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► **To cite this version:**

Ericka L. Fink, Patrick M. Kochanek, Robert C. Tasker, John Beca, Michael J. Bell, et al.. International Survey of Critically Ill Children With Acute Neurologic Insults: The PANGEA study. *Pediatric Critical Care Medicine*, 2017, 4 (18), pp.330-342. 10.1097/PCC.0000000000001093 . hal-01717475

HAL Id: hal-01717475

<https://hal.science/hal-01717475v1>

Submitted on 8 Apr 2019

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Published in final edited form as:

Pediatr Crit Care Med. 2017 April ; 18(4): 330–342. doi:10.1097/PCC.0000000000001093.

International Survey of Critically Ill Children with Acute Neurological Insults: The PANGEA study

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Abstract

Objective—The international scope of critical neurological insults in children is unknown. Our objective was to assess the prevalence and outcomes of children admitted to pediatric intensive care units (PICUs) with acute neurological insults.

Design—Prospective study.

Setting—Multicenter (n=107 PICUs) and multinational (23 countries, 79% in North America and Europe).

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Copyright form disclosure:

The remaining authors have disclosed that they do not have any potential conflicts of interest.

Patients—Children aged 7d–17y admitted to the ICU with new traumatic brain injury, stroke, cardiac arrest, central nervous system infection or inflammation, status epilepticus, spinal cord injury, hydrocephalus, or brain mass.

Interventions—None.

Measurements and main results—We evaluated the prevalence and outcomes of children with pre-determined acute neurological insults. Child and center characteristics were recorded. Unfavorable outcome was defined as change in pre-post insult Pediatric Cerebral Performance Category (PCPC) score ≥ 2 or death at hospital discharge or 3 months, whichever came first. Screening data yielded overall prevalence of 16.2%. Of 924 children with acute neurological insults, cardiac arrest (23%) and traumatic brain injury (19%) were the most common. All-cause mortality at hospital discharge was 12%. Cardiac arrest subjects had highest mortality (24%), and TBI subjects had the most unfavorable outcomes (49%). The most common neurological insult was infection/inflammation in South America, Asia, and the single African site but cardiac arrest in the remaining regions.

Conclusions—Neurological insults are a significant pediatric international health issue. They are frequent and contribute substantial morbidity and mortality. These data suggest a need for an increased focus on acute critical neurological diseases in infants and children including additional research, enhanced availability of clinical resources, and the development of new therapies.

Keywords

child; epidemiology; neurocritical care; outcomes; international

INTRODUCTION

Acute neurological insults due to trauma and non-traumatic cause are leading causes of morbidity and mortality in children.^{1–3} Surviving children are at increased risk of cognitive, physical, and psychological disability, and their families suffer marked emotional, social, and financial strain.^{4–11} Treatment recommendations are largely based on level II or lower evidence due to the lack of high quality prospective research.^{12–14} Cross-sectional epidemiological data can guide allocation of resources to prevent and/or treat these conditions and optimize prospective study design of clinical investigations.¹⁵

The Prevalence of Acute critical Neurological disease in children: a Global Epidemiological Assessment (PANGEA) research program was established with an ultimate goal to provide data to inform clinical research and health care priorities that will lead to future breakthroughs in improving outcome for all children. The aim of this initial report was to describe and better understand the prevalence and outcome of children with acute neurological insults in pediatric intensive care units (PICUs) in largely academic and resource-rich settings.

MATERIALS AND METHODS

PANGEA research program

At the inception of the PANGEA research program (NCT02381977), an international steering committee was formed, and individual PICUs were recruited from professional networks that included: Pediatric Acute Lung Injury VEntilation (PALIVE) study from North America and Europe;¹⁶ the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) and the Pediatric Neurocritical Care Research Group (PNCRG) from North America; the Canadian Critical Care Trials Group; the European Society for Pediatric and Neonatal Intensive Care; the Australia and New Zealand Intensive Care Society; and the World Federation of Pediatric Intensive and Critical Care Societies. Participation was voluntary, and no remuneration was given for involvement. Investigators needed to be fluent in English and have the ability to record data using the study's internet-based platform. Local regulatory approval was obtained at each study site. The Data Coordinating Center was accepted as an exempt protocol by the University of Pittsburgh Institutional Review Board. All centers reported to have obtained a waiver of informed consent, allowing for prevalence calculation.

Case definitions

The international steering committee agreed on the case definitions for acute neurological insult in the critically ill child (Supplementary Data). The inclusion criteria were: 7 days to 17 years old on the study day; admission to the PICU; and, a primary diagnosis of traumatic brain injury, stroke, cardiac arrest, central nervous system (CNS) infection or inflammation, status epilepticus, spinal cord lesion, hydrocephalus, or brain mass. If a child had suffered a perinatal or remote (> 6 months prior to hospitalization) CNS insult without a new, acute neurological insult they did not meet the inclusion criteria.

Point prevalence study design

Four study dates during a 1 year period were chosen, avoiding weekends and holidays to encourage participation: 29 November, 2011; 28 February, 2012; 22 May, 2012; and 24 July, 2012. Centers were instructed to screen all patients in their PICU at 9:00 am local time. Centers recorded the number of children meeting study inclusion criteria, and all but 10 centers provided the total number of children in their PICU on the study day. Based on feedback from study centers, hydrocephalus and brain mass categories were added at the second study date.

