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Nutrition, acid-base status and growth in early childhood

■ **Summary** Optimal growth is only possible in a well-balanced “inner milieu”. Premature infants are especially vulnerable for disturbances of acid-base metabolism with a predisposition to metabolic acidosis due to a transient disproportion between age-related low renal capacity for net acid excretion (NAE) and an unphysiologically high actual renal NAE on nutrition with standard formulas.

During a 50 month period, 452 low birth-weight infants were screened for spontaneous development of incipient late metabolic acidosis (ILMA), an early stage during the development of reten-

tion acidosis, characterized by maximum renal acid stimulation (MRAS, urine-pH < 5.4) on two consecutive days but still compensated systemic acid-base status. Compared with controls, patients with ILMA showed higher serum creatinine values, an increased urinary excretion of sodium, aldosterone and nitrogen, but only slightly lower blood pH (7.38 vs 7.41) and base excess (-2.8 vs. 0.2 mmol/l) with respiratory compensation (PCO₂ 35 vs 37 mm Hg).

Patients with altogether 149 episodes of ILMA were subsequently randomly allocated to either treatment with NaHCO₃ 2 mmol/kg/d for 7 days or no special therapy in protocol I, or NaHCO₃ vs NaCl each 2 mmol/kg/d for 7 days in protocol II. Patients of protocol I with persistent MRAS for 7 days showed lowest weight gain and a tendency for a further increase in urinary aldosterone and nitrogen excretion. NaCl supplementation (protocol II) seemed to promote weight gain without affecting either impaired mineralization or suboptimal nitrogen retention. Patients with alkali therapy

under both protocols showed normal weight gain and normalization of hormonal stimulation, mineralization (protocol II) and nitrogen assimilation.

Modification of the mineral content of a standard preterm formula decreased renal NAE to the low level seen on alimentation with human milk and reduced the incidence of ILMA in preterm and small-for-gestational-age infants to 1%.

The data show that ILMA is associated with impaired growth. Activation of secondary homeostatic mechanisms (extracellular volume contraction, depletion of disposable net base pools) might be important for impaired growth. Production of new formulas for reduced renal NAE could be an effective general preventive measure to reduce the clinical importance of one component of mixed acid-base disorders in early childhood.

■ **Key words** Acid-base balance – Incipient late metabolic acidosis – Infant formula – Renal net acid excretion

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Introduction

There are three major sources of proton generation and turnover. CO₂ – a volatile acid – is transported to the

lungs and eliminated via pulmonary ventilation, thus establishing an ‘open system situation’ for the CO₂/bicarbonate buffer system [1]. Substrate metabolism generates metabolizable acid or base (e. g., by degradation of sulfur containing amino acids). These ‘fixed acids’ are

excreted via the kidneys, associated with regeneration of systemic bicarbonate. Electrolytes, transported from the gut through the body to the kidneys, form so-called 'non-metabolizable' acids or bases. They add to urinary ion excretion, thus, contributing to the resulting net acid excretion [2–8].

Acid-base regulation is primarily based on a strategy to maintain the protein ionization state, and thus protein function constant [9]. This means that all parameters of proton metabolism are controlled within small ranges. Optimal growth is only possible within such a balanced 'inner milieu'.

Premature infants and newborns show a low renal capacity for acid excretion [10–12] and a high rate of cardiopulmonary and transient or inherited metabolic disorders [13, 14]. Furthermore, nutrition with standard formulas already results in a high renal net acid excretion [15, 16]. Thus, in early infancy, complex disorders of acid-base metabolism are frequent, with a predisposition for metabolic acidosis [5, 6, 14].

Renal excretion of acid

The classical operational concept of acid-base metabolism is focused on the kidney [2, 17–20]. NAE is defined as the sum of titratable acidity and ammonium minus bicarbonate [21, 22].

Fig. 1 shows urinary ionograms of preterm infants on nutrition with either human milk or with a standard preterm formula [16, 23]. The urinary excretion of electrolytes is mainly the result of intake, intestinal absorption and retention [4, 24]. According to the principle of

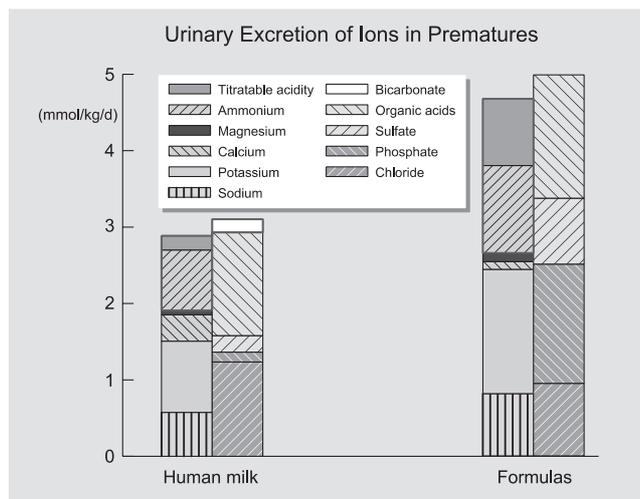


Fig. 1 Urinary ionograms (mmol/kg/day) in premature infants on nutrition with either human milk (left, [23]) or standard formulas for prematures (right, [16]). Renal net acid excretion is defined as the sum of titratable acidity and ammonium minus bicarbonate.

