Reinfection after treatment of first cerebrospinal fluid shunt infection: a prospective observational cohort study

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OBJECTIVE CSF shunt infection requires both surgical and antibiotic treatment. Surgical treatment includes either total shunt removal with external ventricular drain (EVD) placement followed by new shunt insertion, or distal shunt externalization followed by new shunt insertion once the CSF is sterile. Antibiotic treatment includes the administration of intravenous antibiotics. The Hydrocephalus Clinical Research Network (HCRN) registry provides a unique opportunity to understand reinfection following treatment for CSF shunt infection. This study examines the association of surgical and antibiotic decisions in the treatment of first CSF shunt infection with reinfection.

METHODS A prospective cohort study of children undergoing treatment for first CSF infection at 7 HCRN hospitals from April 2008 to December 2012 was performed. The HCRN consensus definition was used to define CSF shunt infection and reinfection. The key surgical predictor variable was surgical approach to treatment for CSF shunt infection, and the key antibiotic treatment predictor variable was intravenous antibiotic selection and duration. Cox proportional hazards models were constructed to address the time-varying nature of the characteristics associated with shunt surgeries.

RESULTS Of 233 children in the HCRN registry with an initial CSF shunt infection during the study period, 38 patients (16%) developed reinfection over a median time of 44 days (interquartile range [IQR] 19–437). The majority of initial CSF shunt infections were treated with total shunt removal and EVD placement (175 patients; 75%). The median time between infection surgeries was 15 days (IQR 10–22). For the subset of 172 infections diagnosed by CSF culture, the mean $\pm$ SD duration of antibiotic treatment was 18.7 ± 12.8 days. In all Cox proportional hazards models, neither surgical approach to infection treatment nor overall intravenous antibiotic duration was independently associated with reinfection. The only treatment decision independently associated with decreased infection risk was the use of rifampin. While this finding did not achieve statistical significance, in all 5 Cox proportional hazards models both surgical approach (other than total shunt removal at initial CSF shunt infection) and nonventriculoperitoneal shunt location were consistently associated with a higher hazard of reinfection, while the use of ultrasound was consistently associated with a lower hazard of reinfection.

CONCLUSIONS Neither surgical approach to treatment nor antibiotic duration was associated with reinfection risk.

ABBREVIATIONS CCC = complex chronic condition; EVD = external ventricular drain; HCRN = Hydrocephalus Clinical Research Network; IQR = interquartile range.

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While these findings did not achieve statistical significance, surgical approach other than total removal at initial CSF shunt infection was consistently associated with a higher hazard of reinfection in this study and suggests the feasibility of controlling and standardizing the surgical approach (shunt removal with EVD placement). Considerably more variation and equipoise exists in the duration and selection of intravenous antibiotic treatment. Further consideration should be given to the use of rifampin in the treatment of CSF shunt infection. High-quality studies of the optimal duration of antibiotic treatment are critical to the creation of evidence-based guidelines for CSF shunt infection treatment.

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KEY WORDS cerebrospinal; shunt; infection; treatment; antibiotic; reinfection; hydrocephalus

WHILE lifesaving and the mainstay of hydrocephalus treatment,¹⁵ CSF shunts can cause new and chronic surgical and medical problems in children with hydrocephalus. Mechanical malfunction is frequent, with 40% of shunts requiring surgical revision within 2 years.²² With each additional CSF shunt surgery, the risk of CSF shunt infection increases.^{2,25,49} CSF shunt infection rates range from 0% to 35% per surgery,^{5,12,20,24,25,28,30,31,33,34,36,56} with an average of 6%–8%.^{18,19} CSF shunt reinfection after an initial infection is frequent, and rates range from 12% to 26%.^{17,21,49}

Three detailed observational studies of treatment of CSF shunt infection with large numbers of children observed reinfection rates of 26% (18 of 70 patients), 20% (10 of 51 patients), and 26% (31 of 118 patients), respectively.^{17,21,39} Investigators have noted considerable variation in surgical and antibiotic decisions for shunt infections that might explain reinfection.^{25,28,37,52}

Surgical decisions in the treatment of CSF shunt infection include either shunt removal with external ventricular drain (EVD) placement followed by new shunt insertion, or shunt externalization followed by shunt replacement once the CSF is sterile. While the benefit of each approach in preventing CSF shunt reinfection remains unclear,^{10,11,14,21,26,43,48,54} the growing consensus within the neurosurgical community has been to perform complete shunt removal at the time of the first infection surgery.^{17,52}

Antibiotic decisions in the treatment of CSF shunt infection include the type and duration of empirical and targeted intravenous antibiotics.^{7,35,50} Here again, evidence is limited because no randomized controlled clinical trials have been conducted, and prior studies have been retrospective and limited in size.⁴³ Duration of intravenous antibiotic use varies widely^{17,38} and depends, in part, on the surgical approach used,^{27,49} pathogen involved,^{7,46,55} CSF laboratory results, and persistence of the pathogen.

We sought a better understanding of the characteristics associated with reinfection following first CSF shunt infection because these may inform optimal treatment strategies at the time of first infection. The Hydrocephalus Clinical Research Network (HCRN) registry provides a unique opportunity to understand reinfection following treatment for CSF shunt infection. This study examines the association of surgical and antibiotic decisions in the treatment of first CSF shunt infection with reinfection.

Methods

Setting

The HCRN is a collaboration of 14 pediatric neurosurgical centers across North America. Of these, 7 were ac-

tive during the study period and participated in this study: Children's of Alabama, Children's Hospital of Pittsburgh, The Hospital for Sick Children, Primary Children's Hospital, Seattle Children's Hospital, Texas Children's Hospital, and St. Louis Children's Hospital. HCRN registry data use was approved by HCRN and the institutional review boards at the University of Utah and Seattle Children's Hospital.

