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Pediatrics in South America (L Landry and WB de Carvalho, Section Editors)

Nutritional Assessment and Body Composition in Critically Ill Children as Prognostic Indicators

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Abstract

Purpose of review Malnutrition is very common in critically ill patients, mainly children and adolescents, and it increases morbidity, length of stay, medical costs, and mortality. Anthropometric and body composition assessment are basic components for monitoring nutritional status. In addition, it appears to be able to predict several clinical outcomes in these patients. This review describes studies evaluating usefulness of nutritional and prognostic assessment tools in critically ill patients.
Recent findings Although anthropometry is difficult to interpret in critically ill patients, it is very useful for classifying nutrition status, as well as for planning nutritional therapy (NT) and nutrition monitoring. Several traditional nutritional markers (zinc, selenium, prealbumin, and HDL) have been used as inflammatory and, consequently, prognostic indicators. Body composition indicators as phase angle obtained by bioelectrical impedance and arm circumference have shown a strong ability to predict outcomes in a wide variety of clinical situations, including critically ill children and adolescents.
Summary Early intervention targeting nutrition assessment can prevent or minimize the complications of undernutrition in the intensive care unit. Thus, improving the accuracy of nutritional and prognostic evaluation is of paramount importance in the clinical management of critically ill patients.

Introduction

Hospital malnutrition (HM) is an important risk factor to increase morbidity, length of stay, medical costs, and mortality in critically ill children and adolescents [1]. Malnutrition can cause severe immune dysfunction and predispose to infections. Disabilities can appear as a consequence of severe sarcopenia and this is one of the most important sequels during admission at de pediatric intensive care unit (PICU) [1–3].

Several studies showed that malnutrition is common at admission and can further intensify during hospitalization period of time. Studies performed in many countries have demonstrated that HM is very frequent reaching up to 50% of these patients [1]. Children and adolescents with chronic diseases present many risk factors for malnutrition: low oral intake, protein hyper catabolism, poor energetic reserve, and higher morbidity. These patients can develop early severe malnutrition during hospitalization. In our PICU, this aspect is clearer with patients with severe liver dysfunction with or without liver transplantation. Stress-induced changes in intermediary metabolism are characterized by increased basal metabolic rate and intensive protein catabolism [2••, 3, 4] which lead to important changes in body composition such as lean mass (LM) reduction.

Protein hyper catabolism: sarcopenia and its influence in prognosis

When dietary protein intake is not enough, muscle is broken down leading to a loss of LM with potentially serious health consequences. LM, or lean body mass (LBM), is a fat-free and bone mineral-free component that includes muscle and other components such as skin, tendons, and connective tissues [3]. Sarcopenia is defined as a decline in skeletal muscle mass and function [3]. Sarcopenia in the critically ill patient is secondary and related to many factors: malnutrition, inflammation, cause of the disease, and immobilization [5]. Studies in critically ill adults in mechanical ventilation demonstrated that this condition is very frequent and can reach 60% of patients [3]. Early sarcopenia is a possible early complication in critically ill patients with significant worsening of prognosis. It is very difficult to estimate the proper requirements of amino acids in the critically ill children and adolescents [2••, 3–5]. In a systematic review, Bechard et al. [6••] found that at least 1.5 g/kg/day of protein intake was necessary to achieve positive protein balance in critically ill children receiving mechanical ventilation. Biolo [5] observed that the amino acid efflux from skeletal muscle provided precursors to "de novo" protein synthesis and energy fuel to the liver and to the rapidly dividing cells of the intestinal mucosa and the immune system. This mechanism is stimulated during critical illness [5]. Unfortunately, low protein delivery is still in use in several PICU, mainly when nutritional support is not based on protocols [7]. Despite the adverse outcomes experienced by critically ill patients with sarcopenia, there is no consensus regarding its management. Combined actions such as nutritional, exercise-based interventions, and future research with neuromuscular electrical stimulation can be useful in a short period of time [3, 8•].

Studies have demonstrated that decreased skeletal muscle mass may be a significant predictor of in-hospital mortality [8•, 9].

