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Clinical Nutrition Approaches to Medical Management of Children with Obesity and Critical Illnesses

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Abstract

Context: Childhood obesity is a serious health problem worldwide and the number of critically ill obese children is rapidly increasing in Pediatric Intensive Care Units (PICUs). Given the importance of optimal energy and nutrient delivery that may lead to improved clinical outcomes in PICUs, we addressed the nutrition support aspects of managing critically ill obese children in PICUs.
Evidence Acquisition: This review was conducted on the National Library of Medicine's PubMed, Scopus, Cochrane, and Embase databases using a combination of relevant MeSH terms and keywords to provide updates on the nutritional management of obese patients in PICUs. The MeSH terms included "Child", "Pediatrics", "Infants", "Obesity", "Morbid Obesity", "Obesity Management", "Complications", "Nutrition Assessment", "Diet Therapy", and "Intensive Care Units". The keywords were as followed: critical care, critical illness, intensive care enteral and parenteral nutrition, morbidity, and mortality. The reference lists of the relevant articles were also reviewed to ensure adequate study identification. Thereafter, 348 records were identified and screened for eligibility in the title and abstract and duplicate publications were removed. Finally, after assessment for eligibility, 42 relevant articles published in English from 1990 to 2018 were obtained and read thoroughly in the reviewing process.
Results: Obese children are at a high risk of nutritional deprivation in PICUs. Obesity, metabolic stress, and inflammation can affect the metabolism of nutrients in critically ill obese children. Screening for potential micronutrient deficiencies, optimal isocaloric feeding with adequate macronutrients, and micronutrients should be considered in critically ill obese children.
Conclusions: This review provided recent evidence to help intensivists for initial nutrition assessment and realistic nutrition care planning for critically ill obese children.

Keywords: Pediatric Obesity, Intensive Care Units, Pediatric, Pediatric; Obesity, Nutrition Assessment, Diet Therapy

1. Context

Childhood obesity is one of the serious health problems in the world. About 14% of Iranian boys and 10% of Iranian girls are suffering from general obesity (1). It is associated with comorbidities and complications including secondary pseudotumor cerebri syndrome, insulin resistance, hyperglycemia, dyslipidemia, increased risk of gastroesophageal reflux disease, hepatitis, liver fibrosis, gallstone, and antibiotic treatment failure (2-5). Endothelial dysfunction and reduced parasympathetic activity in obese children may result in primary arterial hypertension in critically ill patients, followed by larger left ventricular mass and severe hypertension in obese subjects in Pediatric Intensive Care Units (PICUs) (6, 7). Additionally, excess adipose tissue in the body, reduced lean mass and water levels may lead to changes in the volume of drug distribution throughout the body (8).

The airway management of obese patients in PICUs is challenging; for example, obesity may increase the risk of airway intervention requirement, prolonged mechanical ventilation, and obstructive sleep apnea (1, 9-11). Additionally, excess adipose tissue may lead to difficult peripheral and central venous access. Also, because of technical challenges and difficulties in alternative central venous access, catheters may be left longer, which increases the risk of catheter-related complications such as infections, thrombosis, and phlebitis (9). Obesity is an independent risk fac-

tor for surgical outcomes and surgical-related morbidities in children. For example, children with obesity are at an increased risk of post-surgery hernia, nosocomial infections, deep-vein thrombosis, and delayed wound healing (12).

Obesity-related diseases and complications and obesity-related challenges in common procedures in PICUs make it difficult to conduct the medical management of critically ill obese children and obese children are considered to be at a high risk of mortality and morbidity in PICUs (9, 13, 14). Obesity-related challenges in the management of obese children in PICUs are summarized in Figure 1.

In addition to the effects of inflammation and metabolic stress on metabolism nutrients, obesity is associated with alterations in the metabolic process of critically ill obese children due to the high risk of nutritional deprivation in PICUs (13-15). Therefore, it is critical to screen potential nutritional deficiencies and improve the optimal energy and nutrient delivery in obese patients in PICUs (14-16).

While under/overfeeding of critically ill obese children may lead to physiological instability and adverse clinical outcomes, routine behavioral, nutritional, pharmacological, and surgical interventions for obesity treatment are not yet assessed in critically ill PICU patients (17). Previous studies demonstrated inconsistent results in nutritional management strategies regarding calories and macro/micronutrient requirements in the medical management of children with critical illness and obesity. Therefore, the main objective of this study was to elaborate on the nutritional management approaches of critically ill obese children such as nutritional assessment, energy requirement, macro/micronutrient requirement, and additional supplementation intake.