A Case Report Form (CRF) with inclusion and exclusion criteria, study definitions, and guide to data collection was provided to centers and posted as a secure electronic-CRF on the study website (www.pangeastudy.com). CRF composition was based on prior studies, perceived needs of the research community, and input by the Steering Committee, and feedback from PALISI and PNCRG members. Professionals at the Biomedical Telematic Laboratory of the Health Respiratory Network of Fronds de Recherche Sante Quebec, University of Sherbrooke, Canada, designed and maintained the secure website and securely transferred collected study data to the DCC. Data were collected on hospital and study subject characteristics, details about the child's acute neurological insult, monitoring used,

therapies, testing, and outcomes. Details on monitoring and treatments are not included in this manuscript but will be part of secondary data analysis. Components of the Pediatric Index of Mortality-2 (PIM2) scores were embedded into the CRF to allow determination of mortality risk.¹⁷

Outcomes

PICU prevalence of acute neurologic insult was the primary outcome. Secondary outcomes included all-cause mortality, outcome status using the Pediatric Cerebral Performance Category (PCPC) score (unfavorable outcome = change in PCPC pre-insult to study endpoint ≥ 2 or death), lengths of hospital and ICU stay, frequency of new morbidity, and disposition at PICU and hospital discharge. The study's endpoint was hospital discharge or 3 months after the study day, whichever came first. PCPC is a practical, gross measure of neurological status that performs well in comparison with other validated testing instruments.¹⁸ More detailed neuropsychological outcomes were not possible in this study. Centers collected information on the following a priori-specified newly acquired morbidities during this hospital stay: hypertonia, dysautonomia, and placement of a CSF shunt, surgically placed feeding tube, or tracheostomy tube. These morbidities were chosen by the PI and Steering Committee with consideration of prior literature and potential for long-term impact on patients and families, recognizing that the list is not complete and was developed prior to the availability of the Functional Status Score, recently validated in children.^{19,20} Cause of death was taken from the death certificate.

Data management

Data entry was performed by site ICU faculty, ICU fellows, research assistants, or study coordinators depending on resources available at the site. Primary data collection and data quality were managed by site PI. Centers were provided with the CRF that included the study protocol with written instructions, and were given opportunities to discuss questions electronically or over the phone. Centers were provided with regular study updates via email. Personnel from the Clinical Research, Investigation, and Systems Modeling of Acute illness (CRISMA) Center (Department of Critical Care Medicine, University of Pittsburgh) assisted in secondary data quality monitoring along with the study PI and coordinator. Data were screened for missing or implausible information and queries were issued to the site.

Statistical analysis

Descriptive statistics are presented as median (interquartile range [IQR]). Data were analyzed using Kruskal-Wallis, Mann-Whitney, Fisher's exact, and chi-square tests as appropriate. The numerator and denominator for the prevalence calculation came from the screening form. Ten sites did not provide complete screening data (although they did submit all other forms for children who met entry criteria) and thus were excluded from prevalence calculations. Statistical analysis by region was not performed due to the small number of centers and subjects of some regions. The majority of variables had less than 10% missing data, and missing data were not imputed (thus sample sizes for variables and denominators varied slightly). All *p*-values were two-sided, and $p < 0.05$ was considered statistically significant. The Statistical Package for the Social Sciences version 20 (Armonk, NY, USA) and Stata version 12 (College Station, TX, USA) were used for statistical analyses. This

article was written according to the STrengthening the Reporting of OBservational studies in Epidemiology statement.²¹

RESULTS

Study center characteristics

Of the 107 hospitals participating in the PANGEA consortium, 79% were located in North America or Europe (see Figure and Acknowledgments for full list of centers and site personnel). Eighty-six percent of collaborating PICU's were affiliated with a university academic medical center, 75% were located in pediatric hospitals, and there was a wide range in the number of PICU beds and admissions per year (Table 1). The median number of PICU faculty was 8 (6–14), and 69% of centers provide 24-hour, in-house faculty PICU coverage. Seventy-four per cent of hospitals reported a PICU fellowship training program. Forty-eight per cent of the centers reported that they provided a dedicated neurocritical care service while 10% had a PICU follow-up clinic. Most centers were capable of intracranial pressure (93%) and continuous electroencephalography monitoring (78%), but only 14% of centers were able to invasively monitor brain tissue oxygenation.

Point prevalence and subject characteristics

Participating centers who provided complete data (n=97) screened 5,135 children over the 4 study days and 831 met study criteria with resulting prevalence of acute neurological insults of 16.2% (95% confidence interval (CI) 15.2, 17.2)). Total number of subjects enrolled from all 107 centers was 924. The number of subjects enrolled per site ranged from 0–113 over the four study dates. Thirteen centers enrolled 20 or more subjects into the study. Subjects encompassed the full age range (median [IQR] 48 [9–120] months). Females accounted for the 41% of subjects, and 51% were Caucasian, non-Hispanic ethnicity (Table 2). Sixty-two percent of subjects had public insurance or universal health care and 4% had no health insurance. Fifty-eight per cent of subjects had a comorbid condition with neurological being most common (29%), and 61% of subjects had normal PCPC scores before this neurological event and ICU admission.

