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Reduction in CSF shunt infection over a 10-year period associated with the application of concentrated topical antibiotic powder directly to surgical wounds prior to closure

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OBJECT The application of concentrated topical antibiotic powder directly to surgical wounds has been associated with a reduction in wound infection in cardiac, spinal, and deep brain stimulator surgery. As a result of these findings, the corresponding author began systematically applying concentrated bacitracin powder directly to wounds during shunt surgery more than 5 years ago. The object of this study was to evaluate the effectiveness of concentrated bacitracin powder applied directly to wounds prior to closure during cranial shunt surgery and to evaluate the association between shunt infection and other risk factors. A single surgeon's cranial shunt surgery experience, equally divided between periods during which antibiotic powder was and was not applied, was studied to assess the effect of concentrated bacitracin powder application on shunt infection rates.

METHODS This retrospective cohort study included all patients who underwent a cranial shunting procedure at All Children's Hospital performed by a single surgeon (G.F.T.) from 2001 to 2013. The surgeon applied bacitracin powder to all shunt wounds prior to closure between 2008 and 2013, whereas no antibiotic powder was applied to wounds prior to 2008. Both initial and revision shunting procedures were included, and all procedures were performed at a large children's hospital (All Children's Hospital). The primary outcome measure was shunt infection, which was defined using clinical criteria previously used by the Hydrocephalus Clinical Research Network. The association between bacitracin powder use and shunt infection was estimated using hazard ratios (HRs) and 95% CIs from Cox proportional hazard regression models.

RESULTS A total of 47 infections out of 539 shunt operations occurred during the study period, resulting in an overall infection rate of 8.7%. Procedures performed before the use of concentrated bacitracin powder was instituted resulted in a 13% infection rate, whereas procedures performed after systematic use of bacitracin powder had been adopted experienced a 1% infection rate. Bacitracin powder use was associated with a reduced risk of shunt infection in univariate analysis (HR 0.11, 95% CI 0.03–0.34, p = 0.0002) and also in multivariate analysis (HR 0.12, 95% CI 0.04–0.41, p = 0.0006) when controlling for covariates that were associated with infection from the univariate analysis. The presence of a tracheostomy or a gastrostomy tube was also found to be independently associated with shunt infection in multivariate analysis (HR 3.15, 95% CI 1.05–9.50, p = 0.04, and HR 2.82, 95% CI 1.33–5.96, p = 0.007, respectively).

CONCLUSIONS This study suggests, for the first time, that the systematic application of concentrated bacitracin powder to surgical wounds prior to closure during shunt surgery may be associated with a reduction in cranial shunt infection. This initial finding requires validation in a large prospective study before widespread application can be advocated.

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KEY WORDS hydrocephalus; cerebrospinal fluid; infection; antibiotic; powder; bacitracin

ABBREVIATIONS ASA = American Society of Anesthesiologists; GMH = germinal matrix hemorrhage; GT = gastrostomy tube; HCRN = Hydrocephalus Clinical Research Network; HR = hazard ratio.

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Shunt infection is one of the most serious complications of cranial shunt surgery, with published infection rates varying significantly from approximately 1% to 16%.[7,11,18,21,23,24,31,34,35,40,47] Shunt infection causes significant morbidity for patients, including prolonged hospitalization, repeated surgery, lengthy exposure to antibiotics, increased deaths, and possible intellectual consequences.[34] The economic impact of hydrocephalus and associated shunt failure or infection exceeds a billion dollars annually in the US.[24,34,42] Minimizing shunt infection is of paramount importance to neurosurgeons and their patients.

Many factors have been associated with a reduced incidence of shunt infection, including double gloving,[49] preoperative antibiotics,[33] strict adherence to protocols,[7,8,23,32] and prevention of CSF leakage from wounds.[24] Large, federally funded, prospective multiinstitutional trials have attempted to incorporate and control for these factors, but infection rates remained as high as 5.7%, even under these optimized study conditions.[23] Surgical wound infection is not unique to cranial shunt surgery or to neurosurgery as a whole. Other specialties face similar challenges, and efforts to reduce or eliminate surgical infection continue on many fronts.

The irrigation of surgical wounds using dilute antibiotics prior to closure has been commonly performed by surgeons in many specialties for years, with unclear efficacy.[3,4,38,53] More recently, concentrated antibiotic powder and/or antibiotic spheres have been applied directly to surgical wounds just prior to closure, in an effort to further reduce surgical wound infection by achieving higher antibiotic concentrations than those associated with dilute antibiotic irrigation. Large, prospective, randomized trials have shown that the application of topical gentamicin directly to sternal wounds in cardiac surgery has led to a significant reduction in infection rates.[15,16,39] Similarly, the use of vancomycin powder in posterior spinal fusion for trauma has shown reduced infection rates from as much as 13% to as low as 0%.[17,19]

The application of concentrated antibiotics directly to surgical wounds during nonspinal neurosurgical procedures has been more limited. Miller et al. showed that the infusion of concentrated neomycin and polymyxin directly into wounds during deep brain stimulator implantation resulted in a 1.2% infection rate, which was significantly lower than the 5.7% rate reported in their historical cohort in which concentrated antibiotics were not instilled just prior to closure.[27]

In this study, we evaluated the association between concentrated bacitracin powder applied directly to wounds prior to closure during cranial shunt surgery and shunt infection in a large children's hospital. We believe this is the first published report to study the effect of the direct application of a concentrated antibiotic powder to surgical wounds during cranial shunt surgery. We also evaluated the association between shunt infection and other factors such as patient demographics, operative variables, and previous shunt-related procedures.

