Chapter 2
Review of Literature
REVIEW OF LITERATURE

The literature pertinent to this study has been reviewed under the following headings:

2.1. Pediatric general requirements
2.2. Growth and Development
2.3 Definition of Malnutrition
2.4. Prevalence of Malnutrition in Hospitalized Children
2.5. Consequences of Malnutrition
2.6. Metabolic stress response to Critical Illness
2.7. Screening tools to identify children at risk of Malnutrition
2.8. Nutritional Assessment
2.9. Nutritional Support during critical illness
2.10. Routes of Nutrition support
2.11. Early Enteral Nutrition during critical illness
2.12. Under feeding and Over feeding during critical illness
2.13. Barriers to Nutritional support during critical illness
2.1. PEDIATRIC GENERAL REQUIREMENTS

Pediatrics is a branch of medicine which has developed in the mid 19th century. It deals with the care of infants, children and adolescents. Treating a child is not like treating a miniature adult. The obvious body size differences are paralleled by maturational changes. The smaller body of an infant or neonate is physiologically different from that of an adult. There is no other time in life when appropriate nutrition is of greater importance than infancy and childhood (Elizabeth K.E., 2007). During this phase of life, characterized by rapid growth and development of almost all systems, an adequate amount and composition of substrates both in health and disease is of key importance for growth, functioning outcomes such as cognition, immune response and long term well being. Nutrient needs not only reflect rates of growth but energy expended in activity, basal metabolic rates and the interaction of nutrients consumed (Sharma M., 2011).

2.2. GROWTH AND DEVELOPMENT

Growth is the main characteristic of childhood and a sensitive indicator of the child’s nutritional status. From conception to adulthood, growth can be divided into periods: intrauterine, infancy, childhood and adolescence. Each period has its own characteristic pattern and the mechanisms regulating growth differ (fig. 2.1). Deviations in growth, especially reduced growth, are associated with an increased risk of diseases both in the short and long term.
Nutrition has its strongest regulatory effect during early life, growth hormone secretions play an important role during infancy and growth is modified by sex hormones during puberty. Insulin-like growth factor-I (IGFI) mediates the effect of growth hormone on growth, but IGF-I can also be stimulated directly by nutrients. Linear growth velocity and weight gain is highest during the first few months after birth, with monthly increments of about four centimeter and one kilogram. Then growth velocity declines until the pubertal growth spurt, which is earlier in girls than in boys (fig. 2.2). Age at puberty differs considerably between populations with later puberty in populations with a poor nutritional status (Koletzko B. et.al., 2008).

Figure 2.1: The Infancy, Childhood, Puberty (ICP) growth model
Many factors influence growth. Genetic influences are more but can be modified by many environmental factors. Nutrition also has a marked influence on growth, especially during the first years of life as children have limited energy reserves. There are some nutritional problems which affects growth. In a global perspective, the most common cause is a diet in which especially a lack of energy and micronutrients (for example zinc) is important. Protein deficiency can also affect growth. Many acute and chronic diseases, infections with inflammation result in poor appetite which in turn increases the likelihood of developing serious nutritional deficiencies and malnutrition and this may further aggravate when the child is admitted to the hospital for longer
periods of time. Therefore, adequate feeding is essential for complete recovery and normal functioning of a growing child (Koletzko B. et.al., 2008).

2.3. DEFINITION OF MALNUTRITION

Malnutrition is defined as a disorder of body composition characterized by macro and/or micronutrient deficiencies and resulting from reduced nutrient intake or impaired metabolism. 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.

Malnutrition can be of the acute, chronic or a mixed type. Acute malnutrition is the type that usually occurs in critical illness. In developed nations malnutrition is generally secondary to disease and caused by inadequate dietary intake, increased metabolic demands, impaired absorption or increased nutrient losses (Gupte S., 2006). Children with underlying chronic diseases who are admitted to an ICU because of an acute illness can also present with chronic malnutrition (Gupte S., 2006). ICU patients may show a combination of these factors (Corish C.A. et.al., 2000).
2.4. PREVALENCE OF MALNUTRITION IN HOSPITALIZED CHILDREN

The reported prevalence of malnutrition in infants and children admitted to hospital ranges from 6.1 to 40.9%. Most recently, Pawellek I. et.al., (2008), reported about the prevalence of malnutrition in a group of 475 unselected children admitted to a hospital in Munich, Germany. Using cutoff points defined by Waterlow (Weight for Height <80th percentile), they found that 6.1% of the patients were malnourished. With respect to age, the highest risk for malnutrition was found in infants (7.1%) and young children aged 2–5 years (4.3%).

A similar prevalence rate of 7.1 and eight percent respectively, using the same criterion was reported more than 10 years ago by Hendricks K.M. et.al., (1995), in a group of 268 children admitted in Boston, USA and by Hendrikse W. et.al., (1997), in a group of 226 children admitted in Glasgow, UK. Using the two standard deviation criteria for weight for height, Moy R. et.al., (1990), in the UK and Dogan Y. et.al., (2005), in Turkey found 14% and 27.7% malnourishment respectively. Moy R. et.al., (1990), studied a group of 255 patients aged 3 months to 18 years and Dogan Y. et.al., (2005), studied a group of 528 patients aged 1–17 years. Of these 528 children (31.6%) were admitted with an acute disease and 68.4% with a chronic disease.
The remarkably high percentage of malnourishment found by Dogan Y. *et al.*, (2005), was also reported by Ozturk Y. *et al.*, (2003). In this study, a prevalence of 31.8% for malnutrition was found in a group of 170 children admitted to a tertiary center using percentage of ideal body weight less than 80%. Hankard R. *et al.*, (2001) and Marteletti O. *et al.*, (2005), both performed a one day cross-sectional survey in a pediatric population admitted to medical or surgical units in France. Hankard R. *et al.*, (2001), studied a group of 58 children older than six months and hospitalized for more than 48 hour and found 12% of the children to be malnourished, using the BMI criteria below two standard deviation. Marteletti O. *et al.*, (2005), found a prevalence of 11% in a group of 280 children.

