MANAGMENT

7.1. When to begin supplementing sodium?
The addition of salt to solutions must take into account the phase (39). In particular, the sodium supplement must not be given in the prediuretic phase since it may lead to a further expansion of LEC with the risk of pulmonary and peripheral oedema. Sodium must be added to the infused solution after the beginning of the contraction of LEC (40) or after a weight loss of 6% (14). Early administration of sodium causes a persistent expansion with retention of interstitial fluid and a possible increase in the frequency and seriousness of respiratory and cardiac problems such as CLD and PDA. When on the contrary the intake of sodium begins after the weight loss has taken place, the frequency of CLD appears to be lower (17,41-42).

7.2. How much sodium?
The premature infant requires large amounts of sodium secondary to kidney losses and the great need for rapid bone mineralization. Generally speaking, at least 4 mEq/Kg/day are needed unless the mother has been treated with steroids. According to Kloiber, preterms weighing less than 1000g may require from 3 to 8 mEq/Kg/day and sometimes even more. Initially, the sodium is to be administered intravenously, followed by means of milk fortification.

8. HYPO- AND HYPERNATREMIA IN THE PRETERM INFANT: THE CLINICAL PICTURE
Hyponatremia and hypernatremia are often asymptomatic but sometimes produce symptoms such as anorexia, nausea, vomiting, headache, disturbance of equilibrium, cramps, hyporeflexia, convulsions and death in older children and adults. In preterm and term neonates: apnea, bradicardia, lethargy or irritability and convulsions (43). When hyponatremia is chronic, that is, if it appears over a period of days or weeks, the only symptom may be a delay in growth. Hyponatremia or *ample variations in sodium concentration* represent a risk factor independent of adverse outcome (cerebral paralysis, behaviour and memory disturbance) (6,44-45), cerebral haemorrhage (46) and mortality (47) (Table 2). The speed with which hyponatremia takes place significantly influences the severity of neurological manifestations. Hyponatremia is acute and severe when natremia rapidly decreases in less than 48 hours to below 120mEq/L: in this case the cerebral homeostatic mechanisms do not act quickly enough to compensate for such rapid variations. This form is potentially dangerous: the first symptoms are irritability or lethargy. If the hyponatremia is not immediately and aggressively treated it may lead to cerebral oedema, irreversible neurological damage, respiratory arrest, hernia of the cerebral trunk and even death. The cerebral reactions to serum variations of natremia vary with age.In the adult brain hyposmolarity of LEC, secondary to hyponatremia, causes an unbalance in Intracellular Liquid (LIC) and LEC. The interior of the cell becomes hyperosmolar compared to the exterior and, owing to the law of osmotic balance, draws water with a consequent intracellular oedema. After a few hours (the rapid adaptation phase), the cells extrude electrolytes, especially potassium, but also sodium and chlorine, to the outside so as to increase the osmolarity of LEC and lose the excess water. After some days (the slow adaptation phase), the cells eliminate amino acids such as taurine, glutamate, but also myoinositol and phosphates. The brain adapts so as to minimize the symptoms (48).The immature brain presents different phases of adaptation compared to the adult: It is incapable of controlling the volume of cells through the extrusion of ions, but instead

Table 3. Do and don't in neonatal hypo-hypernatremia

DO	DON'Ts
In the first week of life encourage, and not hinder, a weight loss of at least 10-12%	Use humidification of 90-100% ("rain out" danger of infections)
Limit cutaneous water losses by using preferably humidification of 60-80%	Use a high routine water load
In the first 3-4 days of life check weight and supply of liquids at 8-hour intervals; increase by 10-20 ml/Kg/day if: sodium tends to increase and/or there is a weight loss in excess of 2%/day	Apply a routine sodium restriction
Sodium must be added to infused solutions following a contraction of LEC	Perform a rapid correction of hypo- or hypernatremia (>8mEq/L in 24 hours)
Check the amount of "hidden" sodium in the medicines administered	Use concentrated (3%) saline solutions
Optimize hydration through nutrition	

uses the extrusion of organic osmolites (especially taurine). Consequently the rapid adaptation phase is not mediated by the ions but by the intervention of other mechanisms such as the reduced expression of AQP4. This protein is composed of four monomers, each of which presents a foramen through which water freely flows. The AQP4 is situated in the cells of the blood-brain or blood-liqueur interfaces (ependymal, glial cells and astrocyte processes) (9). Other defence mechanisms against oedema are represented by high compliance of the secondary cranium in presence of the then not yet joined fontanelles and sutures.

