NUTRITIONAL ASSESSMENT OF CRITICALLY ILL CHILDREN:
THE SEARCH FOR PRACTICAL TOOLS

CIP-gegevens Koninklijke Bibliotheek, Den Haag

ISBN 90-77595-22-8

Printed by Optima Grafische Communicatie, Rotterdam
Design cover: Estay reclame-adviesbureau, Zwijndrecht
Lay-out: Margo Terlouw-Willeband, Nieuwerkerk aan den IJssel

This research was financially supported by Nutricia Nederland BV, Zoetermeer, the Netherlands and the David Vervat Foundation, Rotterdam, the Netherlands.

NUTRITIONAL ASSESSMENT OF CRITICALLY ILL CHILDREN:
THE SEARCH FOR PRACTICAL TOOLS

Vaststelling van de voedingstoestand van ernstig zieke kinderen
in de dagelijkse praktijk

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus
Prof.dr. S.W.J. Lamberts
en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
donderdag 22 april 2004 om 16.00 uur

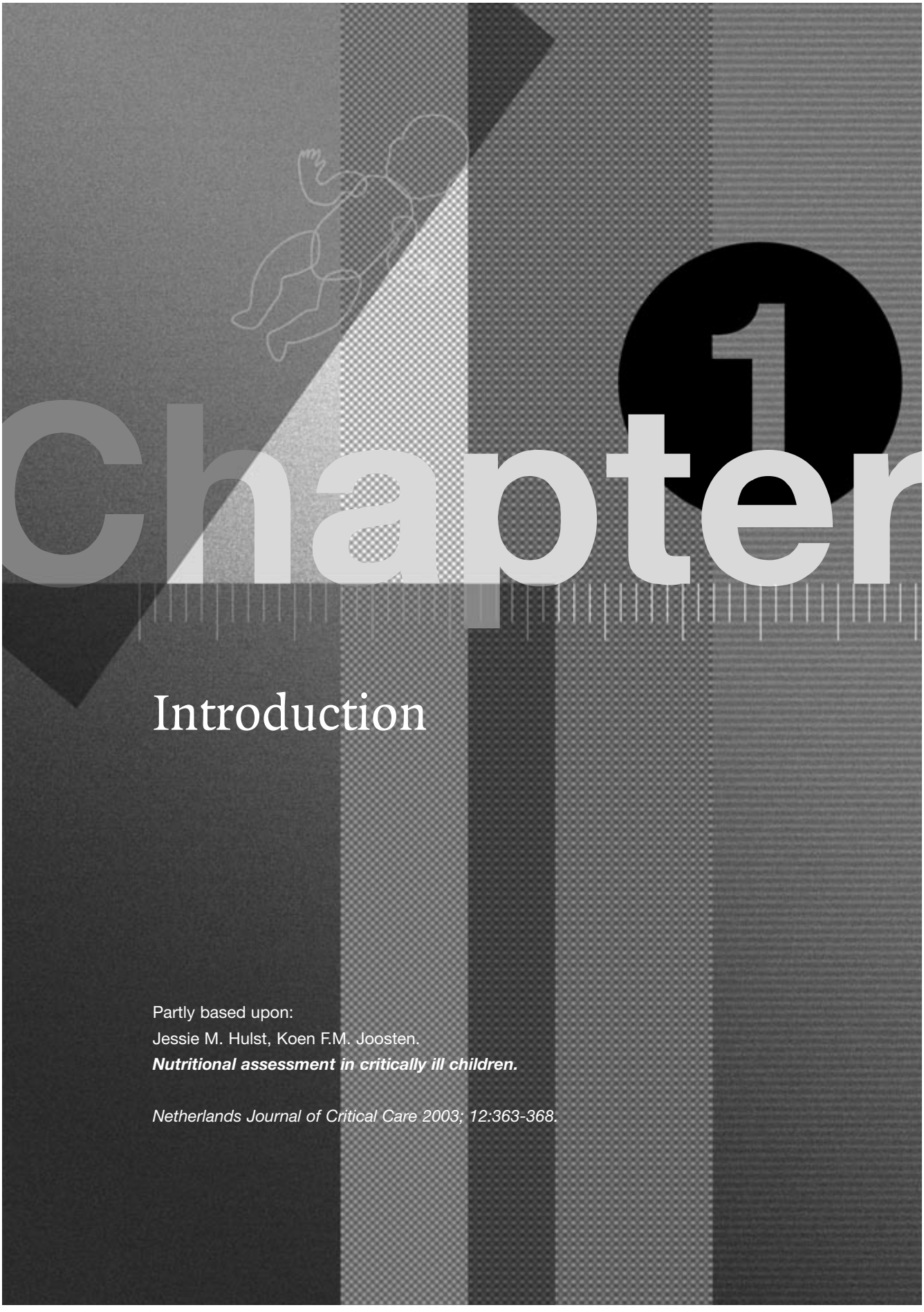
door

Jessie Mathilda Hulst
geboren te Rotterdam

Promotiecommissie:

Promotoren:	Prof.dr. D. Tibboel Prof.dr. J.B. van Goudoever
Overige leden:	Prof.dr. H.A. Büller Prof.dr. H.N. Lafeber Prof.dr. H.J. Bonjer
Copromotor:	Dr. K.F.M. Joosten

Table of Contents



Chapter 1

Introduction

Partly based upon:
Jessie M. Hulst, Koen F.M. Joosten.
Nutritional assessment in critically ill children.

Netherlands Journal of Critical Care 2003; 12:363-368.

General Introduction

Critical illness greatly influences one's nutritional status – child and adult alike – and assessment of nutritional status should therefore be an integral part of patient care. During a child's intensive care (ICU) stay, however, attention is mostly focused on the primary medical problem, e.g. hemodynamic instability, serious infection, congenital anomaly, and not on the child's nutritional status.
As early as 1980, researchers demonstrated protein-energy malnutrition (PEM) in 15-20% of children admitted to the ICU.[1,2] Recent statistics on the prevalence of malnutrition in pediatric ICU's are lacking and studies in populations representing the full range of children admitted to an ICU have not been reported. Nevertheless, factors such as improved intensive care technology, lower age at which major surgery is performed, and altered attitude towards feeding, may have altered the prevalence of malnutrition since then. Furthermore, due to improved technology we are also to reduce mortality in preterm neonates and we are able to lower the gestational age at which very immature infants remain alive. This implies that with the limited maturation of several organs, these infants are very vulnerable with regard to their body reserves. It is very hard to feed those infants adequate and malnutrition is bound to occur during the first weeks of life.[3]

Recent studies among non-critically ill children revealed that 20-25% of children were at risk for malnutrition or were in fact already malnourished, indicating that acute and chronic PEM is still common in hospitalized pediatric patients.[4]
PEM was shown to be associated with increased morbidity and mortality,[5,6] including a higher risk of infections due to poor immune defense, wound healing problems, reduced gut function, longer dependency on mechanical ventilation and longer hospital stay.[7] Furthermore, malnutrition in infancy is associated with poor growth and reduced or delayed mental and psychomotor development.[8,9] Other studies revealed that severe trauma, such as burns, affect children's nutritional status and growth for up to two years.[10,11] All things considered, thorough monitoring of the nutritional status of children admitted to an intensive care seems indispensable. Lacking endogenous stores and having higher baseline requirements, neonates and children under the age of 2 years are particularly susceptible to loss of lean body mass and the inherent risk of increased morbidity and mortality imposed by injury and illness.

It is, therefore, important to have initial nutritional assessment followed by adequate nutritional support as an essential aspect of the clinical management of pediatric intensive care patients. The diversity in clinical presentation and the range in age groups dictate a patient tailored approach.
Quite a few common hospital practices have been identified that may potentially lower the nutritional status of admitted patients (see Table 1).

Table 1 Common hospital practices potentially resulting in deterioration of nutritional status (adapted from Corish et al.)[12]

1.	Diffusion of responsibility for the nutritional care of patients
2.	Lack of interaction between medical, nursing, and dietetic staff
3.	Little emphasis on nutrition education in nursing and medical schools
4.	Limited availability of methods to assess nutritional status
5.	Failure to record patients' height and weight
6.	Failure to observe and record patients' dietary intake
7.	Frequent withholding of food because of diagnostic tests
8.	Delay in commencing nutritional support with prolonged use of glucose administration
9.	Widespread ignorance of the physiological effects of different feeding routes and the composition of nutritional products; this results both in the inappropriate use of route of administration of enteral and parenteral feeds of uncertain composition or inadequate amounts.

In general, the development of malnutrition during an ICU-stay can be related to the disease, to the withholding of nutritional assessment or the establishment of the patient's nutritional needs, or to lack of adequate nutritional support.
One of the reasons why nutritional assessment in the critically ill tends to be overlooked is the lack of a gold standard technique. Available parameters may be less sensitive in critically ill patients, given the combination of pre-existing nutritional status, the severity of the acute episode along with concurrent therapies (e.g. fluid resuscitation), and possible underlying chronic diseases.

The next section elaborates on nutritional assessment, focussing on the usefulness of available nutritional assessment tools in the pediatric intensive care setting.

Critical review of the literature

Definition of malnutrition

Although both under- and overnutrition are forms of malnutrition, the term malnutrition used in this thesis refers to undernutrition. Malnutrition has been defined as a disorder of body composition characterized by macro- and/or micro-nutrient deficiencies and resulting from reduced nutrient intake or impaired metabolism (American Society for Parenteral and Enteral Nutrition, 1995). It describes a broad spectrum of clinical conditions ranging in severity from mild to very severe, which may result in reduced organ function, reduced body mass (muscle wasting and loss of subcutaneous fat), abnormal results in blood chemistry studies, and less favorable clinical outcomes. In developed nations malnutrition is generally secondary to disease and caused by inadequate dietary intake, increased metabolic demands, impaired absorption or increased nutrient losses. ICU-patients may show a combination of these factors.[12] Conditions seen in the neonatal and pediatric ICU with a high risk of poor nutritional status or malnutrition include: prematurity, broncho-pulmonary dysplasia (BPD), cystic

fibrosis (CF), cardiac anomalies, congenital anomalies of the GI-tract (i.e esophageal or intestinal atresias), necrotising enterocolitis (NEC), short bowel syndrome, renal failure, cerebral palsy, and major burns.
Malnutrition can be of the acute, chronic or a mixed type. Acute malnutrition is the type that usually occurs in critical illness, but children with underlying chronic diseases who are admitted to an ICU because of an acute illness can also present with chronic malnutrition.

As nationally or internationally accepted thresholds and guidelines for anthropometric and biochemical variables used to define nutritional status are lacking, the criteria used to define malnutrition vary greatly. However, the diagnosis of PEM is often based on objective measurements, including anthropometric evaluation and assessment of chemical and immunologic parameters reflecting altered body composition. At present, however, there is no (gold standard) test that is both sensitive and specific for diagnosing malnutrition in critically ill patients. All available tests show significant limitations and any application has to be considered in the light of those limitations.[13]

Weight-for-age/Weight-for-height
Several criteria based on weight and length measurements have been used to classify the nutritional status of critically ill children. In order to diagnose acute malnutrition (wasting), different cut-offs have been proposed for weight-for age (WFA) and weight-for-height (WFH).[14-16] Length-for-age (LFA) usually serves to diagnose chronic malnutrition (stunting). Waterlow has classified acute and chronic PEM into four stages, based on the comparison of actual WFH with the 50th percentile in the population for acute malnutrition, and that of the actual LFA with the 50th percentile for chronic malnutrition.[15] Pollack et al. used this index for the initial assessment of children admitted to a pediatric intensive care unit.[2] For children with serious conditions and a high risk of malnutrition due to the primary disease or its treatment, the criteria for malnutrition screening at the population level, such as the Waterlow criteria, may be too low in clinical practice.

SD-scores
Nowadays cut-off values are given in terms of standard deviation (SD) scores (= [measured value – mean value in population]/standard deviation), i.e. SD-scores < -2 for WFA and LFA or decreases of 0.3 SD in these scores over a short period of time. For some congenital syndromes and other health conditions associated with growth abnormalities, the currently available disease-specific growth references are more appropriate for accurately assessing nutritional status.[17]

Definition of nutritional assessment

Nutritional assessment can be defined as the interpretation of data concerning an individual's intake and utilization of nutrients to determine his or her health status. Data must be obtained in a structured way, by different means and interpreted together in order to perform a comprehensive nutritional assessment:

A. General evaluation (including dietary and medical history and physical signs),
B. Severity of illness assessment,
C. Assessment of body composition,
D. Laboratory studies (including the estimation of energy requirements)

Nutritional assessment is necessary to identify patients who have already developed or are at risk of developing PEM, to establish the degree of malnutrition and the risk of developing malnutrition-related complications, and to monitor the adequacy of nutritional support.[18] Accurate assessment of nutritional status in children is complicated by ongoing growth, changing energy needs, varying body composition, and disease.[19]

Nutritional assessment

A. General evaluation

A full medical and dietary history is necessary for an extensive nutritional assessment. Critically ill children with a history of chronic disease may at admission show poor initial nutritional status and thus need extra attention. Physical signs of malnutrition usually do not appear until the malnutrition has been developing for some time and reached a severe stage, but the first impression of the child and subjective assessment of muscle and fat mass can help. Subjective global assessment (SGA) is a clinical technique which assesses nutritional status based on features of the history and physical examination.[20] It has mostly been used in adult and elderly patients[21,22] and not yet in critically ill children.

Measuring current nutritional status identifies only children who are already undernourished, not those at risk of malnutrition. Several nutritional risk assessment and screening tools based on data from both the history and the physical examination were developed to identify adult high-risk patients at the time of admission. Most of them are unsuitable for routine use. Some pediatric nutritional risk scores have been developed, taking into account food intake, presence and/or severity of pain and degree of pathology[23] or a combination of anthropometric and impedance data.[24] These scores have not been validated for children admitted to the ICU.

B. Severity of illness assessment

Objective illness severity scores are quite important in the overall nutritional assessment of a critically ill child during ICU-admission. They provide insight into the degree of

metabolic stress and help to determine the turning point from catabolism to anabolism in the course of disease. Several illness severity scoring systems are available for use in children: the Pediatric Risk of Mortality Score (PRISM)[25] and the Pediatric Index of Mortality (PIM)[26] for the pediatric population; the Clinical Risk Index for Babies (CRIB)[27] and the Score for Neonatal Acute Physiology (SNAP)[28] for preterm neonates.
Furthermore, changes in metabolic, endocrine and inflammatory parameters over time might help to evaluate the severity of illness during ICU-admission. At the moment, however, there is no universal scoring system for severity of disease in relation to nutritional assessment which can be used in daily practice.

C. Assessment of body composition
Currently, there is no consensus on the best method to assess body composition of children admitted to an ICU. A final consensus should be based on practical issues, such as accuracy and precision (reliability), rate at which changes can be detected, and cost-effectiveness. It is, therefore, essential to distinguish between tools that assess initial nutritional status and tools that can be used to identify short-term changes in nutritional status. Characteristics of a desirable method for clinical assessment of body composition during disease and recovery are shown in Table 2.

Body composition can be assessed by classic anthropometry or by newer, more sophisticated methods – e.g. bioelectrical impedance analysis and dual-energy X-ray absorptiometry. Most of these newer methods have severe limitations in the intensive care unit, seeing that practical application is limited because of technical problems, and that validated reference data are lacking. In general, results of body composition measurements may also be affected by the frequent alterations in the child's hydration status during the first stages of critical illness.
The following sections present an overview of body composition measuring techniques, of which the practical and theoretical advantages and limitations for use in critically ill children are summarized in Table 3.

Table 2 Characteristics of a desirable method for clinical assessment of body composition (source: Pichard et al.)[29]

Applicable to all pathology groups
Good precision, accuracy and reproducibility
Observer-independent
Easy to realize
Low degree of invasiveness
Reasonably low cost
Usable at the bedside

Anthropometry

Classic anthropometry is the term describing the measurement of body weight, body length, and head circumference. Additional anthropometric measurements concern circumferences, skinfold thicknesses and measurements of limb lengths, e.g. lower leg length (knemometry). Reference data of anthropometric measures are widely available for all ages, both sexes[30] and for various populations and diseases (e.g. Down's syndrome,[31,32] preterm infants[33,34]).

Weight is still the most important parameter for nutritional assessment of the critically ill child. However, weight is not easy to assess in this group, and changes in weight cannot be ascribed to growth only, because edema also plays an important role. Body length is generally of limited value for nutritional assessment during ICU-admission, because linear growth changes over a short period of admission are minimal. Length measurements are nevertheless important in the initial assessment, to evaluate chronic nutritional status. For newborn infants and children up to 24 months old, heel-to-knee measurement (knemometry) is a promising method for measurement of short term linear growth.[35] It makes use of a hand-held device that can be used inside an incubator and is less interruptive than total body length measurements.

The measurement of head circumference (HC) is an important aspect of nutritional assessment in young children as brain growth is highest in the first 4 years of life. In the ICU, this parameter is used predominantly in the preterm and term neonates, but hardly in children outside this age group. Assessment of HC at admission could signal the presence of severe chronic malnutrition in the past, whereas serial measurements in neonates can help in detecting the development of malnutrition.

Anthropometric measurements that can provide information on fat mass and fat-free mass include body circumferences (mid-upper arm, calf, abdominal) and skinfold thickness. Mid-upper arm circumference (MUAC) is a measure of muscle, fat and bone. It has served as an index of malnutrition in rapid nutritional surveys in which weight and length measurements were not feasible. Triceps skin-fold (TSF) thickness is one of the most valuable anthropometric measures of nutritional status, because (a) it is a good indicator of energy reserves; (b) it correlates well with total body fat stores; and (c) recent reference data are available for all age groups.[30] Combining the TSF measurement with MUAC enables to estimate upper-arm muscle (muscle circumference = MUAC - (0.314*TSF)) and fat stores.[36] The latter correlate well with total body measures of fat mass (FM) and fat-free mass (FFM). Furthermore, measuring arm muscle circumference is quite feasible, the arm is usually free of edema, and the outcome correlates with muscle wastage. Calf circumference was found to be useful for screening of nutritional status in healthy infants, but its utility in disease has not been well documented yet.[37]

Table 3 Nutritional assessment techniques: practical and theoretical advantages and limitations for use in critically ill children

Assessment Tool	What is assessed?	Advantages	Limitations
Subjective Global Assessment (SGA)	Identifies risk factors for malnutrition	▪ Good sensitivity and specificity ▪ Good inter-observer agreement	▪ Subjective ▪ Not validated for critically ill children ▪ Depends on parental co-operation
Functional tests (skeletal muscle function)	Grip strength Respiratory muscle strength Response to electrical stimulation		▪ Not possible in neonates and young children ▪ Relies on degree of patient co-operation ▪ No standardised equipment and procedures ▪ Interference of muscle relaxants and other drugs
Classic anthropometry (weight, height, head circumference)	Total body mass, growth (W) Linear growth (length) Brain growth (HC)	▪ Reference standards available for all ages and sex	▪ Unreliable when oedema is present ▪ Special equipment necessary at the bed-side
Knemometry (KHL)	Short term linear growth	▪ Sensitive to short term changes	▪ Difficult in older children ▪ No reference values available
Circumferences (MUAC, CC)	Body composition: ▪ Indirect measure of somatic protein ▪ Indication of fat mass	▪ Reference standards available for all ages and sex	▪ Values may fall in the normal range in the presence of PEM. ▪ Unreliable when oedema is present
Skin folds (TSF, BSF)	Body composition: ▪ Indication of fat mass	▪ Reference standards available for all ages and sex	▪ Large intra- and inter-observer variability ▪ Unreliable when oedema is present
Bioelectrical impedance analysis (BIA)	Body composition: ▪ Body water : estimation of FFM	▪ Non-invasive ▪ Possible at the bedside ▪ Quick and safe ▪ Small inter-observer variability	▪ No reference standards/equations for all ages ▪ Equations mostly validated in healthy children ▪ Not useful in children with fluid imbalance problems ▪ Influenced by many factors (e.g. skin temperature, prior food, body position)
TOBEC	Body composition: ▪ FFM and FM	▪ Accurate	▪ Not possible at the bed-side ▪ Expensive ▪ Lack of validation in patients undergoing compositional changes.
DEXA	Body composition: ▪ FFM, FM, and BM	▪ Accurate ▪ Low radiation dose ▪ Not relying on equations ▪ Possible at the bedside	▪ Expensive ▪ Technically difficult ▪ Difficult to interpret when oedema is present.

Stable isotope studies	▪ Body composition (deuterium labelled water (^2H_2O)): TBW (FFM) ▪ Estimation of EE (doubly labelled water ($^2H_2{}^{18}O$))	▪ Few exclusion criteria ▪ Very precise	▪ Invasive ▪ Long term assessment ▪ Expensive and scarce ▪ Not routinely possible
Indirect calorimetry	▪ Estimation of EE / 24 hr , RQ ▪ Accurate monitoring of energy needs	▪ Possible at the bed-side ▪ Can be used in mechanically ventilated patients ▪ Non-invasive ▪ Accounts for individual differences ▪ Good follow-up tool of nutritional therapy	▪ Some exclusion criteria ▪ Influenced by metabolic status, fever, activity, thermal effect of food. ▪ Expensive ▪ Maintenance of equipment

CC = calf circumference, DEXA = dual X-ray absorptiometry, EE = energy expenditure, FM = fat mass, FFM = fat free mass, HC = head circumference, L = length, LBM = lean body mass, MUAC = mid upper arm circumference, RQ = respiratory quotient, TBW = total body water, TOBEC = total body electrical conductivity, W = weight

The measuring of soft tissues is generally more difficult in terms of reliability and reproducibility, and requires well-trained anthropometrists. Measurement errors should be considered not only when interpreting a single measurement, but above all when evaluating changes over time.[17]
In summary, besides the problems in accurately performing the measurements, there are several important problems involved with the use of anthropometry in critically ill children. They tend to gain extra weight due to third spacing of fluid in acute metabolic stress, and standard anthropometric measurements may thus result in false outcomes. The individual child, however, may benefit from the initial assessment and follow-up over time.

Bioelectrical methods

Bioelectrical methods measure electrical activity and are based on the principle that lean tissue is far more electrically conductive than fat tissue, due to the much greater content of water and electrolytes in FFM.
One of these methods, bioelectrical impedance analysis (BIA), is a form of body composition analysis that is based on the physical principle that fat has low electrical conductivity and high impedance relative to water (FFM). This technique consists of passing a sensation-free alternating current between electrodes on hands and feet to obtain total body impedance. Total body impedance combines resistance (R) and reactance (Xc) across tissues. These two measures can be converted with age-specific prediction equations to estimate body composition (total body water (TBW) or FFM). Several age-specific prediction equations of TBW and other body compartments, including length and mostly also weight and sex, derived from numerous (small) cross-sectional studies are available.[38-42] Unfortunately, there are almost as many different BIA equations in the literature as there are studies, denoting the population-specific character of these equations. Moreover, equations for neonates and young children are scarce.
BIA was used to study changes in total body water in children < 3 year post-cardiac surgery and was found to be valuable in researching the major water fluxes associated with cardiopulmonary bypass techniques.[43] It also served to assess TBW in preterm neonates receiving intensive care.[44] Chiolero et al[45] showed BIA to be reliable in clinical studies in adult ICU patients, but argued that it is not very accurate for the individual patient. While others also pointed out the lack of accuracy of BIA-based predictions for the individual,[39,46] Robert et al concluded that BIA can be helpful in the monitoring of changes of body composition of adults during an ICU stay.[47]
A recent alternative method, the BIA vector method (RXc graph), generated normal values of the bioelectrical impedance vector from birth to puberty in healthy children.[48-50] This method holds an advantage over the conventional BIA method in that no assumptions regarding body composition and models need be made.[51] Its application in children with altered body composition still needs to be tested.

Although BIA has not been investigated in critically ill children, except for post-cardiac surgery,[43] and little is known about its capability estimating changes in body composition in a longitudinal setting,[52] it has great potential value as it can be carried out easily, quickly, and safely at the patient's bedside, and may show less inter-observer variation than do traditional anthropometric measurements.

Another alternative bioelectrical method, total body electrical conductivity (TOBEC), has been validated for young infants,[37] but it difficult to perform in daily practice, and expensive. Its use, therefore, seems to be limited to the research setting.

Absorptiometry methods

Dual energy x-ray absorptiometry (DEXA) and dual photon absorptiometry (DPA) provide methods to assess three body compartments: bone mass, fat mass and fat-free mass. Because of their varying densities, these tissues attenuate the energy beams or dual photons differentially as they pass through. DEXA causes extremely low radiation exposure and yields precise body composition in infants and children within a few minutes. However, large errors may be anticipated in children with abnormal hydration status because attenuation of water is similar to that of FFM. DEXA nevertheless has a wide application for assessing bone mineral content and body composition in preterm and term neonates,[53,54] patients with cystic fibrosis, Crohn's disease, anorexia nervosa, severe neuromuscular disease and chronic liver, cardiac, and renal disease.[19] Compared with bioelectrical and anthropometric methods of body composition assessment, DEXA has the added advantage of being independent of sample-based equations. A portable DEXA device would be necessary in the ICU-setting.

Muscle function tests

Muscle function tests, such as grip strength, respiratory muscle strength and the response of specific muscles to electrical stimulation, are not very suitable for evaluating nutritional status in young pediatric ICU patients, as their skeletal muscle function can alter rapidly by undernutrition.[55] These tests deserve to be investigated, however, in the older children.

Research tools

Many other methods, such as isotope studies, total body potassium, neutron activation analysis, ultrasonography, computed tomography scanning, or magnetic resonance imaging, have been developed to accurately estimate the body composition of children in a research setting.[56,57] Data on the use of these methods in critically ill children are lacking. So far, these methods have shown practical and logistic limitations in a non-research clinical setting, but they are important as gold standards to which easier methods can be evaluated against.

Total body water (TBW) and consequently FFM can be estimated by dilution methods using stable isotopes of water (deuterium, ^{18}O) that are ingested or infused. They can safely and effectively measure TBW volumes in infants and children.[58] Protein status can be accurately measured using an amino acid labelled with a stable isotope (e.g. ^{13}C leucine).[59] Routine use of stable isotope studies is difficult since the analyses require mass spectrometers which are not available in most hospitals for these purposes.

D. Laboratory assessment

Selected laboratory tests may be useful to identify nutritional deficiencies before clinical findings are evident and may be helpful to monitor clinical recovery from malnutrition.
The clinical use and limitations of laboratory parameters in nutritional assessment of critically ill children are outlined in Table 4 and discussed in more detail in the following sections.

Visceral proteins

Synthesis of visceral proteins is inhibited in the acute phase of trauma and sepsis. In the recovery phase, however, the liver will return to produce visceral proteins which are needed for repair of injured tissue and in children for somatic growth. Various parameters and indexes can describe protein status. Proteins with a short biologic half-life, such as pre-albumin ($t_{1/2}$ = 2 days) and retinol-binding protein ($t_{1/2}$ = 10 hours), are more suited to predict changes in acute nutritional status than are albumin ($t_{1/2}$ = 20 days) and transferrin ($t_{1/2}$ = 8 days), which have longer half-lives. Clinical studies in critically ill infants and preterm infants showed pre-albumin and retinol-binding protein to be the most suitable proteins to evaluate protein nutritional status and protein-energy adequacy.[60,61] Moreover, in growing preterm infants changes in pre-albumin occurred one week before changes in anthropometric measurements.
Various acute phase proteins rise after serious injury or sepsis in association with a drop in visceral proteins. The measurement of a visceral protein as nutritional index should therefore at least be complemented by C-reactive protein (CRP) measurement as an indicator of the presence of an acute phase response, aiding in the interpretation of sequential measurements.[62]
In an attempt to improve the sensitivity and specificity of tests for nutritional assessment, various multiparameter indices – incorporating laboratory parameters and anthropometric – have been developed for the adult population, e.g. the Prognostic Inflammatory and Nutritional Index (PINI),[63] and the Prognostic Nutritional Index (PNI).[64] Chwals et al. used levels of pre-albumin and CRP in combination with total urinary nitrogen excretion and values obtained with indirect calorimetry as guidelines for infant metabolic monitoring during acute stress.[65] Nutritional intake was increased when serial measurements of these metabolic parameters demonstrated a resolution of the acute phase response.

Table 4 Clinical use and limitations of laboratory parameters in nutritional assessment of critically ill children

	Clinical use	Limitations
BIOCHEMICAL		
Albumin	▪ Valuable as a prognostic indicator ▪ Useful for long-term assessments	▪ Affected by many other factors present in ICU patients (e.g. infusion of fluids, capillary leak syndrome) ▪ Long t ½ (15-20 d): levels reflect chronic rather than acute protein depletion
Pre-albumin	▪ Short t ½ (2-3 d) and small body pool: sensitive in evaluating acute changes in nutritional (protein and energy) adequacy	▪ Influenced by liver, renal and inflammatory disease
Transferrin	▪ More sensitive than albumin in reflecting protein depletion	▪ Long t ½ (8 d): more reflective of chronic changes in nutritional status. ▪ Influenced by iron status, liver and inflammatory disease
Retinol binding protein	▪ Short t ½ (12 h) ▪ Decreases rapidly with PEM	▪ Low plasma concentrations ▪ Shows minimal changes in short-term nutritional repletion ▪ Influenced by liver and renal disease
Urinary nitrogen excretion	▪ Marker of protein metabolism ▪ Estimates daily protein losses with reasonable accuracy	▪ Many factors affecting: adequacy of collection, diuretics, renal function and protein intake
Muscle metabolites (urine 3-methylhistidine/ urine creatinine)	▪ Reflects muscle-mass ▪ Correlate with FFM assessed by anthropometry	▪ Influenced by renal function and protein-intake ▪ Not reliable as marker of body composition in conditions in which accelerated rates of protein degradation occur
CRP	▪ Reflects illness severity/acute metabolic response	▪ No direct measure of nutritional status
Markers of immune function (total lymphocyte count, delayed cutaneous hypersensitivity, decreased CD4:CD8 ratio)	▪ Useful in prognostic assessments	▪ Influenced by sepsis, steroids, stress ▪ No value in detection of PEM or monitoring improvement in nutritional status
ENDOCRINE		
IGF-1	▪ Small body pool and short t ½ (2-8 h): sensitive in evaluating acute changes in nutritional (protein and energy) adequacy	▪ No routine laboratory assessment
Thyroid hormones: TSH, T_3, rT_3, T_3/rT_3 ratio	▪ Possible parameter for signaling return to anabolism ▪ Related to severity of illness	▪ No direct measure of nutritional status
Glucose/insulin ratio	▪ Possible parameter for signaling return to anabolism	▪ No direct measure of nutritional status

CRP = C-reactive protein, IGF-1 = insulin-like growth factor I, FFM = fat free mass, PEM = protein energy malnutrition, T3 = triiodothyronine, TSH = thyroid stimulating hormone, rT3 = reverse T3

Total urinary nitrogen and nitrogen balance

Acute metabolic stress will intensify protein breakdown and urinary nitrogen loss. Since urinary excretion is in fact the predominant (> 90%) mechanism of nitrogen removal, measuring urinary nitrogen excretion is sufficient. Patients with uremia and/or renal failure will also experience important gastrointestinal and skin losses. Furthermore, infants after digestive tract surgery will show important fecal nitrogen losses, and losses via nasogastric tubes, enterostomies and wound drains.[66] Daily assessment of nitrogen intake and nitrogen excretion (nitrogen balance) has been used in studies of critically ill children, newborn infants, and infants after surgical procedures to estimate needs, to assess nutritional therapy and to follow metabolic status and the capacity to synthesize protein.[67-73] Protein need is calculated from urinary nitrogen excretion using the formula: protein (g/kg/day) = 6.25 x urinary urea nitrogen excretion. [74] An adjustment can be made for the 10% to 20% of other urinary nitrogen loss such as ammonia, creatinine, and uric and amino acids. A 24 hours urinary collection is preferred but is not always easy in clinical practice; a 6-hr collection or 12-hr collection (preterm neonates) can then be sufficient.

Micronutrients

Hypocalcemia,[75] hypomagnesemia[76] and hypophosphatemia commonly occur in the critically ill[77] it is essential to determine their levels. Serum triglyceride level needs to be assessed initially and followed during nutritional therapy, because of altered fat metabolism in the critically ill child.[78,79] In prolonged critical illness it might be vital to assess levels of vitamins and carnitine sequentially, as decreased nutrient intakes and increased requirements may easily lead to a deficiency state.[80-82]

Other biochemical parameters

Apart from the ones mentioned above, many other biochemical parameters have been used to assess nutritional or protein status. Examples are urinary creatinine excretion, the creatinine-height index,[83] 3-methylhistidine[84,85] and immunological parameters (simple lymphocyte count, ratio of CD4+ to CD8+ lymphocytes, and a cutaneous hypersensitivity test). These parameters, however, are rarely used in the pediatric setting, because they have various practical and methodological limitations in critically ill children and tend to be affected rather by disease than by malnutrition.[19,56,62,86]

Endocrine methods

Endocrine parameters might be used to signal the turning point from catabolism to anabolism in critically ill children and thereby help in optimizing individual nutritional support.

Glucose/Insulin

Initial screening for hypo- and hyperglycemia should be performed in all critically ill children. Hyperglycaemia with high plasma insulin concentrations is the resultant of insulin insensitivity that occurs during stress. Although it occurs frequently in (preterm) neonates it is rare in older pediatric patients[87,88] and the commonly applied intensive insulin therapy in critically ill adult patients has very limited use in critically ill children.[88] Hypoglycemia is predominant in children with sepsis. The use of the ratio glucose/insulin as a marker of nutritional status is worthy of further investigation, since an increase in this ratio after an initial decrease may reflect the transition from catabolism to anabolism. Age-related data on glucose and insulin are available in children after major surgery.[89]

Thyroid hormones

Critical illness causes multiple alterations in the thyroid axis, both in adults and in children. Described as the 'low T_3 syndrome', the 'euthyroid sick syndrome' or 'non thyroidal illness',[90-93] this syndrome combines a low serum triiodothyronine (T_3) level with an increased reverse T_3 concentration and a normal or low thyroxine (T_4) level, all with a normal functioning thyroid gland. This syndrome is generally thought not to produce hypothyroidism, but rather to constitute an adaptation aimed at preventing protein catabolism and lowering energy requirements.[94-97] In critically ill adult patients a component of the alteration in thyroid hormone levels was found to result from the caloric deprivation associated with severe illness,[97] while the magnitude of the T_3 drop within 24 hour reflects the severity of illness.[98] Accordingly, an increase of serum TSH is a hallmark of recovery from severe illness.[99] Moreover, the euthyroid sick syndrome was found to be a predictor of mortality in adult patients.[100-102]

The finding that in critically ill children with meningococcal sepsis the levels of rT_3, T_3 and ratio rT_3/T_3 showed a quick return to normalisation indicates that these levels might be used to prelude anabolism.[87]

IGF-1

The anabolic hormone IGF-1 is often propagated as a marker of nutritional status, as its short half-life allows rapid responses to alterations in nutritional status and because changes in IGF-1 reflect the changes in N-balance and the severity of the nutritional insult.[103-105] In healthy children or children with a chronic disease IGF-1 concentrations are regulated by energy and protein intakes[106,107] and are related with anthropometric parameters of nutritional status.[108,109] Studies among critically ill children show conflicting results, however, on the relationship between IGF-1 concentration and nutritional status.[110,111] The IGF-1 concentration can be expected to increase when the acute stress response has come to a halt and further on when the nutritional status improves. Studies in critically ill children in which IGF-1 levels are assessed over a prolonged period in relation to other nutritional indices and nutritional therapy are

lacking. Such studies are needed to assess the utility of IGF-1 in screening for malnutrition.

Energy requirements

Measuring energy expenditure

Measuring energy expenditure allows for a more accurate monitoring of the child's varying energy needs in the course of critical illness. In the research setting, total and resting energy expenditure can be estimated by using the following methods: indirect calorimetry, doubly labeled water (DLW), whole-body calorimetry, thermic effect of food assessment, and heart rate monitoring.[17] The DLW method is the one mostly used in research and evaluates energy expenditure (EE) over a longer period of time. As the results are not readily available, its use to estimate EE and adjust energy intake in clinical practice is of limited value and restricted to the research setting. Measuring EE by indirect calorimetry is well applicable clinically, at the intensive care unit, and more accurate than estimating individual EE from standard prediction equations.

Indirect calorimetry

Indirect calorimetry provides non-invasive, reliable, repeatable and affordable measurements of actual EE – i.e. resting EE (REE) in non-ventilated children and total daily EE (TDEE) in ventilated children. Quantification of EE is also important for diagnostics in the critically ill child, because it can reveal hyper- or hypometabolic conditions directly related to the individual prognosis. The greatest asset of indirect calorimetry is its potential in designing a nutrition regimen that exactly meets patient's energy requirements while avoiding the complications of overfeeding.[112]

Several factors commonly present in the ICU population might affect measured EE and must be taken into account when interpreting the outcome.[113] These factors are listed in Table 5.

Table 5 Clinical factors influencing energy expenditure (adapted from McClave et al.[113])

Increase in EE	Decrease in EE
Increasing size	Increasing age
Male sex	Female sex
Fever	Progression of sepsis to septic shock
Thermogenesis	Obesity
Weaning from mechanical ventilation	Placement on mechanical ventilation
Flow phase of injury	
Overfeeding	Underfeeding / starvation
Acute hyperventilation	Acute hypoventilation
Drugs: pressor agents, catecholamines, muscle relaxants	Drugs: sedatives, analgesics, beta blockers
Cyclic or bolus feeding	Artefact (leak, calibration, condensation)
Pain, anxiety	

The second parameter obtained from indirect calorimetry, the respiratory quotient (RQ), may help in evaluating substrate utilization and/or nutritional support and in determining overfeeding and underfeeding.[71] Fat oxidation results in an RQ of 0.7, whereas protein and carbohydrate oxidation result in RQ's of 0.83 and 1.0 respectively. Net lipogenesis is shown by an RQ >1.0 which is indicative of overfeeding.

Indirect calorimetry is being widely used as a research tool to determine energy requirements. In most ICUs, however, its routine use is hampered by limited space at the bedside, the cost of multiple metabolic carts, and the lack of trained staff to operate these monitors. In addition, several criteria need to be fulfilled before accurate indirect calorimetry measurements can be performed, some of which are described below:

- Regular and correct calibration of the calorimeter
- A sufficient period of measurement to achieve steady VO_2 and VCO_2 levels.[114]
- Endotracheal tube leakage < 10%[115]
- Inspired oxygen fraction (FiO_2) stable and below 60%
- Steady hemodynamic, respiratory and metabolic states to insure that respiratory gas exchange is equivalent to tissue gas exchange

To date, indirect calorimetry has probably had a greater role in our understanding of energy metabolism and the pathophysiology of disease processes than in guiding individual patient care.[113]

Estimating EE

In clinical practice the use of equations based on weight and sex to estimate REE (e.g. Schofield)[116] can be helpful to guide nutritional support. However, none of them will predict EE with acceptable precision for use in the individual, especially in disease states.

Outline and aims of the thesis

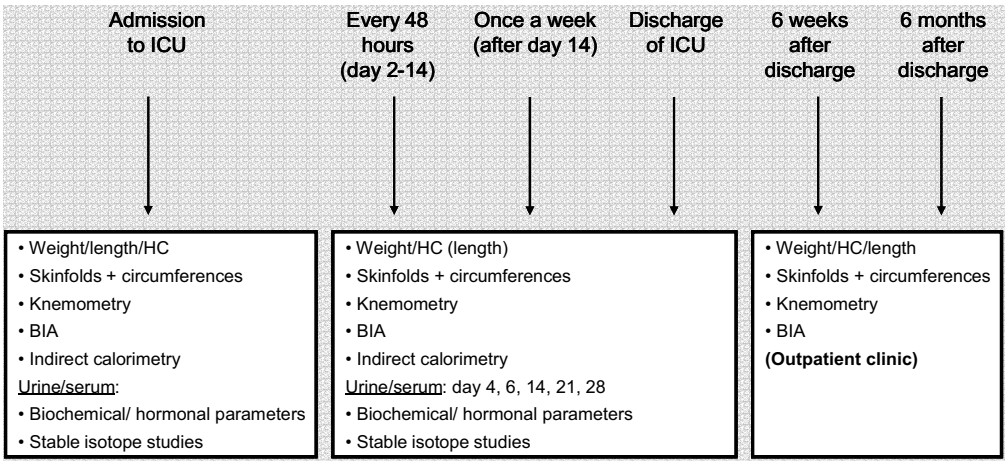
The overall goals of the work presented in this thesis are:

1. to obtain better insight in the prevalence of malnutrition in critically ill children during ICU-admission and follow-up.
2. to determine what nutritional assessment parameters are sensitive in singling out children with poor nutritional status and those at risk for developing malnutrition, with central focus on clinical applicability and routine use feasibility in the pediatric ICU setting.

All studies described in this thesis are based on a one-year prospective observational cohort study in a heterogeneous group of critically ill children admitted to the intensive care unit of the Erasmus MC-Sophia Children's Hospital in 2001. The outline of the study protocol is shown in Figure 1.

Obtaining (parental) informed consent is the first and very important step when performing clinical research in human subjects. In order to establish an adequate and representative sample of the overall population admitted to an ICU, it is important to obtain a high inclusion rate and to characterize those children who could not be included into the study. ***Chapter 2*** describes an evaluation of the possible determinants of obtaining (parental) informed consent for participation of their critically ill child in a clinical study. Moreover, clinical characteristics of the children with informed consent are compared with those of children of whose parents declined consent.

Figure 1 Outline of the study protocol for the prospective, observational cohort study



HC = head circumference, BIA = bio-electrical impedance analysis

In ***Chapter 3*** the anthropometric assessment of critically ill children is described from admission to six months after discharge. Questions to be answered are:

- What are the prevalences of acute and chronic malnutrition in a large cohort of critically ill children at admission to the ICU and during admission?
- What are the groups at risk of developing a poor nutritional status?
- How does the nutritional status of critically ill children discharged from the ICU develop over time?

In ***Chapter 4*** indirect calorimetry is used to study the following issues:

- Can the respiratory quotient be used as a parameter to indicate adequate feeding?
- What is the relation between measured energy expenditure and energy intake?
- What proportion of children receives the adequate amount of energy?

Chapter 5 describes daily and cumulative energy and protein intakes of critically ill children during their first two weeks in the ICU, and compares these with recommended intakes for healthy children (RDA). Furthermore, relationships between accumulated energy and protein intake, measured energy expenditure and changes in anthropometric parameters are examined.

Chapter 6 and ***Chapter 7*** report on the usefulness of various biochemical and hormonal parameters in assessing of nutritional status in critically ill children during their intensive care stay. Issues addressed are:

- Can laboratory parameters help in identifying children at risk for deterioration of their nutritional status during ICU-admission?
- Is it possible to identify hormonal parameters that can be used to predict a return to anabolic metabolism as an important prerequisite to tailor and improve nutritional support?
- Will nutrition influence the course of hormonal parameters during ICU-admission?

The concluding chapters of this thesis search to answer the questions which nutritional assessment tools are suitable for implementation in daily clinical practice (***Chapters 8*** and ***9***). The results are discussed in relation to the reviewed literature and suggestions are made for a new nutritional assessment guideline for routine use in children admitted to an intensive care unit.

References

1. Merritt RJ, Suskind RM. Nutritional survey of hospitalized pediatric patients. Am J Clin Nutr 1979;32:1320-5.
2. Pollack MM, Wiley JS, Holbrook PR. Early nutritional depletion in critically ill children. Crit Care Med 1981;9:580-3.
3. Ehrenkranz RA, Younes N, Lemons JA, Fanaroff AA, Donovan EF, Wright LL, Katsikiotis V, Tyson JE, Oh W, Shankaran S, Bauer CR, Korones SB, Stoll BJ, Stevenson DK, Papile LA. Longitudinal growth of hospitalized very low birth weight infants. Pediatrics 1999;104:280-9.
4. Hendrikse W, Reilly J, Weaver L. Malnutrition in a children's hospital. Clinical Nutrition 1997;16:13-18.
5. Pollack MM, Ruttimann UE, Wiley JS. Nutritional depletions in critically ill children: associations with physiologic instability and increased quantity of care. J Parenter Enteral Nutr 1985;9:309-13.
6. Biolo G, Toigo G, Ciocchi B, Situlin R, Iscra F, Gullo A, Guarneiri G. Metabolic response to injury and sepsis: changes in protein metabolism. Nutrition 1997;13(Suppl):52S-57S.
7. Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient: a meta-analysis. JAMA 1998;280:2013-9.
8. Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. BMJ 1998;317:1481-7.
9. Klein PS, Forbes GB, Nader PR. Effects of starvation in infancy (pyloric stenosis) on subsequent learning abilities. J Pediatr 1975;87:8-15.
10. Hart DW, Wolf SE, Mlcak R, Chinkes DL, Ramzy PI, Obeng MK, Ferrando AA, Wolfe RR, Herndon DN. Persistence of muscle catabolism after severe burn. Surgery 2000;128:312-9.
11. Rutan RL, Herndon DN. Growth delay in postburn pediatric patients. Arch Surg 1990;125:392-5.
12. Corish CA, Kennedy NP. Protein-energy undernutrition in hospital in-patients. Br J Nutr 2000;83:575-91.
13. Cerra FB, Benitez MR, Blackburn GL, Irwin RS, Jeejeebhoy K, Katz DP, Pingleton SK, Pomposelli J, Rombeau JL, Shronts E, Wolfe RR, Zaloga GP. Applied nutrition in ICU patients. A consensus statement of the American College of Chest Physicians. Chest 1997;111:769-78.
14. McLaren DS, Read WW. Classification of nutritional status in early childhood. Lancet 1972;2:146-8.
15. Waterlow JC. Classification and definition of protein-calorie malnutrition. Br Med J 1972;3:566-9.
16. Gomez F, Galvan R, Cravioto J, Frenk S. Malnutrition in infancy and childhood, with special reference to kwashiorkor,. Adv Pediatr 1955;7:131-69.
17. Zemel BS, Riley EM, Stallings VA. Evaluation of methodology for nutritional assessment in children: anthropometry, body composition, and energy expenditure. Annu Rev Nutr 1997;17:211-35.
18. Klein S, Kinney J, Jeejeebhoy K, Alpers D, Hellerstein M, Murray M, Twomey P. Nutrition support in clinical practice: review of published data and recommendations for future research directions. Summary of a conference sponsored by the National Institutes of Health, American Society for

Parenteral and Enteral Nutrition, and American Society for Clinical Nutrition. Am J Clin Nutr 1997;66:683-706.

19. Khoshoo V. Nutritional assessment in children and adolescents. Curr Opin Pediatr 1997;9:502-7.
20. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, Jeejeebhoy KN. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr 1987;11:8-13.
21. Ferguson M, Capra S, Bauer J, Banks M. Development of a valid and reliable malnutrition screening tool for adult acute hospital patients. Nutrition 1999;15:458-64.
22. Duerksen DR, Yeo TA, Siemens JL, O'Connor MP. The validity and reproducibility of clinical assessment of nutritional status in the elderly. Nutrition 2000;16:740-4.
23. Sermet-Gaudelus I, Poisson-Salomon AS, Colomb V, Brusset MC, Mosser F, Berrier F, Ricour C. Simple pediatric nutritional risk score to identify children at risk of malnutrition. Am J Clin Nutr 2000;72:64-70.
24. Edefonti A, Picca M, Paglialonga F, Loi S, Grassi MR, Ardissino G, Marra G, Ghio L, Fossali E. A novel objective nutritional score for children on chronic peritoneal dialysis. Perit Dial Int 2002;22:602-7.
25. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988;16:1110-6.
26. Shann F, Pearson G, Slater A, Wilkinson K. Paediatric index of mortality (PIM): a mortality prediction model for children in intensive care. Int Care Med 1997;23:201-207.
27. The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. The International Neonatal Network. Lancet 1993;342:193-8.
28. Richardson DK, Gray JE, McCormick MC, Workman K, Goldmann DA. Score for Neonatal Acute Physiology: a physiologic severity index for neonatal intensive care. Pediatrics 1993;91:617-23.
29. Pichard C, Genton L, Jolliet P. Measuring body composition: a landmark of quality control for nutritional support services. Curr Opin Clin Nutr Metab Care 2000;3:281-4.
30. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47:316-23.
31. Cronk C, Crocker AC, Pueschel SM, Shea AM, Zackai E, Pickens G, Reed RB. Growth charts for children with Down syndrome: 1 month to 18 years of age. Pediatrics 1988;81:102-10.
32. Cremers MJ, van der Tweel I, Boersma B, Wit JM, Zonderland M. Growth curves of Dutch children with Down's syndrome. J Intellect Disabil Res 1996;40 (Pt 5):412-20.
33. Casey PH, Kraemer HC, Bernbaum J, Yogman MW, Sells JC. Growth status and growth rates of a varied sample of low birth weight, preterm infants: a longitudinal cohort from birth to three years of age. J Pediatr 1991;119:599-605.

