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Brain Injuries and Neurological System Failure are the Most Common Proximate Cause of Death in Children Admitted to a Pediatric Intensive Care Unit

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Abstract

Objective—Mortality rates from critical illness in children have declined over the past several decades, now averaging between 2-5% in most Pediatric Intensive Care Units (PICUs). While these rates, and mortality rates from specific disorders, are widely understood, the impact of acute neurological injuries in such children who die and the role of these injuries in the cause of death are not well understood. We hypothesized that neurological injuries are an important cause of death in children.

Design—Retrospective review.

Setting—PICU at Children's Hospital of Pittsburgh, an academic tertiary care center

Patients—Seventy-eight children who died within the PICU from April 2006-February 2008.

Measurements and Main Results—Data regarding admission diagnosis, presence of chronic illness, diagnosis of brain injury, and cause of death were collected. Mortality was attributed to brain injury in 65.4% (51/78) of deaths. Ninety-six (28/29) percent of previously healthy children died with brain injuries, compared to 46.9% (23/49) of chronically-ill children ($p < 0.05$). The diagnosed brain injury was the proximate cause of death in 89.3% of previously healthy children and 91.3% with chronic illnesses. PICU and hospital length of stay was longer in those with chronic illnesses (38.8 ± 7.0 vs. 8.9 ± 3.7 and 49.2 ± 8.3 vs. 9.0 ± 3.8 , $p < 0.05$ and $p < 0.001$, respectively)

Conclusion—Brain injury was exceedingly common in children who died in our PICU and was the proximate cause of death in a large majority of cases. Neuroprotective measures for a wide variety of admission diagnoses, and initiatives directed to prevention or treatment of brain injury are likely to attain further improvements in mortality in previously healthy children in the modern PICU.

Keywords

Pediatric neurocritical care; mortality; neurological injury; chronic illness; pediatrics; intensive care

Introduction

The mission of pediatrics is to promote the health of children by preventing avoidable disorders and aggressively treating conditions in order to optimize chances for full recovery of function. For pediatric intensivists, this mission begins by limiting mortality for children with critical illnesses or injuries while fostering as full a recovery as possible. In order to fulfill this mission, an understanding of the causes of deaths of children admitted to PICUs is imperative for intensivists as well as a number of other groups, including hospital administrators, health care policy experts, and clinical researchers among others.

The precise causes of any complex process such as death can be inherently difficult to discern due multiple factors. In particular, statistics regarding the mechanisms of death in children are relatively murky from governmentally-derived data from death certificates because single causes are generally required for this form of documentation. According to the most recent data from the CDC, 39,798 child deaths were reported and the leading cause of death for all age categories above 1 year was unintentional injury. Other leading causes in the various age groups were intentional self-harm (suicide), malignant neoplasms, cardiovascular diseases, congenital malformations, influenza and pneumonia, septicemia, and chronic lower respiratory diseases(1). Despite this comprehensively collected data from across the country, the actual cause of each death is unclear. For example, it is likely that “unintentional injury” refers to both severe brain and/or other organ injury and specific reasons for death are not reported. Similarly, children with malignancies often die from complications of their disease or treatments (for example, sepsis due to prolonged immune suppression) and not from direct tumor invasion into surrounding tissues.

While mortality rates are often tracked as part of continuing quality control measures(2), determinations of the proximate causes of death are less common. Vernon and colleagues found that the major diagnoses of children who died in their PICU were post-operative congenital heart disease (18.7%), head injury (12.7%), near-miss sudden infant death syndrome (9.3%), pneumonia (7.3%), sepsis (7.0%), and drowning/near-drowning (7.0%) (3). More recently, Ramnarayan and colleagues studied deaths at their institution over a 7-year period (a total of 1127 deaths) and report that congenital malformations (22.2%), perinatal diseases (18.1%), cardiovascular disorders (14.9%) and neoplasms (12.4%) were the most common diagnoses of children who died(4). However these and other studies have failed to report the precise mechanism of death and have failed to describe if neurological injuries were common in children who died.

