Title

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Intensive Care Unit-Acquired Weakness (ICU-AW) is Associated With Differences in Clinical Outcomes in Critically Ill Children

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Abstract

Objective—Intensive care unit acquired weakness (ICU-AW), comprised of critical illness myopathy (CIM) and critical illness neuropathy (CIN), occurs in a significant proportion of critically ill adults and is associated with high morbidity and mortality. Little is known about ICU-AW among critically ill children. We investigated the incidence of ICU-AW among pediatric intensive care units (PICU) participating in the Virtual PICU Systems (VPS) database. We also sought to identify associated risk factors for ICU-AW and evaluate the hypothesis that ICU-AW is associated with poor clinical outcomes.

Design—Retrospective cohort study.

Setting—Pediatric Intensive Care Unit.

Measurements—VPS was queried for CIM and CIN between 1/2009 and 11/2013. Demographic, admission, and clinical outcome variables including mechanical ventilation days, PICU length of stay (LOS), and discharge disposition were analyzed. The Pediatric Index of Mortality-2 (PIM-2) was used to evaluate and control for illness severity and risk of mortality.

Results—Among 203,875 admissions there were 55 cases of CIM reported and no cases of CIN, resulting in an incidence of 0.02%. Mechanical ventilation days were higher among patients with ICU-AW versus those that did not develop ICU-AW (31.6 ± 28.9 vs 9.3 ±20.6, $p<0.001$). In our multivariable analysis, when controlling for PIM-2, ICU-AW was more frequently reported in those with admission diagnoses of respiratory illness and infection, and the need for mechanical ventilation, renal replacement therapy, extracorporeal life support, and tracheostomy. ICU-AW was associated with a longer PICU LOS, episodes requiring mechanical ventilation, and discharge to an intermediate, chronic care, and rehabilitation care unit. ICU-AW was not independently associated with mortality.

Conclusions—ICU-AW is uncommonly diagnosed among PICU patients reported in VPS. ICU-AW is associated with critical care therapies, invasive procedures and resource utilization. Limitations of our retrospective study include under-recognition of ICU-AW and lack of standardized diagnostic criteria within VPS. Prospective studies are needed to better understand the true incidence, risk factors, and clinical course for patients who develop ICU-AW.

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Keywords

ICU-acquired weakness; critical illness myopathy; critical illness neuropathy

Introduction

Intensive care unit acquired weakness (ICU-AW) is a well-recognized complication in adult patients with critical illness. Critical illness myopathy (CIM) and critical illness neuropathy (CIN) are important causes of ICU-AW with up to 50% of adult patients in the ICU developing weakness of varying severity that can begin within the first few days of illness [1–3]. ICU-AW has been associated with many diseases in adults including asthma, sepsis, systemic inflammatory response syndrome, burns and acute lung injury [2, 4–7]. Acquiring neuromuscular dysfunction during the course of critical illness is associated with increased morbidity in adults with prolonged ICU and overall hospital length of stay, increased days of mechanical ventilation, and poor overall function and quality of life upon discharge from the hospital [8–10]. ICU-AW is also associated with increased mortality among critically ill adults [11, 12].

ICU-AW is largely unexplored in the critically ill pediatric population. The available literature is limited to small case series, with only one longitudinal study in critically ill children [13–15]. As a result, children who are at risk for acquiring neuromuscular dysfunction due to critical illness are less likely to be identified, evaluated and receive appropriate therapies. Furthermore, little is known about important risk factors and how ICU-AW impacts important short and long-term clinical outcomes.

The aim of this study was to establish the incidence of ICU-AW as reported in the Virtual Pediatric Intensive Care Units (PICUs), or VPS, a clinical database with nationally participating pediatric intensive care units (PICUs). We also sought to identify factors associated with ICU-AW, and to test the hypothesis that ICU-AW is associated with poor clinical outcomes among critically ill children in the PICU, including longer length of mechanical ventilation, longer PICU length of stay, and higher mortality.

Methods

Data Source

VPS is a collaboration between the Children’s Hospital Association, the National Outcomes Center of the Children’s Hospital and Health System in Wisconsin, and Children’s Hospital Los Angeles [16]. Participating sites provide encounter-level data on all admissions to the PICU and pediatric cardiac ICU. All sites are required to enter demographic data and clinical elements including diagnoses, data to determine risk of mortality, and interventions such as mechanical intervention and extracorporeal life support (ECLS). A subgroup of sites voluntarily report additional characteristics including functional outcome scores. Annual certifications of data accuracy as well as manual and automated data cleaning are performed to maintain data integrity.