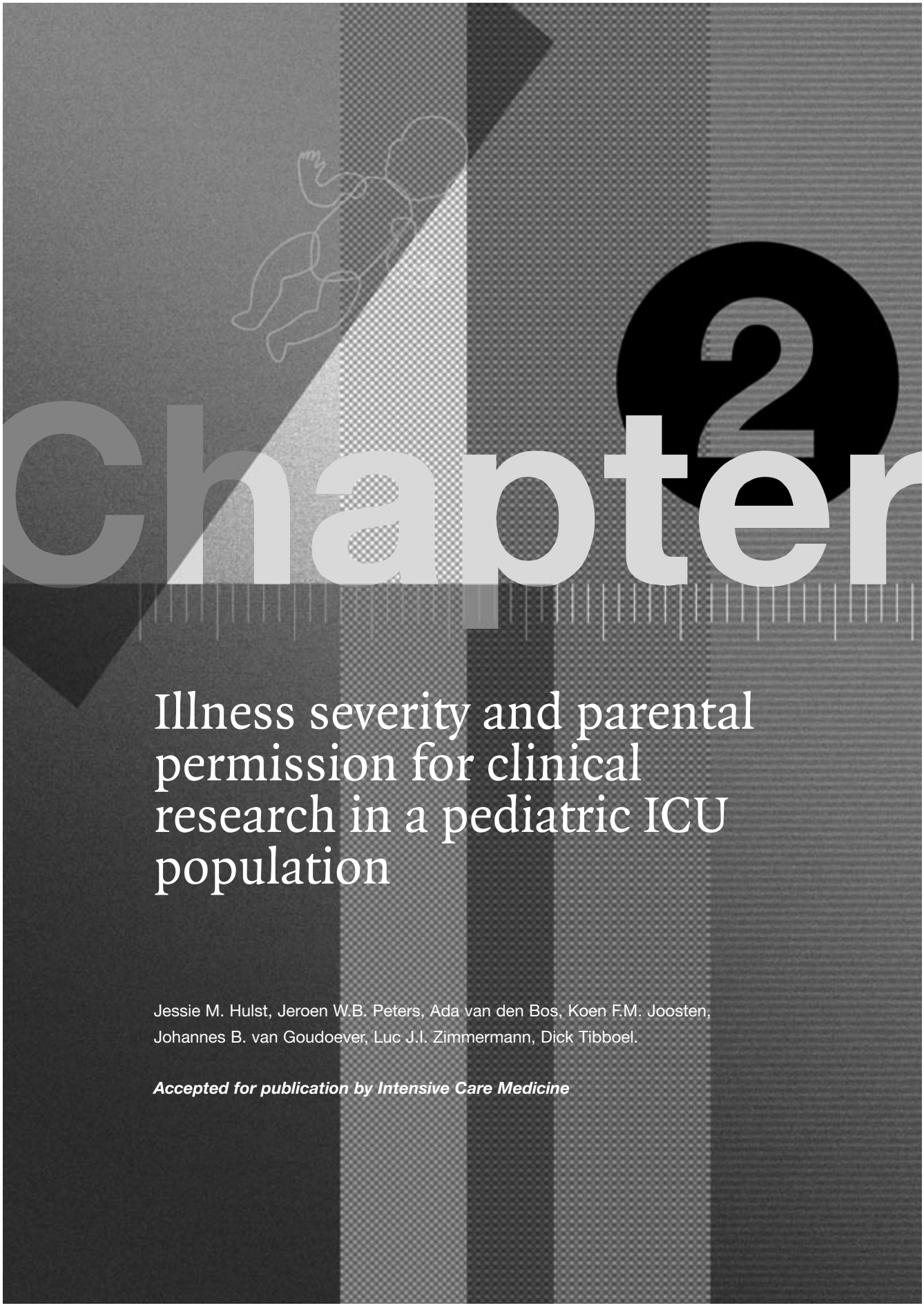
34. Usher R, McLean F. Intrauterine growth of live-born Caucasian infants at sea level: standards obtained from measurements in 7 dimensions of infants born between 25 and 44 weeks of gestation. J Pediatr 1969;74:901-10.
35. Hermanussen M. Knemometry, a new tool for the investigation of growth. A review. Eur J Pediatr 1988;147:350-5.
36. Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. Am J Clin Nutr 1981;34:2540-5.
37. De Bruin NC, Van Velthoven KA, Stijnen T, Juttmann RE, Degenhart HJ, Visser HK. Body fat and fat-free mass in infants: new and classic anthropometric indexes and prediction equations compared with total-body electrical conductivity. Am J Clin Nutr 1995;61:1195-205.
38. Goran M, Kaskoun M, Carpenter W, Poehlman E, Ravussin E, Fontvieille A. Estimating body composition of young children by using bioelectrical resistance. J Appl Physiol 1993;75:1776-1780.
39. Fjeld CR, Freundt-Thurne J, Schoeller DA. Total body water measured by 18-O dilution and bioelectrical impedance in well and malnourished children. Pediatr Res 1990;27:98-102.
40. Kushner RF, Schoeller DA, Fjeld CR, Danford L. Is the impedance index (ht2/R) significant in predicting total body water? Am J Clin Nutr 1992;56:835-9.
41. Deurenberg P, Kusters CS, Smit HE. Assessment of body composition by bioelectrical impedance in children and young adults is strongly age-dependent. Eur J Clin Nutr 1990;44:261-8.
42. Deurenberg P, van der Kooy K, Leenen R, Weststrate JA, Seidell JC. Sex and age specific prediction formulas for estimating body composition from bioelectrical impedance: a cross-validation study. Int J Obes 1991;15:17-25.
43. Maehara T, Novak I, Wyse RK, Elliot MJ. Perioperative monitoring of total body water by bio-electrical impedance in children undergoing open heart surgery. Eur J Cardiothorac Surg 1991;5:258-64; discussion 265.
44. Tang W, Ridout D, Modi N. Assessment of total body water using bioelectrical impedance analysis in neonates receiving intensive care. Arch Dis Child Fetal Neonatal Ed 1997;77:F123-6.
45. Chiolero RL, Gay LJ, Cotting J, Gurtner C, Schutz Y. Assessment of changes in body water by bioimpedance in acutely ill surgical patients. Intensive Care Med 1992;18:322-6.
46. Horlick M, Arpadi SM, Bethel J, Wang J, Moye J, Jr., Cuff P, Pierson RN, Jr., Kotler D. Bioelectrical impedance analysis models for prediction of total body water and fat-free mass in healthy and HIV-infected children and adolescents. Am J Clin Nutr 2002;76:991-9.
47. Robert S, Zarowitz BJ, Hyzy R, Eichenhorn M, Peterson EL, Popovich J, Jr. Bioelectrical impedance assessment of nutritional status in critically ill patients. Am J Clin Nutr 1993;57:840-4.
48. Piccoli A, Fanos V, Peruzzi L, Schena S, Pizzini C, Borgione S, Bertino E, Chiaffoni G, Coppo R, Tato L. Reference values of the bioelectrical impedance vector in neonates in the first week after birth. Nutrition 2002;18:383-7.
49. Savino F, Grasso G, Cresi F, Oggero R, Silvestro L. Bioelectrical impedance vector distribution in the first year of life. Nutrition 2003;19:492-6.

50. De Palo T, Messina G, Edefonti A, Perfumo F, Pisanello L, Peruzzi L, Di Iorio B, Mignozzi M, Vienna A, Conti G, Penza R, Piccoli A. Normal values of the bioelectrical impedance vector in childhood and puberty. Nutrition 2000;16:417-24.
51. Piccoli A, Rossi B, Pillon L, Bucciante G. A new method for monitoring body fluid variation by bioimpedance analysis: the RXc graph. Kidney Int 1994;46:534-9.
52. Phillips SM, Bandini LG, Compton DV, Naumova EN, Must A. A longitudinal comparison of body composition by total body water and bioelectrical impedance in adolescent girls. J Nutr 2003;133:1419-25.
53. Rigo J, Nyamugabo K, Picaud JC, Gerard P, Pieltain C, De Curtis M. Reference values of body composition obtained by dual energy X-ray absorptiometry in preterm and term neonates. J Pediatr Gastroenterol Nutr 1998;27:184-90.
54. Lafeber HN. Nutritional assessment and measurement of body composition in preterm infants. Clin Perinatol 1999;26:997-1005.
55. Russell DM, Leiter LA, Whitwell J, Marliss EB, Jeejeebhoy KN. Skeletal muscle function during hypocaloric diets and fasting: a comparison with standard nutritional assessment parameters. Am J Clin Nutr 1983;37:133-8.
56. Lukaski H. Methods for the assessment of human body composition: traditional and new. Am J Clin Nutr 1987;46:537-56.
57. Ellis KJ. Human body composition: in vivo methods. Physiol Rev 2000;80:649-80.
58. Schoeller DA, van Santen E, Peterson DW, Dietz W, Jaspan J, Klein PD. Total body water measurement in humans with 18O and 2H labeled water. Am J Clin Nutr 1980;33:2686-93.
59. Van Goudoever JB, Sulkers EJ, Halliday D, Degenhart HJ, Carnielli VP, Wattimena JL, Sauer PJ. Whole-body protein turnover in preterm appropriate for gestational age and small for gestational age infants: comparison of [15N]glycine and [1-(13)C]leucine administered simultaneously. Pediatr Res 1995;37:381-8.
60. Chwals WJ, Fernandez ME, Charles BJ, Schroeder LA, Turner CS. Serum visceral protein levels reflect protein-calorie repletion in neonates recovering from major surgery. J Pediatr Surg 1992;27:317-20; discussion 320-1.
61. Polberger SK, Fex GA, Axelsson IE, Raiha NC. Eleven plasma proteins as indicators of protein nutritional status in very low birth weight infants. Pediatrics 1990;86:916-21.
62. Manning EM, Shenkin A. Nutritional assessment in the critically ill. Crit Care Clin 1995;11:603-34.
63. Pressac M, Vignoli L, Aymard P, Ingenbleek Y. Usefulness of a prognostic inflammatory and nutritional index in pediatric clinical practice. Clin Chim Acta 1990;188:129-36.
64. Dempsey DT, Mullen JL, Buzby GP. The link between nutritional status and clinical outcome: can nutritional intervention modify it? Am J Clin Nutr 1988;47:352-6.
65. Chwals WJ. Metabolism and nutritional frontiers in pediatric surgical patients. Surg Clin North Am 1992;72:1237-66.
66. Albers MJ, Steyerberg EW, Rietveld T, Tibboel D. Clinical relevancy of nonurinary nitrogen excretion in newborns and infants after digestive tract surgery. JPEN J Parenter Enteral Nutr 2003;27:327-32.

67. Verhoeven JJ, Hazelzet JA, van der Voort E, Joosten KF. Comparison of measured and predicted energy expenditure in mechanically ventilated children. Intensive Care Med 1998;24:464-8.
68. Salas-Salvado J, Molina J, Figueras J, Masso J, Marti-Henneberg C, Jimenez R. Effect of the quality of infused energy on substrate utilization in the newborn receiving total parenteral nutrition. Pediatr Res 1993;33:112-117.
69. Pierro A, Carnielli V, Filler RM, Smith J, Heim T. Characteristics of protein sparing effect of total parenteral nutrition in the surgical infant. J Pediatr Surg 1988;23:538-42.
70. Bresson JL, Narcy P, Putet G, Ricour C, Sachs C, Rey J. Energy substrate utilization in infants receiving total parenteral nutrition with different glucose to fat ratios. Pediatr Res 1989;25:645-8.
71. Joosten KF, Verhoeven JJ, Hazelzet JA. Energy expenditure and substrate utilization in mechanically ventilated children. Nutrition 1999;15:444-8.
72. Tilden SJ, Watkins S, Tong TK, Jeevanandam M. Measured energy expenditure in pediatric intensive care patients. Am J Dis Child 1989;143:490-2.
73. De Klerk G, Hop WC, De Hoog M, Joosten KF. Serial measurements of energy expenditure in critically ill children: useful in optimizing nutritional therapy? Intensive Care Med 2002;28:1781-5.
74. Mickell JJ. Urea nitrogen excretion in critically ill children. Pediatrics 1982;70:949-55.
75. Chernow B, Zaloga G, McFadden E, Clapper M, Kotler M, Barton M, Rainey TG. Hypocalcemia in critically ill patients. Crit Care Med 1982;10:848-51.
76. Fiser RT, Torres A, Jr., Butch AW, Valentine JL. Ionized magnesium concentrations in critically ill children. Crit Care Med 1998;26:2048-52.
77. Demling RH, DeBiasse MA. Micronutrients in critical illness. Crit Care Clin 1995;11:651-73.
78. Llop J, Sabin P, Garau M, Burgos R, Perez M, Masso J, Cardona D, Sanchez Segura JM, Garriga R, Redondo S, Sagales M, Ferrer D, Pons M, Vuelta M, Fabregas X, Vitales M, Casasi, n T, Marti, nez J, Morato L, Soler M. The importance of clinical factors in parenteral nutrition-associated hypertriglyceridemia. Clin Nutr 2003;22:577-583.
79. Park W, Paust H, Schroder H. Lipid infusion in premature infants suffering from sepsis. JPEN J Parenter Enteral Nutr 1984;8:290-2.
80. Seear M, Lockitch G, Jacobson B, Quigley G, MacNab A. Thiamine, riboflavin, and pyridoxine deficiencies in a population of critically ill children. J Pediatr 1992;121:533-8.
81. Shenkin A. Micronutrients in the severely-injured patient. Proc Nutr Soc 2000;59:451-6.
82. Proulx F, Lacroix J, Qureshi IA, Nadeau D, Gauthier M, Lambert M. Acquired carnitine abnormalities in critically ill children. Eur J Pediatr 1997;156:864-9.
83. Viteri FE, Alvarado J. The creatinine height index: its use in the estimation of the degree of protein depletion and repletion in protein calorie malnourished children. Pediatrics 1970;46:696-706.
84. Maldonado J, Faus MJ, Bayes R, Molina JA, Gil A. Apparent nitrogen balance and 3-methylhistidine urinary excretion in intravenously fed children with trauma and infection. Eur J Clin Nutr 1988;42:93-100.
85. Seashore JH, Huszar GB, Davis EM. Urinary 3-methylhistidine excretion and nitrogen balance in healthy and stressed premature infants. J Pediatr Surg 1980;15:400-4.

86. Twomey P, Ziegler D, Rombeau J. Utility of skin testing in nutritional assessment: a critical review. JPEN J Parenter Enteral Nutr 1982;6:50-8.
87. Joosten KF, de Kleijn ED, Westerterp M, de Hoog M, Eijck FC, Hop WCJ, Voort EV, Hazelzet JA, Hokken-Koelega AC. Endocrine and metabolic responses in children with meningoccocal sepsis: striking differences between survivors and nonsurvivors. J Clin Endocrinol Metab 2000;85:3746-53.
88. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001;345:1359-67.
89. Bouwmeester NJ, Anand KJ, van Dijk M, Hop WC, Boomsma F, Tibboel D. Hormonal and metabolic stress responses after major surgery in children aged 0-3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine. Br J Anaesth 2001;87:390-9.
90. Chopra I. Nonthyroidal illness syndrome or euthyroid sick syndrome? Endocr Pract 1996;2:45-52.
91. Zucker AR, Chernow B, Fields AI, Hung W, Burman KD. Thyroid function in critically ill children. J Pediatr 1985;107:552-4.
92. Hashimoto H, Igarashi N, Yachie A, Miyawaki T, Sato T. The relationship between serum levels of interleukine-6 and thyroid hormone in children with acute respiratory infection. J Clin Endocrinol Metab 1994;78:288-291.
93. Matthews DS, Aynsley-Green A, Matthews JN, Bullock RE, Cooper BG, Eyre JA. The effect of severe head injury on whole body energy expenditure and its possible hormonal mediators in children. Pediatr Res 1995;37:409-17.
94. Carter JN, Eastmen CJ, Corcoran JM, Lazarus L. Inhibition of conversion of thyroxine to triiodothyronine in patients with severe chronic illness. Clin Endocrinol (Oxf) 1976;5:587-94.
95. Chopra IJ, Solomon DH, Chopra U, Wu SY, Fisher DA, Nakamura Y. Pathways of metabolism of thyroid hormones. Recent Prog Horm Res 1978;34:521-67.
96. Moshang T, Jr., Parks JS, Baker L, Vaidya V, Utiger RD, Bongiovanni AM, Snyder PJ. Low serum triiodothyronine in patients with anorexia nervosa. J Clin Endocrinol Metab 1975;40:470-3.
97. Richmand DA, Molitch ME, TF OD. Altered thyroid hormone levels in bacterial sepsis: the role of nutritional adequacy. Metabolism 1980;29:936-42.
98. Rothwell PM, Lawler PG. Prediction of outcome in intensive care patients using endocrine parameters [see comments]. Crit Care Med 1995;23:78-83.
99. Bacci V, Schussler G, Kaplan T. The relationship between serum triiodthyronine and thyrotropin during systemic illness. J Clin Endocrinol Metab 1982;54:1229-1235.
100. Schulte C, Reinhardt W, Beelen D, Mann K, Schaefer U. Low T3-syndrome and nutritional status as prognostic factors in patients undergoing bone marrow transplantation. Bone Marrow Transplant 1998;22:1171-8.
101. Friberg L, Drvota V, Bjelak AH, Eggertsen G, Ahnve S. Association between increased levels of reverse triiodothyronine and mortality after acute myocardial infarction. Am J Med 2001;111:699-703.

102. Iervasi G, Pingitore A, Landi P, Raciti M, Ripoli A, Scarlattini M, L'Abbate A, Donato L. Low-T3 syndrome: a strong prognostic predictor of death in patients with heart disease. Circulation 2003;107:708-13.
103. Hawker FH, Stewart PM, Baxter RC, Borkmann M, Tan K, Caterson ID, McWilliam DB. Relationship of somatomedin-C/insulin-like growth factor I levels to conventional nutritional indices in critically ill patients. Crit Care Med 1987;15:732-6.
104. Unterman TG, Vazquez RM, Slas AJ, Martyn PA, Phillips LS. Nutrition and somatomedin. XIII. Usefulness of somatomedin-C in nutritional assessment. Am J Med 1985;78:228-34.
105. Frayn KN, Price DA, Maycock PF, Carroll SM. Plasma somatomedin activity after injury in man and its relationship to other hormonal and metabolic changes. Clin Endocrinol (Oxf) 1984;20:179-87.
106. Merimee T, Zapf J, Froesch E. Insulin-like growth factor factors in the fed and fasted states. J Clin Endocrinol Metab 1982;55:999-1002.
107. Clemmons DR, Underwood LE, Dickerson RN, Brown RO, Hak LJ, MacPhee RD, Heizer WD. Use of plasma somatomedin-C/insulin-like growth factor I measurements to monitor the response to nutritional repletion in malnourished patients. Am J Clin Nutr 1985;41:191-8.
108. Martinez de Icaya P, Fernandez C, Vazquez C, del Olmo D, Alcazar V, Hernandez M. IGF-1 and its binding proteins IGFBP-1 and 3 as nutritional markers in prepubertal children. Ann Nutr Metab 2000;44:139-43.
109. Brennan BM, Gill M, Pennells L, Eden OB, Thomas AG, Clayton PE. Insulin-like growth factor I, IGF binding protein 3, and IGFBP protease activity: relation to anthropometric indices in solid tumours or leukaemia. Arch Dis Child 1999;80:226-30.
110. Leite HP, Fisberg M, Vieira JGH, De Carvalho WB, Chwals WJ. The role of insulin-like growth factor 1, growth hormone, and plasma proteins in surgical outcome of children with congenital heart disease. Pediatr Crit care Med 2001;2:29-35.
111. Balcells J, Moreno A, Audi L, Roqueta J, Iglesias J, Carrascosa A. Growth hormone/insulin-like growth factors axis in children undergoing cardiac surgery. Crit Care Med 2001;29:1234-8.
112. Brandi LS, Bertolini R, Calafa M. Indirect calorimetry in critically ill patients: clinical applications and practical advice. Nutrition 1997;13:349-58.
113. McClave SA, McClain CJ, Snider HL. Should indirect calorimetry be used as part of nutritional assessment? J Clin Gastroenterol 2001;33:14-9.
114. Joosten KF, Verhoeven JJ, Hop WC, Hazelzet JA. Indirect calorimetry in mechanically ventilated infants and children: accuracy of total daily energy expenditure with 2 hour measurements. Clin Nutr 1999;18:149-52.
115. Knauth A, Baumgart S. Accurate, noninvasive quantitation of expiratory gas leak from uncuffed infant endotracheal tubes. Pediatr Pulmonol 1990;9:55-60.
116. Schofield W. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr: Clin Nutr 1985;39:5-41.



Chapter 2

Illness severity and parental permission for clinical research in a pediatric ICU population

Jessie M. Hulst, Jeroen W.B. Peters, Ada van den Bos, Koen F.M. Joosten, Johannes B. van Goudoever, Luc J.I. Zimmermann, Dick Tibboel.

Accepted for publication by Intensive Care Medicine

Abstract

Objective
Research in child subjects requires parental permission. We aimed to determine if parental authorization of involvement in a clinical study is influenced by the child's severity of illness at the time of the consent decision.

Design and setting
Observational study in a multidisciplinary tertiary pediatric and neonatal intensive care.

Patients
Four hundred twenty-one children (age range from preterm to 18 years) of whom parents were asked to consent for participation in a study within 24 hours after admission to the ICU. The aim of the proposed study was to evaluate the child's nutritional status and included repeated anthropometry, blood sampling and stable isotope studies.

Measurements and results
Severity of illness as well as demographic and clinical factors were compared between the children for whom consent had been obtained and those for whom not. Over 20% of the parents (88/421) refused consent, most of them because they expected the study to be too burdensome for their child. Patient and disease characteristics were comparable in both groups. A higher illness severity score did not decrease the odds for obtaining informed consent. Parents of children with a history of disease were 3.2 times less likely to consent.

Conclusions
Parents of children with higher illness severity scores are not more likely to decline from giving permission to include their child in clinical observational research on the ICU. History of disease and subjectively perceived burden to the child are important factors that have to be taken into account.

Introduction

Against the background of intensifying legislation, privacy rules[1] and ethical discussions about research and the protection of research participants, the issue of informed consent is an important topic. Consent to participate in research is obligatory, as has been clearly recognized by the World Medical Association in the Declaration of Helsinki.[2] When the subject is a minor, permission from a responsible relative can replace that of the subject. This permission is also known as parental informed consent or proxy consent. Four essential components of the informed consent process must be fulfilled before parental consent is considered valid. Parents must be considered to be mentally competent, to have received appropriate information about the purpose and duration of the study and its risk and benefits, to be able to understand the information, and to give consent voluntarily without coercion.[3] Moreover, apart from approval by the local Institutional Review Board (IRB), more and more countries request nation-wide approval of studies conducted in children, e.g. approval by the Central Committee on Research Involving Human Subjects.[4]

In general, the decision to consent or not can be affected by factors relating to the child and his or her illness, to the parents themselves and to the study itself. Previous studies on parental consent have investigated reasons for consenting or declining,[5,6] testing of the validity or quality of the consent process,[5,7,8] general parental attitudes towards research,[9] parental perception of the consent process,[10,11] parents perceptions of research in neonates,[9] and socio-demographic, motivational and psychological factors of parents.[11-13] Possible important factors related to the study itself are type of research, i.e. observational vs. interventional, or therapeutic vs. non-therapeutic; invasiveness and risks, timing of start of the study and the person who asks informed consent.[3,9]

A child's admission to an ICU has an enormous impact, both on the child and the parents. The child usually has to undergo many invasive procedures; the parents, for their part, are overloaded with new information and have unpredictable future perspectives. To our knowledge, no studies have addressed the relation between obtaining informed consent and factors associated to the severity of illness among a heterogeneous group of consecutively admitted children admitted to a mixed neonatal and pediatric ICU. In this study we focused on factors associated with the child and his or her clinical condition. We hypothesized that parents are more likely to decline from giving permission to include their child in a study when the child is more severely ill.
Thus the primary aim of this study was to determine if parental authorization of involvement in a clinical study is influenced by the child's severity of illness at the time of the consent decision. A secondary aim was investigating the importance of other child-related factors on the decision to give parental informed consent.

Materials and Methods

We carried out this study in connection with a prospective observational study performed in our tertiary multidisciplinary intensive care including neonatal, pediatric and pediatric surgical patients. The study population included all parents/legal representatives of children who had been approached for consent to enroll their child in this nutritional assessment study. Children from the age of 12 years were asked for consent themselves at the same time as their parents, provided their condition permitted to do so. Informed consent was requested within 24 hours following admission to the ICU and was obtained by any of the members of the research team according to international guidelines.[14] The team consisted of a full time research physician and five part time research nurses to guarantee daily presence of at least one of the members. The team member present fully explained to the parents (and child, if applicable) the implications of giving consent. Parents were given to understand that their decision would not in any way affect the care for their child and that they were free to withdraw at any time, without stating their reason and with no consequences for the care of their child. Furthermore, they received the outline of the clinical study on paper, summarizing its objective, design, risks and discomforts, and including photographs of the proposed measurements. This informative document adhered to the guidelines of the Central Committee on Research Involving Human Subjects[4] and had been approved by the IRB of our hospital. The parents were given time to read the information, reflect on what was proposed and discuss it together, before giving their decision. Parents who declined consent were asked to reveal the reason for not consenting.

Eligible children were all those admitted to our intensive care unit during the year 2001, from preterm neonates to 18-year-olds. Exclusion criteria were treatment with Extra Corporeal Membrane Oxygenation (ECMO), withholding/withdrawing of treatment, and inclusion into an ongoing nutritional intervention study.

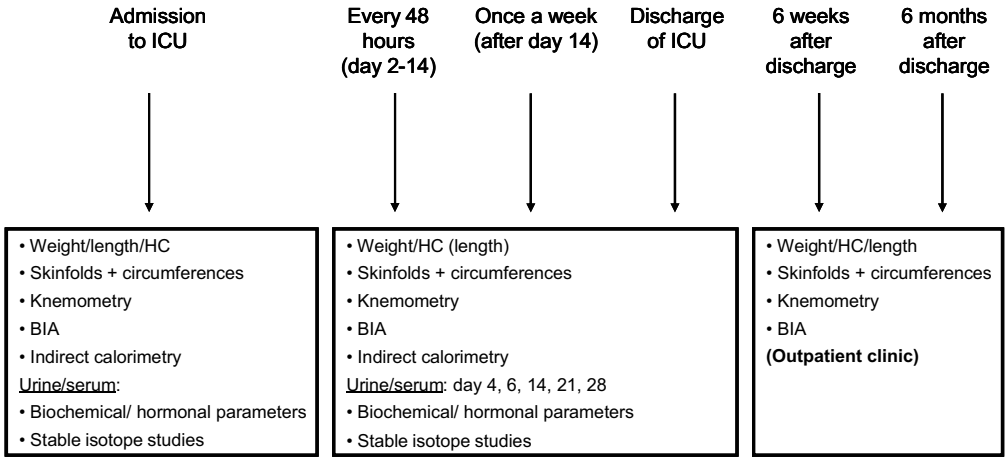
The proposed study was a prospective nutritional assessment study[15] approved by the IRB of our hospital, which was believed to represent minimal risk, a moderate amount of burden and did not directly benefit the child. This study aimed at assessing the nutritional status of critically ill children by different means and monitoring their nutritional status from admission to 6 months after discharge. It included repeated antropometry (weight, length, head circumference, arm circumference, calf circumference and skinfolds of triceps and biceps), knemometry (measuring lower leg length) and bioelectrical impedance analysis (BIA). All these measurements were performed by a member of the research team every other day during the first 2 weeks of admission and weekly thereafter, at a time the child was nursed, thus preventing disruption of sleeping and feeding patterns. Furthermore, if applicable, indirect calorimetry was performed by connecting the ventilator to a metabolic monitor or by putting a canopy over the child

when sleeping. Blood sampling at pre-defined times was also part of the study protocol, but this was only carried out if arterial or venous access was already available (no additional vena puncture). Stable isotope studies, requiring oral administration of the isotope (deuterium labeled water) and urine collection, were performed once a week. Altogether, the different measurements started within the first 24 hours after admission to the unit and continued until the day of discharge from the ICU. The study outline is represented in Figure 1.

Clinical and demographic data were obtained both of children who participated in the nutritional assessment study and those of whom parents withheld permission to the proposed study. These data were used to investigate the effect of severity of illness and other factors on the parental decision to consent or withhold permission. All data could be obtained from the child's file or departmental statistics and were collected by the research team of the nutritional assessment study. These data included severity of illness, (post-conceptional) age, sex, ethnic background, diagnostic group, undergoing surgery or not, length of ICU-stay, death/alive at discharge and, if appropriate, birth weight and gestational age. For the older children we also recorded their previous health status and whether or not the admission was acute or elective. A child admitted to the ICU because of critical illness with no history of disease (e.g. trauma, meningococcal disease) was classified as 'previously healthy', whereas a child with a previous history of chronic disease or numerous hospital admissions was classified as having a 'history of underlying disease'. Severity of illness was assessed by means of two validated scoring systems: the Pediatric Risk of Mortality score (PRISM)[16] and the Clinical Risk Index for Babies (CRIB).[17] The PRISM (score range: 0-76) was used for children from term -18 years, the CRIB for preterm neonates within 12 hours after birth (score range 0-23). A higher PRISM or CRIB score indicates more severe illness.[16,17] Furthermore, the Therapeutic Intervention Scoring System-score (TISS score)[18] was used to estimate the extent of interventions for each child during the first 24 hours. This measure of workload was scored by the ICU-nurses by means of a computerized system.

Children were classified by age into 3 groups: preterm neonates (gestational age < 37 weeks), term neonates (0-30 days) and older children (> 30 days). This grouping of children was chosen because the majority of children admitted to our units are younger than 30 days of age. Since children from the age of 12 years are involved in the consent process, we also looked at this subgroup.

Figure 1 Outline of the protocol of the nutritional assessment study for which informed consent was sought. *(HC = head circumference, BIA = bio-electrical impedance analysis)*



Statistical analysis

Statistical analyses were performed using SPSS software program (version 10.0 for Windows, SPSS, Chicago, Ill., USA). Results are expressed as median and range except when indicated otherwise. Data of the children for whom consent was obtained were compared to the data of children without consent. Parametric data were analyzed using Student's t test. Nonparametric data were analyzed using the Pearson´s X^2-square test or Fisher's exact test, and the Mann-Whitney U-test. In order to adjust for influences of other factors, stepwise multivariate logistic regression analysis with backward elimination (Likelihood Ratio, $P < 0.1$ for entry, $P < 0.05$ for elimination) was carried out to examine what variables affected parents' decision at the time of request.
Factors initially analyzed by this method varied between the 3 age groups. In the preterm and term neonates we checked birth weight, post-conceptional age at admission, illness severity score (CRIB or PRISM score), TISS score and whether or not having to undergo surgery. In the older children additional factors were previous health status and acute/elective admission, while birth weight was left out. A two-tailed *P*-value < 0.05 was considered to indicate statistical significance.

Results

Informed consent was obtained in 333 out of possible 421 cases (79%). Eleven of the twenty-one children aged ≥ 12 y could be involved in the consent process – the other 10

were sedated and/or mechanically ventilated. Thus, eighty-eight parents (5 of whom in line with their child's decision) declined from giving informed consent, for reasons listed in Table 1.

Table 1 Reasons for declining informed consent (n = 88)

Reasons	**n (%)**
Too much (extra) burden on child	59 (67)
Too sick or too small	11 (12)
Child unwilling to participate, parents went along*	5 (6)
Too much to consider for parents	4 (4)
Against research	4 (4)
Infection risk	2 (2)
Do not see the importance	2 (2)
Poor experience with participation in earlier research	1 (1)

**those children aged ≥ 12 years who were able to decide together with their parents.*

All refusers spontaneously expressed or freely revealed the reason for refusal. Most parents (59/88) expected the proposed research to be too burdensome for their child added to the many procedures that he or she had to undergo anyhow.

Patient and disease characteristics, and factors associated with illness severity in both groups are shown in Tables 2a through 2c. Overall, patient characteristics did not differ significantly between children with and children without consent. The distribution of age groups (preterm neonates, term neonates, and older children) within each group was not significantly different, but the percentage of children aged ≥ 12 y was significantly higher in the non-consent group. Regarding factors related to the disease (Table 2b), a significantly higher proportion of older children without consent had a history of underlying disease. All 5 children aged ≥ 12 y who declined to participate had a history of chronic disease and several hospital admissions. Median PRISM and TISS scores were similar in both groups (table 2c), but the median CRIB score of the preterm neonates in the consent group was significantly higher than that of the preterm neonates with no consent. Furthermore, length of stay in this age group was significantly longer in the consent group as compared to the non-consent group. In the older children, the non-consent group showed a higher proportion of deaths during admission (23% vs. 6%, P = 0.016), but their PRISM scores were not significantly higher (median score 21.5 vs. 19, P = 0.829).

Table 2a Patient characteristics.*

	Informed consent (n = 333**)**	**No informed consent** (n = 88)	***P*-value**
Gender (M:F)†	57:43	58:42	NS
Age, d	2 (0-16.9 yr)	2 (0-16.3 yr)	NS
Age groups			NS‡
Preterm neonates†	113 (34)	38(43)	
Gestational age, wk	31.3 (25-36.7)	31.1 (25-36.7)	NS
Birth weight, g	1520 (530-3160)	1600 (650-3205)	NS
Postnatal age, d	0 (0-83)	0 (0-58)	NS
Term neonates†	106 (32)	24 (27)	
Gestational age, wk	39.7 (37-42.1)	39.4 (37-41.9)	NS
Birth weight, g	3305 (1765-5855)	3608 (2470-4475)	NS
Postnatal age, d	1(0-30)	1 (0-30)	NS
Older children†	114 (34)	26 (30)	
Age, y	1.4 (0.1-17.0)	1.4 (0.1-16.3)	NS
Age > 12y†	13 (4)	8 (9)	0.047
Ethnic background†			NS
Caucasian	254 (76)	71 (81)	
Indo-Mediterranean	41 (12)	12 (14)	
African	30 (9)	3 (3)	
Asian	8 (2)	2 (2)	

**Values expressed as median (range), except when indicated otherwise; †expressed as numbers (%) within each consent group; ‡indicates the significance of the difference in age distribution between the groups with and without consent.*

Table 2b Disease characteristics and distribution of diagnoses in the 2 groups*

	Informed consent (n = 333)	**No informed consent** (n = 88)	***P*-value**
Elective admission†	28 (25)	6 (23)	NS
Previous health status†			
Healthy : underlying disease	57: 57 (50:50)	7:19 (27:73)	0.033
Surgery during admission	103 (31)	20 (23)	NS
Diagnostic category‡			NS
Prematurity / dysmaturity	90 (27)	28 (32)	
Congenital anomalies requiring surgery	73 (22)	14 (16)	
Postnatal problems§	26 (8)	10 (11)	
Post-operative monitoring	49 (15)	8 (9)	
Sepsis or meningitis	26 (8)	8 (9)	
Respiratory illness‖	48 (14)	9 (10)	
Other	21 (6)	11 (13)	

**Values expressed as numbers (%) within each consent group; †only the older children (n = 140); ‡Most prominent diagnoses; §e.g. asphyxia, meconium aspiration and infection; ‖e.g. pneumonia, RS-bronchiolitis.*

Table 2c Factors associated with illness severity*

	Informed consent (n = 333)	**No informed consent** (n = 88)	***P*- value**
PRISM†	11 (0-38)	11 (0-33)	NS
CRIB‡	3 (0-16)	1 (0-10)	0.029
TISS§	13.9 (1-47)	13.7 (1-44)	NS
Length of stay, d	7 (1-314)	6 (1-99)	NS
Preterm neonates	12.5 (2-151)	6 (1-99)	0.028
Term neonates	6 (1-314)	6.5 (1-67)	NS
Older children	5 (1-138)	8 (2-88)	NS
Death during admission, n (%)	19 (6)	9 (10)	NS
Preterm neonates, n (%)	6 (5)	3 (8)	NS
Term neonates, n (%)	6 (6)	0 (0)	NS
Older children, n (%)	7 (6)	6 (23)	0.016

PRISM = Pediatric Risk of Mortality; CRIB = Clinical Risk Index for Babies; TISS = Therapeutic Intervention Scoring system.
**Values expressed as median (range), except when indicated otherwise; †in term neonates and older children together (n = 270), also no significant difference found within the 2 age groups; ‡in preterm neonates (n = 110, 41 missing); §in all age groups together (19 values missing); also no significant differences within each age group.*

Logistic regression analyses

In the term neonates none of the predefined demographic and clinical variables explained parent's decision to give informed consent or not (X^2 = 6.88, P = 0.230).
In the preterm neonates a significant model was found (X^2 = 12.85, P = 0.025) using all five predefined demographic and clinical factors. Birth weight (0.009) and post-conceptional age (P = 0.013) were significant contributors. The Nagelkerke R^2, which provides an approximation of the explained variance for a logistic model, revealed that these 5 variables accounted for 17% of the variation. Following backward elimination, birth weight (P = 0.005) and post-conceptional age (P = 0.008) remained in the model (X^2 = 10.54, P = 0.005, Nagelkerke R^2 = 0.142). This model suggests that the odds to obtain informed consent at a certain post-conceptional age decreases when children are born with a higher birth weight (100 g increase in birth weight; OR = 0.76, 95% CI: 0.63-0.92). Independently, the odds to obtain consent were greater at higher post-conceptional ages (1 week increase in post-conceptional age; OR 1.71, 95% CI: 1.15-2.53). A post-hoc analysis was carried out in the preterm neonates without a CRIB score (n = 41, admission later than 12 h after birth), using the variables TISS score, post-conceptional age and birth weight. None of these variables explained parent's decision to give informed consent or not (X^2 = 2.54, P = 0.484).

In the older children, no significant model was found using all six predefined demographic and clinical factors (X^2 = 10.41, P = 0.108). Following backward elimination three variables remained in the model (X^2 = 10.16, P = 0.017): previous health status (P = 0.026), undergoing surgery during admission (P = 0.113), and PRISM score (0.057).

The Nagelkerke R^2 revealed that these 3 variables accounted for 12% of the variation. This model suggests that parents of children with underlying disease were 3.2 times (95% CI 1.1-9.1) less likely to give informed consent for participation in the study, independent of the PRISM score or whether the child had to undergo surgery.

Discussion

Our study showed, contrary to our hypothesis, that a higher degree of actual illness as determined by objective scores did not negatively influence parents' willingness to give informed consent for participation of their critically ill child in a clinical study. In the preterm neonates the illness severity scores were even found to be higher in the group of children for whom consent was obtained. Furthermore, these preterm neonates stayed significantly longer in the ICU, which usually indicates a more complicated course or disease.

The logistic regression analyses revealed some significant child-related factors that influenced parental decision. In the preterm neonates a lower birth weight at a certain post-conceptional age and, independently, a higher post-conceptional age positively influenced parents in their decision to give permission. In the older children, a history of underlying disease negatively influenced parents in their decision to give permission. Since the factors obtained in the logistic regression analysis explained only 12-17% of the variation in the decision to consent or not, we conclude that parents also base their decision on factors other than factors related to illness severity, the child or its disease.
Children aged ≥ 12 years form a special group, because according to national and international legislation, guidelines and recommendations,[4,19,20] these children should be involved in the consent process when considering participation in research. In our study, of those children aged ≥ 12 years who could be involved in the consent process nearly half of the children (5/11) did not want to participate in the proposed research. Since all 5 children who declined participation had a history of chronic disease including several hospital admissions, it seems that both in parents and children this factor is important in contemplating participation in research. Due to the limited number of children that could be involved, further analyses were not performed.

Most of the parents who declined participation did so because they felt the study comprised too many interventions and would be too burdensome for their child in view of their condition. It is imaginable that parents who already had to witness their child undergoing many invasive procedures after admission – and are facing more such procedures – are more likely to decline consent. The initial objective scores of overall workload (TISS), however, did not differ between the consenting and non-consenting group.

Other studies also evaluated parental reasons for refusing consent for participation of their child in clinical studies. Harth and Thong,[12] evaluating parental reasons for not volunteering their child to a placebo-controlled trial of a new asthma drug, found the main reasons to be fear for side effects of the new drug and the inconvenience of frequent visits. Semi-structured interviews with parents who had been asked for consent to neonatal trials[3] have revealed several reasons for refusing, such as perceived risks for or distress of their baby, distrust of research and researchers, dislike of the tone of approach by the doctor, their shock and inability to decide, and the inconvenience of follow-up procedures.

In accordance with our study, Zupansic et al. also evaluated factors related to the child and his or her disease. They found no differences between the neonates in the consent group and in the non-consent group concerning birth weight, gestational age, sex, Apgar score, percentage inborn, score for illness severity and postnatal age.[6] Furthermore the illness severity perceived by parents was similar in the consenters and non-consenters.
Concern has been expressed that, among those parents consenting to research, there may be an overrepresentation of individuals who are unable to understand the information or who are too intimidated to refuse. We did not investigate parental educational background, social economic status or personality; however, previous studies concerning these issues were inconclusive.[7,8,13,21,22] We cannot rule out with certainty that understanding the contents of the study played a role in our study in some individuals, although we put in every effort to ensure that parents understood all details of the study. This was accomplished through our extensive oral explanation and a comprehensible outline of the study in writing. Lynoe et al. showed that the quality of information given to participants can vary, and indicated that optimal information can be provided by researchers who also participated in the design of the study[23] as was the case in our study.

Also the integrity of the consent process can influence parents.[3,6] Parents who reported less freedom to make the decision and who thought that the consent process was too complicated were less likely to permit involvement of their children in a clinical trial.[3,6]
The issue of intimidation or persuasion seems less important in our study since the researchers were not directly involved in the care of the child and the proposed study was not directly related to the reason of ICU admission. Furthermore, the integrity of the consent process in our study was guaranteed as much as possible by the careful approach of the research team member. We believe that a short general informative document explaining which research is being performed at the unit and why, would help to prepare parents for the specific research that will be proposed.
Our study can be seen as non-therapeutic interventional research with minimal risk, but moderate burden on the child[14,24] and it is debatable whether our results can be extrapolated to other types of studies, with different risks and benefits or lower burden.

In this context, Pierro and Spitz[25] observed an increasing rate of parental refusal for non-therapeutic studies from 30% for performing anthropometrical measures to 70% for stable isotope intravenous infusion, gas exchange measurements and blood sampling.

Our results might have differed considerably if the proposed clinical study was directly related to the immediate reason for the ICU care. Also, consent rates might be higher in therapeutic research, as in this type of research the children involved may benefit directly. On the other hand, therapeutic research usually involves a control group not receiving the new treatment. Parents debating to participate in such a study would have to see the benefits for future children with the same diagnosis and give consent for that reason. A blinded randomized placebo controlled study conducted in our hospital, investigating the analgesic effect of routine morphine infusion in preterm ventilated neonates, had an inclusion rate of 71%.[26] This rate is comparable to the hypothetical 78% inclusion rate for studies involving moderate risk but possible major benefits, as reported by Singhal et al.[9] among parents with a child admitted to a neonatal ICU. They investigated the attitudes of parents towards 5 hypothetical research scenarios with varied risks and benefits.
Our present study investigated factors associated to the child and his or her disease. We did not evaluate the validity of the consents and did not ask parents about other influences determining their decision such as their trust in the intensive care providers or researchers. All these factors seem potentially relevant, but were not subject of our study.

We conclude that the severity of illness, as determined by objective scores, was not different between children of whom parents consented and children of whom parents did not consent. This suggests that parents are not influenced by the illness severity of their child in the decision to allow their child to participate in clinical observational research. Other factors, such as the perceived burden to the child, integrity of the consent process, risk and benefit assessments and attitudes towards research are more likely to affect parental decision making, and are subject of further research.

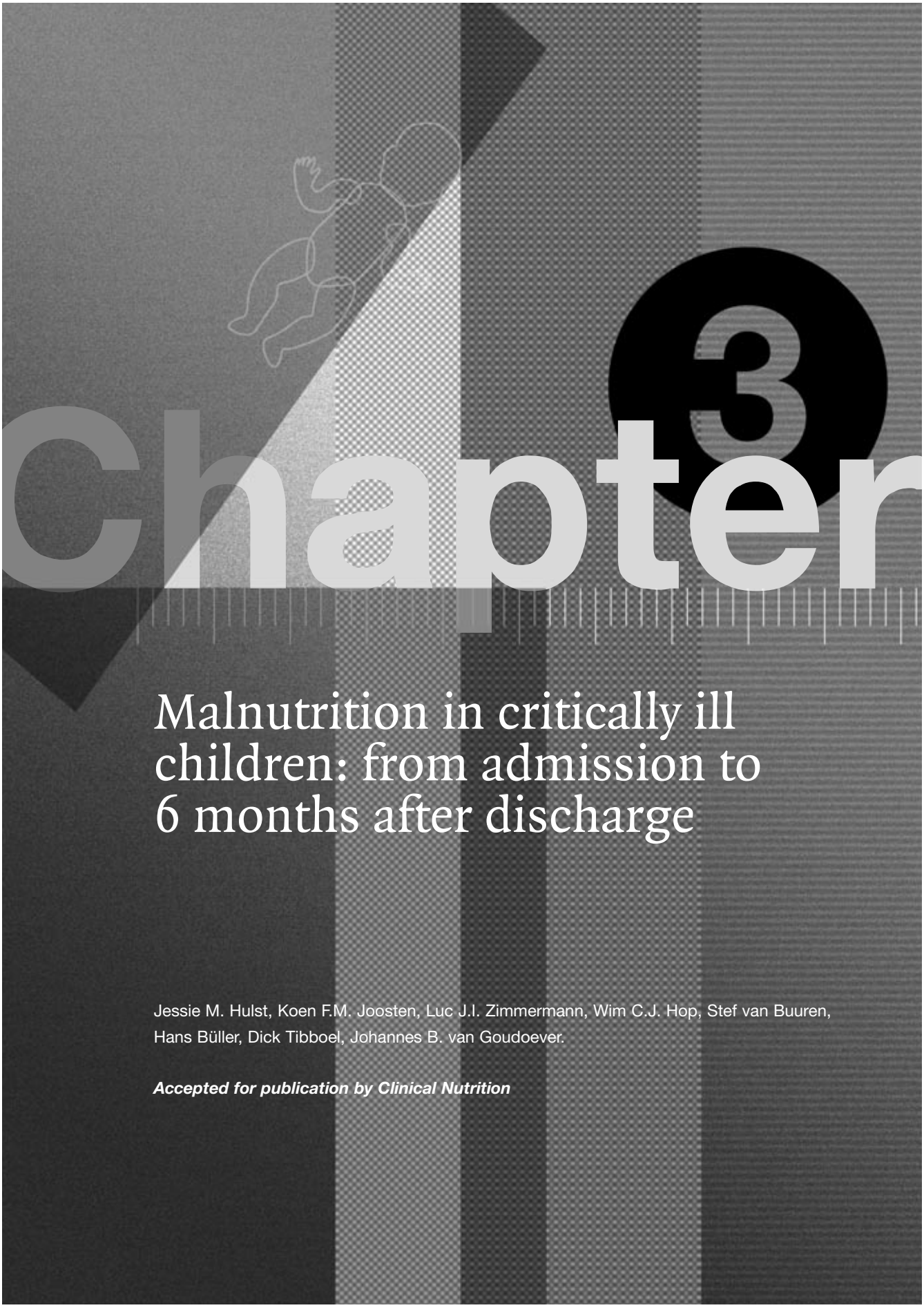
Acknowledgements

The authors would like to acknowledge the research nurses Annelies Bos, Marianne Maliepaard, Marjan Mourik, and Ineke van Vliet for their help in data-collection. The authors thank Ko Hagoort (Erasmus MC, Rotterdam) for his careful editing.

References

1. Office of Civil Rights, Department of Human Services. Standards for privacy of individually identifiable health information. Final rule. Fed Regist 2002;67:53181-273.
2. Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. 52nd General Assembly, Edinburgh, Scotland: World Medical Association; October 2000.
3. Mason SA, Allmark PJ. Obtaining informed consent to neonatal randomised controlled trials: interviews with parents and clinicians in the Euricon study. Lancet 2000;356:2045-51.
4. Manual for the review of medical research involving human subjects-2002. The Hague: Central Committee on Research Involving Human Subjects; September 2002.
5. Mason S. Obtaining informed consent for neonatal randomised controlled trials-- an "elaborate ritual"? Arch Dis Child Fetal Neonatal Ed 1997;76:F143-5.
6. Zupancic JA, Gillie P, Streiner DL, Watts JL, Schmidt B. Determinants of parental authorization for involvement of newborn infants in clinical trials. Pediatrics 1997;99:E6.
7. van Stuijvenberg M, Suur MH, de Vos S, Tjiang GC, Steyerberg EW, Derksen-Lubsen G, Moll HA. Informed consent, parental awareness, and reasons for participating in a randomised controlled study. Arch Dis Child 1998;79:120-5.
8. Tait AR, Voepel-Lewis T, Malviya S. Do they understand? (part I): parental consent for children participating in clinical anesthesia and surgery research. Anesthesiology 2003;98:603-8.
9. Singhal N, Oberle K, Burgess E, Huber-Okrainec J. Parents' perceptions of research with newborns. J Perinatol 2002;22:57-63.
10. Burgess E, Singhal N, Amin H, McMillan DD, Devrome H. Consent for clinical research in the neonatal intensive care unit: a retrospective survey and a prospective study. Arch Dis Child Fetal Neonatal Ed 2003;88:F280-5; discussion F285-6.
11. Harth SC, Thong YH. Parental perceptions and attitudes about informed consent in clinical research involving children. Soc Sci Med 1995;41:1647-51.
12. Harth SC, Thong YH. Sociodemographic and motivational characteristics of parents who volunteer their children for clinical research: a controlled study. BMJ 1990;300:1372-5.
13. Harth SC, Johnstone RR, Thong YH. The psychological profile of parents who volunteer their children for clinical research: a controlled study. J Med Ethics 1992;18:86-93.
14. McIntosh N, Bates P, Brykczynska G, Dunstan G, Goldman A, Harvey D, Larcher V, McCrae D, McKinnon A, Patton M, Saunders J, Shelley P. Guidelines for the ethical conduct of medical research involving children. Royal College of Paediatrics, Child Health: Ethics Advisory Committee. Arch Dis Child 2000;82:177-82.
15. Hulst J, Joosten K, Zimmermann L, Hop W, Van Buuren S, Büller H, Tibboel D, Van Goudoever J. Malnutrition in critically ill children: from admission to 6 months after discharge. Clin Nutr (in press) 2004.

16. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988;16:1110-6.
17. The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. The International Neonatal Network. Lancet 1993;342:193-8.
18. Keene AR, Cullen DJ. Therapeutic Intervention Scoring System: update 1983. Crit Care Med 1983;11:1-3.
19. Gill D, Crawley FP, LoGiudice M, Grosek S, Kurz R, de Lourdes-Levy M, Mjones S, Nicolopoulos D, Rubino A, Sauer PJ, Siimes M, Weindig M, Zach M, Chambers TL. Guidelines for informed consent in biomedical research involving paediatric populations as research participants. Eur J Pediatr 2003;162:455-8.
20. Alderson P. Children's consent to surgery. Buckingham: Open University Press; 1993.
21. Tait AR, Voepel-Lewis T, Siewert M, Malviya S. Factors that influence parents' decisions to consent to their child's participation in clinical anesthesia research. Anesth Analg 1998;86:50-3.
22. Simon C, Zyzanski SJ, Eder M, Raiz P, Kodish ED, Siminoff LA. Groups potentially at risk for making poorly informed decisions about entry into clinical trials for childhood cancer. J Clin Oncol 2003;21:2173-8.
23. Lynoe N, Sandlund M, Dahlqvist G, Jacobsson L. Informed consent: study of quality of information given to participants in a clinical trial. BMJ 1991;303:610-3.
24. Sauer PJ. Research in children. A report of the Ethics Working Group of the CESP. Eur J Pediatr 2002;161:1-5.
25. Pierro A, Spitz L. Informed consent in clinical research: the crisis in paediatrics. Lancet 1997;349:1703.
26. Simons SH, van Dijk M, van Lingen RA, Roofthooft D, Duivenvoorden HJ, Jongeneel N, Bunkers C, Smink E, Anand KJ, van den Anker JN, Tibboel D. Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial. JAMA 2003;290:2419-27.