Identifying the cause of death in an individual child can often be a challenge. In acute disease processes, such as sudden cardiac death from arrhythmia, the cause of death is straightforward. In many other instances, such as children admitted with sepsis, cancer or other conditions, the multi-factorial nature of illnesses make it more difficult (3-6). In our

institution, we observed that many children who died did so after an acute neurological deterioration and we believed that the conventional classification of diseases relating to death may be under-representing neurological conditions. Based on this observation, we theorized that neurological injury and failure was common in children who died and was the proximate cause of death in many cases. Therefore, we choose to evaluate the presence of neurologic organ system failure leading to death. We systematically evaluated the hypothesis that brain injuries were an important cause of death in children who died in our PICU. We further hypothesized that brain injuries were the predominant proximate cause of death in children without previous medical conditions, as children with chronic medical conditions would have some mortality risk from these preexisting disorders. If proven true, this would imply that neuroprotective strategies for children with a wide range of illnesses should be developed in efforts to minimize mortality in the critically-ill child.

Materials and Methods

To prove our hypotheses, we performed a retrospective review of consecutive deaths within our institution. The study was approved by the Committee for Oversight of Research Involving the Dead (CORID) at the University of Pittsburgh. All patients who died under the care of the medical staff of the Pediatric Critical Care Medicine Division at the Children's Hospital of Pittsburgh from April 2006 to February 2008 were prospectively entered into a quality control database and included in this study. This database included all children who were cared for and died within the Pediatric Intensive Care Unit (PICU) and select neonates who were under the care of the members of the Division within the Neonatal Intensive Care Unit (generally referred for Extracorporeal Membrane Oxygenation (ECMO)). However, children admitted to the Cardiac Intensive Care Unit (CICU) were specifically excluded from the analysis.

Definitions

For this study, "brain injury" was defined as an acute disturbance in neurological function that was diagnosed either by new symptomatology or by standardized neurological tests (by neuroimaging or electroencephalogram (EEG)). Such injuries were characterized as "admission brain injuries" if the child had no history of neurological dysfunction prior to the current admission to the PICU but now met the "brain injury" definition above. Similarly, "acquired brain injuries" were defined as an injury that was not present on admission, but developed during hospitalization. The relationship between the brain injury and the cause of death was also extracted. In particular, brain injuries were considered a "proximate cause" of death if the brain injury played a direct role in the pathophysiology leading to the declaration of death or a role in the decision to withdraw life support. For example, the hypoxic/ischemic brain injury was considered a proximate cause of the death in children who suffered a cardiac arrest where return of spontaneous circulation was established but subsequently was declared brain dead (or had life support withdrawn due to profound CNS injury). But brain injury was not considered a proximate cause of death in children who never regained spontaneous circulation after cardiac arrest. Patients were defined as having chronic illnesses if they had a medical condition requiring continuous use of medications or

therapy prescribed by the primary care provider. All other children were considered previously healthy.

Brain injuries were categorized based on the predominant pathophysiology, such as herniation, hypoxic/ischemic injury, hemorrhage, and trauma based on data from the information from medical records (either from extemporaneously dictated attending physician notes or laboratory/radiological tests). Herniation was defined as compression of midbrain structures based on imaging findings. For this analysis, tonsillar and uncal herniation were not distinguished. Hypoxic/ischemic injury was defined as a brain injury that was observed after a documented hypoxic, anoxic or ischemic event from the medical record. Hemorrhage for this study was defined as any type of intracranial hemorrhage such as epidural, subdural, subarachnoid, intraventricular, and intraparenchymal hemorrhages diagnosed by radiological tests. Injuries were categorized as traumatic if they consisted of brain injuries due to traumatic etiologies.