In the case of hypernatremia, the hyperosmolarity of LEC calls for fluids from the cells, thus leading to cell dehydration. The very first compensation phase has been described in the adult and in older children and takes place within an hour if the hyponatremia is not very acute: sodium, potassium, amino acids and organic substances penetrate into the cells and need water. Generally speaking, within a week the brain regains 98% of the water content lost. Naturally, if the hypernatremia is acute and severe the brain is incapable of increasing the intracellular content of solutes enough to preserve its volume. When the cerebral volume is reduced, even by 10-15%, a physical distance is formed between the meninges and the cranium with the possible rupture of the bridge veins and consequent subarachnoid, subdural or even intracerebral haemorrhages (5). If hypernatremia sets in slowly, the neurons have the possibility of re-establishing their intracellular volume and adapting to the situation. The osmolites produced inside the cells cause a gradient of diffusion that brings water into the cells. Retrospective studies demonstrate that the neurological sequels in cases of hypernatremia are significant and include cognitive delay. Mortality varies between 10 and 16% depending on the case history, even with the proper amount of rehydration (43).

9. CORRECTION OF HYPO- AND HYPERNATREMIA AND THE BRAIN

The best practice in the treatment of hypo- and hypernatremia must take into account the risks of hyponatremia against those of the therapy. The best treatment of dysnatremias is represented by the slow correction of the electrolytic unbalance. Brain damage may ensue following rapid correction of a chronic hyponatremia. Extracellular Liquid, following administration of solutions with a high sodium content, becomes relatively hypertonic and this may cause rapid cell dehydration with rupture of the close connections between the endothelial cells, the passage of complementary proteins and cytokines with damage to the oligodendrocytes and demyelination (49). Osmotic myelinolysis may take place

when the speed of the correction exceeds 0.5/mEq/L/h or 12 mEq/L in 24 hours. Bridge and extra-bridge osmotic myelinolysis has been described in adults and children, but cases concerning the unweaned are now beginning to appear in the literature (50). In very low weight preterm infants in whom natremia had been rapidly corrected, a higher incidence of spastic cerebral paralysis, neurosensorial auditory damage and behavioural problems has been observed (51). At present there is no clear consensus concerning the best treatment of symptomatic hyponatremia. In acute forms, where the risk of sequels is greater than that of myelinolysis, the correction must be rapid and, for this reason, according to some authors, it is necessary to consider the use of 3% saline solutions (0.5mEq/cc ev).According to others, the 3% saline solution should be banned in asymptomatic VLBW or Extremely Low Birth Weight (ELBW) preterms with serum sodium <125 (20).Natremia must be monitored every two hours (52). Even in emergency cases the natremia target must be that which allows the patient to become asymptomatic in all certainty; following this, a more gradual correction is to be applied. Plasmatic sodium should not increase more than 8-10 mEq/L in the first 24 hours so as to avoid both cerebral oedema and the risk of myelinolysis. In chronic forms an isotonic saline solution, possibly associated with the use of diuretics, should be preferred.For the reasons given above, also in patients affected by hypernatremia the nervous system may be involved during the rehydration phase when this is performed too quickly (with speed of natremia >0.5-1.0 mmol/L/h) (53). If the natremia is very high, >160mEq/L, it is advisable to administer a 0.9% saline solution so as to reduce the natremia slowly. Subsequently a 0.45% saline solution in 10% glucosate is recommended (54).