The study cohort consisted of all admissions to participating PICUs between January of 2009 and November of 2013. Our initial query of the VPS database were for the International Classification of Disease-9 (ICD-9) codes for Neuropathy, Inflammatory/Toxic/Other (357), Critical Illness Neuropathy (357.82), Myopathy/Muscular Dystrophy NEC (359) and Critical Illness Myopathy (359.81). There were 1246 cases. We further refined our criteria to only include subjects who only had CIM (359.81) or CIN (357.82). To ensure that we identified only cases of acquired myopathy or neuropathy during ICU admission we excluded all patients who had a pre-existing neuromuscular disorder, genetic disorders known to cause neuromuscular weakness (hereditary muscular dystrophy: 359.1, myopathy unspecified: 359.9, infant botulism: 040.41, and specified disorders of metabolism: 277.8). There were 3 cases that had CIM present on admission to the ICU that we also excluded.

Patient Characterization and Data Elements

In addition to basic demographic data, we selected specific risk factors *a priori* to be included in our analysis that might be associated with CIM and/or CIN. Variables include, primary diagnosis and all secondary diagnoses and the pediatric index of mortality-2 (PIM-2). Because previously published data suggest that children with specific diagnostic groups may be at higher risk of developing CIM and/or CIN, we created indicator variables for the following diagnostic categories: congenital heart disease, non-congenital cardiovascular disease, respiratory illness, neurologic abnormalities, hematologic-oncologic disease, infections, and other diagnoses including burns and patients typically immobilized secondary to surgical procedures (e.g., orthopedic operations).

To evaluate the association of CIM and CIN on important clinical outcome variables, we obtained data related to patient morbidity, such as the number of times a patient required mechanical ventilation, the total length of time on mechanical ventilation, and length of PICU stay. We also evaluated the association of ICU-AW with mortality and final disposition status of the patient.

Statistical Analysis

Descriptive statistics are expressed as percentages. For comparisons of demographic, clinical characteristics between ICU-AW and non ICU-AW patient group, Student’s t-test and chi-squared or Fischer’s exact test, as appropriate were used for continuous and categorical variables, respectively. To assess the association between ICU-AW with morbidity, including length of mechanical ventilation and length of ICU stay, and mortality, we used Student’s t-test and Chi-Squared or Fischer’s exact test, as appropriate. Multivariable logistic regression analysis was used to determine the strength of associations of risk factors and ICU-AW. The model adjusted for covariates and other potential confounders including, PIM-2 scores, age in months, the patient’s primary diagnosis and critical care therapies, including mechanical ventilation, extra-corporeal life support (ECLS), renal replacement therapy. This study was approved by the Institutional Review Board at the University of California, Davis.

Results

Between 2009 and 2013, there were 203,875 admissions to 122 PICUs and 107 institutions participating in VPS. There were 55 CIM cases reported and no cases of CIN. As a result, the incidence rate of ICU-AW in the VPS database was 0.02%. The proportion of males who developed ICU-AW (52%) was similar to the proportion of males (56%) who did not develop ICU-AW (Table 1). Patients with a primary admission diagnosis in the respiratory and infectious disease categories had a higher likelihood of developing ICU-AW relative to patients admitted with other primary diagnostic categories. Among patients with ICU-AW, three (5.5%) had asthma. Patients who developed ICU-AW also had a higher mean PIM-2 risk of mortality than patients who did not develop ICU-AW (5.4% vs 2.3%, $p = 0.01$). Patients with ICU-AW were more likely to have received either mechanical ventilation, extracorporeal life support (ECLS), or renal replacement therapy. The mean number of total days on mechanical ventilation was significantly greater among patients who developed ICU-AW than those that did not develop ICU-AW (31.6 ± 28.9 vs 9.3 ± 20.6, $p<0.001$).

The results of our multivariable analysis are shown in Table 2. Factors independently associated with ICU-AW included age, primary diagnosis in the respiratory illness or infectious disease categories, and having received mechanical ventilation, ECLS and renal replacement therapy. We found no association between the development of ICU-AW and a primary diagnosis of cardiovascular disease with and without congenital heart disease. There were too few patients to analyze the association between burn injury and orthopedic procedures and ICU-AW.

ICU-AW was also associated with higher measures of resource utilization (Table 3). Patients with a diagnosis of ICU-AW had a longer mean PICU length of stay (18.8 ± 2.6 vs 3.8 ± 0.02, $p<0.001$), received more tracheostomies (25.5% vs 4.7%, $p <0.001$), and required a higher number of episodes of receiving mechanical ventilation (2.9 ± 0.3 vs 0.6 ± 0.01, $p<0.001$). Furthermore, having a diagnosis of ICU-AW was associated with requiring a higher level of care after PICU discharge, with a greater proportion requiring discharge to an intermediate care unit or a chronic care or rehabilitation facility. While a greater proportion of patients with ICU-AW died, there was not a statistically significant difference in mortality compared to the rest of the VPS cohort (5.2% vs 2.5%, $p=0.1$).