Cardiac arrest was the most frequent neurological insult (23%), followed by traumatic brain injury (19%), status epilepticus (17%), and CNS infection/inflammation (Table 3).

Outcomes

All-cause mortality was 105 (12%). Children admitted after a cardiac arrest had the highest mortality (24%) and Pediatric Index of Mortality (6.6 [2.4–20.6]), both $p < 0.001$ vs. other neurologic insults (Table 3). Cause of death was provided in 49 subjects who died. The most common causes of death were withdrawal of support due to poor neurological status (25%), brain death (11%), and cardiovascular failure (10%). Of subjects with a pre-ICU PCPC of 1 (no disability) with PCPC at hospital discharge or 3 months available, 211/475 (44%) remained PCPC of 1. The remainder of subjects with a pre-ICU PCPC of 1 had PCPC 2 (18%), PCPC 3 (11%), PCPC 4 (13%), PCPC 5 (4%) and PCPC 6 (9%) at the later time point. Subjects with traumatic brain injury had the highest rate of normal baseline PCPC

(82%). Thirty-two percent of subjects had unfavorable outcome, which was most common in subjects with traumatic brain injury (49%) ($p<0.001$).

Hospital and PICU lengths of stay were 22 (8–55) and 13 (4–33) days, respectively, and were longest in children with cardiac arrest (both $p<0.001$). At the study's end point, 58% of subjects were discharged home, and 17% were admitted to an in-patient rehabilitation center. Subjects with traumatic brain injury and spinal cord lesion had the highest frequency of rehabilitation disposition (28% and 37% respectively).

The frequency of new morbidities differed by insult. Feeding tubes were most frequently placed in children with cardiac arrest (30%), and tracheostomy tubes were most frequently placed in children with spinal cord lesion (33%).

Regional data

Subject and PICU characteristics varied by region, including age, type of insurance, number of PICU beds, and neurocritical care service (Tables 1, 2, and 4). Prevalence of acute neurologic insults was highest in North America (18.0 [16.7,19.3]) and Africa (15.8 [6.0,31.3]) and lowest in Asia (9.8 [6.1,14.7]) and Europe (12.7 [10.7,14.8]). The most common acute neurological insult was cardiac arrest in North America, Europe, and Oceania while CNS infection/inflammation were most prevalent in South America, Asia, and Africa (Supplemental Figure). PIM2 scores were highest in Oceania and lowest in South America and Asia. Lengths of stay were longest in Africa and shortest in Oceania and Asia. Mortality was 10–14% except at the single center in Africa, where no subjects died, but 50% had unfavorable outcome.

DISCUSSION

There are three chief findings of this study: 1) Acute neurological insults are common among PICU patients, with global hypoxia-ischemia due to cardiac arrest being the most frequent insult; 2) The consequences of acute neurological insults are serious: mortality was 4 to 6 times that of published PICU mortality rates¹⁹; subjects had long lengths of stay, and survivors frequently acquired new morbidities; and 3) Many regional differences exist among center and subject characteristics with acute neurological insults.

Our study population, and therefore our findings and implications, largely reflect critically ill children admitted to ICU's in academic pediatric hospitals in North America, Europe, and Oceania. The prevalence of acute neurological insults is consistent with an analysis of 3 million pediatric hospital discharges in 11 U.S. states by Moreau et al in which children with neurological insults prompted 10% of pediatric hospital admissions but were responsible for 3 times the proportion of pediatric ICU admissions, longer lengths of stay, higher mortality, and higher cost versus children with non-neurological diagnoses.² Factors that may affect prevalence include the relatively long lengths of stay of children with acute neurological insults (also seen in Moreau et al), and occurrence of adverse events associated with long lengths of stay and severe illness (e.g., hospital acquired infection) or additional organ insults/injuries (e.g., renal failure or acute respiratory distress syndrome); though these were

not assessed in PANGEA.^{2,22} The frequency of new morbidities including the need for new surgical technological supports was high, especially in children with cardiac arrest.

Cardiac arrest, the neurological insult with the highest mortality rate, was also the most common insult overall. Cardiac arrest causes global hypoxia-ischemia, which can lead to varying degrees of post-resuscitation syndrome in which brain injury is often the most significant organ affected long term.²³ Notably, other neurological insults are associated with organ injury outside the CNS, which can affect outcome.^{24–26} Traumatic brain injury was the second most common insult overall in PANGEA, and unintentional injury is the leading cause of death for children aged 10–19 years worldwide.²⁷ Although traumatic brain injury subjects had the highest frequency of unfavorable outcome, children with neurological insults often have great potential for rehabilitation, and assessment of longer-term outcomes is needed.²⁸

The growth of pediatric neurocritical care services in PICUs and development of a pediatric neurocritical care research network reflect the specialty's acknowledgement and commitment to improving outcomes for children with acute neurologic insults.^{29–31} In PANGEA, nearly half of centers reported having a neurocritical care service (of variable make-up), more than double that of a recent survey.³² Data are needed to elucidate the optimal configuration and integration of neurocritical care services that affect outcomes.^{29,30,33,34} Few centers reported having ICU follow-up clinics, an innovative multidisciplinary effort to address recovery from critical illness.³⁵