Metabolic profile in critically ill children and adolescents

The metabolic response of critically ill children and adolescents is characterized, in general, by an increase in resting energy expenditure (REE). The most common equations used in pediatrics to estimate energy expenditure include the Food and Agriculture Organization/World Health Organization/United Nations University (FAO/WHO/UNU) equation [10] and the Schofield-height/weight (Schofield-HW) equation [11]. These are shown in Table 1.

A hyper catabolic state occurs in response to many clinical conditions (sepsis, trauma, burns, etc.) and is characterized by an increase in catabolic hormone concentration and inflammatory cytokines together with an insulin resistance. The systemic inflammatory response activates the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis. There is an increased protein turnover and breakdown with a negative nitrogen balance, and muscle protein loss. At the same time, there is peripheral resistance to insulin, reduced glucose oxidation, and hepatic glycogen storage. Increased lipolysis provides free fatty acids for energy and glycerol for gluconeogenesis. Concentrations of catecholamines, cortisol, glucagon, growth hormone, aldosterone, and antidiuretic hormone are increased, and insulin is generally elevated but insufficiently to impede hyperglycemia. The stress response includes adaptive and compensatory mechanisms with interaction among the nervous, endocrine, and immunologic systems. Sepsis and septic shock are good examples of an exacerbated metabolic response where sarcopenia is a very common finding. Proteolysis releases muscle amino acids to support gluconeogenesis and decreases the risk of hypoglycemia. Patients with systemic inflammatory response syndrome (SIRS) fre-

Table 1. Equations for calculating resting energy expenditure

Author	Equation (calories/day)
FAO/WHO/UNU [10]	Male (3–10 years): REE = [22.7 × weight (kg)] + 495
	Female (3–10 years): REE = [22.5 × weight (kg)] + 499
	Male (10–18 years): REE = [12.2 × weight (kg)] + 746
	Female (10–18 years): REE = [17.5 × weight (kg)] + 651
Schofield-HW [11]	Male (3–10 years): REE = [19.6 × weight (kg)] + [1.033 × height (cm)] + 414.9
	Female (3–10 years): REE = [16.97 × weight (kg)] + [1.618 × height (cm)] + 371.2
	Male (10–18 years): REE = [16.25 × weight (kg)] + [1.372 × height (cm)] + 515.5
	Female (10–18 years): REE = [8.365 × weight (kg)] + [4.65 × height (cm)] + 200

REE, resting energy expenditure

quently present with hyper catabolism and strong muscle proteolysis. This type of response is mediated by the action of cytokines and chemokines, resulting in a negative nitrogen balance, which is usually related to the intensity of the inflammatory process [1, 3, 8•, 12].

Nutritional assessment in the critically ill children and adolescents

Nutritional assessment is the process that defines the diagnosis of patients in regard to their macronutrient and micronutrient needs, aiming to establish prognosis, planning the type of treatment and monitoring its development. For critically ill children and adolescents, the assessment may include the following: anthropometry, measurement of the nutrient balance, measurement of the body composition, measurement of the inflammatory activity, and functional assessments [2••, 13].

Anthropometry

Anthropometry is a basic component of the assessment of the nutritional status, especially in children, since the anthropometric data in this population reflect the child's health status, growth, and development [14].

The use of anthropometry requires two basic items: a marker and a cutting point (reference). The marker or anthropometric index is a measurement or a set of measurements that include additional information, such as age, and reflect different components of the nutritional status. The reference helps distinguish a "normal" nutritional status from malnutrition. Assessment of a healthy child up to 2 years of age includes the main measurements—weight (W), length (L), or height (H), and head circumference (HC)—for which there are growth chart references. By assessing the W and H measurements, it is possible to obtain the three anthropometric indices proposed by the World Health Organization [15] for nutritional classification—weight for age (W/A), height for age (H/A), weight for height (W/H), and/or body mass index for age (BMI/A)—that may be expressed in growth percentiles or *Z* score (*Z*). Besides, anthropometry is very useful for planning nutritional therapy (NT) and monitoring [2••].