Data Extraction

Data were extracted from the medical record. In general, information from the attending history and physical examination, death/discharge summary and autopsy report (when available) was extracted to ascertain the admission diagnosis, pre-existing medical conditions and cause of death. Additional medical information from the patient chart, including daily progress notes and results of diagnostic test reports was examined to determine the timing and symptoms of any brain injury and as needed for demographic and other information. Demographic information including age, sex, PICU and hospital length of stay, were collected. Additionally, information was collected as to the use of CPR, ECMO, and the mode of death (brain death (based on AAP/AAN definition), withdrawal, failure to resuscitate, DNR). Withdrawal of care was performed under the supervision of the Attending Physician. Children were stratified into groups based on the presence of pre-existing medical conditions (those without pre-existing conditions and those with such disorders) for analysis. Groups were compared using X^2 using commercially available software (Sigma Stat, SPSS). Data are expressed as mean $\pm$ SEM, unless otherwise specified. Data was analyzed by 2 independent observers (the first and senior authors) who were blinded to each other's conclusions. Acute neurological injury was determined as the proximate cause of death by each observer, with an inter-rater reliability of 99%. In the one instance where there was disagreement, a more detailed reading of the medical record clarified the cause of death.

Results

The overall mortality rate for all children admitted to our PICU during the 21 month study period was 1.6% (78 deaths/4,694 admissions). Admission demographics are shown in Table 1. Overall, a similar number of males and females died during the study period, with previously-healthy males and chronically-ill females overrepresented within the groups. Children ranged in age from 15 d to 21 y, with a mean of 7.8 y. Children less than 1 year of age accounted for over half of the deaths in previously healthy children. Admission diagnoses varied widely and overall were relatively evenly distributed between respiratory, cardiovascular, traumatic, and gastrointestinal/hepatic disease (Table 1).

Overall, 51 children died with an acute brain injury (65.4% of all deaths, see Tables 2 for categorization and Table 3 for description of injuries). Within this group, 40 children (78.4%) suffered brain injuries at admission and 11 children (21.6%) acquired brain injuries after hospitalization. After stratification based on previous health status, 96.6% (28/29) of previously healthy children had an acute brain injury, with 89.3% (25/28) having admission brain injuries and 10.7% (3/28) having acquired them during hospitalization. Importantly, 89.3% (25/28) of these brain injuries were deemed as the proximate cause of death in these children based on our criteria. For children with chronic conditions, 46.7% (23/49) met the definition of an acute brain injury, with 65.2% (15/23) having admission brain injuries and 34.8% (8/23) having been acquired during hospitalization. Of these injuries, 91.3% (21/23) were determined to be proximate causes of death based on our definitions.

Of the admission brain injuries in the previously healthy cohort, a majority occurred as a result of traumatic brain injury and hypoxic/ischemic injury from cardiac arrest (85.7% (24/28), see Table 4). Of note, 27 children had out of hospital cardiac arrest, and 4 of those required additional CPR during their hospitalization. An additional 16 children, who presented for other reasons, underwent CPR during their hospital stay. Within the chronically-ill cohort, the most common form of brain injury was from hypoxia/ischemia following cardiac arrest, with herniation and cerebral hemorrhage being the other more common causes (see Table 3).

PICU and hospital stays were relatively long in both groups but longer for children with chronic conditions compared to those that were previously healthy (PICU LOS 38.8 ± 7.0 vs. 8.9 ± 3.7 , $p < 0.05$; Hospital LOS 49.2 ± 8.3 vs. 9.0 ± 3.8 , $p < 0.001$). Interestingly, 55% (16/29) of previously healthy children died within 1 day of presentation, compared to 8% (4/49) in chronically-ill children. Of these 16 previously healthy children who died within 1 day of presentation, 10 were declared brain dead and 5 had failed CPR. The last child had severe cardiac failure diagnosed upon admission, had 40 minutes of CPR and was deemed not to be an ECMO or transplant candidate. For this child, care was withdrawn at the behest of the family. Withdrawal of support was the main mode of death in both previously healthy and chronically-ill children (Table 5). Thirty-two of the 78 children who died in this study (41.0%) underwent autopsies or evaluations by the coroner.