2. Evidence Acquisition

This narrative review was conducted to provide updates on the nutritional management of critically ill obese children. The search was performed using a combination of MeSH terms and keywords on the National Library of Medicine's PubMed, Scopus, Cochrane, and Embase as follows: "(((((“Child”[Mesh]) or “Pediatrics”[Mesh]) or “Infant”[Mesh])))) AND ((((((((((mortality) OR Obesity) OR Morbid obesity) OR morbidity) OR Complications) OR obesity Management)) AND (((((Intensive Care Units, Pediatrics) OR intensive care enteral nutrition) OR intensive care parenteral nutrition) OR critical illness) OR critical care))) AND (((Nutrition Assessment) OR Diet Therapy))))".

Relevant publications were identified in English cited from 1st January 1990 to 31st December 2018. The reference lists of the relevant articles were also reviewed to ensure study identification. Any disagreements were discussed and resolved in the focus group panel by all four research investigators. Firstly, 329 articles were retrieved and 19 additional records were identified through other sources and all of them were screened for eligibility in title and abstract by four independent reviewers. Duplications were removed; then, 53 records were identified. The quality assessment of the studies was carried out using “the Cochrane Collaboration's tool for assessing risk of bias in randomized trials” and “the risk of bias in observational studies of exposures” tools in focus group panels (18, 19). Therefore, after the quality assessment for eligibility, 42 studies were included in this narrative review.

3. Results

3.1. Nutritional Assessment of Critically Ill Obese Children

Obese children admitted to PICUs constitute a nutritionally high-risk population (16). The initial nutritional assessment with a nutrition care program is necessary for all critically ill obese children, especially in complicated subjects (14, 16, 20).

The assessment of anthropometric parameters including mid-upper arm circumference (MAC), body weight, height/length, and BMI should be routinely performed to assess and follow the nutrition status of these children (21). Alterations in MAC and weight are correlated with cumulative energy and protein deficiency in PICU patients (22). In addition to the routine monitoring of weight, MAC, and other anthropometric parameters, nitrogen balance should be routinely measured during PICU stay and the diet should be modified in negative nitrogen balance cases (17). Moreover, as an indicator of visceral protein pool, the measurement of pre-albumin may be useful, but this test should be interpreted considering the inflammation phase and illness severity (17).

Obese children are at a higher risk of prolonged stress-induced hyperglycemia than normal subjects (13). Short-time stress could induce hyperglycemia in critically ill patients and remain beneficial since it provides glucose as an energy substrate in the hypermetabolism state to tissues; however, sustaining it in obese children may deteriorate the effect of oxidative stress by increasing free radicals and increased inflammatory cytokines, which may reduce immune system functioning (23).