electroneutrality, renal net acid excretion is determined indirectly by the difference between non-metabolizable urinary anions and cations. That means, net acid excretion, the sum of titratable acidity and ammonium minus bicarbonate, corresponds to the difference in the sum of the important urinary non-carbonic anions (chloride, phosphate, sulfate, and organic acids) minus the sum of the non-metabolizable (non-TA and non-NH₄) cations (sodium, potassium, calcium, magnesium) [6, 7, 25]. In premature infants, the renal net acid excretion was considerably higher on standard preterm formula (1.8 mmol/kg/d) compared to nutrition with human milk (0.8 mmol/kg/d). This unnecessarily reduces renal surplus capacity for acid excretion in preterm infants.

Based on data of age-dependent intestinal absorption and retention rates, a theoretical model has been developed in preterm and term infants to estimate the urinary excretions of anions and cations [6, 26]. In adults, an analogous model allows one to calculate the impact of the composition of a diet on the resulting renal net acid excretion by estimating the so-called potential renal acid load (PRAL) of a given food or diet [7, 8, 27, 28]. Moreover, the effect of modification of the mineral content of a formula on the resulting renal net acid excretion in newborns [15, 29–31] can be estimated.

Renal NAE in infants fed human milk or formulas

György in 1922 was the first to determine excretion of ammonia and titratable acidity in infants. In a study performed at the University of Heidelberg, he observed a much higher ammoniuria in infants fed cow's milk than in infants fed human milk [32].

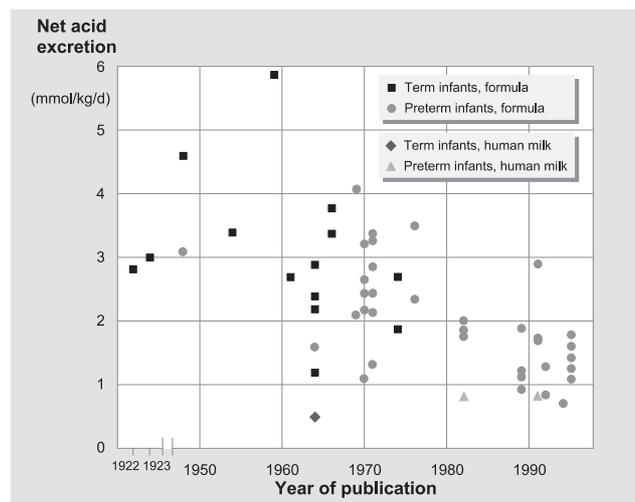


Fig. 2 Data of renal net acid excretion in preterm and term infants on nutrition with human milk or formulas [15, 21, 23, 24, 31–49] according to the year of publication.

Fig. 2 shows literature data for values of renal net acid excretion in preterm and term infants fed different formulas or human milk, according to the year of publication [15, 21, 23, 24, 31–49]. During the last 40 years there has been a continuous trend to lower values of renal NAE. This trend is mainly the result of a higher dilution of raw cow's milk during the production process of infant formula and the use of protein fractions, resulting in lower protein and mineral contents [14].

Renal NAE capacity

One of the first authors who presumed a reduced renal acid excretion capacity due to immaturity was Ylppö. In 1916 he weekly measured urine-pH in a baby with a birth weight of 960 g fed human milk. Urine-pH values were very low during the first few weeks of life and later gradually increased [50].

Fig. 3 gives literature data of maximum renal excretion of net acid and ammonium in preterm and term infants fed human milk or formula. Maximum renal acid stimulation was achieved by acute or chronic acid loading with ammonium or calcium chloride [11, 33, 35, 36, 42, 43, 52–55]. In small preterm babies, renal acid excretion capacity is low compared to term newborns [56]. In both, preterm and term infants, maximum renal net acid excretion improves rapidly during the first few weeks of life.

However, nutrition with standard formulas already results in an actual renal net acid excretion in the range of renal acid excretion capacity in small premature infants [16, 57–59]. Thus, very low birth-weight and premature infants may be assumed to transiently be at a high risk of spontaneously developing acid retention [59, 60].

