Algorithm for Calculating the Protein Intake in Enteral and Parenteral Nutrition in Premature Infants

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ABSTRACT: Introduction. Calculating the exact nutritional balance especially for the premature infant has always been a challenge for the daily practice of the clinician. Purpose: we intend to establish a simplified formula and mathematical algorithms to calculate the necessary amino acids and proteins for the nutrition of the premature newborn, covering most of the international recommendations and also to give to the neonatal intensive care physician the opportunity of their rapid customization for each case. Methods: following an extensive literature revision we have established the protein intake recommendations, indications and contraindications for enteral and parenteral nutrition in premature infants, by age of gestation, birth weight and postnatal age. Then, these recommendations were translated into simplified mathematical equations and we have proceeded to develop logical algorithms to enable the rapid choice of the best equation that fits each individual case with all its peculiarities, at a defined time. Results: for all three premature categories, we have identified intervals for enteral and parenteral nutrition, which were translated into mathematical formulas and management regulations and then transposed into logic algorithms. Conclusions: although mathematically one can use a simplified calculation, for a rapid appreciation, the clinician is still required to go through these algorithms daily and sometimes several times a day. Moreover, to optimize protein intake, we have to calculate the protein / energy ratio and the non-protein calories / gram of protein ratio. This involves extending the calculation for the carbohydrates, fats and calories-practically the entire nutrition.

KEY WORDS: algorithm, nutrition, preterm infant, protein intake

Introduction

Premature birth comes with a significant protein shortage, very difficult to recover [1].

In several studies, early protein intake was associated with nutritional recovery and good neurological development of premature infants with very low birth weight [2-4].

In order to maintain as close to the fetal growth rate as possible, the protein intake should be the sum of the daily protein loss and the need for growth.

Ziegler has approximated the energy loss and the protein needs in order to maintain a positive nitrogen balance and has demonstrated that addressing nutrition through empirical methods brings no positive results [4].

Because these calculations require time, we have found a mathematical approach for assessing the needs and determining the optimal protein intake.

Material and methods

In the absence of a national nutrition guide for the premature babies, we have used the recommendations of the international forums.

We have established ranges for optimal protein needs in enteral and parenteral nutrition, as well as their indications and contraindications.

We have proceeded then to transpose these ratios into mathematical expressions, which were then brought to a simplified form for developing logic algorithms facilitating swift calculation formula.

These algorithms are designed to guide the equation that fits the best the clinical context.

The role of these formulas and algorithms, is to fit the enteral and/or parenteral intake into a rate capable to provide a growth rate as close to the fetal growth rate as possible [4].

Attention should be focused on enteral nutrition. Usually we are trying to initiate the enteral nutrition (EN) with maternal milk (first day of life, or at least the second day) as priming and increasing rapidly with 10-20 ml/kg/day once the residue is minimal, to achieve the optimum as soon as possible [5].

Parenteral nutrition (PN) supports the premature baby until it is able to receive sufficient nutrients by enteral nutrition (until enteral nutrition exceeds 90% of the optimum) [5].

The calculated ratio in the enteral nutrition (REN) should be at least 15% higher than in the parenteral nutrition (the rate of the intestinal absorption of the proteins in premature is~85-90%).

Ziegler estimated a need of 4g/kg/day for the preterm babies about 500-1200g of weight [4].

Finally, there is not a precise consensus on the minimum and maximum permissible, but most committees of international nutrition, recommend the use of large rations (around 4g/kg/day) (see Table 1), and it is likely that further research should establish even higher standards.

Most of the recommendations for optimal protein intake in enteral nutrition are: 4-4,5g/kg/day for the extremely low birth weight (ELBW) infants; 3,5-4,2g/kg/day for the very low birth weight (VLBW) infants and 3-3,6g/kg/day for the LBW infants.

Table 1. Recommendations for enteral protein intake for preterm with very low birth weight

	g/kg/day
Canadian Pediatric Society, 1995*	
Birthweight<1000g	3,5-4,0
Birthweight≥1000g	3,0-3,6
Life Sciences Research Office, 2002[†]	3,4-4,3
AAP Committee on Nutrition, 2004[‡]	3,5-4,0
ESPGHAN, 2010[k]	
Weight up to 1000g	4,0-4,5
Weight 1000-1800g	3,5-4,0

EN initiation should be started from day one [6] so we have to calculate the target for enteral nutrition, usually the initiation is made with a volume of milk of 1-24ml/kg/day [7,8] and progressively increased according to the digestive tolerance (see Table 2). Enteral protein intake (EPI) is calculated by the sum of the proteins contained in the milk volume (maternal+/-formula), protein supplement etc.