Study Population and Data Collection

Within the HCRN registry, data from each neurosurgical admission of each child are collected contemporaneously. Data collection started in April 2008 and, for this study, ended on December 31, 2012, except for children at The Hospital for Sick Children, who underwent follow-up until December 31, 2011. The final cohort included children whose first CSF shunt infection was recorded in the HCRN registry and whose initial CSF shunt placement and all subsequent shunt surgeries were also recorded in the HCRN registry during the study period ($n = 151$) and patients whose shunt surgery history (initial CSF shunt placement and subsequent CSF shunt revisions) was obtained retrospectively ($n = 82$).

The HCRN consensus definition was used for CSF shunt infection:^{19,38,42,45} 1) microbiological determination of bacteria present in a culture or Gram stain of CSF, wound swab, and/or pseudocyst fluid; 2) shunt erosion (visible hardware); or 3) abdominal pseudocyst (without positive culture); or 4) for children with ventriculoatrial shunts, presence of bacteria in a blood culture. The first CSF sample for diagnosis of infection was usually obtained from needle aspiration of the shunt reservoir under sterile conditions and before antibiotic initiation. To ensure that all infections were identified, all neurosurgical admissions involving 2 CSF shunt surgeries and ≥ 48 hours of intravenous antibiotic treatment were reviewed by T.D.S. and local HCRN staff to clarify whether the infection criteria were met.

Outcome Variable

Reinfection was defined using the HCRN consensus definition of infection, as described above. The duration of follow-up for reinfection was through December 31, 2013, resulting in a minimum follow-up duration of 1 year. The at-risk period was defined as the period following first shunt infection in which a shunt was in place. Patients who died during treatment of first infection or who did not subsequently have a shunt in place were censored at day 1 and were excluded from the multivariable models used to predict reinfection.

Predictor Variables

The key surgical predictor variable was the surgical approach to treatment for CSF shunt infection.³⁷ Surgical approach was defined as 1) total shunt removal with EVD placement followed by new shunt insertion once the CSF was sterile, 2) distal shunt externalization followed by shunt replacement (externalization), 3) distal shunt externalization followed by EVD placement followed by new shunt insertion (failed externalization), or, rarely, 4) shunt revision, 5) shunt removal without replacement, or 6) no surgical treatment (i.e., shunt left in place).

The key antibiotic treatment predictor variable was intravenous antibiotic selection and duration,³⁸ which was characterized following review by 2 authors (T.D.S. and M.P.K.) as follows: 1) concordant, defined by the start of intravenous antibiotic(s) to which the organism(s) grown in the CSF culture was sensitive; 2) concordant and appropriate, defined by the start of concordant intravenous antibiotic as previously described at a dose appropriate for weight and with adequate central nervous system penetration; or 3) broad spectrum, defined by the start of intravenous antibiotic(s) to treat gram-positive and gram-negative organisms. When not specifically provided, susceptibilities were anticipated when possible based on the organism (e.g., a methicillin-susceptible *Staphylococcus aureus* isolate was presumed to be susceptible to cefazolin even if not tested directly against it). Drug levels were not available for review in the determination of concordant and appropriate intravenous antibiotic use. Use of intrathecal antibiotics was handled as a dichotomous variable. Use of rifampin was considered synergistic and was not further incorporated into consideration of broad-spectrum or concordant antibiotics because susceptibility data were not available.

Covariates

Baseline characteristics included patient risk factors such as demographics, risk factors prior to initial CSF shunt placement, and treatment decisions at the time of CSF shunt placement and intervening revision surgeries as previously described and shown in Tables 1 and 2.^{38,41,42} Chronological age was handled as both a categorical and continuous variable.^{38,41,42} Complex chronic conditions (CCCs) were classified as previously described.^{38,40} Of note, since June 2007 hospitals in HCRN have instituted an infection prevention bundle that is used at the time of the initial shunt placement and revision(s), although compliance with all aspects is variable.^{18,19}

Factors considered during the treatment of first CSF shunt infection (Table 3) included chronological age, complications after the first shunt infection, shunt location, ultrasound use, endoscope use, and antibiotic-impregnated catheter use. The duration of time between infection surgeries was determined to denote the time span between the first and final surgical approaches for infection treatment (e.g., shunt removal and EVD placement as the first surgery and shunt replacement as the second surgery). Next, we examined diagnostic and microbiological factors in CSF shunt infection (Table 4).⁴⁵ We considered the specific infection criteria that were met; organism(s) recovered in CSF, blood, and wound culture(s); presence of bacteremia (defined as any organism recovered in blood

culture, except from children with ventriculoatrial shunts diagnosed by blood culture); and, where available within 48 hours of infection diagnosis, the results of the first CSF studies, including Gram staining, white and red blood cell counts, and glucose and protein levels.

Among the initial CSF shunt infections diagnosed by CSF culture, we examined additional diagnostic and microbiological factors, including time from first positive culture to first infection surgery, time from first persistently negative culture to final surgical approach for infection treatment, duration of positive CSF cultures, presence of intermittent negative CSF cultures (defined as 2 or more positive CSF cultures with the same organism and at least 1 intervening negative culture), and presence of secondary ventriculitis (recovery of a different organism than that initially recovered in the CSF culture).⁴⁵

Statistical Analyses

The overall study population is described, as well as patients with and without reinfection, using the number and proportion for binary and categorical variables and mean and standard deviation or median (interquartile range [IQR]) for continuous variables. Patient characteristics, treatment decisions at initial CSF shunt placement, CSF shunt revision(s) before initial CSF shunt infection, initial CSF shunt infection (including diagnostic characteristics and surgical and antibiotic treatment decisions, such as antibiotic duration), and interval CSF shunt revision(s) were similarly described. In addition, the characteristics of each shunt revision surgery that occurred after the first CSF shunt infection and prior to CSF shunt reinfection or censoring—including shunt locations, use of ultrasonography and/or endoscopy, and use of antibiotic-impregnated catheter components—are described for patients with and without reinfection. Bivariate analyses of the surgical decisions by the center were conducted to assess systematic differences in surgical and antibiotic treatment decisions.