Discussion

In our study of more than 200,000 PICU admissions reported in the VPS database, we found the incidence rate of ICU-AW to be 0.02%. We also determined that admission diagnoses related to a respiratory or infectious disease process, older age, and the need for several invasive ICU therapies were associated with the development of ICU-AW. The data from VPS also demonstrated that the diagnosis of ICU-AW was associated with poorer outcomes including the need for mechanical ventilation for a longer period of time, a longer PICU length of stay, and a greater likelihood of needing a tracheostomy. We also found that patients who acquired ICU-AW required a higher level of care upon discharge from the PICU.

Our results are similar to studies investigating ICU-AW among adult hospitalized patients in that, like adults, we found the development of ICU-AW in critically ill children to be associated with a primary respiratory or infectious diagnosis [9, 17]. Moreover, ICU-AW in adults is associated with prolonged mechanical ventilation, longer ICU and hospital length of stay, which is similar to our findings among critically ill children [6, 18]. We found older age to be associated with ICU-AW. It is plausible that this may represent a greater challenge in diagnosing ICU-AW in infants and very young children rather than a biologic susceptibility in older children. While there is conflicting data about the influence of age as a risk factor for ICU-AW in adults, the elderly are almost universally at higher risk, even when previously healthy [19].

In our study we found the incidence of ICU-AW among critically ill pediatric patients to be remarkably less than the 30–50% incidence of ICU-AW reported in the adult literature [17]. Moreover, our 0.02% incidence rates is significantly less than the reported 1.7% incidence rate of acquired weakness in the only longitudinal prospective study in critically ill pediatric patients [13]. There are several reasons why the incidence of ICU-AW could be under-reported in this study. First, there may be differential misclassification bias, wherein patients who had ICU-AW were not reported in VPS. This could have significantly reduced the number of cases within the database resulting in an increased number of controls. Another important potential reason for the reported low prevalence of acquired weakness is the under-recognition of the clinical syndrome in critically ill children. It has been noted in previously published literature that ascertaining ICU-AW is challenging and contributes to low reported incidence and prevalence in pediatrics [20]. Studies in adults have demonstrated that clinical assessment alone misses the diagnosis of ICU-AW in up to 50% of patients [21]. Developmental limitations of clinical assessment in the pediatric patient population likely contribute to significant under-recognition of ICU-AW. In fact, the only study to investigate ICU-AW prospectively in critically ill children used only clinical assessment [13]. Furthermore, standard electrodiagnostic tests such as nerve conduction velocity and electromyography are not routinely employed in the critically ill pediatric population because they are technically challenging, invasive, and less well validated in children in comparison to adults. The absence of any CIN cases reflects the low index of suspicion for CIN and limited clinical use of nerve conduction velocities in this population. The lack of identification of CIN as a complication of critical illness likely reflects poor recognition rather than CIN not ever occurring in critically ill children. All of these factors contribute to the under-recognition of ICU-AW in the PICU.

Despite this being the largest study to date to investigate ICU-AW among critically ill children, there are several limitations. While VPS provides some important clinical information about risk factors previously reported to be associated with ICU-AW, the contribution of other important variables including the use of corticosteroids, neuromuscular blockade, the role of inflammation and immobility cannot be determined from this database. Medications that are administered during the course of ICU admission are not recorded within this database. Furthermore, there are no standardized diagnostic criteria for ICU-AW within VPS. This likely contributes to under-reporting and lowers the overall incidence of this disease. We determined that within VPS, children with ICU-AW required a higher level of care upon discharge from the ICU. We could not address functional outcomes, such as the

pediatric cerebral performance category and pediatric overall performance category because these data were not reported in all patients. Functional status scale may also have proved to be a useful outcome measure however these data are not available [22]. VPS captures data just from the PICU portion of hospitalization, thus questions about long-term sequela of acquired neuromuscular weakness during critical illness, including hospital length of stay and outpatient functional outcomes remains unknown. ICU-AW is negatively associated with patient reported and clinician derived outcomes assessing functional capacity and quality of life in adults [4, 7, 17]. Analogous studies have not been done in the critically ill pediatric population. However, there are data both in children with burns and congenital heart disease to suggest that ICU-AW has long-term effects that are only now being appreciated. While our study did not identify cardiovascular disease or congenital heart disease as a risk factor for ICU-AW, children with congenital heart disease who reach adulthood have impaired skeletal muscle and respiratory muscle strength as compared to age matched controls [23]. We had insufficient data to determine the significance of burn injury and ICU-AW from VPS, despite previously published data demonstrating that in children with significant thermal injury who undergo rehabilitation there are significant alterations in metabolism resulting in reduced muscle mass and a predisposition to overweight and obesity [24]. Peripheral neuropathies are reported to arise as a result of the systemic inflammatory response produced by a full-thickness cutaneous burn injury and this has been corroborated with animal models [25]. In patients with thermal burns polyneuropathies and axonal neuropathy were more frequent than mononeuropathy and demyelination and burn associated neuropathy has been observed in pediatric patients.