Although exploratory in this study, regional epidemiological and center differences are important to investigate before planning prospective research studies, allocating health care resources, and developing advocacy programs.^{36–39} For example, CNS infection/inflammation was the most frequent neurological insult in South America, Asia, and the single African site compared with cardiac arrest in the remaining regions. Overall prevalence of acute neurologic insult was highest in North America, nearly double that found in Asian centers, but not the highest length of stay. Centers in Oceania had the highest median risk of mortality scores but not the highest unadjusted mortality rate. Regions showed differences in patient age, sex, and health insurance status, variables associated with outcome^{40–42}. Additionally, regions differed in terms of monitoring and testing capabilities and numbers of personnel providing care in the ICU and in a neurocritical care service, and hospital beds. These findings speak to the idea that the optimal delivery of health care for neurocritical care patients may differ regionally.

These findings, taken together with a dearth of efficacious neuroprotective therapies and overall lack of high quality evidence to support care, represent a compelling case for the need for increased research and healthcare resources to assist in improving outcomes for children with acute neurological insults. Transformational ideas to address these issues are critically needed.^{43,44}

Study Limitations

The strengths and limitations of the point prevalence/cross-sectional method of study have been reviewed and limitations include: 1) findings lack cause and effect conclusiveness;

rather serving as more descriptive purposes; and 2) potential underestimation of rapidly fatal disease processes and infrequently used medications and interventions.⁴⁵ Centers participating in PANGEA are from middle and high-income regions. Therefore, our results are not fully representative of the global health problem of children with neurological insult in need of pediatric critical care in resource-limited settings where most child mortality occurs. PANGEA is also conducting research into the epidemiology and outcomes of acute neurological insult in these settings.^{46,47} Children who died prior to reaching medical care and children with milder injuries who did not require ICU resources were not included in this study. Most participating ICUs were academic, reflecting regionalization typical of pediatric critical care but may limit the generalization of findings. Unfavorable outcome was based on change in PCPC score, which may be less informative in infants than in older children. The wide range of regions and centers collecting PCPC data using the medical chart may have limited its reliability. The deliberate avoidance of choosing study dates on weekends and major holidays may increase the chance of sampling bias. This study focused on primary neurologic insults; inclusion of subjects with secondary neurologic insults, a common cause of mortality and morbidity in critically ill children, would also be valuable to inform our long term objective of improving outcomes for these children.

CONCLUSION

Children with acute neurological insults are common in ICUs and are associated with high morbidity and mortality rates and prolonged ICU stays, posing significant challenges to public, family, and individual health. These data suggest a vital need for resources to assist in the challenge of improving outcomes for these children throughout the span of the periods of emergency care through to rehabilitation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The investigators appreciated the non-financial support of the following groups committed to the provision of excellent clinical care and research: Pediatric Acute Lung Injury and Sepsis Investigators (PALISI), Australian and New Zealand Intensive Care Society (ANZICS), European Society of Paediatric Neonatal Intensive Care (ESPNIC), Canadian Critical Care Trials Group (CCCTG), World Federation of Pediatric Intensive and Critical Care (WFPICCS), and Pediatric Neurocritical Care Research Group (PNCRG). In addition, special thanks to Carrie Pidro (PANGEA study coordinator) and Kyle Landis (PANGEA data management). We are grateful to the staff, nurses, and physicians of all ICU's in this study for their generous efforts to help improve the outcomes of children with critical illness.

Source of Funding: Dr. Fink received funding from the Laerdal Foundation and Department of Critical Care Medicine (University of Pittsburgh Medical Center).

Dr. Fink's institution received funding from Laerdal Foundation, National Institutes of Health (NIH), and Patient Centered Outcomes Research Institute. Dr. Kochanek received funding from SCCM (stipend for serving as the Editor-in-Chief of Pediatric Critical Care Medicine), from serving as an expert witness on several cases over the past 36 months, and has received honoraria from numerous lectures at national meetings and/or as a guest professor at various institutions of higher education. He has also received stipends for editing/authoring books and/or chapters. Dr. Hutchison's institution received funding from Canadian Institutes of Health Research, NIH, and Ontario Neurotrauma Foundation. Dr. Watson's institution received funding from NIH (grant unrelated to the manuscript). He has received funding from SCCM (board review course honorarium and travel), CDC (travel to CDC workshop) and NIH (honorarium for grant review).

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Figure. Participating centers are indicated with black dots. Data in black circles includes the number of centers per region/number of subjects per region. Total number of subjects with acute neurologic insult was 924.