Associations of clinical characteristics and treatment decisions at the time of the first CSF shunt infection with reinfection risk were individually examined in separate Cox proportional hazards models. For these models, because endoscope and ultrasound use tend to be mutually exclusive, we created a visualization use variable at each surgical time point that included only endoscope use, only ultrasound use, use of both, and use of neither. We also trichotomized antibiotic duration at CSF shunt infection as short (< 7 days), intermediate (8–14 days), and long (> 14 days). Time-varying characteristics associated with shunt revisions following first CSF shunt infection were analyzed using the extension of the Cox proportional hazards to the count processes proposed by Andersen and Gill.^{3,44} Factors selected a priori, as well as statistically significant predictors ($\alpha = 0.10$) that were not collinear, were entered into a multivariable Cox proportional hazards model (full model). To ease interpretation, a second version of the full model that includes only children who did not undergo any revisions before reinfection ($n = 147$) is also provided. Factors selected a priori included age, etiology of hydrocephalus, surgical approach to infection treatment, and overall intravenous antibiotic use. Statistically significant predictors ($\alpha = 0.10$) that were not collinear include CCCs,

TABLE 1. Characteristics of children with and without CSF shunt reinfection at the time of initial CSF shunt placement

Characteristic	No Reinfection	Reinfection	Entire Cohort
No. of patients	195	38	233
Median chronological age (IQR), wks	13 (2–54)	20 (9–33)	14 (2–48)
Median gestational age (IQR), wks*†	37 (26–39)	30 (25–38)	36 (26–39)
Sex			
Male	105 (54)	18 (47)	123 (53)
Female	90 (46)	20 (53)	110 (47)
Ethnicity			
Non-Hispanic white	106 (54)	18 (47)	124 (53)
African American	31 (16)	8 (21)	39 (17)
Hispanic	27 (14)	5 (13)	32 (14)
Other*	31 (16)	7 (18)	38 (16)
Insurance			
Public	86 (44)	18 (47)	104 (45)
Private	77 (40)	16 (42)	93 (40)
Self-pay	7 (4)	3 (8)	10 (4)
Other	4 (2)	0 (0)	4 (2)
Government (Canada only)	21 (11)	1 (3)	22 (9)
Mean birth weight (SD), kg‡¶	2.5 (1.2)	1.8 (1.3)	2.3 (1.3)
Median weight at op (IQR), kg§	4.1 (2.8–11.2)	4.2 (3.0–8.6)	4.1 (2.9–10.3)
Etiology of hydrocephalus			
Post-intraventricular hemorrhage due to prematurity*	58 (30)	18 (47)	76 (33)
Congenital (communicating congenital, other congenital, encephalocele, craniosynostosis)	37 (19)	6 (16)	43 (18)
Myelomeningocele	35 (18)	4 (11)	39 (17)
Tumor (supratentorial, posterior fossa, midbrain)	24 (12)	2 (5)	26 (11)
Cyst (posterior fossa, intracranial)¶	9 (4)	5 (13)	14 (6)
Aqueductal stenosis	10 (5)	2 (5)	12 (5)
After head injury	6 (3)	1 (3)	7 (3)
Postinfectious	7 (4)	0 (0)	7 (3)
Other	7 (4)	0 (0)	7 (3)
Spontaneous hemorrhage	2 (1)	0 (0)	2 (1)
CCCs			
0 (except hydrocephalus)	113 (58)	14 (37)	127 (55)
1*	67 (34)	17 (45)	84 (36)
≥2¶	15 (8)	7 (18)	22 (9)
Gastrostomy**	19 (17)	3 (13)	22 (16)
Tracheostomy**	3 (3)	2 (9)	5 (4)

Values are shown as the number of patients (%) unless indicated otherwise.

* Significant difference between groups ($p < 0.10$) according to the unadjusted Cox proportional hazards models.

† Reported for 210 children.

‡ Reported for 160 children.

§ Reported for the prospective cohort of 151 children.

¶ Significant difference between groups ($p < 0.05$) according to the unadjusted Cox proportional hazards models.

** Performed for 137 children.

revisions before initial CSF shunt infection, visualization before initial CSF shunt infection, rifampin use, and, for children with revisions after initial CSF shunt infection, visualization at last surgery before reinfection/censor, revision(s) before reinfection/censoring, and last shunt location. Factors that were not included in models due to collinearity included gestational age and birth weight (col-

linear with etiology of post-intraventricular hemorrhage due to prematurity), shunt locations at all surgical time points before reinfection (collinear with last shunt location), visualization at initial CSF shunt placement (collinear with visualization before initial CSF shunt infection and at last surgery before reinfection/censor), and broad-spectrum intravenous antibiotic use (collinear with overall

TABLE 2. Treatment decisions at the time of initial CSF shunt placement and shunt revision before initial CSF shunt infection in children with and without CSF shunt reinfection

