Risk Factors for First Cerebrospinal Fluid Shunt Infection: Findings from a Multi-Center Prospective Cohort Study

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Objective To quantify the extent to which cerebrospinal fluid (CSF) shunt revisions are associated with increased risk of CSF shunt infection, after adjusting for patient factors that may contribute to infection risk.

Study design We used the Hydrocephalus Clinical Research Network registry to assemble a large prospective 6-center cohort of 1036 children undergoing initial CSF shunt placement between April 2008 and January 2012. The primary outcome of interest was first CSF shunt infection. Data for initial CSF shunt placement and all subsequent CSF shunt revisions prior to first CSF shunt infection, where applicable, were obtained. The risk of first infection was estimated using a multivariable Cox proportional hazard model accounting for patient characteristics and CSF shunt revisions, and is reported using hazard ratios (HRs) with 95% CI.

Results Of the 102 children who developed first infection within 12 months of placement, 33 (32%) followed one or more CSF shunt revisions. Baseline factors independently associated with risk of first infection included: gastrostomy tube (HR 2.0, 95% CI, 1.1, 3.3), age 6-12 months (HR 0.3, 95% CI, 0.1, 0.8), and prior neurosurgery (HR 0.4, 95% CI, 0.2, 0.9). After controlling for baseline factors, infection risk was most significantly associated with the need for revision (1 revision vs none, HR 3.9, 95% CI, 2.2, 6.5; ≥2 revisions, HR 13.0, 95% CI, 6.5, 24.9).

Conclusions This study quantifies the elevated risk of infection associated with shunt revisions observed in clinical practice. To reduce risk of infection risk, further work should optimize revision procedures. *(J Pediatr 2014;164:1462-8)*.

Although placement of cerebrospinal fluid (CSF) shunts successfully treats hydrocephalus, it also frequently leads to new medical and surgical problems. CSF shunt failure is common and necessitates subsequent CSF shunt revision surgery.[1-3] CSF shunt infections are a substantial problem for children with hydrocephalus, their parents, and their caregivers. Infections number up to 2400 admissions and 59 000 hospital days each year in the US.[4] Despite aggressive treatment that typically involves 2 surgeries as well as a prolonged inpatient stay to receive intravenous antibiotics,[5] per patient reinfection rates are high at 20%-25%.[6,7]

Because of the high morbidity associated with CSF shunt infection, it is critical for families and care providers to understand whether certain children undergoing CSF shunt placement are at highest risk for subsequent infection. The association of both patient risk factors and factors at the time of initial CSF shunt placement with first CSF shunt infection is complicated when intervening CSF shunt revisions are required. In addition, risk of infection is not constant, declining with time following a revision.[8] Interval CSF shunt revision(s)[9] and previous infection[6,7,10] have been associated with increased odds of infection. However, the relative contribution of each intervening revision surgery, and its relationship to baseline risk of infection for a given child, was elucidated only recently in a study that assembled a large and detailed retrospective cohort of children at a single center undergoing initial CSF shunt placement. Young age

CSF	Cerebrospinal fluid
EVD	External ventricular drain
HCRN	Hydrocephalus Clinical Research Network
HR	Hazard ratio

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†List of additional members of the HCRN is available at www.jpeds.com (**Appendix**).

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and intervening revision procedures were found to be associated with infection risk, and underlying condition of myelomeningocele demonstrated a protective effect.[11] However, this study was limited by its retrospective design and conduct at a single center.[11]

The object of this study was to quantify the extent to which CSF shunt revision(s) are associated with increased risk of CSF shunt infection, after adjusting for patient factors that may contribute to infection risk, in a large current multicenter prospective cohort of patients undergoing initial CSF shunt placement. We also considered the surgeon as well as medical and surgical decisions at the time of last surgery (either initial shunt placement or revision surgery) as potential confounders.

Methods

The Hydrocephalus Clinical Research Network (HCRN) is a collaboration of pediatric neurosurgical centers conducting systematic investigations in the management of pediatric hydrocephalus.[12-14] The HCRN has maintained a registry with prospectively collected data about neurosurgical procedures at seven centers across North America that first started in 2008. The 7 hospitals contributing to the HCRN registry include Children's Hospital of Alabama and University of Alabama, Children's Hospital of Pittsburgh, Hospital for Sick Children, Primary Children's Medical Center, Seattle Children's Hospital, Texas Children's Hospital, and St. Louis Children's Hospital/Washington University; all except Children's Hospital of Pittsburgh contributed data to this study. The HCRN Data Coordinating Center is housed in Salt Lake City. Use of HCRN registry data was approved by the HCRN and the Institutional Review Boards at the University of Utah and Seattle Children's Hospital.