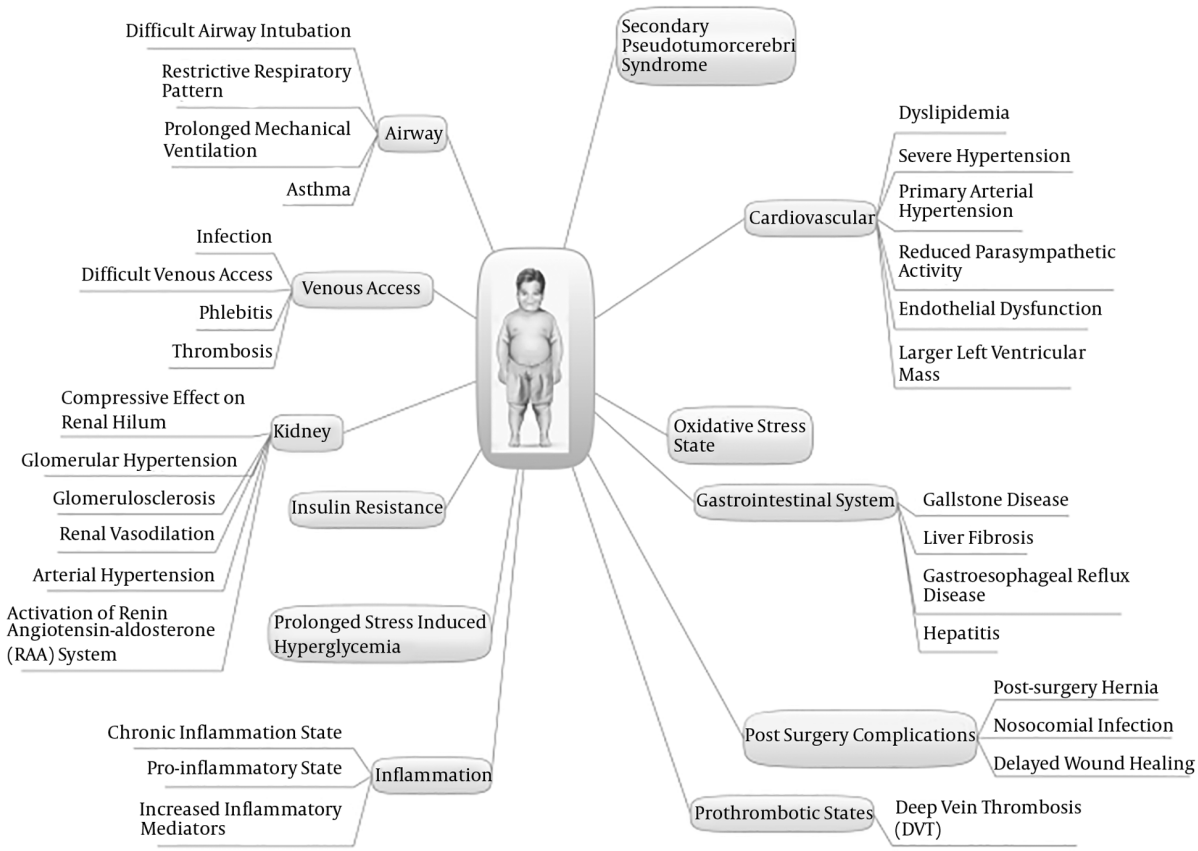

Figure 1. Obesity-related challenges in the management of obese children in pediatric Intensive Care Units (PICUs)

Adipose tissue is not only an inert-fat storing tissue but it is also considered an endocrine organ secreting several hormones including leptin, resistin, visfatin, and adiponectin. These hormones play a major role in various body functions such as nutritional intake, control of sensitivity to insulin, and inflammatory process (24). These hormones can cause the activation of inflammatory pathways and significantly increase pro-inflammatory cytokine levels including tumor necrosis factor-α, interleukin-1b, and interleukin-6, as well as the chronic inflammatory state. Particularly, macrophage-related inflammatory activities may lead to insulin resistance and reduced immunity in obese subjects (25). Therefore, the inflammatory response of obese children to acute injury is differently exacerbated compared with non-obese children (13). Leptin, resistin, adiponectin, and inflammatory mediators secreted by adipose tissue, obesity-related dyslipidemia, and hyperglycemia are other factors involved in the progression of renal dysfunction in obese children admitted to ICUs (13). Chronic inflammation state and increased inflammatory mediators in obese children predispose them to pro-inflammatory and prothrombotic states and oxidative stress (20). Serum C reactive protein (CRP) can also be used as an indicator of inflammation in relation to pre-albumin. In post-surgical cases, a decrease in CRP levels in serum is associated with the elevation of pre-albumin levels, both of which indicate the anabolic phase of metabolism after acute injury (22). The derangements in fatty acid profiles can influence inflammation, organ function, disease process, and survival (26, 27). The derangements in fatty acid profiles may lead to inflammation, organ dysfunction, deterioration of disease process, and reduced survival (25). Finally, childhood obesity may lead to the development of nonalcoholic fatty liver disease (NAFLD) (28). On the other hand, the acute phase response is considered a risk factor for the development of fatty liver disease (29). The recommended routine nutritional assessment of critically ill obese children include lipid profile, glucose, phosphorus,

liver function tests, and complete blood count (15, 30).

3.2. Energy and Macronutrient Requirement

Undernutrition in obese children may result in nutritional deprivation and leads to poor clinical outcomes, especially because of negative protein balance and muscle mass wasting (31, 32).

Overfeeding may result in electrolyte imbalance, respiratory, and cardiovascular complications and increase the length of ICU stay (17). Failure to recognize the hypermetabolic phase of metabolic stress response, reliance on standardized formulae/equations for energy expenditure, inaccurate weight measurements, confusion about which weight to use for obese patients (actual/ ideal body weight), and overestimating the degree of metabolic stress in the era of modern anesthesia and surgery may lead to the overfeeding of these patients in PICUs (10, 31). Optimal energy delivery to such obese patients is essential for sustaining the function of the immune, cardiovascular, and respiratory systems in the acute phase of the inflammatory response (32, 33). Insulin and growth hormone resistance following acute injury caused by increased serum counter-regulatory hormone concentrations could lead to catabolism (34). Optimal nutrition support provision is necessary to prevent the loss of lean body mass in critically ill children. Hypo-caloric feeding is also not recommended during ICU stay since it could increase catabolism in metabolic stress state (15, 17). On the other hand, the transient absence of growth, mechanical ventilation, sedation, activity reduction, and decreased insensible fluid loss during the acute phase of inflammatory response may lead to resting energy expenditure (REE) reduction. Obese children could have various REEs caused by differences in lean body mass, nature, and phases of the acute illness (35).

Table 1 represents cross-sectional/cohort clinical trials of energy expenditure estimation in children with obesity. It summarizes studies on the accuracy of predictive equations in comparison with measured REEs by indirect calorimetry (IC). As noted in Table 1, according to the studies, the most accurate REE predictive equations were SCHOHTWT, Harris-Benedict, and Lazzer, in sequence (36-38). However, in the majority of other studies (80% of all relevant cross-sectional/cohort clinical trials), it is reported that none of the published equations (i.e., World Health Organization (WHO), Schofield and Harris-Benedict, etc.) was accurate (39-47). Notably, in a few studies, one or two equations were developed that were only accurate in the studied population group and had little generalizability (39-45, 47).