Variable	No Reinfection	Reinfection	Entire Cohort
No. of patients	126	25	151
Initial CSF shunt placement			
Shunt location (proximal-distal)			
Ventriculoperitoneal	122 (97)	20 (80)	142 (94)
Cystoperitoneal	3 (2)	1 (4)	4 (2)
Subdural-peritoneal*	0 (0)	2 (8)	2 (1)
Complex peritoneal*	0 (0)	1 (4)	1 (1)
Ventriculoatrial	1 (1)	0 (0)	1 (1)
Subdural-atrial*	0 (0)	1 (4)	1 (1)
Ultrasound use	48 (38)	0 (0)	48 (32)
Endoscope use*	34 (27)	13 (52)	47 (31)
Antibiotic-impregnated catheter use	30 (24)	1 (4)	31 (21)
CSF shunt revisions			
No. before initial infection*†			
0	111 (57)	13 (34)	124 (53)
1*	34 (17)	12 (32)	46 (20)
≥2	50 (26)	13 (34)	63 (27)
Shunt location (proximal-distal)			
Ventriculoperitoneal	118 (93)	18 (72)	136 (90)
Cystoperitoneal	4 (3)	1 (4)	5 (3)
Subdural-peritoneal‡	0 (0)	1 (4)	1 (1)
Complex peritoneal*	2 (2)	3 (12)	5 (3)
Ventriculoatrial	2 (2)	1 (4)	3 (2)
Subdural-atrial*	0 (0)	1 (4)	1 (1)
Ultrasound use*	45 (36)	2 (8)	47 (31)
Endoscope use‡	29 (23)	13 (52)	42 (28)
Antibiotic-impregnated catheter use	34 (27)	4 (16)	38 (25)

Values are shown as the number of patients (%).

* Significant difference between groups ($p < 0.05$) according to unadjusted Cox proportional hazards models.

† For entire cohort of 233 children.

‡ Significant difference between groups ($p < 0.10$) according to unadjusted Cox proportional hazards models.

intravenous antibiotic use). The risks of reinfection associated with each characteristic are reported as hazard ratios and associated 95% confidence intervals.

In addition, 3 alternative model definitions were examined. First, the proportional hazards assumption was challenged by adding the interactions of the time-varying covariates with time since the last procedure. Selection of nonproportional hazards adjustment (time-varying hazards model) was based on the model's stability, Akaike's information criterion, and Bayesian information criterion. Second, automated stepwise model selection was used to reduce the number of terms in the multivariable Cox proportional hazards model (reduced model). Selection criteria for entry and exit were both $\alpha = 0.10$. Finally, to

examine the robustness of the model in a relatively low-risk and homogenous cohort, the time-varying hazards model was applied to the subset of patients with all known shunts placed in the peritoneal location (ventriculoperitoneal shunt model).

All statistical analyses were performed using SAS (version 9.2; SAS Institute).

Results

Study Cohort at Time of CSF Shunt Infection

Of 3131 children in the HCRN registry during the study period, 233 (7.4%) met the inclusion criteria with an initial CSF shunt infection. Of these 233 children, 38 patients (16%) developed reinfection. Baseline patient and treatment factors, including those of patients with and without reinfection, are shown in Tables 1 and 2. Most children underwent initial CSF shunt placement when they were younger than 6 months (156 patients; 67%), at a median age of 14 weeks (IQR 2–48 weeks). The etiology of hydrocephalus was distributed among post-intra-ventricular hemorrhage due to prematurity (76 patients; 33%), congenital (43 patients; 18%), myelomeningocele (39 patients; 17%), tumor (26 patients; 11%), and other etiologies. Significant numbers of children had additional neuromuscular (53 patients; 23%), cardiac (26 patients; 11%), respiratory (25 patients; 11%), and congenital/genetic (22 patients; 9%) CCCs. Cardiac and congenital/genetic CCCs were associated with reinfection (data not shown). The majority of children had 0 CSF shunt revisions (124 patients; 53%) prior to CSF shunt infection. The median time to first infection from previous CSF shunt surgery was 33 days (IQR 15–77 days) (data not shown). At the time of initial CSF shunt infection, the cohort had a median age of 78 weeks (IQR 18–360 weeks). The median duration of follow-up for the entire cohort was 742 days (IQR 406–1260 days), and the median time to reinfection was 44 days (IQR 19–437 days).

The overall diagnostic characteristics of the entire cohort of patients with initial CSF shunt infection and patients with and without reinfection are provided in Table 4. The majority of patients were diagnosed by CSF culture (172 patients; 74%). The most common initial organisms recovered included coagulase-negative staphylococcus (55 patients; 32%), *S. aureus* (49 patients; 28%), and gram-negative bacilli (38 patients; 22%).

Surgical Treatment for First CSF Shunt Infection

The majority of initial CSF shunt infections were treated with total shunt removal and EVD placement (175 patients; 75%). The median time between infection surgeries was 15 days (IQR 10–22 days). As shown in Table 3, the median time from first negative CSF culture to final surgical approach to treat infection was 13 days (IQR 9–20 days).

Antibiotic Treatment for First CSF Shunt Infection

For the subset of 172 infections diagnosed by CSF culture, the mean $\pm$ SD duration of concordant intravenous antibiotic treatment was 18.7 days (SD 12.8 days) (Table 3). The mean duration of concordant and appropriate in-

TABLE 3. Treatment decisions at the time of initial CSF shunt infection and intervening shunt revisions in children with and without CSF shunt reinfection