The HCRN enrolls all children less than 18 years of age in the network registry who receive care at any of the network hospitals and who undergo CSF shunt surgery. Data collection started in April 2008 and, for this study, ended for all procedures occurring on or before December 31, 2011. We assembled a final prospective cohort of 1036 children whose initial CSF shunt placement was recorded in the HCRN registry during the study period. All children in the cohort underwent initial CSF shunt placement, and additionally may have undergone CSF shunt revision(s) and/or infection prior to the end of the study period (**Figure 1**; available at www.jpeds.com).

Within the HCRN registry, data from each neurosurgical admission for each cohort member is collected prospectively. Each member was followed for infection until the end of study follow-up on December 31, 2011, and participants were censored prior to the end of follow-up in the event of death (n = 50), a move out of the network (n = 34), or shunt removal (n = 12). The date a child developed infection, died, moved, or had their CSF shunt removed was the date of censoring. If the date of death was not available (n = 5), we used day after last procedure in registry as censoring date. No patient withdrew consent during the follow-up period.

Primary Outcome Variable

First CSF shunt infection was defined by either microbiological determination of presence of bacteria in a culture or Gram stain of CSF, wound swab, and/or pseudocyst fluid or shunt erosion (visible hardware) or abdominal pseudocyst (even without positive culture). For children with ventriculoatrial shunts, presence of bacteria in a blood culture was diagnostic of infection. This definition of CSF shunt infection was previously developed by consensus among HCRN neurosurgeons.[11,12,15] The first CSF sample for diagnosis of infection usually was obtained from needle aspiration of the shunt reservoir under sterile conditions outside the operating room at a bedside "shunt tap," usually prior to the initiation of antibiotic treatment. In all other neurosurgical admissions that involved 2 CSF shunt surgeries (such as removal and external ventricular drain [EVD] placement followed by new shunt placement) as well as 48 hours or more of intravenous antibiotic treatment, author T.S. and the local research coordinator reviewed the case in detail to review whether cases met infection criteria.

Predictor Variable

The main predictor variable of interest was CSF shunt revision, defined as an operative neurosurgical interventional procedure performed on the CSF shunt. In cases where a staged revision was performed in 2 or more procedures (such as externalization of a shunt followed several days later by re-internalization), the staged revision was handled as a single event and tested as an independent risk factor for infection. The time period between staged procedures was considered noncontributory to infection risk, and details of medical and surgical decisions at the time of only the last neurosurgical procedure were considered in analyses. Any surgical procedure associated with infection treatment was considered the first CSF shunt infection rather than CSF shunt revisions for this study.

Potential Confounding Variables

Potential confounding factors included patient risk factors such as demographics, risk factors prior to initial CSF shunt placement, and risk factors at the time of CSF shunt placement as shown in **Table I** and **Figure 1**. Prior neurosurgeries included endoscopic third ventriculostomy and/or subgaleal and/or reservoir as determined by chart review; and complex chronic conditions were classified as previously described.[4]

In addition to revision procedures and patient factors, we also report the association of surgeon factors and medical and surgical decisions at preceding CSF shunt surgeries (initial CSF shunt placement and/or CSF shunt revision) with CSF shunt infection. Surgeon factors include attending surgeon factors (including surgeon, surgeon's experience defined as years since fellowship, surgeon's volume as number of initial CSF shunt placements per year) and resident surgeon factors (month of year reflecting their experience). Medical and surgical decisions we considered are those