Despite improvements in intensive care technology, feeding possibilities and increased awareness of the significance of adequate nutritional support the prevalence of malnutrition in critically ill children has remained unchanged over the last two decades.

Hulst J. *et al.*, (2004), still found 24% of the children to be acutely and chronically malnourished on admission to the Pediatric Intensive Care Unit (PICU). There was a high (84%) prevalence of underlying growth affecting disease in those with acute malnutrition. On 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.

2.5. CONSEQUENCES OF MALNUTRITION

Malnutrition in infancy is associated with poor growth, reduced or delayed mental and psychomotor development (Galler J.R. et.al., 1975; Lucas A. et.al., 1998). Longitudinal studies have revealed that malnutrition during infancy is associated with increased behavior problems during childhood, including attention deficit and aggressive behavior (Galler J.R. et.al., 2005; Liu J. et.al., 2005).

Early childhood malnutrition has also been related to externalizing behavior in both childhood and adolescence (Barker D.J. et.al., 1993; Liu J. et.al., 2005). Increasing evidence suggests that many common adult diseases have their origins in fetal and early life. It is suggested that poor nutrition during fetal life and early infancy can increase the risk of developing type II diabetes, hypertension and cardiovascular disease in adult life (Barker D.J. et.al., 1993).

Malnutrition has shown to be associated with increased morbidity and mortality in both hospitalized children and adults (Pollack M.M. et.al., 1985; Biolo G. et.al., 1997), including a higher risk of infections due to poor immune
defense, wound healing problems, reduced gut function, longer dependency on mechanical ventilation, longer hospital stay and increased health care costs (Heyland D.K. et.al., 1998).

Just as a wealth of research reveals the harmful outcomes and high costs of malnutrition, many studies also confirm the benefits of nutrition intervention for poorly nourished patients. Providing nutrition support to these patients helps decrease morbidity and mortality, improve quality of life, decrease length of stay and health care costs. American Dietetic Association studies have shown that for every one dollar spent on nutrition screening and intervention, at least 3.25 dollars are saved (Martin C. et.al., 2006).

2.6. METABOLIC STRESS RESPONSE TO CRITICAL ILLNESS

Apart from malnutrition, critical illness also greatly influences one’s nutritional status – child and adult alike. During critical illness children, similar to adults, rely on the metabolic breakdown and transfer of protein, carbohydrates, and lipid to meet the catabolic demands of critical illness. Figure 2.3, illustrates the basic pathways involved in the paediatric metabolic response (Mehta N.M. et.al., 2009).

In general, the metabolic stress response is characterized by an increase in net muscle protein degradation and enhanced movement of the free amino acid products through the circulation. These amino acids serve as the building
blocks for rapid synthesis of proteins that act as inflammatory mediators for tissue repair and the inflammatory response. Remaining amino acids not used in this way are channelled through the liver, where their carbon skeletons are used to create glucose through gluconeogenesis. Although the catabolism of muscle protein is an effective short-term adaptation for the child, it is of limited duration and potentially damaging owing to relative reduction in lean body mass. Carbohydrate and lipid turnover is also increased several fold during the paediatric metabolic response (Mehta N.M. et al., 2009).

Figure 2.3: Basic pathways of the metabolic stress response
Critical illness in a child is also associated with systemic stress response and it is a hyper sympathetic one. At the macro level, gut motility especially of the stomach and small intestines is reduced. Absorption of nutrients and drugs may be erratic secondary to villous atrophy, associated with altered motility secondary to ischemia and necrosis. Consequently increased bacterial and their toxin translocation occur, which may suppress normal immune mechanisms and promote the activation of cytokine synthesis in the liver. Multi organ derangements, particularly of the liver and kidneys affect not only nutrient but also drug metabolism.

At the cellular level, macrophages and polymorph leukocytes release various peptides like cytokines, interleukin one and tumor necrosis factor (Vilcek J. et.al., 1987; Dinarella C.A. et.al., 1998). The stress response is associated with elevated catecholamines, aldosterone, antidiuretic hormone, glucocorticoids, insulin and glucagons (Goldstein S.A. et.al., 1989). Despite elevated insulin levels, hyperglycemia and glucose intolerance are frequently observed because of counter regulatory hormones primarily due to mobilization of alanine, glutamine and other amino acids from muscle and their biosynthesis to glucose and urea by the liver. There is insuppressible lipolysis and reduced ketogenesis. Most critically ill children are in negative nitrogen balance as protein catabolism far exceeds synthesis.
During a child’s intensive care (ICU) stay attention is mostly focused on the primary medical problem, e.g. hemodynamic instability, serious infection, congenital anomaly and much less on the child’s nutritional status and therefore the chances of iatrogenic malnutrition are more.

Apart from this quite a few common hospital practices have also been identified as mentioned below that may potentially lower the nutritional status of admitted patients (Corish C.A. et.al., 2000).

- Diffusion of responsibility for the nutritional care of patients
- Lack of interaction between medical, nursing, and dietetic staff
- Little emphasis on nutrition education in nursing and medical schools
- Limited availability of methods to assess nutritional status
- Failure to record patients’ height and weight
- Failure to observe and record patients’ dietary intake
- Frequent withholding of food because of diagnostic tests
- Delay in commencing nutritional support with prolonged use of glucose administration

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 (Khoshoo V. et.al., 1997). In order, to prevent malnutrition and especially hospital-acquired malnutrition, it is important to have initial
nutritional assessment followed by adequate nutritional support as an essential aspect of the clinical management of pediatric intensive care patients.