Variable	No Reinfection	Reinfection	Entire Cohort
No. of patients	195	38	233
Initial CSF shunt infection			
Median chronological age at infection (IQR), wks	72 (16 to 377)	80 (29 to 292)	78 (18 to 360)
Concordant IV antibiotic use*	144 (98)	24 (96)	168 (98)
Mean duration $\pm$ SD, days	18.8 $\pm$ 13.0	18.3 $\pm$ 11.9	18.7 $\pm$ 12.8
Concordant & appropriate IV antibiotic use*	133 (91)	22 (88)	155 (90)
Mean duration $\pm$ SD, days	15.5 $\pm$ 12.4	17.5 $\pm$ 12.1	15.8 $\pm$ 12.4
Broad-spectrum IV antibiotic use†	164 (84)	30 (79)	194 (83)
Median duration (IQR)	5.2 (2.8 to 12.6)	11.2 (3.0 to 17.5)	5.3 (2.8 to 13.6)
Use of intrathecal antibiotics	130 (67)	23 (61)	153 (66)
Use of rifampin†	34 (17)	2 (5)	36 (15)
Surgical approach to treatment			
Total shunt removal & EVD placement	149 (77)	26 (68)	175 (75)
Externalization	14 (7)	4 (11)	18 (8)
Failed externalization	8 (4)	5 (13)	13 (6)
≥ 1 components revised	6 (3)	2 (5)	8 (3)
Shunt removed after infection treatment	12 (6)	Not at risk	12 (5)
Shunt left in place	4 (2)	1 (3)	5 (2)
Died during treatment	2 (1)	Not at risk	2 (1)
Median time from 1st positive CSF culture to 1st infection op (IQR), days¶	0.3 (−0.1 to 0.8)	0.3 (−0.2 to 0.8)	0.3 (−0.1 to 0.8)
Median time btwn infection surgeries (IQR), days**	14 (10 to 21)	17 (10 to 27)	15 (10 to 22)
Median time from 1st negative CSF culture to final infection op (IQR), days*,††	13 (9 to 18)	16 (9 to 22)	13 (9 to 20)
Complications‡			
Medical	16 (16)	4 (24)	20 (17)
Neurological/surgical	24 (23)	6 (35)	30 (25)
Shunt location (proximal-distal)§,‡‡			
Ventriculoperitoneal	157 (87)	24 (63)	181 (83)
Ventriculoatrial§	8 (4)	6 (16)	14 (6)
Complex peritoneal†	4 (2)	3 (8)	7 (3)
Cystoperitoneal	5 (3)	1 (3)	6 (3)
Ventriculopleural†	3 (2)	2 (5)	5 (2)
Subdural-peritoneal	2 (1)	1 (3)	3 (1)
Complex atrial	1 (0)	1 (3)	2 (1)
Lumboperitoneal	1 (0)	0 (0)	1 (0)
Ultrasound use§,§§	59 (33)	5 (14)	64 (30)
Endoscope use§,§§	52 (29)	21 (57)	73 (34)
Antibiotic-impregnated catheter use§§§	56 (32)	8 (22)	64 (30)
Interval CSF shunt revision			
Revisions after initial infection & before reinfection			
0	121 (62)	26 (68)	147 (63)
1	47 (24)	7 (18)	54 (23)
≥ 2 §	27 (14)	5 (13)	32 (14)
Last known shunt location‡‡			
Ventriculoperitoneal	152 (84)	23 (61)	175 (80)
Ventriculoatrial§	13 (7)	5 (13)	18 (8)
Complex peritoneal§	6 (3)	4 (10)	10 (5)
Cystoperitoneal	2 (1)	1 (3)	3 (1)
Ventriculopleural†	3 (2)	2 (5)	5 (2)
Subdural-peritoneal	2 (1)	1 (3)	3 (1)

CONTINUED ON PAGE 352 »

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TABLE 3. Treatment decisions at the time of initial CSF shunt infection and intervening shunt revisions in children with and without CSF shunt reinfection

Variable	No Reinfection	Reinfection	Entire Cohort
Interval CSF shunt revision (<i>continued</i>)			
Last known shunt location††			
Complex atrial§	0 (0)	2 (5)	2 (1)
Lumboperitoneal	1 (1)	0 (0)	1 (0.5)
Cystoatrial	1 (1)	0 (0)	1 (0.5)
4th ventricle-peritoneal	1 (1)	0 (0)	1 (0.5)
Ultrasound use§,¶¶	53 (30)	4 (11)	57 (26)¶¶
Endoscope use§,¶¶	51 (29)	20 (54)	71 (33)¶¶
Antibiotic-impregnated catheter use¶¶	64 (36)	8 (22)	72 (33)¶¶

Values are shown as the number of patients (%) unless indicated otherwise.

* Reported for the 172 children diagnosed by CSF culture.

† Significant difference between groups ($p < 0.10$) according to the unadjusted Cox proportional hazards models.

‡ Reported for 120 patients. Medical complications included urinary tract infection, sepsis, pneumonia, cardiac arrest, pressure sores, deep venous thrombosis/pulmonary embolism, ascites, and hyponatremia. Neurological/surgical complications included CSF leak, wound infection, seizure, postoperative hemorrhage, pseudomeningocele, over- or underdrainage, intracranial fluid collection, and new neurological deficit.

§ Significant difference between groups ($p < 0.05$) according to the unadjusted Cox proportional hazards models.

¶ Reported for 168 children diagnosed by CSF culture who underwent surgery.

** Reported for the 206 children who had 2 surgeries.

†† Reported for 153 of the 172 children diagnosed by CSF culture.

‡‡ Reported for 219 children whose surgical approach to treatment changed the shunt location.

§§ Reported for 214 children for whom the approach to treatment involved surgery.

