Review article

Muscle weakness and wasting in pediatric critical illness

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Abstract: Muscle weakness and wasting is increasingly recognized as a problem in children admitted to the pediatric intensive care unit (PICU). Muscle weakness and wasting could potentially affect a child's function and development, imposing a burden on the child and their families. We aimed to summarize the literature on muscle weakness and wasting in critically ill children, discuss methods to measure muscle changes as well as areas for future research. Intensive care unit weakness in children has been reported through numerous case reports and a cohort study. These papers demonstrated that muscle weakness can be persistent in critically ill children, with reduced strength reported even after hospital discharge. A prevalence of approximately 2% has been reported in critically ill children, lower than that reported in adults. This may be related to an under-detection of muscle weakness in critically ill children, as identification of muscle weakness and wasting in critically ill children can be challenging. Some methods that have been used to assess muscle changes in critically ill children include arm muscle circumference derived from triceps skinfold thickness and upper-arm circumference, ultrasound-derived limb and diaphragm muscle size, lean body mass from bioelectrical impedance analysis. Using these methods, various patterns have been reported including increase, decrease and no change in muscle. However, studies have not explored the relationship between muscle changes and function. Evidence suggests that there is heterogeneity in the muscle changes that critically ill children may experience. Future research may need to consider differences in age, illness severity and body composition in interpreting changes in muscle size and strength in critically ill children. Importantly, understanding the role of nutrition and physical rehabilitation in relation to muscle changes and function is an important direction in optimizing long-term outcomes in critically ill children.

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Introduction

In the past few years, there has been increasing interest in muscle weakness and wasting, and corresponding consequences, in children admitted to the pediatric intensive care unit (PICU) (1-3). Short-term impact of muscle wasting include prolonged mechanical ventilation (MV) requirement, thus increasing PICU length of stay, healthcare costs and resource utilization (2). Long-term consequences are equally concerning, with muscle weakness and wasting extending beyond PICU stay with the potential to affect a child's physical function and development (4). Functional impairments are one of the types of morbidities observed in the post-intensive care syndrome in children (PICS-p), and these physical limitations can indirectly impact psychological and social function of not only the child, but their siblings and parents as well (5).

However, our understanding of muscle weakness and

wasting in critically ill children is still in its infancy—including identification, trajectory, pathophysiology and mechanisms, at risk groups and strategies to overcome muscle weakness and wasting. In adults, there appears to be a better understanding of muscle weakness and wasting in critical illness and recovery. While not completely translatable, adult data can potentially offer insights into PICU muscle weakness and wasting.

The aim of this review is thus to summarize the literature on muscle weakness and wasting in critically ill children with extrapolation of adult data, where potentially applicable in children. We will discuss the tools used to measure muscle changes in critically ill children, and propose future research areas in the study of muscle weakness and wasting in critically ill children.

Muscle weakness in critically ill adults

The burden of disability following critical illness has gained attention as long-term morbidities in survivors of critical illness have become apparent. This was described in the seminal studies performed by Herridge *et al.*, where survivors of adult acute respiratory distress syndrome were followed up to 5 years after their intensive care unit (ICU) stay (6,7). Survivors reported impairments in physical function, which persisted at 5 years post illness, and was associated with increased medical costs and inability to return to work. It is now recognized that the effects of critical illness are not confined to the ICU; recovery from the sequelae of critical illness can take years following discharge.

Physical impairment due to critical illness has also been extensively reported in other studies (8,9). Survivors not only experience difficulties returning to work, they also have problems with strength, engaging in extensive physical activity and basic activities such as walking independently (7,8). Lung and cardiac dysfunctions have been suggested as reasons for functional impairment, but these deficits usually resolve after ICU stay and do not appear to be responsible for long-term functional impairment (7,10,11). Herridge *et al*. found that survivors of acute respiratory distress syndrome attributed their long-term physical limitations to muscle loss and weakness acquired during ICU stay (6). This muscle loss and weakness is now widely studied, and appears to be the cause of significant medical, financial and social burden to ICU survivors and their families (7,12-15).