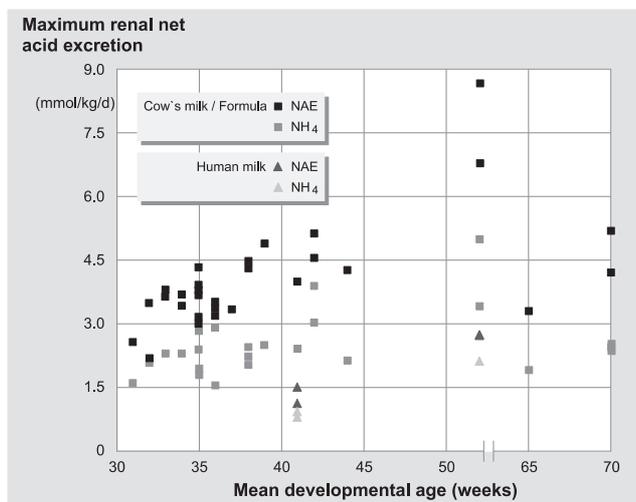


Fig. 3 Maximum renal excretion of net acid and ammonium in preterm and term infants on nutrition with human milk or formulas [11, 33, 35, 36, 42, 43, 52–55].

Late metabolic acidosis (LMA)

In 1964 Kildeberg described late metabolic acidosis (LMA), a manifest retention acidosis in term infants during the first few weeks of life. These patients showed a catabolic metabolic state and growth failure [38]. Kildeberg demonstrated that LMA was caused by an imbalance between the daily load of net acid and the ability of the kidneys to excrete it [61, 62]. In the 1960s and 1970s, renal NAE on nutrition with cow's milk formulas resulted in a renal acid load near renal acid excretion capacity of newborns [10, 11, 42].

Nowadays, reports of LMA are rare as clinical nutrition has generally improved, resulting in a lower dietary net acid load (see Fig. 1). However, manifest late metabolic acidosis may still develop, when the criteria for an imbalance between daily acid load and maximum renal acid excretion capacity are met [63, 64]. In 1990 we described development of manifest LMA in a term baby boy with renal tubular acidosis type 4 who received two cow's milk formulas in succession. Suboptimal mineral composition of the formulas resulting in an unnecessarily high renal net acid excretion (NAE) turned out to be an important risk factor for the development of LMA with growth failure. Only with the start of alkali-therapy on the 33rd day of life was the systemic acid-base status normalized and the boy began to gain body weight [29].

Theoretically, 3 stages during the development of late metabolic acidosis may be distinguished [59]:

1. Development of acute maximum renal acid stimulation (that means actual NAE equals renal NAE capacity).
2. *Incipient LMA* (ILMA) with chronic maximum renal acid stimulation and compensated positive acid balance characterized by still constant acid-base status in the blood.
3. Decompensated retention acidosis with progressive development of metabolic acidosis.

In stages 1 and 2, the diagnostic value of the blood acid-base status is limited. So, up to now, the diagnosis was performed only after full development of the disease at the stage of decompensated retention acidosis.

In the development of LMA [61], retention acidosis presupposes maximum renal acid stimulation (MRAS), usually characterized by urine-pH values of 5.4 or below [65]. We therefore decided to start regular urine pH screening in pretermes and small-for-gestational-age newborns to isolate patients in an early stage of the disease.

Prospective randomized studies in preterm infants

Fig. 4 shows the experimental protocol of two prospective randomized studies [59, 60, 66]. Low birth-weight infants were screened twice weekly for spontaneous de-

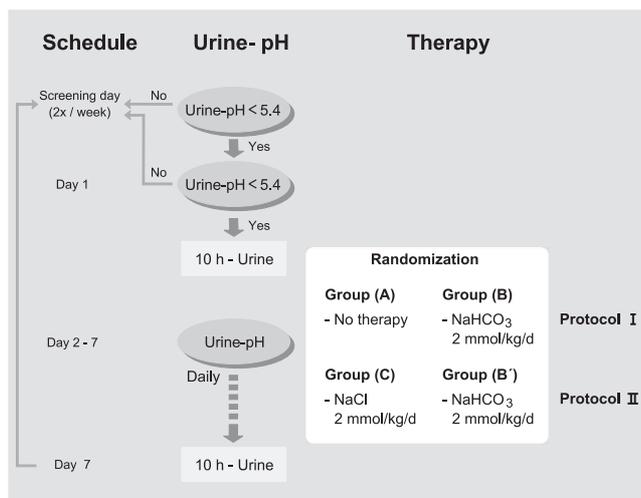


Fig. 4 Experimental protocol of two prospective randomized studies.

velopment of maximum renal acid stimulation (MRAS), characterized by urine-pH values below 5.4. If urine-pH was still below 5.4 on the consecutive day, incipient late metabolic acidosis (ILMA) was diagnosed. Then, regular blood samples were taken and timed urine-samples were collected for 8–12 hours and immediately frozen. Patients with ILMA were randomly allocated to either treatment with sodium bicarbonate, 2 mmol/kg/day for 7 days (group B) or no special therapy (group A) in protocol I, or sodium bicarbonate (group B') versus sodium chloride (group C), each 2 mmol/kg/day for 7 days in protocol II. On day seven, regular blood samples and urine collection were repeated.