Table 1

Center characteristics, /question

Median (interquartile range) or n (%) (n denotes number of centers responding per query sites)	North America n=50 (47)	Europe n=34 (32)	Oceania n=6 (6)	South America n=11 (10)	Asia n=5 (5)	Africa n=1 (1)	Total n=107
No. pediatric hospital beds (n=99)	201 (118–296)	181 (110–280)	248 (189–250)	46 (24–230)	90 (85–170)	279	189 (100–289)
No. pediatric ICU beds (n=101)	29 (14–44)	13 (10–18)	14 (10–18)	11 (7–16)	9 (8–25)	18	16 (11–26)
University-affiliated (n=101)	40 (82)	33 (100)	6 (100)	5 (63)	3 (60)	1 (100)	88 (86)
Pediatric-only hospital (n=96)	41 (87)	21 (70)	6 (100)	1 (14)	2 (40)	1 (100)	72 (75)
ICU admissions/yr. No. centers (%) (n=98)							
1–250	1 (2)	4 (13)	0 (0)	2 (25)	2 (40)	-	9 (9)
251–500	3 (6)	10 (32)	0 (0)	5 (63)	0 (0)	-	18 (18)
501–750	8 (17)	7 (23)	2 (33)	0 (0)	1 (20)	-	18 (18)
751–1000	6 (13)	6 (19)	1 (17)	1 (13)	1 (20)	-	15 (15)
1001–1250	6 (13)	2 (7)	2 (33)	0 (0)	1 (20)	1 (100)	12 (12)
> 1251	23 (49)	2 (7)	1 (17)	0 (0)	0 (0)	-	26 (27)
ICU Personnel							
Total pediatric ICU faculty (n=100)	11 (7–17)	7 (6–10)	7 (5–7)	18 (9–27)	4 (3–5)	4	8 (6–14)
No. faculty in ICU per day (n=100)	2 (1–3)	2 (2–4)	2 (1–2)	4 (3–6)	1 (1–3)	1	2 (2–3)
ICU faculty coverage 24 hr/day (n=100)	27 (56)	25 (78)	4 (67)	7 (88)	5 (100)	1 (100)	69 (65)
Pediatric ICU fellowship program (n=97)	32 (67)	27 (87)	5 (83)	3 (43)	4 (100)	1 (100)	72 (74)
Pediatric ICU fellows (n=97)	5 (0–11)	2 (1–6)	3 (2–12)	0 (0–2)	4 (2–6)	6	3 (0–8)
No. pediatric ICU fellows in ICU per day (n=98)	2 (0–2)	1 (1–2)	1 (1–3)	0 (0–1)	1 (1–3)	5	1 (0–3)
Pediatric residents in pediatric ICU (n=99)	42 (88)	26 (81)	2 (33)	5 (71)	4 (80)	1 (100)	80 (81)
No. residents in ICU per day	3 (2–4)	2 (1–4)	0 (0–2)	2 (0–4)	1 (1–2)	2	3 (1–4)

Median (interquartile range) or n (%) (n) denotes number of centers responding per query (n=99)	North America n=50 (47) sites	Europe n=34 (32)	Oceania n=6 (6)	South America n=11 (10)	Asia n=5 (5)	Africa n=1 (1)	Total n=107
Physician extenders in pediatric ICU (n=97)	32 (65)	20 (65)	2 (33)	3 (50)	3 (60)	0 (0)	60 (62)
No. physician extenders in pediatric ICU per day (n=97)	1 (0-2)	1 (0-3)	0 (0-1)	1 (0-2)	1 (0-1)	0	1 (0-2)
Neurosurgeons available 24 h (n=34)	12 (80)	8 (73)	1 (100)	3 (75)	2 (100)	1 (100)	27 (79)
Neurocritical care service (n=100)	17 (35)	21 (66)	6 (100)	1 (14)	2 (40)	1 (100)	48 (48)
ICU follow-up clinic (n=72)	5 (16)	1 (4)	0 (0)	1 (25)	0 (0)	0 (0)	7 (10)
Center monitoring and testing availability (n=101)							
Central venous catheter	49 (100)	32 (100)	6 (100)	8 (100)	5 (100)	1 (100)	101 (100)
Arterial catheter	49 (100)	31 (97)	6 (100)	8 (100)	5 (100)	1 (100)	100 (99)
Peripherally-inserted central catheter	49 (100)	27 (84)	6 (100)	8 (100)	4 (80)	1 (100)	95 (94)
Intracranial pressure monitoring	48 (98)	29 (91)	6 (100)	7 (88)	3 (60)	1 (100)	94 (93)
Continuous electroencephalography	48 (98)	16 (50)	5 (83)	6 (75)	3 (60)	1 (100)	79 (78)
Near-infrared spectroscopy	33 (69)	16 (52)	4 (67)	2 (25)	0 (0)	1 (100)	56 (57)
Somatosensory evoked potential	18 (37)	14 (44)	4 (67)	2 (25)	1 (20)	0 (0)	39 (39)
Swan-Ganz catheter	26 (53)	2 (6)	1 (17)	3 (38)	0 (0)	0 (0)	32 (32)
Jugular venous oxygen saturation	6 (13)	6 (19)	0 (0)	4 (50)	0 (0)	0 (0)	16 (16)
Brain tissue oxygenation	13 (27)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	14 (14)
Cerebral blood flow	5 (10)	1 (3)	0 (0)	1 (13)	1 (20)	1 (100)	9 (9)
Cerebral microdialysis	6 (12)	0 (0)	0 (0)	1 (13)	1 (20)	0 (0)	8 (8)

ICU, intensive care unit

¹ Some centers did not provide answers to all survey questions, leading to different denominators

Table 2

Subject characteristics.