The weakness responsible for functional impairment occurs in up to 25–33% in patients who are mechanically ventilated for at least 4 to 7 days (14,16), and primarily involves muscle wasting (14,17-19), although in a subset, polyneuropathy may occur (17). However due to the challenges in differentiation and the often co-existence of myopathy and polyneuropathy, an umbrella term "ICU acquired weakness" (ICUAW) is used to describe this phenomenon (20,21). Currently, there is no consensus as to how ICUAW can be diagnosed (22), although a bedside diagnosis of weakness in critically ill patients without an alternate etiology is generally used (21). Manual muscle testing is often performed, most commonly using the Medical Research Council (MRC) muscle strength score (MRC score), which was first validated for use in Guillian-Barre patients (23). This score tests the ability of different muscle groups to overcome varying levels of resistance on a scale of 0 to 5, and a total MRC score of <48 out of 60 has been commonly used as an indicator of ICUAW (21,22).

Muscle weakness and wasting due to critical illness appears to be an increasing and debilitating problem both within and outside the ICU. Besides the long-term functional impairment described above, significant short-term consequences include difficulty in weaning off MV (14,24) and increased risk of mortality (25). Although the exact pathophysiology is unclear, causes of ICU muscle wasting are likely multi-factorial—a combination of critical illness metabolic alterations and ICU therapy (21). Muscle mass is determined by the net balance between protein breakdown and synthesis, which are regulated by catabolic and anabolic pathways respectively (26,27). In most healthy adults, protein breakdown and synthesis are balanced and muscle mass is maintained. Critically ill adults experience elevated muscle breakdown early in the disease course (13,28), and results in a negative protein balance which improves over time (29,30). However, post-discharge data has demonstrated that muscle does not always return to baseline size, indication possible long-term muscle deficits (31).

Muscle weakness and wasting in critically ill children

Muscle weakness has also been reported in critically ill children in the past two decades (32-38). Case reports illustrate clinical observations of flaccid paralysis after weaning of sedatives or failure to extubate from MV, which occurred after 7 to 25 days of PICU stay (33-38). Several risk factors of muscle weakness and wasting have been proposed (39,40). The use of neuromuscular blockade may be a possible risk factor for ICUAW in children, as they were used in all of the case reports and also suggested as the

Table 1 Methods used to assess muscle weakness and wasting in critically ill children

Methodology	Brief description	Advantages	Disadvantages
Medical Research Council (MRC) sum score	Used to gauge strength of limb muscles in relation to the assessor's resistance	Performed at bedside	Subjective
		No equipment necessary	Requires children to be able to understand instructions and cooperate with measurements
Skinfolds and circumference	Skinfolds used to measure fat size and overall body fat percentage. Triceps skinfolds often measured together with arm circumference to determine fat and muscle stores	Bedside measurement	Significant inter/intra-rater variability
		Inexpensive tools required	Accuracy also limited by edema, which is common in critically ill children
Bioelectrical impedance analysis	Sends a weak electrical current through the body, and using values of resistance and reactance, provides an indicator of fat and fat-free mass	Bedside measurement, easy to administer	Equations to estimate fat and fat-free mass are inaccurate in conditions of fluid overload
		Objective	Does not inform on distribution of muscle or fat throughout the body
Ultrasonography	Can be used to assess muscle cross-sectional area, thickness, echogenicity as well as fat thickness. Muscle groups studied: upper and lower limb muscles, diaphragm	Bedside measurement	Ultrasound machine required
		Objective	Measurements can be operator dependent
Computed tomography (CT) and magnetic resonance imaging (MRI)	Imaging methods that use specialized machines to detect specific body tissue components. Muscle and fat size can be measured on each image to provide information on fat and muscle size	Gold standard for identification of specific fat and muscle components	Expensive, specialized manpower and equipment required
			CT scans associated with radiation
			May require sedation for accurate measurement

main cause in several reports (32,35,41). Organ dysfunction score was also higher in children with muscle weakness compared to those without (38). These risk factors are similar to risk factors that have been reported in adult ICU muscle weakness (14,39,40), suggesting similar underlying pathophysiology of ICUAW in adult and children. These include a combination of myopathy and polyneuropathy as a result of disuse and immobilization, inflammation, altered circulating hormones, malnutrition and medication use (20,22). Of note, this phenomenon is different from sarcopenia in older adults, which involves an age-related decline in skeletal muscle mass and function (42).