Fig. 5 shows the structure of these two prospective

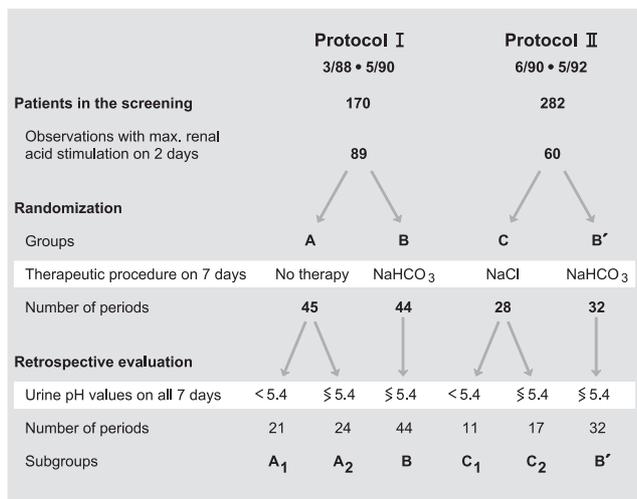


Fig. 5 Numbers of patients in the screening, number of episodes with ILMA (indicated by maximum renal acid stimulation on 2 consecutive days), allocation of patients to the therapeutic procedures and retrospective classification into subgroups based on urine-pH values [60].

randomized studies and gives numbers of patients and episodes with ILMA. During a 50 month period, 452 low-birth weight infants were routinely screened for MRAS. We observed 149 episodes of ILMA. The episodes usually occurred in the second and third week of life. In all patients on alkali-therapy (groups B and B') urine-pH values increased from day 1 to day 7. In contrast, patients of group A with no specific therapy and patients of group C on sodium chloride could be separated into patients with persistent maximum renal acid stimulation (urine-pH < 5.4 on all 7 days, subgroups A1 and C1) and patients with an increase in urine-pH values (urine pH ≥ 5.4 on at least one day of the observation period, subgroups A2 and C2).

The results are presented in two parts. First, characteristic observations in patients on the first day with incipient late metabolic acidosis (ILMA) are compared to control patients without maximum renal acid stimulation, taken from other studies performed in the same ward at the same time [49]. Second, for further analysis, patients with ILMA were followed from day 1 to day 7 of the study, according to the therapy regimen. Special emphasis was laid on the comparison between patients with alkali-therapy (groups B and B') and patients with persistent MRAS (subgroups A1 and C1).

Presentation of selected clinical and biochemical data in patients on the first day with incipient late metabolic acidosis (ILMA)

Analysis of systemic acid base values (determined in capillary samples, Table 1) showed a tendency to lower

Table 1 Clinical data, urine-pH and data of capillary acid-base status (mean ± SD) on day 1 with incipient late metabolic acidosis (ILMA) in 113 premature patients with spontaneous development of 122 episodes with maximum renal acid stimulation (MRAS) and in 51 patients (control group) without MRAS taken from other studies in the same ward at the same time [49].

	ILMA (1 st day) (n=122)	Controls (n=51)	P (ILMA vs controls)
Nutrition	Parenteral and/or oral	Parenteral and/or oral	
Urine-pH	< 5.4	≥ 5.4	
Patients	(n=113)	(n=51)	
Treatment periods	(n=122)	(n=51)	
Gestational age (weeks)	31.9 ± 2.5	31.2 ± 2.7	
Birth weight (kg)	1.44 ± 0.30	1.26 ± 0.30	< 0.01
Actual weight (kg)	1.54 ± 0.25	1.73 ± 0.22	< 0.01
Actual age (days)	17.8 ± 10.8	34.9 ± 15.7	< 0.01
Urine-pH	5.0 ± 0.3	6.1 ± 0.4	
Capillary blood			
pH	7.38 ± 0.05	7.41 ± 0.03	< 0.01
act. HCO ₃ (mMol)	20.9 ± 2.8	23.5 ± 2.4	< 0.01
BE (mMol)	-2.8 ± 2.8	0.2 ± 2.3	< 0.01
PCO ₂ (mmHg)	35.4 ± 5.9	37.6 ± 4.1	< 0.01

base excess (BE) values in prematures with ILMA (resulting in a slightly, but significant lower mean BE). This slight metabolic acidosis in prematures with ILMA was associated with an analogous shift to lower values of CO₂-partial pressure (PCO₂), indicating a small but significant respiratory compensation [67]. However, under clinical conditions, a slight tendency towards metabolic acidosis does not allow diagnosis in an individual patient [68].