Table I. Characteristics of the study cohort

	Prospective cohort (n = 1036)
Demographics	
Sex, n (%)	
Male	582 (56%)
Female	454 (44%)
Race, n (%)	
White	655 (63%)
Other/unknown	199 (19%)
African American	152 (15%)
Asian	20 (2%)
AI/AN/NH/PI	10 (1%)
Insurance status, n (%)	
Public (Medicaid, Medicare)	423 (41%)
Private	409 (39%)
Self-pay	36 (4%)
Other (eg, military)	21 (2%)
Government	147 (14%)
Risk factors prior to initial surgery	
Birth weight (kg),* median (IQR)	3.0 (1.6, 3.4)
Gestational age (wk),* median (IQR)	37 (31, 40)
Length of hospitalization preceding initial shunt placement (d),* median (IQR)	2 (0, 14)
Prior neurosurgery, n (%)	131 (13%)
Risk factors at initial CSF placement	
Chronologic age, n (%)	
0 to <6 mo	577 (56%)
6 to <12 mo	110 (11%)
1 to <2 y	71 (7%)
2 to <9 y	165 (16%)
9-18 y	113 (11%)
Indication for shunt placement, n (%)	
Post-IVH due to prematurity	226 (22%)
Myelomeningocele	164 (16%)
Posterior fossa tumor	109 (11%)
Aqueductal stenosis	84 (8%)
Communicating congenital	80 (8%)
Supratentorial tumor	67 (6%)
Posthead injury	49 (5%)
Other intracranial cyst	44 (4%)
Posterior fossa cyst	40 (4%)
Spontaneous ICH/IVH/SAH	39 (4%)
Post-infectious	38 (4%)
Other	34 (3%)
Other congenital	20 (2%)
Midbrain tumor/lesion	16 (2%)
Encephalocele	15 (1%)
Craniosynostosis	11 (1%)
Weight at surgery (kg), median (IQR)	6.0 (3.3, 13.4)
CCCs, n (%)	
None (excepting hydrocephalus)	727 (70%)
One	247 (24%)
Two or more	62 (6%)
Gastrostomy, n (%)	100 (10%)
Tracheostomy, n (%)	29 (3%)
CSF shunt procedure(s) within 12 mo, n (%)	
One CSF shunt revision	166 (16%)
Two or more CSF shunt revisions	99 (10%)
CSF shunt infection	102 (10%)

AI/AN/NH/PI, American Indian/Alaska Native/ Native Hawaiian/Pacific Islander; *CCC*, complex chronic condition; *ICH*, intracerebral hemorrhage; *IVH*, intraventricular hemorrhage; *SAH*, subarachnoid hemorrhage.
*Data was available for birthweight among 689 children, gestational age and postconceptional age for 908 children, and length of stay for 983 children.

shown in **Figure 2** (available at www.jpeds.com). Complex proximal shunt location was designated when 2 or more catheters were present, and distal shunt location included peritoneal, atrial, and other.

Statistical Analyses

Cohort characteristics at baseline were summarized overall and by subsequent infection status. Binary and categorical variables were described using frequencies and percents, and continuous variables were described using means and SDs or medians and IQRs for duration of follow-up, time to infection, and other skewed variables. Univariate survival analyses were performed to test the associations of each cohort characteristic with infection.

Similarly, the associations of surgeon factors and medical and surgical decisions at preceding CSF shunt surgeries with CSF shunt infection were described using hazard ratios (HRs), a type of rate ratio estimate, and 95% profile likelihood CI. Cox proportional hazard models were used to calculate HR and to test for the association between CSF shunt revision(s) and first CSF shunt infection while controlling for possible confounding baseline characteristics.[16,17] CSF shunt revision(s) were categorized as none, 1, and 2 or more; and were treated as a time-dependent covariate, because an individual child's revision status could change during the study period. For each day on which an infection occurred, this time-dependent model compared the infection hazard among children who had not experienced a shunt revision to date with those who had experienced 1 or 2 or more.

Baseline characteristics included a priori in the multivariable model were age, sex, and indication for shunt placement. Additional baseline characteristics shown in **Table I** were evaluated for inclusion in the model using stepwise regression methodology.[18,19] Using this approach, the model is initiated with a forward selection step in which a single variable is added to the model, and each forward selection step may be followed by one or more backward elimination steps in each of which a single variable may be removed from the model.[20] Criterion for entry into the model was $P \leq .05$; criterion for removal from the model was $P > .05$. Strict criteria were used to reduce error associated with multiple testing and identification of nonsignificant correlated risk factors in the multivariable regression. The HRs from the final multivariable models are presented with 95% profile likelihood CIs.

Sensitivity analyses were performed to investigate whether surgeon factors and medical and surgical decisions (either at initial placement or revision) may mediate the relationship between revisions and infection. We decided a priori to test factors of most interest, which included antibiotic impregnated shunt tubing use, nonperitoneal distal shunt location, complex shunt, staged revision, neuroendoscope use, and ultrasound use, as well as surgeon experience as it was significant in univariate analysis. These factors were evaluated in the final multivariable model as an additional time-dependent factor to determine whether the association between revisions and infections was altered by inclusion of these additional factors. In additional sensitivity analyses, we also considered site as a main effect and tested models without prior neurosurgery because of its association with intraventricular hemorrhage in this dataset.