The prevalence of muscle weakness in critically ill children appears to remains low compared to critically ill adults. In a prospective cohort study, Banwell *et al*. studied the incidence of muscle weakness children admitted to a general PICU for >24 hours over a period of 1 year (n=830). Muscle weakness was defined using a cut-off of MRC grade ≤4 in any muscle group, reduced or absent tendon reflexes and an inability to wean from MV as definitions of muscle weakness (32). The authors reported a prevalence of 1.7% (14/830), which is lower than the median prevalence reported across adult critically care studies of 30% in general ICU cohorts, and 64% in adult sepsis patients (22).

Part of the difference in adults versus children may be the difficulty in muscle strength testing in critically ill children. Siu *et al*. attempted to measure the weekly MRC sum score in critically ill children (43). In a cohort of 33 patients aged 1.1 to 16.1 years, the authors found that the MRC tests could not be completed in almost half of the patients. Aside from patients being sedated or comatose, reasons for non-completion included difficulties in understanding, lack of cooperation and poor neurological status, especially in younger patients.

This demonstrates the need for non-volitional, objective measures to detect muscle weakness and wasting in critically ill children, to be able to better identify and characterize the problem. An option for this is the measurement of body composition and muscle during critical illness. With increasing study on muscle changes in adults during critical illness, interest in muscle and body composition changes in critically ill children have also increased. To date, various methods have been used to determine muscle and body composition in critically ill children (*Table 1*).

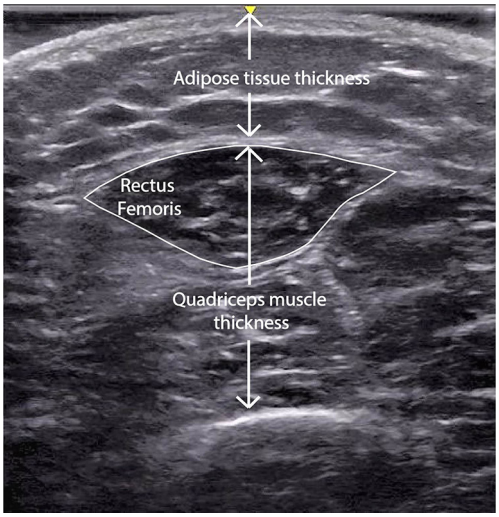

Figure 1 Ultrasound image of a rectus-femoris cross sectional area. Arrows depict the quadriceps muscle thickness and adipose tissue thickness. Solid white outline depicts the rectus femoris cross-sectional area.

Muscle wasting demonstrated by various measurement methodologies

Arm muscle circumference

Traditional anthropometric measurements have included the use of mid-upper arm muscle circumference and triceps skinfold thickness, which can be used to calculate the upper arm muscle circumference and muscle area (44). This method is non-invasive, fast to administer and requires only simple measurement tools such as a tape measure and skinfold calipers.

Zamberlan *et al*. monitored mid-upper arm circumference and triceps skinfold thickness in critically ill children (n=90) on admission and after a week (45). There was an overall reduction in arm circumference, which was attributed to a decrease in triceps skinfold thickness but not arm muscle circumference. Similar findings were reported by Hulst *et al*., who monitored mid upper arm circumference in critically ill children from PICU admission to discharge (46). In 93 children, during their PICU stay, significant decreases in mid upper arm circumference and triceps skinfold thickness were observed, but changes in corresponding arm muscle circumference were not reported.