Discussion

We have found that brain injury and neurological failure are very common in critically-ill children who died in our institution, and brain injury was a precipitating cause of death in an overwhelming majority of cases. We believe that this is the first report that fully describes the impact of brain injuries on mortality in critically-ill children and argues strongly for development of novel neuroprotective strategies, both for preventing brain injuries as well as for multi-factorial conditions that may ultimately lead to neurological dysfunction or failure. Moreover, as institutions focus on neurological outcome as an important outcome of critical illness, including the development of neurocritical care programs, our data serves to highlight the common nature of neurological morbidity and its role in determining mortality in children.

Mortality rates for critically-ill children have been tracked and reported within many contexts for many years, generally demonstrating a decreasing trend as critical care has evolved. In seminal work starting in the mid-1980s, Pollack and colleagues developed the Pediatric Risk of Mortality (PRISM) score(7) to utilize physiological derangements to predict outcome. In doing so, they allowed the calculation of expected mortality rates based on physiological derangements, ultimately leading to expected/observed mortality rates as standardized measures of quality of care(8). In these studies, mortality rates of critically-ill children were reported to range from 2.2 – 16.4%. More recent surveys suggest that overall mortality rates between 2.5(9) to 4.7%(10), with obvious inter-institutional variability. Mortality rates for specific conditions that cause critical illness in children have also been frequently reported. Considerable attention has been given to the mortality of children with cancer who develop respiratory failure or other critical illnesses, with Hallahan reporting a 27% mortality for all children admitted to the PICU with a malignancy(11) and Dursun and colleagues describing a 55% mortality rate for a similar population(12). Mortality rates for severe sepsis in children range from 1 – 3% for previously healthy children and 7 – 10% for children with chronic medical conditions based on compilations of multiple studies(13). Zimmerman and colleagues demonstrated a hospital mortality rate of 18% for children meeting the definition of acute lung injury(14). Moreover, mortality from solid organ transplantation has been reported as near 20% during the first year after transplantation for both liver and lung transplantation(15, 16). The striking nature of these studies, and several others, is the lack of specificity of why the children died and whether neurological injuries contributed to the death.

Our study is the first, to our knowledge, to quantify the extent of serious neurological injury in children who die in the PICU. In recent years, we and others have advocated for specialized neurocritical care efforts within the specialties of Pediatric Critical Care and Pediatric Neurology. Specifically, LaRovere and Riviello reported 557 consults were generated in 2006 in their neurocritical care service in Boston(17), while we reported 373 consults in 14 months at Children's National Medical Center(18). However, neither study addressed the actual burden of neurological injury that causes death in children, which is quite substantial from our findings in the current study. The burden of neurological causes of death is particularly striking in children who were previously healthy, with traumatic brain injury and hypoxic/ischemic brain injury after cardiac arrest being the two most common causes of death. While there are currently two multi-institutional studies determining if early hypothermia improves outcomes from these disorders, our data, should it be corroborated by other institutions, argue for the urgent need for additional novel treatments and greater resources to decrease the mortality of these and other neurological conditions in childhood.

Several studies have demonstrated that chronically ill children are at great risk for more acute critical illnesses, and ours confirms that children with such illnesses are at risk for fatal neurological conditions. Dosa and colleagues demonstrated a RR of 3.3 for children with chronic conditions to be admitted to an intensive care unit, accounting for almost half of elective admissions in a given year(19). In a larger cohort, Feudtner and colleagues found that 60.6% of over 13,000 deaths in children's hospitals occurred in children with 1 or more complex chronic condition, consistent with our findings (49/78, 62.8%)(20). We found that nearly half of these children, who were admitted to the PICU, developed an acute brain

injury in addition to their chronic condition and it was an important cause of death in most of these children. We feel our data illustrates an interesting paradox – in that children with chronic conditions, such as malignancies, chronic organ failure or others are at increased risk for critical illnesses and brain injuries once critically ill, yet are often excluded from clinical trials because their chronic conditions lead to heterogeneous patient populations for such trials. We suggest our data argue that brain injuries should be carefully considered and treated in children with chronic conditions as it appears they are major factors in mortality.