Table 2. Suggestions for premature feeding of the newborn

The day of life	Type of milk	Volume (ml/kgc)	Frequency	Growth
BIRTHWEIGHT BY 1000g				
3-9	Breast milk/Formula	1-2	6-12 hours	-
10-16	Breast milk/Formula	2	2 hours	15ml/kg/day
17-19	Fortified breast milk /Formula for premature	8-9	2 hours	20ml/kg/day
20-21	Fortified breast milk /Formula for premature	12-13	2 hours	20ml/kg/day
BIRTHWEIGHT 1001-1200g				
2-6	Breast milk/Formula	3-5	6 hours	-
7-11	Breast milk/Formula	2	2 hours	20ml/kg/day
12-14	Fortified breast milk /Formula for premature	8-9	2 hours	20ml/kg/day
15-17	Fortified breast milk /Formula for premature	12-13	2 hours	20ml/kg/day
BIRTHWEIGHT 1201-1500g				
2-6	Breast milk/Formula	3-5	6 hours	-
7-11	Breast milk/Formula	2	3 hours	20ml/kg/day
12-14	Fortified breast milk /Formula for premature	8-9	3 hours	20ml/kg/day
15-17	Fortified breast milk /Formula for premature	12-13	2 hours	20ml/kg/day
BIRTHWEIGHT 1501-2000g				
1-3	Breast milk/Formula	5	6 hours	-
4-5	Breast milk/Formula	3	3 hours	-
6-9	Breast milk/Formula	3	3 hours	20ml/kg/day
10-12	Fortified breast milk /Formula for premature	12-14	3 hours	20ml/kg/day
13	Fortified breast milk /Formula for premature	18-20	3 hours	20ml/kg/day

VLBW and ELBW preterms, will have a decreased enteral intake for a period of time due to prematurity, low digestive tolerance or the presence of diseases or complications in the perinatal period. During this period, the enteral nutrition will be supplemented with parenteral amino acid intake (PAI). Parenteral amino acid intake should be started as early as the first 24 hours of life. [9,10] with 1-1,5g/kg/day [11] and the progression will be 1g/kg/day, to achieve the target within 3 days. We shall use for calculating the birthweight for the first 7 days of life, or over that age, the weighed weight. The target is based on birth weight-3,5-4g/kg/day for ELBW and 3,0-3,5g/kg/day for birth weight>1kg [5]. There are however some situations where parenteral intake should be limited (0,5-2g/kg/day): kidney disease; Anionic gap>16, urea>80mg/dL, creatinine>1mg/dl, ALT>80ui, Alk Phos>200U [7].

Results

We have identified 3 periods-the first 3 days (enteral-priming, parenteral-gradual increase of the protein intake); 4-14 days-the gradual increase enteral intake; then stabilizing and decreasing the parenteral intake; after 14 days-exclusively enteral intake. Not all cases follow this pattern and the duration of these intervals is not fixed. In general the parenteral nutrition is maintained until the enteral intake is sufficient to ensure the growth itself.

The calculation must follows 6 steps:

1. Establishing the necessary protein quantity for the enteral nutrition (NPQ).

2. Calculating the enteral protein intake and reporting it to the recommended minimum requirement.

3. Calculation of the enteral gap.

4. Calculation of the landmarks for the parenteral nutrition recommendations (PNR).

5. Calculation of parenteral intake by the landmarks of parenteral nutrition and the enteral gap.

6. The adjustment of the parenteral intake to achieve an optimum ratio between the protein/non-protein calories and calories/gram of protein.