Therefore, critically ill children may be at the risk of under/overfeeding with the estimation of energy requirement based on the development of predictive equations (i.e., WHO, Schofield and Harris-Benedict) and stress correction factors (31). Therefore, it is highly recommended assessing energy requirements with indirect calorimetry as a standard method in terms of accuracy in these critically ill children with obesity (15, 20, 21).

After the determination of energy requirement for these obese patients, the administration of major substrates including carbohydrates, proteins, and lipids should be based upon their metabolism in accordance with the nature and phase of the acute illness (15, 17).

3.3. Micronutrient Requirement

Similar to all patients admitted to PICUs, obese children should be assessed for deficiencies in micronutrients and their RDAs amount (10). Children with a critical illness are at increased risk of vitamin B-1, B-2, and B-6 deficiencies (48). Although obesity in children may lead to vitamin B-12 deficiency, the dietary assessment of obese patients before admission in addition to laboratory assessments should be considered in PICUs (49). Some studies reported that high vitamin B-12 level is associated with high inflammation and mortality rate in critically ill adult patients (50). More studies are needed to identify the state of vitamin B-12 in critically ill obese children.

Most critically ill patients are at the increased risk of vitamin A deficiency development according to their nutrition and metabolic states. The deficiency can be severe in patients with lower hepatic retinol storage that probably occurs in obese patients due to recent dietary restrictions for weight reduction such as skimmed dairy products and eggs as two of the best sources of retinol (50).

Magnesium and vitamin D deficiencies are common in obese children and lower 25(OH) vitamin D and magnesium levels in serum are associated with hyperglycemia and insulin resistance in them (30, 51). Magnesium and vitamin D supplementation may be used as an effective, preventive, and therapeutic treatment in the management of obese patients in PICUs (15, 51).

As a cellular antioxidant, vitamin E plays an important role in oxidative stress status. However, insufficient data are available regarding the determination of the role of vitamin E in such patients (50). Therefore, the best way for the diagnosis of vitamin E state is the adjustment of α-tocopherol to total lipids because of different lipid distributions in critical obesity (50). Serum concentrations of zinc and selenium may decrease in PICU settings in re-

Table 1. Energy Expenditure Estimation in Obese Children

Country	Authors' Names	Number of Participants	Main Findings	Reference
Turkey	Acar-Tek et al.	103 obese children and adolescents	All of the existing predictive equations were inaccurate in the estimation of REE for obese children.A new prediction equation was developed for local use.	(39)
Italy	Marra et al.	264 obese adolescents	None of the previously published equations was accurate.The most suitable equations included the Lazzer equation in both males and females and Schmelz and Henry-1 equations in females.	(38)
Korea	Kim et al.	52 obese children and adolescents	Harris-Benedict, Liu, Mifflin, and Molnar equations were the most accurate predictive equations (accuracy: 73%, 77%, 79%, and 87%, respectively).	(37)
China	Chan et al.	100 obese children	None of the previously developed prediction equations was accurate.A new prediction equation was generated for local use.	(40)
Italy	Lazzer et al.	574 obese children and adolescents	Two new equations were developed based on anthropometric parameters for obese Caucasian children and adolescents.	(42)
Germany	Schmelzle et al.	82 obese children and adolescents	All of the published predictive equations were inaccurate and inclusion of lean body mass in REE prediction improved the accuracy.	(46)
France	Derumeaux-Burel et al.	752 obese children and adolescents (n = 471 derivation and n = 211 validation)	New local accurate equations were established.	(41)
United States of America	McDuffie et al.	502 obese children	None of the World Health Organization, Food and Agriculture Organization, United Nations University, Schofield, Molnar, Maffetis, and Tverskaya equations was accurate.Two new specific equations were developed.	(44)
USA	Tverskaya et al.	110 obese children and adolescents	Previous equations did not accurately predict BMR.A new equation was generated.	(47)
USA	Kaplan et al.	20 obese children	The SCHO-HTWT equation was the best predictive equation (95% +/- 17%).	(36)
Hungary	Molnar et al.	136 obese children and adolescents	Previously published equations overestimated REE.A new predictive equation was established for REE in obese children.	(45)
Italy	Maffeis et al.	130 obese and nonobese prepubertal children	Most of the developed equations overestimated REE in obese subjects and equations were generated.	(43)

sponse to metabolic pathways in systemic inflammation, but there is incomprehensive data in this regard (50).

Although obesity is associated with the increased risk of iron deficiency anemia, screening for iron deficiency is not recommended in critically ill children since the reduction of serum iron level is determined as a protective response against infection and inflammation in acute phase injury (52). However, according to a study, the hepcidin mass spectrometry dosage method is recommended (53). Key nutritional aspects in the management of children with obesity and critical illness are shown in Table 2.

