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RESEARCH **REVIEW ARTICLE**

Pediatric Intensive Care Unit-Acquired Weakness: An Updated Review

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ABSTRACT

Pediatric patients admitted to the intensive care unit may develop a form of muscle weakness termed Intensive Care Unit Acquired Weakness (ICU-AW), which remains relatively challenging to diagnose and manage. This condition may not be as frequent in pediatrics compared to adults, yet it represents a debilitating complication among pediatric ICU patients with notable short and long-term consequences. Diagnosis relies on history and physical examination, aided by electrophysiological studies and muscle biopsies. Serial muscle ultrasound is emerging as a reliable method for early detection of muscle wasting. Preventive measures include modifying risk factors and delaying parenteral nutrition. While no definitive treatment has been identified, early mobilization and limiting the use of sedatives may influence the outcome of this condition in pediatrics. More data is needed to assess the incidence and prognosis of pediatric ICU-AW. New therapeutic strategies are needed to alter the course of the disease.

KEYWORDS - Critical Illness, myopathy, polyneuropathy, acquired weakness, intensive care unit, pediatrics, children.

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INTRODUCTION

Intensive care unit-acquired weakness (ICU-AW) is a clinically detectable weakness in critically ill patients with no plausible etiology other than the critical illness [1]. It is characterized by a diffuse, symmetrical muscle weakness that occurs after the onset of critical illness. It tends to involve the respiratory diaphragm and limb muscles and typically spares the cranial nerves [1]. ICU-AW can be further classified into three subcategories, as shown in Table 1. This condition is being increasingly recognized in critically ill children with prolonged ICU stay and mechanical ventilation (MV) use and is associated with delayed recovery and increased morbidity [2]. Most ICU-AW-related research addresses the adult patient population, while articles related to pediatrics are mostly in the form of case reports and case series (Table 2). This article summarizes current knowledge of epidemiology, risk factors, etiologies, diagnostic approach, management, and prognosis of ICU-AW in pediatrics.

Table 1. Classification of Intensive Care Unit-Acquired Weakness.

ICU-AW type	Main clinical features	Findings on NCS/EMG
Critical illness myopathy (CIM) [1]	Weakness of respiratory diaphragm (difficulty weaning from MV) Flaccid weakness of limb muscles Sparing of cranial nerves and facial muscles	NCS is normal or mildly abnormal EMG shows myopathic changes
Critical illness polyneuropathy (CIP) [1]	Same as CIM Muscle atrophy Sensory deficits Diminished deep tendon reflexes	NCS shows sensorimotor axonal polyneuropathy EMG is normal or shows denervation changes
Critical illness neuromyopathy (CIPNM) [1]	Mixed picture	Mixed picture or inability to fully assess

Table 2. Published case reports, case series, and cohorts of Intensive Care Unit- Acquired Weakness

Reference	Study Design	Patient characteristics	Possible risk factors	Use of NMBAs or Corticosteroids	Test findings	Outcome
Benzig et al 1990 [3]	Case report	Female Age: 2 years	Reactive airway disease	Both	Repetitive stimulation testing: abnormal NCS: normal	Complete recovery
Tsao et al 1995 [4]	Case report	Female Age: 2 years	DIC	Neither	NCS: severely decreased CMAP amplitudes	Complete recovery
Sheth et al 1995 [5]	Case series	n= 4 1 male, 3 females Age range: 6-17 years	Sepsis in 2 patients Asthma in 1 patient	NBMAs alone in one patient Both used in 3 patients	NCS: mild conduction delay in one patient, normal in the rest	Complete recovery: 3 Partial recovery: 1
Dimachkie et al 1995 [6]	Case report	Male Age: 15 years	SIRS	NBMAs only	NCS: abnormal sensory and motor responses	Partial recovery
Petersen et al 1999 [7]	Case series	Patient 1 6-year-old male	Sepsis	NBMAs alone	NCS: decreased CMAP and normal sensory findings	Complete recovery
		Patient 2 2-year-old male	Sepsis	Corticosteroids alone	NCS: decreased CMAP and mild sensory loss	Partial recovery