Methods

Patient Population and Definition of Shunt Infection

The study was approved by the All Children's Hospital Institutional Review Board. A retrospective chart review of all cranial shunt procedures performed by the corresponding author (G.F.T.) between January 2001 and March 2013 was performed by 2 independent reviewers (J.M.B. and L.L.T.). The operating surgeon (G.F.T.) was not involved with data collection. The analysis was limited to operations performed by the corresponding author because he was the only neurosurgeon operating at All Children's Hospital who systematically applied antibiotic powder to all shunt wounds during the study period. The analysis was also limited to this time period because electronic medical records were not readily available for patient care that occurred earlier than 2001. All procedures were performed at a freestanding children's hospital and included patients ranging in age from 1 day to 24 years, i.e., a primarily pediatric population with the exception of a few adults who ethically could not be transferred during acute shunt malfunction. Minimal follow-up duration was 180 days.

Patients were initially identified by searching billing records using Current Procedural Terminology codes that pertained to initial or revision shunt procedures, including ventriculoperitoneal, ventriculoatrial, ventriculopleural, ventriculo-gall bladder, and cystoperitoneal shunts. Of the 658 procedures that were identified through billing records, 119 procedures were excluded from the analysis for the following reasons: a lack of documented 180-day follow-up (n = 73), lumboperitoneal shunt (n = 2), syringo-subarachnoid shunt (n = 1), shunt externalization and placement of an external ventricular drain (n = 28), and procedures for which the corresponding author was listed as an assistant to other attending surgeons (n = 15). The remaining 539 procedures were analyzed.

The primary outcome variable was shunt infection within 1 year of the surgery. Shunt infection was defined in the manner similar to that used in recent studies by the Hydrocephalus Clinical Research Network (HCRN).[22] Shunt infection was considered present if 1 or more of the following criteria were present: 1) positive culture or Gram stain from CSF, wound swab, or pseudocyst fluid; 2) wound breakdown with visible hardware; 3) presence of abdominal pseudocyst (considered infection even in the absence of positive cultures); and 4) positive blood cultures in a patient with a ventriculoatrial shunt.[23]

Other Variables Studied

In addition to the primary outcome of shunt infection, we also collected data on 23 other clinical variables that have been associated with cranial shunt infection in previously published reports or that were anecdotally considered risk factors for infection by the authors. We subdivided these clinical variables into 3 categories: demographics factors, history of previous shunt surgery or shunt infection, and operative factors (Table 1).

The definition of most variables is self-explanatory and is detailed in the tables. More specifically, insurance status was categorized into private and nonprivate (nonprivate included Medicare, Medicaid, self pay, and no charge). Prematurity was defined as birth at less than 36 weeks of gestation. We included "surgery in the first 90 days in a premature child" to delineate the difference

TABLE 1. The 23 factors examined in the study in addition to shunt infection

Demographics
Age
Sex
Race
Health insurance
Etiology of hydrocephalus
Premature birth
Surgery in the first 90 days of life in a premature infant
Tracheostomy present
Gastrostomy tube present
ASA score
Surgical history/history of infection
First shunt operation?
Transition from subgaleal shunt or ventricular reservoir
No. of shunt operations performed within 90 days of surgery
Recent shunt infection (within 1 month)
Operative factors
Operative time
Operating room nursing shift
Shunt type (VP, VA, etc.)
Type of shunt surgery (proximal, valve, distal, etc.)
Neuroendoscopy utilized
Neuronavigation utilized
Use of intrathecal antibiotics
Use of antibiotic-impregnated shunt
Concentrated bacitracin powder

VA = ventriculoatrial; VP = ventriculoperitoneal.

between operating on a child during his/her prematurity versus operating on a child with a history of prematurity, both of which we believed could contribute independently to shunt infection rates. An American Society of Anesthesiologists (ASA) score[51] of 1 or 2 was combined because of their relative similarity and compared independently to an ASA score of 3 and an ASA score of 4. No patients had ASA scores of 5 or 6. "Recent shunt infection" was defined as an infection within 1 month of a shunt operation.

The etiology of hydrocephalus was classified into 1 of 6 categories: congenital, spina bifida, germinal matrix hemorrhage (GMH), acquired, tumor, and pseudotumor. "Congenital" included children with encephalocele, arachnoid cyst, posterior fossa cyst, aqueductal stenosis, and syndromic and genetic hydrocephalus. "Acquired" included children with meningitis, posttraumatic hydrocephalus, and hydrocephalus from hemorrhage other than GMH.

Shunt surgery type was divided into 6 different categories based on a detailed analysis of the operative report: proximal only, proximal plus valve, valve only, distal, and complete. "Complete" shunt surgery type included both de novo shunt placement and complete shunt revision with removal of all shunt components and placement of a new system. Intrathecal antibiotics always included both vancomycin and gentamicin given dose dependently: if the patient was less than 3 months of age, 5 mg of vancomycin and 1 mg of gentamicin were given, and if the child was older than 3 months, 10 mg of vancomycin and 2 mg of gentamicin were given. "Antibiotic-impregnated catheter use" was defined as using an antibiotic-impregnated proximal catheter or distal catheter, or both. The Bactiseal catheter (Codman & Shurtleff) was the antibiotic-impregnated catheter used.