¶¶ For postinfection revisions, 216 children had ultrasound, endoscope, and antibiotic-impregnated catheter use reported.

travenous antibiotic use was 15.8 days (SD 12.4 days). No differences were seen in reinfection for concordant and/or concordant and appropriate intravenous antibiotic use for < 7 days, < 10 days, or < 14 days (data not shown). The median duration of broad-spectrum intravenous antibiotic use, which likely represents empirical antibiotic coverage while waiting for culture results and CSF clearance, was 5.3 days (IQR 2.8–13.6 days). The median duration of time from first negative culture to final surgical approach to treat infection, which best represents the number of days of therapy after CSF sterilization, was 13 days (IQR 9–20 days). A minority of initial CSF shunt infections were treated with additional rifampin (36 patients; 15%). Medical complications were seen in 17% of the cohort and most commonly included hyponatremia (9 patients; 8%) and urinary tract infection (8 patients; 7%). Surgical complications were seen in 25% of the cohort and most commonly included minor CSF leak (8 patients; 7%), wound infection (8 patients; 7%), and seizure (8 patients; 7%) (data not shown).

Association With Reinfection

In all Cox proportional hazards models, neither surgical approach for infection treatment nor overall intravenous antibiotic duration was independently associated with reinfection (Table 5). In the full model that included both the entire cohort and those patients with no revisions after infection, nonmodifiable factors, such as age, number of CCCs, and revisions after initial infection (for the complete cohort), were independently associated with reinfection. The only treatment decision independently associated with decreased infection risk was the use of rifampin.

In the time-varying hazards model, only revision after initial infection was independently associated with reinfection in the complete cohort, and the use of rifampin remained protective (Table 6). However, in the reduced model that used a stepwise approach without any variables forced into the model, 2 risk factors were consistently and independently associated with increased infection risk: 2 or more CCCs and nonventriculoperitoneal shunt location at last surgery. When children with nonventriculoperitoneal shunts were removed from the analysis, no factors were associated with reinfection. While these findings did not achieve statistical significance, both surgical approach other than total shunt removal at initial CSF shunt infection and nonventriculoperitoneal shunt location were consistently associated with a higher hazard of reinfection, while the use of ultrasound was consistently associated with a lower hazard of reinfection in all 5 Cox proportional hazards models.

Discussion

This prospective cohort of 233 children treated for initial CSF shunt infection at 7 hospitals is the largest to date. The majority of patients were surgically treated with total shunt removal with EVD placement. The mean duration of concordant intravenous antibiotic use for those children diagnosed by CSF culture was 19 days. Neither surgical approach to treatment nor antibiotic duration was associated with reinfection risk. Nonmodifiable risk factors, such as age, number of CCCs, and revisions after initial infection, were independently associated with reinfection. The

TABLE 4. Microbiological and diagnostic factors in children with and without CSF shunt reinfection at the time of initial CSF shunt infection

Variable	No Reinfection	Reinfection	Entire Cohort
No. of patients	195	38	233
Diagnosis of infection*			
CSF culture	147 (75)	25 (66)	172 (74)
Wound infection excluding CSF culture	19 (10)	3 (8)	22 (9)
Abdominal pseudocyst	14 (7)	6 (16)	20 (9)
Exposed hardware	13 (7)	2 (5)	15 (6)
Blood culture in ventriculoatrial shunt	1 (1)	2 (5)	3 (1)
Gram stain only	1 (0)	0 (0)	1 (1)
Organism identified†			
Coagulase-negative staphylococcus	48 (33)	7 (28)	55 (32)
<i>Staphylococcus aureus</i>	43 (29)	6 (24)	49 (28)
Other gram-positive organism	18 (12)	7 (28)	25 (15)
Gram-negative organism	34 (23)	4 (16)	38 (22)
≥1 organism	4 (3)	0 (0)	4 (2)
Fungal	0 (0)	1 (4)	1 (1)
Ventriculitis‡	19 (13)	4 (16)	23 (13)
Bacteremia	15 (8)	4 (11)	19 (8)
Intermittent negative cultures‡	23 (16)	2 (8)	25 (15)
No subsequent negative culture‡	6 (4)	1 (4)	7 (4)
Median duration of positive CSF cultures (IQR)*‡	2.7 (1.3–5.6)	2.5 (1.6–4.3)	2.7 (1.4–5.5)
Initial positive Gram stain§	85 (44)	11 (31)	96 (42)
Median initial white blood cell count¶	47 (5–333)	42 (4–233)	47 (5–307)
Median initial red blood cell count (IQR)¶	43 (3–723)	185 (42–881)	59 (4–723)
Median initial glucose (IQR)**	45 (28–60)	41 (25–61)	44 (27–60)
Median initial protein (IQR)**	87 (25–280)	102 (23–499)	90 (25–298)

Values are shown as the number of patients (%) unless indicated otherwise. No significant differences between groups were found according to the unadjusted Cox.

* Diagnosis of infection was assigned in a hierarchical fashion, with CSF culture being the most definitive and wound culture the least definitive.

† Evaluated in 172 children diagnosed by CSF culture.

‡ Seven patients never had a negative culture obtained after the first positive culture.

§ Evaluated for 231 infections.

¶ Evaluated for 224 infections.

** Evaluated for 219 infections.

only treatment decision that was consistently and independently associated with decreased reinfection risk was the use of rifampin. While these findings did not achieve statistical significance, surgical approach other than total shunt removal at initial CSF shunt infection and nonventriculoperitoneal shunt location were consistently associated with a higher hazard of reinfection, while the use of ultrasound was consistently associated with a lower hazard of reinfection in all 5 Cox proportional hazards models.

