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ORIGINAL ARTICLE

Risk Factors Associated with Infections and Need for Permanent Cerebrospinal Fluid Diversion in Pediatric Intensive Care Patients with Externalized Ventricular Drains

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Abstract
Background Externalized ventricular drains (EVDs) are commonly used in pediatric intensive care units (PICU) but few data are available regarding infection rates, infection risks, or factors associated with conversion to permanent cerebrospinal fluid (CSF) diversion.
Methods Retrospective observational study of patients managed with EVDs admitted to a tertiary care PICU from January 2005 to December 2009.
Results Three hundred eighty patients were identified. Neurologic diagnostic groups were externalization of existing shunt in 196 patients (52 %), brain tumor in 122 patients (32 %), intracranial hemorrhage in 23 patients (6 %), traumatic brain injury in 17 patients (5 %), meningitis in 9 patients (2 %), or other in 13 patients (3 %). Six percent of all patients (24/380) had new infections associated with EVD management for an infection rate of 8.6 per 1,000 catheter days. The median time to positive cultures was 7 days (interquartile range 4.75, 9) after EVD placement. Patients with EVD infections had significantly longer EVD duration 6 versus 11.5 days ($p = 0.0001$), and higher maximum EVD outputs 1.9 versus 1.5 mL/kg/h ($p = 0.0017$). Need for permanent CSF diversion was associated with higher maximum EVD drainage (1.3 vs. 1.6 mL/kg/h $p < 0.0001$), longer EVD duration (5 vs. 4 days, $p < 0.005$), and younger age (4.5 vs. 8 years, $p < 0.02$) but not intracranial hypertension (72 vs. 82 % of patients, $p = 0.4$).
Conclusions In our large pediatric cohort, EVD infections were associated with longer EVD duration and higher maximum EVD output. Permanent CSF diversion was more likely in patients with higher maximum EVD drainage, longer EVD duration, and younger age.

Keywords Externalized ventricular drain · Ventricular catheter infection · Pediatric intensive care unit · Neurocritical care · Ventriculoperitoneal shunt · Pediatric

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Introduction

Neurosurgical patients represent a large percentage of patients treated in pediatric intensive care units (PICU) [1]. Externalized ventricular drains (EVD) are commonly used in children with increased intracranial pressure or who require cerebrospinal fluid (CSF) diversion. However, EVDs must be monitored closely due to infection risk [2, 3]. Infection rates in adult neurosurgical intensive care units have ranged between 0 and 45 % [2, 4–6]. Few studies of EVD utilization and infections in children have been conducted, and their sample sizes have been relatively small [3, 7].

With increasing interest in the development of pediatric neurocritical care programs, recent studies have better characterized the pediatric neurocritical care population [1, 8]. Children with EVDs represent a substantial portion of this population and delineation of patient characteristics, risk factors associated with EVD infections and the need for permanent CSF diversion can be utilized to develop future intervention studies on improving EVD management in the pediatric population. Using a large retrospective cohort from a single quaternary care PICU, we aimed to describe the utilization and infection rates of EVDs, determine risk factors associated with EVD infections, and determine risk factors for conversion to permanent CSF diversion.

Patients and Methods

Design

We conducted a retrospective observational study in patients with EVDs admitted to the PICU at The Children's Hospital of Philadelphia between January 1, 2005 and December 31, 2009. The study was approved by the hospital Institutional Review Board and the requirement for informed consent was waived.

Patients were identified by searching the physician order entry database for EVD orders. Inclusion criteria included admission to the PICU and the presence of an EVD or externalized ventricular shunt. During the dates evaluated, no patients were managed with an antimicrobial-impregnated catheter. The medical records of eligible patients were examined. Variables collected included baseline demographics (age, gender, race, and weight), ventriculostomy indication, history of seizures, admission electrolytes, presence of intracranial pressure monitoring, number of days ventriculostomy was present, ventriculostomy disposition, and survival to hospital discharge. Positive CSF cultures obtained at time of EVD placement or externalization of ventriculoperitoneal shunt were not included in overall infection rate. Subsequent positive cultures from patients with previous VPS were included in the overall infection rate only if the CSF cultures were negative or the organism identified on subsequent cultures was different than the initial culture. Daily values were recorded for up to the first 14 days of ventriculostomy drain management which included ventriculostomy output and use of systemic antibiotics. During the study period, there was no standardized protocol for EVD management. For patients with documented infections, sampling was performed by the pediatric neurosurgical team every 48 h.