Table 3. Recommendations for protein intake in enteral nutrition, according to postnatal age

	<7 days	>7 days
ELBW	3,8-4,5 X Bw	3,8-4,5 X Aw
VLBW	3,4-4,2 X Bw	3,4-4,2 X Aw
LBW	2,9-3,6 X Bw	2,9-3,6 X Aw

Stage 1-establishing the needed protein enteral nutrition (Table 3). In the first 7 days of life, the needs relate to the degree of prematurity and the birth weight (Bw). For infants older than 7 days, it relates to the degree of prematurity and the weighed weight (Ww). Usually the premature infant under 32 weeks and 1200g, does not tolerate large volumes of milk so as to cover the need for enteral proteins in the first two weeks after birth (colostrum milk~2g protein/100ml; premature~1.4g protein milk/100ml; mature unfortified milk-protein 1.05g/100ml, after fortifying~2,2-2,4g/100ml; formulas for premature 1,7-2,9g/100ml; protein supplement protein 0.82g/1g). The fortification begins when the digestive tolerance allows a volume of 100ml MM (maternal milk)/kg/day and the protein supplement is recommended for Bw under 1000g-0,4-0,9g/100ml milk. Although the calculation of necessary proteins in enteral nutrition in these circumstances seems unnecessary in the first 2 weeks of life, it helps you to see how high are the standards to be achieved and how far you are from them at the beginning. Even if it starts with priming we recommend to try the progression of the meal from 6am to get a feedback of the digestive tolerance at 8-9pm. Thus, we try to progress daily with the enteral nutrition and we can estimate the tolerated volume of milk for the day and allows us to better approximate the following calculation steps.

Stage 2 involves the calculation of enteral protein intake. Knowing the volume of milk tolerated and approximate concentration of protein in it, we can appreciate the protein enteral intake for the day. We compare the enteral received amount of protein with the recommended minimum requirement of protein enteral intake for the case.

Step 3 The enteral gap is calculated as the difference between the recommended intake and the actual enteral intake of proteins. If enteral gap is greater than zero, we need to calculate the needs for parenteral nutrition, according to each case (GA, BW and AW or by postnatal age).

Step 4-The milestones in parenteral nutrition requirements are individualized by: birth weight (first week) or actual weight (older than 7 days) and the biological status (disease/renal function, hepatic and/or metabolic). It will first inspect the hepato-renal functional status and metabolically abnormal balance sheet as necessary to limit the intake parenteral 0,5-2g/kg/day (regardless of age or weight at birth). If not, protein intake is customized to the age and weight of the

newborn, except for the first 3 days after birth it is recommended to increase in steps: Day 1 with 1-1,5g/kg/day and increased by 1g/kg/day. The aim of the day 3-4-a: 3,5-4g/kg/day for ELBW and 3,0-3,5g/kg/day for birth weight>1kg.

The mathematics transposition of these rules for calculating the minimum parenteral intake for the ELBW neonate becomes: 1g/kg (start)+progression 1g/kg/day. Since for the first day there is no progression, the formula becomes: Bw+1.25 (day-1) BW and it is applied until it reaches 3.5g/kg/day (ie 3,5Gn, day 3th). Elaborating the formula, we obtain: Bw+1,25dBw-1,25Bw=>Bw (1,25d-0.25). For the period day 3 to 7, we are using 3,5Bw. If the age of the baby, is more than 7days, the formula for calculating the minimum parenteral intake will use daily weight (actual weight-Aw): 3.5gAw. The initiation of the parenteral nutrition after the 7th day, no longer requires gradual progression because the newborns are out of the metabolic instability.

The calculation for the upper limit of the reference interval of the parenteral nutrition for the ELBW infant: start at 1.5g/kg/day, the progression is 1.25g/kg/day, the target is 4g/kg/day (day 3). The equation for the first 3 days is: 1,5Bw+1,25(d-1) Bw and by simplifying: Bw (0.25+1,25d). From the day 4: 4Bw; and after Day 7: 4Aw. In these equation we are using the weight in kg and not in grams, the result of the equation is the total grams of protein/24 hours.

For newborns with Bw>1kg-the lower limit for protein requirements in parenteral nutrition is: start on day 1, with 1g/kg/day, gradually increasing to reach 3g/kg/day on day 3th. The equation is: Bw+(d-1) Bw through simplification is: Bw+d Bw-Bw=>d Bw From day 3 to day 7: 3Bw. By Day 8: 3Aw. Upper limit of the interval: start with 1.5g/kg/day, with progressive increase until day 3, and will continue to 3.5g/kg/day. The equation is: 1,5 Bw+(d-1) Bw. Proceed to simplify the equation: 1,5 Bw+dBw-Bw=>Bw (0.5+d). For the interval 3-7 days: 3,5Bw and for babies older than 7 days: 3.5g (Table 4).