All analyses were performed using SAS (v. 9.2, SAS Institute, Cary, North Carolina).

Results

Baseline patient-level risk factors for the 1036 children in the cohort are shown in Table I. The cohort had a median age of 19 weeks (IQR 4, 123), and indication for CSF shunt placement was distributed between postintraventricular hemorrhage because of prematurity (22%), myelomeningocele (16%), posterior fossa tumor (11%), aqueductal stenosis (8%), and other etiologies. Overall 112 (11%) children developed first CSF shunt infection. The majority (102, 91%) of first CSF shunt infection occurred within 12 months of initial placement. During the same time period, CSF shunt revisions occurred in 265 (26%) of the entire cohort and 33 (32%) of those who developed infection. The median duration of follow-up from initial CSF shunt placement in the uncensored cohort was 592 days (IQR 272, 892).

Many infection prevention practices were standardized within the network,[12] including use of prophylactic antibiotics intravenously and intrathecally (data not shown). However, we did observe differences between sites in some surgical practices, such as in type of shunt brand and use of neuroendoscope and ultrasound (data not shown).

There were 112 (11%) children who developed infection over the course of the entire study.Table II presents the baseline patient-level risk factors by infection status, as well as unadjusted associations with risk of CSF shunt infection. In univariate survival analyses, factors that demonstrated a significant association with infection risk included self-pay insurance, cardiac complex chronic condition, presence of a gastrostomy tube, and subsequent CSF shunt revisions. Older gestational age was associated with less infection risk.

Association between Revisions and Infection Risk

Our multivariable model of infection risk demonstrates the HRs for first CSF shunt infection for each of the explanatory variables while controlling for the other explanatory variables (Table III). Gastrostomy tube at initial CSF shunt placement (HR 2.0, 95% CI, 1.1, 3.3) was significantly associated with an increased risk of infection, and age 6-12 months (HR 0.3, 95% CI, 0.1, 0.8) and prior neurosurgery (HR 0.4, 95% CI, 0.2, 0.9) were significantly associated with a decreased risk of infection. When age was handled as a continuous variable, it was not associated with infection.

Infection risk was significantly related to revision after controlling for age, sex, and indication for shunt placement. Infection risk was more than 3 times greater among those with a revision compared with those without a revision (HR 3.9, 95% CI, 2.2, 6.5), and the risk was 13 times greater among those with 2 or more revisions compared with none (HR 13.0, 95% CI, 6.5, 24.9).

Sensitivity Analyses

Sensitivity analyses were performed to determine whether the association between revisions and infections were confounded by surgeon factors and medical and surgical decisions. Only a few surgeon factors, medical and surgical decisions at the preceding surgeries (initial CSF shunt placement and/or CSF shunt revision), were associated with infection hazard in univariate survival analysis; these included less surgeon experience (lower risk) and complex shunt (higher risk) (Figure 2). Medical and surgical decisions of interest, as well as surgeon's experience, were added to the multivariable Cox proportional hazards model in Table III to evaluate whether the association between revisions and infection remained significant. Surgeon experience for those under 5 years remained independently significant with HR 0.5 (95% CI, 0.2, 0.8); however, its addition did not change the HR estimates or significance for revisions substantially. None of the other medical and surgical factors of interest, nor inclusion of site, either demonstrated a significant association with infection hazard or changed the HR estimates or significance for revisions. Exclusion of prior neurosurgery changed the HR estimates for other variables only by making gastrostomy insignificant.

Discussion

In this large prospective multicenter cohort of children undergoing initial CSF shunt placement, 11% developed a first CSF shunt infection. We developed robust models that quantified the relative contributions to the risk of infection of baseline patient factors (including indication for CSF shunt placement) as well as each revision surgery. Baseline patient factors independently associated with first infection included presence of a gastrostomy tube (increased risk) and prior neurosurgery (decreased risk). However, it is revision surgeries that are most significantly associated with infection risk, and this risk increased dramatically with subsequent revisions. Surgeon, site, and medical and surgical decisions involved in shunt surgeries, both at initial placement and revision surgery, did not alter the relationship between revisions and infection. This study decisively quantifies this dramatic and clinically important risk of infection associated with revisions that has been observed in clinical practice.