Feeding the child should be one of the aspect that has to be relegated to the back burner of the typically busy PICU. The diversity in clinical presentation and the range in age groups dictate a patient tailored approach (Ista E. et.al., 2005).

2.7. SCREENING TOOLS TO IDENTIFY CHILDREN AT RISK OF MALNUTRITION

The risk of nutritional depletion needs to be identified at the time of admission because not every patient in the health care setting requires intervention.

A tiered approach is most cost effective:

- First, use of a screening tool to identify which patients are at risk for malnutrition.
- Second, use of a complete assessment tool to identify which of the at-risk patients actually are malnourished.
- Third, development of a nutrition intervention plan for those with confirmed malnutrition.

Numerous nutrition screening and assessment instruments have been validated and are readily available for adult population. Routine nutritional
screening is rarely carried out in pediatric patients due to the lack of a simple and valid nutritional screening tool. Only two screening tools have been published since 2000 to identify children at risk of malnutrition.

Sermet Gaudelus I. et.al. (2000), described a simple pediatric nutritional risk score, which is suitable for routine use to identify patients at risk of malnutrition during hospitalization. Nutritional risk was assessed prospectively in 296 children by evaluating various factors within 48 hour of admission. Multivariate analysis indicated that food intake less than 50%, pain and grades II and III pathologic conditions were associated with weight loss of more than two percent. These significant risk factors were scored (one point for food intake <50%, one for pain, one for grade two pathologic condition, and three for grade III pathologic condition) and add up to a nutritional risk score ranging from zero to five. A score of one or two indicated moderate risk and a score of more than two indicated high risk of malnutrition. Of the patients who lost less than two percent of their reference weights, 25% were in the moderate class and 78% were in the high-risk class. However, this method has its own limitation as it needs 48 hours to complete after admission, hence not being routinely used.

Secker D.J. et.al. (2007), recently reported the use of the Subjective Global Nutritional Assessment (SGNA) screening tool. Prospectively, the preoperative nutritional status of 175 children undergoing major thoracic or
abdominal surgery was evaluated with the use of SGNA and objective measurements. SGNA successfully divided children into well nourished, moderately malnourished, or severely malnourished. SGNA was considered a valid tool for assessing nutritional status in children and identifying those at higher risk of nutrition associated complications and prolonged hospitalizations. However this tool has not been validated for children admitted to the ICU.

2.8. NUTRITIONAL ASSESSMENT

After initial screening, it is essential to perform a thorough nutritional assessment to identify which of the at-risk patients actually are malnourished. 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 (Zemel B.S. et.al., 1997).

Nutritional assessment of the critically ill child is challenging and clinicians use a combination of anthropometric and laboratory data to diagnose undernourishment. However, standard methods of nutritional assessment are either difficult to obtain or impossible to interpret in critically ill patients.

Carefully elicited past history with details of weight gain, dietary history, recent illness and medications may allow identification of risk factors for preoperative malnutrition. Weight on admission to the hospital is important
and may be the only estimate of the actual dry weight before the capillary leak syndrome lead to edema and weight gain. Regular weight monitoring is a valuable index of nutritional status in these patients. Weight changes during the ICU admission should be interpreted in the context of fluid therapy, other causes of volume overload and diuresis (Mehta N.M. et.al., 2009).

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. The measurement of Head Circumference (HC) is an important aspect of nutritional assessment in young children as brain growth is highest in the first four 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 (Fredricks A.M.et.al., 2000).

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 (Fredricks. A.M. et.al., 2000). Combining the TSF measurement with MUAC enables to estimate upper-arm muscle (muscle circumference = MUAC - (0.314*TSF) and fat stores (Frisancho A.R. et.al., 1981). 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 (Bruin D. et.al., 1995). 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 (Zemel B.S. et.al., 1997).

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. Physical examination can be directed toward specific signs of nutritional and metabolic deficiencies. Hair, skin, eyes, mouth, and extremities may reveal stigmata of protein-energy malnutrition or vitamin and mineral deficiencies.

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 (Mehta N.M. et.al., 2009). Serum albumin is frequently used as a tool for nutritional assessment in the ICU. Levels <2.2 g/dl reflect malnutrition. However, the long half-life of albumin (14 to 20 days) makes it less responsive to acute changes in nutritional status. Serum albumin concentrations may be affected by albumin infusion, dehydration, sepsis, trauma and liver disease, independent of nutritional status. Thus, its reliability as a marker of visceral protein status is questionable (Mehta N.M. et.al., 2009). Prealbumin (also known as transthyretin or thyroxine binding prealbumin) is a stable circulating glycoprotein synthesized in the liver. It binds with retinol binding protein and is involved in the transport of thyroxine as well as retinol. Prealbumin, so named by its proximity to albumin on an electrophoretic strip, has a half-life of 24 to 48 hours and reflects more acute nutritional changes. Prealbumin concentration is diminished in renal and liver disease. Chemistry profile should be monitored on admission and repeated periodically (Mehta N.M. et.al., 2009).
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 (Albers M.J. et.al., 2003). 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 (Pierro A. et.al., 1988; Bresson J.L. et.al., 1989; Tilden S.J. et.al., 1989; Salas S.J. et.al., 1993; Verhoeven J.J. et.al., 1998; Joosten K.F. et.al., 1999; Klerk D. et.al., 2002). Protein need is calculated from urinary nitrogen excretion using the formula: protein (g/kg/day) = 6.25 x urinary urea nitrogen excretion (Mickell J.J. et.al., 1982). An adjustment can be made for the 10% to 20% of other urinary nitrogen loss such as ammonia, creatinine, uric and amino acids. A 24 hours urinary collection is preferred but is not always easy in clinical practice; a six hour collection or 12 hour collection (preterm neonates) can then be sufficient.