Withdrawal of medical support was a common mode of death within our intensive care unit, accounting for 66.7% (52/78) of the total deaths. This rate is increased compared to previous studies which demonstrated a 20-55% incidence (3, 6, 21-27). Interestingly, in our study, 77.6% of chronically-ill children had withdrawal of care as their mode of death. In 1992, Mink and Pollack showed that among children with severe chronic disease, which they defined as consisting of a sufficient severity to limit life expectancy or prevent independent functioning as an adult, had 59.0% (13/22) withdrawal of care(27). Unfortunately, the retrospective nature of our study design do not allow for further interrogation of root causes of the family decisions to withdraw care. It appears likely that conditions particular to our institution (staff feelings about withdrawal of care, family/social conditions of the community and others) affected this observed rate of withdrawal of support.

There are several limitations to our study. First, our study population was intentionally limited to critically-ill children admitted to our Pediatric Intensive Care Unit, thereby excluding children who died in our Cardiac Intensive Care Unit, Neonatal Intensive care unit, general medical/surgical wards and the Emergency Department, and those dying at home or in hospice. While a larger survey would have identified more deaths within our institution with inclusion of these areas, our objective was to determine the burden of neurological injuries in children with diverse admission disorders and those that might be most amenable to future institution of neuroprotective strategies. Deaths in the Emergency Department or the medical/surgical ward would not be amenable to future neuroprotective strategies, as these would undoubtedly be due to unsuccessful resuscitation efforts or intentional limitations of support, respectively. We suggest a similar study in children within Cardiac Intensive Care Units would be intriguing, but the dissimilarity between the two populations precludes combining the two groups in our opinion. Secondly, our study did not detect neurological injuries in surviving children, just those that died. We suggest there is a substantial burden of neurological injury, both recognized at admission and during hospitalization, in children who survive critical illnesses and this burden is likely much greater than what we observed in the children who died. However, a paradigm shift in critical care, including acute neurological evaluation during hospitalization and comprehensive neuropsychological testing after discharge, would be required to detect neurological injury. Thirdly, our study was specifically designed to identify cases of brain injury within our patient population. While this leads to a stronger understanding of the impact on neurologic injury, it does not account for the multifactorial nature of disease processes that lead to mortality in critically-ill children and the presence of the number of organ failures at the time of death (or the timing of such failures) was not studied. Lastly, our findings are from a single institution and may not be readily extrapolated to other institutions. Clearly, many factors can lead to prolongation or termination of life support

efforts including cultural views of parents, clinical decisions (both to escalate and de-escalate therapies) by clinicians and availability of resources to name a few. Confirmation of our findings in other populations of critically-ill children will be crucial to fully understand the relationship between brain injuries and mortality in critically-ill children.

In conclusion, our data strongly suggests that children who die in a large, multidisciplinary PICU predominantly have substantial brain injuries that lead to their deaths. This argues for the development of novel neuroprotective strategies in a wide variety of disease conditions that lead to critical illnesses of children. Tasker has stated that “Pediatric neurocritical care is the new frontier in pediatric critical care and pediatric neurology. There is sufficient specialist interest and momentum for the development of a multidisciplinary collaboration that has the aim of improving patient care”(28). Therefore, focusing our clinical efforts to limit these deaths - and improving meaningful survival - appears to be the next step in this new frontier.

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Table 1

Admission Demographics of Patients Who Died in the ICU

	All Patients (n=78)		Previously Healthy (n=29)		Chronically-III (n=49)	
Sex		%		%		%
Male	38	48.7	18	62.1	20	40.8
Female	40	51.3	11	37.9	29	59.2
Age						
Under 1 year	24	30.8	15	51.7	9	18.4
1-4 years	12	15.4	2	6.9	10	20.4
5-14 years	20	25.6	6	20.7	14	28.6
14-21 years	22	28.2	6	20.7	16	32.7
Admission from						
Emergency Department	43	55.1	24	82.8	19	38.8
Inpatient Ward	17	21.8	1	3.4	16	32.7
Operating Room	4	5.1	1	3.4	3	6.1
Outside Hospital Transfer	13	16.7	3	10.3	10	20.4
Primary Admission Diagnosis						
Respiratory failure	16	20.5	3	10.3	13	26.5
Cardiac failure	10	12.8	5	17.2	5	10.2
Sepsis	11	14.1	1	3.4	10	20.4
Traumatic Brain Injury	16	20.5	15	51.7	1	2.0
Neurological disorders [*]	6	7.7	3	10.3	3	6.1
Gastrointestinal/Hepatic disorders	14	17.9	1	3.4	13	26.5
Other	5	6.4	1	3.4	4	8.2