Patients with ILMA demonstrated higher serum creatinine values compared to premature infants without maximum renal acid stimulation (Table 2), thus, pointing to the importance of impaired renal function as a risk factor for the spontaneous development of retention acidosis [14]. The increased ratio of urinary nitrogen excretion to nitrogen intake may indicate suboptimal nitrogen assimilation already on day 1 with diagnosis of ILMA.

Neglecting Na-excretion in feces, apparent Na-retention

(Na-intake – Na-urine) was already negative in premature infants on day 1 with ILMA due to considerably high urinary losses of Na (Table 3), probably indicating that impaired extracellular volume expansion plays an important role as a pathophysiological compensating mechanism in this early stage of retention acidosis [6, 66]. Acute acid-loading, e. g., with ammonium chloride, regularly results in a negative Na-balance and an increased activity of the renin-angiotensin-aldosterone system [69].

Presentation of selected clinical and biochemical data in patients on the first and seventh day with incipient late metabolic acidosis (ILMA)

Table 4 summarizes characteristic clinical and biochemical data on day 1 and day 7 of the study, comparing patients with persistent maximum renal acid stimulation

Table 2 Serum electrolytes, creatinine values and the ratio of urinary nitrogen excretion to nitrogen intake (mean ± SD) on day 1 in 53 premature patients (groups B' and C) with incipient late metabolic acidosis (ILMA), spontaneously developing 60 episodes with maximum renal acid stimulation (MRAS), in a subgroup of 17 patients of groups B' and C with MRAS, and in 17 pair-matched patients (controls) without MRAS, the latter two groups on full oral nutrition with the standard formula F.

	ILMA (1 st day)		Controls	P (subgroup vs controls)
	Groups B', C	Subgroup of groups B', C	Pair-matched to the subgroup	
Nutrition	Parenteral and/or oral	Formula F		
Urine-pH	< 5.4	< 5.4	≥ 5.4	
Patients	(n=53)	(n=17)	(n=17)	
Treatment periods	(n=60)	(n=17)	(n=17)	
Serum				
Sodium (mmol/l)	137.9±3.5	138.1±2.0	136.8±2.2	
Potassium (mmol/l)	40.93±0.59	40.85±0.30	40.77±0.65	
Calcium (mmol/l)	2.39±0.20	2.33±0.19	2.39±0.10	
Chloride (mmol/l)	103.9±4.1	103.9±3.1	101.9±2.8	
Creatinine (µmol/l)	60.1±20.3	55.7±16.8	35.4±10.6	< 0.01
Nitrogen (%) (urinary excr./intake x100)	23.5±10.7	25.9±16.3	18.2±4.5	< 0.05

Table 3 Data for sodium intake and urinary excretion of sodium (mean ± SD), aldosterone, free cortisol and the antidiuretic hormone arginine-vasopressin (median (range)) on day 1 in 77 premature patients (groups A, B, C, B') with incipient late metabolic acidosis (ILMA) spontaneously developing 80 episodes with maximum renal acid stimulation (MRAS), in a subgroup of 19 patients of groups A, B, C, B' with MRAS, and in 19 pair-matched patients (controls) without MRAS, the latter two groups on full oral nutrition with the standard formula F.

	ILMA (1 st day)		Controls	P (subgroup vs controls)
	Groups A, B, B', C	Subgroup (A, B, B', C)	Pair-matched to the subgroup	
Nutrition	Parenteral and/or oral	Formula F		
Urine-pH	< 5.4	< 5.4	≥ 5.4	
Patients (n=77)	(n=19)	(n=19)	(n=19)	
Treatment periods	(n=80)	(n=19)	(n=19)	
Sodium Intake (mmol/kg/d)	2.52±1.2	2.10±0.2	2.24±0.15	
Urine				
Sodium excretion (mmol/kg/d)	3.50±4.2	2.40±2.4	0.97±0.43	< 0.01
Aldosterone* (ng/kg/d)	599 (58–4421)	480 (65–4421)	275 (112–1195)	= 0.06
Cortisol* (µg/kg/d)	2.1 (0.35–8.6)	2.1 (0.24–4.8)	2.6 (1.0–5.3)	
Arg.-vasopressin* (ng/kg/d)	1.3 (0.28–6.3)	1.3 (0.29–3.0)	1.3 (0.61–2.6)	

*Median (range)

Table 4 Clinical and biochemical data of premature patients of different body weight classes on day 1 before therapy and on day 7 after either no therapy (subgroup A1, urine pH < 5.4 for 7 days) or NaHCO₃ therapy (group B) in protocol I and NaCl (subgroup C1, urine pH < 5.4 for 7 days) or NaHCO₃ therapy (group B') in protocol II.