Study data were collected and managed using REDCAP electronic data capture tools hosted at The Children's Hospital of Philadelphia [9]. Continuous variables are presented as medians [IQR25, 75] and categorical variables as numbers and proportions. Univariate analysis was performed using Wilcoxon rank sum for continuous data or Chi squared or Fishers exact test for proportions. All statistics were performed using Stata 10 (College Station, TX).

Results

Three hundred eighty patients were evaluated. Neurologic diagnostic groups for EVD placement were externalization of existing shunt (EXSHUNT) in 196 patients (52 %), brain tumor in 122 patients (32 %), intracranial hemorrhage (ICH) in 23 patients (6 %), traumatic brain injury (TBI) in 17 patients (5 %), meningitis in 9 patients (2 %), or other in 13 patients (3 %). There was no difference in age or sex among neurologic diagnostic groups (Table 1). ICH, TBI, and meningitis had the highest rates of intracranial pressure (ICP) monitoring and intracranial hypertension (ICP $>$ 20 mmHg) (Table 1). Patients with EXSHUNT more commonly had a pre-existing seizure disorder. EVD duration differed significantly between groups: EXSHUNT, ICH, and TBI having the longest durations and tumor having the shortest. EXSHUNT, ICH, and TBI had the highest maximum EVD drain output (Table 1).

One hundred forty-seven patients had CSF cultures obtained on EVD insertion. Ninety percent (133) were for EXSHUNT (Table 2). Sixty-seven (46 %) of cultures sent on EVD insertion were positive and all positive cultures were from the EXSHUNT group. The most common organisms isolated were *Staphylococcus aureus* (39 %) and coagulase negative staphylococcus (34 %) (Table 3). Forty-six percent (67/133) of EXSHUNT group had a positive culture on externalization of the shunt. Six percent (4/67) of patients in the EXSHUNT group who had positive cultures on externalization developed subsequent positive cultures with a different organism and were included in statistical analysis of infection rates and associated risk factors. Ninety-four percent of all patients in the study received at least 24 h of parenteral antibiotics while an EVD was in place.

Table 1 Association of variables with neurologic diagnostic group

	Total $n = 380$	EXSHUNT $n = 196$ (52)	Tumor $n = 122$ (32)	ICH $n = 23$ (6)	TBI $n = 17$ (5)	Meningitis $n = 9$ (2)	Other $n = 13$ (3)	p value
Age (years)		5.2 [1.7, 14]	6.7 [2.2, 12.5]	9.7 [6.4, 14.7]	10.3 [2.6, 14.6]	2.8 [0.7, 8]	11.4 [3.6, 15]	0.29
Sex								
Male	169 (44)	89 (45)	51 (42)	12 (52)	9 (53)	2 (22)	6 (46)	0.66
Female	211 (56)	107 (55)	71 (58)	11 (48)	8 (47)	7 (78)	7 (54)	
Weight (kg)	20.5 [12,50]	17 [10.5, 48.5]	23.5 [13, 50]	44 [18, 55]	31 [15, 70]	14.2 [11, 25]	37 [19.4, 41.8]	0.099
Seizure disorder	73 (19)	56 (29)	12 (10)	2 (9)	0 (0)	0 (0)	3 (23)	<0.001
Maximum daily EVD output (mL)	279 [168, 374]	309 [205, 389]	224 [80, 335]	294 [234, 383]	299 [241, 389]	215 [170, 373]	218 [85, 345]	<0.001
ICP monitored	164 (43)	20 (10)	89 (73)	22 (96)	17 (100)	8 (89)	8 (62)	<0.001
ICP > 20 mmHg	55 (14)	2 (10)	24 (27)	11 (50)	14 (82)	3 (38)	1 (13)	<0.001
EVD duration (days)	6 [4, 10]	8 [5, 12]	4 [3, 6]	8 [4,11]	8 [7,11]	5 [4, 11]	4 [3,5]	<0.001
Mortality	19 (5)	8 (4)	5 (4)	3 (13)	0 (0)	2 (22)	1 (8)	0.07

EVD externalized ventriculostomy drain, *PICU* pediatric intensive care unit, *TBI* traumatic brain injury, *ICH* spontaneous intracranial hemorrhage, *EXSHUNT* externalization of ventriculoperitoneal shunt, *ICP* intracranial pressure, *CSF* cerebrospinal fluid