10. PERSPECTIVE

Neonatologists must thus encourage, and not hinder, a physiological weight loss of 10-15%. They must try to limit insensible losses in the first week of life by means of appropriate environmental humidification and gases administered.The relationship between sodiemia, weight and diuresis must be monitored frequently. Before the beginning of the diuretic phase, sodium must not be added to the solutions (caution in the use of bicarbonate).In calculating the water balance, it is to be kept in mind that children born of mothers who have taken steroids will have skin and kidneys more mature at birth and therefore they will have lower insensible losses of water, but an earlier and more marked diuresis.The younger in gestational age (G.A.) lose more weight than do those born at term owing to their higher water content. Since the correction of a hyponatremia or a hypernatremia may not be a process as innocent as appears, it is best to prefer a slow correction to allow for the shifting of the osmolites and to allow the brain to adjust (Table 3).

11. REFERENCES

1. John M Lorenz: Assessing fluid and electrolyte status in the newborn. National Academy of Clinical Biochemistry. *Clin Chem* 43, 205-10 (1997)

2. Gunnar Sedin, Jon Agren: Water and heat--the priority for the newborn infant. *Ups J Med Sci* 111, 45-59 (2006)

3. Masaki Wada, Satoshi Kusuda, Naoto Takahashi, Hiroshi Nishida: Fluid and electrolyte balance in extremely preterm infants <24 weeks of gestation in the first week of life. *Pediatr Int* 50, 331-6 (2008)

4.John M Lorenz: Fluid and electrolyte therapy and chronic lung disease. *Curr Opin Pediatr* 16, 152-6 (2004)

5. Michael L Moritz, Juan Carlos Ayus: Disorders of water metabolism in children: hyponatremia and hypernatremia. *Pediatr* Rev 23, 371-80 (2002)

6. Louis Baraton, Pierre Yves Ancel, Cyril Flamant, Jean Luc Orsonneau, Dominique Darmaun, Jean Christophe Rozé: Impact of changes in serum sodium levels on 2-year neurologic outcomes for very preterm neonates. Pediatrics 124, e655-61 (2009)

7. Jinan Al-Dahhan, Leila Jannoun, George Haycock: Effect of salt supplementation of newborn premature infants on neurodevelopmental outcome at 10–13 years of age. Arch Dis Child 86, F120–F123 (2002)

8. Zuzanna Gawlowski, Narendra Aladangady, Pietro G Coen: Hypernatraemia in preterm infants born at less than 27 weeks gestation. J Paediatr Child Health 42, 771-4 (2006)

9. Mario C Papadopoulos, Alan S Verkman: Aquaporin-4 and brain edema. Pediatr Nephrol 22, 778-84 (2007)

10. Endre Sulyok: Renal aspects of sodium metabolism in the fetus and neonate. In: Questions and controversies in neonatology series. Renal/fluids and electrolytes. Ed by W. Oh, J.P. Guignard, S Baumgart. Philadelphia: Saunders Elsevier, 23-53 (2008)

11. Søren Nielsen, Kwon Tae-Hwan, Jørgen Frøkiær, Mark A Knepper: Key Roles of Renal Aquaporins in Water Balance and Water-Balance Disorders. *News Physiol Sci* 15, 136-143 (2000)

12. Michel Baum, Raymond Quigley: Ontogeny of renal sodium transport. *Semin Perinatol* 28, 91-6 (2004)

13. John M Lorenz: Fluid and Electrolyte Therapy in the Very Low-birthweight Neonate. *NeoReviews* 9, e102 (2008)

14. Neena Modi: Management of fluid balance in the very immature neonate. *Arch Dis Child Fetal Neonatal* 89, F108-11 (2004)

15. Jean M Chow, Davina Douglas: Fluid and electrolyte management in the premature infant. *Neonatal Netw* 27, 379-86 (2008)

16. Gabriel Dimitriou, Valia Kavvadia, Markella Marcou, Anne Greenough: Antenatal steroids and fluid balance in very low birthweight infants. *Arch Dis Child Fetal Neonatal* 90, F509-13 (2005)

17. Gary Hartnoll: Basic principles and practical steps in the management of fluid balance in the newborn. *Semin Neonatol* 8, 307-13 (2003)

18. Tsutomu Ohno: Fluid and electrolyte balance in extremely low birth weight infants. *Perinat Med Jpn* 27, 523-9 (1997)