This study augments a similar analysis performed in a single center retrospective cohort.[11] In the current study, we found that shunt placement at 6-12 months of age was protective. In our previous work, age 0 to <6 months at CSF shunt placement was significantly associated with an increased risk of infection (HR 2.4, 95% CI, 1.02, 6.7). The association of age with infection risk appears as inconsistent across ours and other studies.[21,22]

In this larger study, we found that presence of a gastrostomy tube was associated with infection risk. We did not assess gastrostomy risk in our previous analysis. Physically, it makes some sense that the presence of a gastrostomy tube could confer infection risk when a ventriculoperitoneal

Table II. Association of characteristics in the cohort with first CSF shunt infection

	First CSF shunt Infection (n = 112)	No CSF shunt infection (n = 924)	Unadjusted HR (95% CI)*
Demographics			
Sex, n (%)			
Male	61 (54%)	521 (56%)	0.9 (0.6, 1.3)
Female	51 (46%)	403 (44%)	Referent
Race, n (%)			
White	65 (58%)	590 (64%)	Referent
Other/unknown	23 (21%)	176 (19%)	1.2 (0.8, 2.0)
African American	22 (20%)	130 (14%)	1.5 (0.9, 2.3)
Asian	1 (1%)	19 (3%)	0.5 (0.0, 2.3)
AI/AN/NH/PI	1 (1%)	9 (1%)	1.0 (0.1, 4.3)
Ethnicity, n (%)			
Latino	18 (16%)	127 (14%)	1.3 (0.7, 2.0)
Not Latino	72 (64%)	629 (68%)	Referent
Unknown	22 (20%)	168 (18%)	1.2 (0.7, 1.8)
Insurance status, n (%)			
Public (Medicaid, Medicare)	46 (41%)	377 (41%)	1.1 (0.7, 1.8)
Private	39 (35%)	370 (40%)	Referent
Self-pay	9 (8%)	27 (3%)	**2.9 (1.3, 5.6)**
Other (eg, military)	2 (2%)	19 (2%)	1.1 (0.2, 3.5)
Government	16 (14%)	131 (14%)	1.2 (0.7, 2.1)
Risk factors prior to initial surgery			
Birth weight (kg), median (IQR)	2.7 (1.0, 3.2)	3.0 (1.7, 3.4)	0.8 (0.7, 1.02)
Gestational age (wk), median (IQR)	36 (26, 39)	38 (32, 40)	**0.95 (0.92, 0.98)**
Length of hospitalization preceding initial shunt placement (d), median (IQR)	4 (1, 21)	2 (0, 14)	1.0 (0.99, 1.01)
Prior surgery (neurosurgical), n (%)	13 (12%)	118 (13%)	0.9 (0.5, 1.6)
Risk factors at initial CSF placement			
Chronologic age, n (%)			
0 to <6 mo	73 (65%)	504 (55%)	1.0 (0.6, 2.0)
6 to <12 mo	10 (9%)	100 (11%)	0.7 (0.3, 1.6)
1 to <2 y	7 (6%)	64 (7%)	1.4 (0.6, 3.1)
2 to <9 y	10 (9%)	155 (17%)	0.7 (0.3, 1.5)
9 to 18 y	12 (11%)	101 (11%)	Referent
Postconceptional age (wk), median (IQR)	2 (-3, 31)	9 (-1, 70)	1.0 (0.99, 1.01)
Indication for shunt placement, n (%)			
Post-IVH due to prematurity	36 (32%)	190 (21%)	1.5 (0.8, 3.4)
Tumor (posterior fossa, supratentorial, midbrain)	15 (13%)	177 (19%)	0.8 (0.3, 1.9)
Myelomeningocele	15 (13%)	149 (16%)	0.8 (0.4, 1.9)
Congenital (communicating, other, encephalocele, craniosynostosis)	13 (12%)	113 (12%)	0.9 (0.4, 2.2)
Cyst (posterior fossa, intracranial)	12 (11%)	72 (8%)	1.4 (0.6, 3.4)
Aqueductal stenosis	9 (8%)	75 (8%)	Referent
Posthead injury	5 (4%)	44 (5%)	0.9 (0.3, 2.7)
Spontaneous ICH/IVH/SAH	2 (2%)	37 (4%)	0.5 (0.1, 2.0)
Postinfectious	3 (3%)	35 (4%)	0.7 (0.2, 2.3)
Other	2 (2%)	32 (3%)	0.5 (0.1, 2.0)
Weight at surgery (kg), median (IQR)	4.1 (2.9, 9.7)	6.3 (3.4, 13.9)	1.0 (0.99, 1.01)
CCCs, n (%)			
None (excepting hydrocephalus)	72 (64%)	655 (71%)	Referent
One	30 (27%)	217 (23%)	1.3 (0.8, 1.9)
Two or more	10 (9%)	52 (6%)	1.8 (0.9, 3.3)
Neuromuscular CCC, n (%)	15 (13%)	100 (11%)	1.3 (0.7, 2.1)
Cardiac CCC, n (%)	14 (13%)	69 (7%)	**1.9 (1.1, 3.3)**
Respiratory CCC, n (%)	11 (10%)	78 (8%)	1.2 (0.6, 2.1)
Renal CCC, n (%)	2 (2%)	7 (1%)	2.1 (0.3, 6.6)
Gastrointestinal CCC, n (%)	4 (4%)	12 (1%)	2.4 (0.7, 5.8)
Hematologic CCC, n (%)	0 (0%)	1 (0%)	n/a
Metabolic CCC, n (%)	2 (2%)	5 (1%)	2.8 (0.5, 8.7)
Congenital/genetic CCC, n (%)	6 (5%)	44 (5%)	1.2 (0.5, 2.4)
Malignancy CCC, n (%)	1 (1%)	26 (3%)	0.3 (0.0, 1.4)
Gastrostomy, n (%)	19 (17%)	81 (9%)	**2.0 (1.2, 3.2)**
Tracheostomy, n (%)	5 (4%)	24 (3%)	1.7 (0.6, 3.7)
CSF shunt revision(s) within 12 mo, n (%)			
No CSF shunt revisions	79 (71%)	692 (75%)	Referent
One CSF shunt revision	19 (17%)	147 (16%)	**3.6 (2.1, 5.9)**
Two or more CSF shunt revisions	14 (12%)	85 (9%)	**11.9 (6.1, 21.6)**