Table 2 Cerebrospinal fluid cultures by neurologic diagnostic group

	All	EXSHUNT	Tumor	ICH	TBI	Meningitis	Other	p value
Culture sent on EVD insertion	147	133	3	1	0	7	3	<0.001
EVD insertion culture positive	67	67	0	0	0	0	0	
Subsequent positive culture	24	15	4	1	3	1	0	0.145
Infection rate (per 1,000 catheter days)	8.6	8.6	6.9	4.9	21	14	0	0.387

EXSHUNT was classified as having a subsequent positive culture only if initial CSF culture on EVD insertion or shunt externalization was negative or the organism identified on subsequent cultures was different than the organism identified on initial culture

EVD externalized ventricular drain, *EXSHUNT* externalization of previous ventriculoperitoneal shunt, *ICH* spontaneous intracranial hemorrhage, *TBI* traumatic brain injury

Table 3 Initial positive cultures

All	67 (100)
Staphylococcus aureus	26 (39)
Staphylococcus coagulase negative	23 (34)
Propionibacterium	5 (7)
Pseudomonas	2 (3)
Streptococcus mitis	2 (3)
E. coli	2 (3)
Streptococcus pneumoniae	1 (1)
Neisseria meningititidis	1 (1)
Klebsiella	1 (1)
Morganella morganii	1 (1)
Enterococcus	1 (1)
Listeria	1 (1)
Corynebacterium	1 (1)

Six percent of all patients (24/380) had subsequent new infections with an infection rate of 8.6 per 1,000 catheter days. The median time for subsequent new positive cultures was 7 days [4.5, 9], and 88 % of infections occurred within the first 10 days of management with an EVD (Fig. 1). The most common organism isolated was coagulase negative staphylococcus (50 %) (Table 4). There was no difference in infection rates between neurologic diagnostic groups (Table 2). Patients with positive CSF cultures after EVD placement had significantly longer EVD days and higher maximum EVD outputs compared to patients without positive cultures (Table 5).

Overall mortality rate prior to hospital discharge was 5 % (19/380). Patients with meningitis had the highest mortality at 22 % (2/9) (Table 1). Eleven patients died with an EVD in place. Excluding the EXSHUNT group, twenty-nine percent (54/184) of patients had an internalized shunt placed prior to discharge. Thirty-five percent (43/122) of tumor patients required shunt placement prior to discharge. Endoscopic third ventriculostomy without shunt placement was rarely performed 1 % (4/380). Shunt placement was associated with higher maximum EVD drainage, longer EVD duration, and younger age (Table 6). Monitoring of ICP and episodes of ICP > 20 mmHg were not associated with the need for permanent CSF diversion.

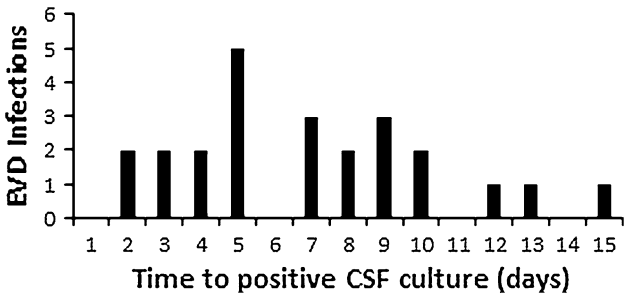

Fig. 1 Externalized ventriculostomy drain (EVD), cerebrospinal fluid (CSF)

Table 4 Subsequent positive cultures

All	24 (100)
Staphylococcus coagulase negative	12 (50)
Staphylococcus aureus	4 (17)
Propionibacterium	2 (8)
E. coli	1 (4)
Streptococcus mitis	1 (4)
Bacillus	1 (4)
Enterococcus	1 (4)
Enterobacter	1 (4)
H. influenza	1 (4)

Table 5 Characteristics associated with infection

	No positive culture $n = 356$	Positive culture $n = 24$	p value
Age	6.6 [2, 13.9]	5.1 [2.3, 14]	0.99
ICP monitoring	156 (43)	8 (33)	0.396
ICP > 20 mmHg	50 (32)	5 (21)	0.12
Maximum EVD output (mL/kg/h)	1.5 [0.93, 1.9]	1.9 [1.5, 2.6]	0.0017
Shunt placement	225 (63)	17 (71)	0.517
Mortality	19 (5.3)	0 (0)	0.621
EVD duration (days)	6 [4,9]	11.5 [8,15]	0.0001