Chapter 3

Malnutrition in critically ill children: from admission to 6 months after discharge

Jessie M. Hulst, Koen F.M. Joosten, Luc J.I. Zimmermann, Wim C.J. Hop, Stef van Buuren, Hans Büller, Dick Tibboel, Johannes B. van Goudoever.

Accepted for publication by Clinical Nutrition

Abstract

Background & Aims
Little is known about the nutritional status of critically ill children during hospitalisation in and after discharge from an intensive care unit. We set up a prospective, observational study to evaluate the nutritional status of children in an intensive care unit from admission up to six months after discharge. A secondary aim was identifying patient characteristics that influence the course of the various anthropometric parameters.

Methods
The nutritional status of 293 children – 104 preterm neonates, 96 term neonates and 93 older children – admitted to our multidisciplinary tertiary pediatric and neonatal intensive care unit was evaluated by anthropometry upon and during admission, at discharge and 6 weeks and 6 months following discharge.

Results
Upon admission, 24% of all children appeared to be undernourished. Preterm and term neonates, but not older children, showed a decline in nutritional status during admission. At six months after discharge almost all children showed complete recovery of nutritional status. Length of stay and history of disease were the parameters that most adversely affected the nutritional status of preterm and term neonates at discharge and during follow-up.

Conclusions
While malnutrition is a major problem in pediatric intensive care units, most children have good long-term outcome in terms of nutritional status after discharge.

Introduction

Critical illness has a major impact on the nutritional status of both children and adults. Studies conducted more than twenty years ago already demonstrated that 15-20% of children admitted to pediatric intensive care units were acutely or chronically malnourished.[1-4] Recent data on the prevalence of malnutrition in pediatric intensive care units are not available. It is not unimaginable, however, that this prevalence has changed, on account of improved intensive care technology, lowering of the age at which major surgery is performed and increased awareness of the significance of adequate nutritional support.
While follow-up studies concerning nutritional status in premature neonates are available.[5-7] the nutritional status of critically ill children after discharge from an intensive care unit (ICU) has not been documented. The available follow-up studies focus on mortality and functional outcome,[8,9] rather than on nutritional status. Studies in specific subsets of patients, e.g. those with severe burns,[10,11] reveal impaired growth for up to 2 years.

The protein-energy malnutrition that may develop during ICU-stay is associated with an increase in morbidity and mortality,[3,12] whereas malnutrition in infancy is associated with poor growth and reduced or delayed mental and psychomotor development.[5,13-15] Recent studies in critically ill children showed a wide variation in individual energy expenditure.[16,17] This phenomenon would make them more vulnerable for energy malnutrition, seeing that a standard feeding protocol fails to take inter-individual differences into account. Moreover, individual assessment of a patient's nutritional status as guidance for nutritional support is not part of the routine procedures upon admission to a pediatric ICU. Because none of the available methods – including weight measurements, biochemical parameters, and dual-energy X-ray absorptiometry (DEXA) – is free from pitfalls, there is no single best test for nutritional assessment in ICU patients. Newly introduced non-invasive techniques, such as bioelectrical impedance analysis (BIA) and DEXA, have shown to be difficult in practice and very demanding, and most have not been validated for critically ill children, notably the very young.[18,19]
Furthermore, in the acute setting hormonal and biochemical nutritional assessment parameters are predominantly useful as markers of disease severity and not of nutritional status per se.[20] This leaves anthropometry as the best tool currently available for assessing the nutritional status of a heterogeneous group of critically ill children, the more so because recent reference values are available for the different age groups and sexes.[21]
We conducted a prospective observational study to determine the nutritional status of a cohort of critically ill children by means of anthropometric parameters from admission to 6 months after discharge from a tertiary intensive care unit. Furthermore we set out to identify risk factors for poor nutritional status at admission and during follow-up.

Materials and Methods

Children admitted during the year 2001 to our level III multidisciplinary neonatal and pediatric/ surgical intensive care unit (ICU) with an expected stay of at least 48 hours were included in the study, provided written parental informed consent had been obtained. Exclusion criteria were withholding or withdrawing of treatment, inclusion into another nutritional intervention study, and treatment with Extra Corporeal Membrane Oxygenation (ECMO). Most patients on ECMO develop extreme generalised oedema, and consequently their anthropometric measurements are unreliable. The institutional review board of Erasmus MC approved the study protocol.

We recorded the patients' sex, age, surgical status, pre-existent health status, severity of illness, duration of mechanical ventilation and length of stay at the ICU (LOS). The patients were classified by age into 3 age groups in order to differentiate between growth patterns: preterm neonates (gestational age < 37 weeks; post-conceptual age ≤ 40 wk), term neonates (0-30 days), and older children (> 30 days). Patients were also classified by diagnosis into seven categories (Table 1). Pre-existent health status was defined as either 'previously healthy with normal growth' or 'history of growth-affecting disease' (e.g. congenital anomaly, chromosomal abnormalities, dysmaturity or chronic systemic disease).

Severity of illness was measured at admission by either of two validated scores: the Pediatric Risk of Mortality score (PRISM) for the term neonates and older children (score range 0-76);[22] the Clinical Risk Index for Babies (CRIB) for the preterm neonates (score range 0-23).[23] All infants were enterally and/or parenterally fed according to the current feeding protocol.
Within 24 hours after admission anthropometric measurements were performed including weight, length, head circumference (HC), mid upper arm circumference (MUAC), calf circumference (CC) and the skinfold thicknesses of biceps (BSF) and triceps (TSF). These measurements (except head circumference and length) were repeated every other day during the first 2 weeks and weekly thereafter. A reassessment was performed at discharge for most anthropometric parameters. Length and head circumference were measured at discharge in a selected group consisting of children less than 2 years of age with LOS of at least 12 and 6 days, respectively. When a child's reassessment on the day of discharge was not possible, the previous measurements taken closest to discharge were used, provided the period between this day and discharge was within 20% of the total duration of stay. Otherwise, the measurements were considered to be missing. Full anthropometric evaluation was repeated at 6 weeks and 6 months after discharge from the ICU.

Table 1 Patient characteristics and diagnoses (n = 293).

Patient characteristics		
M:F	n (%)	167:126 (57:43)
Age	Median (range), d	2 (0 d-17 y)
Age groups		
Preterm neonates	n (%)	104 (35%)
Gestational age	Mean (SD), wk	31.4 (2.7)
Postconceptual age	Mean (SD), wk	31.9 (2.9)
Term neonates	n (%)	96 (33%)
Gestational age	Mean (SD), wk	39.4 (1.5)
Postnatal age	Median (range), d	1 (0-30)
Older children	n (%)	93 (32%)
Age	Median (range), y	1.4 (31 d-17 y)
PRISM (n = 189)	Median (range)	11 (0-38)
CRIB (n = 76)	Median (range)	3 (0-16)
Length of stay	Median (range), d	7 (2-314)
Mechanical ventilation	n (%)	211 (72)
Duration	Median (range), d	3 (0-53)
History of growth-affecting disease	n (%)	123 (42)
Surgery	n (%)	92 (31)
Diagnostic groups		
Prematurity / dysmaturity	n (%)	84 (29)
Congenital anomalies	n (%)	65 (22)
Post-operative monitoring	n (%)	44 (15)
Respiratory illness*	n (%)	41 (14)
Postnatal problems†	n (%)	24 (8)
Sepsis or meningitis	n (%)	22 (8)
Other	n (%)	13 (4)

CRIB = Clinical Risk Index for Babies; PRISM = Pediatric Risk of Mortality.
**Includes pneumonia, RS-bronchiolitis; †Includes asphyxia, meconium aspiration, infection.*

Body weight, without diapers and clothes, was measured to the nearest 0.01 kg in a standardised way using calibrated scales. Length was obtained to the nearest 0.1 cm by measuring crown-heel length in the supine child. During the follow-up visits, standing height was measured by a stadiometer in the children who were able to stand. HC was measured with a tape around the head at the most protruding points of the occiput and forehead. TSF and BSF served to establish subcutaneous fat stores, and were measured to the nearest 0.1 cm with a Harpenden skin fold caliper (UK), using the mean of three separate readings.[24] The caliper was applied while keeping the skinfold between thumb and forefinger, and had to remain in position until the measurement had stabilised (2-5 seconds). Neonates with body weight < 1000 grams were excluded from skin fold measurements. MUAC and CC were measured to the nearest 0.1 cm.

Intra-observer and inter-observer studies performed prior to the study had shown good reproducibility of measurements with coefficients of variation < 3% for MUAC and CC, and < 7% for BSF and TSF.

All anthropometric data were compared with recently published standards based on a Dutch reference population and transformed into standard deviation scores (SD-scores) by means of a software program (TNO, Prevention and Health, Leiden, the Netherlands).[21] Acute malnutrition was defined as a standard deviation score (SDS) for weight-for-age (WFA-SDS) of more than 2 below the mean. Chronic malnutrition was defined as a SDS for length-for-age (LFA-SDS) of more than 2 below the mean. SD-scores of CC and MUAC more than 2 below the mean are associated with inadequate protein stores and acute malnutrition whereas a SDS of TSF < -2 is associated with deficient fat stores and chronic malnutrition.[25] Children with a decrease in SDS between admission and discharge of > 1SD were included in the analyses as well.

In neonates up to a post-conceptual age of 41 weeks the calculation of SD-scores for weight, length and head circumference was based on the intra-uterine growth curves of Usher and McLean.[26] SD-scores for weight, length and head circumference for older children were derived from the recently published standards of a Dutch population study in 1997.[21] The individual measurements of MUAC, CC, TSF and BSF of all children starting from term age were compared with normative data of a Dutch reference population and also expressed in SD-scores in children.[27] The ages of prematurely born children with postnatal age < 2 years were corrected for prematurity.

Statistical analyses

The Statistical Package for Social Sciences (version 10.0, SPSS Inc., Chicago, IL) was used for statistical analyses. Longitudinal analysis of the growth data, including the comparison of mean values, allowing for missing data, was performed using repeated measures analysis of variance (PROC MIXED, SAS, Cary, NC) on the 3 subsets based upon age.

Clinical factors suspected to influence the changes in SD-scores were analyzed in order to determine the major factors related to outcome. The dependent variables were the SD-scores at discharge, 6 weeks after discharge and 6 months after discharge for WFA and LFA. Variables initially tested for association in univariate regression analysis included age, gender, severity of illness (PRISM or CRIB), length of stay at the ICU, duration of ventilation, having undergone surgery, and previous health status. All analyses were adjusted for the SDS at admission. Variables associated with the dependent variable in the univariate analysis ($P < 0.05$) were entered in a stepwise linear regression with backward elimination. Paired percentages were compared using the McNemar test. We considered $P < 0.05$ to be significant.

Results

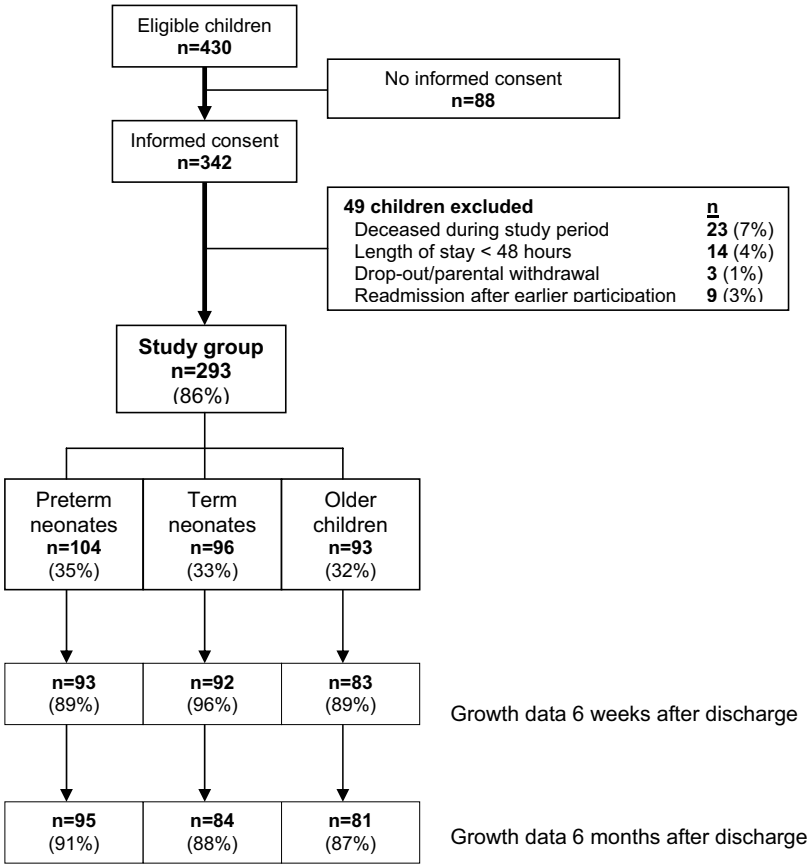
Subjects

A total of 342 children were enrolled in the study. For various reasons 49 of them were not included in the analyses (Figure 1). The characteristics and diagnoses of the remaining 293 children are shown in Table 1.

The first and second follow-up measurements actually took place after a mean (SD) of 6.3 ± 1.8 weeks and 26.6 ± 3.3 weeks after discharge, respectively. We collected data of 268 (91%) children at first follow up and 260 (89%) children at second follow up.

Table 2 shows the SD-scores of all parameters upon admission, discharge and follow up. The course of the WFA-SDS over time is shown in Figure 2.

Figure 1 Flow chart of the study population.



Nutritional status upon admission

The mean SD-scores of all anthropometric parameters of the 3 age groups upon admission, except length in the term neonates and head circumference in all children, were significantly below zero ($P < 0.001$). In 15% of the children a WFA-SDS < -2 was found indicating acute malnutrition (14% of the preterm, 9% of the term neonates and 24% of the older children). In 84% of these children a history of growth-affecting disease was identified. In 20% of the children a LFA-SDS < -2SD was found indicating chronic malnutrition (26% of the preterm, 11% of the term and 22% of the older children). Overall, 24% of the children showed signs of acute and/or chronic malnutrition upon admission. Furthermore, 81%, 65% and 67% of term neonates had a score < -2 for CC-SDS, MUAC-SDS, and TSF-SDS, respectively. Percentages for the older children were 20%, 15% and 10%, respectively.

Nutritional status at discharge

Preterm neonates

Preterm neonates showed a significant decrease in mean WFA-SDS (Figure 2a) (– 0.92 SD, $P < 0.001$) from admission to discharge. The proportion of preterm neonates classified as acutely malnourished had increased significantly at discharge (14 to 32%, $P < 0.001$), of which 55% were new cases. In 44% of the preterm infants a more than 1 SD drop in WFA was observed between admission and discharge.

Also the mean LFA-SDS-score (–1.03 SD, $P < 0.001$) and mean HC-SDS (– 0.85 SD, $P < 0.001$) decreased significantly. The proportion of children with a LFA-SDS < -2 increased significantly to 63% ($P = 0.013$).

Term neonates

Term neonates showed a significant decrease in mean WFA-SDS (Figure 2b) (– 0.67 SD, $P < 0.001$) from admission to discharge. The proportion of term neonates classified as acutely malnourished had increased significantly at discharge (9% to 23%, $P < 0.001$), of which 62% were new cases. In 28% of the term infants a more than 1 SD drop in WFA was observed between admission and discharge. The mean LFA-SDS-score (–1.11 SD, $P < 0.001$) and HC-SDS (–0.54 SD, $P < 0.001$) also decreased from admission to discharge in the selected groups.

The proportion of children with a LFA-SDS < -2 was comparable (16%) with that upon admission. SD-scores for CC, MUAC, TSF and BSF remained low during ICU-hospitalization. The proportions of children with a CC-, MUAC-, or TSF-SDS < -2 did not change significantly (78%, 63% and 66%, respectively).

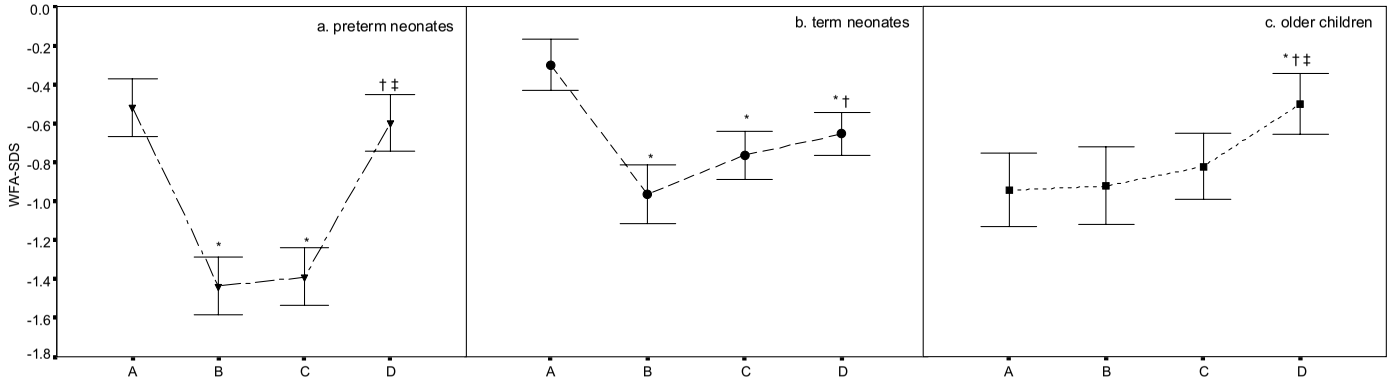


Figure 2 Standard deviation scores for Weight-For-Age upon admission, at discharge and 6 weeks and 6 months after discharge from the ICU for the 3 age groups (a. preterm neonates, b. term neonates, c. older children).

All values expressed as mean ± SEM. WFA-SDS = SD-score for weight-for-age; A: admission, B: discharge, C: 6 weeks after discharge, D: 6 months after discharge
**Value is significantly different when compared to admission, P < 0.05; †value is significantly different when compared to discharge, P < 0.05; ‡value is significantly different when compared to 6 weeks after discharge, P < 0.05.*

Older children
The mean WFA-SDS (Figure 2c), LFA-SDS and HC-SDS were not significantly affected during IC-stay. The proportions of children classified as acutely (22%) or chronically (11%) malnourished upon discharge did not significantly differ from those upon admission. Only 4% of the older children dropped > 1 SD in WFA between admission and discharge. The SD-scores for CC, MUAC and TSF showed a small but significant decline during the ICU-stay. The proportions of children with a CC-, MUAC-, or TSF-SDS < -2 did not significantly change (32%, 20% and 16%, respectively).

Nutritional status following discharge
Preterm neonates
Mean SD-scores of LFA and HC, but not WFA, increased significantly from discharge to 6 weeks after discharge (Table 2). At 6 months after discharge the mean outcomes of all parameters were either not different from or higher than those upon admission.
At 6 months after discharge 15% of the preterm neonates were acutely malnourished, which compares to the proportion upon admission. Thirteen percent had a LFA < -2, which was a significantly lower proportion (P = 0.021) than that upon admission (26%).

Term neonates
Most SD-scores improved significantly from discharge to 6 weeks after discharge (Table 2). At 6 months after discharge the mean SD-scores for WFA (Figure 2b) and HC had not yet been restored to the admission scores (P = 0.01 and P = 0.025 respectively).
At 6 months after discharge the percentage of children classified as acutely malnourished was 12%, which compares to the proportion upon admission. Only 2% had a LFA-SDS < -2, which was a significantly lower proportion (P = 0.008) than that upon admission (11%).

Older children
SD-scores of WFA, CC and MUAC at 6 months after discharge were significantly higher than those upon admission. All other SD-scores did not significantly differ from those upon admission (Table 2). At 6 months after discharge 10% of children were classified as acutely malnourished which was significantly (P = 0.008) lower than that upon admission. Thirteen percent had a LFA < -2, which was significantly (P = 0.031) lower than the proportion upon admission (22%).

Effect of various factors on nutritional status
Severity of illness, age and sex were not found to have a significant influence on the course of the WFA-and LFA-SDS over time in all age groups.
In the preterm neonates a longer LOS was significantly related to a decrease in WFA-SDS at discharge (each doubling of LOS was associated with a decrease of – 0.24 SD between admission and discharge). Both longer LOS and surgery negatively influenced

the WFA and LFA-SDS during follow up. Preterm neonates with a WFA-SDS < -2 (SGA) upon admission showed a smaller decline in SDS between admission and discharge than children with a SD-score in the normal range did (–0.43 vs. –1.0 SD, respectively, P = 0.003).

Table 2 Standard deviation scores (SDS) of the different growth parameters upon admission, at discharge and 6 weeks and 6 months after discharge for the 3 different age groups

GROWTH PARAMETER (SDS)	Admission	Discharge	6 weeks after discharge	6 months after discharge
Preterm neonates (n = 104)				
WFA	-0.52 ± 0.15	-1.44 ± 0.15‡	-1.39 ± 0.15‡	-0.60 ± 0.15§,¶
LFA	-1.31 ± 0.17	-2.72 ± 0.28‡	-1.66 ± 0.17‡	-0.39 ± 0.14‡,¶
LFA* (n = 52)	-1.69 ± 0.28	-2.72 ± 0.28‡	-2.16 ± 0.26§	-0.90 ± 0.20‡,§,¶
HC	-0.19 ± 0.12	-	-0.27 ± 0.13	0.12 ± 0.13‡,¶
HC† (n = 72)	-0.37 ± 0.15	-1.22 ± 0.17‡	-0.43 ± 0.16§	-0.02 ± 0.15‡,§,¶
MUAC	-	-	-2.41 ± 0.14	-0.26 ± 0.13¶
CC	-	-	-2.17 ± 0.13	0.26 ± 0.16¶
TSF	-	-	-1.93 ± 0.08	-1.00 ± 0.08¶
BSF	-	-	-1.30 ± 0.09	-0.50 ± 0.08¶
Term neonates (n = 96)				
WFA	-0.30 ± 0.13	-0.97 ± 0.15‡	-0.76 ± 0.12‡	-0.65 ± 0.11‡,§
LFA	-0.28 ± 0.13	-	-0.50 ± 0.13	-0.23 ± 0.12¶
LFA* (n = 23)	0.20 ± 0.24	-0.91 ± 0.25‡	-0.76 ± 0.18‡	-0.19 ± 0.23§,¶
HC	-0.01 ± 0.14	-	-0.28 ± 0.13‡	-0.28 ± 0.11‡
HC† (n = 53)	0.02 ± 0.20	-0.53 ± 0.17‡	-0.34 ± 0.18‡	-0.25 ± 0.15
MUAC	-2.26 ± 0.01	-2.25 ± 0.01	-1.68 ± 0.11‡,§	0.06 ± 0.12‡,§,¶
CC	-2.68 ± 0.11	-2.68 ± 0.10	-1.49 ± 0.11‡,§	0.45 ± 0.12‡,§,¶
TSF	-2.10 ± 0.05	-2.10 ± 0.05	-1.65 ± 0.06‡,§	-1.07 ± 0.10‡,§,¶
BSF	-1.38 ± 0.05	-1.37 ± 0.04	-1.08 ± 0.06‡,§	-0.39 ± 0.09‡,§,¶
Older children (n = 93)				
WFA	-0.94 ± 0.19	-0.92 ± 0.20	-0.82 ± 0.17	-0.50 ± 0.15‡,§,¶
LFA	-0.79 ± 0.21	-	-0.89 ± 0.18	-0.64 ± 0.15¶
LFA* (n = 13)	-0.68 ± 0.43	-0.42 ± 0.43	-1.08 ± 0.30§	-0.90 ± 0.32
HC	-0.24 ± 0.16	-	-0.41 ± 0.14‡	-0.17 ± 0.14¶
HC† (n = 32)	-0.83 ± 0.32	-0.92 ± 0.32	-1.02 ± 0.26	-0.76 ± 0.25
MUAC	-0.28 ± 0.21	-0.54 ± 0.21‡	-0.33 ± 0.19	0.27 ± 0.20‡,§,¶
CC	-0.76 ± 0.17	-0.95 ± 0.17‡	-0.45 ± 0.17‡,§	0.02 ± 0.17‡,§,¶
TSF	-0.62 ± 0.16	-0.89 ± 0.14‡	-0.50 ± 0.17§	-0.34 ± 0.16§
BSF	-0.34 ± 0.13	-0.39 ± 0.12	-0.16 ± 0.14§	-0.15 ± 0.16

*All values expressed as mean ± SEM; WFA = weight-for-age, LFA = length-for-age, HC = head circumference, CC = calf circumference, MUAC = mid upper arm circumference, TSF = triceps skinfold, BSF = biceps skinfold. *Only children with LOS > 12 days and age < 2 years.*
†Only children with length of stay > 6 days and age < 2 years.
‡Value is significantly different when compared to admission, P < 0.05; §Value is significantly different when compared to discharge, P < 0.05; ¶Value is significantly different when compared to 6 weeks after discharge, P < 0.05.

In term neonates LOS, gestational age and previous health status upon admission were significantly related to WFA-SDS at 6 weeks after discharge. In children with a history of disease, however, LOS had no additional negative effect upon the effect of their previous health status on the WFA-SDS at 6 weeks after discharge. At 6 months after discharge, LOS and previous health status negatively influenced the WFA-SDS. However, LOS had impact in the previously healthy population only. In the children with a history of growth-affecting disease no additional negative effect of LOS was observed. The LFA-SDS at 6 weeks after discharge was related to gestational age with a positive effect of 0.24 SD/week of gestational age. At 6 months after discharge LFA-SDS was negatively related to the LOS.

Older children who underwent a surgical intervention during admission had a mean WFA-SDS at 6 weeks after discharge that was 0.30 SD lower than that in the children without surgery.

Discussion

This study aimed at evaluating how admission to a specialized intensive care unit affects children's nutritional status during hospitalization and up to 6 months after discharge. It yielded some remarkable findings on the prevalence of malnutrition upon admission and follow-up, and on the risk factors as well. The novelty of this study lies in starting nutritional assessment measurements as early as in the acute phase of the critical illness. While several studies have been performed in small, selected groups in the acute phase, such as in burn patients, most studies focused on nutritional assessment starting in the recovery period or after the ICU-stay.[28-30]

Our primary observation is that critically ill children admitted to the ICU are in a poorer nutritional status than the general population. Overall, 24% of the children were acutely and/or chronically undernourished. The period of illness prior to the admission and/or the high prevalence of underlying disease in these children (84%) could explain this high proportion. It may also be speculated that being malnourished increases the chance of being admitted to an ICU as a consequence of disease. The proportion of malnourished children in our study population compares to findings from Pollack et al[1-3] in the 1980s, which would seem to indicate that the problem of malnutrition at pediatric intensive units has not improved at all.

Secondly, we found that at discharge, on average for the preterm and term neonates together, acute and chronic malnutrition rates had increased to 26 and 48%, respectively, whereas the prevalence of malnutrition in the older children was found not to have changed during the ICU-stay. Moreover, in 30% of all children the WFA-SDS

had dropped > 1 SD between admission and discharge, indicating acute malnutrition. In the older children the decline of SD-scores for mid upper arm circumference, calf circumference and skinfolds represented a diminished protein and fat condition. These measurements could provide a useful tool for assessing nutritional status during ICU-stay in this group of children.

Our third observation is very important in that almost all children showed complete recovery of their nutritional status within 6 months after discharge. Interestingly, most parameters were even higher than upon admission, with the exception of WFA in term infants. The complete recovery of nutritional status is surprising in view of findings from the few studies performed in subgroups of critically ill pediatric patients. Children with severe burns showed long term negative effects on nutritional status i.e. an exaggeration of hypermetabolism and catabolism for at least 9 months after injury, a decline in lean body mass until 9-12 months after the burn,[11] and a delay in linear growth for 2 years after injury.[10] We speculate that the overall rate of catabolism in our group was lower than that in the patients with thermal injury, which resulted in faster recovery.
Identifying risk factors for poor nutritional status, we found different factors per age group. In general, the length of stay appeared to be the factor with the most negative effect on the course of the SD-scores over time. Meritt and Suskind[4] also found an association between prolonged hospitalization and low anthropometric scores. The ICU-stay affected neonates (preterm and term) the most, which can be explained by the higher metabolic rate and energy requirement per kg body weight and the higher protein turnover compared to older children. These factors together will lead to a higher rate of catabolism in situations of critical illness and suboptimal nutritional support.[31-33]

Furthermore, neonates are in a period of rapid growth in which it is crucial to consume the optimal amount of calories and protein.
Another important factor with a negative influence on recovery was a child's previous health status. The children in our study group with a history of disease or associated anomalies showed a high prevalence of malnutrition upon admission and during follow up. Andrassy et al,[34] in evaluating the nutritional status of patients operated for oesophageal atresia in a long-term follow-up study, also found that children with a history of associated anomalies or illnesses frequently demonstrated the most severe depletions.

A limitation of nutritional assessment studies is the choice of reference standards for growth parameters. For children with a post-conceptual age < 41 weeks we used growth charts that take differences in gestational age into account,[26] but we realize that it might not be fully appropriate to use intra-uterine growth data after birth.
Furthermore, the use of universal growth standards for the entire group might not be appropriate in view of the differences in growth patterns and growth velocity of different

ethnic groups[35] and children with a history of disease, congenital anomalies or chromosome disorder. As every child, irrespective of ethnicity or underlying disease, will follow a certain individual growth curve, using the same standards for different groups will only have minor influence on the change in scores associated with longitudinal data.

The predicting factors we evaluated are not fully explanatory. The most important predisposing factor for the development or persistence of a negative nutritional status during ICU-stay is probably the inadequate intake of nutrients as a result of underprescribing or interruption of feeding.[36-38] Therefore, the roles of cumulative energy and protein deficits as well as type of feeding during ICU-stay in relation to growth parameters during follow-up need further investigation. Our study, for that matter, was merely of an observational nature, and only intended to quantify the malnutrition rate in a mixed population of children admitted to an ICU, including almost all admitted patients.
It was the epidemiological approach and mixed study population that made us choose anthropometric parameters to define the nutritional status of critically ill children. We are aware, however, that newer techniques, i.e. BIA and DEXA, have been applied in other populations such as children with inflammatory bowel disease (IBD) or cystic fibrosis (CF). However, in view of the impracticality of these methods and the lack of reference values for the younger age groups, we feel that they are still of limited value in the ICU setting with its heterogeneous set of patients. Furthermore, biochemical assessment, besides its disputable usefulness, would not have been routinely possible during follow-up visits. In other epidemiologically based studies that estimate the prevalence of malnutrition in hospital populations, anthropometric criteria were used as well.[39-42]
Nevertheless, we are aware that anthropometric methods have limitations in critically ill children, who frequently show edema, water imbalance and renal, circulatory and hepatic problems. The presence of edema upon admission will lead to an overestimation of SD-scores. The decrease in SD-scores seen at discharge will be influenced by the disappearance of the edema and may, therefore, seem stronger than it really is. Even so, because we also found a decline in SD-scores between admission and 6 weeks after discharge and a return to admission levels at 6 months, we believe that our results hold up.

We conclude that although the long-term outcome in terms of nutritional status is relatively good for the majority of children discharged from the pediatric or neonatal intensive care unit, there remains a considerable proportion who are malnourished and need more attention during ICU-stay. The risk of developing malnutrition during a child's stay at the intensive care unit can only be minimized by starting standardized nutritional assessment upon admission, which should enable to identify children at higher risk and optimize their nutritional support.

Acknowledgements

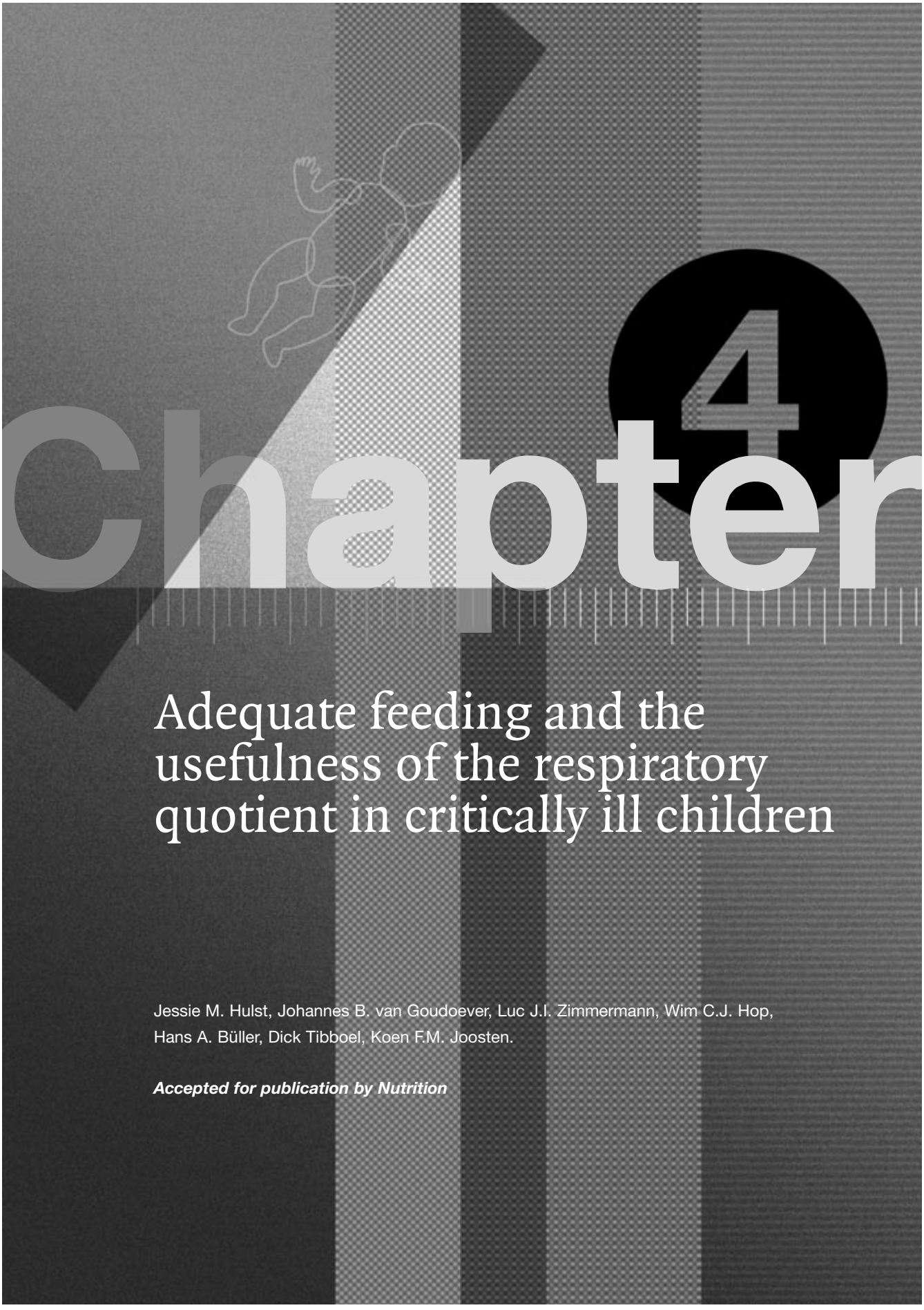
The authors thank the participating children and their parents. Our gratitude goes out to the nursing and medical staff of the Neonatal, Pediatric and Surgical Intensive care unit and the outpatient clinic of the Erasmus MC-Sophia Children's hospital, without whose support this study would not have been possible. We also thank Ko Hagoort (Erasmus MC, Rotterdam) for his careful editing.
Source of Support: Nutricia Nederland BV, Zoetermeer, the Netherlands.

References

1. Pollack MM, Wiley JS, Holbrook PR. Early nutritional depletion in critically ill children. Crit Care Med 1981;9:580-3.
2. Pollack MM, Wiley JS, Kanter R, Holbrook PR. Malnutrition in critically ill infants and children. J Parenter Enteral Nutr 1982;6:20-4.
3. Pollack MM, Ruttimann UE, Wiley JS. Nutritional depletions in critically ill children: associations with physiologic instability and increased quantity of care. J Parenter Enteral Nutr 1985;9(3):309-13.
4. Merritt RJ, Suskind RM. Nutritional survey of hospitalized pediatric patients. Am J Clin Nutr 1979;32:1320-5.
5. Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. BMJ 1998;317:1481-7.
6. Ruiz-Extremera A, Robles-Vizcaino C, Salvatierra-Cuenca MT, Ocete E, Lainez C, Benitez A, Cruz F, Miranda MT, Salmeron J. Neurodevelopment of neonates in neonatal intensive care units and growth of surviving infants at age 2 years. Early Hum Dev 2001;65 Suppl:S119-32.
7. Kitchen WH, Doyle LW, Ford GW, Callanan C. Very low birth weight and growth to age 8 years. I: Weight and height. Am J Dis Child 1992;146:40-5.
8. Butt W, Shann F, Tibballs J, Williams J, Cuddihy L, Blewett L, Farley M. Long-term outcome of children after intensive care. Crit Care Med 1990;18:961-5.
9. Gemke RJ, Bonsel GJ, van Vught AJ. Long-term survival and state of health after paediatric intensive care. Arch Dis Child 1995;73:196-201.
10. Rutan RL, Herndon DN. Growth delay in postburn pediatric patients. Arch Surg 1990;125:392-5.
11. Hart DW, Wolf SE, Mlcak R, Chinkes DL, Ramzy PI, Obeng MK, Ferrando AA, Wolfe RR, Herndon DN. Persistence of muscle catabolism after severe burn. Surgery 2000;128:312-9.
12. Biolo G, Toigo G, Ciocchi B, Situlin R, Iscra F, Gullo A, Guarneiri G. Metabolic response to injury and sepsis: changes in protein metabolism. Nutrition 1997;13(Suppl):52S-57S.
13. Klein PS, Forbes GB, Nader PR. Effects of starvation in infancy (pyloric stenosis) on subsequent learning abilities. J Pediatr 1975;87:8-15.
14. Winick M. Malnutrition and brain development. J Pediatr 1969;74:667-79.
15. Grantham-McGregor SM, Powell C, Stewart M, Schofield WN. Longitudinal study of growth and development of young Jamaican children recovering from severe protein-energy malnutrition. Dev Med Child Neurol 1982;24:321-31.
16. Verhoeven JJ, Hazelzet JA, van der Voort E, Joosten KF. Comparison of measured and predicted energy expenditure in mechanically ventilated children. Intensive Care Med 1998;24:464-8.
17. Briassoulis G, Venkataraman S, Thompson AE. Energy expenditure in critically ill children. Crit Care Med 2000;28:1166-72.
18. Lafeber HN. Nutritional assessment and measurement of body composition in preterm infants. Clin Perinatol 1999;26:997-1005.

19. Pichard C, Genton L, Jolliet P. Measuring body composition: a landmark of quality control for nutritional support services. Curr Opin Clin Nutr Metab Care 2000;3:281-4.
20. Fuhrman MP. The albumin-nutrition connection: separating myth from fact. Nutrition 2002;18:199-200.
21. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47:316-23.
22. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988;16:1110-6.
23. The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. The International Neonatal Network. Lancet 1993;342:193-8.
24. Gerver WJ, de Bruin R. Body composition in children based on anthropometric data. A presentation of normal values. Eur J Pediatr 1996;155:870-6.
25. Frisancho AR. Triceps skin fold and upper arm muscle size norms for assessment of nutrition status. Am J Clin Nutr 1974;27:1052-8.
26. Usher R, McLean F. Intrauterine growth of live-born Caucasian infants at sea level: standards obtained from measurements in 7 dimensions of infants born between 25 and 44 weeks of gestation. J Pediatr 1969;74:901-10.
27. Gerver W, Bruin Rd. Paediatric Morphometrics: a reference manual. Utrecht: Bunge; 1996.
28. Cezard J, Touati G, Alberti C, Hugot J, Brinon C, Czernichow P. Growth in Paediatric Chron's Disease. Hormone Research 2002;58(suppl 1):11-15.
29. Brunton JA, Saigal S, Atkinson SA. Growth and body composition in infants with bronchopulmonary dysplasia up to 3 months corrected age: a randomized trial of a high-energy nutrient-enriched formula fed after hospital discharge. J Pediatr 1998;133:340-5.
30. Stettler N, Kawachak DA, Boyle LL, Propert KJ, Scanlin TF, Stallings VA, Zemel BS. A prospective study of body composition changes in children with cystic fibrosis. Ann N Y Acad Sci 2000;904:406-9.
31. Denne SC, Rossi EM, Kalhan SC. Leucine kinetics during feeding in normal newborns. Pediatr Res 1991;30:23-7.
32. van Goudoever JB, Sulkers EJ, Lafeber HN, Sauer PJ. Short-term growth and substrate use in very-low-birth-weight infants fed formulas with different energy contents. Am J Clin Nutr 2000;71:816-21.
33. Kien CL, Rohrbaugh DK, Burke JF, Young VR. Whole body protein synthesis in relation to basal energy expenditure in healthy children and in children recovering from burn injury. Pediatr Res 1978;12:211-6.
34. Andrassy RJ, Patterson RS, Ashley J, Patrissi G, Mahour GH. Long-term nutritional assessment of patients with esophageal atresia and/or tracheoesophageal fistula. J Pediatr Surg 1983;18:431-5.

35. Goldenberg RL, Cliver SP, Cutter GR, Hoffman HJ, Cassady G, Davis RO, Nelson KG. Black-white differences in newborn anthropometric measurements. Obstet Gynecol 1991;78:782-8.
36. De Jonghe B, Appere-De-Vechi C, Fournier M, Tran B, Merrer J, Melchior JC, Outin H. A prospective survey of nutritional support practices in intensive care unit patients: what is prescribed? What is delivered? Crit Care Med 2001;29:8-12.
37. Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatrics 2001;107:270-3.
38. McClave SA, Sexton LK, Spain DA, Adams JL, Owens NA, Sullins MB, Blandford BS, Snider HL. Enteral tube feeding in the intensive care unit: factors impeding adequate delivery. Crit Care Med 1999;27:1252-6.
39. Edington J, Boorman J, Durrant ER, Perkins A, Giffin CV, James R, Thomson JM, Oldroyd JC, Smith JC, Torrance AD, Blackshaw V, Green S, Hill CJ, Berry C, McKenzie C, Vicca N, Ward JE, Coles SJ. Prevalence of malnutrition on admission to four hospitals in England. The Malnutrition Prevalence Group. Clin Nutr 2000;19:191-5.
40. Ravasco P, Camilo ME, Gouveia-Oliveira A, Adam S, Brum G. A critical approach to nutritional assessment in critically ill patients. Clin Nutr 2002;21:73-7.
41. McWhirter JP, Pennington CR. Incidence and recognition of malnutrition in hospital. BMJ 1994;308:945-8.
42. Hendrikse W, Reilly J, Weaver L. Malnutrition in a children's hospital. Clinical Nutrition 1997;16:13-18.



Chapter 4

Adequate feeding and the usefulness of the respiratory quotient in critically ill children

Jessie M. Hulst, Johannes B. van Goudoever, Luc J.I. Zimmermann, Wim C.J. Hop, Hans A. Büller, Dick Tibboel, Koen F.M. Joosten.

Accepted for publication by Nutrition

Abstract

Objective
To determine incidences of underfeeding and overfeeding in children admitted to a multidisciplinary tertiary pediatric intensive care and to evaluate the usefulness of the respiratory quotient (RQ) obtained from indirect calorimetry for assessing feeding adequacy.

Research methods and procedures
Children up to the age of 18 years who fulfilled the criteria for indirect calorimetry entered our prospective, observational study and were studied until day 14. Actual energy intake was recorded, compared to required energy intake (measured energy expenditure + 10%), and classified as underfeeding (< 90% of required), adequate feeding (90-110% of required), or overfeeding (> 110% of required). We also evaluated the adequacy of a measured RQ < 0.85 to identify underfeeding, and a RQ > 1.0 to identify overfeeding.

Results
Ninety-eight children underwent a total of 195 calorimetry measurements. Underfeeding, adequate feeding and overfeeding occurred on 21, 10 and 69% of days, respectively. RQ < 0.85 to identify underfeeding showed low sensitivity (63%) and high specificity (89%) and negative predictive value (90%). RQ > 1.0 to indicate overfeeding showed poor sensitivity (21%), but a high specificity (97%) and positive predictive value (93%). Food composition, notably a high carbohydrate intake, was responsible for RQ exceeding 1.0 in the overfed group.

Conclusion
Children admitted to the intensive care unit receive adequate feeding on only 10% of measurement days during the first 2 weeks of admission. The usefulness of RQ in monitoring feeding adequacy is limited to identifying (carbohydrate) overfeeding and excluding underfeeding.

Introduction

Nutritional support of critically ill children is essential in the care for critically ill children since inadequate feeding can increase morbidity and mortality rates.[1] Critically ill children receiving adequate nutritional support have shown significant improvement in physiological stability and outcome.[2,3] Furthermore, the goal of supporting critically ill children is not only to restore a normal functioning level but also to meet the requirements for growth and development. Thus clinicians in the pediatric intensive care unit (ICU) are challenged to provide adequate energy for optimal tissue synthesis and immune function while avoiding complications of overfeeding.
The major problem in clinical practice, however, is to define nutritional requirements for critically ill children, as demands range widely with altered metabolic states determined by the children's age, state of health, and nutritional status. Moreover, metabolic responses may greatly vary as well, depending on the nature of the injury and the variability of the individual response to the same type of injury.[4,5] Because standard feeding protocols do not provide for inter-individual differences in energy requirements and also because the available prediction equations are inadequate for calculating energy needs in critically ill children, these children are more vulnerable to complications arising from underfeeding or overfeeding.

It is important, therefore, to monitor whether children admitted to an ICU are adequately fed. Indirect calorimetry provides a method that can help in this matter. In studies in adults, feeding adequacy was determined by the ratio of energy intake/ (measured energy expenditure + 10% for activity).[6] A second parameter derived from indirect calorimetry is the respiratory quotient (RQ), which is the ratio of the carbon dioxide produced to the oxygen consumed. The role of the RQ as a marker of substrate use is controversial in critical illness, however, because the body's ability to use nutrient substrates may be altered. Also, the clinical usefulness of the RQ as an indicator of underfeeding or overfeeding was found to be limited in critically ill adult patients due to its low sensitivity and specificity.[7] McClave et al. concluded that its clinical usefulness is restricted to a marker of test validity and a marker of respiratory tolerance of the nutritional support regimen.[7] Previous studies among critically ill children using indirect calorimetry do not specify criteria for adequate feeding; the only criterion specified to define overfeeding is a measured RQ > 1.0.[4,8]

We set up a study with a twofold aim: A) to determine the incidences of underfeeding and overfeeding in a heterogeneous cohort of children admitted to the pediatric ICU of our level III children's hospital, based on the criterion used in adults, and B) to evaluate whether the RQ would enable to monitor whether these children are adequately fed.

Materials and methods

Subjects

Over a one-year period (2001), children up to the age of 18 years admitted to our level III multidisciplinary pediatric/surgical ICU with an expected stay of at least 48 hours were studied repeatedly by indirect calorimetry during the first 14 days of admission. The institutional review board of the Erasmus MC approved the study protocol, and written (parental) informed consent before subjects entered the study. Exclusion criteria for this study were withholding/withdrawing of treatment, and inclusion into a nutritional intervention study. Furthermore, children were excluded if they did not fulfill the inclusion criteria for indirect calorimetry measurements. The following inclusion criteria had to be satisfied for indirect calorimetry in ventilated children:

a. mechanical ventilation with a Servo ventilator 300 (Siemens-Elema, Solna, Sweden);
b. inspired oxygen fraction (FiO_2) less than 60%;
c. tube leakage < 10% (considered not to significantly affect the measurements; determined by comparing inspired and expired tidal volumes measured by the ventilator assuming an absence of air leaks in the patient-ventilator circuit);[9]
d. a hemodynamic stable condition (within 2 SD of age-related values for blood pressure and heart rate.[10]

Non-ventilated children receiving supplementary oxygen were excluded from the measurements because of the technical issues involved.

Clinical data collected included age, gender, weight, primary diagnosis, surgical status, days on mechanical ventilation, length of ICU-stay, route of nutritional support, and energy intake. The severity of illness on admission was assessed by the pediatric risk of mortality score (PRISM).[11] Weight was measured on each measurement day according to the methods described by Gerver and De Bruin.[12]

Energy expenditure

Indirect calorimetry measurements were started as soon as technically possible after admission to the ICU and continued on each subsequent day, either in respiratory or canopy mode depending on the child's need for mechanical ventilation. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and RQ standardized for temperature, barometric pressure, and humidity were measured using the Deltatrac II MBM-200 (Datex Division Instrumentarium, Helsinki, Finland) metabolic monitor, and measured energy expenditure (MEE) was calculated using the modified Weir formula.[13] The properties of the Deltatrac metabolic monitor have been described previously.[14] Before each study the calorimeter was calibrated with a reference gas mixture (95% O_2, 5% CO_2, Datex Division Instrumentarium Corp.). Data for the first 5 minutes were routinely discarded to exclude artifacts arising during connection of the calorimeter to the patient. Measurements in the ventilated children lasted at least 2 h. Measurements in

non-ventilated children lasted at least 20 minutes. Placed in an airtight transparent plastic canopy, these children were either sleeping or quietly resting in supine position and had not been exposed to diagnostic or therapeutic procedures in the previous 30 minutes. Flow range and canopy-size were in conformity with the manufacturer's instructions. Measurement results in canopy mode were only used in the analysis if steady states in O_2 and CO_2 concentrations had been obtained. Steady-state criteria were defined as a variation coefficient of the VO_2 and VCO_2 levels of ≤ 10% for at least 15 minutes.