Usually, critically ill children are bedridden, making it difficult to accurately measure height. In addition, due to the metabolic changes that occur, especially in the initial phase of the aggression, they commonly present with electrolyte imbalances, renal and hepatic dysfunction with edema and ascites, or tumor masses that affect the quality of the weight measurement. Inaccurate measurements of weight and height may compromise the diagnosis of nutritional status, as well as the planning of NT and its monitoring. For this reason, in addition to anthropometry, it has been suggested to include in the nutritional evaluation of these patients measures of inflammatory activity and body composition [2••]. We agree that anthropometry is part of the nutritional assessment, and it must be performed in the PICU. However, the role of exclusive anthropometric data to determine accurately nutritional status in critically ill children is still moot.

Inflammatory activity

Cytokine concentrations are determinants to modify body composition during inflammatory response. Changes in metabolic substrates are common during this kind of response. Lipid metabolism has been studied and may be used as a marker of modifications in metabolism in critical ill disease. Studies in adult patients with severe sepsis have shown that the concentrations of total cholesterol (TC) and lipoproteins decrease in the early stages of critical illness as part of the host response. In a study performed in our PICU, in a developing country, we observed significantly lower TC, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) concentrations in every child and adolescent admitted to the PICU with severe sepsis/septic shock compared with controls. On the other hand, the levels of C-reactive protein (CRP) and triacylglycerol (TG) were significantly higher in septic pediatric patients compared with controls. Similar to other studies [16], it was demonstrated that the degree of inflammation correlates with the severity of hypocholesterolemia. Our data suggested that in septic pediatric patients, a negative correlation exists between the severity of inflammation (as measured by serum CRP values) and TC, HDL, and apolipoprotein A-1 levels.

Biochemical indices are often deranged in severe illness or trauma [13, 17]. Other nutritional biomarkers frequently are utilized: serum albumin, serum prealbumin, zinc, selenium, retinol-binding protein, transferrin, fibronectin, lymphocytes count, etc. Nevertheless, there is low evidence that they can offer a good follow-up to evaluate nutritional condition during hospitalization, including the prognostic aspect [18••].

Body composition

Several methods are available for measuring body composition of neonates and infants. A number of non-invasive methods have emerged that can provide additional information about the composition of the body that may aid in the nutritional management of infants. The most frequently used, body composition model splits body weight (Wt) into two compartments: fat mass (FM) and fat-free mass (FFM) [13].

For the nutritional model, total body water (TBW) is also the main component of FFM. Hence, if body water can be measured and the ratio of TBW to FFM is known, then FM can be calculated:

$$FM = Wt - (k_1 \times TBW)$$

This approach is reasonably consistent for healthy adults because the hydration of lean tissues remains relatively constant ($k_1 = 0.732 \pm 3\%$) at these ages. However, for neonates and infants, FFM hydration is not constant ($k_1 = 0.90$–0.77), decreases immediately after birth, and continues to show a decline throughout healthy infancy. Sick infants can have erratic fluctuations in body water. TBW is also the major contributor to Wt [13].

Body composition assessment is able to provide accurate information about the body compartments as well as the physiological or pathological changes that occur during the growth or course of a disease. The identification of prognostic factors in many diseases is relevant for their clinical management [19, 20•]. Among the simple techniques, we highlight arm measurements and bioelectrical impedance (BIA).

Circumferences and skinfolds

Muscle measurements of the limbs are basically used to measure the quantity and the variation rate of the skeletal muscle protein. Two measurements are needed to calculate the amount of muscle in a limb: the circumference of the limb and the corresponding skinfold. The WHO recommends measurement of the arm circumference (AC) as the anthropometric nutritional parameter to estimate total skeletal muscle protein [21], for it represents the sum of all areas that compose the arm's bone, muscle, and fat tissues. Skinfold measurement is a means to indirectly establish body mass fat [22, 23]. Given that there are reference values for its measurement, tricipital skinfold (TSF) is the most adopted measurement used to assess body composition, especially in pediatrics. Furthermore, it is a good marker of energy reserves in the organism and is satisfactorily correlated to total body fat [24].

Some authors have suggested that AC seems to better discriminate malnutrition when compared to W/H or BMI/I in critically ill children [25]. In previous study, we evaluated NT administered to 90 consecutive patients who were hospitalized for 7 days in a tertiary pediatric intensive care (PICU) and we found higher frequency of malnutrition determined by AC when compared to BMI/I (47% vs 13%, respectively) [25]. The comparative analysis between the initial assessment (admission) and the seventh day of hospitalization showed that there was a statistically significant difference in AC measures (decrease), denoting that arm measures, especially AC, are able to evidence body composition changes in a short period of time which are those occurring in the critically ill patients in the ICU.