Therapy	Subgroup A1 none Urine-pH < 5.4 for 7 days		Group B NaHCO ₃		Subgroup C1 NaCl Urine-pH < 5.4 for 7 days		Group B' NaHCO ₃	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
Body weight class kg	n = 9		1.5–1.9 kg n = 20		n = 8		1.5–1.9 kg n = 23	
Episodes with ILMA	n = 9		n = 20		n = 8		n = 23	
Blood (capillary)								
pH	7.396±0.003	7.392±0.034	7.386±0.060	7.412±0.043	7.378±0.031	7.370±0.058	7.388±0.037	7.421±0.047
BE (mmol/l)	-2.1±2.1	-0.6±1.8	-1.9±2.7	2.1±3.6	-4.3±2.2	-2.4±2.6	-3.1±2.8	1.1±3.0
Weight gain (7 days) (g)	138±55		202±55		190±60		218±58	
Nitrogen (Urinary excr./ intake×100) (%)	19.8±6.8	22.7±9.4	22.4±9.4	19.2±6.5	27.2±4.2	20.8±6.6	24.2±10.6	16.0±4.5
Calcium Intake (mmol/kg/d)					2.69±0.55 (7)	3.20±0.11 (8)	2.40±0.95 (23)	3.13±0.79 (23)
Urinary excretion (µmol/kg/day)	not determined		not determined		64.0±31.8 (7)	86.3±36.5 (7)	55.0±32.5 (18)	49.3±41.8 (22)
Body weight class	n = 21		1.0–2.4 kg n = 44		n = 11		1.0–1.9 kg n = 32	
Episodes with ILMA	n = 21		n = 44		n = 11		n = 32	
Aldosterone-18- glucuronide* (ng/kg/d)	396 (14)**	562 (14)	636 (14)	203 (14)	734 (7)	555 (7)	1115 (24)	432 (24)

* Median values, ** No. of samples

(protocol I: group A1; protocol II: group C1) and patients on alkali-therapy (protocol I: group B; protocol II: group B').

■ **Blood acid-base status.** On day 1 with diagnosis of ILMA only slightly acidotic values of blood-pH and base-excess (BE) were observed. As the development of ILMA probably takes a few days, compensating mechanisms may have enough time to counteract the positive acid-base balance, thus, veiling maximum renal acid stimulation (MRAS) by seemingly (almost) normal results of blood acid-base status [59]. No patient from subgroup A1 or subgroup C1 developed manifest late metabolic acidosis. Remarkably, these patients with persistent MRAS even showed a trend to increased values of base-excess, again pointing to activation of compensating mechanisms lifting the renal bicarbonate threshold (the plasma bicarbonate level at which urine-pH equals 6.1) to a higher plasma bicarbonate level [6, 60].

■ **Growth.** Weight gain between day 1 and day 7 of the treatment period was compared between the different therapeutic regimens in patients with ILMA of the body weight class 1.5 to 1.9 kg. Patients of subgroup A1 with persistent maximum renal acid stimulation with no special therapy showed impaired weight gain compared to

patients of groups B and B' on alkali therapy. Supplementation with sodium chloride (subgroup C1) seemed to promote weight gain [66].

■ **Nitrogen assimilation.** Assuming constant ratios of fecal N-excretion to N-intake, a decrease in the ratio of urinary N-excretion to N-intake from day 1 to day 7 corresponds to an increasing rate of N-retention and improved N-assimilation and vice versa [59, 60]. Patients on alkali therapy under both protocols (groups B and B') and patients with sodium chloride supplement (subgroup C1) showed improved nitrogen assimilation. Patients of protocol I with no specific therapy (subgroup A1), however, showed a tendency for a further increase in urinary nitrogen excretion, corresponding to a higher catabolic rate. Thus, growth retardation in ILMA seems to be attributed both to a reduced gain of extracellular volume [70] and diminished cellular growth as well [66].

■ **Intake and urinary excretion of calcium (protocol II).** Intake of calcium was similar in patients of protocol II with either sodium chloride supplement (subgroup C1) or alkali-therapy (group B') on day 1 and day 7. In contrast to patients of group B' on alkali therapy, patients with ILMA and persistent maximum renal acid stimulation on sodium chloride (subgroup C1) demonstrated a trend for a higher urinary calcium excretion, tentatively

pointing to impaired bone mineralization processes in these patients at an early stage of metabolic acidosis [71, 72]. These observations support the hypothesis that net bone alkali release is involved in systemic hydrogen ion buffering in vivo [73, 74], probably preserving acid-base balance at the expense of bone mineral metabolism [75].

■ **Urinary aldosterone excretion.** In patients of groups B and B' on alkali therapy and patients of subgroup C1 with the sodium chloride supplement, urinary aldosterone excretion showed a decrease towards normalization [76]. Only patients of subgroup A1 with persistent ILMA and no special therapy showed a tendency for a further increase in urinary aldosterone excretion from day 1 to day 7 of the observation period, indicating a further stress of the hormonal milieu in patients with ILMA [14].