^{*} Neurological disorders exclude traumatic brain injuries

Table 2

Precipitating Cause of Brain Injury

	All Children n=51	Previously Healthy n=28	Chronically-III n=23	Admission Brain Injury			Acquired Brain Injury		
				Admission Brain Injury n=40	Previously Healthy n=25	Chronically-III n=15	Acquired Brain Injury n=11	Previously Healthy n=3	Chronically-III n=8
Cardiac Arrest/Respiratory Arrest	22	7	15	19	7	12	3	0	3
Traumatic Brain Injury	16	15	1	16	15	1	0	0	0
CNS Infection	6	4	2	4	3	1	2	1	1
Spontaneous Intracranial Hemorrhage*	3	0	3	0	0	0	3	0	3
ECMO with Intracranial Hemorrhage	2	2	0	0	0	0	2	2	0
Demyelinating Brain Injury	1	0	1	0	0	0	1	0	1
Posterior Reversible Encephalopathy Syndrome	1	0	1	1	0	1	0	0	0

* Spontaneous intracranial hemorrhage excludes intracranial hemorrhages acquired while on ECMO

Table 3
Characteristics of Children with Brain Injury

Previously Healthy Children with Brain Injury (N=28)

- 15 Traumatic brain injury
 - 7 with concern for non-accidental trauma
- 16 Cardiac arrest (acute hypoxic/ischemic brain injury) at or prior to admission
 - 8 of which also had traumatic brain injury
 - 1 had primary diagnosis of meningitis
- 2 Meningitis, both with cerebral edema upon CT scan
 - 1 cerebral herniation
- 2 Status Epilepticus
 - 1 cerebral herniation
 - 1 with encephalopathy, refractory status epilepticus
- 2 ECMO therapy with resultant brain hemorrhage and herniation

Chronic Illness Children with Brain Injury (N=23)

- 1 Traumatic brain injury
- 11 Cardiac arrest (acute hypoxic/ischemic brain injury) at or prior to admission
- 1 ECMO therapy for dermatomyositis, respiratory failure and PRES with resultant intracranial hemorrhage
- 3 s/p Multivisceral transplants, all 3 developed intracranial hemorrhages
- 2 Multivisceral transplant evaluations
 - 1 with severe hydrocephalus with multiple hypoxic ischemic events due to CPR and hemorrhages
 - 1 with intracranial hemorrhage
- 1 Cryptococcal meningitis with herniation
- 1 Fanconi's anemia s/p BMT with demyelinating brainstem injury
- 1 Omphalocele, line sepsis with cardiac arrest and hypoxic/ischemic injury
- 1 Osteosarcoma with arrest during chemotherapy
- 1 Cystic fibrosis with respiratory arrest

Table 4
Mechanisms of Brain Injury

	Previously Healthy (n=29)	%	Chronically-III (n=49)	%
Herniation	9	32.1	8	34.8
Hypoxia/Ischemia	25	89.3	19	82.6
Hemorrhage	14	50.0	7	30.4
Epidural	2	6.9	1	2.0
Subdural	11	37.9	2	4.0
Subarachnoid	6	20.7	1	2.0
Intraventricular	2	6.9	2	4.0
Intraparenchymal	6	20.7	5	10.2

Table 5
Modes of Death Among All Children Admitted to the ICU

	Previously Healthy (n=29)	%	Chronically-III (n=49)	%
Brain Death	13	44.8	3	6.1
Failure to Resuscitate	2	6.9	5	10.2
Withdrawal	14	48.3	38	77.6
Due to Neurological Futility	13	44.8	20	40.8
DNR	0	0.0	3	6.1