In their study, Israëls et al. [26] assessed children and adolescents with cancer using the W/A, H/A, and W/H, as well as AC and TSF. They determined that the arm measurements were more sensitive for severe malnutrition diagnosis in their patients. Of the 128 children studied, 59.3% presented AC values below the fifth percentile.

Despite the practical applicability and ability to discriminate malnutrition and changes in body composition, arm measurements may be influenced by non-nutritional factors and evaluator person ability.

Bioelectrical impedance

Bioelectrical impedance (BIA) is a simple, portable, non-invasive, and easy-to-reproduce method for assessing the body composition of outpatients and inpatients in various clinical situations, which is based on the passage of an electric current of low intensity (800 μA) and fixed frequency (50 kHz) by the body, measuring primary components—resistance (R), reactance (Xc), and phase angle (PA)—and estimating by mathematical equations: FFM and TBW [27–29].

The principle is that the lean tissues are highly conductive of electrical current, because they contain large amounts of water and electrolytes, and therefore a low resistance. On the other hand, fat and bone are poor conductors, with fewer amounts of fluids and electrolytes and greater electrical resistance. R is defined as the opposition offered by the body to the electric current, primarily related to the amount of water present in the tissues, and Xc or capacitance is the resistive effect produced by the interfaces of tissues and cell membranes [27, 29, 30].

A multitude of factors may influence the reliability of BIA measurement and intra-instrumental variability should be limited until the device is calibrated before use, besides electrodes should not be cleaved and they can be used only once. In addition, the position of electrodes is essential. Specifically, active and recording electrodes should be separated by a 5-cm distance in order to avoid magnetic interference [31]. In addition, skin conductibility is improved treating the sites where electrodes will be placed with alcohol, in order to remove secretions and peeled skin cells. Another relevant issue in predicting FFM is related to age. BIA assessment takes that body is considered as a single conductive cylinder and the relationship between the main cross-sectional areas remains the same. The model changes when considering older subjects, since with aging, the decrease in skeletal muscle mass and a redistribution of adipose tissue from the limbs to the trunk give rise to narrower diameters for the conductive volumes (cylinders) of the limbs. Hydration of the fat-free body also varies more in the elderly than in younger age groups. This difference in hydration interferes with the accuracy of estimates of older people's body composition using prediction equations derived from younger ones [32]. Thus, to minimize this bias, many prediction equations that take into account values of weight, height, sex, age, and physiological conditions have been developed to estimate FFM and TBW [33, 34]. Finally, in hydric retentive conditions or in the presence of dehydration, using BIA for FFM estimation, respectively, leads to FFM over- and underestimation, respectively [32].

In summary, we can say that estimates made by the BIA are based on two assumptions: that tissue hydration is the same in all individuals and that the body behaves like a cylinder that conducts the electric current uniformly. Thus, BIA does not seem to be a good method to evaluate body composition in situations where these two principles are not valid, such as obesity, patients with hydration disorders, ascites, or edema, and some critically ill patients. Our recommendation for patients in the ICU is to use the primary components measured by the device, such as *R*, Xc, and PA that can provide information about body water balance and nutritional status.

Body composition and prognosis

Phase angle

BIA was introduced by Lukaski et al. [35] in 1985 as a simple method of estimating body composition. As it has already been mentioned, this is not considered a good tool in situations with hydration changes. On the other hand, the BIA provides the measurement of PA, which is an easy and fast measure, and indirectly reflects MLG [36] without the interference of body water and the need to use prediction equations.

PA is formed when part of the electric current is stored in the cell membrane, thus creating a phase change that is quantified geometrically by the angular transformation of the ratio Xc/R $[(Xc/R) \times (180°/¶)]$ [37]. It has been considered a marker of cellular health, where higher values reflect higher content and integrity of cell membranes, as well as best cellular function [27, 37]. This concept can be extrapolated to the nutritional condition, since all the electrical properties of the cell membrane are influenced by changes in cellular mass, which in turn is dependent on metabolic rate and nutrition [38].