n/a, not applicable.
Bolded values are stastically significant.

Table III. Results from multivariable Cox proportional hazard model for the association between revisions and first CSF shunt infection, adjusting for baseline characteristics and confounders*

	Adjusted HR (95% CI)
Revision procedure	
2 or more	**13.0 (6.5, 24.9)**
1	**3.9 (2.2, 6.4)**
None	Referent
Chronologic age at initial shunt placement	
0 to <6 mo	0.7 (0.3, 1.7)
6 to <12 mo	**0.3 (0.1, 0.8)**
1 to <2 y	0.8 (0.3, 1.9)
2 to <9 y	0.6 (0.2, 1.3)
9 to 18 y	Referent
Female sex	1.1 (0.8, 1.7)
Indication for initial shunt placement	
Myelomeningocele	0.7 (0.3, 1.8)
Post-IVH due to prematurity	1.9 (0.9, 4.2)
Posthead injury	0.7 (0.2, 2.2)
Tumor (posterior fossa, midbrain, supratentorial)	0.7 (0.3, 1.8)
Cyst (other intracranial, posterior fossa)	1.6 (0.7, 3.9)
Spontaneous ICH/IVH/SAH	0.5 (0.1, 2.0)
Postinfectious	0.6 (0.1, 1.9)
Congenital (communicating, other, encephalocele, craniosynostosis)	0.9 (0.4, 2.2)
Other	0.5 (0.1, 2.4)
Aqueductal stenosis	Referent
Gastrostomy tube	**2.0 (1.1, 3.3)**
Prior neurosurgery	**0.4 (0.2, 0.9)**

Bolded values are stastically significant.
*Baseline characteristics included a priori were age, sex, and indication for shunt placement. Additional baseline characteristics shown in Table I were evaluated for inclusion in the model using stepwise regression methodology. Criterion for entry into the model was $P \leq .05$; criterion for removal from the model was $P > .05$.

shunt is present. However, it may also be a marker for medical complexity. Unfortunately, we do not have data on the timing of gastrostomy tube placement in this cohort, limiting our ability to understand the nature of its timing with infection risk. Presence of a gastrostomy tube represents an important risk factor to consider in clinical practice as well as future studies.