Application of Bacitracin and Routine Surgical Technique

We initiated the use of bacitracin powder based on previously published results in other types of surgery. We chose bacitracin as the antibiotic of choice because it is readily available, inexpensive, and has been used safely and routinely in a dilute form during shunt operations for decades. When bacitracin antibiotic powder was used in this study, it was placed in all wounds as the final step just prior to closure, following strict hemostasis and thorough irrigation of all wounds with dilute bacitracin irrigation (50,000 U/L of saline). The dry, granular form of the antibiotic was placed in all wounds, but not in a precise dose-dependent manner. Powder chunks were generally tucked under wound edges with forceps, and the fine powder was simply applied to the wound prior to closure (Fig. 1). The powder would typically turn into a thick slurry as it mixed with the surrounding serous fluid and residual blood products. For children of adult size, an entire bottle (50,000 U) was commonly used to fill all of the wounds. Smaller doses were used in premature infants and infants, but a strict weight-dependent formula was not used. The wound was then closed in the typical fashion without washing away any of the bacitracin powder.

All shunts were placed with the help of an assistant (usually a neurosurgical resident) at a freestanding children's hospital. Standard operating procedures that did not change during the study period included the following: minimal hair removal using clippers, pre-preparation with topical chlorhexidine (Hibiclens) and 3% isopropyl alcohol, wound infiltration with local anesthetic containing epinephrine, skin preparation with either povidone-iodine gel or Prevail solution (CareFusion), use of povidone-iodine–impregnated adhesive drapes over all exposed skin, the use of double gloves by all staff, multiple wound irrigations with bacitracin solution (50,000 U mixed with 1 L of lactated ringers solution), and application of antibiotic ointment to the closed wound at the end of the procedure with only rare use of any sort of surgical dressing. The corresponding author did not use the "no touch" technique for shunt placement nor did he strictly limit operating room traffic. Hand washing techniques were varied between traditional scrubbing and antiseptic solution. Shunt surgeries were performed using antibiotic-impregnated or standard nonantibiotic systems, with pressure-controlled or programmable valves. Endoscopy and/or neuronavigation were intermittently used for catheter placement.

Statistical Analysis

Descriptive data were summarized by infection status using counts (with percentages) for categorical vari-

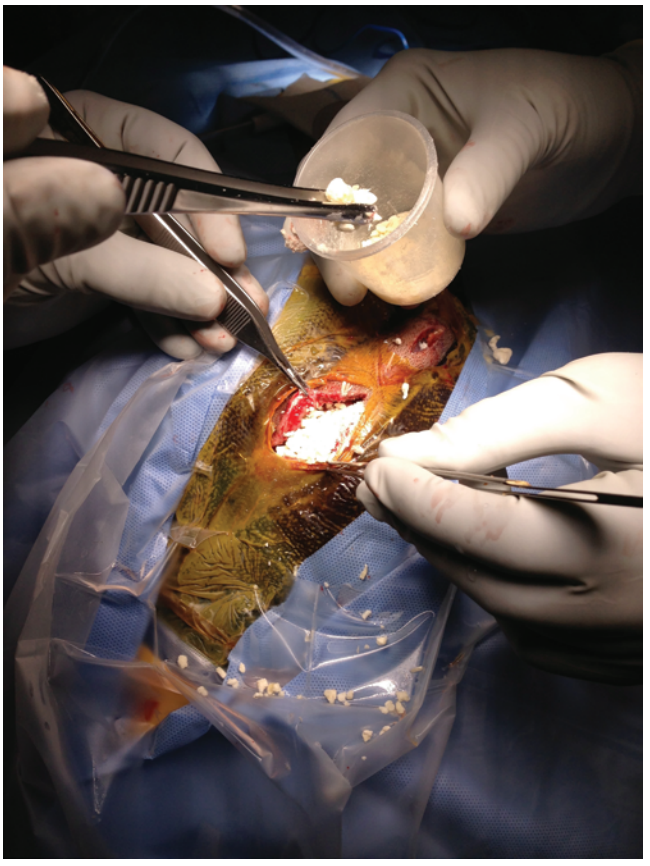

FIG. 1. Photograph of bacitracin powder being placed in a wound just prior to closure. Figure is available in color online only.

ables and medians (with ranges) for continuous variables. Kaplan-Meier analysis was used to estimate infection-free survival probabilities for the 2 time periods and the differences between the periods were compared using a log-rank test. Cox proportional hazards regression that accounts for repeated events (some patients had undergone surgical shunt procedures several times during the study period) was used to estimate the hazard ratios (HRs) and 95% CIs for the association between bacitracin powder use and the development of a postoperative shunt infection, while adjusting for potential confounders. Time to infection was defined as the time from surgical shunt procedure by the principal investigator to the development of the first recorded infection. Patients who did not develop infection were censored at the time of a subsequent surgery (by the principal investigator or another surgeon), death, or last documented contact. Potential confounding factors were evaluated in univariate analyses and factors with a p value < 0.2 were included in a multivariable model to control for their effect on the association between bacitracin powder use and the development of a postoperative shunt infection. We also constructed another multivariate model that included factors previously reported to be associated with shunt infection. Statistical analyses were performed using SAS (version 9.3, SAS Institute). All statistical tests were 2-sided and a p value < 0.05 was considered statistically significant.