Given its close correlation with nutritional status, PA seems useful in clinical practice, since it has made it possible to identify patients with increased risk of malnutrition as well as reduced survival [36]. In a recent systematic review, of the 455 articles evaluated with the variables of interest PA and mortality/survival, the authors extracted 48 studies, which allowed them to conclude that PA seems to be a good indicator of mortality in many clinical situations and can be used to estimate patient's outcome [39••].

We tested in a previous study the association of body composition indicators (AC and PA) with pediatric ICU length of stay (LOS) and mortality in critically ill patients. Data from children aged 2 months–18 years were collected, and BIA was performed to obtain PA. Receiver operating characteristic (ROC) curve was used to analyze the association of phase angle with 30-day mortality and to find the best cutoff point. Survival probabilities and PICU length of stay were estimated using the Kaplan–Meier method. We evaluated 247 children with a median age of 4.8 years and PA cutoff associated with mortality found by the ROC curve analysis in this population was 2.8° (AUC = 0.65; 95% CI 0.58–0.71), with a sensitivity of 37.1% and a specificity of 86%. Survival curves showed higher survival in patients with PA > 2.8° compared with patients with PA ≤ 2.8° (53 vs 23 days, respectively; $p < 0.0001$). Kaplan–Meier time-to-event analysis showed that children who did not die and had lower PA values were more likely to stay longer in the PICU (HR 1.84; $p = 0.003$). The results suggest that PA may be useful not only for nutrition diagnosis and monitoring but also as an additional indicator for outcome evaluation. Our study is one of the first in recent years to explore the use of nutritional indicators of body composition, particularly PA, as a potential prognostic indicator in critically ill children, including a determining cutoff point associated with mortality in this population [40]. It should be noted, however, that Azevedo et al. [41] had already investigated the behavior of *R* and Xc (related to the PA) in critically ill pediatric patients, evaluated for lung injury, severity of sepsis, and multiple organ dysfunction.

Similar studies have been conducted in critically ill adults, such as Stapel et al. [42] that found higher values of PA in individuals who survived when compared with those who died (5.0 ± 1.3 vs. 4.1 ± 1.2, $p < 0.001$). In addition, PA < 4.8° (ideal cutoff point found by the ROC curve) was an independent predictor of 90-day ICU mortality (OR adjusted for BMI, sex, age, and severity score = 3.65, 95% CI 1.34–9.93, $p = 0.011$). Thibault et al. [35] evaluating more than 900 adult patients obtained similar results. FFM indirectly measured by PA on ICU admission was associated with 28-day mortality, suggesting that this measure could be used to chart the patient's prognosis upon admission to the unit.

Table 2 summarizes the recent studies evaluating PA and mortality in critically ill patients.

Arm circumference

As numerous nutritional indicators [18, 47], the evaluation of body composition has been used as a marker of prognosis in critically ill patients; since in addition to identifying the body compartments in the nutritional aspect itself, it may be able to predict clinical outcomes, which is extremely important, since

Table 2. Summary of studies evaluating PA and mortality in critically ill patients

Reference	Country	Population (*n*)	Cutoff point PA (degrees)	Age (median)	Follow-up time	Association with mortality
Díaz-De Los Santos et al. [43]	Peru	Septic shock (30)	6.0	60.0	8 days	Yes
Berbigier et al. [44]	Brazil	Septic patients (50)	5.0	65.6	28 days	No
Da Silva et al. [45]	Brazil	Admitted to the ICU (95)	5.1	63.7	28 days	No
Lee et al. [46]	Korea	Admitted to the ICU (66)	–	63.1	–	Yes
Thibault et al. [36]	France	Admitted to the ICU (931)	4.1	61.0	28 days	Yes
Stapel et al. [42]	Holanda	Admitted to the ICU (196)	4.8	64.8	90 days	Yes
Zamberlan et al. [40]	Brazil	Admitted to the ICU (247)	2.8	4.8	30 days	Yes

the early identification of severity allows the anticipation of therapeutic measures that might be crucial for the patient's outcome.

In the anthropometric assessment, AC has been highlighted as a good discriminator of malnutrition in critically ill patients as well as a good predictor for worse clinical prognosis.