Pathophysiological model of incipient late metabolic acidosis (ILMA)

Fig. 6 presents a scheme of our pathophysiological model of incipient late metabolic acidosis (ILMA). ILMA is proposed to result from the intake of a suboptimally composed formula, an age-related low capacity for renal net acid excretion, and individual functional and biochemical characteristics. Our observations suggest an activation of potent compensatory pathophysiological mechanisms defending systemic acid-base homeostasis in spite of persistent positive acid balance [77]. These mechanisms tend to increase tubular bicarbonate reabsorption and to promote a pool of transiently disposable net base [14, 78]. Extracellular volume, disposing net base by volume contraction [69] and the bone re-

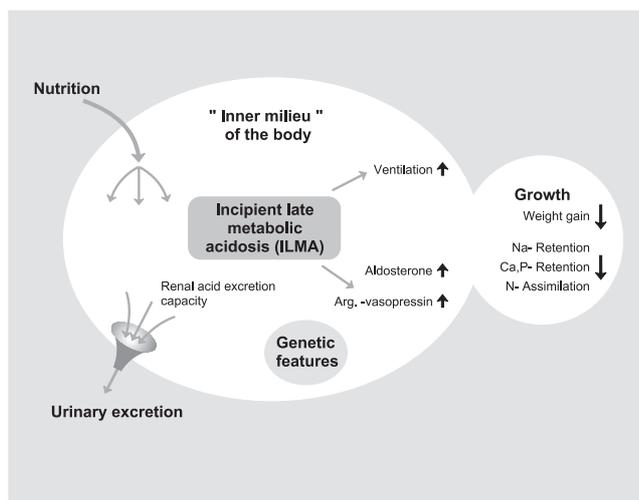


Fig. 6 Pathophysiological mechanisms in premature infants with incipient late metabolic acidosis (ILMA).

leasing sodium, potassium, calcium and carbonate [73, 74] might be such pools.

The compensatory mechanisms result in an amazing pathophysiological stability of ILMA for about 10 to 14 days, until the positive acid balance situation is terminated due to further maturation of renal acid excretion. (In fact, only 1 infant not included in the study population, was observed with manifest late metabolic acidosis). However, the organism has to pay a heavy price for this amazing pathophysiological stability during episodes with ILMA: a decreased growth rate, a stressed hormonal milieu, wasted net base pools and a higher degree of instability due to reduced surplus capacities for adaptive responses to further challenges. So far, we do not know if episodes with ILMA are associated with functional sequelae during further development.

Reduction of alimentary acid load

Individual bicarbonate therapy invariably resulted in termination of ILMA. Table 5 shows the estimated composition of human milk [79] and the analysis of two formulas. The standard preterm formula F is higher in protein and mineral content compared to human milk. Nutrition with this standard formula is known to result in a considerably higher actual renal acid load than seen on nutrition with human milk. In order to reduce renal net acid excretion in preterm infants to the low level seen on alimentation with human milk, the mineral content of the standard formula F was modified, resulting in an increased alkali excess (sodium + potassium – chloride) in formula FB (Table 5).

In 11 premature infants on the modified formula FB, renal net acid excretion was reduced to about 0.6 mmol/kg/d compared to about 1.7 mmol/kg/d in 23 premature infants on nutrition with the standard formula F. In a further prospective study, the incidence of ILMA in preterm and small-for-gestational-age infants on nutrition with the modified formula was reduced to only 1% [31].

Efforts to reduce the potential renal load of a diet may

Table 5 Composition of human milk (MM: estimated data), compared to analysis of a preterm formula FB with reduced acid load (AL ↓) and a standard preterm formula (F) with considerably high acid load (AL ↑)

	MM (estimated)	FB (AL ↓)	F (AL ↑)
Protein (g/dl)	1.0	1.8	1.8
Fat (g/dl)	4.0	4.0	4.0
Carbohydrate (g/dl)	7.0	8.0	8.0
Na (mmol/l)	7.0	17.4	13.4
K (mmol/l)	15.0	26.1	20.3
Cl (mmol/l)	12.0	14.1	13.4
(Na + K – Cl) (mmol/l)	10.0	29.4	20.3

also be helpful in elderly patients with an age-related decline of renal function to avoid pathophysiological sequelae of compensating mechanisms in early stages of systemic retention acidosis [78, 80].

Pulmonary versus renal responses in premature infants with different alimentary acid load

Blood acid-base status and renal acid excretion were analyzed in three groups of premature infants on nutrition with different alimentary acid loads (Table 6): group MM was on nutrition with human milk, group FB was nurtured with the formula FB with reduced alimentary acid load (achieved by modification of the mineral content) [31], and group F was on the standard preterm formula F with relatively high renal acid load.