Results

Shunt Infections

Our database contained information on 539 shunt procedures (initial and revision) performed by the corresponding author at All Children's Hospital between 2001 and 2013. A total of 47 shunt infections, as defined by the criteria set forth above,[23] were encountered in our cohort. Thirty of these infections had positive CSF cultures, with the majority consisting of *Staphylococcus* species (n = 18). There were a total of 9 wound breakdowns, 7 pseudocysts, and no infections associated with bacteremia in a ventriculoatrial shunt (Table 2). There were no complications from the use of topical bacitracin, including no cases of anaphylaxis or wound breakdown.

Time Period Comparisons

The infection rate for the early time period (2001–2005), when bacitracin powder was not used, was 13%. The infection rate dropped to 1% in the later time period (2008–2013), when concentrated bacitracin antibiotic powder was uniformly applied. No data were analyzed in 2006 or 2007 because the corresponding author practiced at a different facility during that time period.

Variable frequencies were then compared between the two time periods to analyze potential changes in the patient population and the surgical technique over the 12-year period (Table 3). Patient characteristics were similar between the time periods, aside from a greater percentage of patients without private insurance and of Hispanic and African-American descent in the later time period. Patients were also less likely to have undergone a shunt operation in the 90 days prior to the index shunt procedure and less likely to have had a previous shunt infection in the 2008–2013 time period. Patients were more likely to have had their shunt operation during the daytime nursing shift in the later time period and they were also more likely to have had just a distal revision of their shunt. Neuronavigation and antibiotic-impregnated catheters were also more commonly used in the later time period (Table 3).

Comparison of Variables Among Operations

A Kaplan-Meier analysis showed that patients in the 2001–2005 period were more likely to develop an infection compared with those in the 2008–2013 period ($p < 0.001$, log-rank test; Fig. 2). While shunt infection rates significantly declined in the later time period, when antibiotic bacitracin powder was applied, there were also some changes in practice pattern and surgical technique during this 12-year period. To evaluate if the observed decline in infection due to bacitracin was independent of these other factors, all the data from 2001 to 2013 were pooled and analyzed using univariate and multivariate Cox proportional hazard regression models, with the presence or absence of a shunt infection as the outcome (Table 4). The results of these analyses are described in the sections that follow.

Univariate Analysis

Patient factors that were significant ($p < 0.05$) in the univariate analysis were as follows: the presence of a tra-

TABLE 2. Infection characteristics with or without bacitracin powder

Infection Criteria	No Powder (n = 336)	Powder (n = 203)
Total infections by HCRN criteria	44 (13%)	3 (1%)
Positive CSF culture or Gram stain		
S. epidermidis	8	—
MSSA	5	1
Enterobacter species	3	—
MRSA	2	—
Abiotrophia species	1	—
Coagulase-negative staphylococci	1	—
Gram-positive rods	1	—
Diphtheroids	1	—
Group A *Streptococci*	1	—
Haemophilus influenza	1	—
Propionibacterium acnes	1	—
Pseudomonas aeruginosa	1	—
Serratia marcescens	1	—
S. auricularis	1	—
S. hominis	1	—
S. viridans	1	—
Wound breakdown		
Culture negative	8	—
CSF + (MSSA)	1	—
Pseudocyst, no growth		
Culture negative	4	2
Culture + (diphtheroid)	1	—
Bacteremia w/ VA shunt	—	—

MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*.

cheostomy ($p < 0.0001$); presence of a gastrostomy tube (GT; $p < 0.0001$); an ASA score of 4 ($p = 0.02$); the number of shunt operations in the previous 90 days ($p = 0.01$; this was run as an ordinal variable, meaning that there was a trend toward infection as the number of operations increased); recent shunt infection ($p < 0.0001$); ventriculopleural shunt compared with ventriculoperitoneal shunt ($p = 0.02$); and the lack of use of bacitracin powder just prior to closure ($p = 0.008$; Table 4). These should not be considered independent risk factors for infection due to possible confounders, which was assessed in the multivariate analysis.

Factors not found to be significant in the univariate analysis but with a p value < 0.2 in the univariate analysis included prematurity, ASA score of 3, revision versus initial surgery, and the use of standard shunt hardware instead of antibiotic-impregnated catheters (Table 4). Notable factors that did not show a significant association with shunt infection ($p \geq 0.2$) were age, sex, race, type of health insurance, etiology of hydrocephalus, and the nursing shift during which the operation was performed. Although the etiology of GMH had a p value of less then 0.2, the Type-3 p value for etiology as a whole was 0.44, so it was not included in the multivariate analysis. The same was true for the "proximal + valve" revision type (Type-3 p value = 0.29). Type-3 p values are not listed in Table 4. We chose

TABLE 3. Variable frequency in two separate 5-year periods: 2001–2005 (no antibiotic powder) and 2008–2013 (bacitracin powder)