In the current study, we found that prior neurosurgery was protective. Although we considered prior neurosurgery in previous work and it was not associated with infection, it was assessed from *International Classification of Disease, Ninth Revision, Clinical Modification* codes rather than chart review and, unlike this study, included consideration of EVDs. In our previous work, myelomeningocele was significantly associated with a decreased risk of infection (HR 0.4, 95% CI, 0.2, 0.8); we wondered if the routine use of exposure to antibiotics intravenously seen in children with myelomeningocele might explain the protective effect in the single center study. The protective effect of myelomeningocele was not replicated in this larger cohort. One possible explanation for the protective effect of prior neurosurgery in this study, which we did not test, again could be prior exposure to antibiotics intravenously.

None of the associations of baseline factors in this or the previous study was as strong as performance of CSF shunt revision. Taking both studies together, 1 CSF shunt revision was associated with 3- to 4-fold higher hazard of infection whereas 2 or more CSF shunt revisions were associated with 6- to 13-fold higher infection hazard. Our finding of each subsequent CSF shunt revision increasing infection risk for a patient also is consistent with previous work.[9] Each surgery likely represents an opportunity to introduce new organisms into the CSF and onto shunt hardware. Each surgical exposure of the shunt apparatus may represent an opportunity to further colonize a shunt apparatus in a sterile setting, with an additive effect over time. Future research efforts should focus on modalities to reduce microbial exposure during the perioperative period to optimize revision procedures and reduce risk of subsequent infection.

Conclusions about medical and surgical decisions, as well as surgeon's volumes and experience, can be limited as they vary between and are highly confounded by surgeon and study site.[23] However, many medical and surgical decisions to prevent infection, including prophylactic use of antibiotics,[24,25] site preparation including hair clipping,[26,27] type of skin cleanser,[26,28] double gloving,[25] prophylactic intraventricular antibiotic use,[28-31] and use of a wound dressing were standardized within the HCRN.[12] By reducing background variation, this standardization permitted us to more concisely address baseline risk factors associated with infection risk. Areas of ongoing controversy in the prevention of CSF shunt infection include use of antibiotic impregnated shunt tubing,[32-35] distal shunt location,[22,36-40] and use of neuroendoscope.[10,25] In this study, surgeon, study site, or medical and surgical decision did not substantially contribute to infection risk beyond CSF shunt revision itself.

This work has several limitations. The conduct of this study at a group of centers adhering to a common checklist of medical and surgical practices to prevent shunt infection reduces generalizability of findings outside of the HCRN. The small number of surgeons and hospitals limits the ability to systematically study surgeon and hospital effects on patient outcome. However, the multi-institutional nature of this study gives it greater generalizability than previous studies. Certain patient risk factors may not have been captured in this analysis. Missing data on gestational age and birth weight limits our ability to draw conclusions about these patient factors, and we did not collect data on use of antibiotic-impregnated EVD or postoperative wound care practices. Outcomes were all collected passively. Our definition of infection was developed by consensus within the HCRN and does not permit easy comparison with infection rates at non-HCRN sites or those used by hospital infection control groups. For neurosurgical procedures, the assumption is that patients return to the same center for care. Death as an outcome depends on the neurosurgical center staff knowledge of a child's demise. If children moved to a different location, they were lost to follow-up.

Families of and care providers for children with recurrent CSF shunt revisions should be aware of their increased odds of CSF shunt infection. Further research is needed to optimize strategies for revision procedures and to reduce risk of subsequent infection. ■

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Appendix

Additional members of HCRN include:

Amita Bey, MPH (Children's Hospital of Alabama and University of Alabama); Arlene Luther, BS, RN (Children's Hospital of Pittsburgh); Lindsay O'Connor, MSc and Megha Agrawal (Hospital for Sick Children); Tracey Habrock-Bach, BS (Primary Children's Medical Center); Amy Anderson, BSN, RN (Seattle Children's Hospital); Sheila Ryan, MPH, JD (Texas Children's Hospital); and Deanna Mercer (Washington University).

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Collaborating HCRN investigator: Chevis N. Shannon, PhD (Children's Hospital of Alabama and University of Alabama during study period, now Department of Neurosurgery, Vanderbilt University).