Chetaille et al 2000 [8]	Case report	Female Age: 11 years	Solid organ transplant	Both	NCS: normal EMG: myopathic changes Biopsy: loss of filaments	Complete recovery
Tabarki et al 2002 [9]	Case series	n= 4 2 males, 2 females Age range: 2-14 years	Solid organ transplant in 2 patients SIRS in 1 patient Status asthmaticus and SIRS in 1 patient	NBMAs alone in one patient Both used in 4 patients	NCS: decreased CMAP in 3 patients, normal in one patient	Complete recovery: 3 Partial recovery: 1
Banwell et al 2003 [10]	Prospective cohort	n= 14 5 males, 9 females Age range: 1-17 years	Multiple organ failure in 9 patients Solid organ transplant in 8 patients. Aminoglycoside use in 7 patients	Corticosteroids in 9 patients NBMAs in 9 patients	Needle EMG in 4 of 5 patients: myopathic changes. NCS in 4 of 7 patients: sensory and motor abnormalities.	Complete recovery: 1 Partial recovery: 10 Death or lost follow up: 3
Vondracek et al 2006 [11]	Case series	Patient 1 15-year-old female	SIRS, multiple organ failure	NBMAs only	NCS: decreased CMAP and sensory loss	Partial recovery
		Patient 2 13-year-old male	SIRS, multiple organ failure	NBMAs only	NCS: decreased CMAP and sensory loss	Partial recovery
Charisius et al 2010 [12]	Case report	Male Age: 17 years	SIRS, acute leukemia	Corticosteroids only	NCS: abnormal sensory and motor responses CSF analysis: unremarkable	Partial recovery
Field-Riley et al 2016 [2]	Retrospective cohort	n= 55 29 males Age range: 1-13 years	Respiratory illness in 27 patients Infectious disease in 7 patients Other: MV, ECLS, and renal replacement therapy	Not determined	N/A Retrospective database analysis of clinical data	Increased morbidity with longer PICU stays, longer MV period, higher level of care upon discharge
Mudawi et al 2018 [13]	Case report	Male Age: 3 years	Sepsis	Both	NCS: normal conduction velocity with reduced amplitude.	Complete recovery
Avila-Smirnow et al 2022 [14]	Case series	Patient 1 17-year-old male	Respiratory infection and obesity	Both	NCS: abnormal sensory and motor responses	Partial recovery
		Patient 2 0.8-year-old female	Respiratory infection and obesity	Both	NCS: abnormal sensory and motor responses	Complete recovery
Chalipat et al 2024 [15]	Case report	Male Age: 10 years	Sepsis	Neither	NCS: abnormal sensory and motor responses	Complete recovery

NBMA, neuromuscular blocking agent; SIRS, systemic inflammatory response syndrome; DIC, disseminated intravascular coagulation; CMAP, compound muscle action potential; NCS, nerve conduction studies; CSF, cerebrospinal fluid; MV, mechanical ventilation; ECLS, extracorporeal life support.

METHODS

Pubmed, MEDLINE and Google Scholar were searched for combinations of "critical illness," "critically ill," or "ICU" with "polyneuropathy," "myopathy," "neuromyopathy," and "acquired weakness" from January 1980 to April 2024 and we chose the studies that contained pediatric patients. We screened the reference lists of the included articles for relevant publications not retrieved in the initial search. We also screened citing articles and related references for relevant articles. We limited the search to articles in English. For sections with no available pediatric-specific information (mainly risk factors and pathophysiology), we relied on studies from the adult population for completeness.

INCIDENCE

The reported incidence of ICU-AW varies depending on the studied patient population, risk factors, diagnostic criteria, and the method used for diagnosis. Little information is available regarding the incidence of ICU-AW in pediatrics [10,16–18]. A study of 830 pediatric ICU patients relied on physical exam and reported that 1.7% had generalized weakness [10]. A cohort of selected pediatric ICU patients where NCS/EMG was used reported a critical illness polyneuromyopathy (CIPNM) incidence of 32% [16,18]. Another prospective study that also used electrophysiology screened 481 pediatric ICU patients and reported that only 2 patients developed ICU-AW [17]. This suggests that ICU-AW may be less common in children compared to adults, where the incidence can be more than 70 % [19] [20], but this could also be due to the low sensitivity of the methods used to identify cases and the variability of the criteria used for diagnosis.

PATHOPHYSIOLOGY

The underlying mechanisms of ICU-AW are complex but remain incompletely understood. It has not been specifically studied in pediatric patients.