Table 4. Setting the interval for parenteral nutrition. Bw-birth weight; Aw-actual weight-expressed in Kg; d-age in postnatal days

	The first 3 days		Days 3-7		>7 days	
	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum
Bw <1kg	Bw(1,25z-0,25)	Bw(0,25+1,25z)	3,5Bw	4Bw	3,5Aw	4Aw
Bw ≥ 1kg	zBw	Bw(0,5+z)	3Bw	3,5Bw	3Aw	3,5Aw

If the nutrition is totally parenteral, the computation stops at the 4-th step. If the nutrition is partially parenteral, will need to calculate the 5th stage.

Stage 5-calculating the parenteral need for amino acids, according to the recommendations and the enteral intake. Because the cellular metabolism of the proteins is the same, regardless of the route of administration, it should be considered for the enteral and parenteral intake to be in a correlation so as to avoid excessive administration. The enteral route will be the reference, and the parenteral pathway will be the variable that can be changed. Thus, as the enteral intake increases, the parenteral intake will be lowered, such that total protein intake (enteral+parenteral) approximates at least the minimum score in the nutrition recommendations. Mathematically: the minimal reference mark for enteral nutrition-enteral intake=enteral gap. The enteral gap will be "filled" by parenteral nutrition. Referring to the enteral gap, to the recommendations of

parenteral nutrition, we have the following 3 situations:

A) The value of the enteral gap is bigger than the maximum admissible value of parenteral nutrition recommendations. In this case, the parenteral intake will be limited to the maximum recommendation and we`ll try to increase the enteral intake.

B) The value of the enteral gap is within the recommended interval in parenteral nutrition. In this case, parenteral intake may cover the enteral gap. There remains an increase in enteral intake, and any progression of this may lead to a decrease in parenteral intake. If parenteral intake is not decreased, then the sum of parenteral+enteral intake will be higher than the recommended minimum in enteral nutrition, with caution not to exceed the maximum admissible limit.

C) The enteral gap value is below the minimum limit of parenteral nutrition recommendations. The logic scheme is synthesized in Fig.1.
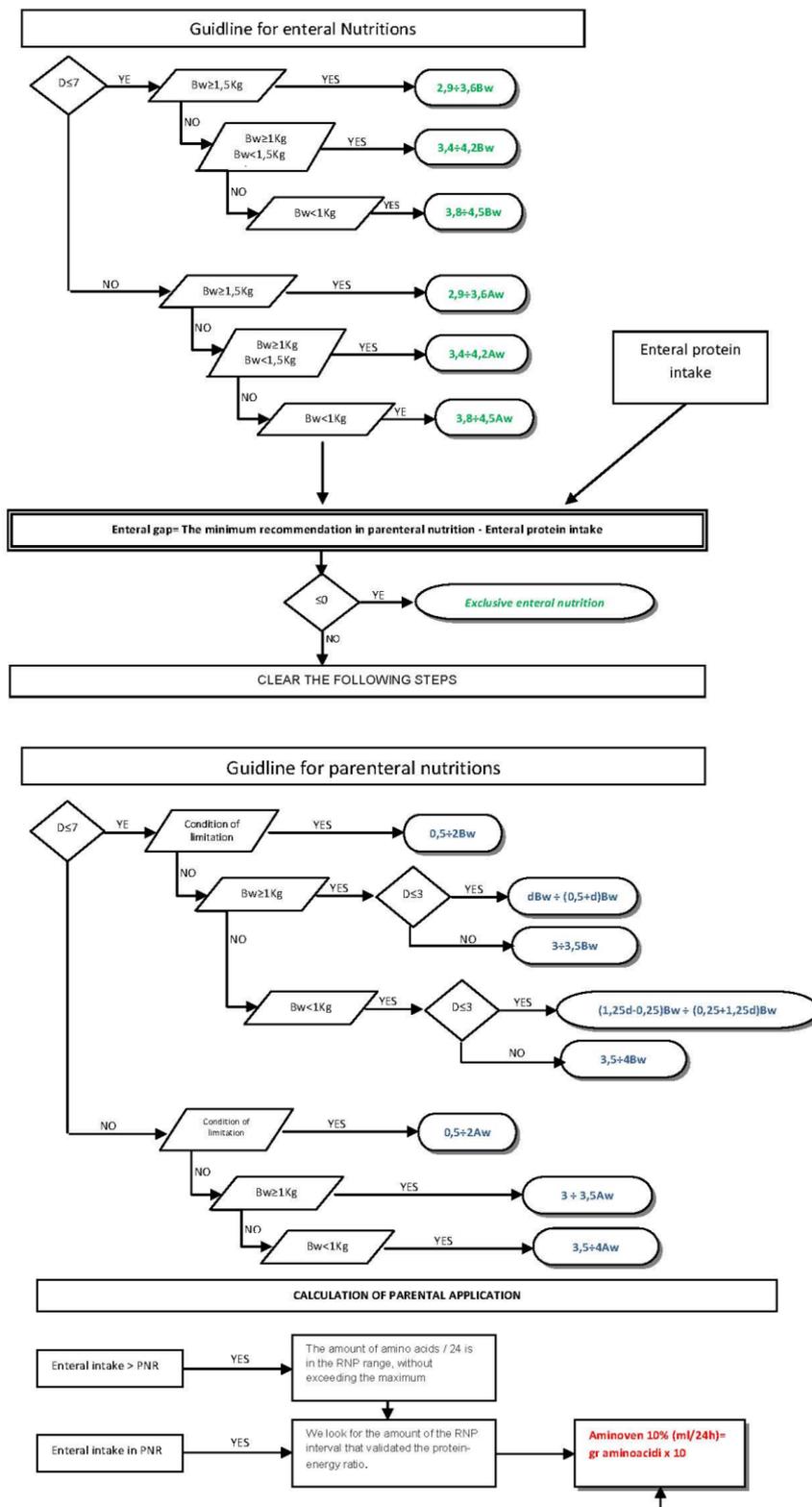
**Fig.1. Integration of recommendations in parenteral and enteral nutrition
or calculating the intravenous amino acid requirement**