4. Conclusions

In addition to the necessity of preventive strategies for the reduction of childhood obesity prevalence, nutrition planning for the management of obese children admitted to PICUs is of high importance. Optimal energy and nutrient delivery can play an important role in the clinical outcomes of critically ill obese children. These patients constitute a nutritionally high-risk group for whom initial nutritional assessment with suitable nutrition care programs is necessary.

Optimal isocaloric feeding with adequate macronutrients and micronutrients should be administered in critically ill obese children. Since hypocaloric feeding is not recommended in critically ill obese children due to increased catabolism in the metabolic stress state, assessing energy requirement by indirect calorimetry may prevent overfeeding/underfeeding in obese children in PICUs. Further clinical studies, particularly randomized clinical trials, are necessary for the development of nutritional principles in energy requirement, macro/micronutrient delivery, and necessary supplementations.

Table 2. Key Nutritional Aspects in the Management of Critically Ill Obese Children

Step of Nutrition Support	Recommendation	References
Nutritional assessment	**Anthropometric parameters**	(21, 22)
	MAC	
	Bodyweight	
	Height/length	
	BMI	
	Nitrogen balance	(17)
	Pre-albumin	(17)
	CRP	(22, 27)
	Possible/potential laboratory abnormalities	
	Complete blood count	(15, 30)
	Glucose	(13, 15)
	Phosphorus	(15)
	Lipid profile	(15, 25)
	Total cholesterol	
	HDL cholesterol	
	LDL cholesterol	
	Triglycerides	
	Liver function tests	(15, 28, 29)
	AST	
	ALT	
	Direct bilirubin	
	GGT	
Energy requirement	Indirect calorimetry is recommended	(15, 17)
Macronutrient requirements	Based upon carbohydrate, protein, and lipid metabolism depending on the nature and phase of acute illness	(10, 15, 17)
Micronutrient requirements	**Routines in RDAs amount**	(10, 15, 17)
	Assessment of possible/potential micronutrients deficiencies and treatment of documented deficiencies	
	Vitamin B-1, B-2, and B-6, B-12	(48-50)
	Vitamin A	(50)
	Vitamin D	(30, 51)
	Magnesium	(15, 51)
	Zinc	(50)
	Selenium	(50)

Abbreviations: ALT, alanine amino transaminase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C reactive protein; GGT, γ-glutamyl transpeptidase; MAC, mid-upper arm circumference.

Footnotes

Authors' Contribution: Study concept and design: Mohsen Nematy, Gholamreza Khademi, and Fatemeh Roudi. Acquisition of data: Golnaz Ranjbar, Mahdieh Pouryazdanpanah, Rahele Rahimi, and Fatemeh Roudi. Interpretation of data: Gholamreza Khademi, Mohsen Nematy, Golnaz Ranjbar, Mahdieh Pouryazdanpanah, Rahele Rahimi, and Fatemeh Roudi. Drafting of the manuscript: Gholamreza Khademi, Mohsen Nematy, Golnaz Ranjbar, Mahdieh Pouryazdanpanah, and Fatemeh Roudi. Critical revision of the manuscript for important intellectual content: Mohsen Nematy and Golnaz Ranjbar. Study supervi-