Patients with positive cultures on initial insertion or externalization were classified in the positive culture group only if the organism identified on subsequent cultures was different than the organism identified on initial culture

EVD externalized ventricular drain, *ICP* intracranial pressure

Discussion

Of 380 children managed with EVDs in our PICU, EVD infections were uncommon with 6 % of patients developing a positive culture during EVD management, resulting in an infection rate of 8.6 per 1,000 catheter days. Higher CSF output and longer duration of EVD were risk factors associated with EVD infections. Excluding patients with existing shunts, 30 % of patients had an internalized shunt placed prior to discharge with higher CSF output, longer duration of EVD management, younger age, and neoplasm associated with an increased risk for permanent CSF diversion. Interestingly, intracranial hypertension was not a risk factor for EVD infections or permanent CSF diversion in our pediatric patient population.

Table 6 Characteristics associated with permanent CSF diversion

	No $n = 130$	Yes $n = 54$	p value
Age (years)	8 [2.7, 14.1]	4.5 [1.2, 12.1]	<0.02
Maximum 24 h EVD output (mL/kg/h)	1.3 [0.6, 1.8]	1.6 [1.1, 2.1]	<0.001
Diagnostic group			
Tumor	79 (61)	43 (80)	0.18
ICH	19 (15)	4 (7)	
TBI	15 (11)	2 (4)	
Meningitis	7 (5)	2 (4)	
Other	10 (8)	3 (5)	
EVD days	4 [3, 6]	5 [4, 8]	<0.005
ICP monitored	105 (81)	30 (72)	0.2
ICP > 20	41 (39)	12 (31)	0.4
Mortality	11 (8)	0 (0)	<0.01

CSF cerebrospinal fluid, *EVD* externalized ventricular drain, *ICP* intracranial pressure, *TBI* traumatic brain injury, *ICH* intracranial hemorrhage

The 8.6 per 1,000 catheter day infection rate is lower than that reported for adults with standard non-antimicrobial-impregnated catheters. A recent meta-analysis of antimicrobial-impregnated catheters in adults observed an overall infection rate of 13.7 % in standard catheters. In our cohort, intracranial pressure >20 mmHg was not a risk factor for EVD infection, but has been reported as a risk factor in adult patients [6]. Patients with TBI and meningitis had the highest incidence of EVD infection but this difference did not reach statistical significance, potentially related to the small number of patients in each of these neurologic diagnosis subgroups. Longer EVD durations and higher maximum EVD output were the only risk factors associated with EVD infections (Table 6). Previous studies have reported conflicting results regarding EVD duration as a risk factor for EVD infection [3, 6, 7, 10, 11]. Similar to several other studies, the majority of EVD infections (88 %) in our cohort were observed in the first 10 days after EVD placement (Fig. 1). The majority of patients with EXSHUNT (63/67, 94 %) with initial positive cultures did not have subsequent positive culture with a different organism and were classified as no infection for analysis. Typically, these patients would have relatively longer EVD durations, but we still observed a strong association between EVD duration and subsequent positive

cultures in our EVD patient population. Clinicians may want to consider evaluating for infection when encountering patients with larger than expected EVD outputs.

Use of systemic prophylactic antibiotics to prevent EVD infections is controversial with conflicting results reported in previous studies [12–15]. The majority of the patients (94 %) in this study received at least 24 h of prophylactic antibiotics and all patients who developed subsequent EVD infections had received at least 24 h of systemic antibiotic prophylaxis prior to positive cultures. Due to the variability of systemic antibiotic duration and choice of antibiotics in this cohort, it is difficult to draw any conclusions on the efficacy of antibiotic prophylaxis. Antimicrobial-impregnated catheters have recently demonstrated efficacy in preventing EVD-associated infections [16, 17]. Studies of antimicrobial-impregnated ventricular catheters in the pediatric population are lacking and were not in use at our institution during the study period.