Key questions in the treatment of CSF shunt infection still include determination of the appropriate surgical therapy and appropriate duration of antibiotic therapy.^{43,54} While not statistically significant, a surgical approach other than total shunt removal at initial CSF shunt infection was consistently associated with a higher hazard of reinfection in this study. Additionally, the current study adds to the existing literature^{39,47} and, importantly, suggests the feasibility of controlling and standardizing the surgical approach (total shunt removal with EVD placement) to remove potential confounding effects in a trial aimed at identifying

an optimal antibiotic regimen. Significant variation in antibiotic treatment decision making in the treatment of CSF shunt infection has been previously demonstrated.^{23,38,52} This study confirms that considerable variation, and therefore equipoise, exists in the duration and selection of intravenous antibiotic treatment.¹⁷ We believe future studies of the optimal duration of intravenous antibiotic treatment are critical to the creation of high-quality, evidence-based guidelines for CSF shunt infection treatment. A reasonable first step toward a randomized controlled trial would be to standardize treatment of CSF shunt infection and use standard surgical therapy for shunt removal and EVD placement and standard intravenous antibiotic therapy according to duration^{38,46} and organism, as outlined in recent guidelines from the Infectious Diseases Societies of America.⁴⁷

The only treatment decision that was consistently and independently associated with decreased reinfection risk in this cohort was the use of rifampin, which is thought to be effective against biofilms. Rifampin has been reported to be beneficial in case reports,^{4,13,29} case series,⁹ and re-

TABLE 5. Factors independently associated with CSF shunt reinfection among children with infection

Variable	Adjusted OR (95% CI)	
	Full Model for Full Cohort	Children w/ No Revisions Btwn Infection & Reinfection (n = 147)
Chronological age at initial shunt placement		
0–1 mos	0.3 (0.1–0.9)	0.4 (0.1–1.5)
1–6 mos	0.7 (0.3–1.7)	0.2 (0.1–0.9)
6 mos–4 yrs	Referent	Referent
>4 yrs	0.1 (0.0–0.6)	NR
Etiology of hydrocephalus		
Post-IVH due to prematurity	0.6 (0.3–1.5)	1.2 (0.3–4.5)
Cyst (other intracranial, posterior fossa)	NR	
CCCs		
0 (except hydrocephalus)	Referent	Referent
1	2.0 (0.8–5.1)	2.9 (0.7–13.0)
≥2	3.4 (1.1–10.5)	5.6 (1.1–32.0)
Revisions before initial CSF shunt infection		
0	Referent	Referent
1	1.9 (0.7–4.9)	1.2 (0.3–4.2)
≥2	1.1 (0.4–2.9)	0.8 (0.2–2.5)
Visualization used before initial CSF shunt infection		
Both	NR	NR
Endoscope	1.4 (0.5–3.8)	1.0 (0.3–3.4)
Ultrasound	0.5 (0.1–2.2)	0.4 (0.0–4.3)
Neither	Referent	Referent
Unknown	0.4 (0.1–1.4)	0.3 (0.0–1.9)
Surgical approach to treatment of initial infection other than total removal	1.7 (0.6–4.2)	3.2 (0.8–11.7)
No use of rifampin at initial CSF shunt infection	4.2 (1.1–27.6)	7.9 (1.1–173.1)
Duration of overall IV antibiotic use		
<7 days	0.4 (0.0–1.7)	2.2 (0.3–13.7)
8–14 days	Referent	Referent
>14 days	1.5 (0.6–3.7)	1.9 (0.5–7.9)
Visualization used at initial CSF shunt infection/last op prior to censor/reinfection		
Endoscope	0.9 (0.3–2.2)	2.8 (0.8–10.9)
Ultrasound	0.3 (0.0–1.5)	0.4 (0.0–2.1)
Neither	Referent	Referent
Nonventriculoperitoneal shunt location last known op prior to censor/reinfection	1.6 (0.6–3.9)	1.9 (0.6–6.3)
Revisions after initial CSF shunt infection & before censor/reinfection		
0	Referent	
1	1.7 (0.5–4.7)	
≥2	7.0 (1.8–25.0)	

IVH = intraventricular hemorrhage; NR = not reportable.
 Boldface type indicates statistical significance.

view articles.⁷ Rifampin use was either not reported^{17,21} or not beneficial³⁹ in more recent studies. Further consideration should be given to the use of rifampin in the treatment of CSF shunt infection,¹ and rifampin use is recommended for susceptible organisms in recent guidelines from the Infectious Diseases Societies of America.⁴⁷

Nonmodifiable risk factors, such as the number of CCCs and revisions after initial infection, were independently associated with reinfection in this cohort, which

was not observed in earlier detailed studies of reinfection risk.^{17,21,39} While not statistically significant in this study, nonventriculoperitoneal shunt location was consistently associated with a higher hazard of reinfection, as observed in earlier work.³⁹

We observed consistent approaches to visualization during neurosurgical procedures within centers, as well as within a given patient over time. While not statistically significant, the use of ultrasonography was consistently as-