CIM is a heterogenous entity, and underlying pathological changes include myosin loss, necrosis, and muscle fiber membrane dysfunction. Proposed etiologies for axonal injuries in CIP include microcirculatory changes associated with systemic inflammation leading to distal nerve ischemia and degeneration, increased vascular permeability within the endoneurial space leading to edema, and sodium channel inactivation resulting leading to decreased excitability of peripheral nerves. [21,22]

Studies have reported that electrophysiological changes involving both muscles and nerves can start within hours of admission to the ICU. [23]

EPIDEMIOLOGY AND RISK FACTORS

Prospective studies aiming to identify the risk factors for ICU-AW in pediatric populations are lacking. Pediatric cases reported in the literature were associated with older age, longer ICU stays, mechanical ventilation, sepsis, and solid organ transplant [2,10]. (See Table 2). Multiple risk factors are mentioned in the adult literature, including female sex, obesity, duration of ICU stay, mechanical ventilation, sepsis, parenteral nutrition, prolonged immobilization, and the use of drugs such as corticosteroids, aminoglycosides, neuromuscular blockers, and sedatives. Other factors include metabolic derangements such as hyperglycemia, hyponatremia, high lactate level, high blood urea nitrogen, as well as, organ dysfunction, and extra-renal replacement therapy [10,24–26].

CLINICAL MANIFESTATIONS

The clinical presentation of ICU-AW in pediatric patients is similar to adults. Critical illness myopathy (CIM) typically presents with diaphragm weakness, leading to difficulty weaning from MV along with symmetrical and flaccid limb muscle weakness, while typically sparing ocular and facial muscles [6,10,27]. However, a recent case report described visual disturbances in a 3-year-old boy with ICU-AW that resolved over time [13]. Critical Illness Polyneuropathy (CIP) presents similar to CIM, but the main features include muscle atrophy, diminished deep tendon reflexes, and distal sensory loss [6,12,28]. It can be difficult to clinically distinguish between CIM and CIP based on clinical presentation, especially in sedated patients where it is hard to check for sensory deficits, thus a diagnosis of combined CIM and CIP (Termed critical illness polyneuromyopathy or CIPNM) can be made [29].

DIAGNOSIS

HISTORY AND PHYSICAL EXAMINATION - A thorough history is required to uncover preexisting conditions and assess possible etiologies. It is also important to evaluate the ICU course and any associated complications and co-morbidities, as pediatric patients have been shown to develop CIM/CIP within a week of critical illness [30].

INVESTIGATIONS - Laboratory tests are of limited value in confirming the diagnosis of ICU-AW, except to rule out other etiologies of muscle weakness and check for preexisting neurological conditions (Table 3). Electrophysiological studies (NCS/EMG) should be considered in pediatric ICU patients with unexplained weakness to confirm the diagnosis of ICU-AW and differentiate it from other causes of weakness. In CIP, NCS shows findings of axonal neuropathy and could affect both compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs), while EMG could show denervation abnormalities [11,18]. In the adult literature, a decrease of the SNAP or CMAP of more than 20-25% of the maximum amplitude in one nerve is sufficient [17,31]. In CIM, NCS studies tend to be normal or may show a decrease in CMAP, and the EMG shows myopathic changes. These studies may not be helpful in differentiating CIP from CIN in sedated patients and those unable to activate muscles [11,17].

A muscle biopsy confirms the diagnosis and extent of ICU-AW but is not always feasible. In CIP, it shows it shows denervation changes with atrophy of both type 1 and type 2 fibers. In CIM, the biopsy shows selective thick filament myosin loss along with necrosis, fibrosis, and fat atrophy. In CIPNM, muscle biopsy shows denervation atrophy and myopathic changes [22,32]. Serial measurements of arm muscle circumference can be used to assess muscle wasting, but it is subject to interrater variability and can be affected by fluid status in critically ill children [27].

Multiple studies have looked at the use of serial ultrasound (US) measurements to screen for muscle wasting among ICU patients and showed that it can be reliably used in adults [33]. A study from 2016 looked at the use of US to assess thigh muscles among ICU patients, included 30 children, and concluded that US might be reliably used in adults but not in pediatric patients [34]. Subsequent studies used US to serially measure the thickness of the diaphragm and the quadriceps femoris muscle in critically ill children and concluded that it can be used reliably to assess for muscle wasting [35–38]. US has the advantage of being noninvasive and objective. Still, it is operator-dependent; thus, more studies are needed in the pediatric population to assess its reliability and usefulness in diagnosing ICU-AW. Other modalities used in assessing skeletal muscle bulk include Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), but these modalities are expensive and not readily available, in addition to the potential harm from radiation exposure with serial CT scans [39,40]