Other proteins used for nutritional assessment include, retinol binding protein, transferrin, fibronectin and insulin-like growth factor 1(IGF-1). Other laboratory
tests that help in overall nutritional assessment include serum electrolytes, blood urea nitrogen, glucose, coagulation profile, iron, magnesium, calcium, and phosphate. The adequacy of cellular immunity can be estimated through the measurement of Total Lymphocyte Count (TLC) (Mehta N.M. et.al., 2009). In an attempt to improve the sensitivity and specificity of tests for nutritional assessment, various multi parameter indices incorporating laboratory parameters and anthropometric have been developed for the adult population, e.g. the Prognostic Inflammatory and Nutritional Index (PINI), (Pressac M et.al.,1990) and the Prognostic Nutritional Index (PNI). Chwals W.J. et.al., (1992), 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. Nutritional intake was increased when serial measurements of these metabolic parameters demonstrated a resolution of the acute phase response.

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 (Laren M. et.al., 1972).
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 malnutrition is often based on objective measurements, including anthropometric evaluation and assessment of chemical and immunologic parameters reflecting altered body composition. The acceptance of such methods in clinical practice, for the whole spectrum of hospitalized patients, is limited due to the lack of adequate validation studies, use of subjective criteria (Detsky A.S. et al., 1982), restriction to selected patient groups, low feasibility and need for highly trained personnel.

At present, however, there is no gold standard test that is both sensitive and specific for diagnosing malnutrition in critically ill pediatric patients. All available tests show significant limitations and any application has to be considered in the light of those limitations (Cerra F.B. et al., 1997). Therefore, more research should be focused on validation of an assessment tool which includes both subjective as well as objective data and should be able to correctly identify malnourished patients so that appropriate tailor-made nutritional support could be provided to such individuals.

2.9. NUTRITIONAL SUPPORT DURING CRITICAL ILLNESS

Nutritional support after initial nutritional assessment should be an essential aspect of the clinical management of patients in the PICU. It is defined as the
provision of energy in the form of glucose, protein, or lipid to provide calories and substrate for metabolism. Some would define metabolic support as provision of these calories at basal metabolic rate, without any intention of supporting anabolic activities such as growth or activities of daily living. Accordingly, metabolic support is a form of nutritional supports (Ista E. et.al., 2005).

PROTEIN METABOLISM DURING CRITICAL ILLNESS AND ITS REQUIREMENTS

Amino acids are the key building blocks required for growth and tissue repair. The vast majority (98%) is found in existing proteins, with the remainder residing in the free amino acid pool. Proteins themselves are not static as they are continually degraded and synthesized in the process of protein turnover. The reuse of amino acids released by protein breakdown is extensive, protein turnover contributes more than two times the amino acids derived from protein intake. As a reference, healthy newborns have a protein turnover of approximately 6.7 g/kg/d and adults have a protein turnover of approximately 3.5 g/kg/d. An advantage of high protein turnover is that a continuous flow of amino acids is available for synthesis of new proteins. In this way, maximal physiologic adaptability is present at times of injury or illness.
In the metabolically stressed patient, with significant cardio-respiratory failure requiring Extracorporeal Membrane Oxygenation (ECMO), protein turnover is double that of normal subjects (Jaksic T. et al., 1999; Keshen T. et al., 2001). Specifically, this process involves a redistribution of amino acids from skeletal muscle to the liver, wound and other tissues taking part in the inflammatory response. The mediators of the inflammatory response such as enzymes, serum proteins, and glucose (via gluconeogenesis) are thus synthesized. Evidence for this process can be seen in the serum by the marked increase in hepatically derived acute phase reactants (C-reactive protein, fibrinogen, α1-antitrypsin, α-1-acid glycoprotein) and the reduction in transport proteins such as albumin and retinol binding protein. Importantly, although children with critical illness have increases in both whole body protein degradation and whole body protein synthesis, it is the former that predominates during the stress response. Thus, these patients manifest net negative protein and nitrogen balance. Clinically significant negative protein balance is characterized by skeletal muscle wasting, weight loss and immune dysfunction.

Apart from the need for acute-phase protein production in the inflammatory response, another driving force for increased protein catabolism is the obligate production of glucose from amino acids through the process of gluconeogenesis. This process is essential as glucose is the preferred substrate for the brain, erythrocyte and renal medulla and is a versatile
energy source for tissues involved in the inflammatory response. From neonates to adults, increased gluconeogenesis is known to occur during illness and injury. On a per kilogram basis, this process is particularly prominent in patients with low body weight, presumably because of an elevated brain to body weight ratio and hence an increased requirement for glucose as an energy source (Jaksic T. *et al.*, 1999). Although the catabolism of muscle protein to generate glucose and inflammatory response proteins is an excellent short term adaptation, it is ultimately limited because of the reduced protein stores available in children and neonates. Interestingly, unlike during starvation, the provision of dietary glucose alone is ineffective in reducing the endogenous glucose production via gluconeogenesis in the metabolically stressed state (Keshen T. *et al.*, 2001).

During critical illness, loss of diaphragmatic and intercostal muscle mass leads to respiratory compromise and the subsequent loss of cardiac muscle predisposes to fatal arrhythmia. Fortunately, the provision of amino acid nutritional supplementation has been shown to improve overall protein balance in the premature neonate (Van Lingen R.A. *et al.*, 1992; Rivera A. *Et al.*, 1993) The mechanism for this change appears to be an increase in protein synthesis, whereas the rate of protein degradation remains constant (Duffy B. *Et al.*, 1996). As expected, the amount of protein required to optimally enhance protein accretion is higher in critically ill than in healthy children. The provision of dietary protein sufficient to optimize protein
synthesis, facilitate wound healing and the inflammatory response and preserve skeletal muscle protein mass is the single most important nutritional intervention in critically ill children. The quantities of protein recommended for critically ill children are outlined in Table 2.1.