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References

1. Veyckemans F. Child obesity and anaesthetic morbidity. *Curr Opin Anaesthesiol*. 2008;**21**(3):308–12. doi: 10.1097/ACO.0b013e3282f82bbb. [PubMed: 18458546].
2. Khajavi L, Khademi G, Mehramiz M, Norouzy A, Safarian M. Association of dysglycemia with mortality in children receiving parenteral nutrition in pediatric intensive care unit. *Turk J Pediatr*. 2018;**60**(2):134–41. doi: 10.24953/turkjped.2018.02.003. [PubMed: 30325118].
3. Banna Zadeh V, Khademi G, Rakhshanizadeh F, Imani B, Abdollahpour N, Sezavar M. Impact of hyperglycemia duration on mortality and ventilator dependence in Neonatal Intensive Care Unit. *Iran J Neonatol*. 2017;**8**(2):36–43.
4. Camilleri M, Malhi H, Acosta A. Gastrointestinal complications of obesity. *Gastroenterology*. 2017;**152**(7):1656–70. doi: 10.1053/j.gastro.2016.12.052. [PubMed: 28192107]. [PubMed Central: PMC5609829].
5. Longo C, Bartlett G, Macgibbon B, Mayo N, Rosenberg E, Nadeau L, et al. The effect of obesity on antibiotic treatment failure: A historical cohort study. *Pharmacoepidemiol Drug Saf*. 2013;**22**(9):970–6. doi: 10.1002/pds.3461. [PubMed: 23733599].
6. Raj M. Obesity and cardiovascular risk in children and adolescents. *Indian J Endocrinol Metab*. 2012;**16**(1):13–9. doi: 10.4103/2230-8210.91176. [PubMed: 22276248]. [PubMed Central: PMC3263181].
7. Liao D, Rodriguez-Colon SM, He F, Bixler EO. Childhood obesity and autonomic dysfunction: Risk for cardiac morbidity and mortality. *Curr Treat Options Cardiovasc Med*. 2014;**16**(10):342. doi: 10.1007/s11936-014-0342-1. [PubMed: 25143120]. [PubMed Central: PMC4159679].
8. Harskamp-van Ginkel MW, Hill KD, Becker KC, Testoni D, Cohen-Wolkowiez M, Gonzalez D, et al. Drug dosing and pharmacokinetics in children with obesity: A systematic review. *JAMA Pediatr*. 2015;**169**(7):678–85. doi: 10.1001/jamapediatrics.2015.132. [PubMed: 25961828]. [PubMed Central: PMC4494887].
9. Alurkar S, Vyas H. Obesity and critical care in children. *Paediatrics and Child Health*. 2013;**23**(4):180–2. doi: 10.1016/j.paed.2012.12.007.
10. Mehta NM, Compher C; A. S. P. E. N. Board of Directors. A.S.P.E.N. Clinical Guidelines: nutrition support of the critically ill child. *JPEN J Parenter Enteral Nutr*. 2009;**33**(3):260–76. doi: 10.1177/0148607109333114. [PubMed: 19398612].
11. Malhotra A, Hillman D. Obesity and the lung: 3. Obesity, respiration and intensive care. *Thorax*. 2008;**63**(10):925–31. doi: 10.1136/thx.2007.086835. [PubMed: 18820119]. [PubMed Central: PMC2711075].
12. Roupakias S, Mitsakou P. Surgical morbidity in obese children. *Asian J Surg*. 2012;**35**(3):99–103. doi: 10.1016/j.asjsur.2012.06.008. [PubMed: 22884265].
13. Donoso Fuentes A, Cordova LP, Hevia JP, Arriagada SD. The obese child in the Intensive Care Unit. Update. *Arch Argent Pediatr*. 2016;**114**(3):258–67. doi: 10.5546/aap.2016.eng.258. [PubMed: 27164340].
14. Ross PA, Newth CJ, Leung D, Wetzel RC, Khemani RG. Obesity and mortality risk in critically ill children. *Pediatrics*. 2016;**137**(3). e20152035. doi: 10.1542/peds.2015-2035. [PubMed: 26908670].
15. Jesuit C, Dillon C, Compher C, Lenders CM; American Society for Parenteral; Enteral Nutrition Board of Directors. A.S.P.E.N. clinical guidelines: Nutrition support of hospitalized pediatric patients with obesity. *JPEN J Parenter Enteral Nutr*. 2010;**34**(1):13–20. doi: 10.1177/0148607109354088. [PubMed: 20054058]. [PubMed Central: PMC3235913].