Variable	2001–2005	2008–2013	p Value
Demographics			
No. of patients	336	203	
Age (days)			0.95
Median	3066.5	2990.9	
Range	1–8850	2–7974	
Sex (%)			0.53
Female	175 (52)	100 (49)	
Male	161 (48)	103 (51)	
Race (%)			0.0012
Caucasian	247 (73)	124 (61)	
African American	63 (19)	44 (22)	
Hispanic	26 (8)	35 (17)	
Health insurance (%)			<0.0001
Not private	139 (41)	140 (69)	
Private	131 (39)	59 (29)	
Missing	66 (20)	4 (2)	
Etiology (%)			0.23
Congenital	120 (36)	63 (31)	
Spina bifida	52 (15)	41 (20)	
GMH	100 (30)	62 (31)	
Acquired	21 (6)	9 (4)	
Tumor	29 (9)	24 (12)	
Pseudotumor	13 (4)	3 (1)	
Missing	1 (0)	1 (1)	
Premature (%)			0.49
No	195 (58)	125 (62)	
Yes	138 (41)	78 (38)	
Missing	3 (1)	0 (0)	
Surgery in first 90 days in premature child (%)			0.88
No	120 (36)	69 (34)	
Yes	18 (5)	11 (5)	
Missing	198 (59)	123 (61)	
Tracheostomy (%)			0.08
No	272 (81)	196 (97)	
Yes	11 (3)	2 (1)	
Missing	53 (16)	5 (2)	
GT (%)			0.51
No	226 (67)	165 (81)	
Yes	53 (16)	33 (16)	
Missing	57 (17)	5 (3)	
ASA (%)			0.19
1 & 2	40 (12)	67 (33)	
3	108 (32)	121 (60)	
4	8 (2)	14 (6)	
Missing	180 (54)	1 (1)	

(continued)

TABLE 3. Variable frequency in two separate 5-year periods: 2001–2005 (no antibiotic powder) and 2008–2013 (bacitracin powder) *(continued)*

Variable	2001–2005	2008–2013	p Value
Surgical history/history of infection			
Initial vs revision operation (%)			0.36
Revision	274 (82)	159 (78)	
Initial	62 (18)	44 (22)	
Transition from subgaleal shunt (%)			0.11
No	334 (99)	198 (98)	
Yes	2 (1)	5 (2)	
No. of shunt operations in previous 90 days (%)			0.047
0	212 (63)	147 (72)	
1	69 (21)	28 (14)	
2	21 (6)	16 (8)	
3 or more	34 (10)	12 (6)	
Recent shunt infections (%)			<0.0001
No	310 (92)	202 (100)	
Yes	26 (8)	1 (0)	
Time to event (days)			0.25
Median	352	407	
Range	1–4888	1–341	
Operative factors			
Operative time (min)			0.24
Median	41	42	
Range	12–253	15–242	
Nursing shift (%)			0.0001
Day	194 (58)	145 (72)	
Afternoon	128 (38)	43 (21)	
Night	14 (4)	15 (7)	
Shunt type (%)			0.044
Ventriculoperitoneal	276 (82)	181 (89)	
Ventriculoatrial	50 (15)	20 (10)	
Ventriculopleural	7 (2)	0 (0)	
Ventriculo–gall bladder	3 (1)	2 (1)	
Shunt surgery type (%)			0.002
Complete	141 (42)	74 (36)	
Proximal only	114 (34)	70 (34)	
Proximal & valve	42 (13)	12 (6)	
Distal	28 (8)	33 (16)	
Valve only	11 (3)	14 (7)	
Neuroendoscopy (%)			0.43
No	274 (82)	171 (84)	
Yes	62 (18)	32 (16)	
Neuronavigation (%)			0.037
No	331 (99)	194 (96)	
Yes	5 (1)	9 (4)	
Operative factors *(continued)*			
Intrathecal antibiotics (%)			<0.0001
No	193 (57)	183 (90)	
Yes	0 (0)	18 (9)	
Missing	143 (43)	2 (1)	
Antibiotic-impregnated catheter (%)			<0.0001
No	285 (85)	116 (57)	
Yes	46 (14)	84 (41)	
Missing	5 (1)	3 (1)	
Bacitracin powder			<0.0001
No	336 (100)	0 (0)	
Yes	0 (0)	203 (100)	
Infection according to HCRN criteria (%)			<0.0001
No	292 (87)	200 (99)	
Yes	44 (13)	3 (1)	
Time to infection (days)			<0.0001
Median	32	47	
Range	1–341	23–78	

to exclude the ASA classification from the multivariate analysis, even though there was an association with shunt infection, because almost half of the patients were missing data, which would severely underpower our final analysis.

Lastly, use of intrathecal antibiotics could not be calculated using Cox proportional hazard analysis because it was not used in the historical cohort (Table 3) and, of the 18 patients to whom it was given, none developed an infection (Table 4), rendering a zero value. Any analysis would ultimately lead to a value of infinity. Due to the low numbers of patients who received intrathecal antibiotics (n = 18) and significant missing data (roughly one-third of the population; Table 4), the authors believe that analysis including the covariate would be underpowered to make any substantial conclusions.

Multivariate Analysis

A multivariate Cox proportional hazard analysis showed that topical bacitracin powder had an independent association with shunt infection (HR 0.12, 95% CI 0.04–0.41, p = 0.0006; Table 5). The HR for bacitracin powder use in the multivariate analysis was 0.12, indicating bacitracin powder had a protective effect on shunt infection (88% reduction in shunt infection). Both the presence of a tracheostomy and GT were also independent risk factors for shunt infection (p = 0.04 and p = 0.007, respectively).