Stage 6. The adjustment of the values described in point 5 regarding the amount of protein to meet the criteria for the optimum protein/calory and non-protein/protein gram ratio. It includes also the calculation of the lipid and glucose intake, as well as the calories provided by them. The optimization of the protein-calory ratio will be done through the fine variation in the amount of protein described in stage 5, but also the amount of carbohydrates

and lipids in the recommended range to change the caloric intake of the equation. Recommended: 25-30kcal non-protein/1g protein and 3-4g protein/100kcal [12]. A suboptimal energy-protein ratio will encourage catabolism of amino acids in order to produce energy. Finally, the grams of amino acids calculated in this step will be converted to 10% Aminoven Infant Volume by multiplying by 10. It remains to calculate the perfusion rate (if you are given the amino acids separately) and, moreover, the osmolarity of the solution (if you prepare a Mixture of amino-glucose-electrolyte) given the route of administration (peripheral or central).

It is recommended to represent graphically the necessary and the protein intake as long as enteral nutrition is not complete. For example, the evolution of the protein intake in the first 21 days of life in a newborn weighing 1000g, represented in Fig.2 and 3. In Fig.2, the landmarks of the customized recommendations are shown with a continuous green line for enteral nutrition and a purple discontinuous line for the parenteral nutrition. The daily intake of protein from the enteral nutrition is represented as a vertical bar with a brown color, and below it, also as a vertical bar, in blue, the daily intake from the parenteral source.
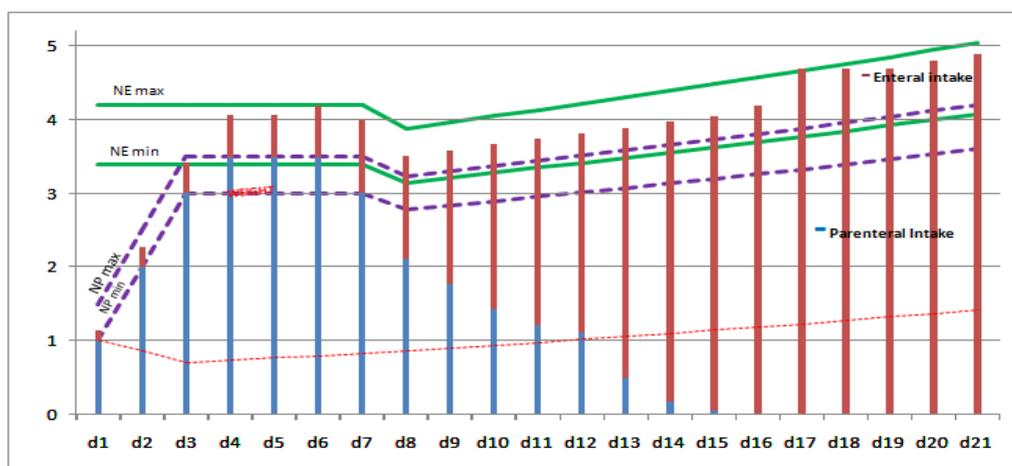