Additional limitations to our study include the fact that VPS contains only data that has been voluntarily reported by a relatively small proportion of the nation’s PICUs. There is also an overrepresentation of university-affiliated hospitals compared to smaller or community-based hospitals. Thus the use of VPS may result in biased findings. Also, there are limited data elements that are required to be reported as a member of VPS. The diagnoses of critical illness myopathy and critical illness neuropathy are not required variables in the VPS dataset, and likely result in under-reporting compared to a database specifically developed to identify patients who acquire ICU-AW.

In conclusion, we found that ICU-AW was reported in only 0.02% of patients hospitalized in PICUs reporting to the VPS database. We also found that the diagnosis of ICU-AW is associated with high rates of invasive PICU therapies, higher resource use, and poor outcomes among critically ill children. It is likely that the low incidence is due to both under-reporting and less than optimal clinical detection in children managed in the PICU setting. The retrospective design of this study limits our ability to determine the true impact of ICU-AW on morbidity and mortality in critically ill children. Prospective studies are needed to better characterize the disease incidence using standard electrodiagnostics such as electromyography and nerve conduction velocities. Muscle ultrasound can identify acute skeletal atrophy in critical illness in adults but has not been used in critically ill children [3, 26]. Identifying patients who may be at risk and ascertaining the long-term impact of ICU-AW by assessing functional outcomes is of vital importance so that future studies can be aimed at the development of therapies that assist with prevention and recovery.

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Table 1

Patients Demographics with ICU-AW

	ICU-AW (n=55)	Non ICU-AW (n=203,875)	p value
Male, N (%)	29 (52)	113,633(56)	0.90
Race, N (%)			
Caucasian/European, Non-African-American	25 (47%) 10 (19%)	82,317 (42%) 30,581(15%)	< 0.01
Hispanic	9 (13%)	33,216 (16%)	
Asian/Indian/Pacific-Islander	4 (8%)	5,273 (2%)	
Unspecified/Unknown	6 (11%)	42,990 (21%)	
Other/Mixed	1(10%)	7,856 (4%)	
Primary Diagnoses, N (%)			
Respiratory	27(49%)	55,159 (27%)	< 0.01
Infectious	7 (12%)	8,411(4%)	
Cardiovascular (not CHD)	1 (1.8%)	19,692 (9.6%)	
CHD	2 (3%)	6,652 (3%)	
Neurologic	5 (9%)	28,992 (14%)	
Hematologic/oncologic	2 (4%)	10,163 (5%)	
Other Diagnoses	11 (20%)	73,395 (36%)	
PIM 2 risk of mortality, mean % (SD)	2.3(1.7)	0.9(1.5)	>0.01
Age in years, mean (SD)	7.6(5.9)	6.4(5.9)	0.12
Mechanical Ventilation Days, mean (SD)	31.6 (28.9)	9.3 (20.6)	<0.001

Abbreviations: CHD=congenital heart disease, PIM=Pediatric Index of Mortality-2

Table 2

Multivariable Regression of Risk Factors Associated with ICU-AW

Risk Factor	Odds ratio	95% CI	P value
PIM-2	0.9	0.7–1.1	0.3
Age in Years	1.1	1.0–1.1	<0.001
Respiratory Diagnosis	3.4	1.9–6.1	<0.01
Infectious Diagnosis	3.5	1.4–8.5	0.006
Renal Replacement Therapy	3.6	1.1–11.4	0.03
ECLS	11.2	4.8–26.4	<0.001
Mechanical Ventilation	21.5	8.5–54.1	<0.001

Table 3

ICU Outcomes Among Patients with ICU-AW

Outcomes	ICU-AW	VPS	p-value
Number of mechanical ventilation events, mean (SD)	2.9 (2.2)	0.6 (1.1)	<0.001
PICU LOS, days (SD)	20.4 (18.4)	4.1 (9.7)	<0.001
Tracheostomy, N (%)	14 (25.5%)	9,585 (4.7%)	<0.001
Disposition, N (%)			
Home	9 (16%)	50,271 (25%)	
General ward	23 (42%)	118,743 (58%)	
Intermediate unit	15 (27%)	20,605 (10%)	
Chronic/Rehabilitation facility	3 (5%)	1,661 (0.8%)	
Other	1 (2%)	3,997 (2%)	<0.001
Mortality, N (%)	3 (5.5%)	4837(2.1%)	0.1

Abbreviations: LOS=length of stay