Multivariate Analysis of Factors Previously Shown to Be Associated With Shunt Infection

To further evaluate factors that could be associated

with shunt infection and possibly confound our results, we performed an a priori multivariate analysis strictly including factors that have been shown to be statistically significant in previous studies but not necessarily in our univariate analysis. These factors included operative time,[47] antibiotic-impregnated catheters,[1,21,31,33,48] sex,[34] GT,[29,40] age,[13,24,26,34,36,40,43,49,50] prematurity,[24,26] etiology of hydrocephalus,[13,34,50] initial versus revision surgery,[13,40,43] and recent shunt infection.[26] These studies differ vastly with respect to design, procedure volume, definition of shunt infection, and statistical methodology, but the authors believe they are nonetheless important to evaluate. The results of this analysis once again showed both topical bacitracin and GT remained statistically significant ($p = 0.016$ and $p = 0.002$, respectively; Table 5) in their association with shunt infection. Interestingly, operative time was also statistically significant ($p = 0.041$), although only limited conclusions can be drawn from this finding.

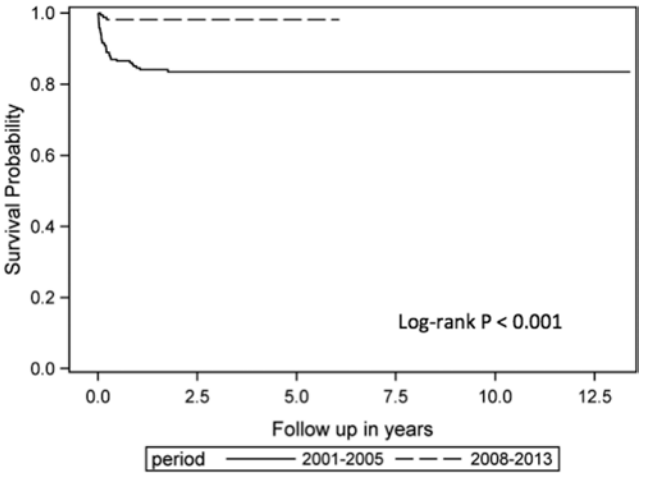

FIG. 2. Kaplan-Meier plot of infection-free survival for patients in the 2001–2005 (no bacitracin) and 2008–2013 (bacitracin powder) time periods.

Discussion

Bacitracin Powder and Shunt Infection

Our retrospective multivariate analysis of 539 shunt operations over a 10-year period showed that the application of bacitracin powder to shunt wounds was independently associated with a reduction in shunt infection. We also found the presence of a tracheostomy or a GT to independently increase shunt infection rates by 3-fold.

The corresponding author began systematically utilizing antibiotic powder during shunt surgery based on reports of infection reduction with similar techniques in other types of surgery. Bacitracin was chosen, rather than other antibiotics such as vancomycin or gentamycin, because it was inexpensive, readily available, and had been used routinely as an irrigant in a dilute form by the corresponding author and many other neurosurgeons inserting cranial shunts in the US for many years. The authors recognized that while dilute bacitracin irrigation solution (5 U/ml) is widely applied and is associated with low complication rates, its effectiveness in reducing infection in shunt surgery or other types of surgery has not been proven or universally accepted.[3,4,38] Dilute bacitracin irrigation was routinely used in all surgeries performed in this series. The concentrated bacitracin powder was used only in the operations performed after 2005.

While our study is the first to address the impact of the direct application of antibiotics to surgical wounds in CSF shunt surgery specifically, many previous studies have evaluated this concept with other surgical procedures. Huiras et al. recently reviewed the use of local antibiotics across multiple subspecialties including dermatology, orthopedics, colorectal surgery, general surgery, and cardiothoracic surgery.[20] Previously published studies have reported conflicting results, and there is a lack of Level I evidence to support the routine use of topical antibiotics in surgical wounds at this time. However, some well-designed studies have shown encouraging results.

The use of local concentrated vancomycin powder is prevalent in the orthopedic and neurosurgical spine literature. There are multiple retrospective studies that support the use of 1–2 grams of topical vancomycin in the wound for reducing both deep and superficial infections.[28,30,46] Local gentamicin is prevalent in the cardiovascular literature but has had inconsistent results. In the Local Gentamicin for Sternal Wound Infection Prophylaxis (LOGIP) trial (a prospective randomized controlled trial with 2000 procedures), the placement of collagen-gentamicin sponges (with 260 mg gentamicin) within the sternotomy wound prior to closure reduced infection rates from 9% to 4.3%.[15,16] These findings were confirmed with another prospective randomized controlled trial in 2012 showing infection reduction from 3.5% to 0.56%.[39] However, 2 randomized controlled trials in 2005 and 2010 failed to show a significant change in infection with topical antibiotics.[20]

As Alves and Godoy stated in their recent review, compared with other specialties, there have been very few neurosurgical studies that evaluated the role of topical antibiotics in infection prevention.[2] In one of the few neurosurgical publications on this topic, Miller et al. reported that local neomycin and polymyxin combined with systemic antibiotics were superior to systemic antibiotics alone in reducing stereotactic and functional hardware infection, with no associated complications.[27]

We found the use of bacitracin powder to be economical and safe. The typical uses of bacitracin as a dilute wound irrigant during surgery and as a topical ointment applied to the skin have been associated with relatively few serious complications.[6] Bacitracin as a dilute irrigant has been rarely associated with anaphylaxis.[6,10] Bacitracin as an ointment has been associated with wound irritation and some increase in wound breakdown.[12] Nephrotoxicity has also rarely been reported when used via the intramuscular route.[14] In our study, concentrated bacitracin powder applied to the wound was not associated with wound breakdown or anaphylaxis. We did not specifically measure wound irritation in the bacitracin powder group, but the authors have noted no increase in wound problems after many years of concentrated bacitracin utilization. Finally, the use of bacitracin powder did not appear to select for unusual or antibiotic-resistant organisms in this study.