Table 3. Differential diagnoses of muscle weakness in critically ill children

Disease	Main clinical features	Findings on NCS/EMG
Rhabdomyolysis	Muscle weakness, myalgia Red urine	Elevated levels of serum creatine phosphokinase
Gullain Barre syndrome	Ascending symmetrical flaccid muscle weakness Diminished deep tendon reflexes Paraesthesia	Elevated CSF protein with normal cell count Electrophysiological studies
Botulinum Toxicity	History of exposure to the toxin Cranial nerve palsies Descending, symmetrical flaccid muscle weakness	Serum and stool assay for Botulinum neurotoxin Electrophysiological studies
Poliomyelitis	Asymmetrical flaccid weakness Affects lower limbs more than upper limbs	Positive polymerase chain reaction test Electrophysiological studies
Myasthenia Gravis	Muscle weakness that increases with fatigue and may involve ocular muscles	Positive anti-acetylcholine receptor antibodies and other autoantibodies Electrophysiological studies
Myotonic Dystrophy	Myotonia and distal muscle weakness	Genetic testing for CTG trinucleotide repeats Electrophysiological studies

DIFFERENTIAL DIAGNOSIS

There is a wide differential diagnosis for muscle weakness in critically ill patients [30,41]. Electrolyte imbalances such as hypokalemia and hypophosphatemia can cause muscle weakness. Drug-induced muscle weakness can be associated with corticosteroids, neuromuscular blockers, calcium channel blockers, statins, chemotherapeutic medications, and other drugs [17,42]. Adrenal insufficiency can cause muscle weakness in critically ill children [43]. It presents with muscle weakness, fatigue, and hypotension and

can be ruled out by measuring a morning level of serum cortisol [44,45]. Thyroid dysfunction can also be associated with muscle weakness in critically ill patients [46]. Guillain-Barré syndrome (GBS) can present similar to ICU-AW and can lead to ICU admission in 30% of patients [47]. Pediatric patients with GBS present with lower limb weakness, gait instability, diminished deep tendon reflexes, and neuropathic pain. A key difference between ICU-AW and GBS is that the former usually occurs after prolonged mechanical ventilation, while GBS is usually preceded by a gastrointestinal or upper respiratory tract infection, and the weakness tends to be the presenting symptom. GBS is diagnosed clinically, but helpful tests include increased protein and normal cell count on cerebrospinal fluid analysis. NCS shows demyelinating changes with decreased velocity and a conduction block [47,48]. Other neurological disorders to be considered are listed in Table 3.

MANAGEMENT

The management of ICU-AW requires a multidisciplinary approach involving medical and rehabilitation specialists. Thus far, no specific therapeutic intervention has been identified, including no pharmacological agents. However, supportive and preventive measures aimed at modifying risk factors and improving outcomes have been studied in both adults and pediatrics [49–57].

GLYCEMIC CONTROL - Studies in adult ICU patients have demonstrated a risk reduction of ICU-AW with the implementation of tight glycemic control (TGC), which aims for blood glucose levels between 80–110 mg/dl [49] [50]. However, the broad implementation of this intervention in critically ill adult patients brings further risks, such as a higher incidence of hypoglycemia and increased mortality [58]. No studies have looked at whether TGC influences the incidence of pediatric ICU-AW. However, studies that looked at such intervention among critically ill children compared to the conventional glycemic control, which targets a blood glucose < 180 mg/dl, showed no difference in mortality, and even though TGC was associated with a lower rate of acquired infections, it significantly increased the risk of hypoglycemic episodes which adversely affects developing brains [59,60].

NUTRITION - Multiple pediatric studies have examined the effect of the timing of initiating parenteral and enteral nutrition on the overall outcome of critically ill children, including muscle weakness. The multicenter PEPaNIC study concluded that early parenteral nutrition has not been shown to improve outcomes but carries the risk of side effects and is associated with a higher risk of nosocomial infections [61]. Early enteral nutrition is associated with decreased morbidity and mortality, but nutrient restriction early on can be beneficial in pediatric patients by stimulating the catabolic stress response and enhancing autophagy, which in turn maintain muscle integrity. [62]. Similarly, in the adult literature, late parenteral nutrition initiation significantly reduced the incidence and the duration of muscle weakness [51].