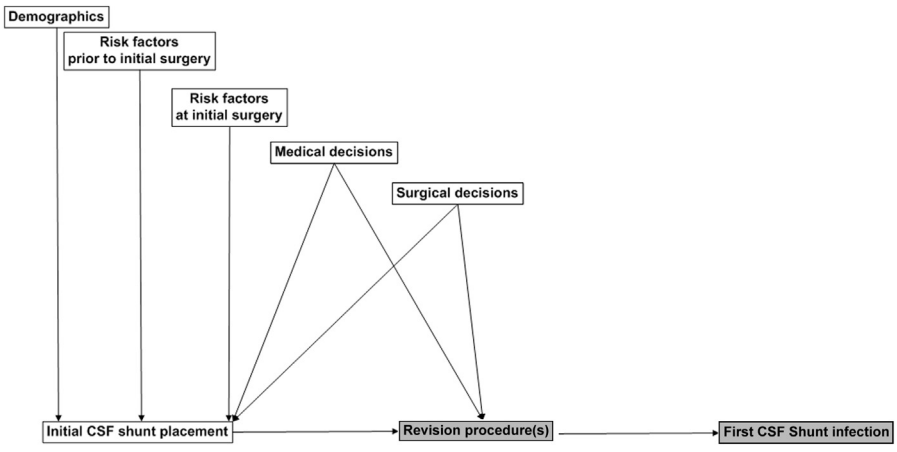

Figure 1. Timeline of events for each patient in cohort. *Shading* indicates event did not occur for all children.

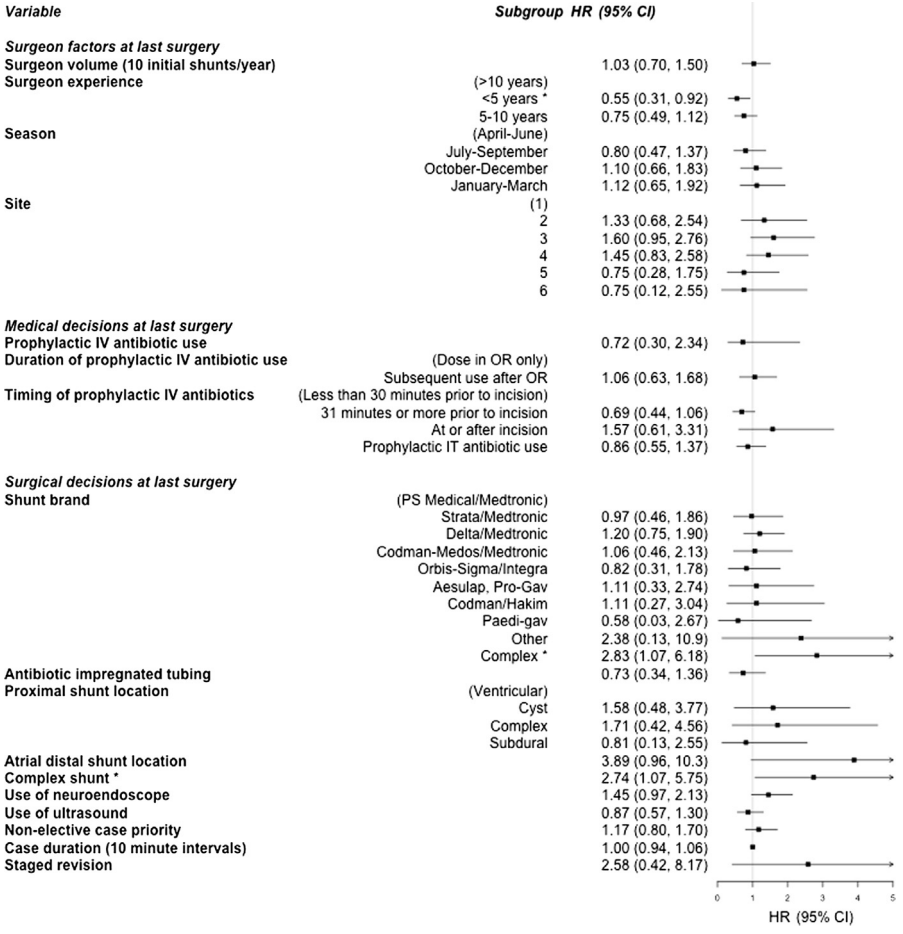

Figure 2. Association of surgeon, medical, and surgical characteristics in the cohort with first CSF shunt infection in univariate survival analyses. *Significant in univariate survival analysis. *IV*, intravenous; *IT*, intrathecal.