Skinfold measurements are subject to inter-rater differences, which can limit the accuracy of longitudinal changes (47). In addition, edema can affect the accuracy of arm muscle area and skinfolds measurements, which can limit its utility in children who experience significant fluid shifts (48).

Computed tomography (CT) and magnetic resonance imaging (MRI)

CT and MRI scans are considered one of the most accurate methods in visualizing and differentiating between different body tissue components (49,50). Using specialized software and established greyscale thresholds for various tissue components (e.g., skeletal muscle, visceral adipose tissue), skeletal muscle and various adipose tissue components can be measured from MRI and CT images. Our group has used these imaging methods to assess skeletal muscle mass and adipose tissue size at PICU admission (51). Using imaging data from 92 children, we found that higher skeletal muscle and adipose tissue size at PICU admission was associated with functional impairment that persisted to hospital discharge (51). However, CT and MRI scans have not been used to study longitudinal skeletal muscle changes in critically ill children. Part of this reason is the that CT and MRI imaging is rarely done in critically ill children due to the radiation involved in CT scans, as well as the need for specialized equipment and manpower. The low frequency of measurements thus limits the utility of these imaging methods to assess skeletal muscle changes in pediatric critical illness.

Ultrasonography

Muscle ultrasonography in critically ill children has gained recent interest after the use of this method to identify muscle wasting in critically ill adults (52). However, muscle imaging using ultrasound has been used for over two decades in monitoring of changes in neuromuscular diseases such as spinal muscular atrophy and Duchenne muscular dystrophy (53,54).

Limb muscle

Limb muscles play a large role in movement and autonomy, and thus have been monitored in muscle disorders (55-58). In pediatric neuromuscular disease, ultrasounds demonstrate decreasing limb muscle thickness as well as an increase in muscle echogenicity, an indication of progression of disease (56,59). Muscle size and echogenicity measurements have both been shown to correlate with physical function and strength (55,56,59).

In critically ill children, both upper and lower limb

muscles have been studied. The most commonly studied muscle has been the quadriceps muscle (*Figure 1*) (2,3,60), partly due to ease and accessibility of measurement in the immobile, supine state during critical illness. The quadriceps muscles also play an important role in mobility, which is one aspect of physical function that has been shown to be impaired in critically ill adults (7). Other limbs measured include the biceps brachii and tibialis anterior (2).

Overall, ultrasounds demonstrate decreases in muscle size during critical illness. Adults have reported an average decrease in quadriceps muscle size of 2% to 3% per day during critical illness (13,61). Two studies have reported similar rates of muscle wasting in critically ill children. In a dual-center study, Valla *et al*. found a decrease in quadriceps thickness of 9.8% [interquartile range (IQR), 0–13.3%] on day 5 of PICU stay, while Johnson *et al*. reported a decrease in quadriceps thickness of 1.5% per day (2). In comparison, Johnson *et al*. found that there were no significant decreases in biceps or tibialis muscles, indicating differences in vulnerability of muscle groups to atrophy during critical illness, and emphasizing the effects of critical illness (2). Factors associated with loss of quadriceps muscles in bivariate analyses included age >1 year, traumatic brain injury and greater body mass index, although these did not remain significant in the final multiple regression model.

Diaphragm muscle

Ultrasound of the diaphragm muscle has been recently studied to understand the rate of diaphragm atrophy, as well as to predict extubation success. Diaphragm ultrasound is most commonly performed between the right anterior and the mid-axillary lines, at the intercostal space between the eighth or the tenth ribs (62-64). Overall rates of diaphragm atrophy in children range from approximately 2.0% to 3.4% per day (2,62,64), lower than rates of 6% to 7.5% reported in adults (65,66). In both children and adults, rates of diaphragm atrophy are the fastest in the first 2 to 3 days, tapering off in subsequent days (62,67). One factor that has been reported to be associated with diaphragm atrophy was the use of neuromuscular blockade, although this was not consistent across studies (2,64).