Energy intake

The children were enterally and/or parenterally fed on the guidance of the current feeding protocol and the judgment of the physician clinically responsible for the individual child, independent of the study. During the first 12-24 hours a glucose infusion was given. Fluid and electrolyte intakes were adjusted to individual requirements. For neonates the amount of enteral or parenteral feeding was increased postnatally in accordance with increasing fluid intake until the amount of ≥ 150-180 ml/kg.d at day 7 postnatally. If enteral feeding could not be started on the second day, total parenteral feeding was started within 24-48 h after admission, either by peripheral infusion or by a central venous line (Intralipid 20%, Pharmacia Upjohn, the Netherlands; Primene 10% (body weight ≤ 5kg), Clintec Baxter, Canada; Aminovenös N-paed 10% (body weight > 5 kg), Fresenius, the Netherlands). On the first day of parenteral feeding the amounts of protein and fat amounted to 50% of the aimed intake according to hospital practice (1-2.4 g/kg.d and 2-4 g/kg.d, respectively, depending on age). Enteral feeding was started as soon as possible in all children, either continuously or intermittently through a nasogastric tube (drip or bolus) or nasoduodenal tube (drip), consisting of human milk or standard formula according to parents' preference (Nenatal for preterm neonates; Nutrilon Premium for children aged < 1 m; Nutrison Pediatric Standard for children aged 1 m-1y; Nutrison Multi Fibre for children aged >1 y, Nutricia, Zoetermeer, the Netherlands).

Actual total daily energy intake (kcal/day) was determined by patient intake records on the day of calorimetry, after which the ratio of energy intake/measured energy expenditure (MEE) could be calculated. We corrected for additional protein calories from sources such as plasma and/or albumin infusions and for extra carbohydrate calories from medication solutions. Energy intakes on the day of admission and the day of discharge were extrapolated to a 24h-intake. In order to determine the composition of feeding, a RQ of the administered macronutrients (RQ_{macr}) was obtained from the modified Lusk table after determining the carbohydrate to fat ratio for the total non-protein calories of the nutrients.[15]

Energy requirements (kcal/day) were defined as MEE plus 10% for patient activity related to nursing care (110% of MEE) as used by McClave et al. in critically ill adults.[6]

Consequently, the degree of feeding was defined by the ratio of energy intake/(MEE+10%). Underfeeding was defined as a ratio < 90%, adequate feeding as a ratio of 90-110%, and overfeeding as a ratio > 110%. The adequacy of feeding as classified by the ratio energy intake/(MEE+10%) was compared to the classification based on the measured RQ.[7] Using the measured RQ, underfeeding was defined as a RQ < 0.85 and overfeeding as RQ > 1.0. We calculated the specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) of a measured RQ < 0.85 and > 1.0 to correctly identify underfeeding and overfeeding, respectively.

Statistical analysis

Statistical analyses were performed using SPSS 11.0 for Windows, SPSS software (Chicago, Ill., USA). Results are expressed as mean ± SEM or median and range. To allow optimally for the variable number of measurement days while taking account of between and within patient variations, repeated measures analysis of variance (PROC MIXED, SAS, Cary, NC) was used to compare mean values and examine relationships between various parameters. This analysis served to examine relationships between RQ and various clinical factors (day after admission, ratio energy intake/MEE, RQ_{macr}, carbohydrate intake (mg/kg/min), fat intake (g/kg/day), route of feeding (enteral, parenteral or combination), age and PRISM scores). Two-tailed *P*-values < 0.05 were considered significant.

Results

Clinical characteristics

One hundred twelve children were eligible for this study. However, 14 children were excluded from analysis because of invalid results (e.g. failure to reach steady state) or incomplete nutritional data. Ninety-eight children thus comprised the final study group of whom the clinical characteristics at admission are shown in table 1.

A total of 195 measurements – 83 in canopy and 112 in respiratory mode – were performed. In 49 (50%) children more than one valid indirect calorimetry measurement could be obtained during the first 14 days of admission. Measurement characteristics are shown in table 2. As additional protein and carbohydrate losses from wounds or drained pleural and peritoneal effusions were not significant on the measurement days, these were not adjusted for in the energy intake calculations.

Table 1 Patient characteristics and diagnostic information*

	Total group (n = 98)
M:F[2]	50:48
Age at admission, d	14.5 (0d-15.2y)
Length of stay, d	7 (2-314)
Days on mechanical ventilation, d	3 (0-47)
PRISM score at admission	12 (0-38)
Diagnostic groups[†,‡]	
Congenital anomalies	36
Postnatal problems[§]	14
Post-operative monitoring	116
Sepsis or meningitis	10
Respiratory illness[¶]	15
Other	7
Surgical:non-surgical[†]	45:53

*PRISM, Pediatric Risk of Mortality; *Values expressed as median and range, except when indicated otherwise; [†]Expressed as numbers; [‡]Predominant diagnoses; [§]Includes asphyxia, meconium aspiration, infection; [¶]Includes pneumonia, rs-bronchiolitis.*

Table 2 Characteristics of indirect calorimetry measurements and days on which the measurements were performed*

	All measurements (n = 195)
Measurement mode: canopy vs. respiratory	83:112 (43:57)
Day of measurement	
Respiratory mode	2 (0-14)
Canopy mode	4 (0-14)
Total	4 (0-14)
Day of first measurement	2 (0-14)
Number of measurements per child	2 (1-7)
Duration of measurements (minutes)	
Respiratory mode	119 (60-794)
Canopy mode	24 (15-47)
Medication	
Sedatives	112 (57)
Cardiotonics	15 (8)
Muscle relaxants	8 (4)
Ventilator characteristics	
Tube leakage (%)	1 (0-10)
PRVC:VS:PS	79:32:1 (71:28:1)
Nutritional support	
Parenteral nutrition	38 (19)[†]
Combination of parenteral and enteral nutrition	80 (41)
Enteral nutrition	77 (40)

*PRVC = pressure regulated volume control, VS = volume support, PS = pressure support; *All values expressed as median (range) or numbers (%). [†]Five children received a glucose infusion exclusively.*

For the total study population, the mean ratio energy intake/ MEE increased with increasing time on the ICU (Figure 1), with 8.1 ± 1.2% per day (P < 0.001). Altogether, on 21% (41/195) of measurement days energy intake was below MEE and on 79% of days energy intake exceeded MEE.
The positive relationship between the ratio energy intake/MEE and measured RQ was highly significant, as shown in Figure 2 *(P* < 0.001). Three other clinical factors were independently related to RQ. In addition to the ratio energy intake/MEE, positive relationships were found with day after admission (*P* = 0.0001), ratio energy intake/MEE (*P* < 0.001), and carbohydrate intake (*P* = 0.003). A negative association was found for fat intake (*P* < 0.001). Route of feeding, age, and PRISM score at admission were not significantly related to RQ.

Sensitivity, specificity, positive and negative predictive values of RQ.
Underfeeding, adequate feeding and overfeeding were noted on 21, 10 and 69% of measurement days, respectively. Table 3 shows the relationship between the classification based on measured RQ and the degree of feeding using all measurements (n = 195). Using a measured RQ < 0.85 to identify underfeeding had a low sensitivity of 63% and a specificity of 89%. The positive predictive value was 60% and the negative predictive value was 90%. Using a measured RQ > 1.0 to identify overfeeding had a poor sensitivity of 21% and a specificity of 97%. The positive predictive value was 93% and the negative predictive value was 35%.
Similar values for sensitivity, specificity, PPV and NPV were found when measurements were broken down according to admission day.

Discrepancies between criteria
When comparing the days with and without a measured RQ < 0.85 in the underfeeding category (n = 40), the mean carbohydrate intake was found to be significantly lower on days with a RQ < 0.85 (3.1 ± 0.3 vs. 4.4 ± 0.4 mg/kg/min; *P* < 0.001). No significant differences were found for fat intake and RQ_{macr}. Comparison of the days with overfeeding (n = 135) with and without an RQ > 1 revealed that the ratio energy intake/MEE did not significantly differ (*P* = 0.834). Significantly higher mean carbohydrate intakes (8.1 ± 0.3 vs. 7.2 ± 0.2, *P* = 0.007) and significantly lower mean fat intakes (3.0 ± 0.3 vs. 3.8 ± 0.2 g/kg/d, *P* = 0.018) were registered on those days with a RQ > 1.0. This resulted in a higher RQ_{macr} on days with a RQ > 1.0 (0.890 ± 0.007 vs. 0.860 ± 0.004, *P* < 0.001). Only on 2 of the 30 measurement days with a RQ > 1.0 no overfeeding occurred; a high carbohydrate intake (3.2 and 6.0 mg/kg.min) could not explain the finding of a RQ > 1.0 in these 2 measurements.

Figure 1 Relation between the ratio energy intake/MEE and day after admission.
Data points (n = 195) with fitted regression line generated by 'repeated measures analysis of variance'. The area between the dashed lines indicates the reference range for adequate feeding defined as 90-110% of the ratio energy intake/ (MEE+10%).

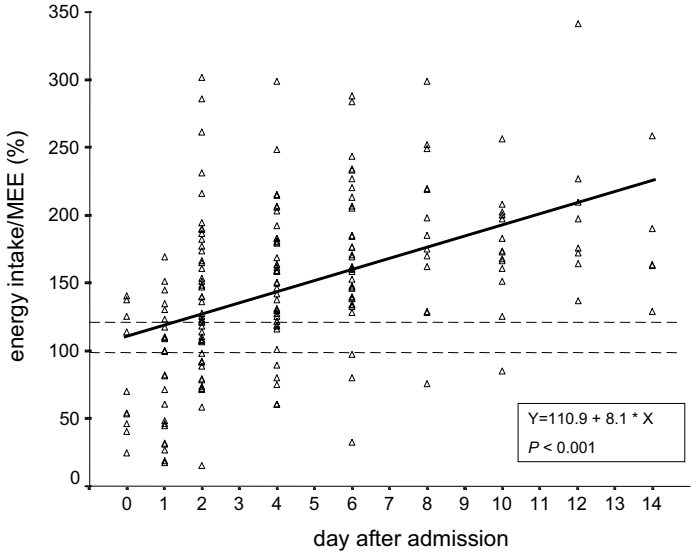


Figure 2 Relation between the ratio energy intake/MEE and measured RQ.
Data points (n = 195) with fitted regression line generated by 'repeated measures analysis of variance'. Dashed lines border the range of adequate feeding according to measured RQ.

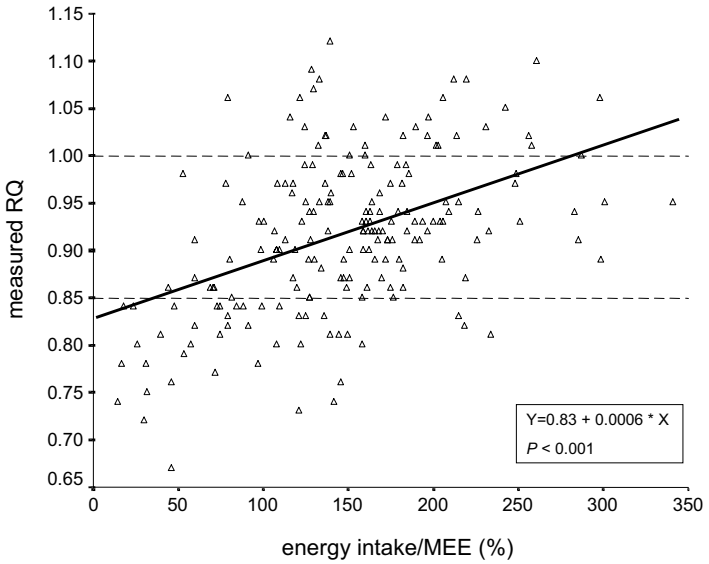


Table 3 Measured RQ in relation to the degree of feeding (n = 195).

	Measured RQ		
	< 0.85	0.85-1.0	> 1.0
Degree of feeding			
Underfeeding (n = 40)	25 (63)	14 (35)	1 (2)
Adequate feeding (n = 20)	5 (25)	14 (70)	1 (5)
Overfeeding (n = 135)	12 (9)	95 (70)	28 (21)

Data represent numbers of measurement days with percentages in parentheses.

Discussion

In this study we analyzed relationships between measured energy expenditure, actual energy intake and measured respiratory quotient in a mixed cohort of children admitted to our ICU. On 21% and 79% of measurement days energy intake was found to be below and above MEE, respectively. Applying a classification used for adults,[6,7] only on 10% of days children would have received adequate nutrition, whereas on 21% and 69% of days children would have been underfed and overfed, respectively.

The high proportion of overfeeding noted in this study is remarkable. The cut-off value of 110% of the ratio energy intake/(MEE+10%) to indicate overfeeding (which corresponds to 121% of MEE), as used by McClave for adults, is beyond discussion for critically ill children in the acute phase of metabolic stress.[8] However, McClave's criterion for overfeeding is arguable in critically ill children who have resumed somatic growth. As opposed to critically ill adults, the feeding regimen for children must also take into account the energy for this growth.[16,17] As growth-related energy can only partly be measured with indirect calorimetry the limits for adequate and overfeeding will be rather different dependent on the age of the child. It is not exactly known, however, when the acute phase turns into the recovery phase. A recent study in critically ill children using endocrine parameters showed that return to anabolism may already occur within the first few days after admission.[18] Another post-operative study evaluating hormone profiles in children of different age groups revealed that the metabolic stress response is significantly shorter in children as compared to adults.[19] Previous studies in critically ill children on mechanical ventilation and children with burns suggested that 20-50% should be added to the MEE in order to reach adequate nutrition and achieve a positive nitrogen balance.[20-22] In recovering young infants this amount of energy might arguably be even higher in case of catch-up growth.[16,17]

Currently there is no uniform standard for defining underfeeding and overfeeding in critically ill children in relation to possible adverse effects such as protein-energy malnutrition for underfeeding, and respiratory problems or liver steatosis for

overfeeding.[8,23] Therefore, there is need for a tool to assess adverse consequences of inadequate feeding and to indicate when nutritional support should be adjusted, for each individual child. Our question was if the measured RQ-value could be such a tool in critically ill children. In theory, the overall measured RQ should reflect the used proportions of fat, protein and carbohydrates, considering that each of these substrates has its unique RQ. Consequently, energy overfeeding or carbohydrate intake in excess of oxidation capacity with resulting lipogenesis, will increase the RQ to a level above 1.0. The use of endogenous fat stores during underfeeding in order to meet caloric requirements will decrease the RQ below 0.85. Used in this way, the measured RQ will alert to the adverse consequences of inadequate feeding and can therefore theoretically be used to evaluate nutritional adequacy.

With regard to all measurement days, an increase in the ratio energy intake/MEE resulted in a significant increase in measured RQ. This might plea for the usefulness of the RQ as a tool to assess feeding adequacy. However, evaluating the usefulness of a single measured RQ in a specific range to classify the degree of feeding, we found poor sensitivity (63% for underfeeding; 21% for overfeeding), which is in accordance with McClave's findings in adults.[7] This means that the RQ is not reliably reflected in the same way in all children in response to overfeeding and underfeeding and that consequently factors other than energy intake relative to MEE must be important. These issues limit the overall value of the RQ in monitoring the adequacy of nutritional support. As opposed to low values for sensitivity, high values were found for specificity to identify overfeeding (97%) and underfeeding (89%) when using a RQ > 1.0 and < 0.85, respectively. This means that only a few measurement days were indicated as days with underfeeding and overfeeding by RQ when actually there was no underfeeding or overfeeding (false positives). The usefulness of the RQ to correctly classify feeding adequacy in practice could be more directly assessed from the positive and negative predictive values. Considering the high negative predictive value (90%) of a RQ < 0.85, we may conclude that the finding of a RQ > 0.85 with reasonable certainty can exclude underfeeding. Furthermore, given the very high chance of correctly classifying a child as overfed when finding an RQ > 1.0 (positive predictive value = 93%), a measured RQ > 1.0 can be useful in clinical practice. The usefulness of the RQ to recognize (carbohydrate) overfeeding has also been demonstrated in other studies in critically ill children and adults.[4,8,24]

We found that the levels of carbohydrate intake and energy intake relative to MEE were independently related to RQ-value. We also showed that on those days with overfeeding with a RQ > 1.0 a significantly different composition of feeding (higher carbohydrate intake, lower fat intake) was administered than on the days with overfeeding with a RQ < 1.0. In clinical practice this means that when an RQ > 1.0 is found the carbohydrate intake and/or the total energy intake has to be adjusted.

Our study has some limitations, however. First, looking into reasons for feeding days to fall in an RQ-range that did not correspond to the feeding degree (discrepancies between criteria) we focused on composition of feeding. It is known, however, that numerous factors – related and unrelated to feeding – can alter the value of measured RQ in critically ill patients, e.g. hyperventilation, acidosis, effects of cardiotonic agents and neuromuscular blocking, and the individual unique response to a given substrate load, injury or disease.[25] In addition, the ongoing use of endogenous fuels (protein catabolism, lipolysis), found even when supplying adequate amounts of exogenous substrates, can result in discrepancies between measured RQ and the amount of energy provided.
Second, our study group consisted of a heterogeneous group of children with different ages, diagnoses, and illness severity scores. In addition, measurements were performed in both ventilatory and non-ventilatory mode under different nutritional support regimens. We deliberately opted for this epidemiological approach – including almost all admitted patients – aiming at investigating the metabolic monitor as a clinical tool in a pediatric population representative for any pediatric ICU. The study described here is embedded in a study that aims to provide guidelines for nutritional and metabolic monitoring in daily clinical practice, taking into account the patient mix usually seen in pediatric ICUs. We are aware that this inhomogeneity has various drawbacks and makes it difficult to interpret our results for specific groups of critically ill children such as septic or post-operative patients. We considered several possible influencing factors and found that route of feeding, age and illness severity score at admission did not significantly affect the RQ.

In conclusion, applying the criteria used in critically ill adults, we found that critically ill children were overfed on most measurement days. Nevertheless, only on 20% of these days there appeared to be chance to develop adverse consequences of overfeeding (RQ> 1.0). In the pediatric ICU-setting, the usefulness of the RQ to monitor feeding adequacy and to adjust nutritional support is limited due to poor sensitivity and large inter-individual variability. However, the extreme values of RQ can well be used to indicate two clinically relevant issues. An RQ-value > 0.85 reliably indicates the absence of underfeeding and an RQ-value > 1.0 reliably indicates the presence of (carbohydrate) overfeeding.

Summary

In this study among critically ill children the usefulness of the respiratory quotient to monitor feeding adequacy was investigated and found to be of limited value due to low sensitivities. RQ-values above 0.85 and above 1.0 reliably exclude underfeeding and indicate carbohydrate and/or actual overfeeding, respectively, and call for adjustment of nutritional support.

Acknowledgements

Our gratitude goes out to Ada van den Bos, Annelies Bos, Marjan Maliepaard, Marianne Mourik, and Ineke van Vliet for their help with the collection of data. We also thank Ko Hagoort (Erasmus MC, Rotterdam) for his careful editing.
Supported, in part, by Nutricia Nederland BV, Zoetermeer, the Netherlands.

References

1. Biolo G, Toigo G, Ciocchi B, Situlin R, Iscra F, Gullo A, Guarneiri G. Metabolic response to injury and sepsis: changes in protein metabolism. Nutrition 1997;13(Suppl):52S-57S.
2. Pollack MM, Ruttimann UE, Wiley JS. Nutritional depletions in critically ill children: associations with physiologic instability and increased quantity of care. J Parenter Enteral Nutr 1985;9:309-13.
3. Coss-Bu J, Jefferson L, Walding D, David Y, Smith EO, Klish WJ. Resting energy expenditure and nitrogen balance in critically ill pediatric patients on mechanical ventilation. Nutrition 1998;14:649-652.
4. Joosten KF, Verhoeven JJ, Hazelzet JA. Energy expenditure and substrate utilization in mechanically ventilated children. Nutrition 1999;15:444-8.
5. Phillips R, Ott L, Young B, Walsh J. Nutritional support and measured energy expenditure of the child and adolescent with head injury. J Neurosurg 1987;67:846-51.
6. McClave SA, Lowen CC, Kleber MJ, Nicholson JF, Jimmerson SC, McConnell JW, Jung LY. Are patients fed appropriately according to their caloric requirements? J Parenter Enteral Nutr 1998;22:375-81.
7. McClave SA, Lowen CC, Kleber MJ, McConnell JW, Jung LY, Goldsmith LJ. Clinical use of the respiratory quotient obtained from indirect calorimetry. J Parenter Enteral Nutr 2003;27:21-6.
8. Chwals WJ. Overfeeding the critically ill child: fact or fantasy? New Horiz 1994;2:147-55.
9. Knauth A, Baumgart S. Accurate, noninvasive quantitation of expiratory gas leak from uncuffed infant endotracheal tubes. Pediatr Pulmonol 1990;9:55-60.
10. Report of the Second Task Force on Blood Pressure Control in Children-- 1987. Task Force on Blood Pressure Control in Children. National Heart, Lung, and Blood Institute, Bethesda, Maryland. Pediatrics 1987;79:1-25.
11. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988;16:1110-6.
12. Gerver W, De Bruin R. Paediatric Morphometrics: a reference manual. Utrecht: Bunge; 1996.
13. Weir J. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol 1949;109:1-9.
14. Joosten KF, Jacobs FI, van Klaarwater E, Baartmans MG, Hop WC, Merilainen PT, Hazelzet JA. Accuracy of an indirect calorimeter for mechanically ventilated infants and children: the influence of low rates of gas exchange and varying FIO2. Crit Care Med 2000;28:3014-8.
15. McClave SA, Snider HL. Use of indirect calorimetry in clinical nutrition. Nutr Clin Pract 1992;7:207-21.
16. Ashworth A, Millward DJ. Catch-up growth in children. Nutr Rev 1986;44:157-63.
17. Fjeld CR, Schoeller DA, Brown KH. Body composition of children recovering from severe protein-energy malnutrition at two rates of catch-up growth. Am J Clin Nutr 1989;50:1266-75.

18. Joosten KF, de Kleijn ED, Westerterp M, de Hoog M, Eijck FC, Hop WCJ, Voort EV, Hazelzet JA, Hokken-Koelega AC. Endocrine and metabolic responses in children with meningoccocal sepsis: striking differences between survivors and nonsurvivors. J Clin Endocrinol Metab 2000;85:3746-53.
19. Bouwmeester NJ, Anand KJ, van Dijk M, Hop WC, Boomsma F, Tibboel D. Hormonal and metabolic stress responses after major surgery in children aged 0-3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine. Br J Anaesth 2001;87:390-9.
20. De Klerk G, Hop WC, De Hoog M, Joosten KF. Serial measurements of energy expenditure in critically ill children: useful in optimizing nutritional therapy? Intensive Care Med 2002;28:1781-5.
21. Goran MI, Peters EJ, Herndon DN, Wolfe RR. Total energy expenditure in burned children using the doubly labeled water technique. Am J Physiol 1990;259:E576-85.
22. Briassoulis G, Tsorva A, Zavras N, Hatzis T. Influence of an aggressive early enteral nutrition protocol on nitrogen balance in critically ill children. Journal of Nutritional Biochemistry 2002;13:560-569.
23. Vo N, Waycaster M, Acuff R, Lefemine A. Effect of postoperative carbohydrate overfeeding. Ann Surg 1987;53:632-635.
24. Bresson JL, Bader B, Rocchiccioli F, Mariotti A, Ricour C, Sachs C, Rey J. Protein-metabolism kinetics and energy-substrate utilization in infants fed parenteral solutions with different glucose-fat ratios. Am J Clin Nutr 1991;54:370-6.
25. McClave S, Snider HL, Greene L, Lowen C, Cornelius M, Samuelson S, Dukes L. Effective utilization of indirect calorimetry during critical care. Intensive Care World 1992;9:194-200.

Chapter 5

The effect of cumulative energy and protein deficiency on anthropometric parameters in a pediatric ICU population

Jessie M. Hulst, Johannes B. van Goudoever, Luc J.I. Zimmermann, Wim C.J. Hop, Marcel J.I.J. Albers, Dick Tibboel, Koen F.M. Joosten

Accepted for publication by Clinical Nutrition

Abstract

Background & Aims

Nutritional support is essential in the care of critically ill children since inadequate feeding increases morbidity and negatively affects growth. We aimed to compare cumulative energy and protein intakes with recommended dietary intakes (RDA) and examine relationships between accumulated balances and anthropometric parameters.

Methods

Prospective, observational study. Total daily energy and protein intakes were determined during a maximum of 14 days in 261 children admitted to our multidisciplinary tertiary pediatric ICU. Actual intakes were subtracted from RDA and cumulative balances were calculated. Relations between cumulative balances, various clinical factors and changes in anthropometry (weight, arm and calf circumference) were analyzed using regression analysis.

Results

At 14 days after admission children showed significant cumulative nutritional deficits compared to RDA. These deficits were on average 27, 20, 12 kcal/kg and 0.6, 0.3, and 0.2g protein/kg per day for preterm neonates (n = 103), term neonates (n = 91) and older children (n = 67), respectively. Age at admission, length of ICU-stay and days on mechanical ventilation were negatively related to cumulative balances. Cumulative energy and protein deficits were associated with declines in SD-scores for weight and arm circumference.

Conclusions

Children admitted to the ICU accumulate substantial energy and protein deficits when compared to RDA. These deficits are related to decreases in anthropometric parameters.

Introduction

It is generally acknowledged that nutritional support is essential in the care for children with (chronic) disease since inadequate feeding may increase morbidity and mortality and negatively affect body composition and growth.[1,2] There are, however, limited prospective data available describing non-selected groups of children admitted to a pediatric intensive care unit (ICU). Protein-energy malnutrition has been found to occur in 15-20% of critically ill children.[3-6] Lacking endogenous stores of protein and fat and having higher baseline requirements, neonates and children under the age of 2 are particularly susceptible to loss of lean body mass and its related morbidity.[7]
In critically ill children sustained catabolism may lead to severe protein-energy malnutrition. Although in this situation both protein synthesis and protein breakdown are intensified, the latter predominates. Thus, critically ill children manifest a net negative protein balance, which may clinically be noted by weight loss, negative nitrogen balance and skeletal muscle wasting. Fortunately, supplementation of amino acids does improve protein balance by increasing protein synthesis.[8,9] Providing adequate dietary protein is, therefore, a very important nutritional intervention in critically ill children.

Nutritional regimens for energy and protein at an ICU are usually based on recommended intakes for healthy children (RDA). Complying with these reference values is controversial, however, in the first stage of acute illness when energy needs might be lower or higher than RDA and protein needs might be higher.[10,11] A more precise, individual estimation of energy requirements can be obtained by measuring an infant's actual energy expenditure.
Once nutritional support is started, its adequacy may be assessed by parameters of nutritional status, such as anthropometric measurements. Studies in preterm infants showed a significant accumulation of nutrient deficits in the first few weeks of postnatal life resulting in severe growth retardation.[12-14] Cumulative nutritional deficits have not yet been investigated in other age groups admitted to an ICU, except in critically ill infants with lower respiratory tract infections, though without paying attention to impact on growth or changes in body composition.[15]

The first aim of our study was to prospectively assess daily and cumulative energy and protein intakes of a cohort of critically ill children during their first 14 days in the ICU, and to compare these intakes to the RDA. The second purpose was to examine relationships between accumulated energy and protein intake and changes in anthropometric parameters.

Patients and Methods

Subjects

Children admitted during the year 2001 to our level III multidisciplinary neonatal and pediatric/surgical ICU with an expected stay of at least 48 hours were included in the study, provided written parental informed consent had been obtained. Exclusion criteria were withholding or withdrawal of treatment, inclusion into another nutritional study, or treatment with Extra Corporeal Membrane Oxygenation (ECMO). The institutional review board of Erasmus MC approved the study protocol.

The patients were grouped into 3 age categories to differentiate between groups with different nutritional needs, i.e. preterm neonates (gestational age < 37 wk), term neonates (gestational age ≥ 37 wk; age 0-30 d) and older children (age 30 d-18 y).

Energy intake

The children were enterally and/or parenterally fed on the guidance of the current feeding protocol and the judgement of the physician clinically responsible for the individual child, independent of the study. During the first 12-24 hours a glucose infusion was given. Fluid and electrolyte intakes were adjusted to individual requirements. For neonates the amount of enteral or parenteral feeding was increased postnatally in accordance with increasing fluid intake until the amount of ≥ 150-180 ml/kg.d at day 7 of life. If enteral feeding could not be started on the second day, parenteral feeding was started within 24-48 h after admission by either peripheral or central venous line (Intralipid® 20%, Fresenius, 's Hertogenbosch, the Netherlands; Primene® 10% (body weight ≤ 5kg), Clintec Baxter, Clintec Benelux N.V., Brussel, Belgium; Aminovenös N-paed® 10% (body weight > 5 kg), Fresenius, 's Hertogenbosch, the Netherlands). On the first day of parenteral feeding the amount of protein and fat was 50% of the aimed intake according to hospital practice (1-2.4 g/kg.d and 2-4 g/kg.d, respectively, depending on age). Enteral feeding was started as soon as possible in all children, either continuously or intermittently with a nasogastric tube (drip or bolus) or nasoduodenal tube (drip) with human milk or standard formula according to parents' preference (Nenatal for preterm neonates; Nutrilon Premium for children aged < 1 month; Nutrison Pediatric Standard in children aged 1 month-1 year; Nutrison Multi Fibre in children aged > 1 year, Nutricia, Zoetermeer, The Netherlands).

Intake vs. RDA

Actual total daily intake was determined by patient intake/output records until discharge from the ICU or during the first 14 full days of ICU-admission if admission continued after day 14. In order to calculate daily balances, actual daily energy and protein intakes were subtracted from the recommended daily allowances (RDA) for age and sex for healthy children.[16,17] Daily balances were totaled to calculate cumulative balances. Weight at

admission was used for all calculations on energy and protein intake throughout the study period.
In those children who stayed at least 7 days at the ICU, we investigated relationships between cumulative energy and protein balances and changes in anthropometric parameters of nutritional status during admission. Weight, mid upper arm circumference (MUAC) and calf circumference (CC) were measured within 24 hours after admission, at discharge or at day 14 after admission if admission continued after day 14. Measurements were performed according to the methods described for Dutch reference values.[18] Intra-observer and inter-observer studies performed prior to the study had shown good reproducibility of measurements with coefficients of variation < 3% for MUAC and CC. Measurements of weight (all children), MUAC (term neonates and older children) and CC (term neonates and older children) were converted to standard deviation (SD) scores using recent Dutch reference standards[19] for term neonates and older children and intra-uterine growth curves for preterm neonates.[20] The changes in SD-scores for weight-for-age (WFA-SDS), MUAC (MUAC-SDS) and CC (CC-SDS) between admission and discharge or between admission and day 14 of admission in case of prolonged admission were calculated. Since no SD-scores for MUAC and CC can be calculated for the preterm neonates, absolute changes in MUAC and CC were used for these measurements.

Other clinical data collected were age, gender, birth weight, gestational age, primary diagnosis, surgical status, days on mechanical ventilation, length of ICU-stay and route of nutritional support. The severity of illness on admission was assessed by the Pediatric RISk of Mortality score (PRISM)[21] for the term neonates and older children or the Clinical Risk Index for Babies (CRIB) in the preterm neonates.[22]

Statistical analyses
Results are expressed as mean ± SEM except when indicated otherwise. Longitudinal analysis of the intake data and growth parameters, including the comparison of mean values, allowing for missing data (e.g. earlier discharge than day 14), was performed using repeated measures analysis of variance (PROC MIXED, SAS, Cary, NC) on the 3 subsets based upon age. Kaplan-Meier analysis,[23] taking account of length of ICU-stay, was used to determine the median day after admission at which an intake ≥ 90% of RDA was reached for at least 3 consecutive days.
Regression analysis was used to examine relationships between cumulative energy and protein deficits at discharge or day 14 after admission and various clinical parameters. Variables initially tested for association in univariate regression analysis included age, gender, gestational age, birth weight, severity of illness (PRISM or CRIB), length of ICU-stay and days on mechanical ventilation at the endpoint, having undergone surgery, and previous health status. Variables associated with the dependent variable in the univariate analysis ($P < 0.05$) were entered in a stepwise linear regression with

backward elimination. Stepwise regression analysis was also used to examine the relationship between changes in SDS and cumulative energy and protein deficits. Variables initially tested for association in univariate regression analysis included energy or protein deficit, age group and length of ICU-stay. A two-tailed *P*-value < 0.05 was considered to indicate statistical significance.

Results

A total of 342 children were enrolled in the study, of which 81 children were not included in the analyses for various reasons (Figure 1). The characteristics and diagnoses of the remaining 261 children are shown in Table 1. Frequencies of routes of nutritional support changed during the ICU-stay. Overall, 59% of the children on day 1 received parenteral feeding exclusively (21% only glucose solution), a proportion which gradually decreased to 10% on day 14. Administration of enteral feeding (full or partial) increased from 41% on day 1 to 90% on day 14.

Figure 1 Flow chart describing the study population.
**LOS = length of stay; in these patients anthropometric parameters were evaluated.*

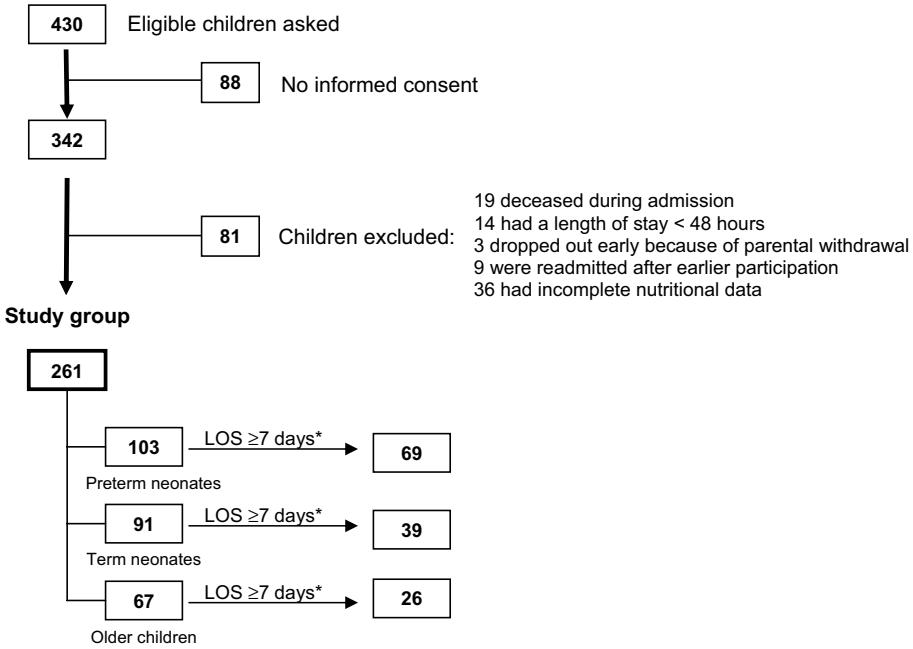


Table 1 Patient characteristics and diagnoses*

	Preterm neonates (n = 103)	Term neonates (n = 91)	Older children (n = 67)
M:F[†]	62:41	46:45	36:31
Age at admission, d	0 (0-83)	1.0 (0-30)	0.5y (32d-17y)
Gestational age, wk	31.1 (27-36.7)	39.7 (37-42)	-
Birth weight, g	1500 (530-3160)	3310 (1765-5855)	5.7 (2.3-60)[‡]
Length of stay, d	12 (2-151)	6 (2-314)	5 (2-138)
Days on ventilation, d	3 (0-42)	3 (0-53)	2 (0-35)
Severity of illness score[§]	3 (0-16)	14 (0-38)	9 (0-31)
Diagnostic groups[†,¶]			
Prematurity / dysmaturity	83	0	0
Congenital malformations	9	37	11
Postnatal problems[#]	0	24	0
Postoperative monitoring	8	5	20
Sepsis or meningitis	0	5	15
Respiratory illness**	2	16	18
Other	1	4	3
Surgical:non-surgical	17:87	35:55	27:40

**Values expressed as median (range), except when indicated otherwise; [†]Expressed as numbers; [‡]Weight at admission in kg; [§]Clinical Risk Index for Babies (CRIB score) in the preterm neonates (n = 77), Pediatric Risk of Mortality Score (PRISM) in term neonates and older children; [¶]Most prominent diagnoses; [#]Includes asphyxia, meconium aspiration, infection; **Includes pneumonia, rs-bronchiolitis.*

Daily energy and protein intake

For the total group, the ratio energy intake/ RDA (Figure 2) and protein intake/RDA increased significantly with increasing time on the ICU ($P < 0.001$). The median day at which a child reached an energy intake of ≥ 90% of RDA was day 10 for the preterm neonates and day 8 for the term neonates and older children. A protein intake of ≥ 90% of RDA was reached at a median of 10 days after admission in the preterm neonates, 5 days for the term neonates and 6 days for the older children.

Cumulative energy and protein intake in relation to RDA

Daily cumulative energy and protein deficits during the first 14 days of admission are presented in Figure 3a and 3b respectively. At day 14, cumulative deficits were significantly different between the three age groups, with the preterm neonates accumulating the largest deficits (380 ± 15, 285 ± 18, and 162 ± 27 kcal/kg and 7.9 ± 0.4, 4.8 ± 0.6, and 2.4 ± 0.8 g protein/kg for the preterm neonates, term neonates and older children, respectively). These deficits correspond to mean daily deficits of 27 ± 1, 20 ± 1, and 12 ± 2 kcal/kg (23, 20, and 13% of RDA) and 0.56 ± 0.03, 0.34 ± 0.04, and 0.17 ± 0.06 g protein/kg (19, 14, and 9% of RDA) for the preterm neonates, term neonates and older children respectively.

Figure 2 Actual energy intake expressed as a percentage of RDA during the first 14 days of ICU-admission for a) preterm neonates (n = 103), b) term neonates (n = 91) and c) older children (n = 67).

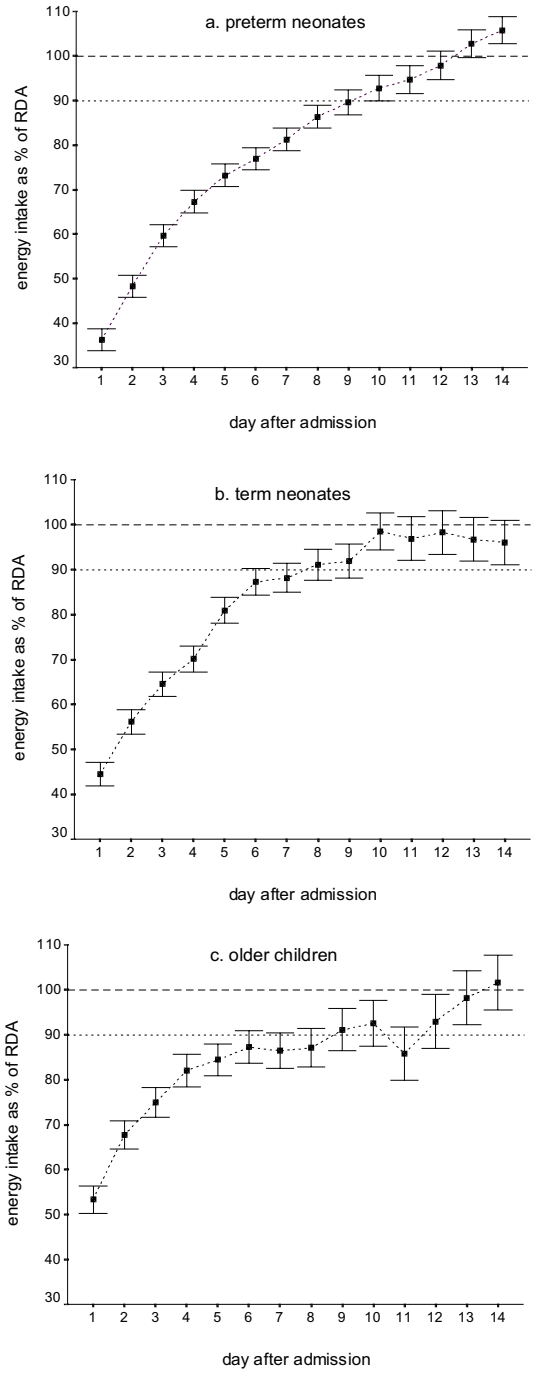


Figure 3a Mean cumulative energy deficits (intake - RDA) during the first 14 days of admission for the 3 age groups. *All values expressed as mean ± SEM; data were analyzed using ANOVA and were based on 103 preterm neonates, 91 term neonates and 67 older children. *Cumulative energy deficits on day 14 were significantly different between all age groups.*

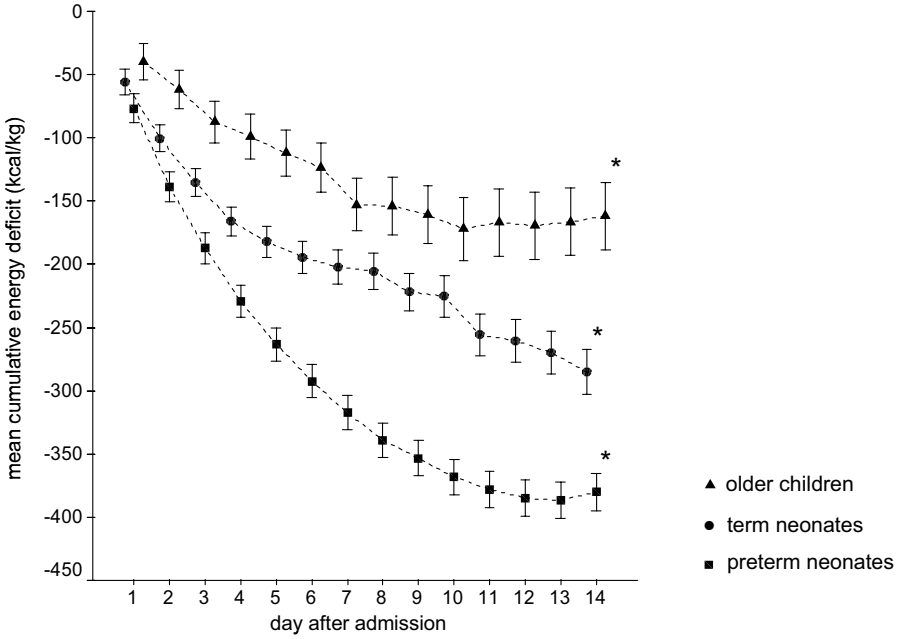
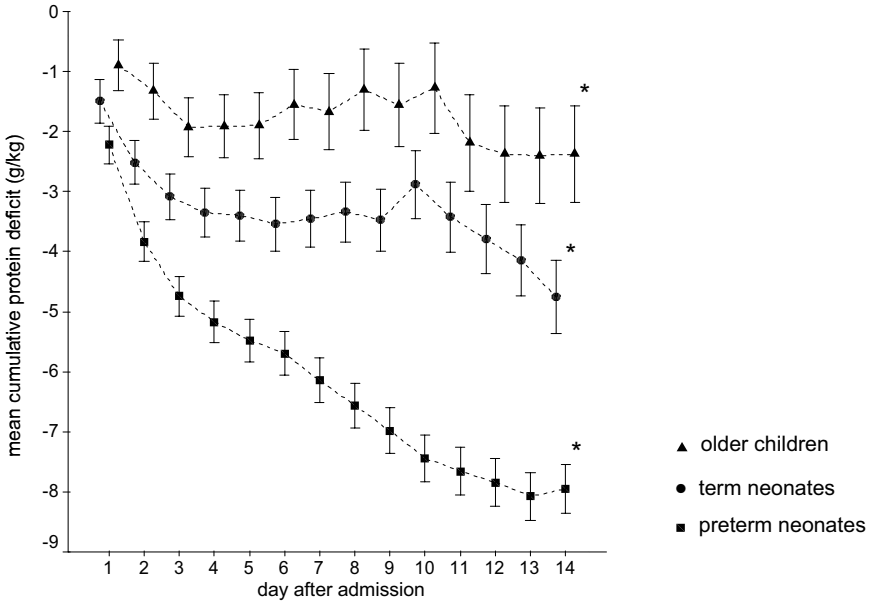


Figure 3b Mean cumulative protein deficits (intake - RDA) during the first 14 days of admission for the 3 age groups. *All values expressed as mean ± SEM; data were analyzed using ANOVA and were based on 103 preterm neonates, 91 term neonates and 67 older children. *Cumulative protein deficits on day 14 were significantly different between all age groups.*



Different clinical factors were significantly related to the deficits in stepwise regression analysis for the three age groups. In the preterm neonates, cumulative energy balances were significantly negatively related to length of ICU-stay (P = 0.006), days on mechanical ventilation (P < 0.001), and having undergone surgery (P = 0.018). Cumulative protein balance was significantly negatively related to length of ICU-stay (P < 0.001). In the term neonates, cumulative energy deficits were significantly related to length of ICU-stay (P < 0.001) and age at admission (P < 0.001). In the older children, only the length of ICU-stay negatively influenced cumulative energy balance (P = 0.012). No significant relations were found between any clinical factor and cumulative protein balance for term neonates and older children.

Change in growth parameters

Changes in growth parameters between admission and discharge/day 14 (endpoint) were determined in fifty-one percent (n = 134) of the children, those who had an ICU-stay of ≥ 7 days. The mean changes in WFA-SDS between admission and endpoint were significantly different between age groups. The mean change in WFA-SDS only significantly differed from zero for the preterm and term neonates (-0.95 ± 0.08, -0.24 ± 0.09, and 0.16 ± 0.14 respectively for the preterm neonates, term neonates and older children). The mean changes in SD-scores for MUAC-SDS and CC-SDS were similar for the term neonates and older children. Mean change in MUAC-SDS was significant in the older children (-0.20 ± 0.09, P = 0.041). For CC-SDS no significant changes were found in term neonates and older children. In the preterm neonates no significant differences in absolute MUAC and CC between admission and endpoint were found. Length of ICU-stay was not significantly related to changes in any growth parameter between admission and discharge/day 14 (all P-values > 0.2) for the three age groups

Cumulative energy deficits (RDA) and change in growth parameters

Taking all age groups together, the change in WFA-SDS from admission to the endpoint was significantly related to cumulative energy deficits (P < 0.001). Age group and cumulative energy deficits were found to explain 39% (R^2) of the variation in WFA-SDS. Allowing for the significant differences in change of WFA-SDS between age groups, a cumulative energy deficit of 100 kcal/kg was associated with a decrease of WFA-SDS of 0.06 (95% CI: 0.01-0.1) (Figure 4a), an effect which did not significantly differ between age groups. The change in MUAC-SDS between admission and discharge/day 14 was significantly related to cumulative energy deficits when term neonates and older children were taken together (P = 0.025). A cumulative energy deficit of 100 kcal/kg was associated with a decrease of MUAC-SDS of 0.07 (95% CI: 0.009-0.1) and there was no effect of age group. Cumulative energy deficits were found to explain 10% (R^2) of the variation in MUAC-SDS. Changes in CC-SDS for all age groups and changes in absolute CC and MUAC in the preterm neonates were not significantly related to cumulative energy deficits during admission.

Figure 4a Relationship between cumulative energy balance (EI - RDA) and the change in WFA-SDS between admission and discharge/day 14. *Data points with fitted regression lines for the 3 age groups; data were analyzed using ANOVA and were based on 69 preterm neonates, 39 term neonates, and 26 older children. Mean differences between groups: 0.35 between older children (1) and term neonates (2), P = 0.041; 0.61 between term neonates (2) and preterm neonates (3), P < 0.001; 0.96 between preterm neonates (3) and older children (1), P < 0.001.*

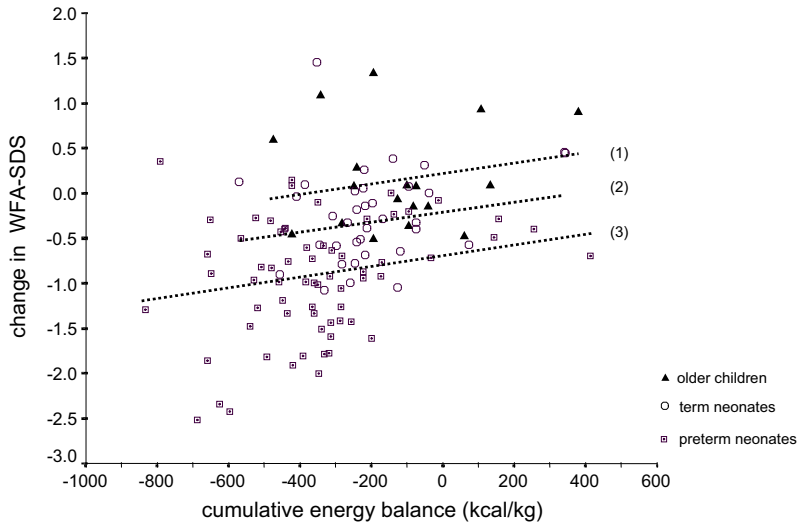
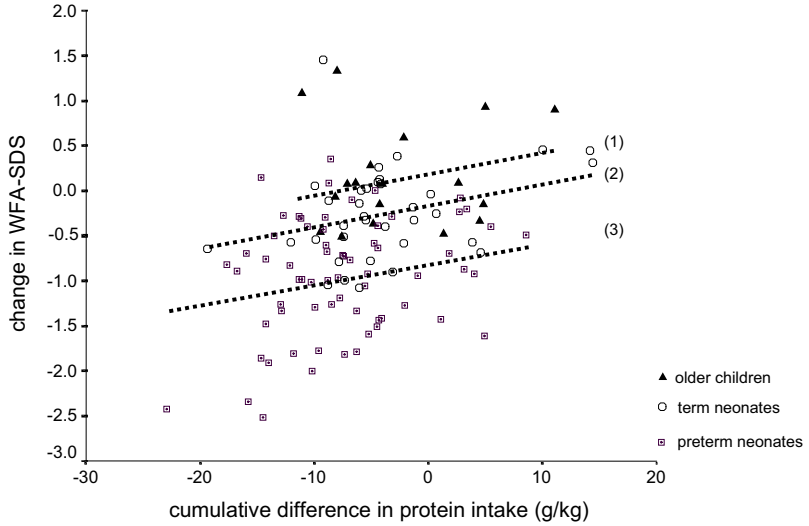


Figure 4b Relationship between cumulative protein balance (protein intake - RDA) and the change in WFA-SDS between admission and discharge/day 14. *Data points with fitted regression lines for the 3 age groups; data were analyzed using ANOVA and were based on 69 preterm neonates, 39 term neonates, and 26 older children. . Mean differences between groups: 0.38 between older children (1) and term neonates (2), P = 0.029; 0.62 between term neonates (2) and preterm neonates (3), P < 0.001; 0.997 between preterm neonates (3) and older children (1), P < 0.001.*



Cumulative protein balance (RDA) and change in growth parameters

Taking all age groups together, the change in WFA-SDS between admission and discharge/day 14 was significantly related to cumulative protein deficits ($P < 0.001$). Age group and cumulative protein deficits were found to explain 40% (R^2) of the variation in WFA-SDS. Allowing for the significant differences in change of WFA-SDS between age groups, a cumulative protein deficit of 10 g/kg was associated with a decrease in WFA-SDS of 0.2 (95% CI: 0.07-0.4) (Figure 4b). A cumulative protein deficit of 10 g/kg was associated with a decrease of MUAC-SDS of 0.2 (95% CI: 0.02-0.4, $P = 0.033$) when term neonates and older children were taken together. Changes in CC-SDS were not significantly related to cumulative protein deficits, but a cumulative protein deficit of 10 g/kg was associated with a decrease in absolute CC of 0.4 cm (95% CI: 0.1-0.7 cm; $P = 0.005$) in the preterm neonates (14% of variation explained). The absolute changes in MUAC were not significantly related to cumulative protein deficits.