Median (interquartile range) or n (%) (n) denotes number of subjects with data per query	North America n=661 (72) subjects	Europe n=156 (17)	Oceania n=42 (5)	South America n=37 (4)	Asia n=22 (2)	Africa n=6 (1)	Overall n=924
<i>Subject demographics</i>							
Age, months (n=913)	48 (9–120)	24 (9–102)	30 (12–108)	24 (10–84)	10 (3–48)	54 (12–60)	48 (9–120)
Weight, kg (n=915)	16 (7–35)	12 (7–25)	14 (9–31)	14 (8–27)	8 (4–15)	18 (10–18)	15 (7–31)
Female sex (n=918)	267 (41)	73 (47)	16 (40)	10 (27)	12 (55)	2 (33)	380 (41)
<i>Race/Ethnicity (n=850)</i>							
Caucasian, not-Hispanic	309 (50)	83 (65)	29 (76)	11 (30)	0 (0)	1 (17)	434 (51)
Caucasian, Hispanic	110 (18)	15 (12)	0 (0)	20 (54)	0 (0)	0 (0)	145 (17)
Black	116 (19)	9 (7)	0 (0)	1 (3)	0 (0)	2 (33)	128 (15)
Asian	27 (4)	10 (8)	3 (8)	0 (0)	19 (86)	0 (0)	59 (7)
Other	57 (9)	10 (8)	6 (16)	5 (14)	3 (14)	3 (50)	84 (10)
<i>Health Insurance (n=875)</i>							
Public	263 (42)	24 (16)	20 (50)	2 (5)	0 (0)	0 (0)	309 (35)
Private	239 (38)	3 (2)	4 (10)	10 (27)	4 (18)	1 (17)	261 (30)
Universal coverage	88 (14)	110 (75)	16 (40)	17 (46)	3 (14)	0 (0)	234 (27)
Self-pay	7 (1)	0 (0)	0 (0)	1 (3)	8 (36)	0 (0)	16 (2)
No insurance	12 (2)	1 (1)	0 (0)	7 (19)	7 (32)	5 (83)	32 (4)
Other	15 (2)	8 (5)	0 (0)	0 (0)	0 (0)	0 (0)	23 (3)
<i>Pre-hospital and admission data</i>							
<i>Scene and Interfacility transport (n=884)</i>							
Emergency medical system	159 (25)	48 (31)	8 (20)	13 (36)	5 (23)	4 (67)	237 (27)
Specialized pediatric team	237 (38)	59 (38)	18 (45)	14 (39)	3 (14)	0 (0)	331 (37)
Physician on transport	100 (17)	96 (62)	21 (54)	25 (69)	4 (18)	0 (0)	246 (29)
<i>Source of ICU admission (n=918)</i>							
Transfer from outside study hospital	238 (36)	62 (40)	16 (40)	10 (27)	2 (9)	1 (17)	329 (36)

Median (interquartile range) or n (%) (n) denotes number of subjects with data per query	North America n=661 (72) subjects	Europe n=156 (17)	Oceania n=42 (5)	South America n=37 (4)	Asia n=22 (2)	Africa n=6 (1)	Overall n=924
Emergency department	226 (34)	33 (21)	12 (30)	13 (35)	12 (55)	4 (67)	300 (33)
Ward	84 (13)	32 (21)	6 (15)	8 (22)	5 (23)	0 (0)	136 (15)
Operating room	93 (14)	22 (14)	5 (13)	6 (16)	3 (14)	1 (17)	129 (14)
Other	17 (3)	6 (4)	1 (3)	0 (0)	0 (0)	0 (0)	24 (3)
Admission Category (n=918)							
Medical	383 (58)	96 (62)	23 (58)	23 (62)	19 (86)	4 (67)	548 (60)
Trauma	120 (18)	29 (19)	7 (18)	6 (16)	1 (5)	1 (17)	164 (18)
Surgical, scheduled	104 (16)	14 (9)	4 (10)	1 (3)	1 (5)	0 (0)	124 (14)
Surgical, unscheduled	51 (8)	16 (10)	5 (15)	7 (19)	1 (5)	1 (17)	82 (9)
Co-morbid Conditions (any)	405 (62)	78 (50)	22 (52)	19 (51)	10 (45)	1 (17)	538 (58)
Seizure disorder (n=802)	132 (23)	13 (9)	5 (13)	7 (23)	3 (14)	0 (0)	160 (20)
Static encephalopathy (n=793)	52 (9)	9 (6)	4 (11)	6 (21)	1 (5)	0 (0)	72 (9)
Neurological – other (n=763)	118 (22)	21 (15)	4 (11)	1 (4)	2 (10)	1 (25)	147 (19)
Congenital heart disease (n=853)	127 (21)	25 (17)	5 (13)	3 (11)	4 (19)	1 (17)	165 (19)
Acquired heart disease (n=729)	38 (7)	11 (9)	2 (5)	1 (4)	0 (0)	0 (0)	52 (7)
Chronic pulmonary disease (n=848)	90 (15)	11 (7)	3 (8)	4 (13)	0 (0)	1 (17)	109 (13)
Chronic ventilatory support (n=721)	58 (11)	6 (5)	2 (6)	5 (18)	3 (17)	0 (0)	74 (10)
Prematurity (n=818)	87 (15)	17 (11)	4 (10)	3 (10)	0 (0)	0 (0)	111 (14)
Congenital syndrome (n=785)	63 (11)	13 (9)	3 (8)	2 (7)	1 (5)	0 (0)	82 (10)
Oncologic disease (n=911)	49 (7)	9 (6)	1 (2)	5 (14)	1 (5)	0 (0)	65 (7)
Transplant (n=338)	16 (7)	2 (4)	2 (3)	0 (0)	0 (0)	0 (0)	20 (6)
Other (n=911)	95 (15)	16 (11)	4 (10)	3 (8)	2 (10)	1 (17)	121 (13)