MINIMIZING SEDATION AND EARLY MOBILIZATION - The implementation of strategies aimed at minimizing sedation and early mobilization is emerging as an effective approach to improving the overall outcome in critically ill children [63]. While these studies didn't specifically look into ICU-AW in children, two randomized trials in critically ill children demonstrated that the length of mechanical ventilation and length of ICU stay were significantly reduced in the interrupted as compared to the continuous group of sedation [64,65].

Studies in adult ICU patients demonstrate the clinical benefits of early mobilization in decreasing the incidence of ICU-AW, improving the functional capacity, and increasing the number of ventilator-free days in the ICU setting [52–55]. One recent randomized controlled trial assessing the effect of early mobilization on acquired muscle weakness among 80 pediatric critically ill patients found that ambulation distance at ICU discharge was increased among the intervention group, with a significant difference between the two groups in the length of hospital stay [66]. Passive mobilization has also been shown to be beneficial [67]. However, fewer than 25% of critically ill children mobilize early in the children's PICU stay, considering that early mobilization in pediatric ICU has proven to be generally safe [68–70].

NEUROMUSCULAR ELECTRICAL STIMULATION (NMES) - This modality has been suggested as an alternative to early mobilization since a considerable number of patients in the ICU have a decreased level of consciousness and decreased activity. NMES involves repetitive electrical impulses which are directed at a target muscle group to induce muscle contractions and effectively enhance muscle function and strength [52,56,57]. This intervention is showing promising results in adults, and one case report has mentioned its use in the rehabilitation of a child with ICU-AW [71].

It is worth noting that two clinical trials currently in process are looking into the effect of

certain interventions on outcome measures in critically ill pediatric patients, including muscle weakness. The first one is examining the effect of neuromuscular blockade use, and the second aims to assess the effect of early mobilization [72,73].

PHARMACOTHERAPY - Limited studies have looked into the effect of pharmacological interventions on the ICU course in both adults and pediatrics [74]. Both Oxandrolone and propranolol have been used in adult patients with some success [75]. Oxandrolone is an anabolic steroid that promotes the growth of muscle mass and has been used in critically ill pediatric burn patients and showed improvement in lean body mass [76,77]. Propranolol may reduce the catabolic response seen in critically ill children. It has been studied in pediatric burn patients and led to less reduction in lean body mass [78,79]. Further studies are needed to assess the benefit of these medications in pediatric ICU-AW. Growth hormone, glutamine, and immunoglobulins have not shown significant benefits in adults and have not been studied in pediatrics. Novel agents such as myostatin inhibitors and BGP-15 present promising pharmacological agents for future research [80,81].

PROGNOSIS

Studies on the prognosis, both short- and long-term outcomes in pediatric ICU-AW patients, are lacking.

SHORT TERM OUTCOME - In adult studies, outcomes spanned a spectrum from spontaneous recovery occurring over months to permanent residual deficits, mainly distal muscle weakness and sensory deficits [82].

One study found that pediatric patients diagnosed with ICU-AW had a worse outcome, including a longer stay in the ICU and a longer duration of mechanical ventilation. They were more likely to require a tracheostomy and required a higher level of care upon discharge from the pediatric ICU [2]. However, the study's retrospective nature imposes some limitations and highlights the need for further prospective studies.

LONG TERM OUTCOME - A meta-analysis of studies conducted in adult patients with ICU-AW revealed an overall 70% chance of full recovery, with a relatively better outcome in patients with CIM compared to CIPNM [83]. A study from 2006 followed 2 pediatric patients with CIPNM for 1 year and reported significant but incomplete recovery [11]. More recent studies looked at the overall outcome of patients admitted to the pediatric ICU 2 months after discharge and up to 3 years after discharge and showed evidence of limitation in physical abilities, though none specifically evaluated patients diagnosed with pediatric ICU-AW [84,85].

CONCLUSION AND FUTURE DIRECTIONS

We present an overview of pediatric ICU-AW, including the epidemiology, diagnostic approach, strategies for prevention and management, and overall outcome. While no definitive treatments exist, supportive and preventative measures should be established to help reduce the burden of pediatric ICU-AW. Multiple knowledge gaps have been identified, highlighting the need for additional prospective studies on incidence, risk modification, earlier detection, and short- and long-term outcome measures.

AUTHORS' CONTRIBUTIONS

All authors contributed to writing the first draft of the manuscript. Abu-Libdeh and Loubani provided direct feedback, guidance, and corrections to the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

DISCLAIMER

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