In a previous study, we demonstrated that AC was the indicator that best discriminated malnutrition in 90 children and adolescents evaluated in a tertiary PICU [25]. Studies such as those by Bechard et al. [48] have shown that low *Z* BMI/I values are an independent indicator of poor clinical prognosis and that weight loss implies an increased risk of mortality. However, it is speculated that the deleterious effects attributed to malnutrition actually result from the depletion of lean mass and not from loss of body weight. Our study seems to corroborate this idea since FFM depletion at PICU admission demonstrated by low percentile AC values (≤ 5) increased 30-day mortality and LOS in the PICU [40]. Grippa et al. [49] observed that the middle upper arm muscle area (MUAC) for age and W/A and H/A were able to predict the duration of mechanical ventilation in 72 children and adolescents in the PICU. In adults, Ravasco et al. [50] also observed a higher mortality rate in critically ill adults whose MUAC values were $<$ 5th percentile.

Practical approach

Nutritional prognosis and evolution of the patient during admission in the PICU are linked as a result of intense protein hyper catabolism and metabolic adaptation during inflammatory response. Actually, those considered exclusively nutritional biomarkers have been considered inflammatory parameters to monitor these patients. In fact, the first one that was used for this outcome was albumin (with stronger evidence in adults) [51]. Nevertheless, hypoalbuminemia has multifactorial etiology and spontaneous normalization of concentrations in the recovery phase of the disease. Other traditional nutritional markers (zinc, selenium, prealbumin, and HDL) have been used as inflammatory and, consequently, prognostic indicators. These markers can be associated to other parameters, mainly anthropometric measurements, to evaluate nutritional and clinical conditions in critically ill patients [47].

Nutrition care studies have proposed that an early intervention targeting nutritional assessment can prevent or minimize undernutrition complications [52]. For this reason, nutritional evaluation of the patients early after admission is essential to promote sufficient and proper nutrition support.

Anthropometry is a basic component of the nutritional assessment because it presents standardized reference values by age group, unlike biochemical indicators. Furthermore, anthropometry is very useful for classifying nutrition status, as well as for planning NT and nutrition monitoring [50]. Although anthropometry is difficult to interpret in critically ill patients, we believe it is important and we recommend that it be performed on admission and repeated weekly during the whole hospitalization for nutritional status monitoring.

Besides, identifying body compartments in the nutrition aspect and body composition seems to be able to predict clinical outcomes such as mortality and length of hospital stay. Thus, we suggest including the body composition assessment in the admission nutritional assessment.

There are several techniques to assess body composition, such as arm measures and BIA. Among the BIA parameters, PA which indirectly represents FFM is the most clinically established as it has shown a strong ability to predict outcomes in a wide variety of clinical situations, including critically ill children, as we showed in a previous study [40]. In patients with lower PA values, a higher survival rate was reported (*reference*). Besides, the Kaplan–Meier time-to-event analysis showed that children with lower PA values (who did not die) were more likely to remain in the PICU. We have suggested that BIA for PA estimation should be performed on admission to the PICU as an additional indicator in the estimation of the risk of death and LOS.

AC is a simple, quick, and inexpensive measure that has been shown to be a suitable discriminator of malnutrition in critically ill patients, as well as an outcome predictor for mortality and LOS in these patients [40, 50]. We recommend including AC in routine nutritional assessment in the ICU. It should be performed on admission and repeated periodically (every 7 to 10 days) for nutritional monitoring of the patient.

Conclusion

Nutritional assessment is essential in the prognosis of critically ill children and adolescents and it should be based on anthropometric (W/A, H/A, H/W, BMI/A) and body composition measurements. Undernourished patients are at risk for immune depression with higher risk of morbidity, infections, and mortality. Several nutritional biomarkers have been used to assess nutritional status as well as to predict clinical outcomes. New parameters (HDL, zinc, selenium) seem to be worthwhile but more studies are needed. Body composition assessment by new tools as BIA (with PA cutoff points for specific populations) may help to improve the prognosis and nutritional status evaluation.

Compliance with Ethical Standards

Conflict of Interest

Patrícia Zamberlan declares that she has no conflict of interest. Werther Brunow de Carvalho declares that he has no conflict of interest. Artur Figueiredo Delgado declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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