Fig.2. Directions for customized recommendations to a newborn of 1000g are shown with a continuous green line for enteral nutrition and a discontinuous purple line for parenteral nutrition. The daily intake of protein from the enteral nutrition is represented as a vertical bar with a claret color, and below it, also as a vertical bar, in blue, the daily intake from the parenteral source. Stacking them shows total protein intake. Attempts to maintain a total protein intake that ranges between the recommended range for enteral nutrition. With a bold red line, the weight curve is shown

In Fig.3, the representation is by horizontal vectors (green color is the result of the enteral source-purple color and parenteral source-red color), reported on a scale with customized parenteral and enteral nutrition markers.
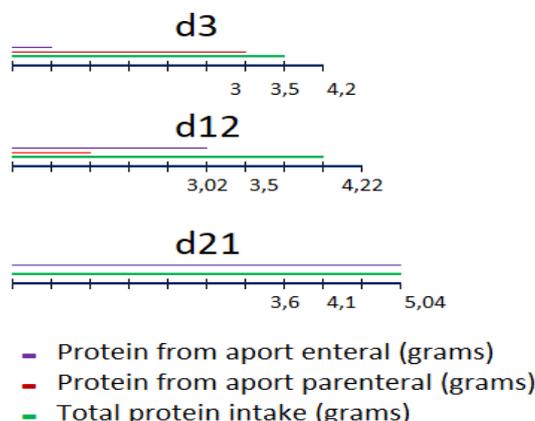

Fig.3. Vector representation of enteral (purple line), parenteral (red color) and resultant (green color) for day 3, 15 and 21 in a newborn with 1000 g Gn. The graduated scale contains recommendations for parenteral and enteral nutrition, tailored to the case

Discussions

In recent years, there have been numerous support programs for parenteral computer assisted feeding. All these systems are trying to reduce the time needed to make parenteral nutrition solutions, and to eliminate errors [13].

From a safety point of view, information technology can handle better than the man's medication and ordering PN, based on the guidelines contained in his program [14,15].

Since its introduction in the 1980s [16,17], computer aided programs are widely used in hospitals in Europe and the United States [18]. Unlike humans, computerized programs are not susceptible to fatigue or mathematical errors [14,19].

Through computerized programs, we can individualize PN prescriptions for each patient using such treatment, thereby improving biochemical control and reducing n. premature. Puangco and co-authors [14,20] found that the automation of writing and delivery of PN commands saved time because repetitive tasks and tedious calculations required earlier by neonatologists, dieticians and pharmacists were eliminated. Moreover, they have shown that the PN ordering of PCs has led to the improvement of nutrient content of PN solutions (energy, protein, calcium and phosphate).

This has helped achieve earlier caloric and protein goals, and has led to lower levels of alkaline phosphatase-a marker of better mineral status [14,20].

Such a computerized nutritional software offers a low cost and effective nutrient data are easy to use, the doses correctly calculated.

The PN-assisted PN prescription should become available as this can save time, reduce time spent on calculations, optimize composition of solutions and improve the quality of nutritional care.

Such computerized programs will most likely guide the physician to use appropriate standardized solutions and optimize the use of personalized solutions [21].

Conclusions

The method allows a rapid and accurate calculation of daily protein requirements. It is a "soft" method with the gradual increase of protein intake during the metabolic instability period and it is accurate and appropriate for the period of partial parenteral alimentation and allows a gradual and well-quantified decrease of the parenteral intake when enteral intake becomes dominant. The period of metabolic instability is the most difficult period in which a positive nitrate balance must be ensured (daily protein loss is estimated at 0.7g/kg/day), metabolic stress should be avoided and at the same time a sufficient intake to ensure a quick recovery must be provided. The period during which the nutrition is partially parenteral requires additional efforts to calculate the contribution from the enteral source and the proper adaptation of the perfusions. Another "sensitive" issue is the rate of the parenteral intake reduction and the optimal stopping time. The method gives a certain confidence during the ablation of the parenteral source avoiding the overestimate of the enteral intake or to produce a deficit in the nitrate balance for a significant amount of time.