**Table 2.1: Protein Requirements**

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Protein Requirements (g/kg/day)</th>
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<tbody>
<tr>
<td>&lt;1</td>
<td>2.0-2.5</td>
</tr>
<tr>
<td>1-6</td>
<td>1.5-2.0</td>
</tr>
<tr>
<td>7-18</td>
<td>1.0-1.5</td>
</tr>
</tbody>
</table>

Source: Raju U, Choudhary S, Harjai MM. Nutritional Support In The Critically Ill Child. MJAFI, 61: 2005, 47

Certain severely stressed states, such as significant burn injury or patients requiring Extracorporeal Membrane Oxygenation (ECMO), may require additional protein supplementation to meet metabolic demands. Hence, growth rates and other indices for protein accretion must be monitored closely in chronically ill patients. Excessive protein administration should be avoided as toxicity has been documented, particularly in children with marginal renal and hepatic function. Studies using high protein allotments of four to six g/kg/d have been associated with adverse effects such as azotemia, metabolic acidosis and neuro developmental abnormalities (Premji S. *et.al.*, 2006). During critical illness, the short-term adaptive benefit of metabolic response is, in time, outweighed by the loss of protein in critical organs and the consequent morbidity seen after the exhaustion of limited
protein reserves. This sustained protein breakdown cannot be stopped by optimal caloric provision alone (as in starvation), but protein balance may be restored by optimal (probably individual and disease-specific) quantities of protein intake during this state.

ENERGY METABOLISM DURING CRITICAL ILLNESS AND ITS REQUIREMENTS

During critical illness, increases in the metabolic turnover of protein, carbohydrate and lipid result in an increased basal energy requirement for the pediatric patient. Administration of high-caloric (glucose load) diets in the early phase of critical illness may exacerbate hyperglycemia, increase carbon dioxide generation with increased load on the respiratory system, promote hyperlipidemia resulting from increased lipogenesis and result in a hyperosmolar state. On the other hand, hypocaloric diet may have a protein sparing effect and demonstrable benefits in critically ill obese patients. Some investigators have recently proposed hypocaloric diets during critically ill patients (Patino J.F. et.al., 1999; Mc Cowen K.C. et.al., 2000). Although, overfeeding critically ill children is also associated with net lipogenesis, hepatic steatosis and liver dysfunction, as well as increased carbon dioxide production and difficulty in ventilator weaning (Macintyre N.R. et.al., 2001), it is uncertain if administration of lower caloric intakes are appropriate for this group. The risks and benefits of a hypocaloric regimen will need to be carefully examined in children before its implementation in practice. Thus, a
careful appraisal of energy requirements in the critically ill paediatric patient is mandatory.

Previous recommendations for energy requirements were based on estimates of Basal Metabolic Rate (BMR) or resting energy expenditure derived either by indirect calorimetry or by standard equations. Since, these methods have proven inaccurate in determining individual energy requirements in our population, the preferred method of estimating the energy requirements is using kcal/kg standards (Hunter D.C. et.al., 1988) as presented in Table 2.2. Once protein needs have been met, safe caloric provisions using carbohydrate and lipid energy sources is recommended.

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Energy Requirements (kcal/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>100-120</td>
</tr>
<tr>
<td>1-6</td>
<td>75-90</td>
</tr>
<tr>
<td>7-18</td>
<td>60-75</td>
</tr>
</tbody>
</table>

Source: Raju U, Choudhary S, Harjai MM. Nutritional Support In The Critically Ill Child. MJAFI, 61: 2005, 47

**CARBOHYDRATE METABOLISM DURING CRITICAL ILLNESS AND ITS REQUIREMENTS**

Glucose production and availability are a priority of the metabolic response in critically ill children. Glucose is the primary energy used by the brain, erythrocyte and renal medulla and is useful in the repair of injured tissue.
Glycogen stores are limited and quickly depleted in illness or injury, resulting in the need for gluconeogenesis. In injured and septic adults, a three-fold increase in glucose turnover and oxidation has been demonstrated as well as an elevation in gluconeogenesis (Long C.L. et.al., 1976). As mentioned earlier, a significant feature of the metabolic stress response is that the provision of dietary glucose does not halt gluconeogenesis. Consequently, the catabolism of muscle protein to produce glucose continues unabated (Long C.L. et.al., 1976). However, it is clear that a combination of dietary glucose and amino acids effectively improves net protein balance in critical illness. This occurs primarily through the augmentation of protein synthesis and has little, if any, effect on protein breakdown (Duffy B. et.al., 1986). In early nutritional support regimens for critically ill patients, excessive glucose allotments were used to attempt to overcome the need for gluconeogenesis and in effect, protein degradation. As expected, the excess glucose was converted to fat, resulting in the net generation of carbon dioxide. The synthesis of fat from glucose has a Respiratory Quotient (RQ) of approximately 8.7. Clinically, this high RQ is not attained, as glucose is never purely used for fatty acid synthesis. Nonetheless, the provision of excess glucose results in an elevated RQ and thus increases the ventilatory burden on the child. Thus, avoidance of excess calories from glucose provisions and the use of a mixed-fuel system employing both carbohydrates and lipid are theoretically and practically useful in critically ill children, many of whom already have respiratory challenges from the nature of their illness. 55-65% of
total kilocalories of carbohydrate is recommended in critically ill children. This approach also helps to alleviate difficulties with hyperglycemia in the relatively insulin resistant stressed child (Laird A.M. et.al., 2004).