TABLE 4. Frequency and univariate analysis of variables as they relate to shunt infection

Variable	Frequency		Univariate Analysis		
	No Infection	Infection	HR	95% CI	p Value
Demographics					
Age (days)			1.0	1.0–1.0	0.76
Median	3055	2699			
Range	1–8850	60–7268			
Sex (%)			1.39	0.77–2.45	0.28
Female	255 (52)	20 (43)			
Male	237 (48)	27 (57)			
Race (%)					
Caucasian	335 (68)	36 (77)	Ref.		
African American	99 (20)	8 (17)	0.76	0.35–1.64	0.49
Hispanic	58 (12)	3 (6)	0.48	0.15–1.58	0.23
Health Insurance (%)			1.24	0.66–2.33	0.49
Not private	258 (52)	21 (45)			
Private	172 (35)	18 (38)			
Missing	62 (13)	8 (17)			
Etiology (%)					
Congenital	170 (35)	13 (28)	Ref.		
Spina bifida	86 (17)	7 (15)	0.98	0.39–2.45	0.96
GMH	143 (29)	19 (40)	1.73	0.86–3.51	0.13
Acquired	29 (6)	1 (2)	0.47	0.06–3.61	0.47
Tumor	47 (10)	6 (13)	1.79	0.68–4.71	0.24
Pseudotumor	15 (3)	1 (2)	0.98	0.13–7.48	0.98
Missing	2 (0)	0 (0)			
Premature (%)			1.63	0.92–2.89	0.09
No	297 (60)	23 (49)			
Yes	192 (39)	24 (51)			
Missing	3 (1)	0 (0)			
Surgery first 90 days in premature child (%)			0.49	0.12–2.12	0.35
No	167 (34)	22 (47)			
Yes	27 (5)	2 (4)			
Missing	298 (61)	23 (49)			
Tracheostomy (%)			8.45	3.55–20.1	<0.0001
No	432 (88)	36 (77)			
Yes	7 (1)	6 (13)			
Missing	53 (11)	5 (10)			
GT (%)			4.18	2.27–7.72	<0.0001
No	367 (75)	24 (51)			
Yes	68 (14)	18 (38)			
Missing	57 (11)	5 (11)			
ASA (%)					
1 and 2	104 (21)	3 (6)	Ref.		
3	210 (43)	19 (40)	3.37	0.10–11.4	0.05
4	19 (4)	3 (6)	6.25	1.26–31	0.02
Missing	159 (32)	22 (47)			
Surgical history/history of infection					
Initial vs revision operation (%)			0.45	0.18–1.12	0.09
Revision	391 (79)	42 (89)			
Initial	101 (21)	5 (11)			

(continued)

TABLE 4. Frequency and univariate analysis of variables as they relate to shunt infection *(continued)*

Variable	Frequency		Univariate Analysis		
	No Infection	Infection	HR	95% CI	p Value
Surgical history/history of infection *(continued)*					
Transition from subgaleal shunt or reservoir (%)			1.50	0.21-10.9	0.69
No	486 (99)	46 (98)			
Yes	6 (1)	1 (2)			
No. of shunt ops in previous 90 days (%)			1.40	1.08-1.81	0.010
0	335 (68)	24 (51)			
1	86 (18)	11 (23)			
2	30 (6)	7 (15)			
3 or more	41 (8)	5 (11)			
Recent shunt infection			5.90	2.75–12.6	<0.0001
No	473 (96)	39 (83)			
Yes	19 (4)	8 (17)			
Time to event (days)			—	—	—
Median	450	32			
Range	1–4888	1–341			
Operative factors					
Op time (min)			1.00	0.99–1.01	0.33
Median	41	45			
Range	12–253	13–184			
Nursing shift (%)					
Day	312 (63)	27 (57)	Ref.		
Afternoon	153 (31)	18 (38)	1.42	0.78–2.57	0.25
Night	27 (6)	2 (4)	1.09	0.26–4.59	0.90
Shunt type (%)					
Ventriculoperitoneal	421 (85)	36 (77)	Ref.		
Ventriculoatrial	62 (13)	8 (17)	1.60	0.75–3.45	0.22
Ventriculopleural	5 (1)	2 (4)	5.82	1.40–24.2	0.02
Ventriculo–gall bladder	4 (1)	1 (2)	2.99	0.41–21.8	0.28
Shunt surgery type (%)					
Complete	194 (39)	21 (45)	Ref.		
Proximal only	171 (35)	13 (28)	0.75	0.37–1.49	0.40
Proximal + valve	46 (9)	8 (17)	1.72	0.76–3.89	0.19
Distal	57 (12)	4 (8)	0.63	0.22–1.84	0.40
Valve only	24 (5)	1 (2)	0.40	0.05–3.01	0.38
Neuroendoscopy (%)			0.80	0.36–1.78	0.58
No	405 (82)	40 (85)			
Yes	87 (18)	7 (15)			
Neuronavigation (%)			0.83	0.12–6.05	0.86
No	479 (97)	46 (98)			
Yes	13 (3)	1 (2)			
Intrathecal antibiotics (%)			—	—	—
No	343 (70)	33 (70)			
Yes	18 (4)	0 (0)			
Missing	131 (26)	14 (30)			
Antibiotic-impregnated catheters (%)			0.53	0.24–1.18	0.12
No	363 (74)	38 (81)			
Yes	123 (25)	7 (15)			
Missing	6 (1)	2 (4)			

(continued)

TABLE 4. Frequency and univariate analysis of variables as they relate to shunt infection *(continued)*

Variable	Frequency		Univariate Analysis		
	No Infection	Infection	HR	95% CI	p Value
Operative factors *(continued)*					
Bacitracin powder (%)			0.11	0.03–0.34	0.0002
No	292 (59)	44 (94)			
Yes	200 (41)	3 (6)			

Ref. = reference.