Intracranial pressure was measured in all diagnostic groups excluding EXSHUNT, 78 % (144/184). Episodes of intracranial hypertension were observed in 14 % of all patients and most commonly found in patients with TBI or ICH, but these patients were least likely to require permanent CSF diversion. There is a paucity of data on conversion rates and the risk factors associated with need for permanent CSF diversion in pediatric patients with EVDs. A recent retrospective study of 180 pediatrics patients over a 20-year period reported a conversion rate of 25 % to permanent CSF diversion, which varied by diagnosis with TBI having the lowest rate [18]. Excluding the EXSHUNT group, we observed a similar conversion rate of 30 % (56/184) with the TBI group having the lowest conversion rate (12 %) in our similar sized but more contemporary cohort.

We identified several factors that were associated with the need for permanent CSF diversion. Patients requiring permanent CSF diversion were younger, had a higher maximum EVD output, and a longer EVD duration. In a recent study, pediatric patients with neoplasm were also more likely to require a shunt with a 40 % conversion to VPS which is similar to our observed rate of 35 % for tumor patients [18]. Interestingly, intracranial hypertension was not associated with the need for permanent CSF diversion in our pediatric population, which is in contrast to adult patients [19, 20]. Patients in our pediatric cohort with ICH or TBI had lower conversion rates as well as shorter durations of EVD placement compared to reported conversion rates of 21–28 % in adults [19, 20]. Our data highlight some of the unique responses of the pediatric brain compared to the adult brain. To the best of our knowledge, this is the first adult or pediatric study to report an association between maximum EVD drain output and need for permanent CSF diversion.

There are several limitations to our study that must be considered when attempting to generalize our findings. This retrospective study was limited to one large quaternary PICU where clinical practice such as criteria for transfer to the regular inpatient care setting may vary compared to other similar institutions. All patients in this study remained in the ICU during the duration of their EVD management, undergoing daily rounds with the critical care team and daily discussions with the neurosurgical team, which may have contributed to the relatively low infection rate in our report. However, this practice was also a strength in our study, as we were able to fully collect daily data for up to the first 14 days of EVD placement. The distribution of patients by neurologic diagnostic group was heavily weighted to externalization of previous VPS or brain tumors, with smaller numbers of patients with TBI or ICH. Our experience may not be representative of infection and CSF diversion rates at other institutions with different neurocritical patient populations [3, 18]. The TBI patient population in our study was relatively small compared to the EXSHUNT and tumor groups, and is not representative of the total TBI population. This is in part due to the fact that a large portion of TBI patients during the study period were not managed with an EVD. Eleven percent of TBI patients in our cohort underwent conversion to permanent CSF diversion, a higher proportion than has been previously reported [18]. However, our TBI cohort represents a distinct population as we observed a 0 % mortality in the TBI patients managed with EVDs. Furthermore, it has been previously reported that continuous versus intermittent drainage can alter EVD output, intracranial pressure, as well as CSF biomarkers in patients suffering from traumatic brain injury [21]. EVD management was clinician dependent in our small retrospective TBI cohort which precludes any conclusions about the impact of continuous versus intermittent drainage on EVD output, need for permanent CSF diversion, or infection rates. In the newly funded comparative effectiveness trial in pediatric TBI, CSF diversion is one of the modalities that will be specifically examined to get further insight to optimize care for these patients [22]. Finally, antibiotic prophylaxis after EVD placement was administered in the majority of our patients, but the variation in antibiotic choice and the duration of antibiotic prophylaxis in our study population limited any conclusions about its efficacy.

Conclusion

In summary, to the best of our knowledge this is the largest cohort of pediatric patients with EVDs assessing EVD utilization and risk factors for infection and need for permanent CSF diversion. Positive CSF cultures during EVD management were uncommon, with a 6 % incidence in our cohort. Higher maximum drain output was found to be

associated with EVD infections. Clinicians should consider infectious etiologies for unexplained high-volume draining EVDs in pediatric patients. Permanent CSF diversion was more likely in patients with higher maximum EVD drain output, younger age, and longer EVD duration but not in patients with intracranial hypertension during their hospitalization. Future prospective studies using a comparative effectiveness approach may be able to establish whether varying infection prevention and management strategies impact outcome and whether varying practices regarding permanent CSF diversion impact long-term outcome.

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Conflict of interest Alexis A Topjian, Amber Stuart, Alyssa A. Pabalan, Ashleigh Clair, Todd J. Kilbaugh, Nicholas S. Abend, Robert A. Berg, Gregory G. Heuer, Phillip B. Storm Jr., Jimmy W. Huh, and Stuart H. Friess declare that they have no conflict of interest.

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