19. Val A Harpin, Nick Rutter: Humidification of incubators. *Arch Dis Child* 60, 219-24 (1985)

20. Stephen Baumgart: What's new from this millennium in fluids and electrolyte management for VLBW and ELBW prematures. *Journal of Neonatal-Perinatal Medicine* 2, 1-9 (2009)

21. Rachel Porat, Nancy Brodsky: Effect of Tegederm use on outcome of extremely low birth weight (ELBW) infants. *Pediatr Res* 33, 231 (1993)

22. Mavis L Donahue, Phelps L Dale, Susan E Richter, Jonathan M Davis: A semipermeable skin dressing for extremely low birth weight infants. *J Perinatol* 16, 20-6 (1996)

23. Amy Jo Nopper, Kimberly A. Horii, Sharon Sookdeo-Drost, Tung Ho Wang, Anthony J. Mancini, Alfred T. Lane: Topical ointment therapy benefits premature infants. *J Pediatr* 128, 660-9 (1996)

24. Judith R Campbell, Elena Zaccaria, Carol J. Baker: Systemic candidiasis in extremely low birth weight infants receiving topical petrolatum ointment for skin care: a case-control study. *Pediatrics* 105, 1041-5 (2000)

25. Robert Zietse, Roeland Zoutendijk, Ewout J Hoorn: Fluid, electrolyte and acid-base disorders associated with antibiotic therapy. *Nat Rev Nephr*ol 5, 193-202 (2009)

26. Modi Neena: Clinical implications of postnatal alterations in body water distribution. *Semin Neonatol* 8, 301-6 (2003)

27. Robert L Chevalier: The moth and the aspen tree: sodium in early postnatal development. *Kidney Int* 59, 1617-25 (2001)

28. Ulla Holtbäck, Anita C Aperia: Molecular determinants of sodium and water balance during early human development. *Semin Neonatol* 8, 291-9 (2003)

29. Leonard G Feld: Hyponatremia in infants and children: A practical approach. *J Nephrology* 9, 5 (1996)

30. Neena Modi: Hyponatraemia in the newborn. *Arch Dis Child Fetal Neonatal Ed* 78, F81–F84 (1998)

31. Laetitia Martinerie, Eric Pussard, Laurence Foix-L'Hélias, Francois Petit, Claudine Cosson, Pascal Boileau, Marc Lombès: Physiological partial aldosterone resistance in human newborns. *Pediatr Res* 66, 323-8 (2009)

32. Teresa D Puthoff: Fluids and electrolytes management. *Newborn and Infant Nursing Reviews* 4, 98-105 (2004)

33. Mikko Hallman M, Allen T Merritt, Kristina Bry, Colin Berry: Association between neonatal care practices and efficacy of exogenous human surfactant: results of a bicenter randomized trial. *Pediatrics* 91, 552-60 (1993)

34. Sung Min Kim, Edward Y Lee, Jie Chen, Steven Alan Ringer: Improved care and growth outcomes by using hybrid humidified incubators in very preterm infants. *Pediatrics* 125, e137-45 (2010)

35. Luc P Brion, Deborah E Campbell: Furosemide for symptomatic patent ductus arteriosus in indomethacin-treated infants. *Cochrane Database Syst Rev* 3:CD001148 (2001)

36. Peter Andriessen, Nicole C Struis, Hendrik Niemarkt, Sidarto Bambang Oetomo, Ronald B Tanke, Bart Van Overmeire: Furosemide in preterm infants treated with indomethacin for patent ductus arteriosus. *Acta Paediatr* 98, 797-803 (2009)

37. Arpitha Chiruvolu, Mambarath A Jaleel: Therapeutic management of patent ductus arteriosus. *Early Hum Dev* 85, 151-5 (2009)

38. Meera Narayanan-Sankar, Ronald I Clyman: Pharmacology Review Pharmacologic Closure of Patent Ductus Arteriosus in the Neonate. *NeoReviews* 4, 215-221 (2003)

39. Atsuko Tanaka, Ligia M Rugolo, Antero F Miranda, Cleide E Trindade: Fractional sodium excretion, urinary osmolality and specific gravity in preterm infants fed with fortified donor human milk. *Jornal de Pediatria* 82, 335-40 (2006)