16. Bechard LJ, Duggan C, Touger-Decker R, Parrott JS, Rothpletz-Puglia P, Byham-Gray L, et al. Nutritional status based on body mass index is associated with morbidity and mortality in mechanically ventilated critically ill children in the PICU. *Crit Care Med*. 2016;**44**(8):1530–7. doi: 10.1097/CCM.0000000000001713. [PubMed: 26985636]. [PubMed Central: PMC4949117].
17. Mehta NM, Skillman HE, Irving SY, Coss-Bu JA, Vermilyea S, Farrington EA, et al. Guidelines for the provision and assessment of nutrition support therapy in the pediatric critically ill patient: Society of Critical Care Medicine and American Society for parenteral and enteral nutrition. *JPEN J Parenter Enteral Nutr*. 2017;**41**(5):706–42. doi: 10.1177/0148607117711387. [PubMed: 28686844].
18. Bero L, Chartres N, Diong J, Fabbri A, Ghersi D, Lam J, et al. The risk of bias in observational studies of exposures (ROBINS-E) tool: Concerns arising from application to observational studies of exposures. *Syst Rev*. 2018;**7**(1):242. doi: 10.1186/s13643-018-0915-2. [PubMed: 30577874]. [PubMed Central: PMC6302384].
19. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;**343**:d5928. doi: 10.1136/bmj.d5928. [PubMed: 22008217]. [PubMed Central: PMC3196245].
20. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: The linking mechanism and the complications. *Arch Med Sci*. 2017;**13**(4):851–63. doi: 10.5114/aoms.2016.58928. [PubMed: 28721154]. [PubMed Central: PMC5507106].
21. Mehta NM, Duggan CP. Nutritional deficiencies during critical illness. *Pediatr Clin North Am*. 2009;**56**(5):1143–60. doi: 10.1016/j.pcl.2009.06.007. [PubMed: 19931068]. [PubMed Central: PMC4641569].
22. Hulst JM, van Goudoever JB, Zimmermann LJ, Hop WC, Albers MJ, Tibboel D, et al. The effect of cumulative energy and protein deficiency on anthropometric parameters in a pediatric ICU population. *Clin Nutr*. 2004;**23**(6):1381–9. doi: 10.1016/j.clnu.2004.05.006. [PubMed: 15556260].
23. Karlsson M, Marild S, Brandberg J, Lonn L, Friberg P, Strandvik B. Serum phospholipid fatty acids, adipose tissue, and metabolic markers in obese adolescents. *Obesity (Silver Spring)*. 2006;**14**(11):1931–9. doi: 10.1038/oby.2006.225. [PubMed: 17135608].
24. Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: An endocrine organ. *Arch Med Sci*. 2013;**9**(2):191–200. doi: 10.5114/aoms.2013.33181. [PubMed: 23671428]. [PubMed Central: PMC3648822].
25. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest*. 2003;**112**(12):1821–30. doi: 10.1172/JCI19451. [PubMed: 14679177]. [PubMed Central: PMC296998].
26. Letton RW, Chwals WJ, Jamie A, Charles B. Early postoperative alterations in infant energy use increase the risk of overfeeding. *J Pediatr Surg*. 1995;**30**(7):988–92. discussion 992-3. doi: 10.1016/0022-3468(95)90327-5. [PubMed: 7472959].
27. Bechard LJ, Ziegler J, Duggan C. Is energy expenditure of infants predictable after surgery? A review of the evidence. *Infant Child Adolesc Nutr*. 2010;**2**(3):170–6. doi: 10.1177/1941406410370850.
28. Feldstein AE, Patton-Ku D, Boutelle KN. Obesity, nutrition, and liver disease in children. *Clin Liver Dis*. 2014;**18**(1):219–31. doi: 10.1016/j.cld.2013.09.003. [PubMed: 24274876]. [PubMed Central: PMC4008146].