Mean values of capillary acid-base values did not differ between the three groups (Table 6). Base excess (BE) values showed a broad interindividual scattering between minus 5 and plus 5 mmol/l. As expected, individual values of CO₂-partial pressure (P CO₂) were proportional to BE, indicating a continuous fine adjustment of pulmonary ventilation to the metabolic parameter of acid base status [67]. This continuous pulmonary regulation was mirrored by a linear correlation between PCO₂ (y) and base excess (x), found to be uniform in preterm infants of all three groups: $y = 0.655x + 37.76$ ($p < 0.001$).

Regarding renal acid excretion, all infants on formula FB with reduced acid load showed urine-pH values between 6.3 and 7.3; that means no infant developed maximum renal acid stimulation (MRAS) on this modified formula. In contrast, some premature infants on human

milk (group M) and on the standard formula F with high acid load (group F) as well, developed incipient late metabolic acidosis (ILMA), indicated by MRAS. A further analysis showed no increase in ammoniogenesis in those premature infants of groups F and MM with MRAS, pointing to immature or impaired renal mechanisms of ammoniogenesis when compared to adults [81]. For a given urine-pH value, ammoniuria was lower in premature infants on nutrition with human milk compared to premature infants on nutrition with the standard formula F with a higher protein content. Thus, a high protein content of the formula (or diet) may promote renal ammoniogenesis, a hypothesis that was already discussed earlier to explain observations in preterm infants [11, 53] and adults [27]. An increase in the glomerular filtration rate and/or in plasma glutamate and glutamine concentrations induced by a higher protein content of the formula [82, 83] could probably contribute to this 'protein effect' on renal ammoniogenesis, thus, enabling the kidney to meet acid-base demands more efficiently [27].

Conclusions

Preterm infants are at a high risk for metabolic acidosis due to an age-related low maximum renal acid excretion capacity and a frequently high actual renal net acid load (due to suboptimal composition of formulas). A normal or almost normal acid-base status is no guarantee of an undisturbed acid-base metabolism; the development of incipient late metabolic acidosis (ILMA) is indicated by a urine-pH value below 5.4.

Infants with incipient late metabolic acidosis (ILMA) show a ventilatory response (slight increase of pulmonary ventilation), impaired growth (decreased retention of nitrogen, Na, Ca), and adaptive hormonal reactions (increase of urinary aldosterone excretion). These characteristic reactions are probably due to activation of potent secondary mechanisms (CO₂-disposal, extracellular volume contraction, depletion of disposable net base pools) defending systemic acid-base homeostasis.

Regular measurement of urine-pH is a useful non-invasive method for early diagnosis of incipient late metabolic acidosis (ILMA), thus, allowing early effective alkali therapy on an individual basis.

Production of new formulas with reduced renal net acid excretion could be an effective general preventive measure for reducing the incidence of one component of mixed acid-base disorders in early childhood.

Speculation

The renal response to a given alimentary acid load seems to be dependent on the composition of the for-

Table 6 Clinical characteristics and data (mean \pm SD) for capillary acid-blood values and for pH and acid excretion in collected urine in 28 premature infants on nutrition with human milk (group MM), in 11 premature infants (group FB) on nutrition with a preterm formula FB with reduced acid load (AL \downarrow), and in 23 premature infants (group F) on nutrition with a standard preterm formula (F) with considerably high acid load (AL \uparrow)

	Group MM (n = 28)	FB (AL \downarrow) (n = 11)	F (AL \uparrow) (n = 23)
Gestational age (weeks)	32.8 \pm 2.7	31.5 \pm 2.4	30.9 \pm 3.0
Actual age (days)	26.7 \pm 16.4	34.1 \pm 20.3	38.8 \pm 15.8
Actual body weight (kg)	1.73 \pm 0.26	1.96 \pm 0.11	1.91 \pm 0.10
Capillary samples			
pHc	7.40 \pm 0.05	7.40 \pm 0.04	7.42 \pm 0.03
PCO ₂ (mm Hg)	37.8 \pm 5.5	39.6 \pm 5.0	36.5 \pm 3.5
HCO ₃ (mmol/l)	23.0 \pm 2.5	24.6 \pm 2.5	23.5 \pm 2.4
BE (mmol/l)	-0.8 \pm 2.2	0.6 \pm 2.2	0.0 \pm 2.2
Urine (collected)			
pH	5.76 \pm 0.53	6.80 \pm 0.30**	6.00 \pm 0.60
NAE (mmol/kg/d)	0.94 \pm 0.52	0.60 \pm 0.70	1.70 \pm 0.70**
TA (mmol/kg/d)	0.31 \pm 0.14	0.29 \pm 0.14	0.64 \pm 0.30
NH ₄ ⁺ (mmol/kg/d)	0.78 \pm 0.26	0.80 \pm 0.10	1.22 \pm 0.44*

* $p < 0.05$, ** $p < 0.01$

mula (thus, differing from a seemingly uniform pulmonary response). We speculate that in prematures with renal acid stimulation, renal ammoniogenesis may be promoted by a high protein content of the formula.

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