40. Stephen Baumgart: Sodium intake in very low birth weight infants: is more always better? *Jornal de Pediatria* 82, 317-8 (2006)

41. William Oh, Brenda B Poindexter, Rebecca Perritt, James A Lemons, Charles R Bauer, Richard A Ehrenkranz, Barbara J Stoll, Kenneth Poole, Linda L Wright; Neonatal Research Network: Association between fluid intake and weight loss during the first ten days of life and risk of bronchopulmonary dysplasia in extremely low birth weight infants. *J Pediatr* 147, 786-90 (2005)

42. Andrew T Costarino Jr, Jeffrey A Gruskay, Linda Corcoran, Richard A Polin, Stephen Baumgart: Sodium restriction versus daily maintenance replacement in very low birth weight premature neonates: a randomized, blind therapeutic trial. *J Pediatr* 120, 99-106 (1992)

43. Catherine H Chung, Donald Zimmerman: Hypernatremia and Hyponatremia: Current understanding and management. *Clinical Pediatric Emergency Medicine* 10, 272-278 (2009)

44. Tibor Ertl, Kinga Hadzsiev, Olga Vincze, József Pytel, István Szabo, Endre Sulyok: Hyponatremia and sensorineural hearing loss in preterm infants. *Biol Neonate* 79, 109-12 (2001)

45. Deirdre J Murphy, Peter L Hope, Ann Johnson: Neonatal risk factors for cerebral palsy in very preterm babies: case-control study. *BMJ* 314, 404-8 (1997)

46. Yue Feng Li, George J Lu, Young Kue Han: Risk factors for intracranial hemorrhage in very low birth weight infants. *Zhongguo Dang Dai Er Ke Za Zhi* 9, 297-300 (2007)

47. Naseer Ahmed Mir, Arif M Faquih, Mabrouka Legnain: Perinatal risk factors in birth asphyxia: relationship of obstetric and neonatal complications to neonatal mortality in 16,365 consecutive live births. *Asia Oceania J Obstet Gynaecol* 15, 351-7 (1989)

48. Horacio J Adrogué, Nicolaos E Madias: Hyponatremia. *N Engl J Med* 342, 1581-9 (2000)

49. Takashi Murase, Yoshihisa Sugimura, Seiko Takefuji, Yutaka Oiso, Yoshiharu Murata: Mechanisms and therapy of osmotic demyelination. *Am J Med* 119, S69-73 (2006)

50. Hakkı Muammer Karakaş, Gülnur Erdem, Cengiz Yakinci: Osmotic demyelination syndrome in a 40 day old infant. *Diagn Interv Radiol* 13, 121-124 (2007)

51. Samina B Bhatty, Anna Tsirka, Patricia Bigini-Quinn, Edmund F La Gamma, Joseph D De Cristoforo: Rapid correction of hyponatremia in extremely low birth weight (ELBW) premature neonates is associated with long term developmental delay. *Pediatr Research* 41, 140A (1997)

52. Dimon D Whyte: Perioperative fluid and electrolyte balance in children. *Anaesthesia and Intensive Care Med* 10, 93-97 (2009)

53. Sevim Unal, Ebru Arhan, Nazli Kara, Nermin Uncu, Didem Aliefendioğlu: Breast-feeding-associated hypernatremia: Retrospective analysis of 169 term newborns. *Pediatr Int* 50, 29-34 (2008)

54. Ian A Laing: Hypernatraemic dehydration in newborn infants. *Acta Pharmacol Sin* 23, S48-51 (2002)

55. Garth I Leslie, Kalaw MB, Jennifer R Bowen, John D Arnold: Risk factors for sensorineural hearing loss in extremely premature infants. *J Paediatr Child Health* 31, 312-6 (1995)

Send correspondence to: Vassilios Fanos, Dept Paediatrics and Clinical Medicine-Section of Neonatal Intensive Care Unit, University of Cagliari, Italy, Tel.: 390706093403, Fax: 390706093495, E-mail: vafanos@tin.it