Due to the highly significant correlation ($r_s = 0.55$, $P < 0.001$) between cumulative energy and cumulative protein deficits, it was not possible to differentiate between these effects on growth parameters.

Discussion

This observational study shows that under the current feeding regimen, and using the RDA as the value for optimal energy and protein intake, an unselected group of children admitted to the ICU suffers from considerable cumulative energy and protein deficits.

The cumulative deficits in energy and protein intake relative to RDA were related to decreases in anthropometric variables between admission and discharge/day 14 after admission. This relationship underscores the inadequacy of nutritional support in critically ill children in general and implies the need for optimizing nutritional care.

The accumulated deficits relative to RDA were significantly different between the three age groups, with the youngest children accumulating the highest deficits. This finding is in accordance with previous studies regarding cumulative intake in preterm or very low birth weight (VLBW) neonates.[12,14] In the preterm neonates, the deficits corresponded with a mean daily shortage of 23% of energy and 19% of protein needed according to RDA. In the term neonates and older children these proportions were 13 and 9%, respectively.

While measured resting energy expenditure is considered the minimum value for energy intake, it remains questionable what the optimal energy intake is during the acute and recovery phases of critical illness. In the recovery phase, when energy is needed for tissue repair – e.g. in case of wound healing – and when growth is regained, energy intake should be increased. Previous studies in ventilated critically ill children showed that adequate nutrition was in the range of 1.2-1.5 times measured EE.[24-27] Given that

our study showed a negative relation between accumulated energy deficits and changes in growth parameters, one could speculate that energy requirements in the recovery phase would be close to or even above RDA levels.
The relationship we found between cumulative protein deficits and growth indicates that protein intake is important and should be increased, possibly to levels above RDA in diseases with high metabolic stress. Protein makes up 10-12% of all newly formed tissue. Thus, for example, in a preterm neonate with a body weight of 1 kg, a protein deficit of 8 g/kg after 14 days is equivalent to a loss of about 80g/kg body weight. Daily assessment of nitrogen balance would seem helpful in estimating the actual protein balance of each child.[26]

Few studies have been performed that relate nutritional support to growth parameters in critically ill children. A study by Embleton et al[12] among preterm infants revealed cumulative energy deficits at 14 days of life for infants ≥ 31 weeks gestation equaling the deficits found in our group of preterm neonates with a mean gestational age of 31.1 weeks. However, the protein deficits in their study were higher. Moreover, Embleton et al. concluded that poorer growth was primarily related to inadequate energy intake. In a study by Carlson and Ziegler among VLBW infants, weight gain was found mainly to result from adequate protein intake.[13]
Interestingly, we found several clinical factors, varying among the three age groups that influenced cumulative nutritional balances. Overall, obviously the most important factor was length of ICU-stay, which was negatively related to the energy and protein balances. Moreover, more days on mechanical ventilation was related to larger cumulative deficits, independent of ICU-stay. Undergoing surgery was related to a more negative cumulative energy balance in preterm neonates. Furthermore, the deficits accumulated most rapidly during the first days of admission. Thus, special attention should be paid to the adequacy of feeding during the first days of admission, when the child is ventilated or in post-operative state.

The variation in change of SD-scores of anthropometric parameters between admission and discharge/day 14 could be explained for up to 40% by cumulative intake deficits and age group. A substantial proportion of the variation was not explained, which reflects the heterogeneity of the group and underlines the importance of factors other than nutrition responsible for changes in growth parameters. As described previously,[28] factors such as a history of disease or undergoing surgery may also negatively influence growth outcome at discharge.

In general, accumulation of nutritional deficits can be due to underprescribing, inadequate delivery of nutrients (e.g. interruptions caused by digestive intolerance, airway management, and diagnostic procedures) or a combination. Several studies in critically ill adult patients[29-31] showed that while 66-78% of calories required was

prescribed, 51-71% was effectively delivered. We only studied the total amount of calories and proteins actually delivered to the child, which precludes drawing conclusions about the reasons for the deficits noted. It seems likely, however, that critically ill children are also subject to cessations of nutrient administration attributable to avoidable causes.

Some limitations of the study must be pointed out. First, our choice of anthropometric parameters to define changes in nutritional status rests on the epidemiological approach of this study and the mixed study population. We are aware that newer techniques, i.e. bioelectrical impedance analysis (BIA) and dual-energy X-ray absorptiometry (DEXA) are available. However, in view of the limitations of these methods in daily use and the lack of reference values for the younger age groups, we feel that they are still of limited value in the ICU setting with its heterogeneous set of patients. Nevertheless, we realize that anthropometric methods have limitations in critically ill children who frequently show fluid retention with resulting edema, especially in the first days after admission.
Secondly, the maximum study duration was set at 14 days. The relationship between intake deficits and growth parameters might have been stronger if collection of data on intake and growth had been continued until discharge for all children. Yet, given that the mean length of stay of critically ill pediatric patients in Dutch intensive care units is 4.7 days,[32] overall results would have been strongly influenced by a selected group of children with prolonged ICU-stays.

However, this study was not initiated to determine the optimal feeding regimen, but merely to describe how a mixed population of ICU patients is fed in relation to recommended intakes. Optimal feeding would be defined as a feeding regimen enabling to achieve normal growth rates which, as shown, our current feeding protocol fails to achieve.
We conclude that critically ill children during ICU-admission accumulate substantial energy and protein deficits that exert negative effects on growth. A more aggressive feeding regimen, especially during the first days after admission, might help to minimize the accumulation of deficits. Future research must show the safety and practical implication of such a strategy in selected patient groups.

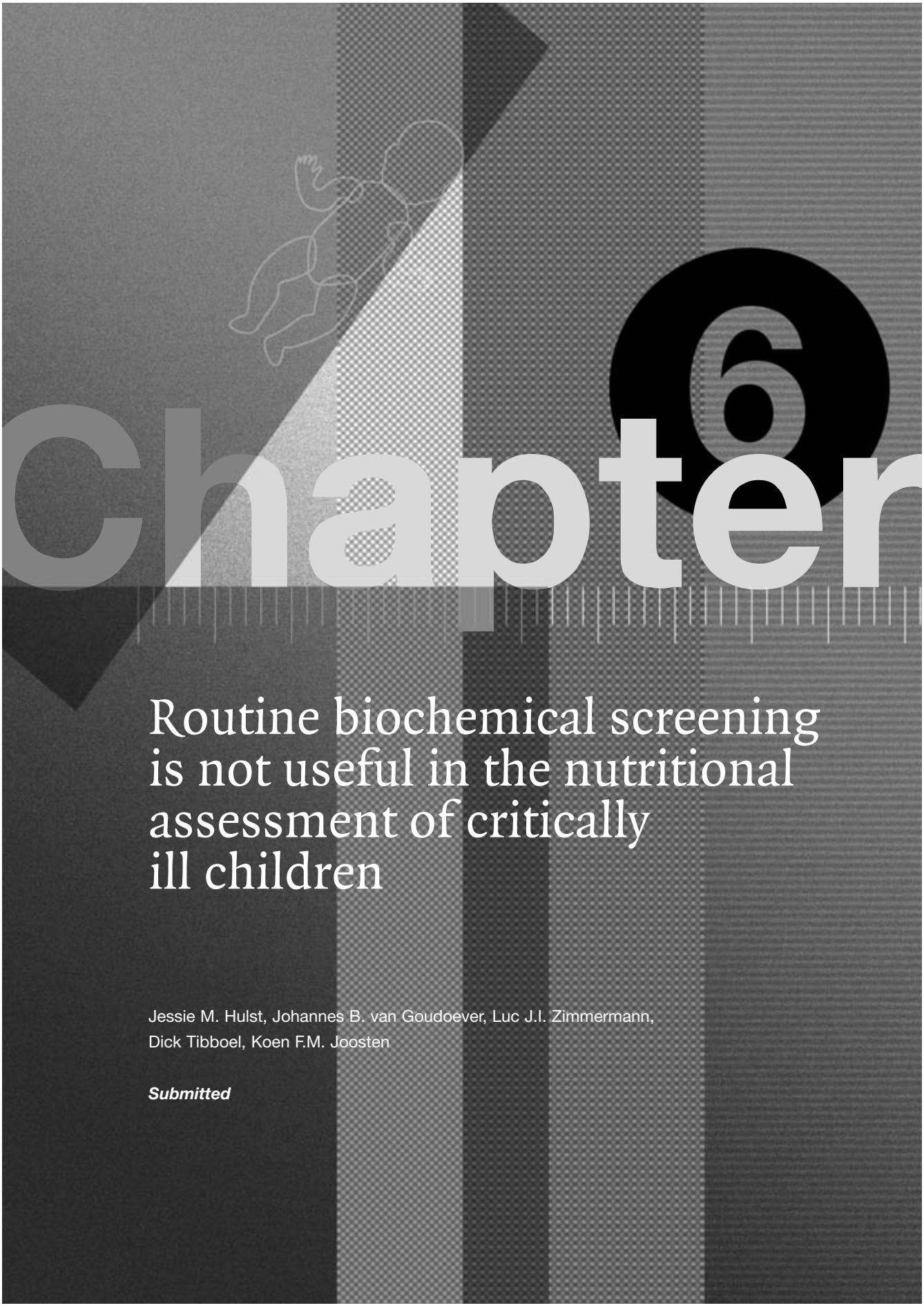
Acknowledgements

The authors thank the participating children and their parents. We also thank Ada van den Bos, Annelies Bos, Marianne Maliepaard, Marjan Mourik and Ineke van Vliet for their great help with data collection and inclusion of patients. Furthermore, our gratitude goes out to the nursing and medical staff of the Neonatal, Pediatric and Surgical Intensive care unit of the Erasmus MC-Sophia Children's hospital, for their support. We also thank Ko Hagoort (Erasmus MC, Rotterdam) for his careful editing.
Source of support: Nutricia Nederland BV, Zoetermeer, the Netherlands.

References

1. Motil KJ, Grand RJ, Davis-Kraft L, Ferlic LL, Smith EO. Growth failure in children with inflammatory bowel disease: a prospective study. Gastroenterology 1993;105:681-91.
2. Stettler N, Kawachak DA, Boyle LL, Propert KJ, Scanlin TF, Stallings VA, Zemel BS. A prospective study of body composition changes in children with cystic fibrosis. Ann N Y Acad Sci 2000;904:406-9.
3. Pollack MM, Wiley JS, Kanter R, Holbrook PR. Malnutrition in critically ill infants and children. J Parenter Enteral Nutr 1982;6:20-4.
4. Pollack MM, Wiley JS, Holbrook PR. Early nutritional depletion in critically ill children. Crit Care Med 1981;9:580-3.
5. Pollack MM, Ruttimann UE, Wiley JS. Nutritional depletions in critically ill children: associations with physiologic instability and increased quantity of care. J Parenter Enteral Nutr 1985;9:309-13.
6. Merritt RJ, Suskind RM. Nutritional survey of hospitalized pediatric patients. Am J Clin Nutr 1979;32:1320-5.
7. Agus MS, Jaksic T. Nutritional support of the critically ill child. Curr Opin Pediatr 2002;14:470-81.
8. van Lingen RA, van Goudoever JB, Luijendijk IH, Wattimena JL, Sauer PJ. Effects of early amino acid administration during total parenteral nutrition on protein metabolism in pre-term infants. Clin Sci (Lond) 1992;82:199-203.
9. Van Goudoever JB, Colen T, Wattimena JL, Huijmans JG, Carnielli VP, Sauer PJ. Immediate commencement of amino acid supplementation in preterm infants: effect on serum amino acid concentrations and protein kinetics on the first day of life. J Pediatr 1995;127:458-65.
10. Chwals WJ. Overfeeding the critically ill child: fact or fantasy? New Horiz 1994;2:147-55.
11. Coss-Bu JA, Klish WJ, Walding D, Stein F, Smith EO, Jefferson LS. Energy metabolism, nitrogen balance, and substrate utilization in critically ill children. Am J Clin Nutr 2001;74:664-9.
12. Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatrics 2001;107:270-3.
13. Carlson SJ, Ziegler EE. Nutrient intakes and growth of very low birth weight infants. J Perinatol 1998;18:252-8.
14. Fenton TR, McMillan DD, Sauve RS. Nutrition and growth analysis of very low birth weight infants. Pediatrics 1990;86:378-83.
15. Fitch CW, Neville J. Nutrient intake of infants hospitalized with lower respiratory tract infections. J Am Diet Assoc 2001;101:690-2.
16. Health Council of the Netherlands. Dietary Reference Intakes: energy, proteins, fats and digestible carbohydrates. The Hague: Health Council of the Netherlands, 2001; publication no. 2001/19.
17. Tsang RC, Lucas A, Uany R, Zlotkin S, editors. Nutritional needs of the preterm infant. Baltimore, MD: Williams &Wilkins; 1993.
18. Gerver W, De Bruin R. Paediatric Morphometrics: a reference manual. Utrecht: Bunge; 1996.

19. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47:316-23.
20. Usher R, McLean F. Intrauterine growth of live-born Caucasian infants at sea level: standards obtained from measurements in 7 dimensions of infants born between 25 and 44 weeks of gestation. J Pediatr 1969;74:901-10.
21. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988;16:1110-6.
22. The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. The International Neonatal Network. Lancet 1993;342:193-8.
23. Peto R, Pike M, Armitage P, Breslow N, Cox D, SV H, Mantel N, McPherson K, Peto J, Smith P. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. Br J Cancer 1977;35:1-39.
24. Briassoulis G, Venkataraman S, Thompson AE. Energy expenditure in critically ill children. Crit Care Med 2000;28:1166-72.
25. Pollack M. Nutritional support of children in the intensive care unit. In: Suskind R, Lewinter-Suskind L, editors. Textbook of pediatric nutrition. 2nd ed. New York: Raven Press, Ltd.; 1993. p. 207-216.
26. De Klerk G, Hop WC, De Hoog M, Joosten KF. Serial measurements of energy expenditure in critically ill children: useful in optimizing nutritional therapy? Intensive Care Med 2002;28:1781-5.
27. Goran MI, Peters EJ, Herndon DN, Wolfe RR. Total energy expenditure in burned children using the doubly labeled water technique. Am J Physiol 1990;259:E576-85.
28. Hulst J, Joosten K, Zimmermann L, Hop W, Van Buuren S, Büller H, Tibboel D, Van Goudoever J. Malnutrition in critically ill children: from admission to 6 months after discharge. Clin Nutr (in press) 2004.
29. McClave SA, Sexton LK, Spain DA, Adams JL, Owens NA, Sullins MB, Blandford BS, Snider HL. Enteral tube feeding in the intensive care unit: factors impeding adequate delivery. Crit Care Med 1999;27:1252-6.
30. De Beaux I, Chapman M, Fraser R, Finnis M, De Keulenaer B, Liberalli D, Satanek M. Enteral nutrition in the critically ill: a prospective survey in an Australian intensive care unit. Anaesth Intensive Care 2001;29:619-22.
31. De Jonghe B, Appere-De-Vechi C, Fournier M, Tran B, Merrer J, Melchior JC, Outin H. A prospective survey of nutritional support practices in intensive care unit patients: what is prescribed? What is delivered? Crit Care Med 2001;29:8-12.
32. Gemke RJ, Bonsel GJ. Comparative assessment of pediatric intensive care: a national multicenter study. Pediatric Intensive Care Assessment of Outcome (PICASSO) Study Group. Crit Care Med 1995;23:238-45.



Chapter 6

Routine biochemical screening is not useful in the nutritional assessment of critically ill children

Jessie M. Hulst, Johannes B. van Goudoever, Luc J.I. Zimmermann, Dick Tibboel, Koen F.M. Joosten

Submitted

Abstract

Aims

To determine whether abnormal values of routine laboratory parameters at admission predict outcome and changes in nutritional status in critically ill children during intensive care unit stay (ICU).

Study design

Prospective descriptive study in a tertiary multidisciplinary pediatric ICU. Serum urea, albumin, triglycerides, and magnesium were measured in samples obtained from 105 children (age 7d-16y) within the first 24 hours after admission. The prevalences of abnormalities in these parameters were assessed, as well as possible associations with outcome (length of stay, days on mechanical ventilation) and changes in nutritional status (changes in SD-scores for weight, mid upper arm and calf circumference) between admission and discharge.

Results

Prevalences of hypomagnesemia, hypertriglyceridemia, uremia, and hypoalbuminemia were 20, 25, 30, and 52%, respectively, with no significant associations between the different disorders. Except for uremia, no significant associations were found between abnormalities in biochemical parameters and changes in SD-scores of anthropometric measurements. Children with uremia showed larger declines in SD-scores for weight and arm circumference between admission and discharge than children without uremia did (median change in SD-scores for weight: -0.51 vs. -0.04 SD, $P < 0.05$; median change in SD-scores for arm circumference: -0.70 vs. -0.12; $P < 0.001$). Children with hypertriglyceridemia had longer ventilator dependency ($P < 0.01$) and length of stay ($P < 0.001$) than children with normal triglyceride levels on admission had.

Conclusions

Abnormalities in routine nutritional laboratory parameters were frequently noted in critically ill children at admission, but were not (strongly) predictive of changes in nutritional status between ICU admission and discharge.

Introduction

Malnutrition in the pediatric ICU population is a widely acknowledged problem, which may intensify underlying illnesses, increase the risk of complications and affect growth and development.[1,2] Nutritional assessment on admission to the ICU is necessary to identify children at risk and to guide nutritional support during intensive care stay. The repertoire of routine laboratory parameters includes several markers (e.g. albumin, urea, triglycerides, electrolytes) that can provide useful and easily obtainable information regarding nutritional status and requirements.[3] Abnormalities in these parameters reflect derangements in several metabolic pathways and may represent the severity of depletions occurring during critical illness. Previously we have shown the nutritional status of children admitted to an ICU to deteriorate during admission.[4] By determining these biochemical parameters we aim at identifying specific derangements that may be related to the development of malnutrition in the ICU.
So far, data are lacking on the usefulness of an initial biochemical screen on children's admission to the ICU as part of a comprehensive nutritional assessment including the implications for nutritional support and as a prognostic marker.
We set up a study to determine the prevalence of abnormalities in routinely available laboratory parameters related to nutritional status in critically ill children on admission to the ICU, and to investigate their usefulness in identifying children at risk of decline in nutritional status.

Methods and Materials

The children described in this study participated in a prospective observational study on different aspects of nutritional assessment. The primary clinical results of this comprehensive study, encompassing all children admitted to the neonatal and pediatric ICU of our hospital in a one-year-period (2001) for at least 48 hours, were published previously.[4] Patients aged > 7 days and < 18 years were eligible for this part of the study. We excluded preterm neonates, and also children in whom treatment was withheld or withdrawn. The institutional review board of the Erasmus MC approved the study protocol, and written (parental) informed consent was obtained before subjects entered the study (within the first 24 hours after admission).

Clinical parameters
Clinical data collected included age, sex, surgical status, days on mechanical ventilation, length of ICU-stay, and mortality. The patients were classified in five diagnostic groups as shown in table 1. The severity of illness on admission was assessed by the Pediatric Risk of Mortality Score (PRISM).[5]

Table 1 Patient characteristics (n = 105)*

Patient characteristics	
M:F	57:48 (54:46)
Age, y	0.8 (8 d-15.5 y)
Age groups	
Term neonates	19 (18)
Older children (> 30 d)	86 (82)
PRISM score	10 (0-31)
Length of stay, d†	6 (2-35)
Mechanical ventilation	68 (65)
Duration, d†	2 (0-35)
Surgery during ICU admission	45 (41)
Reason for ICU care	
Respiratory illness	37 (35)
Sepsis	16 (15)
Cardiac disease	21 (20)
Neurological/trauma	13 (12)
Other	18 (17)
Deceased during admission	7 (7)

**Values expressed as median (range) or numbers (percentage); †Excluding the deceased children.*

Blood samples and measurements

Blood samples were taken for urea, albumin, triglycerides, and magnesium within the first 24 hours after admission. Samples for all biochemical parameters could be obtained if an indwelling arterial line was present. Parameters could be missing for children in whom only a capillary blood puncture was possible. Exclusion criteria for the analysis of albumin included prior administration of hyperoncotic albumin solution (20%), fresh frozen plasma or pasteurized plasma solution. For the analysis of triglycerides, the administration of parenteral lipid emulsions was an exclusion criterion. Cut-off values were conform the levels used by our clinical laboratory. Hypomagnesemia was defined as a serum magnesium level < 0.76 mmol/l for neonates and < 0.70 mmol/L for infants and children. Hypertriglyceridemia was defined as a serum triglyceride concentration > 1.47 mmol/l. Uremia was defined as a serum urea level > 4.2 mmol/l for neonates and > 5.6 mmol/l for infants and children. Albumin concentrations < 35 mmol/l and < 25 mmol/l were used as cut-off values for hypoalbuminemia in children and neonates, respectively. For continuous analysis of the levels of the different parameters we adjusted for age by calculating the percentages of the lower limit (albumin, magnesium) or percentages of the upper limit (urea). All levels were determined on a routine clinical chemistry analyzer (Hitachi 912, Roche Diagnostics, Almere, the Netherlands).

Anthropometry

Weight, mid upper arm circumference (MUAC) and calf circumference (CC) were measured within 24 hours after admission, and at discharge from the ICU.

Measurements were performed according to the methods described for Dutch reference values.[6] Intra-observer and inter-observer studies performed prior to the study had shown good reproducibility of measurements with coefficients of variation < 3% for MUAC and CC. Measurements of weight, MUAC and CC were converted to standard deviation (SD) scores using recent Dutch reference standards.[7] The changes in SD-scores for weight-for-age (WFA-SDS), MUAC (MUAC-SDS) and CC (CC-SDS) between admission and discharge were calculated.

Statistical analysis

Results are expressed as median (range) unless specified otherwise. The Mann-Whitney U-test was used to compare levels of biochemical parameters between survivors and non survivors and to compare PRISM scores, outcome variables (length of stay, length of mechanical ventilation, death) and changes in anthropometric measurements between children with and without abnormalities in biochemical parameters. Spearman's correlation analysis was used to examine relationships between individual biochemical parameters and changes in SD-scores of anthropometric values. Chi-square tests (Pearson, Fisher-Exact, Exact) were used to determine differences in prevalence of abnormalities between the different diagnostic groups and different age groups, and relationships between the different abnormalities. A *P*-value < 0.05 was considered statistically significant.

Results

A total of 105 children were included in the analyses. Their characteristics are presented in Table 1**.** Seven of them died after a median stay in the PICU of 13.5 days (range 2-83).

Table 2 shows the prevalence of hypomagnesemia, hypertriglyceridemia, uremia, and hypoalbuminemia, together with the median values and range of parameters per age group. No significant associations between abnormalities in individual parameters were found. The group of children with hypoalbuminemia consisted predominantly of children older than 30 days (25 out of the 27 children with hypoalbuminaemia, $P < 0.01$). Significant differences for the prevalence of uremia were found between the five diagnostic groups ($P < 0.001$). Uremia was noted in 63% of children with sepsis and 60% of children with cardiac anomalies (9, 25 and 13% for respiratory disease, trauma/neurological problems, and other diagnoses, respectively).

Table 2 Median level of biochemical parameters within the first 24-h after admission and prevalence of abnormal values.

	n	Concentrations within first 24 h on ICU*	Normal reference	Prevalence of abnormal values† (%)
Magnesium, mmol/l	**76**	**0.81 (0.40-1.21)**		15 (20)
Neonates (0-30 d)	12	0.81 (0.67-0.99)	0.76-1.17	
Age > 30 d	64	0.81 (0.40-1.21)	0.70-0.95	
Albumin, g/l	**52**	**32 (20-49)**		27 (52)
Neonates (0-30 d)	14	32 (20-35)	25-30	
Age > 30 d	38	32 (20-49)	35-50	
Urea, mmol/l	**99**	**3.8 (0.9-24)**		30 (30)
Neonates (0-30 d)	17	3.4 (1.0-11.2)	1.7-4.2	
Age > 30 d	82	3.9 (0.9-24)	2.6-5.6	
Triglycerides, mmol/l	**55**	**0.94 (0.14-2.51)**	< 1.47	14 (25)

**Values expressed as median (range); †rows correspond to hypomagnesemia, hypoalbuminaemia, uremia, hypertriglyceridemia, respectively.*

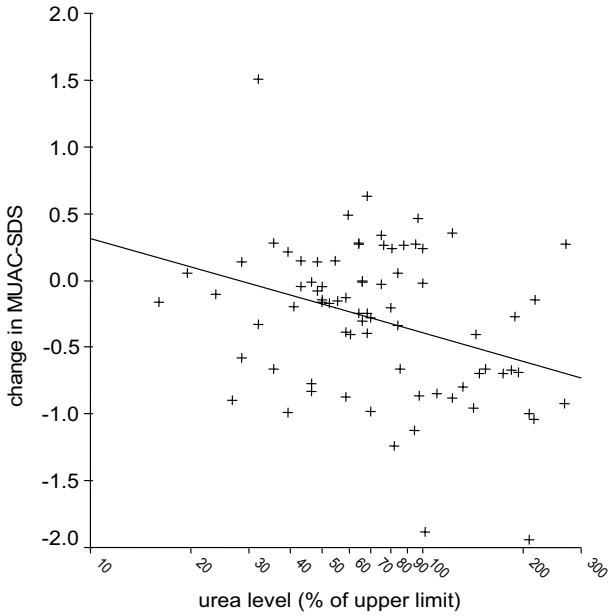
Severity of illness and outcome

Children with uremia had a median PRISM score of 18 (0-31), which was significantly higher (P < 0.001) than that in children without uremia (9 (0-27)). Children with hypertriglyceridemia had a significantly higher PRISM score (P < 0.05), longer duration of mechanical ventilation (P < 0.01) and length of ICU-stay (P < 0.001) than children with no hypertriglyceridemia. No significant relationships were found for albumin, urea and magnesium level and the number of days on mechanical ventilation or length of ICU stay. The seven children who died had a significantly higher median PRISM score (P < 0.001) and urea level (P < 0.05) on admission than the survivors.

Relation with nutritional status

Median changes in WFA-SDS, MUAC-SDS and CC-SDS between admission and discharge were -0.15 SD (range: -1.6-2.06), -0.18 SD (range: -1.94-1.51) and -0.15 SD (range: -1.78-1.81), respectively. Urea level was significantly negatively correlated to the change in MUAC-SDS between admission and discharge (r_s = -0.28, P = 0.013) (Figure 1). Furthermore, those children with uremia showed larger declines in WFA-SDS and MUAC-SDS between admission and discharge than children without uremia (median change in WFA-SDS: -0.51 vs. -0.04 SD, P < 0.05; median change in MUAC-SDS: -0.70 vs. -0.12; P < 0. 001). No relationships were found between abnormalities of the other biochemical parameters on admission and changes in nutritional anthropometric parameters from admission to discharge.

Figure 1 Relationship between urea level at admission (expressed as the percentage of the upper limit) and change in MUAC-SDS between admission and discharge.



Discussion

In order to minimize the deterioration of children's nutritional status during ICU-admission, it would be helpful if those at risk could be identified at admission, so that nutritional care could be tailored to their (individual) needs. Routine laboratory parameters may possibly serve as easily obtainable indicators.[3]
In the present study we found considerable proportions of abnormalities in biochemical parameters routinely used for initial screening of pediatric ICU patients. Except for urea, however, none of these were predictive of changes in nutritional status as assessed by changes in anthropometric measurements during ICU admission. Apart from hypertriglyceridemia, no relationships were found between levels of these nutritional parameters and outcome variables such as length of ICU-stay and duration of mechanical ventilation.

Considerable proportions of abnormal levels of albumin, urea and magnesium on admission were also found in previous studies in critically ill adults and children.[8-13] To our knowledge, abnormalities in fasting triglyceride level have not been reported before. So far, determination of serum triglycerides only served to check for parenteral nutrition-

associated hypertriglyceridemia and to monitor safety of parenteral fat administration.[14-16] With regard to the clinical consequences of the abnormal levels, it is obvious that low levels of albumin and magnesium will be treated. It is questionable, however, whether high levels of urea and triglycerides on admission to the ICU will modify nutritional support strategies.

Furthermore, several other metabolic parameters, which may not be measured easily in plasma, will show high prevalences of abnormalities as well. For example, hypomagnesemia is strongly associated with hypokalemia and hypocalcemia.[17-20] and low levels of phosphorus, selenium, zinc and manganese are also commonly found in critical illnesses.[21] It might be postulated that combinations of those unidentified and untreated deficiencies may delay recovery, as they all play key roles in many of the metabolic processes that promote recovery from critical illness.[21] While this study revealed hypertriglyceridemia to be related with poorer outcome variables, previous studies in critically ill adults and children revealed associations between hypoalbuminemia[8,9,22] and hypomagnesemia[19,23-25] with increased likelihood of mortality, morbidity, prolonged ventilator dependency, and prolonged ICU and hospital stay. Perhaps the fact that most children in our study were treated (data not shown) explains why we did not find any association between hypoalbuminemia or hypomagnesemia and outcome variables. The clinical significance of the association between hypertriglyceridemia and length of stay and duration of mechanical ventilation still has to be determined. Yet our data suggest that it may just reflect a higher severity of illness , a finding that was also observed in adult intensive care patients.[26]

Serum urea levels can indicate the degree of catabolic stress and level of protein breakdown associated with illness, surgery or trauma.[3] In this study we demonstrated that children with high urea levels on admission had larger declines in SD-scores for weight-for-age and mid upper arm circumference (indicating loss of muscle mass) during ICU-stay than children with low urea levels on admission had. However, we must take into account that factors such as impaired renal function, dehydration, polyuria or severe sweating on admission may cause increased urea levels. The children with sepsis or cardiac anomalies in this study showed the highest prevalences of uremia, which can be explained both from the degree of catabolism and the degree of impairment of renal function.

As none of the other laboratory parameters were related to changes in anthropometric measurements, we conclude that, the panel of parameters we used does not seem to be very useful for prediction of growth in critically ill children at the end of ICU admission.

The limitations of our study should be noted. First, although it represents an analysis of prospectively collected data, the fact that our study protocol did not allow us to obtain all biochemical parameters in all children might have led to selection bias with overrepresentation of the more severely ill children. As they usually have indwelling arterial lines, blood samples are easier to obtain from these children. Furthermore,

although all were severely ill, the heterogeneity of our study population might explain the lack of associations. Some of the parameters studied could well be useful in more specific diagnostic groups. Second, we did not correct for possible other factors, such as use of medication, acidosis, gastro-intestinal losses, which may influence the levels of the different biochemical parameters. Third, because of the limited number of children we did not examine the usefulness of combinations of different routine biochemical and anthropometric data (prognostic score) in predicting outcome and changes in nutritional status during ICU-admission, as has been done in some adult studies.[27-29]

In conclusion, this study showed that, although frequently abnormal, the levels of the routinely available biochemical parameters albumin, triglycerides and magnesium were not associated with changes in nutritional status during admission. The clinical importance of the found associations between uremia and changes in anthropometric parameters and those between hypertriglyceridemia and outcome parameters has to be evaluated in future studies.

Acknowledgements

The authors would like to acknowledge the research nurses Ineke van Vliet, Marjan Mourik, Marianne Maliepaard, Ada van den Bos, and Annelies Bos for their assistance in data-collection. We also thank Wim C.J. Hop (Department of Epidemiology and Biostatistics, Erasmus MC, Rotterdam, the Netherlands) for his statistical advice and Ko Hagoort (Erasmus MC, Rotterdam) for his careful editing.

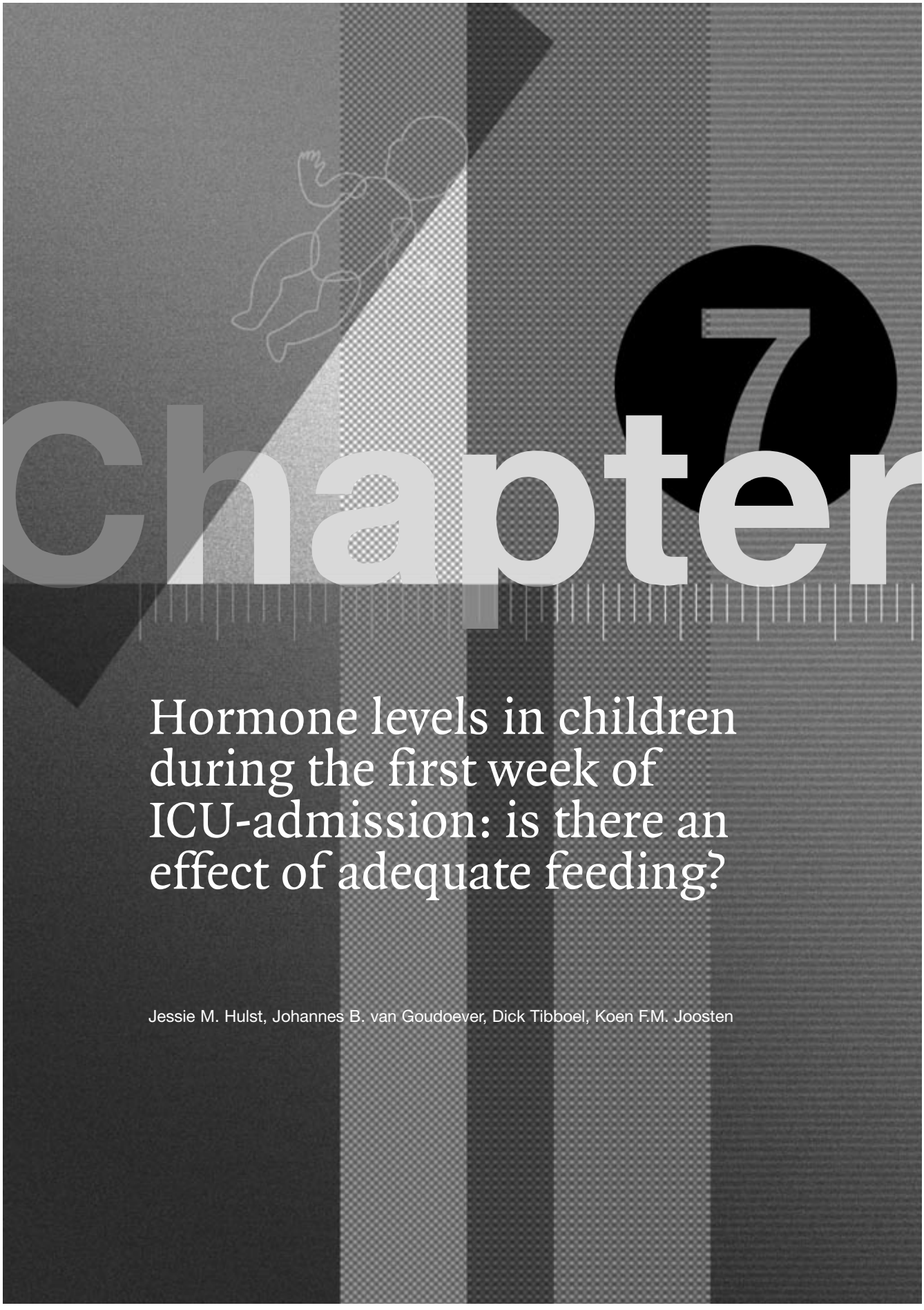
Source of Support: Nutricia Nederland BV, Zoetermeer, the Netherlands.

References

1. Pollack MM, Ruttimann UE, Wiley JS. Nutritional depletions in critically ill children: associations with physiologic instability and increased quantity of care. JPEN J Parenter Enteral Nutr 1985;9:309-13.
2. Pollack MM, Smith D. Protein-energy malnutrition in hospitalized children. Hosp Formul 1981;16:1189-90, 1192-3.
3. Selberg O, Sel S. The adjunctive value of routine biochemistry in nutritional assessment of hospitalized patients. Clin Nutr 2001;20:477-85.
4. Hulst J, Joosten K, Zimmermann L, Hop W, Van Buuren S, Büller H, Tibboel D, Van Goudoever J. Malnutrition in critically ill children: from admission to 6 months after discharge. Clin Nutr (in press) 2004.
5. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988;16:1110-6.
6. Gerver W, De Bruin R. Paediatric Morphometrics: a reference manual. Utrecht: Bunge; 1996.
7. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47:316-23.
8. Vincent JL, Dubois MJ, Navickis RJ, Wilkes MM. Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. Ann Surg 2003;237:319-34.
9. Durward A, Mayer A, Skellett S, Taylor D, Hanna S, Tibby SM, Murdoch IA. Hypoalbuminaemia in critically ill children: incidence, prognosis, and influence on the anion gap. Arch Dis Child 2003;88:419-22.
10. Verive MJ, Irazuzta J, Steinhart CM, Orlowski JP, Jaimovich DG. Evaluating the frequency rate of hypomagnesemia in critically ill pediatric patients by using multiple regression analysis and a computer-based neural network. Crit Care Med 2000;28:3534-9.
11. Deshmukh CT, Rane SA, Gurav MN. Hypomagnesaemia in paediatric population in an intensive care unit. J Postgrad Med 2000;46:179-80.
12. Fiser RT, Torres A, Jr., Butch AW, Valentine JL. Ionized magnesium concentrations in critically ill children. Crit Care Med 1998;26:2048-52.
13. Chernow B, Smith J, Rainey TG, Finton C. Hypomagnesemia: implications for the critical care specialist. Crit Care Med 1982;10:193-6.
14. Deutschman CS. Nutrition and metabolism in the critically ill child. In: Rogers, editor. Pediatric Intensive Care; 1997. p. 1109-1131.
15. Park W, Paust H, Schroder H. Lipid infusion in premature infants suffering from sepsis. JPEN J Parenter Enteral Nutr 1984;8:290-2.
16. Llop J, Sabin P, Garau M, Burgos R, Perez M, Masso J, Cardona D, Sanchez Segura JM, Garriga R, Redondo S, Sagales M, Ferrer D, Pons M, Vuelta M, Fabregas X, Vitales M, Casasi, n T, Marti,

nez J, Morato L, Soler M. The importance of clinical factors in parenteral nutrition-associated hypertriglyceridemia. Clin Nutr 2003;22:577-583.

17. Whang R, Ryder KW. Frequency of hypomagnesemia and hypermagnesemia. Requested vs routine. Jama 1990;263:3063-4.
18. Ryzen E, Wagers PW, Singer FR, Rude RK. Magnesium deficiency in a medical ICU population. Crit Care Med 1985;13:19-21.
19. Rubeiz GJ, Thill-Baharozian M, Hardie D, Carlson RW. Association of hypomagnesemia and mortality in acutely ill medical patients. Crit Care Med 1993;21:203-9.
20. Salem M, Munoz R, Chernow B. Hypomagnesemia in critical illness. A common and clinically important problem. Crit Care Clin 1991;7:225-52.
21. Demling RH, DeBiasse MA. Micronutrients in critical illness. Crit Care Clin 1995;11:651-73.
22. Rady MY, Ryan T. Perioperative predictors of extubation failure and the effect on clinical outcome after cardiac surgery. Crit Care Med 1999;27:340-7.
23. Chernow B, Bamberger S, Stoiko M, Vadnais M, Mills S, Hoellerich V, Warshaw AL. Hypomagnesemia in patients in postoperative intensive care. Chest 1989;95:391-7.
24. Soliman HM, Mercan D, Lobo SS, Melot C, Vincent JL. Development of ionized hypomagnesemia is associated with higher mortality rates. Crit Care Med 2003;31:1082-7.
25. Munoz R, Laussen PC, Palacio G, Zienko L, Piercey G, Wessel DL. Whole blood ionized magnesium: age-related differences in normal values and clinical implications of ionized hypomagnesemia in patients undergoing surgery for congenital cardiac disease. J Thorac Cardiovasc Surg 2000;119:891-8.
26. Lind L, Lithell H. Impaired glucose and lipid metabolism seen in intensive care patients is related to severity of illness and survival. Clin Intensive Care 1994;5:100-5.
27. Mullen JL, Buzby GP, Waldman MT, Gertner MH, Hobbs CL, Rosato EF. Prediction of operative morbidity and mortality by preoperative nutritional assessment. Surg Forum 1979;30:80-2.
28. Buzby GP, Williford WO, Peterson OL, Crosby LO, Page CP, Reinhardt GF, Mullen JL. A randomized clinical trial of total parenteral nutrition in malnourished surgical patients: the rationale and impact of previous clinical trials and pilot study on protocol design. Am J Clin Nutr 1988;47:357-65.
29. Ingenbleek Y, Carpentier YA. A prognostic inflammatory and nutritional index scoring critically ill patients. Int J Vitam Nutr Res 1985;55:91-101.



Chapter 7

Hormone levels in children during the first week of ICU-admission: is there an effect of adequate feeding?

Jessie M. Hulst, Johannes B. van Goudoever, Dick Tibboel, Koen F.M. Joosten

Abstract

Background & Aims
To evaluate the course of hormonal parameters in relation to clinical parameters, illness severity and nutritional intake in children admitted to the pediatric ICU during the first week of admission.

Methods
Prospective, observational study. Levels of triiodothyronine (T_3), reverse T_3 (rT_3), ratio T_3/rT_3 and insulin-like growth factor I (IGF-1) were evaluated in 84 critically ill children (50 term neonates and 34 children aged 32 d-15 y) admitted to our multidisciplinary tertiary pediatric intensive care unit within 24 hours after admission, on day 4 and day 6 after admission. Changes in hormones levels over time were related to illness severity, C-reactive protein-levels and the adequacy of feeding.

Results
For both age groups IGF-1 levels remained low until day 4, but at day 6 IGF-1 levels were significantly higher than admission level. In 88 and 89% of the older children, T_3 levels remained below normal at day 4 and 6, respectively. In both age groups, rT_3 levels declined significantly over time, whereas the ratio T_3/rT_3 increased. The increases in IGF-1, T_3 and ratio T_3/rT_3 and decrease in rT_3 were significantly associated with decreases in CRP-levels. No significant relations were found between changes in IGF-1 and thyroid hormone levels during admission and the adequacy of energy and protein intake.

Conclusions
During the first week of ICU-admission, abnormalities in levels of IGF-1, T_3 and rT_3 were frequently observed in critically ill children, especially in the children aged > 1 month. The adequacy of feeding did not seem to affect the normalization of IGF-1 and thyroid hormone levels.

Introduction

Critical illness leads to a spectrum of metabolic and neuroendocrine changes which comprise the metabolic stress response. Alterations in the GH-IGF-1 axis and hypothalamic-pituitary-thyroid axis have been described in studies of critically ill adult and pediatric patients.[1-5]
Studies in critically ill patients concerning the GH-IGF-1 axis revealed augmented basal GH levels with reduced oscillatory activity, low GH-binding capacity, and low serum levels of IGF-1, a combination interpreted as a GH-resistant state.[6]
The multiple alterations in the thyroid axis seen both in adults and children with critical illness have been described as the 'low T_3 syndrome' or 'euthyroid sick syndrome' or 'nonthyroidal illness syndrome (NTIS)'.[4,7-9] The hallmark of this syndrome is a decrease in circulating T_3 with a reciprocal increase in reverse T_3 (rT_3), the inactive metabolite of thyroxin, in patients with nonthyroidal illness. There remains much controversy regarding the precise etiology but several mechanisms have been proposed.[10,11]

In critically ill adult patients the alteration in thyroid hormone levels was found to be partly due to the caloric deprivation associated with severe illness.[12] Furthermore, a number of studies have demonstrated marked increases in rT_3 and decreases in T_3 levels during short-term fasting and long-term deficient diets.[13-15] In healthy adults and children[16] or children with stable or chronic disease[17-19] the IGF-1 concentration is regulated by energy and protein intake. This relationship was not supported by a study among children undergoing cardiac surgery[20] that found no relationship between nitrogen balance and IGF-1.

Furthermore, the magnitude of changes in the GH-IGF-1 axis and hypothalamic-pituitary-thyroid axis associated with critical illness reflect the severity of metabolic stress.[21] The magnitude of stress may be established by measuring the plasma concentrations of counter regulatory hormones and by acute phase proteins such as C-reactive protein.[22]
An increase in anabolic hormones can be expected when the acute stress response has come to a halt and further on when the nutritional status improves. No studies in critically ill children have been performed in which IGF-1 or thyroid hormones were assessed over a prolonged period in relation to nutritional intake.
The present study was undertaken to evaluate the serum levels of IGF-1, T_3 and rT_3 during the first 6 days of ICU-admission in a mixed cohort of critically ill children and to relate these levels to severity of illness parameters and nutritional intake. We hypothesized that illness would suppress anabolic hormone levels but that in due course with decreasing illness severity and increasing nutritional intake hormone levels would return to normal values.

Materials and methods

Subjects

The subjects described in this study took part in a nutritional assessment study performed in 2001 among children admitted to our level III multidisciplinary pediatric / surgical ICU with an expected stay of at least 48 hours.[23] Exclusion criteria for this study were treatment with Extra Corporeal Membrane Oxygenation (ECMO), withholding/withdrawing treatment, and inclusion into a nutritional intervention study. The institutional review board of the Erasmus MC approved the study protocol, and written informed consent was obtained from parents before entering the study. Only those children were included in whom

1. blood samples for hormonal parameters could be collected during the first 24h after admission and possibly on day 4 and 6 after admission by means of an indwelling arterial line or when a blood drawing could be combined with a scheduled vena puncture, and
2. complete nutritional intake data were available.

Preterm neonates were excluded. Clinical data collected included age, gender, (birth) weight, gestational age, primary diagnosis, surgical status, days on mechanical ventilation, and length of ICU-stay. The patients were grouped into 2 age categories: term neonates (gestational age ≥ 37 wk; age 0-30 d) and older children (age > 30 d).
The severity of illness on admission was assessed by the pediatric risk of mortality score (PRISM).[24] The level of C-reactive protein was assessed as a parameter of metabolic stress, and use of dopamine was also evaluated due to its potential effect on thyroid hormone levels.[25]

Hormone assays

Plasma T_3 and reverse T_3 (rT_3) were measured by established radioimmunoassay procedures as previously described[26,27] and levels were expressed as nmol/L. From the values of T_3 and rT_3 the ratio T_3/rT_3 was calculated. Within-assay CV's were 2-6% for T_3 and 3-4% for rT_3, whereas between-assay CV's were 8% for T_3, and 9-16% for rT_3. Age-specific reference values obtained by our laboratory were used for comparison. IGF-I was measured using an immunometric technique on an Advantage Chemiluminescense System (Nichols Institute Diagnostics, San Juan Capistrano, USA) in the laboratory of Utrecht Medical Center, Utrecht, The Netherlands. The lower limit of detection was 6.0 ng/mL and inter-assay variation was 8,7; 5,8 and 6,5% at mean IGF-I plasma levels of 33; 174 and 445 ng/l, respectively (n = 115). This method is comparable to the RIA used in previous studies.[28] The levels of plasma total IGF-1 were expressed as nmol/L and converted to SD-scores. Due to the lack of reference values for children younger than 6 months of age, the IGF-1 values of these children were compared to levels of children aged 6 months.

Nutritional intake

The children were enterally and/or parenterally fed on the guidance of the current feeding protocol and the judgment of the physician clinically responsible for the individual child, independent of the study. During the first 12-24 hours a glucose infusion was given. Fluid and electrolyte intakes were adjusted to individual requirements. For neonates the amount of enteral or parenteral feeding was increased postnatally in accordance with increasing fluid intake until the amount of ≥ 150-180 ml/kg.d at day 7 of life. If enteral feeding could not be started on the second day after admission, parenteral feeding was started within 24-48 h after admission according to standard hospital practice (Intralipid® 20%, Fresenius, 's Hertogenbosch, the Netherlands; Primene® 10% (body weight ≤ 5kg), Clintec Baxter, Clintec Benelux N.V., Brussel, Belgium; Aminovenös N-paed® 10% (body weight > 5 kg), Fresenius, 's Hertogenbosch, the Netherlands). On the first day of parenteral feeding the amount of protein and fat was 50% of the aimed intake (1-2.4 g/kg.d and 2-4 g/kg.d, respectively, depending on age). Enteral feeding was started as soon as possible in all children, either continuously or intermittently with a nasogastric tube (drip or bolus) or nasoduodenal tube (drip) with human milk or standard formula according to parents' preference (Nutrilon Premium for children aged < 1 month; Nutrison Pediatric Standard in children aged 1 month-1 year; Nutrison Multi Fibre in children aged > 1 year, Nutricia, Zoetermeer, The Netherlands). Actual daily nutritional intake was determined by patient intake/output records and compared to the recommended daily allowances (RDA) for age and sex for healthy children.[29] For each day the ratio intake/RDA was calculated and mean ratios up to day 4 and up to day 6 of admission were determined. These mean ratios express the adequacy of feeding. The weight at admission was used for all calculations on energy and protein intake throughout the study period.

Statistical analyses

Results are expressed as mean ± SEM except when indicated otherwise. Logarithmic transformations were applied to normalize variables and minimize the influence of outliers, when appropriate. Longitudinal analysis of the hormone, including the comparison of mean values, allowing for missing data, was performed using repeated measures analysis of variance (PROC MIXED, SAS, Cary, NC) on the 2 subsets based upon age.

The relationship between various clinical parameters and hormone levels at admission was examined with regression analysis. Variables initially tested for association in univariate regression analysis included age, gender, gestational age, (birth) weight, severity of illness (PRISM), and dopamine use. Variables associated with the dependent variable in the univariate analysis ($P < 0.05$) were entered in a stepwise linear regression with backward elimination. Linear regression analysis was also used to examine the relationship between changes in hormone levels and CRP levels from admission to day 4 or day 6 after admission and for the relationship of changes in

hormone levels and adequacy of feeding up to day 4 and day 6. These analyses were performed for both age groups separately. A two-tailed *P*-value < 0.05 was considered to indicate statistical significance.