ICU, intensive care unit

Table 3

Frequency, risk of mortality, and outcome by type of acute neurologic insult.¹

Median (interquartile range) or n (%) (n) denotes number of subjects with data per query	Cardiac arrest n=215 (23) subjects	Traumatic brain injury n=171 (19)	Status epilepticus n=157 (17)	CNS infection /inflammation n=144 (16)	Stroke n=86 (9)	Brain mass n=81 (9)	Hydrocephalus n=42 (5)	Spinal cord injury n=28 (3)	Overall n=924 ¹	p-value ²
PIM 2 (n=918)	6.6 (2.4–20.6)	3.1 (1.1–4.9)	3.3 (1.3–5.3)	2.2 (0.9–4.3)	4.1 (1.2–11.4)	1.0 (0.4–2.8)	1.3 (1.1–3.9)	3.2 (0.9–4.2)	3.2 (1.1–6.4)	<0.001
Hospital LOS, d (n=809)	48 (19–95)	16 (7–33)	13 (4–42)	29 (12–54)	30 (13–75)	10 (5–31)	12 (3–37)	34 (10–77)	22 (8–55)	<0.001
ICU LOS, d (n=826)	33 (12–70)	9 (4–19)	8 (2–28)	13 (6–32)	16 (5–42)	6 (2–14)	7 (2–18)	21 (11–33)	13 (4–33)	<0.001
Mortality ³ (n=876)	50 (24)	15 (9)	15 (10)	13 (9)	10 (13)	1 (1)	0 (0)	1 (4)	105 (12)	<0.001
Unfavorable outcome ³ (n=772)	72 (43)	70 (49)	30 (21)	39 (32)	21 (33)	10 (13)	1 (3)	5 (21)	248 (32)	<0.001
PCPC Pre-insult										n/a
1	106 (54)	121 (82)	60 (41)	97 (73)	49 (64)	51 (66)	10 (28)	17 (65)	511 (61)	
2	34 (17)	10 (7)	21 (14)	18 (14)	11 (14)	18 (23)	9 (25)	2 (8)	123 (15)	
3	26 (13)	4 (3)	22 (15)	11 (8)	6 (8)	7 (9)	9 (25)	3 (12)	88 (11)	
4	22 (11)	9 (6)	41 (28)	6 (5)	8 (11)	1 (3)	8 (22)	3 (12)	98 (12)	
5	8 (4)	4 (3)	2 (1)	1 (1)	2 (3)	0 (0)	0 (0)	1 (4)	18 (2)	
PCPC HD/3 mo										n/a
1	30 (17)	37 (25)	34 (24)	50 (40)	17 (26)	36 (47)	8 (22)	11 (46)	223 (28)	
2	35 (20)	30 (20)	20 (14)	24 (19)	17 (26)	21 (28)	9 (25)	2 (8)	158 (20)	
3	24 (14)	27 (18)	23 (16)	12 (10)	13 (20)	12 (16)	12 (33)	5 (21)	128 (16)	
4	23 (13)	35 (23)	44 (31)	21 (17)	7 (11)	5 (7)	7 (19)	5 (21)	147 (19)	
5	11 (6)	5 (3)	4 (3)	4 (3)	2 (3)	1 (1)	0 (0)	0 (0)	27 (3)	
6	50 (29)	15 (10)	15 (11)	13 (10)	10 (15)	1 (1)	0 (0)	1 (4)	105 (13)	
Change in PCPC pre-insult to HD/3 mo										n/a