LIPID METABOLISM DURING CRITICAL ILLNESS AND ITS REQUIREMENTS

Analogous to protein and carbohydrate metabolism, lipid turnover is generally accelerated by critical illness, surgery, and trauma (Jeevanadham M. et.al., 1990). Although lipid use is compromised in the initial, brief ebb phase following acute trauma or sepsis, overall lipid turnover increases dramatically during the predominant flow phase. Critically ill patients demonstrate two to fourfold increase in lipid turnover compared with healthy controls and this increase is proportional to the degree of illness (Nordenstrom J. et.al., 1998). This process involves the recycling of free fatty acids and glycerol into and from triglycerides. Approximately 30 to 40% of the free fatty acid moieties are oxidized for energy and the RQ values post injury are approximately 0.8. Infants and children subjected to uncomplicated abdominal surgery have also shown a reduction in RQ along with a decline in plasma triglyceride levels (Powis M.R. et.al., 1998). Recently, it has been shown that critically ill children do, indeed, have a higher rate of fat oxidation (Coss-Bu J.A. et.al., 2001). Thus, this suggests that fatty acids are, in fact, the prime source of energy in metabolically stressed children. Glycerol, released along with free fatty acids from the breakdown of triglycerides, may
be converted to pyruvate and thereby shunted into the gluconeogenesis pathway. Again similar to protein catabolism, the provision of dietary glucose does not decrease glycerol clearance or overall lipid turnover. Because of the increased demand for lipid use in critical illness coupled with the limited lipid stores in the pediatric patient, critically ill children are susceptible to the evolution of biochemically detected essential fatty acid deficiency if administered a fat-free diet (Friedman Z. et.al., 1960; Paulsrud et.al., 1972).

In infants, linoleic and linolenic acid are considered essential, whereas arachidonic acid and docosahexaenoic acid are thought to be conditionally essential. If the body lacks dietary linoleic acid, the formation of arachidonic acid (a tetraene) by desaturation and chain elongation cannot take place. The same pathway then converts available oleic acid to 5,8,11-eicosatrienoic acid (a triene), resulting in an elevated triene-to-tetraene ratio, which is empirically characteristic of essential fatty acid deficiency (Holman R.T. et.al., 1960).

Clinically, this syndrome presents as dermatitis, alopecia, thrombocytopenia, and increased susceptibility to bacterial infection. To avoid essential fatty acid deficiency in critically ill or injured infants, the allotment of linoleic and linolenic acid is recommended at concentrations of 4.5 and 0.5% of total calories, respectively (Agget P.J. et.al., 1991). The provision of commercially available lipid solutions to parenterally fed critically ill children reduces the risk of essential fatty acid deficiency, results in improved protein use, and does not significantly increase carbon dioxide production or metabolic rate (Van Aerde J.E. et.al., 1994). There are disadvantages, however, with lipid
administration, including hyper triglyceridemia, increased rates of infection, and decreased alveolar oxygen diffusion capacity (Periera G.R. et al., 1980; Cleary T.G. et al., 1983; Freeman J. et al., 1990). Most centers, therefore, start lipid supplementation in ill children at one g/kg/d and advance over a period of days to two to four g/kg/d, with monitoring of triglyceride levels. Lipid administration is generally restricted to a maximum of 30 to 40% of total calories.

**ELECTROLYTE METABOLISM**

Requirements for the basic electrolytes sodium, potassium, chloride, bicarbonate and calcium must be evaluated frequently in the critically ill patient. In addition to routine electrolyte monitoring, careful attention to phosphate and magnesium levels is recommended. Hypophosphatemia may lead to hemolytic anemia and respiratory muscle dysfunction and may also be seen with refeeding syndrome in the ill child. Renal failure can result in the retention of phosphate and nutritional allotments must be reduced accordingly. Deficiency of magnesium can cause fatal cardiac arrhythmia. Abnormalities of acid–base physiology in the critically ill child can also influence the nutritional regimen. For example, head-injured patients often develop an iatrogenically induced respiratory alkalosis. If a metabolic alkalosis secondary to active diuresis or gastric suction is also present, chloride administration should be used to correct the alkalosis. Untreated alkalemia tends to inhibit the respiratory drive, shift potassium intracellularly
and decrease ionized calcium concentrations by increasing the affinity of albumin for calcium. Metabolic acidosis can also be seen in critically ill children, often from associated hypotension or ischemic etiologies. In this case, the provision of acetate instead of chloride is recommended so as not to worsen the existing acidemia. The provision of excess acetate at one mEq/kg/d is usually a safe adjunct to limit metabolic acidosis (Mehta N.M. et.al., 2009).

**VITAMIN AND TRACE MINERAL METABOLISM**

Vitamin and trace mineral metabolism in critically ill and postoperative patients has not been extensively studied. For the neonate and the child, required vitamins include fat-soluble vitamins (A, D, E, and K) and water-soluble vitamins (ascorbic acid, thiamin, riboflavin, pyridoxine, niacin, pantothenate, biotin, folate and vitamin B12) and these are routinely administered. Because vitamins are not stoichiometrically consumed in biochemical reactions but rather act as catalysts, the administration of large supplements of vitamins in stressed states is not logical from a nutritional standpoint. The trace minerals required for normal development are zinc, iron, copper, selenium, manganese, iodide, molybdenum, and chromium. Trace minerals are used in the synthesis of active sites of a ubiquitous and extraordinarily important class of enzymes termed metalloenzymes. As with vitamins, the role of metalloenzymes is to act as catalysts. Hence, unless there are excessive losses, such as increased zinc loss with severe diarrhea,
large nutritional requirements in critical illness should not be anticipated. The Recommended Dietary Allowances of vitamin and trace mineral needs of healthy children and neonates are reviewed periodically and are well defined in the literature (Goran M.I. et.al., 1994). These recommended levels have been used in critically ill patients and little evidence exists that they are nutritionally inadequate. In children with severe hepatic failure, copper and manganese accumulation can occur thus trace mineral supplementation should be reduced.