Results

The study group consisted of 84 children – 50 term neonates and 34 children older than 1 month — of whom the clinical characteristics and diagnoses are shown in Table 1. Altogether, 155 hormonal assays were obtained; 84 within the first 24 hours, 47 at day 4 and 24 at day 6 after admission, with a median of 2 per child (range 1-3).
Table 2 shows the mean values of the hormone levels for the 2 age groups at the 3 time points, as calculated by repeated measures analyses, and a graphical interpretation is given in Figure 1 and 2.

Table 1 Patient characteristics and diagnoses

Patient characteristics (n = 84)		
M:F	n (%)	44:40
Age groups		
Term neonates (n)	n (%)	50
Gestational age, wk	Median (range)	40 (37-42)
Age, d	Median (range)	0.5 (0-28)
Older children (n)	n (%)	34
Age, y	Median (range)	0.6 (32 d-15.2y)
PRISM score	Median (range)	15 (0-38)
Length of ICU-stay, d	Median (range)	6.5 (2-314)
Mechanical ventilation	n (%)	73
Duration, d	Median (range)	3.5 (0-53)
Surgery	n (%)	31
Dopamine use (1st 24h, day 4, day 6)		
Term neonates	n (%)	10 (20), 12 (39), 5 (33)
Older children	n (%)	7 (21), 1 (6), 2 (22)
Diagnostic groups*		
Congenital malformations	n (%)	22 (26)
Respiratory illness†	n (%)	19 (23)
Postnatal problems‡	n (%)	16 (19)
Post-operative monitoring	n (%)	11 (13)
Sepsis or meningitis	n (%)	13 (15)
Other	n (%)	3 (4)

*PRISM = Pediatric Risk of Mortality, CRIB = Clinical Risk Index for Babies; *Most prominent diagnosis; †includes pneumonia, rs-bronchiolitis; ‡includes asphyxia, meconium aspiration, infection.*

Table 2 Values of IGF-1, IGF-1 SDS, T_3, rT_3, and T_3/rT_3 ratio for the 2 age groups at the 3 time points*

	First 24H	Day 4	Day 6
Term neonates	(n = 50)	(n = 31)	(n = 15)
IGF-1 (nmol/l)	2.00 ± 0.19	2.20 ± 0.25	2.64 ± 0.37
IGF-1 SDS	-2.77 ± 0.18	-2.54 ± 0.26	-2.13 ± 0.36
T_3 (nmol/l)	1.17 ± 0.11	1.28 ± 0.12	1.40 ± 0.16
rT_3 (nmol/l)	2.10 ± 0.14	1.46 ± 0.09	1.31 ± 0.13
Ratio T_3/rT_3	0.56 ± 0.07	0.83 ± 0.08	1.08 ± 0.12
Older children	(n = 34)	(n = 16)	(n = 9)
IGF-1 (nmol/l)	4.12 ± 0.48	4.25 ± 0.63	6.52 ± 1.23
IGF-1 SDS	-1.97 ± 0.26	-1.98 ± 0.25	-0.95 ± 0.36
T_3 (nmol/l)	0.72 ± 0.08	1.14 ± 0.14	1.27 ± 0.19
rT_3 (nmol/l)	1.09 ± 0.09	0.79 ± 0.06	0.58 ± 0.08
Ratio T_3/rT_3	0.66 ± 0.10	1.37 ± 0.18	1.98 ± 0.29

*IGF-1 = insulin growth factor-1, T_3 = triiodothyronine, rT_3 = reverse T_3, SDS = standard deviation score; *All values expressed as mean ± SEM, as derived from repeated measures analyses.*

IGF-1 - term neonates

Admission

The multivariate analysis of variance revealed that in the term neonates, weight at admission was significantly positively related to IGF-1 concentration ($P < 0.001$, $R^2 = 0.30$,). Dopamine administration, CRP concentration and PRISM score were not associated with IGF-1 levels (absolute and SD-scores) on admission.

Time course

Levels did not increase between the first 24 h after admission and day 4, but at day 6 IGF-1 levels were significantly higher than in the first 24 h after admission. SD-scores of IGF-1 were below -2 in 69, 64, 60% of neonates within 24 hours after admission, on day 4 and day 6, respectively.

Change in hormone levels

Univariate analysis showed that the increase in IGF-1 level between admission and day 6 was significantly associated with a decrease in CRP-level ($P = 0.004$, $R^2 = 0.63$).

IGF-1 – older children

Admission

In the older children age was significantly positively correlated with the IGF-1 level at admission ($P < 0.001$, $R^2 = 0.48$). No associations were found between IGF-1 levels (absolute and as SDS) and dopamine use, CRP or PRISM score.

Time course

IGF-1 levels did not increase between the first 24 h after admission and day 4, but at day 6 IGF-1 levels were significantly higher than in the first 24 h after admission. On all assessment days, IGF-1 levels were significantly higher than those of the term neonates, but SD-scores of IGF-1 were below -2 in 42, 43, 49% of children within 24 hours after admission, on day 4 and day 6, respectively.

Change in hormone levels

No association was found between changes in CRP levels and IGF-1 levels between admission and later days.

Thyroid hormones - term neonates

Admission

Post-conceptual age was significantly positively associated with levels of T_3 (P = 0.006, R^2 = 0.15) and T_3/rT_3 ratio (P < 0.001, R^2 = 0.29), and negatively with rT_3 (P = 0.007, R^2 = 0.15). No differences were found in absolute hormone levels in children with and without continuous dopamine administration. Furthermore, CRP concentration or PRISM score were not associated with levels of T_3, rT_3 or T_3/rT_3 ratio.

Figure 1 Course of IGF-1 level during the first week of admission for the 2 age groups.
**indicates significant difference compared to admission level, †indicates significant difference compared to day 4.*

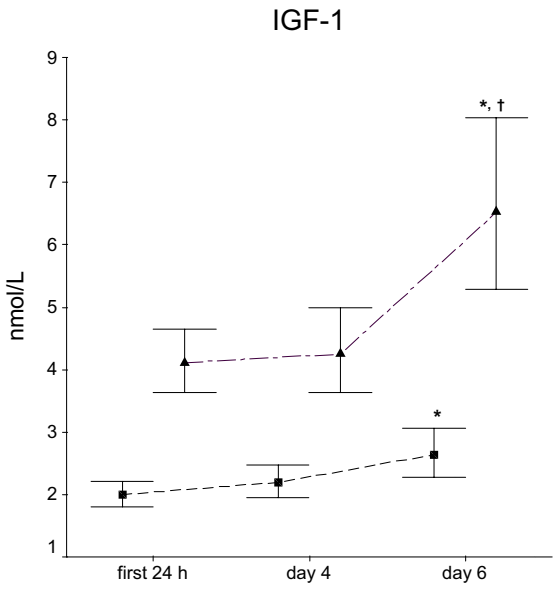
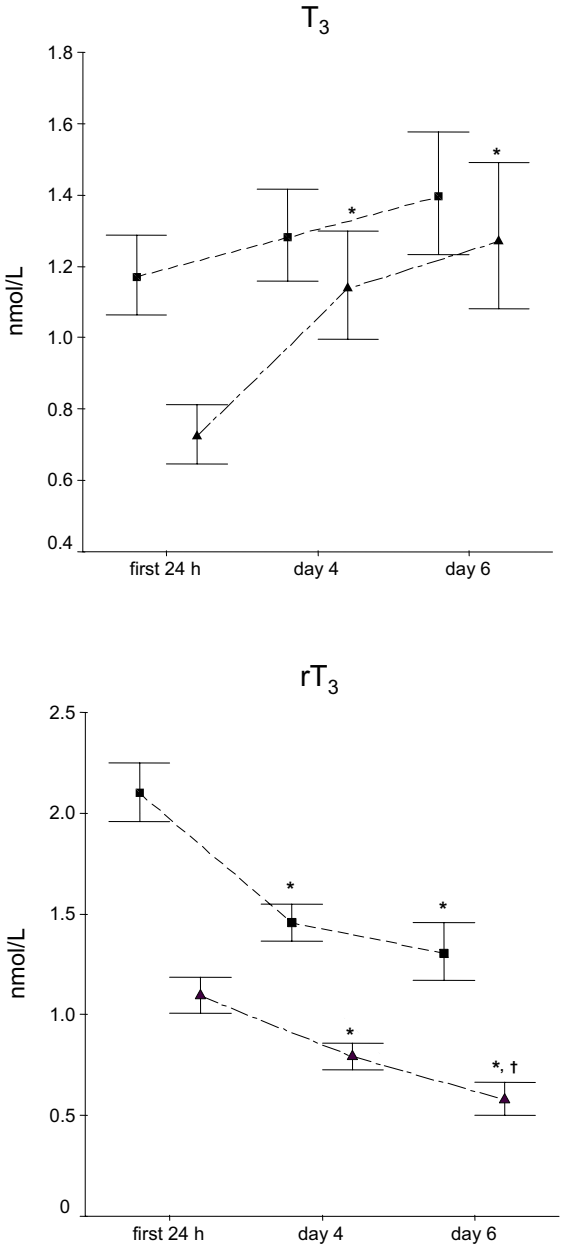
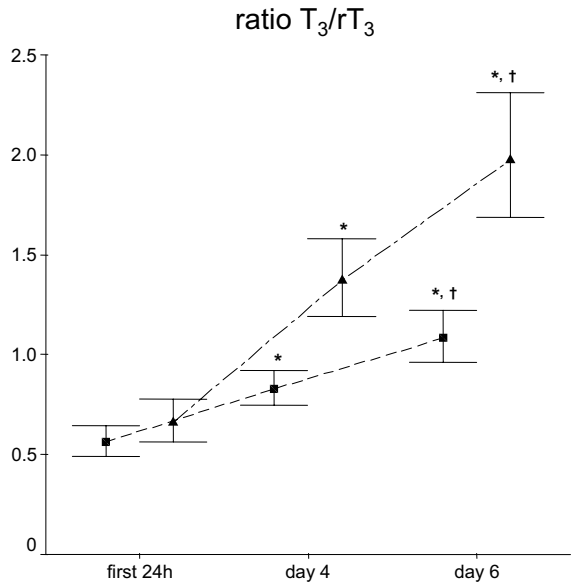


Figure 2 Course of T_3, rT_3 and the ratio T_3/rT_3 during the first week of admission for the 2 age groups. **indicates significant difference compared to admission level, † indicates significant difference compared to day 4.*





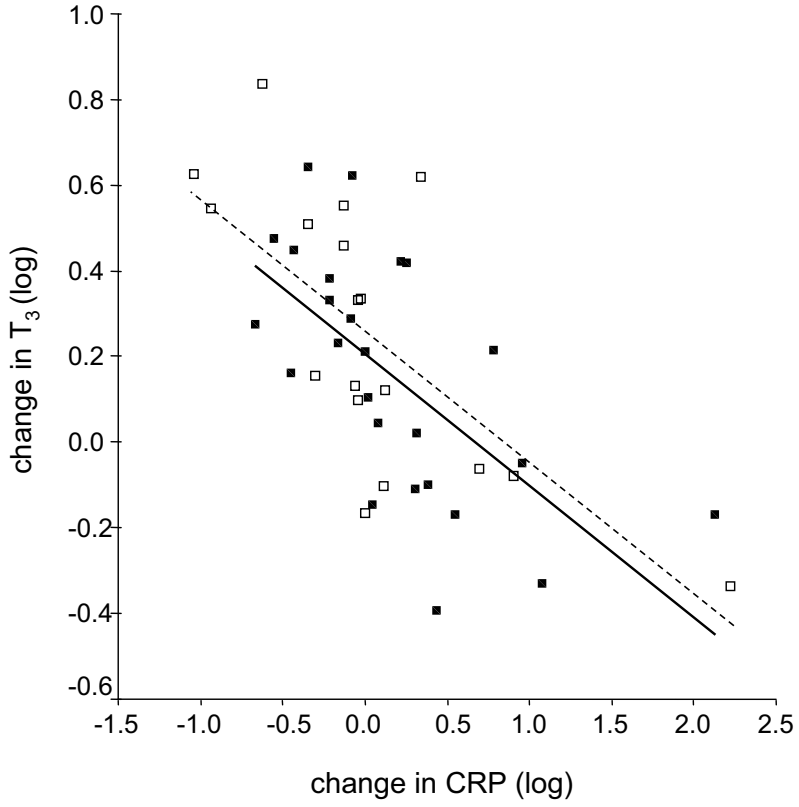
Time course

For T_3 levels, no significant changes occurred between the various days, whereas levels of rT_3 decreased significantly from admission to day 4 ($P < 0.001$) and from admission to day 6 ($P < 0.001$). Concentrations of rT_3 were significantly higher than those of the older children during the total study period. A total of 8%, 10% and 7% of children had a T_3 level below the lower limit of normal within the first 24 h, on day 4 and day 6, respectively. For rT_3 13%, 3% and 0% of children had levels above the upper limit of normal within the first 24 h, on day 4 and day 6, respectively, whereas the ratio T_3/rT_3 was below the lower limit of normal in 4%, 3% and 7% of children respectively.

Change in hormone levels

Significant inverse relationships were found between changes in CRP levels and changes in T_3 between admission and day 6 ($P = 0.004$, $R^2 = 0.67$) and the change in ratio T_3/rT_3 between admission and day 4 or day 6 ($P = 0.002$, $R^2 = 0.58$ and $P = 0.013$, $R^2 = 0.56$). Furthermore a decrease in rT3 between admission and day 4 was significantly associated with a decrease in CRP–level ($P = 0.004$, $R^2 = 0.52$) (Figure 3).

Figure 3 Relationship between change in T_3 levels and CRP levels between admission and day 4 and admission and day 6 for the total group.
Data points (day 4 = closed squares; day 6 = open squares) with fitted regression lines (thick line: change between admission and day 4; dashed line: change between admission and day 6) for the 2 study days; data were analyzed using ANOVA.



.

Thyroid hormones - older children

Admission

A high PRISM score was associated with lower levels of T_3/rT_3 ratio (P = 0.037), and higher levels of rT_3 (P = 0.009). Children who received dopamine had a significantly lower T_3 and T_3/rT_3 level (P = 0.004 and P = 0.01). Furthermore, CRP level was associated with low T_3 levels (P = 0.004) and low levels of the T_3/rT_3 ratio (P = 0.001).

Time course

A significant increase in T_3 was found on day 4 (P = 0.001) and day 6 (P = 0.004) after admission when compared to admission level. A total of 79%, 88% and 89% of children had a T_3 level below the lower limit of normal within the first 24 h, on day 4 and day 6,

respectively. Levels of rT_3 decreased significantly from admission to day 4 ($P < 0.001$) and from admission to day 6 ($P < 0.001$) and were found to be above the upper limit of normal in 74%, 63% and 22% of children within the first 24 h, on day 4 and day 6, respectively. The ratio T_3/rT_3 was below the lower limit of normal in 71%, 69% and 56% of children within the first 24 h, on day 4 and day 6, respectively.

Change in hormone levels
A significant inverse relationship was found between changes in CRP levels and changes in T_3 between admission and day 4 ($P = 0.025$, $R^2 = 0.44$).

Relation with adequacy of feeding
In the term neonates, the mean ratios of intake/RDA up to day 4 and 6 were 55% and 69% for energy and 72% and 82% for protein, respectively. For the older children, these percentages were respectively 61 and 67% for energy and 72% and 89% for protein. Overall, taking into account the different age groups and different days, no significant relations were found between changes in T_3, rT_3, ratio T_3/rT_3 and IGF-1 levels from admission to day 4 or day 6 and the adequacy of energy and protein intake up to day 4 and 6 respectively.

Discussion

In this study we showed that in children older than 1 month the thyroid hormone and IGF-1 levels changed significantly during the first week after ICU-admission but levels remained abnormal in the majority of the children. The hormonal changes were significantly related to changes in levels of CRP but not related to nutritional intake. In neonates, IGF-1 levels remained low and thyroid hormone levels changed less markedly than in older children.
We tried to evaluate whether thyroid hormone and IGF-1 levels could be used as parameters to signal the turning point from catabolism to anabolism eventually in relation with feeding adequacy. In our study older children showed significantly changes in the hormonal levels but still on day 6 decreased levels of T_3 and IGF-1 (respectively in 89% and 49% of children) were seen. This might indicate that in those children, who are still admitted to an ICU on day 6, the stress response is still not resolved and return to anabolism is not completed in most of these children. Interestingly we found a significant relation in changes of thyroid hormones and changes in CRP level. One could speculate that the recovery of the acute stress response is expressed by the decline in CRP level, which dictates the changes in thyroid hormone and IGF-1 levels more than adequacy of feeding in the first week after ICU-admission. Our finding of decreased levels of IGF-1 in the first week of admission was also observed in previous studies of children who underwent cardiac surgery[20,30] and decreased levels of IGF-1 coincided with increased

levels of CRP.[30] In contrast to the results we found in children, Richmand et al[12] found a link between the adequacy of feeding and thyroid hormones in critically ill adults. In this study hormone levels of groups of patients with the same illness severity, but different feeding regimes (dextrose or total parenteral nutrition) were compared, which made it possible to unravel the effects of adequate nutrition and stress on hormone levels.

Concerning the neonates, we found less markedly changes in levels of thyroid hormones and IGF-1. Compared to normal reference values, only a minority of neonates showed abnormal levels of thyroid hormones whereas levels of IGF-1 were low in almost half of the neonates. An important reason for the little changes in thyroid hormones in neonates could be due to the fact that thyroid levels can vary greatly in the first weeks after birth; rT_3 is initially high after birth and will decrease to "reference values of older children" 2-4 weeks after birth.[31] For T_3, levels are low at birth, show a manifold peak during the first hours after birth, a further sustained increase during the first days of life, followed by a slight decrease to normal prepubertal values in the first weeks. For this reason the use of detecting levels of thyroid hormones in relation with follow-up and adequacy of feeding will be very limited in neonates. The use of IGF-1 in relation to adequacy of feeding was previously studied in premature infants.[19] Serum IGF-1 correlated strongly with length of gestation, day since birth and with calorie and protein intake. In our group of term neonates weight was positively related with IGF-1 but there was not a relation with adequacy of feeding. As also reported in young infants who underwent cardiac surgery,[20,30] IGF-1 levels hardly changed in the first week of admission and remained low, while in this group of neonates a significant negative relationship between levels of CRP and IGF-1 and thyroid hormones was observed. One can speculate that especially in the neonate the resumption of growth, which coincides with increased levels of IGF-1, will only occur if there is complete restoration of anabolism. The period of our study was too short to draw further conclusions concerning this speculation.

There are some limitations with respect to the study population and study design that should be discussed. Firstly, SD-scores for IGF-1 for children less than 6 months of age were calculated with reference data from children with an age of 6 months, which might have influenced the interpreting of results. Secondly, this study was not designed to investigate the hormonal changes with various nutritional intake regimes. Therefore the influence of the adequacy of nutrition on the normalization of hormone levels in critically ill children should further be evaluated in a prospective randomized controlled trial with different feeding regimen that has to go beyond the first week of admission. Lastly, a larger study population is needed to investigate the independent effect of various clinical parameters, e.g. nutrition, pain, dopamine use, and illness severity, on the course of hormone levels during ICU-admission. As such, our study provides baseline data in a limited group of critically ill newborns and children on the hormonal stress response.

These data should be interpreted in line with other data from our group in post-operative children 0-3 years of age.[32]

In conclusion, this study showed that after one week of ICU-admission, levels of IGF-1 remained low in all children, whereas abnormalities in thyroid hormone levels were found in the majority of children older than 1 month. Furthermore, we showed that adequate feeding did not affect the changes in hormone levels occurring between admission and later days.

Acknowledgements

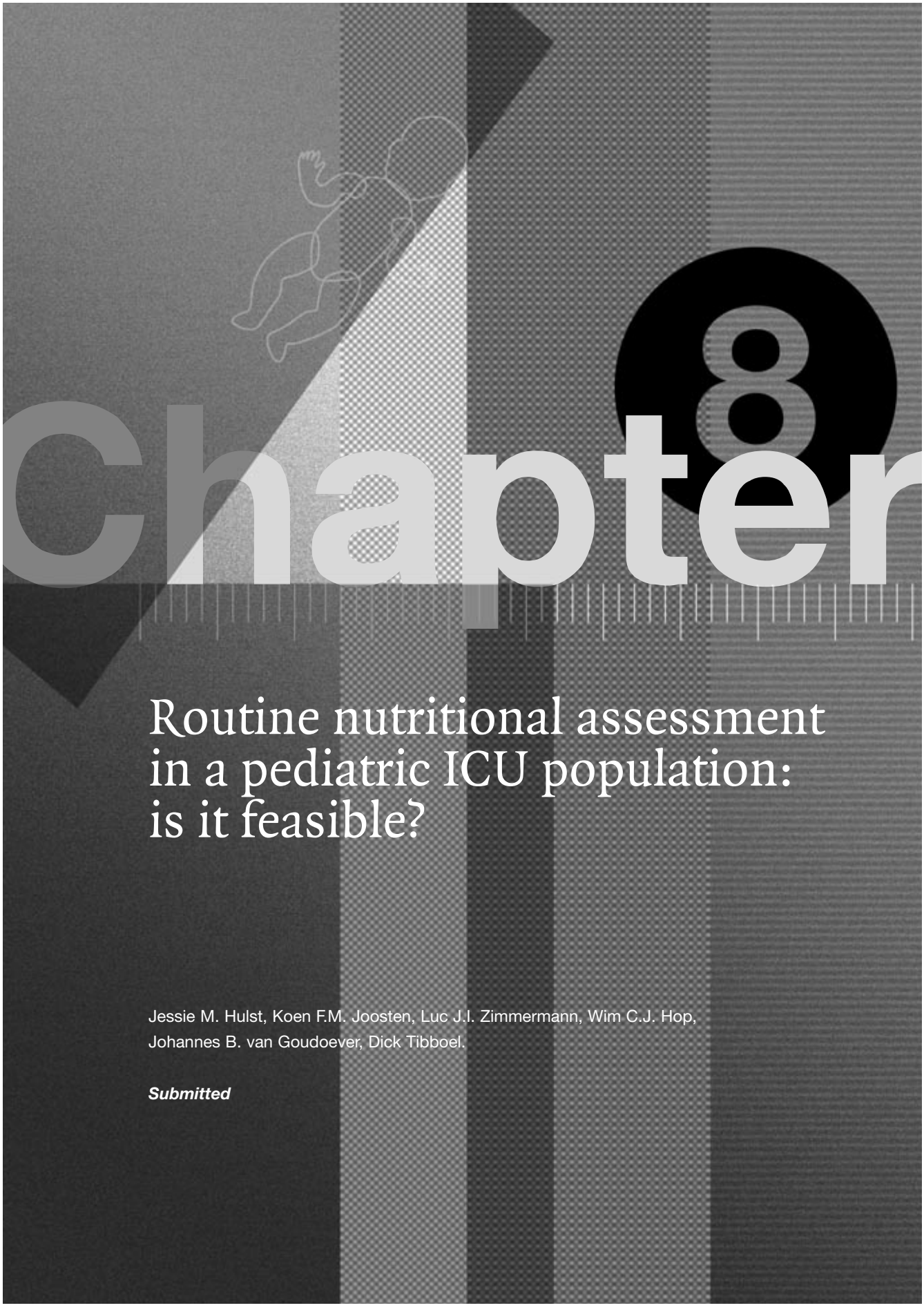
The authors thank Ada van den Bos, Annelies Bos, Marianne Maliepaard, Marjan Mourik and Ineke van Vliet for their great help with data. Furthermore, our gratitude goes out to the nursing and medical staff of the Neonatal, Pediatric and Surgical Intensive care unit of the Erasmus MC-Sophia Children's hospital, for their support. We also thank Wim C.J. Hop (Department of Epidemiology and Biostatistics, Erasmus MC, Rotterdam, the Netherlands) for his statistical advice and Ko Hagoort (Erasmus MC, Rotterdam) for his careful editing.
Partly supported by: Nutricia Nederland BV, Zoetermeer, The Netherlands.

References

1. Frayn KN, Price DA, Maycock PF, Carroll SM. Plasma somatomedin activity after injury in man and its relationship to other hormonal and metabolic changes. Clin Endocrinol (Oxf) 1984;20:179-87.
2. Van den Berghe G. Novel insights into the neuroendocrinology of critical illness. Eur J Endocrinol 2000;143:1-13.
3. De Groof F, Joosten KF, Janssen JA, de Kleijn ED, Hazelzet JA, Hop WC, Uitterlinden P, van Doorn J, Hokken-Koelega AC. Acute stress response in children with meningococcal sepsis: important differences in the growth hormone/insulin-like growth factor I axis between nonsurvivors and survivors. J Clin Endocrinol Metab 2002;87:3118-24.
4. Zucker AR, Chernow B, Fields AI, Hung W, Burman KD. Thyroid function in critically ill children. J Pediatr 1985;107:552-4.
5. Uzel N, Neyzi O. Thyroid function in critically ill infants with infections. Pediatr Infect Dis 1986;5:516-9.
6. Ross R, Miell J, Freeman E, Jones J, Matthews D, Preece M, Buchanan C. Critically ill patients have high basal growth hormone levels with attenuated oscillatory activity associated with low levels of insulin-like growth factor-I. Clin Endocrinol (Oxf) 1991;35:47-54.
7. Chopra I. Nonthyroidal illness syndrome or euthyroid sick syndrome? Endocr Pract 1996;2:45-52.
8. Hashimoto H, Igarashi N, Yachie A, Miyawaki T, Sato T. The relationship between serum levels of interleukine-6 and thyroid hormone in children with acute respiratory infection. J Clin Endocrinol Metab 1994;78:288-291.
9. Matthews DS, Aynsley-Green A, Matthews JN, Bullock RE, Cooper BG, Eyre JA. The effect of severe head injury on whole body energy expenditure and its possible hormonal mediators in children. Pediatr Res 1995;37:409-17.
10. De Groot LJ. Dangerous dogmas in medicine: the nonthyroidal illness syndrome. J Clin Endocrinol Metab 1999;84:151-64.
11. Docter R, Krenning EP, de Jong M, Hennemann G. The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism. Clin Endocrinol (Oxf) 1993;39:499-518.
12. Richmand DA, Molitch ME, TF OD. Altered thyroid hormone levels in bacterial sepsis: the role of nutritional adequacy. Metabolism 1980;29:936-42.
13. Merimee TJ, Fineberg ES. Starvation-induced alterations of circulating thyroid hormone concentrations in man. Metabolism 1976;25:79-83.
14. Carlson HE, Drenick EJ, Chopra IJ, Hershman JM. Alterations in basal and TRH-stimulated serum levels of thyrotropin, prolactin, and thyroid hormones in starved obese men. J Clin Endocrinol Metab 1977;45:707-13.
15. Visser TJ, Lamberts SW, Wilson JH, Docter R, Hennemann G. Serum thyroid hormone concentrations during prolonged reduction of dietary intake. Metabolism 1978;27:405-9.

16. Smith WJ, Underwood LE, Clemmons DR. Effects of caloric or protein restriction on insulin-like growth factor-I (IGF-I) and IGF-binding proteins in children and adults. J Clin Endocrinol Metab 1995;80:443-9.
17. Merimee T, Zapf J, Froesch E. Insulin-like growth factor factors in the fed and fasted states. J Clin Endocrinol Metab 1982;55:999-1002.
18. Clemmons DR, Underwood LE, Dickerson RN, Brown RO, Hak LJ, MacPhee RD, Heizer WD. Use of plasma somatomedin-C/insulin-like growth factor I measurements to monitor the response to nutritional repletion in malnourished patients. Am J Clin Nutr 1985;41:191-8.
19. Smith WJ, Underwood LE, Keyes L, Clemmons DR. Use of insulin-like growth factor I (IGF-I) and IGF-binding protein measurements to monitor feeding of premature infants. J Clin Endocrinol Metab 1997;82:3982-8.
20. Balcells J, Moreno A, Audi L, Roqueta J, Iglesias J, Carrascosa A. Growth hormone/insulin-like growth factors axis in children undergoing cardiac surgery. Crit Care Med 2001;29:1234-8.
21. Rothwell PM, Lawler PG. Prediction of outcome in intensive care patients using endocrine parameters [see comments]. Crit Care Med 1995;23:78-83.
22. Chwals WJ, Fernandez ME, Jamie AC, Charles BJ. Relationship of metabolic indexes to postoperative mortality in surgical infants. J Pediatr Surg 1993;28:819-22.
23. Hulst J, Joosten K, Zimmermann L, Hop W, Van Buuren S, Büller H, Tibboel D, Van Goudoever J. Malnutrition in critically ill children: from admission to 6 months after discharge. Clin Nutr (in press) 2004.
24. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988;16:1110-6.
25. Van den Berghe G, de Zegher F, Lauwers P. Dopamine suppresses pituitary function in infants and children. Crit Care Med 1994;22:1747-53.
26. Visser T, Docter R, Hennemann G. Radioimmunoassay of reverse tri-iodothyronine. J Endocr 1977;73:375-396.
27. Bauer A, Wilson J, Lamberts S, Docter R, Hennemann G, Visser T. Handling of iodothyronines by the liver and kidney in patients with chronic liver disease. Acta Endocrinol (Copenh) 1987;116:339-346.
28. Rikken B, van Doorn J, Ringeling A, Van den Brande JL, Massa G, Wit JM. Plasma levels of insulin-like growth factor (IGF)-I, IGF-II and IGF-binding protein-3 in the evaluation of childhood growth hormone deficiency. Horm Res 1998;50:166-76.
29. Health Council of the Netherlands. Dietary Reference Intakes: energy, proteins, fats and digestible carbohydrates. The Hague: Health Council of the Netherlands, 2001; publication no. 2001/19.
30. Leite HP, Fisberg M, Vieira JGH, De Carvalho WB, Chwals WJ. The role of insulin-like growth factor 1, growth hormone, and plasma proteins in surgical outcome of children with congenital heart disease. Pediatr Crit care Med 2001;2:29-35.
31. Fisher D, Klein A. Thyroid development and disorders of thyroid function in the newborn. N Engl J Med 1981;304:702-712.

32. Bouwmeester NJ, Anand KJ, van Dijk M, Hop WC, Boomsma F, Tibboel D. Hormonal and metabolic stress responses after major surgery in children aged 0-3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine. Br J Anaesth 2001;87:390-9.



Chapter 8

Routine nutritional assessment in a pediatric ICU population: is it feasible?

Jessie M. Hulst, Koen F.M. Joosten, Luc J.I. Zimmermann, Wim C.J. Hop, Johannes B. van Goudoever, Dick Tibboel.

Submitted

Abstract

Objective
To assess the feasibility of routinely performing nutritional assessment using non-invasive methods in critically ill children.

Design
Prospective observational study

Setting
Level III multidisciplinary pediatric surgical intensive care unit (ICU).

Patients
All consecutively admitted neonates and children with an ICU-stay of ≥ 48 hours in 2001.

Measurements and main results
The feasibility of anthropometric measurements (weight, length, circumferences of mid upper arm and calf, skinfolds of biceps and triceps, and knee-heel length), bio-electrical impedance analysis (BIA) and indirect calorimetry was assessed by a research team within 24 hours after admission in all children, and in children with an ICU-stay ≥ 7 d also at various moments during admission and at discharge. The frequency in which each measurement could be performed and could be interpreted as reliable (by subjective assessment) was determined and reasons for inability/unreliability were obtained. A total of 316 children were included comprising 784 measuring moments.
Anthropometric and BIA measurements were reliably obtained in 56-91% of children, depending on the moment and type of measurement. Indirect calorimetry could be performed in 70-80% of eligible children. Most common reasons for measurements to be impossible or unreliable were instability/pain, agitation, and presence of edema or bandages/tubes/splints that hindered measurements. Furthermore, measurements were more difficult to obtain with increasing illness severity, increasing age and during the earlier stages of admission.

Conclusions
Reliable assessment of nutritional status using non-invasive methods is possible in daily pediatric ICU practice, but is unfortunately less feasible in the most seriously ill children, the ones who might benefit the most from it. Implementation of a standardized nutritional assessment strategy can help to individualize patient care.

Introduction

Studies have demonstrated that acute and/or chronic protein-energy malnutrition (PEM) is present in 15-24% of children admitted to an intensive care unit (ICU).[1-3] Since malnutrition may predispose patients to a wide variety of complications and negatively affects body composition and growth,[4,5] it is clinically important to identify the children who suffer from PEM or are at risk of developing PEM. This is one of the goals of nutritional assessment. The other two goals are to quantify the risk of developing malnutrition-related medical complications and to monitor the adequacy of nutritional therapy.[6] In many ICUs, however, malnutrition is not recognized and nutritional assessment has not become a routine procedure because of vague responsibilities, low priority, lack of equipment, insufficient knowledge and lack of procedures or guidelines.[7,8]

For nutritional assessment to become routine in critically ill children, minimally invasive, easily obtainable, and reliable instruments are needed that can be used at the bed-side. Of the numerous available nutritional assessment tools for assessing body composition, anthropometry seems currently the best option as a routine tool, although inter-rater variability and changes in the child's hydration status may limit data interpretation.[9,10] Apart from these limitations, anthropometry can provide a good overall evaluation of nutritional status when performed by trained individuals and by comparing the anthropometric measurements to appropriate reference standards, which are widely available.[11,12] A relatively newer rapid, non-invasive, and portable technique to measure body composition is bio-electrical impedance analysis (BIA). BIA has previously been studied in the ICU setting for the evaluation of total body water in neonates[13] and children after cardiac surgery,[14] and of body composition changes in critically ill adult patients.[15] Individual energy expenditure and feeding adequacy can be monitored with indirect calorimetry measurements. Indirect calorimetry can be performed at the bed-side, provided several inclusion criteria are fulfilled.[16]

Although practical and methodological limitations have been described for each technique in general,[10,17,18] no data are available that quantify the feasibility of these measurements as an element of routine nutritional assessment in a pediatric ICU population.
The primary aim of this study was to quantify the feasibility of routinely performing non-invasive nutritional assessment measurements (anthropometry, BIA, and indirect calorimetry) in daily practice in a heterogeneous group of children admitted to the neonatal and pediatric ICU. Furthermore, we tried to identify common pitfalls and limitations in the routine use of the different methods.

Patients and methods

The data described in this study were obtained from a prospective observational nutritional assessment study in children admitted during the year 2001 to our level III multidisciplinary neonatal and pediatric/ surgical ICU with a length of stay (LOS) of at least 48 hours.[3] The overall study investigated several methods for assessing nutritional status including anthropometric measurements, bioelectrical-impedance analysis (BIA), indirect calorimetry, biochemical parameters and stable isotope studies. Exclusion criteria were withholding or withdrawing of treatment, inclusion into a nutritional intervention study, and treatment with Extra Corporeal Membrane Oxygenation (ECMO). Written parental informed consent was obtained in all children and the institutional review board of Erasmus MC approved the study protocol.

In this paper we focus on the feasibility of routinely performing the non-invasive methods: anthropometry, BIA-measurements and indirect calorimetry. In the overall assessment study, these measurements were scheduled to be performed, if possible, once within 24 hours after admission, every other day during the first 2 weeks and weekly thereafter (except head circumference and length). Head circumference was scheduled to be measured on admission in all children and weekly in children < 2 y. Length measurements were planned at admission for all children and every other week in children aged < 2 y. A reassessment was scheduled at discharge for all anthropometric parameters (except length, and head circumference) and BIA. When discharge followed within 24 hours of an earlier assessment, measurements were not repeated and the previous assessment was interpreted as the discharge assessment.
Using this measurement scheme, we analysed the feasibility of performing measurements within 24 hours after admission to the ICU in all children, and on day 6, 14, 21 and 28 after admission (follow-up) and in the last 24 h before discharge from the ICU in all children with a LOS ≥ 7 days. For the indirect calorimetry measurements, we evaluated the feasibility during the first 48 hours instead of the first 24 hours after admission.
Six observers carried out the measurements, after intensive training and having reached good reproducibility (intra-observer and inter-observer variability) of the individual measurements with coefficients of variation < 0.6% for knee-heel length, < 3% for circumferences of mid-upper arm and calf, and < 7% for skinfolds of biceps and triceps. On each measurement day, they carried out a subjective clinical assessment evaluating the presence of generalized edema and edema at the different measurement sites (head, arms, legs). Reasons for inability to perform measurements and reasons for possible unreliability of the measurements were recorded and ranked according to frequency. Only those measurements interpreted as reliable were recorded as successful measurements. The feasibility of each type of measurement was expressed as the percentage of successful attempts on each assessment moment.

Anthropometry

Each assessment included measurements of weight (W), supine length (L), mid-upper arm circumference (MUAC), and calf circumference (CC) in all children, skinfolds of biceps (BSF) and triceps (TSF) in children with a weight > 1000 g, and knee-heel length (KHL, knemometry) in children < 2 y. Measurements were performed at the times the child was nursed, according to the methods described by Gerver and de Bruin,[19] except for knemometry. Weight measurements were performed by the nursing staff conform standard protocol. Supine length was measured to the nearest 0.1 cm using a calibrated instrument suitable for measurements in the incubator or hospital bed. KHL, which is a parameter for short-term linear growth,[20] was measured in children < 2 y using an electronic knemometer with a digital display and a resolution of 0.01 mm. The mean of 5 separate readings was taken as outcome.

BIA

Bio-electrical impedance analysis was conducted using the tetrapolar single frequency, phase-sensitive impedance analyzer (STA/BIA Soft Tissue Analyser®, Akern-RJL Systems, Florence, Italy). The instrument applies a 50-kHz oscillating current of 800 μA and is connected to surface electrodes placed on the child's wrist and ankle.

Indirect calorimetry

Indirect calorimetry measurements were performed either in respiratory or canopy mode – depending on the child's need for mechanical ventilation – using the Deltatrac II MBM-200 (Datex Division Instrumentarium, Helsinki, Finland) metabolic monitor. The properties of the Deltatrac metabolic monitor have been described previously.[21]

The following inclusion criteria had to be satisfied for indirect calorimetry in ventilated children:

a. mechanical ventilation with a Servo ventilator 300 (Siemens-Elema, Solna, Sweden);
b. inspired oxygen fraction (FiO_2) less than 60%;
c. tube leakage < 10% (considered not to significantly affect the measurements; determined by comparing inspired and expired tidal volumes measured by the ventilator assuming an absence of air leaks in the patient-ventilator circuit);[22]
d. hemodynamically stable condition (within 2 SD of age-related values for blood pressure and heart rate.[23]

In non-ventilated children, those receiving supplementary oxygen were excluded from indirect calorimetry because of the technical hitches involved. According to our protocol, measurements had to last at least 2 h in ventilated children and at least 20 minutes in non-ventilated children. Placed in an airtight transparent plastic canopy, the latter group was either sleeping or quietly resting in supine position and had not been exposed to diagnostic or therapeutic procedures in the previous 30 minutes.

Table 1 Patient characteristics and diagnostic information (n = 316).

Patient characteristics		
M:F	n (%)	176:140 (56:44)
Age groups		
Preterm neonates	n (%)	112 (35%)
Gestational age	Median (range), wk	31.2 (25-36.7)
Postconceptional age	Median (range), wk	31.4 (25-41.1)
Term neonates	n (%)	102 (32%)
Gestational age	Median (range), wk	39.7 (37-42.1)
Postconceptional age	Median (range), d	40 (37-44.6)
Older children	n (%)	102 (32%)
Age	Median (range), y	1.4 (31 d-17 y)
PRISM (n = 204)	Median (range)	11 (0-38)
CRIB (n = 84)	Median (range)	3 (0-16)
Length of stay*	Median (range), d	7 (2-314)
Mechanical ventilation	n (%)	231 (73)
Duration*	Median (range), d	3 (0-53)
Surgery	n (%)	100 (32)
Diagnostic groups[†]		
Prematurity / dysmaturity	n (%)	89 (28)
Congenital anomalies	n (%)	72 (23)
Post-operative monitoring	n (%)	46 (15)
Respiratory illness[‡]	n (%)	42 (13)
Postnatal problems[§]	n (%)	25 (8)
Sepsis or meningitis	n (%)	23 (7)
Other	n (%)	19 (6)
Mortality	n (%)	19 (6)

*CRIB = Clinical Risk Index for Babies; PRISM = Pediatric Risk of Mortality. *Deceased children excluded; [†]Most prominent diagnoses; [‡]Includes pneumonia, rs-bronchiolitis; [§]Includes asphyxia, meconium aspiration, infection.*

Clinical data

We recorded the child's sex, age, gestational age, birth weight, surgical status, severity of illness, duration of mechanical ventilation, and LOS. The patients were classified into three age groups: preterm neonates (gestational age < 37 weeks), term neonates (0-30 days) and older children (> 30 days). Patients were also classified by diagnosis into seven categories (Table 1). The severity of illness on admission was assessed by the Clinical Risk Index for Babies (CRIB) in preterm neonates (score range 0-76),[24] and the Pediatric Risk of Mortality (PRISM) score in the term neonates and older children (score range 0-23).[25]

Statistical analyses

All values are described as median and range or as frequencies. Paired percentages were compared using the McNemar test (dichotomous variables). The Mann Whitney U test or Chi-square test were used to assess differences in clinical parameters (age,

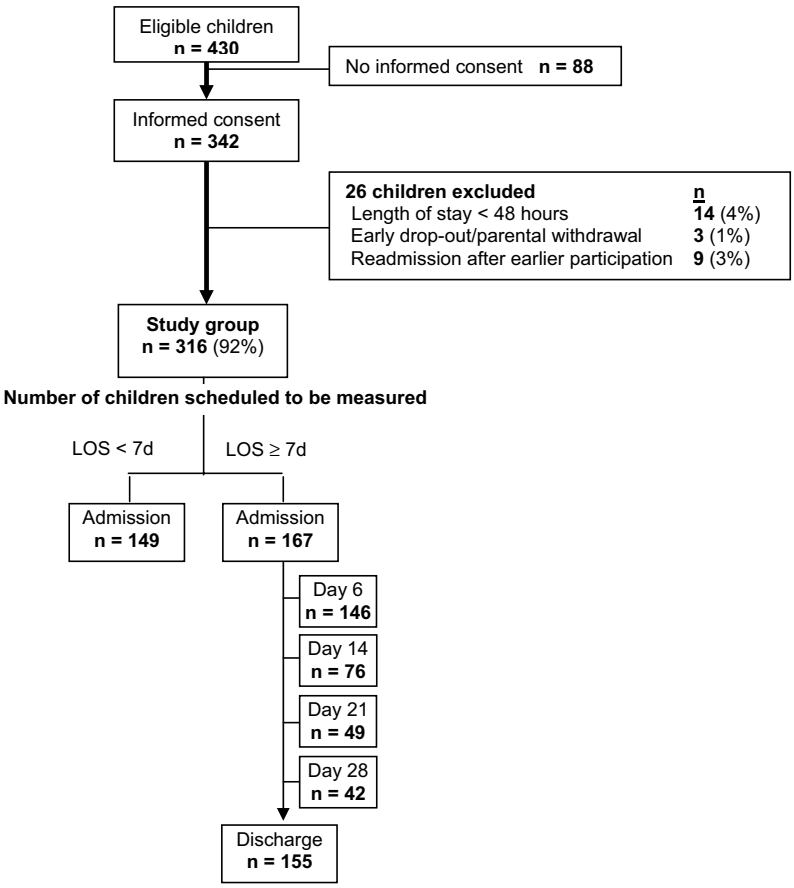
weight, gestational age, PRISM, CRIB, duration of mechanical ventilation, LOS, and diagnostic group) between children in whom measurements could or could not be obtained. We considered *P*-values < 0.05 to be statistically significant.

Results

Patients

Of the 342 children included in our nutritional assessment study,[3] 316 children (92%) comprised the final study group (Figure 1). Patient characteristics, admission information, and diagnoses are shown in Table 1. Altogether, 784 assessment moments were identified. The numbers of children to be measured at admission, discharge and follow-up assessments are shown in figure 1.

Figure 1 Flowchart of the study population



Anthropometry

The frequencies in which each anthropometric measurement could be performed and was interpreted as reliable (by subjective assessment) out of those planned at admission, during the follow-up measurements and at discharge are shown in Table 2.

Table 2 Feasibility of obtaining anthropometric measurements and BIA-measurements at different moments during admission expressed as the percentage of performed and reliable measurements out of all scheduled measurements.

	At admission (n = 316)		**During follow-up (n = 313)‡**		**At discharge (n = 155)**	
	P*	R*	P	R	P	R
W	84 (85)	81 (80)	81 (69-96)	72 (56-91)	89	88§
L†	82 (78)	81 (77)	86 (83-88)	84 (81-87)	91	91
HC†	85 (80)	76 (69)	85 (79-92)	76 (72-82)	93	89§
MUAC	89 (86)	76 (68)	92 (86-93)	77 (71-84)	85	82§
BSF†	86 (82)	74 (66)	86 (78-92)	74 (69-81)	82	79§
TSF†	86 (81)	74 (65)	86 (78-85)	74 (69-81)	81	78§
CC	91 (87)	77 (68)	91 (86-94)	79 (75-86)	85	82§
KHL†	82 (78)	73 (68)	88 (84-92)	82 (78-87)	79	75
BIA	74 (65)	-	84 (81-88)	-	80§	-

P = percentage performed, R = percentage reliable, W = weight, L = length, HC = head circumference, MUAC = mid upper arm circumference, BSF = biceps skinfold, TSF = triceps skinfold, CC = calf circumference, KHL = knee-heel length, BIA = bio-electrical impedance analysis.
**Percentages for children with LOS ≥ 7d in parentheses; †Total number of planned measurements is different from numbers above columns (see methods); ‡Follow-up consists of day 6, 14, 21, and 28 after admission, mean % and ranges given for these days; §Significant difference when compared to percentage of (reliable) measurements at admission in children with LOS ≥ 7 d.*

Differences in feasibility between admission and discharge for the children with a LOS ≥ 7 days are indicated for each individual measurement. On day 6, feasibility percentages were the lowest, especially for weight (56%) and skinfolds (69%). Overall, the different anthropometric measurements showed comparable feasibilities, with the skin fold and KHL assessments showing the lowest rates. In those children without a reliable weight measurement (n = 59) on admission, at least one of the other anthropometric measurements could be obtained in 90% of children. Frequencies ranged from 48-69% depending on the type of measurement (e.g. 48% for KHL, 56% for skinfolds, 69% for CC). In the children aged < 2 y, KHL measurements were less feasible than length measurements at admission (73 vs. 84%, $P < 0.001$), but equally feasible at the later assessments.

In 10% (n = 75) of moments no measurements, or no measurements in addition to weight measurements performed by nurses, could be obtained. Most of these missed assessments were recorded at admission (n = 27) and at discharge (n = 24).

The main reasons for inability to perform the measurements or unreliability of the outcome, subdivided into general reasons and reasons related to the child's clinical status or to the specific measurements are described and ranked in Table 3.

Table 3 Reasons for measurements to be not performed or interpreted as unreliable

	Measurements influenced	First 24h	Day 6-28	Discharge
Related to the child's condition				
Too unstable/painful	All measurements	++	+	-
Too agitated	L, KHL, SF	-	+	+
Edema (generalized or focal)	W, MUAC, CC, SF, KHL	+	+	-
Skin lesions	SF, BIA	+	+/-	+/-
Minimal handling (preterm neonates)	W	-	+	-
Logistic problems				
Hindrance of measurement*	L, HC, KHL, MUAC, CC, SF, BIA	+	+	-
Child cannot be measured with ordinary tools†	W, L	+	+	+
Devise not functional	BIA	+/-	+/-	+/-
General reasons				
No opportunity/lack of time/sudden discharge	All measurements	+/-	+/-	++
Parent/Child refuses	All measurements	+/-	+/-	+/-

*W = weight, L = length, HC = head circumference, MUAC = mid upper arm circumference, SF = skinfolds, CC=calf circumference, KHL = knee-heel length, BIA = bio-electrical impedance analysis; ++ very important factor, + important factor, +/- somewhat important factor, - no important factor; *The presence of splints/lines/ bandages at measurement sites impeding accurate measurements or appropriate placement of electrodes; †Child too heavy to be weight on a baby scale or too tall to be measured accurately in bed.*

The children in whom anthropometric measurements could not be performed reliably in the first 24 hours after admission had significantly higher mean illness severity scores (L, HC, MUAC, CC, BSF, TSF; all P-values < 0.01), higher age (weight, *P* < 0.001), longer ventilator dependency (HC, MUAC, CC, BSF, TSF; all *P*-values < 0.01) and longer LOS (HC, MUAC, CC, BSF, TSF; all *P*-values < 0.01) than the children in whom measurements could reliably be performed.

BIA

The percentages in which BIA-measurements could be performed out of those scheduled are shown in table 2 and the reasons why BIA measurements could not be obtained are presented in table 3. The most frequent reason for unobtainability of BIA-measurements was the presence of splints, lines or bandages at wrists and ankles preventing appropriate placement of the electrodes. Children in whom no BIA measurements could be obtained within the first 24 hours were significantly younger (*P* = 0.031), had a lower birth weight (*P* = 0.016), higher PRISM (*P* < 0.001) and CRIB scores (*P* = 0.01) and longer ventilator dependency (*P* = 0.003) and longer LOS (*P* = 0.003) than the children who could be measured. The distribution of diagnostic categories also significantly differed between children who could and could not be assessed (*P* = 0.012), with sepsis showing the lowest frequency (52%). BIA measurements could be obtained in 71% of children without a reliable weight measurement (n = 59) on admission.

Indirect calorimetry

Within the first 48 hours after admission, 106 children (34%) fulfilled the inclusion criteria for indirect calorimetry. The other 210 children were excluded because of the following reasons: mechanical ventilation with another ventilator (e.g. Babylog 8000; Sensormedics HFO) than the Servo ventilator 300/nasopharyngeal tube/supplementary oxygen (n=201), FiO_2 > 60% (n = 6), and tube leakage > 10% (n = 3). Indirect calorimetry could actually be performed in 86 of eligible children (80%), 39 times in respiratory mode (45%) and 47 times in canopy mode (55%). This group consisted of 13 preterm neonates (all canopy mode), 31 term neonates (22 canopy, 9 respiratory) and 42 older children (30 respiratory, 12 canopy). Of those children with an ICU-stay ≥ 7 days, 21-32% were eligible for calorimetry measurements at the various follow-up moments during admission. Calorimetry was performed on average in 70% of children during the follow-up assessments. Reasons for not being able to carry out calorimetry were: no occasion, child too agitated to perform canopy measurement, measurement not successful, and parents gave no permission for canopy measurement. Children who underwent calorimetry during the first 48 hours were significantly older (*P* < 0.001) than those who could not undergo calorimetry. They also had lower CRIB-scores (preterm neonates, *P* = 0.029), but comparable PRISM-scores (term neonates and older children, *P* = 0.448).