Diaphragm thickening fraction (DTF), which is commonly measured using M-mode ultrasound, has been used to predict extubation success (62,63). DTF is calculated using the equation [(diaphragm end-inspiratory thickness – end-expiratory thickness) ÷ end-expiratory thickness]. In critically ill children, a DTF cut-off of ≥17% and ≥21% have been reported to predict extubation success in mechanically ventilated children (62,63).

One limitation of ultrasonography is its highly operator-dependent nature, implying that accuracy of measurements can depend on the person performing the measurement (68). Clear protocols and repeated training as well as inter-operator reliability testing would help in improving accuracy and reducing human error in measurements (69,70).

Bioelectrical impedance analysis (BIA)

BIA utilizes electrical currents to inform body fluid status and composition. Based on the respective resistance (R) and reactance (X_c) of current speeds in different medium, BIA is capable of detecting the total body water (71). Resistance and reactance values can also be put into pre-established equations to estimate body fat and fat-free mass components (71). BIA measurements are non-invasive, easy to administer and relatively inexpensive, making it ideal for the PICU setting. However, BIA is subject to fluid shifts—a common occurrence in critically ill patients, which limits the accuracy of the equations used to estimate body composition, and thus the accuracy in informing changes in body composition during critical illness.

With the inaccuracies of fat and fat-free mass estimations during periods of fluid shifts, researchers have shifted towards the use of raw data of resistance and reactance, which are less influenced by fluid status compared to equations used to estimate fat and fat-free mass (72). Resistance and reactance can then be used to calculate phase angle using the equation: arctangent ($X_c \div R$) × ($180 \div \pi$). Phase angle has been used to gauge the general health of a cell, and an indirectly, muscle mass (73,74). In critically ill adults, several observational studies have reported that lower phase angle on admission was associated with mortality (75-78). Various cut-offs of phase angle reported to be predictive of mortality include <3.49° to <4.8° (77,78). Importantly, Looijaard *et al*. described a decrease in phase angle, albeit non-significant, in a small cohort (n=15) of critically ill adults (79). This study also reported a correlation between greater protein intake and increases in phase angle, although this could have been confounded by other non-nutritive factors fluid balance.

BIA-derived resistance, reactance and phase angle has also been studied in critically ill children. In a mixed PICU cohort of 247 patients, Zamberlan *et al*. demonstrated that a phase angle on admission ≤2.8° was associated with higher risk of mortality and a longer PICU stay (80).

The authors also found that this phase angle cut-off was able to differentiate between those with a mid-upper arm circumference ≤5th percentile for age, suggesting phase angle as a possible alternative method to identify low nutritional status in critically ill children.

To understand longitudinal BIA changes, Azevedo *et al.* conducted BIA measurements in a general PICU cohort of 332 children requiring MV at admission and discharge (72). The authors found that reactance and resistance generally increased from 48 hours of PICU admission to PICU discharge, with a greater increase in reactance compared to resistance and an overall increase in phase angle. The authors also found that survival was generally associated with an increase in resistance from PICU admission to discharge, while in non-survivors there was a trend of decrease in either resistance or reactance.

These studies suggest potential for the use of resistance, reactance and phase angle in predicting outcomes in critically ill children. However, how these parameters correlate with nutritional intake and body composition during critical illness remains unclear. In addition, before BIA can be used for body composition analysis in critically ill children, it requires further study, including ensuring that the measurements are able to account for gender, age and ethnic differences in body composition (81).