Although the algorithm allows the rapid choice of the appropriate calculation formula, although the calculation formulas have been simplified, although the total calculation time is so low, however, the method remains laborious for the period when the enteral source and the calculation stage giving the optimal protein-energy ratio (where glucose and lipid intake should also be taken into account). Given that these recommendations can be translated into logical algorithm and expressed in mathematical equations, the use of computing is more plausible. An application using the Excel platform has been developed in this direction, with very good results, but for easier accessibility, it is working to translate into the web application (see Fig.4). The working time is very short, and this algorithm allows data to be kept and compare the evolution, also it allows the user to make more "scenarios" and choose the optimal one, the calculation of the infusion solutions being automatic, it is flexible by personalizing the calculations according to the clinical situation and the biological parameters.
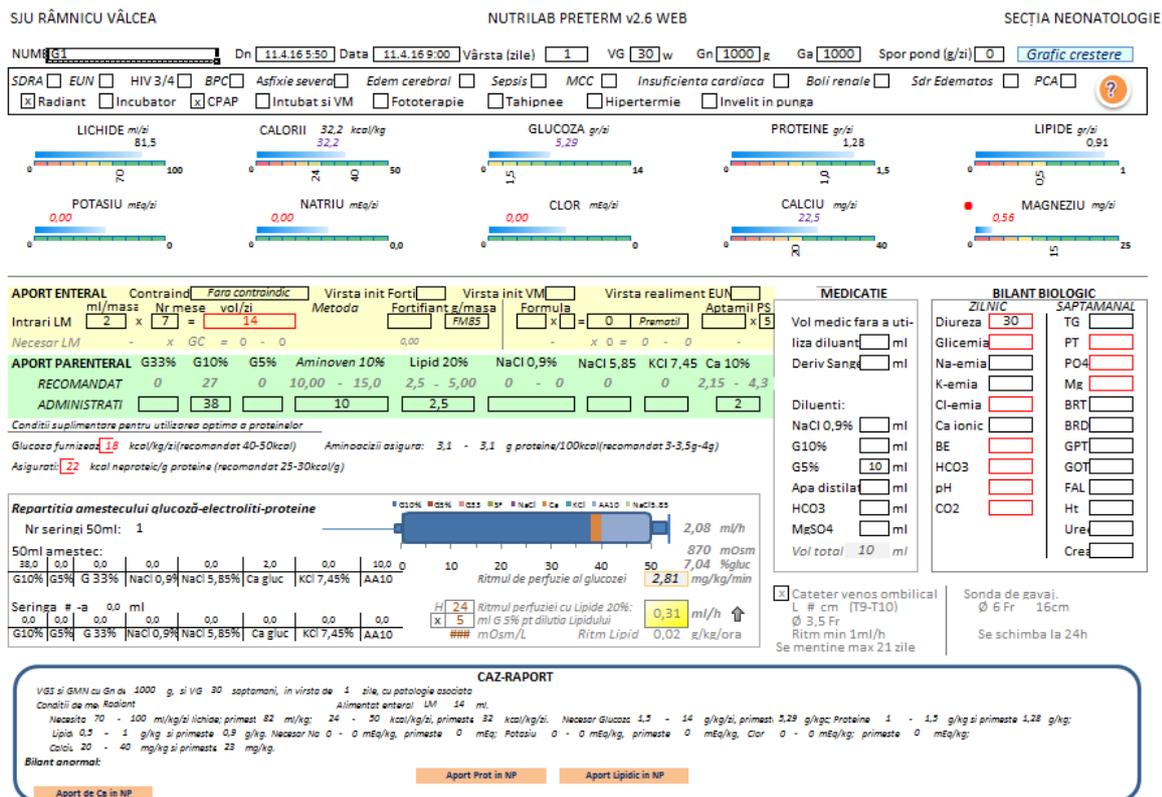
Fig.4. Interface of the nutrition program to the premature newborn (using the Excel platform)-authors' own concept

Abbreviations

Bw - birth weight, 5, 6, 7

d-1 - in ecuation, day-1, 7

ELBW - Extremely low birth weight, 4, 6, 7

EN - Enteral nutrition, 3, 4

LBW - Low birth weight, 4, 12

MM - maternal milk, 5

NPQ - the amount of protein needed in enteral nutrition, 5

PAI - Parenteral Aminoacid intake, 4

Parenteral nutrition - PN, 3

PNR - Parenteral nutrition recommandations, 5 ratio in the enteral nutrition

REN, 4

VLBW - Very low birth weight, 4

Ww - Weighed weight, 5

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