29. Paquot N, Delwaide J. Fatty liver in the intensive care unit. *Curr Opin Clin Nutr Metab Care*. 2005;**8**(2):183–7. doi: 10.1097/00075197-200503000-00013. [PubMed: 15716798].
30. Via M. The malnutrition of obesity: Micronutrient deficiencies that promote diabetes. *ISRN Endocrinol*. 2012;**2012**:103472. doi: 10.5402/2012/103472. [PubMed: 22462011]. [PubMed Central: PMC3313629].
31. Hulst JM, van Goudoever JB, Zimmermann LJ, Hop WC, Buller HA, Tibboel D, et al. Adequate feeding and the usefulness of the respiratory quotient in critically ill children. *Nutrition*. 2005;**21**(2):192–8. doi: 10.1016/j.nut.2004.05.020. [PubMed: 15723748].
32. Martinez EE, Ariagno KA, Stenquist N, Anderson D, Munoz E, Mehta NM. Energy and protein delivery in overweight and obese children in the Pediatric Intensive Care Unit. *Nutr Clin Pract*. 2017;**32**(3):414–9. doi: 10.1177/0884533616670623. [PubMed: 28490231].
33. Abad-Jorge A. Nutrition management of the critically ill pediatric patient: Minimizing barriers to optimal nutrition support. *Infant Child Adolesc Nutr*. 2013;**5**(4):221–30. doi: 10.1177/1941406413492821.
34. Elijah IE, Branski LK, Finnerty CC, Herndon DN. The GH/IGF-1 system in critical illness. *Best Pract Res Clin Endocrinol Metab*. 2011;**25**(5):759–67. doi: 10.1016/j.beem.2011.06.002. [PubMed: 21925076]. [PubMed Central: PMC3788574].
35. Aspen Board of Directors; the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr*. 2002;**26**(1 Suppl):1SA–138SA. [PubMed: 11841046].
36. Kaplan AS, Zemel BS, Neiswender KM, Stallings VA. Resting energy expenditure in clinical pediatrics: measured versus prediction equations. *J Pediatr*. 1995;**127**(2):200–5. doi: 10.1016/s0022-3476(95)70295-4. [PubMed: 7636642].
37. Kim MH, Kim JH, Kim EK. Accuracy of predictive equations for resting energy expenditure (REE) in non-obese and obese Korean children and adolescents. *Nutr Res Pract*. 2012;**6**(1):51–60. doi: 10.4162/nrp.2012.6.1.51. [PubMed: 22413041]. [PubMed Central: PMC3296923].
38. Marra M, Montagnese C, Sammarco R, Amato V, Della Valle E, Franzese A, et al. Accuracy of predictive equations for estimating resting energy expenditure in obese adolescents. *J Pediatr*. 2015;**166**(6):1390–6 e1. doi: 10.1016/j.jpeds.2015.03.013. [PubMed: 25872963].
39. Acar-Tek N, Agagunduz D, Celik B, Bozbulut R. Estimation of resting energy expenditure: Validation of previous and new predictive equations in obese children and adolescents. *J Am Coll Nutr*. 2017;**36**(6):470–80. doi: 10.1080/07315724.2017.1320952. [PubMed: 28749749].
40. Chan DF, Li AM, Chan MH, So HK, Chan IH, Yin JA, et al. Validation of prediction equations for estimating resting energy expenditure in obese Chinese children. *Asia Pac J Clin Nutr*. 2009;**18**(2):251–6. [PubMed: 19713185].
41. Derumeaux-Burel H, Meyer M, Morin L, Boirie Y. Prediction of resting energy expenditure in a large population of obese children. *Am J Clin Nutr*. 2004;**80**(6):1544–50. doi: 10.1093/ajcn/80.6.1544. [PubMed: 15585766].
42. Lazzer S, Agosti F, De Col A, Sartorio A. Development and cross-validation of prediction equations for estimating resting energy expenditure in severely obese Caucasian children and adolescents. *Br J Nutr*. 2006;**96**(5):973–9. doi: 10.1017/bjn20061941. [PubMed: 17092390].
43. Maffeis C, Schutz Y, Micciolo R, Zoccante L, Pinelli L. Resting metabolic rate in six- to ten-year-old obese and nonobese children. *J Pediatr*. 1993;**122**(4):556–62. doi: 10.1016/s0022-3476(05)83535-8. [PubMed: 8463900].
44. McDuffie JR, Adler-Wailes DC, Elberg J, Steinberg EN, Fallon EM, Tershakovec AM, et al. Prediction equations for resting energy expenditure in overweight and normal-weight black and white children. *Am J Clin Nutr*. 2004;**80**(2):365–73. doi: 10.1093/ajcn/80.2.365. [PubMed: 15277157]. [PubMed Central: PMC2267722].
45. Molnar D, Jeges S, Erhardt E, Schutz Y. Measured and predicted resting metabolic rate in obese and nonobese adolescents. *J Pediatr*. 1995;**127**(4):571–7. doi: 10.1016/s0022-3476(95)70114-1. [PubMed: 7562278].
46. Schmelzle H, Schroder C, Armbrust S, Unverzagt S, Fusch C. Resting energy expenditure in obese children aged 4 to 15 years: Measured versus predicted data. *Acta Paediatr*. 2004;**93**(6):739–46. doi: 10.1111/j.1651-2227.2004.tb01000.x. [PubMed: 15244220].
47. Tverskaya R, Rising R, Brown D, Lifshitz F. Comparison of several equations and derivation of a new equation for calculating basal metabolic rate in obese children. *J Am Coll Nutr*. 1998;**17**(4):333–6. doi: 10.1080/07315724.1998.10718771. [PubMed: 9710841].
48. 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**(4):533–8. doi: 10.1016/s0022-3476(05)81140-0. [PubMed: 1403385].
49. Pinhas-Hamiel O, Doron-Panush N, Reichman B, Nitzan-Kaluski D, Shalitin S, Geva-Lerner L. Obese children and adolescents: A risk group for low vitamin B12 concentration. *Arch Pediatr Adolesc Med*. 2006;**160**(9):933–6. doi: 10.1001/archpedi.160.9.933. [PubMed: 16953016].
50. Dao DT, Anez-Bustillos L, Cho BS, Li Z, Puder M, Gura KM. Assessment of micronutrient status in critically ill children: Challenges and opportunities. *Nutrients*. 2017;**9**(11). doi: 10.3390/nu9111185. [PubMed: 29143766]. [PubMed Central: PMC5707657].
51. Olson ML, Maalouf NM, Oden JD, White PC, Hutchison MR. Vitamin D deficiency in obese children and its relationship to glucose homeostasis. *J Clin Endocrinol Metab*. 2012;**97**(1):279–85. doi: 10.1210/jc.2011-1507. [PubMed: 22072738]. [PubMed Central: PMC3251943].
52. Nead KG, Halterman JS, Kaczorowski JM, Auinger P, Weitzman M. Overweight children and adolescents: A risk group for iron deficiency. *Pediatrics*. 2004;**114**(1):104–8. doi: 10.1542/peds.114.1.104. [PubMed: 15231915].
53. Lasocki S, Puy H, Mercier G, Lehmann S; Hepcidane study group. Impact of iron deficiency diagnosis using hepcidin mass spectrometry dosage methods on hospital stay and costs after a prolonged ICU stay: Study protocol for a multicentre, randomised, single-blinded medico-economic trial. *Anaesth Crit Care Pain Med*. 2017;**36**(6):391–6. doi: 10.1016/j.accpm.2017.04.009. [PubMed: 28919067].