Discussion

This survey describes the feasibility of standard assessment of nutritional status by means of non-invasive methods in infants and children admitted to a specialized pediatric ICU. Our results show that performing reliable anthropometric and BIA measurements was possible in the majority of children on admission, during follow-up and at discharge. Measurements were more difficult to obtain on admission, in children with a higher degree of illness and with increasing age. A minority of children fulfilled the inclusion criteria for indirect calorimetry, and measurements were possible in 70-80% of them.
Weight on admission is an important parameter in critically ill children, not only for the prescription of medication, but also for initial assessment of the nutritional status. Furthermore, serial weight measurements are necessary to evaluate the rapid changes caused by fluid retention and to monitor growth of children with a prolonged ICU-stay. In 19% of our study population, no reliable weight measurement was obtained within the first 24 hours after admission, mostly due to the overall instability of the children. In most children in this group, however, it was possible to perform other anthropometric measurements providing information about the nutritional status. Concerning the feasibility of the anthropometric measurements, percentages were similar for follow-up and discharge assessments. While on admission not being able to perform (reliable) anthropometric measurements was mainly due to instability, during the later assessments the child's agitation and minimal handling were important reasons for impeding measurements. Overall, measurements were hindered mostly by edema and by practical problems such as the presence of splints or bandages at measurement sites preventing accurate measurements.

We expected to find a higher percentage of reliable measurements of knee-heel length compared to the traditional length measurements in children < 2 y of age, but found that length measurements on admission had a significantly higher feasibility than measurements of knee-heel length. This initial difference in performance can mainly be explained by the presence of edema in newborns after birth. We and others[26-28] believe that, especially in preterm neonates, the less interruptive character of knemometry as compared to length measurements, makes it a routinely applicable measurement for longitudinal assessment of short-term linear growth.
The BIA measurements could be performed in frequencies that were comparable to most anthropometric measurements, but the reasons for inability were somewhat different. Apart from the above-mentioned problems hindering anthropometric measurements, BIA measurements were also impeded by technical problems with the device and by the presence of skin lesions.
Previous studies that looked specifically into the feasibility of non-invasive nutritional assessment methods, such as anthropometry in the critically ill, are limited and mostly

focus on adult patients. In a study assessing the prevalence of malnutrition in 337 patients using length, weight, and body circumference measurements, both length and weight could be obtained in 65% of admissions, whereas MUAC measurements could be obtained in all patients.[29] In other studies MUAC was propagated as a feasible method with prognostic value for the ICU.[30] Studies identifying (critically ill) children with malnutrition predominantly use weight and length measurements,[31-33] but provide no information on the numbers of children that could not be assessed or in which measurements were unreliable.
The feasibility of performing routine indirect calorimetry was affected by the many criteria that have to be satisfied before measurements can be obtained. Only 21-34% of the children were eligible, a proportion that was lower than that in the population described by Verhoeven et al.,[34] of which 63% of children fulfilled the inclusion criteria. This discrepancy might be explained by the fact that our study, unlike the other, included preterm neonates on ventilators that are unsuitable for performing indirect calorimetry as they lack continuous gas flow. In the group of eligible children, it was nevertheless possible to perform reliable measurements in 70-80% of the children.

The main goal of routine nutritional assessment is to prevent deterioration of nutritional status during ICU stay. It is to be feared, however, that those unstable and painful children who cannot be assessed on admission are the very ones that have the highest risk of developing malnutrition. It is, therefore, important to take illness severity and degree of metabolic stress into account when aiming at identifying children with a poor nutritional status on admission or those at risk for developing malnutrition.
Furthermore, it should be noticed that all measurements, except weight measurement, were performed by trained researchers. Therefore, successful implementation of standard nutritional assessment will necessitate training of nurses or other caregivers.
Some limitations of our study need to be discussed. First, weight measurements were not done according to a standard protocol by researchers, but by nurses conform the attending physician's policy. Having nurses perform routine weight measurements on admission, at regular intervals during admission and at discharge according to a standard protocol using practical scales, might well improve the success rate of weight measurements. Second, according to the study protocol, the other measurements could not start before parental informed consent was obtained. This has probably limited the number of children that could reliably be assessed within 24 hours after admission. It is to be expected that assessment rates will rise if assessment of nutritional status should be integrated routinely in the admission procedure.

In summary, reliable assessment of nutritional status using non-invasive methods is feasible in daily pediatric ICU practice, but is difficult in the most seriously ill children. Notwithstanding the availability of newer techniques to assess body composition, such as BIA, obtaining reliable assessments in all admitted children will remain difficult. In

spite of these limitations, we would recommend the implementation of a standardized nutritional assessment strategy to improve the quality of ICU-care, with initial assessment of each child's nutritional status firmly incorporated in the ICU admission procedure.

Acknowledgements

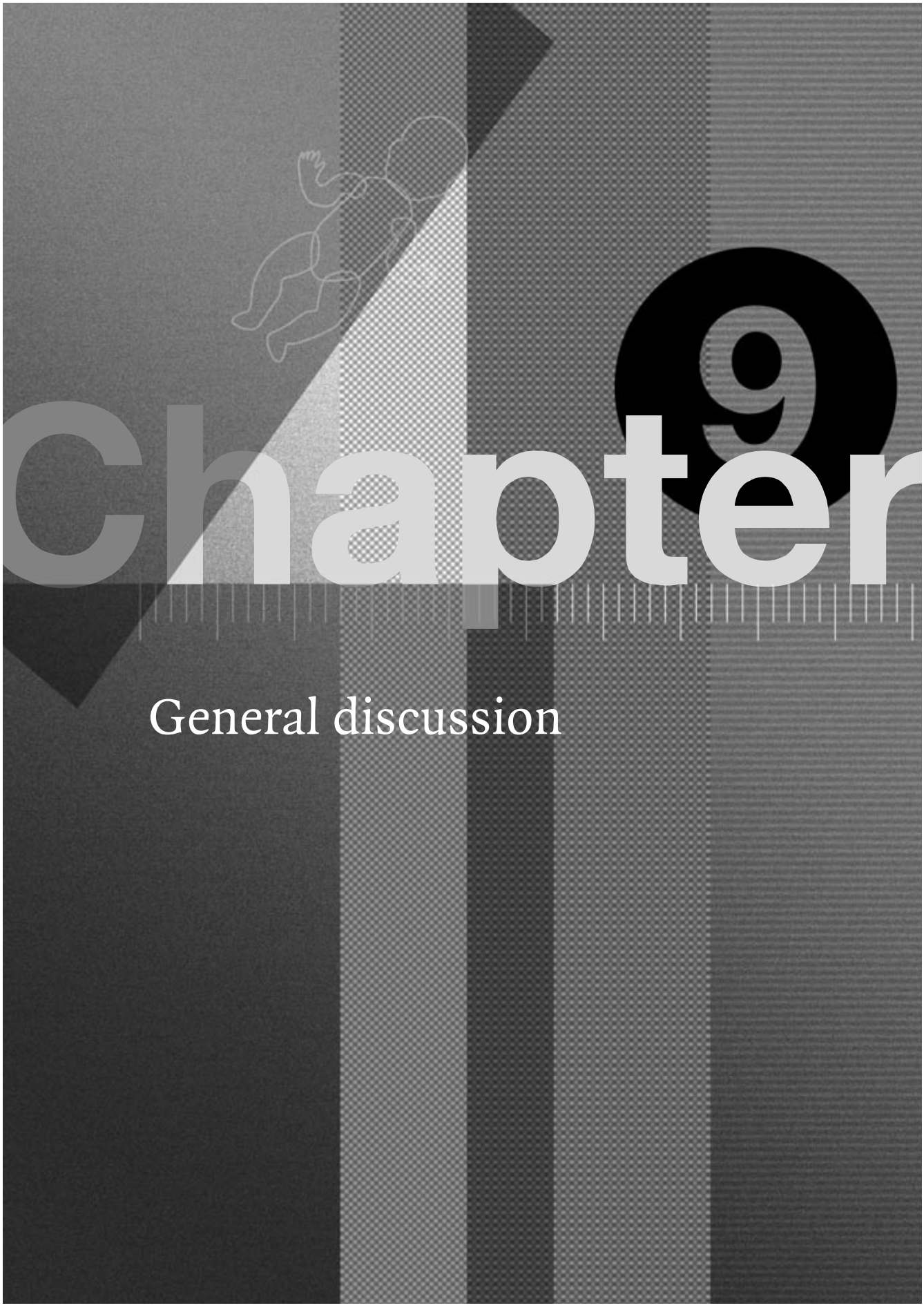
The authors would like to acknowledge the research nurses Ineke van Vliet, Marjan Mourik, Marianne Maliepaard, Ada van den Bos and Annelies Bos for their great assistance in data-collection. We also thank Ko Hagoort (Erasmus MC, Rotterdam) for his careful editing.
Financial support: Nutricia Nederland BV, Zoetermeer, the Netherlands.

References

1. Merritt RJ, Suskind RM. Nutritional survey of hospitalized pediatric patients. Am J Clin Nutr 1979;32:1320-5.
2. Pollack MM, Wiley JS, Holbrook PR. Early nutritional depletion in critically ill children. Crit Care Med 1981;9:580-3.
3. Hulst J, Joosten K, Zimmermann L, Hop W, Van Buuren S, Büller H, Tibboel D, Van Goudoever J. Malnutrition in critically ill children: from admission to 6 months after discharge. Clin Nutr (in press) 2004.
4. Pollack M, Ruttimann U, Wiley J. Nutritional depletions in critically ill children: asociates with physiologic instability and increased quantity of care. J of Parenter Enteral Nutr 1985;9:309-313.
5. Biolo G, Toigo G, Ciocchi B, Situlin R, Iscra F, Gullo A, Guarneiri G. Metabolic response to injury and sepsis: changes in protein metabolism. Nutrition 1997;13(Suppl):52S-57S.
6. Klein S, Kinney J, Jeejeebhoy K, Alpers D, Hellerstein M, Murray M, Twomey P. Nutrition support in clinical practice: review of published data and recommendations for future research directions. Summary of a conference sponsored by the National Institutes of Health, American Society for Parenteral and Enteral Nutrition, and American Society for Clinical Nutrition. Am J Clin Nutr 1997;66:683-706.
7. Lennard-Jones J, Arrowsmith H, Davison C, Denham A, Micklewright A. Screening by nurses and junior doctors to detect malnutrition when patients are first assessed in the hospital. Clinical Nutrition 1995;14:336-340.
8. Rasmussen HH, Kondrup J, Ladefoged K, Staun M. Clinical nutrition in Danish hospitals: a questionnaire-based investigation among doctors and nurses. Clin Nutr 1999;18:153-8.
9. Manning EM, Shenkin A. Nutritional assessment in the critically ill. Crit Care Clin 1995;11:603-34.
10. Zemel BS, Riley EM, Stallings VA. Evaluation of methodology for nutritional assessment in children: anthropometry, body composition, and energy expenditure. Annu Rev Nutr 1997;17:211-35.
11. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47:316-23.
12. Usher R, McLean F. Intrauterine growth of live-born Caucasian infants at sea level: standards obtained from measurements in 7 dimensions of infants born between 25 and 44 weeks of gestation. J Pediatr 1969;74:901-10.
13. Tang W, Ridout D, Modi N. Assessment of total body water using bioelectrical impedance analysis in neonates receiving intensive care. Arch Dis Child Fetal Neonatal Ed 1997;77:F123-6.
14. Novak I, Davies PS, Elliott MJ. Noninvasive estimation of total body water in critically ill children after cardiac operations. Validation of a bioelectric impedance method. J Thorac Cardiovasc Surg 1992;104:585-9.
15. Robert S, Zarowitz BJ, Hyzy R, Eichenhorn M, Peterson EL, Popovich J, Jr. Bioelectrical impedance assessment of nutritional status in critically ill patients. Am J Clin Nutr 1993;57:840-4.

16. Joosten KF, Verhoeven JJ, Hop WC, Hazelzet JA. Indirect calorimetry in mechanically ventilated infants and children: accuracy of total daily energy expenditure with 2 hour measurements. Clin Nutr 1999;18:149-52.
17. Baxter JP. Problems of nutritional assessment in the acute setting. Proc Nutr Soc 1999;58:39-46.
18. Goulet O. Assessment of nutritional status in clinical practice. Baillieres Clin Gastroenterol 1998;12:647-69.
19. Gerver W, De Bruin R. Paediatric Morphometrics: a reference manual. Utrecht: Bunge; 1996.
20. Hermanussen M. Knemometry, a new tool for the investigation of growth. A review. Eur J Pediatr 1988;147:350-5.
21. Joosten KF, Jacobs FI, van Klaarwater E, Baartmans MG, Hop WC, Merilainen PT, Hazelzet JA. Accuracy of an indirect calorimeter for mechanically ventilated infants and children: the influence of low rates of gas exchange and varying FIO2. Crit Care Med 2000;28:3014-8.
22. Knauth A, Baumgart S. Accurate, noninvasive quantitation of expiratory gas leak from uncuffed infant endotracheal tubes. Pediatr Pulmonol 1990;9:55-60.
23. Report of the Second Task Force on Blood Pressure Control in Children-- 1987. Task Force on Blood Pressure Control in Children. National Heart, Lung, and Blood Institute, Bethesda, Maryland. Pediatrics 1987;79:1-25.
24. The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. The International Neonatal Network. Lancet 1993;342:193-8.
25. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988;16:1110-6.
26. Hermanussen M, Seele K. Mini-knemometry: an accurate technique for lower leg length measurements in early childhood. Ann Hum Biol 1997;24:307-13.
27. Bloomfield FH, Knight DB, Breier BH, Harding JE. Growth restriction in dexamethasone-treated preterm infants may be mediated by reduced IGF-I and IGFBP-3 plasma concentrations. Clin Endocrinol (Oxf) 2001;54:235-42.
28. Gibson AT, Pearse RG, Wales JK. Knemometry and the assessment of growth in premature babies. Arch Dis Child 1993;69:498-504.
29. Kelly IE, Tessier S, Cahill A, Morris SE, Crumley A, McLaughlin D, McKee RF, Lean ME. Still hungry in hospital: identifying malnutrition in acute hospital admissions. Qjm 2000;93:93-8.
30. Ravasco P, Camilo ME, Gouveia-Oliveira A, Adam S, Brum G. A critical approach to nutritional assessment in critically ill patients. Clin Nutr 2002;21:73-7.
31. Pollack MM, Wiley JS, Kanter R, Holbrook PR. Malnutrition in critically ill infants and children. J Parenter Enteral Nutr 1982;6:20-4.
32. Leite HP, Isatugo MK, Sawaki L, Fisberg M. Anthropometric nutritional assessment of critically ill hospitalized children. Rev Paul Med 1993;111:309-13.

33. Hendricks KM, Duggan C, Gallagher L, Carlin AC, Richardson DS, Collier SB, Simpson W, Lo C. Malnutrition in hospitalized pediatric patients. Current prevalence. Arch Pediatr Adolesc Med 1995;149:1118-22.
34. Verhoeven JJ, Hazelzet JA, van der Voort E, Joosten KF. Comparison of measured and predicted energy expenditure in mechanically ventilated children. Intensive Care Med 1998;24:464-8.



Chapter 9

General discussion

Introduction

Malnutrition due to lack of food is a common health problem in developing countries.[1] By contrast, the malnutrition seen in critically ill patients in Western countries is usually the result of disease, and is called disease-related malnutrition.[2] This type of malnutrition may develop from inadequate dietary intake, increased metabolic demands, impaired absorption or increased nutrient losses in disease. Much more than adults, critically ill children are at high risk of clinical depletions because they have limited body reserves of fat and protein, higher energy expenditure, and increased energy requirements for growth and development. This is particularly relevant in preterm neonates.

The acute effects of malnutrition include poor wound healing, higher risk of infections due to poor immune defense, reduced gut function, longer dependency on mechanical ventilation and longer hospital stay.[3] Considering that malnutrition might also jeopardize future growth and development,[4] it seems all-important to identify on admission to the ICU, those children with pre-existing poor nutritional status and those at risk for developing malnutrition, in view of tailoring their nutritional care. Various tools are available for nutritional assessment. To this specific aim we need to identify one that can easily be used in the intensive care setting, is patient friendly, portable, and has enough sensitivity/specificity to distinguish children with poor nutritional status from children with normal nutritional status.

Possible relationships between nutritional assessment, nutritional status, malnutrition and severity of disease are fundamental issues in discussions about nutritional assessment and guidelines for nutritional support. A formal nutritional assessment arguably does not define the presence and extent of malnutrition at the time of assessment, but rather identifies the metabolic consequences of an underlying disease state defined by parameters that are also deranged in pure starvation. The results of nutritional assessment in a critically ill patient, therefore, reflect metabolic consequences of both undernutrition and the underlying disease. In this context, nutritional assessment and subsequent nutritional support are directed not only at treating malnutrition but also at supporting the patient nutritionally and metabolically to prevent further physiologic deterioration under primary disease-directed therapy.[5] Furthermore, in critically ill children we must also aim at improving their nutritional status to ascertain normal growth and development, especially when a high metabolic demand is expected – e.g. in case of burns or neurotrauma – and if they show preexisting (chronic) undernutrition.

In the studies described in this thesis, we investigated various aspects of nutritional assessment in children admitted to a multidisciplinary neonatal, pediatric, and pediatric surgical intensive care unit. The novelty of our research lies in starting nutritional assessment measurements as early as the acute phase of critical illness. True, some

previous studies focused on small, selected groups in the acute phase, e.g. burn patients. Most studies, however, concentrated on nutritional assessment starting in the recovery period, i.e. after major metabolic instability had subsided or even after discharge from the ICU.[6-8] Furthermore, we used an epidemiological approach and did not apply case selection, in contrast to previous studies. The ultimate goal was to set a standard for performing nutritional assessment in daily practice.

The previous research of our group[9] distinguished four levels of nutritional assessment in the pediatric ICU population, corresponding to phase and severity of illness. These levels were described as follows:

Level 1 All patients at admission: weight, height, head circumference and illness severity scores.

Level 2 Patients with present protein-energy malnutrition on admission or expected prolonged ICU stay (> 3 days): biochemical parameters, indirect calorimetry, and nitrogen balance.

Level 3 Prolonged critical illness (> 3 days): cortisol, vitamin status, carnitine.

Level 4 Methods of which the value has not been established yet (research tools): different laboratory (e.g. urine 3-methyl histidine) and hormonal parameters (e.g. IGF-1, rT_3, T_3), body composition techniques (BIA, DEXA, TOBEC, knemometry) and research methods (isotope studies).

The studies by Joosten et al.[9] had a special focus on the use of indirect calorimetry, whereas we predominantly evaluated the practical use of several level 1 and level 2 assessment tools, and some level 4 methods.

In the following section we discuss the main findings of this thesis in relation to other studies. We elaborate on the implications for clinical practice and propose a guideline for implementation of nutritional assessment in daily ICU-practice. Furthermore, we debate the problems encountered in performing a clinical study in a heterogeneous group of patients. Finally, we recommend future research using the knowledge obtained from our studies.

Major Findings

Prevalence of malnutrition

Studies performed in the 1980s revealed that about 20% of the children admitted to a pediatric intensive care unit were in poor nutritional state.[10-13] Despite improvements in intensive care technology, feeding possibilities and increased awareness of the significance of adequate nutritional support, we found still 24% of the children to be

acutely and/or chronically malnourished on admission to the ICU (Chapter 3). The fact that the incidence had not gone down may be explained by certain developments in the care for critically ill children in recent years. As a result of these developments, more and more children with chronic disease or major congenital anomalies survive to older age, and these are more likely to be in poor nutritional state on admission to the ICU than are previously healthy children. The high prevalence of underlying growth-affecting disease (84%) in those with acute malnutrition in our cohort underlines this issue. Previous studies in children with chronic disease, such as cystic fibrosis, inflammatory bowel disease, severe handicaps or neuro-muscular diseases, have already demonstrated the beneficial effect of nutritional intervention.[14,15]

We showed that notably preterm and term neonates were vulnerable for worsening of their nutritional status during ICU-stay compared to the older age group. This is in line with findings from previous studies in which children under 2 years of age showed a higher prevalence of malnutrition than did older children.[10,16] The latter is highly relevant to clinical practice, as most children admitted to an ICU are younger than 2 years of age (84% of children in our study. Showing the largest decrease in anthropometric parameters between admission and discharge, indicating reduced growth, the preterm neonates form a special group within the pediatric ICU population. We found 44% of preterm neonates to have a WFA-SDS < -2 at discharge, a pattern emerging from earlier studies as well.[17]
Apart from age and a history of growth-affecting disease, two other factors negatively influenced anthropometric parameters of nutritional status during admission and follow-up in our study: previous surgery, and prolonged length of ICU-stay.

Assessment of nutritional status

Clinical anthropometric assessment

In most children anthropometric assessment of nutritional status could be performed on admission, during the course of admission and at discharge, but measurements were less feasible on admission and in the most seriously ill children (Chapter 8). Other factors associated with difficulties in performing reliable anthropometric measurements were the presence of edema, higher age, longer ventilator dependency and longer length of stay.

The results from Chapter 7 indicate that the ability of anthropometric assessment tools to detect malnutrition or changes in nutritional status depends on the patient's age. In the preterm neonates, SD-scores of the conventional measurements of weight, length and head circumference showed significant changes over time. As reference values for body circumferences, skinfolds, and knee-heel length for the Dutch preterm population are lacking, we were unable to calculate changes in SD-scores for these measurements. In practice, however, a previous measurement may serve as reference for the

longitudinal assessment of the individual child, enabling to calculate and follow growth rates over time. In the term neonates, SD-scores of WFA, LFA and HC showed significant changes over time, whereas the mean changes in SD-scores of MUAC, CC, and skinfolds were not significant over the course of admission, but did increase in the follow-up period after admission. In the older children (> 30d -17 y), SD-scores for weight and length might not be sensitive enough to detect deterioration of nutritional status during ICU-admission. On the other hand, measurements of MUAC, CC and skinfolds, representing the protein and fat condition, showed significant changes and could therefore provide a useful tool for assessing (changes in) nutritional status during ICU-stay in this group of children.
As the period between admission and discharge is variable, the discharge assessment might already represent an increase in nutritional status compared to earlier time points during admission, especially in children with prolonged ICU-stay. Regular assessment, e.g. once a week, may therefore be beneficial in detecting the most vulnerable period during admission.

Follow-up anthropometric assessment
Follow-up studies after intensive care admission addressing growth and parameters of nutritional status have predominantly been performed in preterm neonates.[4,18-21] Although previous research has addressed the prevalence of acute and chronic malnutrition in children requiring intensive care treatment,[10,22-25] none of these studies followed up measurements of initial nutritional status over the course of ICU stay or after discharge. Our follow-up measurements during admission and up to six months after discharge are therefore of great value (Chapter 3). Over admission we observed a decline in anthropometric parameters in the preterm and term neonates, but not in the older children. At 6 weeks after discharge the nutritional status of most neonates had not yet returned to admission level, but at 6 months after discharge almost all neonates showed complete recovery. Considering that our study was of an observational nature and we did not influence the nutritional intake of the children after discharge, it can be argued that nutritional status might have improved faster with an individual dietary advice or with a special post-discharge formula.[26-29]

Biochemical assessment
In Chapter 6 we focused on a limited panel of routinely available biochemical parameters and determined whether abnormal values of these parameters in critically ill children at admission would predict outcome and changes in nutritional status during the ensuing ICU-stay. We opted for this limited set of parameters because it is easy to obtain as routine screening using little blood. The analyses revealed high prevalences of abnormalities – 20% hypomagnesemia, 25% hypertriglyceridemia, 30% uremia, and 52% hypoalbuminemia. The highest prevalences were found in the most severely ill children, but no strong relationships were found between these abnormalities and

changes in nutritional status over ICU-stay.
Furthermore, it can be argued that biochemical parameter levels at admission will be of limited value in distinguishing children with pre-existing malnutrition, as they reflect metabolic consequences of both nutritional status and the underlying disease.
Other potential biochemical assessment parameters, such as pre-albumin and cytokines, should in future studies be investigated in relation to changes in nutritional status. These, however, require more blood and consequently informed consent and IRB approval.
We conclude that biochemical assessment at admission is useful, seeing that it revealed high prevalences of abnormalities that should be taken into account in clinical practice. In our opinion, these abnormalities reflect a higher illness severity and do not identify those children at risk for a decline in nutritional status over admission.

Endocrine assessment
In Chapter 7 we evaluated the courses of hormonal parameters in relation to clinical parameters, illness severity and nutritional intake in children during the first week of admission to the pediatric ICU. We hypothesized that illness would suppress anabolic hormone levels but that with decreasing illness severity and increasing nutritional intake hormone levels would return to normal values in due course. The results showed frequent deviations in levels of IGF-1, T_3 and rT_3 in critically ill children aged > 1 month at admission, which in most of them persisted until day 6 after admission. The significant negative relationship between changes in CRP and hormone levels led us to speculate that the recovery of the acute stress response is reflected by the decline in CRP level, which might predominantly dictate the changes in thyroid hormone and IGF-1 levels. In our study, adequacy of feeding did not seem to affect normalization of IGF-1 and thyroid hormone levels, but this could be due to the heterogeneity of the study group with different types of feeding. Until now, no prospective studies in critically ill children have been performed evaluating the use of endocrine parameters in relation to standard feeding protocols. The effect of feeding on anabolic hormone levels will probably be more pronounced after resolution of the acute stress response. Therefore, our 6-day study period might have been too short, and future studies should encompass a longer time span, as in previous studies monitoring the responses of preterm neonates to feeding.[30]

Assessment of nutritional needs
Monitoring of feeding adequacy is one of the goals of a comprehensive nutritional assessment. But how can feeding adequacy be evaluated? The ultimate goal is growth and recovery, but first of all we need to know how nutritional intake compares to a nutritional standard according to age or how energy intake compares to measured energy expenditure.
Nutritional requirements in children who are under stress from critical illness may be

significantly different from those of healthy children or children who are less severely ill. Moreover, metabolic responses may greatly vary as well, depending on the nature of the injury and the variability of the individual response to the same type of injury.[31,32] This inter-individual difference essentially only leaves the option of measuring individual energy expenditure (EE), for instance by indirect calorimetry, but this only provides the minimum requirements, disregarding the energy needed for growth and recovery. When indirect calorimetry is not possible, equations such as the equation of Schofield[33] can help to estimate EE. However, this has proven to be inaccurate in critically ill patients.[34,35]

Measured energy expenditure and respiratory quotient

In Chapter 4 we compared the actual energy intake with measured EE, which is the minimum level of energy requirements. On 21% of assessment days energy intake was found to be below the minimum requirement of measured EE. This mainly occurred during the first two days of ICU admission, which means that in order to prevent shortage in energy supply, attention should specifically be paid to the first days of admission.

We also investigated the usefulness of the respiratory quotient (RQ) in determining the adequacy of feeding (Chapter 4). RQ was found to be of limited value as a parameter to indicate adequate feeding due to poor sensitivity and large inter-individual variability, a finding also emerging from previous studies in critically ill adult patients admitted to an ICU.[36] However, we found the two extreme values of RQ to be useful to indicate clinically relevant issues. An RQ-value > 0.85 reliably indicates the absence of underfeeding and an RQ-value > 1.0 reliably indicates the presence of (carbohydrate) overfeeding. The usefulness of the RQ to recognize (carbohydrate) overfeeding has also been demonstrated in other studies in critically ill children and adults[31,37,38] In practice, RQ > 1.0 signals the necessity of reducing either total caloric intake or carbohydrate intake in order to prevent otherwise adverse effects, such as inability to wean the patient from the ventilator. Furthermore, RQ < 0.85 implicates an increase in caloric intake.

As indirect calorimetry has several technical limitations, only a limited group of children at the ICU can be assessed, which has implications for clinical practice. Thus, only 21-34% of children in our study group were eligible for indirect calorimetry on the different assessment moments during admission (Chapter 8). Measurements could be actually performed in 70-80% of eligible children, in general the older and less severely ill children.

Recommended daily allowance

In our studies we also compared energy intake with the recommended daily allowance (RDA),[39] which is the optimal requirement for healthy children allowing for energy

needed for growth and recovery. During the first days of critical illness RDA will overestimate energy requirements in most children, as appears from indirect calorimetry studies showing that measured EE was below RDA.[31,34] Measured EE, however, is no more than an initial guide during the first days, which would underestimate energy needs during the later stages of admission. In the recovery phase, when growth resumes, RDA levels would be a more appropriate reference for energy requirements. The exact time point to switch to RDA is hard to determine in the individual patient.

Energy and protein deficits

We compared the actual energy and protein intakes of all admitted children with optimal requirements according to RDA throughout the first 14 days of admission and found substantial daily and cumulative discrepancies. Furthermore, the cumulative deficits negatively influenced several anthropometric parameters (Chapter 5). This association underlines the importance of assessing cumulative energy and protein balances in relation to a feeding standard or in relation to measured EE. Preterm neonates showed the largest cumulative deficits; other children at risk for developing significant deficits were those who had to undergo surgery, had a longer duration of ICU-stay, longer ventilator dependency or younger age.

Deficits may develop either from underprescription of nutrients or from interrupted administration of feeding. These causes represent differences in optimal versus prescribed, optimal versus delivered and prescribed versus delivered nutrients.

Previous studies among adults,[40-42] and premature neonates[17] admitted to an ICU showed large differences between prescribed and actually delivered nutritional intake (22-23%), and between prescribed and required/optimal nutrition (22-35%). The main reasons for these deficits were material-related factors, gastrointestinal intolerance, slow gastric emptying, airway management, fasting in anticipation of diagnostic and surgical procedures, and underprescription. Because we only assessed actual intakes and did not investigate differences between prescribed and delivered nutrition, we can not document the reasons for these inadequacies: underprescription or problems with the delivery.

Conclusion

For most of the single nutritional assessment parameters that we studied, we found a relevant application in clinical practice. However, owing to the limitations of the various methods not one specific parameter could be identified that is applicable to the overall neonatal and pediatric ICU population. This means that information on the different levels of a comprehensive nutritional assessment (body composition, laboratory parameters, estimation of nutritional needs, and illness severity) must be obtained from different measurements geared to the child's characteristics and his or her disease state and therefore implies a patient tailored assessment.

Furthermore, various combinations of methods are useful in different groups of critically ill children.

Methodological considerations

Study population

As we had set only a few exclusion criteria, a large number of children were eligible for inclusion during the one-year study period. The inclusion rate was 80%, which can be interpreted as good in view of the observational nature of the study combined with the severe impact of critical illness on parents. The results described in Chapter 2 showed that the characteristics of children who participated in the study were comparable with those children whose parents declined informed consent. This means that we established a representative sample of the overall population of children admitted to a pediatric ICU, rather than studying a selection of children.

The loss to follow-up was limited to about 10 percent of children and was evenly distributed among the different age groups. The results of the follow-up assessments were very valuable, therefore, and represented the outcome of the total group.
The large diversity in age, diagnosis, and illness severity, which is characteristic of most level III pediatric ICUs, makes it difficult to draw a singular conclusion about the best method for nutritional assessment in daily clinical practice. We classified children into three age groups: preterm neonates (gestational age < 37 weeks), term neonates (0-30 days) and older children (> 30 days). This classification is rather practical than well-balanced, and an additional breakdown of the older children into smaller groups might have been more helpful to answer specific research questions.

Study design

In contrast to most research on nutritional assessment in pediatric ICU-populations,[10,22,31] we chose to perform a prospective study enabling us to follow the course of nutritional status over time, and to trace possible influencing factors.
The combined observational and epidemiological approach used for our studies, including almost all children admitted during a one-year-period, from preterm neonates to 18-year-olds, must be taken into consideration when interpreting our results. For some topics addressed in this thesis a different study design would have been more appropriate. For instance, we chose not to perform extra vena punctures in order to obtain the highest possible parental consent rate for inclusion in the overall study, thereby guaranteeing an adequate and representative sample size. This limitation certainly had an impact on the results of the studies described in Chapters 6 and 7 regarding the usefulness of biochemical and hormonal parameters. In these studies blood samples could only be obtained when indwelling arterial catheters were present or

when sampling could be combined with a vena puncture or blood draw ordered by the attending physician. Consequently, individual biochemical parameters could be missing for children in whom these parameters were not routinely ordered by the attending physician or could not be combined with another clinical assessment later on in the first 24 hours. Furthermore, the evaluation of the clinical usefulness of hormone levels as a potential landmark for the turning point from catabolism to anabolism was limited by the lack of serial data in the majority of children, especially after day 4, and of aged-matched reference values.

Methods used for nutritional assessment

We predominantly used non-invasive methods of nutritional assessment and based the prevalence of malnutrition on anthropometric parameters. This was inherent to the mixed study population and the epidemiological approach. Other nutritional assessment methods have been developed and studied in more and more specific populations. However, as they lack cut-off values and reference values and are often impractical, these methods have limited application in the heterogeneous ICU population. Nevertheless, we are aware that anthropometry has its limitations in critically ill children, who frequently show edema or water imbalance.

Information on illness severity or degree of physiologic stress forms an important component of a comprehensive nutritional assessment, especially in the more severely ill children in whom other measures of nutritional assessment are more difficult to obtain.[43] We used initial objective illness severity scores (PRISM and CRIB)[44,45] obtained at admission, but it would have been very informative to obtain daily validated scores in conjunction with e.g. serial CRP levels to detect changes in illness severity over time. Daily PRISM scores might have been an option, although this scale was not intended and validated for this particular use.

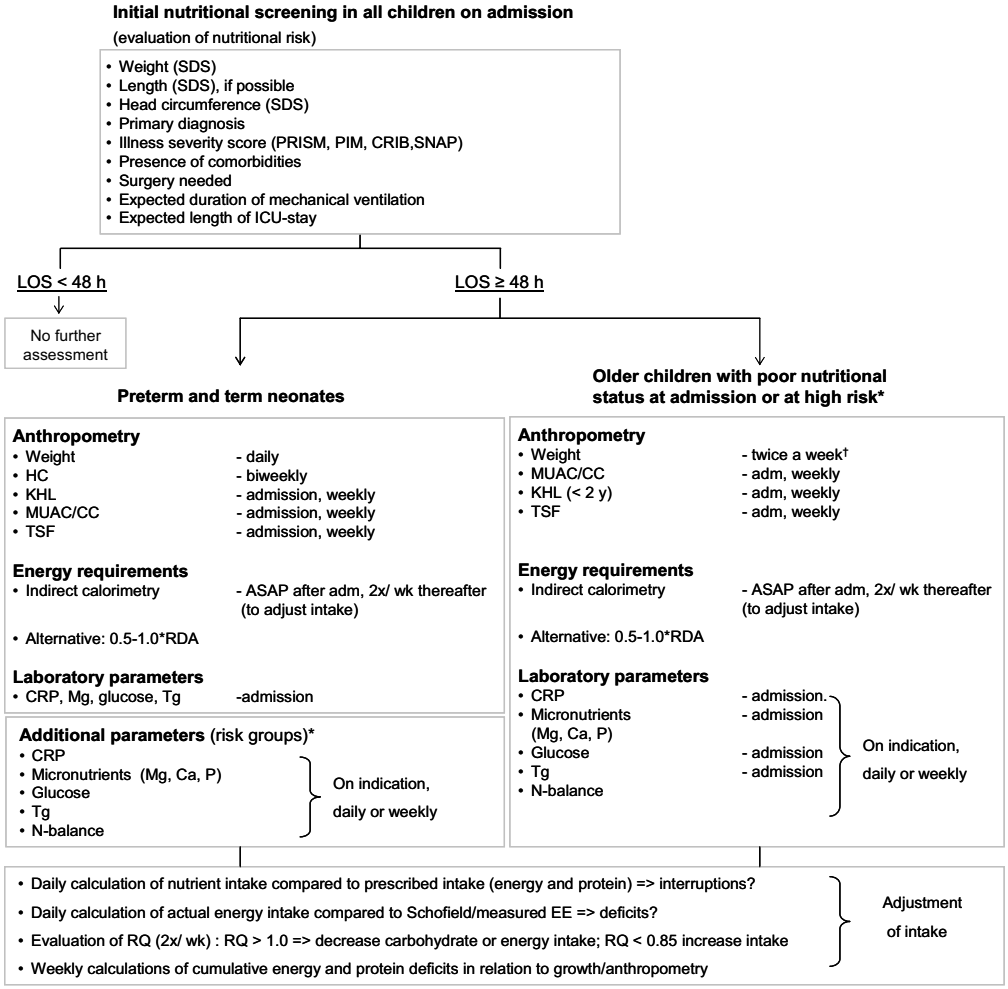
Implications for clinical practice

The results of our studies highlight the importance of including a form of routine nutritional assessment in the daily care of critically ill children. This will allow us to identify those children at nutritional risk on admission or those children with a deteriorating nutritional status over admission. This does not mean that a full nutritional assessment – anthropometry, laboratory parameters and metabolic monitoring – should be performed in all children admitted to an ICU.

In Figure 1, we propose an algorithm for performing nutritional assessment in routine clinical practice based on the findings from our research and the current literature. It consists of a simple initial screening on admission aimed at identifying children at nutritional risk. This initial screening should be incorporated in the admission procedure

and can be performed by the attending nurse and/or physician. The identification of risk patients is important, because assessments other than the conventional weight and length measurements are not necessary in all children admitted to an ICU.

Figure 1 Proposed standard of nutritional assessment in the pediatric ICU population.



adm = admission, ASAP = as soon as possible, CC = calf circumference, CRIB = Clinical Risk Index for Babies, CRP = C-reactive protein, EE = energy expenditure, IC = indirect calorimetry, IGF-1 = insulin like growth factor-1, KHL = knee-heel length, MUAC = mid upper arm circumference, PIM = Pediatric Index of Mortality, PRISM = Pediatric Risk of Mortality, rT_3 = reverse T_3, RQ = respiratory quotient, SDS = standard deviation score, SNAP = Score for Neonatal Acute Physiology, T_3 = triiodothyronine, TSF = triceps skinfold.
**poor nutritional status: WFA-SDS or LFA-SDS or WFL-SDS < -2; risk groups: prolonged expected ICU-stay, prolonged duration of mechanical ventilation, children undergoing surgery, children with underlying growth-affecting disease such as children with major congenital malformations, cardiac anomalies, CF, IBD, HIV-infection (see text for details); †depending on age of the child.*

Risk groups

We could identify several groups of children at nutritional risk by means of our anthropometry parameters and assessment of nutritional deficits (Chapters 3 and 5). Translating these factors into clinical practice implies that during ICU-admission special attention should be directed to the (initial) nutritional status and nutritional intake of:

- Neonates, especially the preterm neonates;
- Children with a history of chronic disease;
- Children with a compromised nutritional status on admission (WFA-SDS < -2 or (LFA-SDS < -2 or WFH-SDS < -2);
- Children who have to undergo surgery;
- Children with an expected prolonged ICU-stay, e.g. preterm neonates and children with major congenital anomalies;
- Children with an expected prolonged ventilator–dependency, e.g. preterm neonates with BPD and children with congenital anomalies of the lungs.

We realize that on admission one cannot always predict the probable length and course of ICU stay because unforeseen complications may necessitate longer intensive care treatment. The nutritional status of a child with an initially expected stay < 48 hours who develops serious complications should be re-evaluated at that point and assessed according to the appropriate standard for age.

Within our mixed group of critically ill children we did not aim at identifying specific diagnostic groups with increased risk of poor nutritional status. Previous research, however, has identified several such groups, including children with cardiac problems, chronic lung disease (e.g. cystic fibrosis and broncho-pulmonary dysplasia), diseases of the GI-tract (e.g. intestinal atresia, necrotising enterocolitis, short bowel syndrome, inflammatory bowel disease), cancer, HIV-infection, renal disease, and cerebral palsy.[16,46-51] These children's nutritional status and nutritional strategy need extra attention during admission to an intensive care unit.

Other determinants that help to identify patients at risk for malnutrition have been used in the subjective global assessment in adult patients[52] and may also be applicable to children. These anamnestic items are:

- recent weight loss
- deficient intake due to pain
- recently increased nutrient losses, as manifested by e.g. vomiting and diarrhea

Unlike in adults, cut-off levels can not be determined for children because of ongoing growth, and therefore anthropometric parameters have to be compared with age–specific reference data of healthy children or syndrome-specific reference values.[53] Furthermore, in the individual child the values of the different assessment parameters (anthropometry, laboratory, EE) obtained at admission can serve as reference values for later assessments.

After the initial screening, additional anthropometric measurements and, if possible, indirect calorimetry have to be performed within 24-48 hours after admission, and limited initial biochemical parameters should be obtained in children with an expected stay of ≥ 48 hours. These should be followed by an individual determination of macro- and micronutrient needs.
Additional laboratory parameters need to be obtained in children with poor nutritional status on admission (WFA-SDS < -2 or LFA-SDS < -2 or WFH-SDS < -2) and those with a high degree of metabolic stress, i.e. in case of sepsis, burns, or neurotrauma. Furthermore, nutritional screening should be repeated regularly to monitor alterations in nutritional status and in diagnoses or conditions that might put the child at nutritional risk, and also to monitor the efficacy of nutritional support (see Figure 1). Though frequency of nutritional monitoring should be adjusted to the severity of the clinical condition, degree of malnutrition, level of metabolic stress and existing nutritional deficiencies, a general guideline is given in Figure 1.

Implementation
As stated earlier, the initial screening – including measurement of weight, height and head circumference – can be performed by the attending nurse and/or physician conform standard protocol. Given the known limitation (high inter-observer variability) of anthropometric measurements such as arm circumference and skinfolds, it is of great importance that the persons performing these measurements are well trained and carry out the measurements conform a standard protocol.[54] It is questionable whether nurses caring for the child are the appropriate persons to perform these assessments. Ideally, a 'nutritional assessment team' consisting of specialized ICU-nurses or dieticians should be available to perform and interpret the anthropometric measurements together with the indirect calorimetry. If available, ICU-staff are recommended to alert this specialized team as soon as possible after admission of a child shown to be at risk at the initial screening.

The indirect calorimetry measurements must be interpreted as soon as possible in order to establish the child's minimal energy needs. Later measurements must be evaluated during the daily clinical rounds along with the data on intake. Individual patient digital monitoring systems (PDMS) can be helpful in this matter, as they facilitate calculations of nutritional intake and comparisons between nutritional intake and measured and estimated needs. Furthermore, the differences between prescribed and delivered nutrition must be evaluated and acted upon when necessary.

Improvement of patient care
The specialized nutritional assessment team can also be of major importance in the education of physicians, nurses and dieticians regarding nutritional assessment and nutritional support.[55] They can emphasize the need of performing standard

anthropometric assessments, provide clear guidelines with regard to optimal nutrition, and give ongoing education about enteral and parenteral feeding.

Future perspectives

Many topics relating to nutritional assessment and nutritional support in critically ill children are still subject for future studies. The information gained from our studies can be used in future research, e.g. anthropometric parameters can serve as assessment parameters in nutritional intervention studies, and the baseline hormonal data can be used in studies investigating the effect of different feeding regimens on the return to anabolism in critically ill children. Three areas of future research are discussed below.

A. Alternative tools for nutritional assessment

Applying the levels of nutritional assessment as proposed by Joosten[9] together with the obtained knowledge from our studies and previous research, the usefulness of the following nutritional assessment measurements needs to be assessed for use in daily clinical practice.

- Bio-electrical impedance analysis (BIA): as more and more reference data become available even in young infants,[56-58] the use of BIA in the routine assessment of body composition in the neonatal and pediatric ICU population deserves to be evaluated, especially in view of its non-invasive character.
- Functional tools: as changes in muscle function induced by nutritional therapy were found to occur more rapidly than changes in body composition,[59] the use of e.g. grip strength in children of risk groups from the age of 8 years needs further investigation.
- The use of biochemical and hormonal parameters in relation to acute phase proteins to detect the turning point from catabolism to anabolism.

B. Nutritional intervention studies

Our study was of an observational nature and therefore not designed to evaluate the effects of different nutritional support regimens on outcome of critically ill children. Although many nutritional intervention studies have been performed in critically ill adults, the number of prospective randomized controlled trials (RCTs) evaluating the effect of nutritional support in critically ill children is limited.[60] In preterm neonates, however, a large body of data on different nutritional intervention trials is available, although almost all of these studies started in the phase after the acute illness period. Examples of issues related to nutritional support studied in this population are different feeding

modes (formula vs. breast milk), routes of feeding, diets supplemented with specific agents, and early weaning.[61-64]

Given the differences between adults and children in their tolerance to the adverse effects of malnutrition and in their growth needs, findings from studies in adults can not be extrapolated to pediatric patients.
Studies in the area of nutritional support are difficult to conduct, especially in ICU–patients, who often present with multiple pathologies and advanced supportive therapies. This sample heterogeneity dictates large groups of patients for nutritional interventions to demonstrate improvement.[65]

For setting up a valid randomized controlled trial it is essential to

1. Have a sound hypothesis and study design.
2. Identify children who may benefit from nutritional intervention.
3. Choose meaningful outcome parameters that can be related to nutritional intervention:
4. General: mortality, morbidity, length-of-stay, immune function, cost-effectiveness;
5. Nutritional variables: growth, preservation of LBM, nitrogen balance.
6. Choose an assessment tool that can evaluate short-term changes in nutritional status
7. Study a sufficiently large group (power-calculation)
8. Characterize children in terms of underlying pathology, reason for ICU admission, severity of illness, supportive therapy, indications for nutritional support, and rate and severity of complications.
9. Assess the pre-illness nutritional status of the child, because malnourished patients tend to benefit from nutritional support, in contrast to the well-nourished ones. This is necessary to avoid the mistake of attributing positive results to a particular formula when what was being observed was the benefit derived from the feeding itself.
10. Check the route of nutritional support, because clinical benefits arising from adding a nutrient is to TPN, for example, can not be extrapolated to enteral feeding and vice versa. The confounding factor is that patients who are successfully fed enterally often have a better prognosis because their illness is not so severe as to prevent them from tolerating the diet.
11. Use feedings with equal caloric and protein content when studying the effect of certain supplemented components.
12. Use an intention-to-treat analysis in order to prevent bias.

C. Optimal nutritional support

Although we did not aim at finding the optimal nutritional support regimen in critically ill children, it is a topic which is inextricably bound up with nutritional assessment and should be studied in future research.
Nutritional support is defined as the provision of nutrients orally, enterally or parenterally with therapeutic intent. It is used to avoid the development of malnutrition resulting from insufficient energy and nutrient intake in the face of increased energy needs.

The future studies should incorporate several aspects of nutritional support in order to find the optimal feeding:

- Quick identification of the children at risk
- Composition (macronutrients, micronutrients, specific agents)
- Timing – starting as early as possible
- Route of feeding – enteral vs. parenteral, transpyloric vs. gastric
- Monitoring of energy requirements by indirect calorimetry in relation to improvements in patient outcome
- Follow-up of nutritional support by means of anthropometry and selected laboratory parameters
- Recognition of overfeeding and underfeeding in the individual patient
- The eventual goal must be reduced mortality and morbidity, but most importantly the resuming of normal growth and development.

Nutri-pharmaceuticals
Apart from improving the amounts of nutrients administered to the critically ill child, we need to further evaluate the effects of specific nutrients on outcome and growth. Feedings containing so-called immuno-modulating agents (immunonutrition) were the subject of many recent studies in critically ill adults.[66-68] Examples of these so-called nutri-pharmaceuticals are glutamine, arginine, fatty acids, nucleotides, and anti-oxidants. The future optimal feeding of specific groups of critically ill children might contain one of these agents that are now not yet present or present in low concentrations only.

Glutamine and alanine have been classified as conditional essential amino acids with special usefulness in the critically ill patient. Immunomodulation, gut protection, and prevention of protein depletion are mentioned among their positive effects in such circumstances. Glutamine supplementation has predominantly been studied in adults, but some studies have been done in infants and children, showing contradictory results.[69-71] The reported benefits of enteral glutamine supplementation in very low birth weight infants were reduced sepsis, increased feeding tolerance and reduced costs.[72-74] Enjoying the full benefits of glutamine use or other nutri-pharmaceuticals in pediatrics is

likely to require a major research effort with large multicenter clinical trials to achieve sufficient power.

Modulators of metabolic response
As hormonal and cytokine mediated metabolic alterations are better understood, therapeutic interventions may become available to directly modulate the metabolic response to illness. In the near future optimal nutritional and metabolic support may therefore also include the administration of hormones that can attenuate the catabolic response. This modulation of the hormonal response to injury may be helpful in augmenting protein preservation. Proposed hormones are insulin, IGF-1, growth hormone, and thyroid hormones. In a large prospective, randomized controlled trial among critically ill adults, maintenance of normal glucose levels with insulin infusion produced wide ranging significant benefits, including a reduction in mortality.[75] On the other hand, a prospective randomized controlled trial on the effects of growth hormone administration in critically ill adults showed increased mortality in the growth hormone group.[76] Only few studies are available on the use of these hormones in critically ill neonates and children, and so far no indication for use of these modulators in practice has been found. Future studies should aim at the groups of children at risk.

Concluding remarks

The results from our studies emphasize the importance of nutritional assessment and adequate feeding in children admitted to a pediatric intensive care unit. A simple and integrated nutritional screening should be part of the admission procedure, to be followed by additional measurements in particular groups of children, including the assessment of nutritional requirements. In addition, nutritional screening should be repeated regularly during ICU-admission in order to monitor changes in nutritional status, diagnoses or conditions that might put the child at nutritional risk and to monitor the efficacy of nutritional support. Until more information is available, nutritional support of critically ill children should focus primarily on preventing the development of nutritional deficiencies rather than on modulation of the metabolic response by specific nutrients, hormones or cytokines.