TABLE 6. Factors independently associated with CSF shunt reinfection

Factor	Adjusted OR (95% CI)		
	Time-Varying Hazards Model	Reduced Model	VP Shunt Model
Chronological age at initial shunt placement			
0–1 mos	0.4 (0.1–1.3)	NR	0.3 (0.0–2.1)
1–6 mos	0.7 (0.3–1.8)	NR	0.3 (0.1–1.0)
6 mos–4 yrs	Referent	NR	Referent
>4 yrs	0.2 (0.0–1.2)	NR	ND
Etiology of hydrocephalus			
Post-IVH due to prematurity	0.7 (0.3–1.8)	NR	1.6 (0.4–7.0)
Cyst (other intracranial, posterior fossa)	NR	NR	NR
CCCs			
0 (except hydrocephalus)	Referent	Referent	Referent
1	1.7 (0.6–4.7)	1.9 (0.8–4.5)	3.6 (0.8–17.3)
≥2	3.1 (1.0–9.9)	5.6 (2.0–14.9)	3.8 (0.6–26.5)
Revisions before initial CSF shunt infection			
0	Referent	NR	Referent
1	1.3 (0.4–3.6)	NR	1.4 (0.3–6.0)
≥2	0.9 (0.3–2.4)	NR	1.0 (0.2–4.5)
Visualization used before initial CSF shunt infection			
Both	NR	NR	NR
Endoscope	2.0 (0.7–5.8)	2.2 (1.0–5.1)	1.1 (0.2–6.7)
Ultrasound	0.7 (0.1–3.4)	0.4 (0.1–1.6)	NR
Neither	Referent	Referent	Referent
Unknown	0.5 (0.1–2.3)	0.4 (0.1–1.6)	0.8 (0.1–6.0)
Surgical approach to treatment of initial infection other than total removal	2.0 (0.6–5.5)	NR	4.6 (0.9–22.1)
No use of rifampin at initial CSF shunt infection	6.5 (1.2–121.6)	NR	4.8 (0.7–96.3)
Duration of overall IV antibiotic use			
<7 days	0.7 (0.1–3.5)	NR	2.1 (0.2–15.2)
8–14 days	Referent	NR	Referent
>14 days	1.8 (0.7–5.1)	NR	1.0 (0.2–4.2)
Visualization used at initial CSF shunt infection/last op prior to censor/reinfection			
Endoscope	0.9 (0.3–2.7)	NR	5.0 (0.9–35.5)
Ultrasound	0.2 (0.0–1.0)	NR	0.2 (0.0–2.6)
Neither	Referent	NR	Referent
Nonventriculoperitoneal shunt location last known op prior to censor/reinfection	1.7 (0.6–4.6)	2.6 (1.2–5.5)	NA
Revisions after initial CSF shunt infection & before censor/reinfection			
0	Referent	NR	Referent
1	5.4 (1.1–24.6)	NR	9.2 (0.6–104.0)
≥2	NR	NR	NR

NA = not applicable; ND = not determined.

Boldface type indicates statistical significance.

sociated with a lower hazard of reinfection in all 5 Cox proportional hazards models. This study adds to the literature by suggesting that the use of ultrasonography⁵¹ is associated with a lower risk of shunt failure⁶ or is of uncertain benefit.^{8,53} Although statistical significance was not observed in this cohort, the use of an endoscope before infection was associated with a higher hazard of reinfection in several models. This study adds to the literature by suggesting that the use of an endoscope either is not as-

sociated with reduced shunt failure¹⁶ or is associated with a higher risk of shunt failure.³² These findings suggest that efforts to minimize instrumentation of the CSF may reduce infection risk.

This work has several limitations. The relatively low reinfection rate with a moderate sample size limits our power and ability to adjust for multiple variables, particularly those variables that are not significantly associated with reinfection or correlated with other predictors. Incon-

porating variables with true predictive association with reinfection can reduce unexplained variance and illuminate associations with residual variance. However, we also challenged this by using both judicious model construction and reduced models. Conducting this study at HCRN centers that were adhering to an infection prevention bundle^{18,19} reduces generalizability of the findings outside of HCRN. However, the HCRN prevention bundle has been widely disseminated and implemented in the past 5 years. In addition, the multiinstitutional nature of this study gives it greater generalizability than previous studies. The potential confounding of factors associated with treatment decision making and reinfection risk, such as the center, continues to be problematic. Surgeons may take into consideration individual patient and infection characteristics that are believed to be important enough to influence treatment and are likely to also be associated with treatment outcomes. For example, infection with a difficult-to-treat organism may result in a longer duration of antibiotic administration and may also be likely to reoccur. Our ability to disentangle these associations is limited in this study. Additional aspects of the management of CSF shunt infection—including but not limited to the number, frequency, and method of CSF culturing obtained through EVDs; flushing of EVDs; replacement of EVDs; and the use of antibiotic-impregnated EVDs—are not standardized in HCRN and were subject to variation within and between participating centers. Our definition of infection was developed by consensus within HCRN and does not permit easy comparison with infection rates at non-HCRN centers or those used by hospital infection control groups. For neurosurgical procedures, the assumption is that patients return to the same center for care, and therefore subsequent infections would be captured in our data. Drug levels were not available for the review and determination of concordant and appropriate intravenous antibiotic use.

Conclusions

Neither surgical approach to treatment nor antibiotic duration was associated with reinfection risk. While this finding did not achieve statistical significance, a surgical approach other than total shunt removal at initial CSF shunt infection was consistently associated with a higher hazard of reinfection in this study and suggests the feasibility of controlling and standardizing the surgical approach (shunt removal with EVD placement). Considerable variation, and therefore equipoise, exists in the duration and selection of intravenous antibiotic treatment. The only treatment decision that was consistently and independently associated with decreased reinfection risk in this cohort was the use of rifampin, and further consideration should be given to its use in the treatment of CSF shunt infection. High-quality studies of the optimal duration of antibiotic treatment are critical to the creation of evidence-based guidelines for CSF shunt infection treatment. A reasonable first step toward a randomized controlled trial would be to standardize the treatment of CSF shunt infection by standardizing both surgical shunt removal with EVD placement and intravenous antibiotic therapy and duration according to the recovered organism.

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Appendix

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Conception and design: Simon, Whitlock, Mayer-Hamblett, Oakes. Acquisition of data: Simon. Analysis and interpretation of data: Simon, Kronman, Whitlock, Gove. Drafting the article: Simon. Critically revising the article: Kronman, Whitlock, Gove, Mayer-Hamblett, Holubkov, Kulkarni, Langley, Riva-Cambrin, Rozzelle, Whitehead, Kestle. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Simon. Statistical analysis: Whitlock, Gove. Study supervision: Simon.

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