**2.10. ROUTES OF NUTRITIONAL PROVISION**

Following the estimation of energy expenditure and requirement in the critically ill child, the next challenge is to facilitate the provision of nutritional support. Although nutrition can be provided to critically ill children enterally or parenterally, the enteral route is preferred as shown in figure 2.4 (Curley M.A. et.al.,1998).

![Figure 2.4: Routes of Nutrition Support](image)
Enteral nutrition is physiologic and has been shown to be more cost-effective without the added risk of nosocomial infection (Letton R.W. et.al., 1995). The postpyloric feeding tube, placed at the bedside or with fluoroscopic guidance, helps to decrease the risk of aspiration and is a useful tool in the nutritional management of the critically ill child. Continuous feedings using standard formulas can adequately nourish the majority of injured patients. Diarrhea can often be avoided by carefully controlling the infusion rate until tolerance is established.

Early enteral nutrition has been shown to decrease infectious episodes and decrease length of hospital stay in critically ill patients (Zaloga G.P. et.al., 1997). The enteral route has been successfully used for nutritional support of the critically ill child (Chellis M.J. et.al., 1996; Briassoulis G.C. et.al., 2001). At the time of extubation, tube feeds are held for six to 12 hours to lower the corresponding risk of aspiration. It is also recommended not to use enteral feeds with patients who are hypotensive or who have evidence of bowel ischemia so as to limit the risk of small bowel necrosis associated with rapid enteral feeding (Moore F.A. et.al., 1992).

However, many studies have shown inability to achieve the set nutritional goal. In a study examining the endocrine and metabolic response of children with meningococcal sepsis, nutritional goal was achieved in only 25% of the cases (Rogers E.J. et.al., 2003). Similar observations have been made in a
group of 95 children in a pediatric ICU (PICU) where patients received a median of 58.8% of their estimated energy requirements. In this review, enteral feeding was interrupted on 264 occasions to allow clinical procedures. Consistently underachieved enteral nutrition goals are thought to be perhaps responsible for the absence of beneficial effect in multiple studies and meta-analysis of the efficacy of immunonutrition in preventing infection (Gianotti L. et.al., 1994).

In another review of nutritional intake in 42 patients in a tertiary-level pediatric ICU over 458 ICU days, actual energy intake was compared with estimated energy requirement (Rogers E.J. et.al., 2003). Only 50% of patients were reported to have received full estimated energy requirements after a median of seven days in the ICU. Prolonged fluid resuscitation was a major factor hindering the achievement of estimated energy requirements despite maximizing the energy content of feeds. Other contributing factors included interruption of feeds for procedures, enteral feed intolerance.

Protocols for feeding use of transpyloric feeding tubes and changing from bolus to continuous feeds during brief periods of intolerance are strategies to achieve estimated energy requirements in this population. Enterally administered feeds meet nutritional requirements in critically ill children with functional gastrointestinal system and have the advantages of cost, manageability, safety and preservation of gastrointestinal function. Early
introduction of enteral feeds in critically ill patients helps to achieve positive protein and energy balance and restores nitrogen balance during the acute state of illness. It maintains gut integrity and elicits release of growth factors and hormones that maintain gut integrity and function (Briassoulis G.C. et al., 2001).

Despite its perceived benefits, current practice in ICUs shows a significant proportion of eligible patients deprived of enteral feeds (Heyland D.K. et al., 1998). Enteral feedings are indicated early on the course of critical illness if peristalsis has been established. Postpyloric feedings are recommended, due to gastric distension and hypomotility. Feeds can be administered into the stomach or jejunum with the aid of feeding tubes inserted nasally or orally. Intragastric or intrajejunal tip placement is confirmed by radiograph. Postpyloric feeding is increasingly adopted to feed children with reflux or delayed gastric emptying who are at risk of aspiration. Surgical placement of gastrostomy or jejunostomy tube allows long-term enteral feeding and administration of drugs in selected patients during intensive care and after discharge from the ICU. The advent of percutaneously placed gastric and jejunal tubes has minimized cost, time and morbidity. Stoma site infection, obstruction, and tube dislodgement are common complications and must be identified and managed early. Tube tip malposition is frequently encountered with any of these devices either at placement or during the course of its use. Bed-side screening methods for correct tip position range
from auscultation during air insufflation to ultrasound-guided tip localization. However, feeds should be held when malposition of tip is suspected and when in doubt, radiographic confirmation of correct tip position must be obtained before recommencing feeds (Mehta N.M. et.al., 2009).

2.11. EARLY ENTERAL NUTRITION DURING CRITICAL ILLNESS

Zaloga and Roberts (1997), reviewed the results of early Enteral Nutrition in animal and human adult studies. Animal studies showed that early EN improved gut blood flow and gut mass, diminished the invasiveness of gut bacteria, protected the liver and prevented injury during shock, improved protein synthesis and the rate of wound healing and increased survival after critical illness. More importantly, prospective, randomized trials in humans have indicated that early EN improved outcome during critical illness. Studies in premature and low birth-weight infants found that the lack of enteral feeding may result in an absence of the natural stimulus for growth of the intestinal mucosa, as well as diminished production of intestinal mucins, which acts as a barrier to bacterial translocation (Wesley J.R. et.al., 1994). Further proof of the efficacy and safety of early enteral feeds was given in the form of case reports and case series of burn patients (Engelhardt V.J. et.al., 1994; Trocki O. et.al., 1995). Chellis M.J. et.al., (1996) performed a study in forty two critically ill children to evaluate the feasibility and safety of early enteral feedings. All patients were able to achieve caloric goals within 48 hours of beginning enteral feedings and there were no documented complications,
such as aspiration or abdominal distention (Chellis M.J. et al., 1996). A more recent retrospective study in 95 critically ill children showed that it was possible to start EN within 24 hours after admission in most children (Taylor R.M. et al., 2003).