Understanding muscle wasting and areas of future research

Relationship between muscle and function

While several studies have demonstrated muscle loss in critically ill children (2,3), none have yet correlated muscle changes with physical function in survivors of pediatric critical illness. In adults, recovery from ICU muscle weakness can take time, and physical impairments are seen up to 5 years post critical illness in adults (7). In PICU functional outcome studies, there is evidence that the impairment can also be prolonged (82,83). In the cohort study (n=830) eluded to earlier on the prevalence of muscle weakness in critically ill children, muscle weakness persisted in majority (89%) of the patients at 3 months after discharge, with reported poor physical endurance at 18 months post-discharge in one of the patients (32). Case reports of PICU muscle weakness during also described children suffering from prolonged impairments of certain areas of function despite strength recovery. For example, an 18-month-old girl reported being easily fatigued after strength recovery at 5 months (84), while another patient (21 months) experienced developmental delay including motor delay after strength recovery at 16 months (33). Although this motor delay might not necessarily be due to muscle deficits, they have been reported in children with liver-failure associated muscle wasting, which improved with restoration of weight and muscle mass (85). Determining recovery in children requires not just a return to baseline, but also a catch-up to their peers. This may differ depending on the developmental age and plasticity of the children. Thus, assessing age-appropriate functions in PICU survivors is important to avoid overlooking functional disabilities during the growing ages.

Nutritional and rehabilitative strategies

The evidence for nutritional strategies in improving muscle wasting and physical function remains unclear. In adults, while observational studies have reported reduced muscle wasting with greater energy adequacy (86,87), nutritional interventions have failed to translate to improvements in muscle mass in randomized controlled trials (RCTs). For example, in the Early versus Late Parenteral Nutrition in Critically Ill adults (EPaNIC) RCT, early parenteral protein and energy provision did not ameliorate muscle wasting or result in better physical function, and instead was associated with more muscle weakness and slower recovery (88,89). The Early Versus Delayed Enteral Feeding (EDEN) trial also did not find a difference in physical function between trophic and full enteral feeding in critically ill adults in the first week of ICU stay (90). Individualized, targeted nutrition did not result in better physical quality of life compared to standard of care in the Early Goal-Directed Nutrition in ICU Patients (EAT-ICU) trial (91). A possible explanation for this may be an impaired mitochondrial function and dysregulation of skeletal muscle bioenergetics, as intramuscular adenosine triphosphate content and substrates were found to correlate with muscle loss in critically ill adults (92). These trials collectively suggest the need for further considerations with regards to the timing, substrate and amount of feeding in critical illness.

Early mobilization (EM) is another aspect of care that has been studied in reducing muscle weakness and wasting. In critically ill adults, EM helps to improve function in the adult ICU (93), but there is a lack of consensus and perceived acceptable thresholds for safety guidelines of early rehabilitation in critically ill children (94). While these definitions of EM and safety thresholds differ across

units, rehabilitation has generally shown to be safe within the PICU (95). A recent point-prevalence study of physical rehabilitation efforts within the PICUs in the United States demonstrated that children with better pre-PICU function are less likely to receive rehabilitation compared to children of poor pre-PICU function (96), although these children have shown to be at greater risk for functional impairment post-PICU stay (82,97). However, the impact of early rehabilitation on physical function post-PICU stay has not yet been demonstrated. Choong *et al*. conducted a pilot trial evaluating in-bed cycling in PICU patients, but did not observe a difference in physical function in the intervention group (98).

Research on nutrition and rehabilitation during pediatric critical illness in relation to muscle wasting and functional outcomes is still in its infancy. Extrapolation of adult evidence to the pediatric population must be done with caution, and be respectful of the differences in protein homeostatic responses between adults and children. Interventions that may not have been effective in adults may have different effect on children. For example, feeding has been shown to be highly anabolic in younger children, especially neonates, compared to adults (99). Trials on both nutrition and early rehabilitation are needed in critically ill children to determine its effect on muscle wasting and functional outcomes. Further, it may be important to understand the synergistic combination of nutrition and exercise during critical illness, as is being done in adults in the Nutrition and Exercise in Critical Illness (NEXIS) trial (100).

Conclusions

While evidence demonstrates of muscle weakness and wasting in critically ill children, there is insufficient understanding of the pathophysiology, risk factors and long-term consequences on child function and development. Incorporating non-invasive, objective, bedside methods such as ultrasonography and BIA in the assessment of muscle and body composition changes together with measurement of function and development may help overcome this. Research efforts addressing these can benefit the understanding of the PICS-p.

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