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Median (interquartile range) or n (%) (n) denotes number of subjects with data per query	Cardiac arrest n=215 (23) subjects	Traumatic brain injury n=171 (19)	Status epilepticus n=157 (17)	CNS infection /inflammation n=144 (16)	Stroke n=86 (9)	Brain mass n=81 (9)	Hydrocephalus n=42 (5)	Spinal cord injury n=28 (3)	Overall n=924†	p-value ²
-4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	1 (0)	
-3	4 (2)	2 (1)	1 (1)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	8 (1)	
-2	2 (1)	3 (2)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	7 (1)	
-1	5 (3)	2 (1)	4 (3)	4 (3)	1 (2)	1 (1)	2 (6)	1 (4)	20 (3)	
0	52 (31)	46 (32)	90 (64)	60 (49)	28 (44)	53 (71)	29 (85)	13 (54)	371 (48)	
+1	33 (20)	21 (15)	15 (11)	19 (15)	13 (20)	10 (13)	2 (6)	4 (17)	117 (15)	
+2	20 (12)	28 (19)	11 (8)	12 (10)	12 (19)	5 (7)	1 (3)	3 (13)	92 (12)	
+3	15 (9)	29 (20)	8 (6)	16 (13)	2 (3)	4 (5)	0 (0)	2 (8)	76 (10)	
+4	16 (10)	4 (3)	7 (5)	6 (5)	3 (5)	1 (1)	0 (0)	0 (0)	37 (5)	
+5	21 (13)	9 (6)	4 (3)	5 (4)	4 (6)	0 (0)	0 (0)	0 (0)	43 (6)	
Feeding tube (n=884)	59 (30)	35 (23)	32 (22)	22 (16)	17 (24)	9 (11)	3 (8)	7 (25)	184 (22)	0.006
CSF Shunt (n=308)	3 (4)	9 (19)	0 (0)	5 (12)	5 (20)	16 (37)	14 (64)	4 (29)	56 (18)	<0.001
Hypertonia (n=845)	45 (23)	32 (21)	15 (10)	16 (12)	15 (21)	8 (10)	5 (14)	5 (18)	141 (17)	0.014
Tracheostomy tube (n=847)	42 (21)	24 (16)	14 (10)	12 (9)	6 (8)	8 (10)	4 (11)	9 (33)	119 (14)	<0.001
Dysautonomia (n=847)	17 (9)	15 (10)	8 (5)	11 (8)	6 (8)	3 (4)	0 (0)	7 (25)	67 (8)	0.011
Hospital disposition among survivors (n=819)										0.006
Home	77 (63)	77 (58)	95 (77)	79 (72)	36 (64)	60 (80)	26 (74)	12 (52)	462 (68)	
Inpatient rehabilitation	22 (18)	39 (30)	13 (11)	21 (19)	12 (21)	9 (12)	5 (14)	8 (35)	129 (19)	
Skilled nursing facility	7 (6)	6 (5)	10 (8)	6 (5)	3 (5)	0 (0)	1 (3)	1 (4)	34 (5)	
Other	16 (13)	10 (8)	5 (4)	4 (4)	5 (9)	6 (8)	3 (9)	2 (9)	51 (8)	

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IQR, interquartile range; CNS, central nervous system; PIM2, Pediatric Index of Mortality; HD, hospital discharge; NA, not applicable; CSF, cerebrospinal fluid; PCPC, Pediatric Cerebral Performance Category

Outcomes occurred at hospital discharge or 3 months after the study date, whichever came first.

¹See Supplementary Data for definitions

²Clinical variables and outcomes were compared among the 8 acute neurologic insult categories

Table 4

Regional analysis.

Median (interquartile range) or n (%)	North America n=661 (72 subjects)	Europe n=156 (17)	Oceania n=42 (5)	South America n=37 (4)	Asia n=22 (2)	Africa n=6 (1)	Overall n=924
Prevalence (95% CI) [/]	18.0 (16.7,19.3)	12.7 (10.7,14.8)	13.9 (9.4,19.6)	13.5 (9.0,19.2)	9.8 (6.1,14.7)	15.8 (6.0,31.3)	16.2 (15.2,17.2)
Insult							
Cardiac arrest	155 (23)	38 (24)	10 (24)	6 (16)	6 (27)	0 (0)	215 (23)
Traumatic brain injury	120 (18)	34 (22)	7 (17)	7 (19)	2 (9)	1 (17)	171 (19)
Status epilepticus	113 (17)	26 (17)	8 (19)	6 (16)	4 (18)	0 (0)	157 (17)
CNS infection/ inflammation	96 (15)	21 (13)	8 (19)	8 (22)	8 (36)	3 (50)	144 (16)
Brain mass	64 (10)	9 (6)	1 (2)	5 (14)	1 (5)	1 (17)	81 (9)
Stroke	60 (9)	17 (11)	6 (14)	2 (5)	1 (5)	0 (0)	86 (9)
Hydrocephalus	30 (5)	7 (4)	2 (5)	3 (8)	0 (0)	0 (0)	42 (5)
Spinal cord injury	23 (3)	4 (3)	0 (0)	0 (0)	0 (0)	1 (17)	28 (3)
Risk of Mortality and Outcomes							
PIM2	3.1 (1.1–6.1)	3.6 (1.3–7.7)	5.6 (3.3–13.5)	1.9 (0.8–4.0)	1.8 (0.8–4.0)	3.2 (0.9–3.9)	3.2 (1.1–6.4)
Hospital LOS, d	21 (8–54)	30 (11–75)	23 (9–65)	27 (8–57)	19 (9–22)	50 (38–63)	22 (8–55)
ICU LOS, d	13 (4–33)	13 (5–40)	8 (4–23)	15 (2–26)	11 (5–20)	27 (11–42)	13 (4–33)
Mortality	75 (12)	20 (14)	4 (10)	4 (13)	2 (11)	0 (0)	105 (12)
Unfavorable outcome	184 (32)	49 (40)	7 (22)	5 (22)	0 (0)	3 (50)	248 (32)

[/] Prevalence based on screening data from 97 sites

ICU, intensive care unit; CNS, central nervous system; PIM2, Pediatric Index of Mortality 2; LOS, length of stay; CI, confidence interval