References

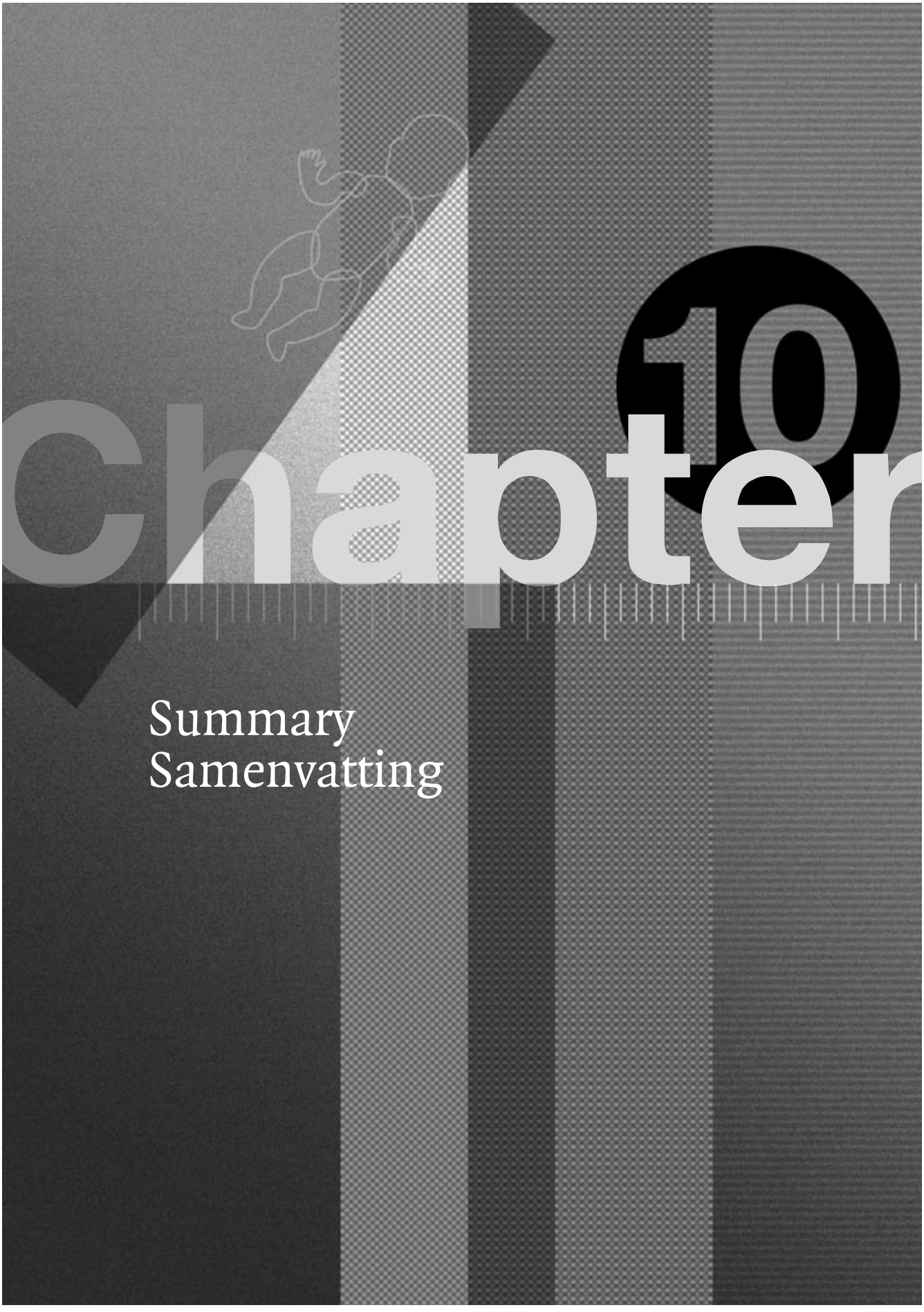
1. Heikens G. Rehabilitation of sick malnourished children: environment, requirements, prognosis and feasibility (PhD thesis). Amsterdam: University of Amsterdam; 2003.
2. Stratton R, Green C, Elia M. Disease-related malnutrition: an evidence-based approach to treatment. Oxon: CAB International; 2003.
3. Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient: a meta-analysis. JAMA 1998;280:2013-9.
4. Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. BMJ 1998;317:1481-7.
5. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr 2002;26:1SA-138SA.
6. Stettler N, Kawachak DA, Boyle LL, Propert KJ, Scanlin TF, Stallings VA, Zemel BS. A prospective study of body composition changes in children with cystic fibrosis. Ann N Y Acad Sci 2000;904:406-9.
7. Brunton JA, Saigal S, Atkinson SA. Growth and body composition in infants with bronchopulmonary dysplasia up to 3 months corrected age: a randomized trial of a high-energy nutrient-enriched formula fed after hospital discharge. J Pediatr 1998;133:340-5.
8. Cezard J, Touati G, Alberti C, Hugot J, Brinon C, Czernichow P. Growth in Paediatric Chron's Disease. Hormone Research 2002;58:11-15.
9. Joosten K. Metabolic, endocrine and nutritional aspects of critically ill children (PhD thesis). Rotterdam: Erasmus University; 1999.
10. Pollack MM, Wiley JS, Holbrook PR. Early nutritional depletion in critically ill children. Crit Care Med 1981;9:580-3.
11. Pollack MM, Wiley JS, Kanter R, Holbrook PR. Malnutrition in critically ill infants and children. J Parenter Enteral Nutr 1982;6:20-4.
12. Pollack MM, Ruttimann UE, Wiley JS. Nutritional depletions in critically ill children: associations with physiologic instability and increased quantity of care. J Parenter Enteral Nutr 1985;9:309-13.
13. Merritt RJ, Suskind RM. Nutritional survey of hospitalized pediatric patients. Am J Clin Nutr 1979;32:1320-5.
14. Shepherd RW, Holt TL, Cleghorn G, Ward LC, Isles A, Francis P. Short-term nutritional supplementation during management of pulmonary exacerbations in cystic fibrosis: a controlled study, including effects of protein turnover. Am J Clin Nutr 1988;48:235-9.
15. Morin CL, Roulet M, Roy CC, Weber A, Lapointe N. Continuous elemental enteral alimentation in the treatment of children and adolescents with Crohn's disease. JPEN J Parenter Enteral Nutr 1982;6:194-9.
16. Hendricks KM, Duggan C, Gallagher L, Carlin AC, Richardson DS, Collier SB, Simpson W, Lo C. Malnutrition in hospitalized pediatric patients. Current prevalence. Arch Pediatr Adolesc Med 1995;149:1118-22.

17. Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatrics 2001;107:270-3.
18. Ruiz-Extremera A, Robles-Vizcaino C, Salvatierra-Cuenca MT, Ocete E, Lainez C, Benitez A, Cruz F, Miranda MT, Salmeron J. Neurodevelopment of neonates in neonatal intensive care units and growth of surviving infants at age 2 years. Early Hum Dev 2001;65 Suppl:S119-32.
19. Georgieff MK, Mills MM, Zempel CE, Chang PN. Catch-up growth, muscle and fat accretion, and body proportionality of infants one year after newborn intensive care. J Pediatr 1989;114:288-92.
20. Georgieff MK, Hoffman JS, Pereira GR, Bernbaum J, Hoffman-Williamson M. Effect of neonatal caloric deprivation on head growth and 1-year developmental status in preterm infants. J Pediatr 1985;107:581-7.
21. Kitchen WH, Ryan MM, Rickards A, McDougall AB, Billson FA, Keir EH, Naylor FD. A longitudinal study of very low-birthweight infants. IV: An overview of performance at eight years of age. Dev Med Child Neurol 1980;22:172-88.
22. Briassoulis G, Zavras N, Hatzis T. Malnutrition, nutritional indices, and early enteral feeding in critically ill children. Nutrition 2001;17:548-57.
23. Almeida Santos L, Ruza F, Guerra AJ, Alves A, Dorao P, Garcia S, Santos NT. [Nutritional evaluation of children with respiratory failure (RF): anthropometric evaluation upon admission to the pediatric intensive care units]. An Esp Pediatr 1998;49:11-6.
24. Leite HP, Isatugo MK, Sawaki L, Fisberg M. Anthropometric nutritional assessment of critically ill hospitalized children. Rev Paul Med 1993;111:309-13.
25. Pollack MM, Smith D. Protein-energy malnutrition in hospitalized children. Hosp Formul 1981;16:1189-90, 1192-3.
26. Lucas A, Fewtrell MS, Morley R, Singhal A, Abbott RA, Isaacs E, Stephenson T, MacFadyen UM, Clements H. Randomized trial of nutrient-enriched formula versus standard formula for postdischarge preterm infants. Pediatrics 2001;108:703-11.
27. Cooke RJ, Embleton ND, Griffin IJ, Wells JC, McCormick KP. Feeding preterm infants after hospital discharge: growth and development at 18 months of age. Pediatr Res 2001;49:719-22.
28. Cooke RJ, McCormick K, Griffin IJ, Embleton N, Faulkner K, Wells JC, Rawlings DC. Feeding preterm infants after hospital discharge: effect of diet on body composition. Pediatr Res 1999;46:461-4.
29. Cooke RJ, Griffin IJ, McCormick K, Wells JC, Smith JS, Robinson SJ, Leighton M. Feeding preterm infants after hospital discharge: effect of dietary manipulation on nutrient intake and growth. Pediatr Res 1998;43:355-60.
30. Smith WJ, Underwood LE, Keyes L, Clemmons DR. Use of insulin-like growth factor I (IGF-I) and IGF-binding protein measurements to monitor feeding of premature infants. J Clin Endocrinol Metab 1997;82:3982-8.
31. Joosten KF, Verhoeven JJ, Hazelzet JA. Energy expenditure and substrate utilization in mechanically ventilated children. Nutrition 1999;15:444-8.

32. Phillips R, Ott L, Young B, Walsh J. Nutritional support and measured energy expenditure of the child and adolescent with head injury. J Neurosurg 1987;67:846-51.
33. Schofield W. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr: Clin Nutr 1985;39:5-41.
34. Briassoulis G, Venkataraman S, Thompson AE. Energy expenditure in critically ill children. Crit Care Med 2000;28:1166-72.
35. Verhoeven JJ, Hazelzet JA, van der Voort E, Joosten KF. Comparison of measured and predicted energy expenditure in mechanically ventilated children. Intensive Care Med 1998;24:464-8.
36. McClave SA, Lowen CC, Kleber MJ, McConnell JW, Jung LY, Goldsmith LJ. Clinical use of the respiratory quotient obtained from indirect calorimetry. J Parenter Enteral Nutr 2003;27:21-6.
37. Chwals WJ. Overfeeding the critically ill child: fact or fantasy? New Horiz 1994;2:147-55.
38. Bresson JL, Bader B, Rocchiccioli F, Mariotti A, Ricour C, Sachs C, Rey J. Protein-metabolism kinetics and energy-substrate utilization in infants fed parenteral solutions with different glucose-fat ratios. Am J Clin Nutr 1991;54:370-6.
39. Health Council of the Netherlands. Dietary Reference Intakes: energy, proteins, fats and digestible carbohydrates. The Hague: Health Council of the Netherlands, 2001; publication no. 2001/19.
40. De Jonghe B, Appere-De-Vechi C, Fournier M, Tran B, Merrer J, Melchior JC, Outin H. A prospective survey of nutritional support practices in intensive care unit patients: what is prescribed? What is delivered? Crit Care Med 2001;29:8-12.
41. McClave SA, Sexton LK, Spain DA, Adams JL, Owens NA, Sullins MB, Blandford BS, Snider HL. Enteral tube feeding in the intensive care unit: factors impeding adequate delivery. Crit Care Med 1999;27:1252-6.
42. Adam S, Batson S. A study of problems associated with the delivery of enteral feed in critically ill patients in five ICUs in the UK. Intensive Care Med 1997;23:261-6.
43. Tormoen S, Powell RW, Luterman A. Injury severity score as a guide to nutritional management of the pediatric trauma patient. Am Surg 1995;61:475-80.
44. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988;16:1110-6.
45. The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. The International Neonatal Network. Lancet 1993;342:193-8.
46. Moy R, Smallman S, Booth I. Malnutrition in a UK children's hospital. Journal of Human Nutrition and Dietetics 1990;3:93-100.
47. Cameron JW, Rosenthal A, Olson AD. Malnutrition in hospitalized children with congenital heart disease. Arch Pediatr Adolesc Med 1995;149:1098-102.
48. Stallings VA, Charney EB, Davies JC, Cronk CE. Nutritional status and growth of children with diplegic or hemiplegic cerebral palsy. Dev Med Child Neurol 1993;35:997-1006.
49. Smith DE, Stevens MC, Booth IW. Malnutrition at diagnosis of malignancy in childhood: common but mostly missed. Eur J Pediatr 1991;150:318-22.

50. Sentongo TA, Semeao EJ, Piccoli DA, Stallings VA, Zemel BS. Growth, body composition, and nutritional status in children and adolescents with Crohn's disease. J Pediatr Gastroenterol Nutr 2000;31:33-40.
51. Pereira AM, Hamani N, Nogueira PC, Carvalhaes JT. Oral vitamin intake in children receiving long-term dialysis. J Ren Nutr 2000;10:24-9.
52. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, Jeejeebhoy KN. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr 1987;11:8-13.
53. Zemel BS, Riley EM, Stallings VA. Evaluation of methodology for nutritional assessment in children: anthropometry, body composition, and energy expenditure. Annu Rev Nutr 1997;17:211-35.
54. Gerver W, De Bruin R. Paediatric Morphometrics: a reference manual. Utrecht: Bunge; 1996.
55. Jonkers CF, Prins F, Van Kempen A, Tepaske R, Sauerwein HP. Towards implementation of optimum nutrition and better clinical nutrition support. Clin Nutr 2001;20:361-6.
56. Piccoli A, Fanos V, Peruzzi L, Schena S, Pizzini C, Borgione S, Bertino E, Chiaffoni G, Coppo R, Tato L. Reference values of the bioelectrical impedance vector in neonates in the first week after birth. Nutrition 2002;18:383-7.
57. Savino F, Grasso G, Cresi F, Oggero R, Silvestro L. Bioelectrical impedance vector distribution in the first year of life. Nutrition 2003;19:492-6.
58. De Palo T, Messina G, Edefonti A, Perfumo F, Pisanello L, Peruzzi L, Di Iorio B, Mignozzi M, Vienna A, Conti G, Penza R, Piccoli A. Normal values of the bioelectrical impedance vector in childhood and puberty. Nutrition 2000;16:417-24.
59. Russell DM, Leiter LA, Whitwell J, Marliss EB, Jeejeebhoy KN. Skeletal muscle function during hypocaloric diets and fasting: a comparison with standard nutritional assessment parameters. Am J Clin Nutr 1983;37:133-8.
60. Klein S, Kinney J, Jeejeebhoy K, Alpers D, Hellerstein M, Murray M, Twomey P. Nutrition support in clinical practice: review of published data and recommendations for future research directions. Summary of a conference sponsored by the National Institutes of Health, American Society for Parenteral and Enteral Nutrition, and American Society for Clinical Nutrition. Am J Clin Nutr 1997;66:683-706.
61. Fewtrell MS, Morley R, Abbott RA, Singhal A, Isaacs EB, Stephenson T, MacFadyen U, Lucas A. Double-blind, randomized trial of long-chain polyunsaturated fatty acid supplementation in formula fed to preterm infants. Pediatrics 2002;110:73-82.
62. Butte NF, Wong WW, Hopkinson JM, Smith EO, Ellis KJ. Infant feeding mode affects early growth and body composition. Pediatrics 2000;106:1355-66.
63. Thompson SW, McClure BG, Tubman TR. A Randomized, Controlled Trial of Parenteral Glutamine in Ill, Very Low Birth-weight Neonates. J Pediatr Gastroenterol Nutr 2003;37:550-3.
64. Marriott LD, Foote KD, Bishop JA, Kimber AC, Morgan JB. Weaning preterm infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2003;88:F302-7.

65. Preiser JC, Chiolero R, Wernerman J. Nutritional papers in ICU patients: what lies between the lines? Intensive Care Med 2003;29:156-66.
66. Tepaske R, Velthuis H, Oudemans-van Straaten HM, Heisterkamp SH, van Deventer SJ, Ince C, Eysman L, Kesecioglu J. Effect of preoperative oral immune-enhancing nutritional supplement on patients at high risk of infection after cardiac surgery: a randomised placebo-controlled trial. Lancet 2001;358:696-701.
67. Griffiths RD, Jones C, Palmer TE. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. Nutrition 1997;13:295-302.
68. Grimm H, Kraus A. Immunonutrition--supplementary amino acids and fatty acids ameliorate immune deficiency in critically ill patients. Langenbecks Arch Surg 2001;386:369-76.
69. Ball PA, Hardy G. Glutamine in pediatrics: where next? Nutrition 2002;18:451-4.
70. Lacey JM, Crouch JB, Benfell K, Ringer SA, Wilmore CK, Maguire D, Wilmore DW. The effects of glutamine-supplemented parenteral nutrition in premature infants. JPEN J Parenter Enteral Nutr 1996;20:74-80.
71. Poindexter BB, Ehrenkranz RA, Stoll BJ, Koch MA, Wright LL, Oh W, Papile LA, Bauer CR, Carlo WA, Donovan EF, Fanaroff AA, Korones SB, Laptook AR, Shankaran S, Stevenson DK, Tyson JE, Lemons JA. Effect of parenteral glutamine supplementation on plasma amino acid concentrations in extremely low-birth-weight infants. Am J Clin Nutr 2003;77:737-43.
72. Roig JC, Meetze WH, Auestad N, Jasionowski T, Veerman M, McMurray CA, Neu J. Enteral glutamine supplementation for the very low birthweight infant: plasma amino acid concentrations. J Nutr 1996;126:1115S-20S.
73. Neu J, Roig JC, Meetze WH, Veerman M, Carter C, Millsaps M, Bowling D, Dallas MJ, Sleasman J, Knight T, Auestad N. Enteral glutamine supplementation for very low birth weight infants decreases morbidity. J Pediatr 1997;131:691-9.
74. Dallas MJ, Bowling D, Roig JC, Auestad N, Neu J. Enteral glutamine supplementation for very-low-birth-weight infants decreases hospital costs. JPEN J Parenter Enteral Nutr 1998;22:352-6.
75. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001;345:1359-67.
76. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, Hinds CJ. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 1999;341:785-92.



Chapter 10

Summary
Samenvatting

Summary

Critically ill children are at risk of deteriorating nutritional status when admitted to an intensive care unit. This may lead to malnutrition, which is associated with increased morbidity and mortality. While adequate feeding is essential for complete recovery and normal functional outcome of the growing child, caregivers on admission tend to focus on the primary medical problem. In order to provide good nutritional care it seems essential to fully assess the child's nutritional status and needs. Various methods are available, and it is the child's age, clinical presentation, and illness severity that determine which of them is most suitable as individual approach.
This thesis describes the prevalence of malnutrition in critically ill children and investigates the applicability and usefulness of the available assessment methods for identifying children with poor initial nutritional status or at risk of developing malnutrition. We focused on the feasibility of routine use in the pediatric ICU setting.

In **Chapter 1** we provide the background and aims of the studies presented in this thesis. We describe the various components of a comprehensive nutritional assessment: general evaluation, severity of illness assessment, assessment of body composition, and laboratory studies – including the estimation of energy and protein requirements. Furthermore, we review the available literature on different nutritional assessment methods, specifically for applicability in daily practice in children admitted to a pediatric ICU. Each method appeared to have its drawbacks and limitations. A golden standard assessment is not available for the pediatric ICU population.

In this thesis we analyzed data obtained from a cohort of children receiving intensive care in the Erasmus MC-Sophia Children's Hospital during the year 2001. This cohort consisted of preterm neonates, term neonates and older children aged 30 days-16 years.

Before reporting our findings from the use of the various assessment tools, we first describe what factors influenced parents to consent in participation of their critically ill child in the nutritional assessment study (**Chapter 2**). We compared characteristics of children of whom parents gave permission (n = 333) with those of children whose parents refused consent (n = 88). Our primary observation was that a higher degree of actual illness – as determined by objective scores at the time of the consent decision – did not negatively influence parents' willingness to give permission. A history of (chronic) disease did lower the informed consent rate, especially for the children aged 12 years and older, the ones that participated in the informed consent process themselves. Secondly, the most frequent reason for parents to refuse permission was that they felt the study comprised too many interventions and would be too burdensome for their child in view of its condition. Overall, other demographic, clinical and disease characteristics

were comparable between the children with and without consent.
The findings from this chapter also indicate that the group of children in which we evaluated nutritional status by different methods, adequately represents the total group of children admitted to an ICU.

In **Chapter 3,** we prospectively determined the prevalence of malnutrition in our study group, on admission to the ICU, at discharge and after 6 weeks and 6 months after discharge by means of anthropometry. Overall, in 24% of the 293 children signs of acute and/or chronic malnutrition were present on admission. Furthermore, our study group was found to be in a poorer nutritional status than the general pediatric population as SD-scores of the various anthropometric parameters were found to be below mean values.
Preterm and term neonates' nutritional status declined over admission, as expressed by decreasing SD-scores for weight, length, head circumference and additional anthropometric parameters. In the older children, SD-scores of arm circumference, calf circumference and skinfolds decreased, but weight, length or head circumference were not affected. At six months after discharge almost all children had shown complete recovery of nutritional status. Parameters that most adversely affected preterm and term neonates' nutritional status at discharge and during follow-up were found to be length of stay and history of disease.

In **Chapter 4,** we performed indirect calorimetry measurements in a group of 98 children admitted to the pediatric ICU to determine the respiratory quotient (RQ) and energy requirements during the first 14 days of admission. Comparing actual energy intakes with energy requirements as defined by a classification used for adults (measured energy expenditure plus an additional 10% for activity), it appeared that these children received adequate nutrition on only 10% of days, and were underfed and overfed on 21% and 69% of days, respectively. However, we pointed out that the use of this adult classification is arguable in critically ill children who have resumed somatic growth.
The usefulness of the RQ to assess feeding adequacy was found to be limited due to poor sensitivity and large inter-individual variability. This means that the RQ is not reliably reflected in the same way in all children in response to overfeeding and underfeeding and that consequently factors other than energy intake relative to energy requirements must be important. The study revealed, however, that the extreme values of RQ can well be used to indicate two clinically relevant issues: RQ > 0.85 reliably indicates the absence of underfeeding, and RQ > 1.0 reliably indicates the presence of (carbohydrate) overfeeding.

In **Chapter 5**, we analyzed in a group of 261 children the relationships between cumulative energy and protein balances, various clinical factors and changes in anthropometry (weight, arm and calf circumference) during the first 14 days of admission

to the ICU. In order to calculate cumulative balances, actual energy and protein intake were compared with recommended intakes for healthy children and summed. The results showed significant cumulative nutritional deficits, with a mean of 27, 20, 12 kcal/kg and 0.6, 0.3, and 0.2g protein/kg per day for preterm neonates, term neonates and older children, respectively. Age at admission, length of ICU-stay and days on mechanical ventilation were negatively related to cumulative balances. Moreover, the cumulative energy and protein deficits were associated with declines in SD-scores for weight and arm circumference.

Chapter 6 describes the usefulness of routine laboratory parameters (urea, albumin, magnesium and triglycerides) in the identification of children at risk for deterioration of nutritional status during ICU-stay. Although abnormalities in these biochemical parameters were found in prevalences up to 52%, these abnormalities, except uremia, were not strongly associated with changes in SD-scores of anthropometric measurements between admission and discharge. Children with uremia showed larger declines in SD-scores for weight and arm circumference between admission and discharge than did children without uremia, but factors other than merely protein breakdown, such as impaired renal function, were identified that could attribute to their high urea level. This complicates the drawing of conclusions about the suitability of using serum urea levels in detecting children at risk for decline of their nutritional status between admission and discharge from the ICU. We conclude, therefore, that the panel of parameters used does not seem to be very useful for predicting growth in critically ill children at the end of ICU admission.

In **Chapter 7,** we studied in critically ill term neonates (n = 50) and children aged > 1 month (n = 34) during the first week of ICU-admission the courses of the hormonal parameters IGF-1, T_3, rT_3 and ratio T_3/rT_3 in relation to severity of illness and feeding adequacy. The concentrations of IGF-1, T_3 and the ratio T_3/rT_3 inclined between admission and day 6, whereas the rT_3 level significantly declined over this period. Abnormalities in levels of IGF-1, T_3 and rT_3 were frequently observed, especially in the children aged > 1 month. Furthermore, in many children of this age group, levels of the anabolic hormones IGF-1 and T_3 had not yet normalized on day 6 after admission. This implies that total resolution of the acute stress response has not taken place at this time point and that return to anabolic metabolism has not been completed. Feeding adequacy did not seem to affect the normalization of IGF-1 and thyroid hormone levels, but the changes in T_3 levels showed a significant negative association with changes in CRP levels, whereas changes in rT_3 coincided with changes in CRP. This may indicate that during the first week of ICU-admission recovery of the acute stress response, as expressed by declining CRP level, more prominently dictates the changes in thyroid hormone and IGF-1 levels than does feeding adequacy. Our findings suggest that it

seems useful to study the relation between hormonal parameters and energy and protein intake over a longer period.

In **Chapter 8,** we determined feasibility and reliability of routine non-invasive measurements of nutritional status and nutritional needs – anthropometry, BIA, and indirect calorimetry – in 316 children admitted to the pediatric ICU. To this aim we evaluated the performance of measurements at different moments: within 24 hours after admission, weekly during admission and at discharge. The results showed that reliable assessment of nutritional status using these non-invasive methods is routinely possible in daily pediatric ICU practice. However, several factors were found to complicate (reliable) measurements, e.g. instability/pain, agitation, the presence of edema, or the presence of splints or bandages at measurement sites. In addition, measurements were more difficult to perform in the initial stage of admission, with increasing illness severity and with increasing age. This knowledge underlines the need for a patient tailored approach and the need for continuing the search for non-invasive tools that can be applied even in the most seriously ill children.
Due to the strict criteria to be met before indirect calorimetry can be performed, only a minority of children (21-34%) was eligible for this type of assessment. It proved possible, however, to perform reliable measurements in 70-80% of the eligible children.

In **Chapter 9,** we discuss our findings in context with the literature and enlarge upon the benefits and limitations of the chosen study design and study population. Furthermore, we discuss the implications of our findings for clinical ICU practice and suggest a guideline for routine nutritional assessment in critically ill children. In this proposed guideline we discriminate between different age groups, expected durations of stay, initial levels of nutritional status and risk groups.

The main **conclusions** obtained from the studies described in this thesis are the following:

- Twenty-four percent of the neonates and children admitted to a pediatric intensive care unit have poor nutritional status on admission.
- The nutritional status of critically ill children, as expressed by anthropometric parameters, worsened during admission, predominantly in the preterm and term neonates.
- At six months after discharge, standard deviation scores of the different anthropometric parameters have returned to admission levels in most children.
- The usefulness of the RQ in monitoring feeding adequacy is limited to identifying (carbohydrate) overfeeding and excluding underfeeding.
- The cumulative energy and protein deficits during the first 14 days of ICU-admission, as shown from comparing intakes to the recommended intakes for

healthy children, are most pronounced in the preterm neonates and are related to decreases in anthropometric parameters.

- The routine assessment of nutritional status using non-invasive methods is feasible in daily pediatric ICU practice.

Samenvatting

De letterlijke betekenis van de term ondervoeding is een lichamelijke toestand waarbij sprake is van een verminderde biologische functie als gevolg van een tekort aan voedingsstoffen. Als we deze definitie hanteren, is er in westerse landen nauwelijks sprake van ondervoeding. Ondervoeding in Nederland is vooral gerelateerd aan het hebben van een ziekte. Enerzijds heeft de ziekte zelf een katabole of weefselafbrekende invloed op het lichaam, en anderzijds kan bij ziekte de voedselinname, -opname en/of -benutting verlaagd zijn, kunnen er abnormale verliezen aan voedingstoffen optreden en/of kan de voedingsbehoefte verhoogd zijn. Kinderen zijn in vergelijking met volwassenen extra gevoelig voor het ontstaan van ondervoeding tijdens ziekte doordat hun reserves aan voedingstoffen in het lichaam relatief kleiner zijn. Onderzoek uit de jaren tachtig liet zien dat 15-20% van de kinderen opgenomen op een intensive care (IC) afdeling acuut of chronisch ondervoed was. Cijfers over de huidige prevalentie van ondervoeding bij kinderen opgenomen op een IC-afdeling zijn niet voorhanden.

Het gestandaardiseerd bepalen van de voedingstoestand (*nutritional assessment*) bij (ernstig) zieke kinderen is van uitermate groot belang voor het opsporen van kinderen met reeds bestaande ondervoeding en kinderen die een verhoogd risico lopen op het ontstaan van ondervoeding. Tevens kan dit dienen voor het vaststellen van de mate van ondervoeding en het evalueren van het ingestelde voedingsbeleid.

Voor de bepaling van de voedingstoestand zijn verschillende methoden beschikbaar, waarvan de klinische toepasbaarheid afhangt van de leeftijd van het kind, de ernst van ziekte en de presentatie van de ziekte. Hierdoor is het tot op heden niet mogelijk gebleken om de voedingstoestand van ernstig zieke kinderen uit te drukken door middel van een enkele parameter. In dit proefschrift worden dan ook verschillende methoden toegepast. Dit leidt tot conclusies over de prevalentie van acute en chronische ondervoeding bij kinderen opgenomen op een IC-afdeling. Tevens hadden de studies die beschreven worden in dit proefschrift tot doel te bepalen welke methoden het best onderscheidend en toepasbaar zijn bij ernstig zieke kinderen in de dagelijkse praktijk van een IC-afdeling.

In **hoofdstuk 1** worden de achtergronden en doelstellingen beschreven van de studies die in dit proefschrift gepresenteerd worden. Een overzicht van de mogelijke methoden voor het vaststellen van de voedingstoestand wordt gegeven, met de nadruk op de dagelijkse praktische toepasbaarheid van deze methoden bij ernstig zieke kinderen opgenomen op een IC-afdeling. Een aantal van deze methoden wordt toegepast in de studies beschreven in de verschillende hoofdstukken van dit proefschrift.
De kinderen waarbij onderzoek werd verricht varieerden in leeftijd (van pasgeborenen, zowel prematuur als à term, tot kinderen van 1 maand tot 16 jaar), soort en ernst van

ziekte of aandoening, maar waren allen enige tijd opgenomen op de neonatale, kindergeneeskundige of chirurgische intensive care van het Erasmus MC-Sophia Kinderziekenhuis in het jaar 2001.

Alvorens op de resultaten betreffende de verschillende *nutritional assessment* methoden in te gaan, wordt gekeken naar de samenstelling van de studiegroep. Voor het verrichten van onderzoek bij kinderen is het verplicht toestemming te vragen aan ouders of verzorgers; dit wordt ook wel aangeduid met de term *informed consent*. In **hoofdstuk 2** wordt een vergelijking gemaakt tussen de 333 kinderen waarvoor ouders (en/of het kind) toestemming gaven voor deelname aan het onderzoek en de 88 kinderen waarvan ouders niet toestemden. We waren in het bijzonder geïnteresseerd of de ernst van de ziekte een rol speelde in de beslissing van ouders. Uit de resultaten blijkt dat dit niet het geval was. De ziekte-ernst – uitgedrukt in gevalideerde scores – van de kinderen die wel deelnamen verschilde niet significant van die van de andere kinderen. Ook andere demografische, ziekte-ernst gerelateerde en ziekte-gerelateerde factoren waren niet van invloed op het verlenen van *informed consent*, behalve dat een mogelijke voorgeschiedenis van ziekte en ziekenhuisopnames van het kind de mate van toestemming geven significant negatief beïnvloedden, met name bij de kinderen van 12 jaar en ouder die zelf konden meebeslissen. Van de ouders die deelname aan het onderzoek weigerden, gaven de meesten als reden aan de extra belasting van hun kind boven de al veelvuldige invasieve ingrepen en procedures op de IC-afdeling.
De resultaten van dit hoofdstuk geven verder aan dat de bestudeerde groep kinderen een representatieve afspiegeling vormt van de totale populatie kinderen opgenomen op een IC-afdeling.

Hoofdstuk 3 beschrijft het verloop van verschillende anthropometrische parameters (gewicht, lengte, hoofdomtrek, bovenarm- en kuitomtrek en huidplooien) bij 293 kinderen vanaf opname op de IC-afdeling tot 6 maanden na ontslag. Bij opname werd een prevalentie van 24% gevonden voor het bestaan van acute en/of chronische ondervoeding. Een groot aantal van deze kinderen met een slechte voedingstoestand bij opname had een chronisch ziekte of een ziekte die gepaard gaat met groeivertraging. De groep kinderen die wij bestudeerd hebben waren gemiddeld genomen in een slechtere voedingstoestand bij opname dan kinderen uit de Nederlandse populatie. Tijdens de opname op de IC-afdeling treedt een verslechtering op van de voedingstoestand, met name bij pasgeborenen. Andere risicofactoren voor het verslechteren van de voedingstoestand zijn een langere opnameduur en het hebben van een onderliggende (chronische) ziekte of aandoening. De poliklinische vervolgonderzoeken na ontslag lieten zien dat de voedingstoestand van het merendeel van de pasgeborenen 6 weken na ontslag nog niet hersteld is, maar dat 6 maanden na ontslag de waarden van de anthropometrische parameters gelijk zijn aan of hoger liggen dan de waarden bij opname op de IC-afdeling.

De basis voor een goede voedingstherapie is het vaststellen van de voedingsbehoefte. Deze voedingsbehoefte is bij ernstig zieke kinderen sterk individueel bepaald. In **hoofdstuk 4** wordt met behulp van zogeheten indirecte calorimetrie het energieverbruik van 98 kinderen gemeten gedurende de eerste 14 dagen van de opname op de IC-afdeling. Met behulp van deze methode worden de in– en uitgeademde gasvolumes en de concentraties zuurstof en kooldioxide bepaald. Hieruit kunnen de hoeveelheid geproduceerde kooldioxide, de verbruikte hoeveelheid zuurstof en de verhouding tussen beide waarden, de respiratoire quotiënt (RQ), bepaald worden, alsmede het energieverbruik. Wanneer de energie-inname van deze kinderen wordt vergeleken met hun energiebehoefte, de laatste bepaald op basis van een bij volwassen IC-patiënten gebruikte formule (gemeten energieverbruik plus een extra 10% voor activiteit), is er op slechts 10% van de meetdagen sprake van adequate voeding. Volgens deze rekenmethode treedt onvoldoende energie-inname, maar vooral overmatige energie-inname veelvuldig op (respectievelijk op 21 en 69% van de dagen) en dan met name gedurende de latere dagen van opname. Het gebruik van deze “volwassen” formule bij kinderen voor het bepalen van de energiebehoefte is echter controversieel in de fase dat kinderen weer gaan groeien. Deze studie laat tevens zien dat de RQ onvoldoende selectief is om vast te stellen of de toegediende hoeveelheid voeding voldoende is. De RQ is klinisch wél te gebruiken om (koolhydraat)overvoeding te signaleren (RQ > 1.0) en ondervoeding (RQ < 0.85) uit te sluiten.

In **hoofdstuk 5** worden de dagelijkse energie- en eiwitinname van 261 kinderen gedurende de eerste 14 dagen van IC-opname vergeleken met de aanbevolen dagelijkse hoeveelheid (ADH) voor energie en eiwit voor gezonde kinderen. Deze ADH levert voldoende energie voor het groeiende kind. De dagelijkse verschillen tussen ADH en werkelijke inname werden opgeteld, en de resultaten lieten duidelijke cumulatief innametekorten zien van gemiddeld 27, 20, en 12 kcal/kg/dag en 0.6, 0.3, en 0.2 g eiwit/kg/dag voor respectievelijk de preterme pasgeborenen, à terme pasgeborenen en oudere kinderen. De tekorten namen toe gedurende de opnameperiode en waren vooral aanzienlijk bij premature pasgeborenen. Andere factoren met een significante negatieve invloed op de grootte van de ontstane tekorten zijn een chirurgische ingreep en een langere beademings- of opnameduur. Bovendien bestaat er verband tussen de mate van cumulatieve tekorten aan energie en eiwit en de verandering in anthropometrische parameters (gewicht, armomtrek en kuitomtrek), waarbij de voedingstoestand van de kinderen met de grootste tekorten significant meer verslechtert.

Hoofdstuk 6 beschrijft de waarde van het bepalen van een panel van routine-laboratorium parameters (ureum, albumine, magnesium en triglyceriden) bij opname op de IC-afdeling voor het identificeren van kinderen die risico lopen op een verslechtering van hun voedingstoestand gedurende de IC-opname. Hoewel er een groot aantal afwijkingen werd gevonden kon er geen duidelijke relatie worden gelegd tussen de

waarden van deze parameters en veranderingen in de voedingstoestand. Weliswaar vonden we dat kinderen met een verhoogd ureumgehalte bij opname een sterkere daling van gewicht en armomtrek vertoonden tijdens opname in vergelijking met kinderen met een normaal ureumgehalte, maar naast een mogelijke sterkere spierafbraak waren in deze groep kinderen nog andere factoren aanwezig die het ureumgehalte in het bloed kunnen verhogen. Dit maakt het moeilijk te concluderen of het ureumgehalte van nut is voor het opsporen van kinderen met een verhoogd risico op verslechtering van hun voedingstoestand. We concluderen dan ook dat het gebruik van dit minimale pakket laboratoriumbepalingen niet bruikbaar is bij het voorspellen van groei bij ernstig zieke kinderen aan het einde van de IC-opname.

In **hoofdstuk 7** hebben we het optreden van hormonale veranderingen (IGF-1, schildklierhormonen) bij ernstig zieke pasgeborenen (n = 50) en kinderen > 1 maand (n = 34) bestudeerd in de eerste week van opname, in relatie met de ernst van de ziekte en de voedingsinname. Zowel de concentratie van IGF-1, T_3 als de ratio T_3/rT_3 lieten een stijging zien tussen opname en dag 6, terwijl de rT_3 concentratie in deze periode duidelijk afnam. Bij een groot aantal van de kinderen ouder dan 1 maand zijn de waarden van T_3 en IGF-1 op dag 6 echter nog niet genormaliseerd. Dit impliceert dat bij deze kinderen de acute stress-respons nog niet is verdwenen en dat er dus nog geen sprake is van anabolisme. In onze studie werd geen verband gevonden tussen verbeteringen van de hormoonspiegels en de mate van energie- en eiwitinname gedurende de eerste week na opname, maar de veranderingen in hormoonspiegels vertoonden een significante relatie met veranderingen in het niveau van het acute fase eiwit CRP. Dit zou kunnen betekenen dat het herstel van de acute stress-respons wordt uitgedrukt door dalende CRP-concentraties, wat dan weer overwegend bepalend is voor de concentraties van IGF-1 en schildklierhormonen. Naar aanleiding van onze bevindingen lijkt het zinvol om de mogelijke relatie tussen veranderingen in hormoonspiegels en de mate van energie- en eiwitinname te bestuderen gedurende een langere periode.

In **hoofdstuk 8** zijn de uitvoerbaarheid en betrouwbaarheid in kaart gebracht van het routinematig toepassen van weinig belastende methoden (anthropometrie, bio-electrische impedantiemeting en indirecte calorimetrie) voor het vaststellen van de voedingstoestand en de voedingsbehoefte van 316 kinderen opgenomen op een IC-afdeling. Hiertoe werden metingen geëvalueerd die verricht werden op verschillende meetmomenten, namelijk binnen 24 uur na opname op de IC, wekelijks gedurende de opname, en bij ontslag van de IC. De resultaten laten zien dat bij de meeste kinderen de diverse anthropometrische metingen op deze momenten goed en betrouwbaar te verrichten waren. Er zijn echter een aantal factoren geïdentificeerd die een goede anthropometrische beoordeling in de weg staan, namelijk instabiliteit/pijn, onrust, de aanwezigheid van oedeem of de aanwezigheid van pleisters, infusen of spalken op de

meetplaatsen. Tevens is het verrichten van deze metingen moeilijker gebleken tijdens de eerste dagen van opname, naarmate het kind zieker is, en naarmate het kind ouder is. Deze gegevens benadrukken de noodzaak tot een patiëntgerichte benadering en versterken de behoefte om te blijven zoeken naar niet belastende en nauwkeurige methoden die ook toepasbaar zijn bij de meest zieke kinderen.
Gezien de strenge voorwaarden voor het toepassen van indirecte calorimetrie, kwam slechts een minderheid (21-34%) van de kinderen in aanmerking voor deze meting. Bij de kinderen die in aanmerking kwamen, lukte het in 70-80% van de gevallen om de meting goed te verrichten.

In **hoofdstuk 9** worden de voornaamste bevindingen van onze studies besproken in relatie met de gegevens uit eerder beschreven onderzoeken. De sterke punten en beperkingen van de gekozen studieopzet en studiepopulatie worden besproken. Tevens worden de klinische implicaties van onze resultaten toegelicht en wordt een voorstel gedaan voor het doen van routinematige “nutritional assessment” op de kinder-IC-afdeling. Dit voorstel maakt onderscheid tussen verschillende leeftijdsgroepen, de duur van opname, de voedingstoestand bij opname en het al dan niet behoren tot een risicogroep voor het ontstaan van ondervoeding.

De voornaamste **conclusies** resulterend uit dit proefschrift zijn de volgende:

- Vierentwintig procent van de kinderen opgenomen op een IC-afdeling heeft al een slechte voedingstoestand bij opname.
- De voedingstoestand van deze ernstig zieke kinderen, uitgedrukt in anthropometrische parameters, verslechtert gedurende de opname, met name bij preterme en à terme pasgeborenen.
- Zes maanden na ontslag zijn de anthropometrische parameters van de meeste kinderen weer terug op het niveau van opname.
- De respiratoire quotiënt is bruikbaar voor het vaststellen van een overmatige voedingsinname en het uitsluiten van een tekort aan voedingsinname.
- De cumulatieve energie- en eiwittekorten die optreden gedurende de eerste 14 dagen van IC-opname, bij vergelijking van de inname met de aanbevolen dagelijkse inname voor gezonde kinderen, zijn het grootst bij de preterme pasgeborenen en zijn gerelateerd aan verslechtering van anthropometrische parameters.
- Het routinematig en betrouwbaar uitvoeren van weinig belastende metingen is mogelijk bij de meerderheid van kinderen opgenomen op een IC-afdeling.

Dankwoord

Na een intensieve onderzoeksperiode van ruim drie jaar geeft het een geweldig gevoel het eindresultaat in handen te hebben! Dit was niet gelukt zonder de hulp van velen. Iedereen hartelijk bedankt!

Mijn grootste dank gaat uit naar de deelnemende kinderen en hun ouders die belangeloos hebben meegewerkt. Dankzij jullie en uw medewerking zijn we weer een stap verder gekomen in het optimaliseren van de zorg voor ernstig zieke kinderen.

Dr. K.F.M. Joosten, mijn copromotor; beste Koen, ontzettend bedankt voor je uitstekende begeleiding, inzet, scherpe blik en enthousiasme. Je hebt een zeer belangrijke rol gespeeld bij de totstandkoming van dit proefschrift.

Mijn promotoren, Prof. dr. D. Tibboel en Prof. dr. J.B. van Goudoever. Beste Dick, in 2000 vroeg je me voor dit grootschalig onderzoek, ik ben blij dat ik je aanbod heb geaccepteerd ook al was de uitwerking van de data niet altijd even gemakkelijk. Ik bewonder je gedrevenheid en enthousiasme en wil je bedanken voor het in het oog houden van de grote lijnen. Beste Hans, bedankt voor je begeleiding, positivisme en de goede samenwerking. Ik vind het erg leuk om als eerste een promovendus van je te zijn!

Prof. dr. H.A. Büller, beste Hans, mede-initiator van dit project, ik dank je voor de interessse die je gedurende de afgelopen jaren hebt getoond en het nuttige commentaar op de stukken.

Dr. L.J.I Zimmerman, beste Luc, iets meer op de achtergrond was jij betrokken bij mijn onderzoek. Hartelijk dank voor het meedenken en je commentaren.

Prof. dr. H.N. Lafeber en Prof. dr. H.J. Bonjer wil ik bedanken voor de snelle beoordeling van mijn manuscript. Prof. dr. F.W.J. Hazebroek en Prof. dr. H. van Vught dank ik voor hun bereidheid plaats te willen nemen in de grote commissie.

De researchverpleegkundigen Marjan, Ada, Ineke, Marianne en Annelies, ontzettend bedankt voor jullie hulp en inzet bij de opzet van het onderzoek, het maken van de database en het verzamelen en invoeren van de data. We waren een superteam...nog maar een 3-IC studie?

De verpleegkundigen en artsen van de IC-afdelingen dank ik voor hun medewerking. De medewerkers van het lab (AKC-Sophia en lab Interne III, Erasmus MC; endocrinologisch lab, UMC) voor hun hulp bij de verwerking van de bloed- en urinemonsters.
De secretaresses van de IC-afdelingen, poli-assistentes en portiers van het ziekenhuis: zonder jullie logistieke hulp was het allemaal niet zo gesmeerd verlopen.

Dr. W.C.J. Hop, beste Wim, heel wat uren hebben we doorgebracht achter jouw PC en menig keer heb je me duidelijk gemaakt hoe ontzettend moeilijk het analyseren van data afkomstig van IC-patiënten is. Ik ben blij dat we volgehouden hebben en ben je dankbaar voor je hulp en de goede samenwerking. Ik heb veel van je geleerd!

Mede-onderzoekers op de ICN, Sinno Simons en Niesje Jongeneel dank ik voor het gecombineerd toestemming vragen, veelal in de nachtelijke uurtjes!

Ko Hagoort, beste Ko, enorm bedankt voor je hulp bij de bewerking van de tekst tot prachtige Engelse volzinnen, great job!

Margo Terlouw, beste Margo, het boekje ziet er prachtig uit dankzij jou secure opmaak. Ontzettend bedankt!

Glenn van den Bos, ik bedank jou en je team voor de geweldige creatieve bijdrage aan de cover en vormgeving!

De grote groep collega-onderzoekers van de kindergeneeskunde en kinderchirurgie, in het bijzonder Daphne, Sophie, Sacha, Carola, Venje, Manon, Marieke (B), Maaike (2x), Geert, bedankt voor de gezelligheid, borrels, AIO-weekenden en adviezen!
Kamergenootjes Janine en Sandra, bedankt voor jullie support in de laatste fase. Collega-assistenten kindergeneeskunde, ik kijk uit naar de komende jaren!

Lieve Mariek en Bar, ik vind het super dat jullie mijn paranimfen zijn! Onwijs bedankt voor alle gezelligheid, hulp en steun gedurende de afgelopen jaren en vooral tijdens de laatste drukke periode. Heel veel succes met jullie eigen ‘boekjes’!

Lieve atletiekvriendinnen en -vrienden, dank voor jullie luisterend oor en afleiding. Ik heb de afgelopen maanden regelmatig verstek laten gaan op de baan, maar ben van plan jullie binnenkort mijn hielen weer te laten zien!

Mijn ouders, lieve Peet en Let, erg bedankt voor jullie onvoorwaardelijke liefde, steun en geloof in mij. Ik ben erg blij dat ik uit zo’n warm nest kom.
Lieve Joyce, Jon, Harold, Jennifer, familie en vrienden, bedankt voor jullie interesse, vertrouwen en nodige afleiding na weer een lange dag achter de compu. Joycie, tweelingzus, ik ben trots op je, bedankt voor je input!

Lieve Jim, een paar zinnen in je moedertaal speciaal voor jou. Tusen takk for din støtte og kjærlighet gjennom disse ti årene. Uten din hjelp hadde ikke denne oppgaven vært ferdig ennå. Jeg håper på at 2004 blir et stort år for deg også... Jeg elsker deg!

Curriculum vitae

Jessie Hulst was born on July 31st, 1973, as the second child of a twin pair in Rotterdam, the Netherlands. She attended the secondary school St. Laurenscollege in Rotterdam and passed the VWO exam in 1991. In the same year she started her medical training at the Faculty of Medicine and Health Sciences of the Erasmus University, Rotterdam. During her study she performed athletics at a national level which resulted in a 2-year athletic scholarship at the University of Texas at El Paso, USA from August 1993 to June 1995. In September 1995 she resumed her medical studies and participated in a study on the long term outcome of prematurely born infants at the neonatology department of the Sophia Children's Hospital (1997). She obtained her medical degree in January 2000. From February until December 2000 she worked as a resident at the pediatric surgical intensive care unit of the Sophia Children's Hospital, Rotterdam. In December 2000, she started working as a research physician for the project "Nutritional assessment of critically ill children: a prospective, longitudinal follow-up study" which is presented in this thesis. The study was performed at the Intensive care units of the Sophia Children's Hospital and supervised by Prof. Dr. D. Tibboel, Prof. Dr. J.B. van Goudoever and Dr. K.F.M. Joosten. In January 2004 she started her clinical pediatric residency in training (AGIO) at the Erasmus MC-Sophia Children's Hospital, Rotterdam (head Prof. Dr. H.A. Büller and Prof. Dr. A.J. van der Heijden). She is living together with Jim Svenøy.

List of abbreviations

BIA	Bio-electrical impedance analysis
BSF	Biceps skin fold
CC	Calf circumference
CRIB	Clinical Risk Index for Babies
DEXA	Dual energy x-ray absorptiometry
DLW	Double labelled water
FFM	Fat-free mass
EE	Energy expenditure
HC	Head circumference
HFA	Height-for-age
ICU	Intensive care unit
IGF-1	Insulin like growth factor-1
IRB	Institutional review board
KHL	Knee-heel length
LFA	Length-for-age
LOS	Length of stay
MEE	Measured energy expenditure
MUAC	Mid upper arm circumference
NICU	Neonatal intensive care unit
PEM	Protein energy malnutrition
PICU	Pediatric intensive care unit
PIM	Pediatric Index of Mortality
PRISM	Pediatric Risk of Mortality Score
RDA	Recommended daily allowance
REE	Resting energy expenditure
RQ	Respiratory quotient
rT_3	Reverse T_3
SDS	Standard deviation score
SGA	Subjective global assessment
SNAP	Score for Neonatal Acute Physiology
T_3	Triiodothyronine
TBW	Total body water
TDEE	Total daily energy expenditure
TISS	Therapeutic Intervention Scoring System
TOBEC	Total body electrical conductivity
TSF	Triceps skin fold
VO_2	Oxygen consumption
VCO_2	Carbon dioxide production
WFA	Weight-for-age
WFH	Weight-for-height