### 2.12. UNDERFEEDING AND OVERFEEDING DURING CRITICAL ILLNESS

Overfeeding has important adverse effects during critical illness. Excess carbohydrate intake can increase carbon dioxide production and impede ventilator weaning. Excess protein does not prevent catabolism and can even increase catabolism of body protein (Shew S.B. et al., 1999; Stroud M. et al., 2007). High caloric intake can increase fat deposition, including in the liver (Chwals W.J. et al., 1994; Zaloga G.P. et al., 1994; Hart D.W. et al., 2002).

In animal models, lower calorific goals were associated with weight loss and improved survival from critical illness (Yamazaki K. et al., 1986; Alexander J.W. et al., 1989). Some adult human studies suggest that underfeeding during critical illness is associated with improved survival and reduced length of stay in hospital (Dickerson R.N. et al., 2003; Krishnan J.A. et al., 2003; Jeejeebhoy K.N. et al., 2004; Ash J.L. et al., 2005; Boitano M. et al., 2006). This is compatible with the finding in many types of animals that a 30% to 50% restriction of calories increased their lifespan and resistance to diseases.
of aging and oxidative damage (with similar pathophysiology to critical illness inflammatory cascades) (Bordone L. et.al., 2005).

2.13. BARRIERS TO NUTRITIONAL SUPPORT DURING CRITICAL ILLNESS

Although importance of nutrient delivery in critically ill patients is well recognized, it is not possible to give all critically ill children the maximum required amount of enteral feeding according to RDA. Barriers to optimal delivery of nutrients at the bedside still persist (Adam S. et.al., 1997; Rogers E.J. et.al., 2003). The care of a critically ill patient involves multiple interventions, which often compete with the delivery of nutrients in the intensive care setting. Elective procedures, unplanned interventions, or diagnostic tests often require a fasting state, requiring interruption of nutrition support. In addition, feed intolerance or contraindications to feeding related to the disease processes may require feeding to be postponed or discontinued in the PICU. However, a significant number of eligible patients are deprived of nutrition support during critical illness because of avoidable factors, such as suboptimal prescription, failure to initiate nutritional support early, or frequent and prolonged interruptions to nutritional support. Delayed initiation and subsequent interruptions contribute to suboptimal nutrient administration in the PICU.
Enteral feeding in critically all children should be started as soon as possible. If critically ill children are haemodynamically stabilized even if high doses of inotropics are necessary small amounts of enteral feeding can be started. Because critically ill children suffer from gastric dysmotility and emptying difficulties, transpyloric tube feeding is the preferred route. Total parenteral feeding is indicated when the gastric–intestinal tract is nonfunctional, when it is impossible to obtain enteral access, or when EN alone is not able to meet the child's energy requirements. Nutritional support in the critically ill child has not been well investigated and is a controversial topic in paediatric critical care medicine. There are no clear guidelines for the optimal timing and forms of nutritional support in these children (Mehta N.M. et.al., 2009).

2.14. GUIDELINES FOR OPTIMAL NUTRITION DURING CRITICAL ILLNESS

In 2009, American Society of Parenteral and Enteral Nutrition Support published Grade B nutrition support guideline recommendations for critically Ill children (Mehta N.M. et.al., 2009). These are as follows:

1. 1A) Children admitted with critical illnesses should undergo nutrition screening to identify those with existing malnutrition and those who are nutritionally-at-risk.
1B) A formal nutrition assessment with the development of a nutrition care plan should be required, especially in those children with premorbid malnutrition.

2. 2A) Energy expenditure should be assessed throughout the course of illness to determine the energy needs of critically ill children. Estimates of energy expenditure using available standard equations are often unreliable.

2B) In a subgroup of patients with suspected metabolic alterations or malnutrition, accurate measurement of energy expenditure using Indirect Calorimetry (IC) is desirable. If IC is not feasible or available, initial energy provision may be based on published formulas or nomograms. Attention to imbalance between energy intake and expenditure will help to prevent overfeeding and underfeeding in this population.

3. There are insufficient data to make evidence-based recommendations for macronutrient intake in critically ill children. After determination of energy needs for the critically ill child, the rational partitioning of the major substrates should be based upon understanding of protein metabolism and carbohydrate- and lipid-handling during critical illness.

4A) In critically ill children with a functioning gastrointestinal tract, enteral nutrition should be the preferred mode of nutrient provision, if tolerated.
4B) A variety of barriers to EN exist in the Pediatric Intensive Care Unit (PICU) clinicians must identify and prevent avoidable interruptions to EN in critically ill children.

4C) There are insufficient data to recommend the appropriate site (gastric vs post-pyloric/transpyloric) for enteral feeding in critically ill children. Post-pyloric or transpyloric feeding may improve caloric intake when compared to gastric feeds. Post-pyloric feeding may be considered in children at high risk of aspiration or those who have failed a trial of gastric feeding.

5. Based on the available pediatric data, the routine use of immunonutrition or immune-enhancing diets/nutrients in critically ill children is not recommended.

6. A specialized nutrition support team in the PICU and aggressive feeding protocols may enhance the overall delivery of nutrition, with shorter time to goal nutrition, increased delivery of EN, and decreased use of parenteral nutrition. The effect of these strategies on patient outcomes has not been demonstrated.

The lack of controlled research and clinical trials in critically ill children has resulted in an absence of widely accepted evidence based guidelines for optimal nutritional management in this group (Van der Kuip M. et.al., 2004). However many western PICU’s have implemented local guidelines for
introducing and establishing enteral nutrition in their critically ill populations as shown in figure 2.4 (Duggan C, 2008). Similarly, development of an Indian as well as institution specific guideline addressing nutritional assessment, introduction and management of nutritional support is an essential requisite in treating the malnourished patient in the PICU.

Figure 2.5: Feeding Algorithm