Local administration of antibiotics is attractive because high concentrations can be achieved in the wound with limited systemic toxicity. Local hematomas, seromas, and areas of tissue necrosis are often present despite the most meticulous surgical technique.[44] These areas are at highest risk of infection and have the lowest penetration of systemically administered antibiotics. Essentially, this technique allows antibiotics to be placed where they are needed the most, regardless of their mechanism of action.

Other Variables Associated With Shunt Infection

Nine factors other than bacitracin powder had a p value of less than 0.2 in our univariate analysis: the presence of a tracheostomy, presence of a GT, high ASA score, prematurity, a recent shunt infection, revision surgeries, shunt type (ventriculopleural), the use of antibiotic-impregnated shunt components, and the number of shunt operations in the previous 90 days (Table 4). Even though 7 of the 9 factors (tracheostomy, GT, ASA score of 4, number of shunt operations in the previous 90 days, recent shunt infection, shunt type [ventriculopleural], and bacitracin powder) reached significance in the univariate analysis, only bacitracin powder, tracheostomy, and GT maintained statistical significance in the multivariate analysis, thereby showing an independent association with shunt infection.

Both a tracheostomy and the presence of a GT were recently evaluated by Simon et al. in their prospective investigation of shunt infection risk factors.[40] They found that the presence of a GT resulted in a 2-fold increased risk of infection in their multivariate analysis. This is logical, as it appears a direct communication between the peritoneal cavity and the skin would confer increased risk of infection in ventriculoperitoneal shunts.[40] Unfortunately, neither our study nor theirs could collect data on the timing of GT placement compared with shunt insertion, so our understanding of that correlation is limited. Nabika et al., however, retrospectively assessed a small cohort of 23 adult patients in Hiroshima and concluded that there was an increased risk of infection when a percutaneous endoscopic gastrostomy was placed within a month after ventriculoperitoneal shunt placement.[29] Further studies would need to assess this.

To our knowledge, this is the only study to find the presence of a tracheostomy to be an independent risk factor for infection. Both Simon et al.[40] and Nabika et al.[29] failed to show this correlation. Our findings of relating both tracheostomy and GT to infection could simply confer medical complexity and a generalized increased risk for morbidity. Nevertheless, these should be considered important risk factors during operative planning and patient counseling.

Lastly, we believe this is the first study to evaluate a patient's ASA score and its relationship to shunt infection. ASA scores of of 3 ($p = 0.05$) and 4 ($p = 0.02$) were shown to be associated with subsequent infection in the univariate analysis (Table 4). This may suggest a link between comorbidities and rate of shunt infection (i.e., tracheostomy and GT above); however, there was a significant amount of missing data (roughly one-third, foregoing placement into the multivariate analysis) so we cannot conclude that they are independent risk factors for infection in this study.

Variables Associated With Infection in Previous Studies

Some results in our study contradicted results from previously published studies. Sex, race, age, health insurance type, and etiology of hydrocephalus are demographic factors that have been associated with infection in previous studies but were not correlated with infection in our study. Previous studies regarding sex are inconsistent, with Reddy et al. showing an increase in infection in males, while Simon et al. showed increased infection in females.[34,41] Our results were more consistent with those of Renier et al., McGirt et al., and Theophilus et al., who showed no correlation between infection rates and a patient's sex.[26,36,47]

The literature on race is inconsistent as well. Simon et al. showed increased infection rates in Asian and African-American children.[41] Our results were more consistent with the findings of Reddy et al. and Theophilus et al., who reported a similar distribution of infection across races.[34,47] Similarly, studies have shown conflicting associations with age at the time of surgery. Some studies have seen no difference in infection rates based on age (comparing < 1 month, 1–6 months, 6–12 months, 12–18 months, and > 24 months, or comparing "neonate," "infant," "child," and "adult")[7,11,47] and others show increased risk with younger age (varying from less than 4 months to less than 11.3 years).[13,34,36,43,49,50] Although our infection group tended to be younger, age was not found to be a statistically significant predictor of infection. To further assess the effect of patient age, we examined prematurity and assessed the following factors: surgery in the first 90 days after premature birth, and patients with a history of prematurity regardless of age at the time of surgery. The published evidence on this factor is inconsistent, with some studies showing an increase in infection and others showing no difference.[11,21,24,26] Our results showed that any history of prematurity had a weak association with infection, but surgery within 90 days after premature birth did

TABLE 5. Risk factors for shunt infection determined by multivariate analyses

Variable	HR	95% CI	p Value
Multivariate analysis*			
Prematurity	1.34	0.70–2.55	0.38
Initial shunt operation	0.37	0.11–1.31	0.12
Type of shunt revision	0.67	0.13–3.61	0.64
No. of shunt operations within 90 days	1.11	0.77–1.61	0.58
Antibiotic-impregnated catheters	1.06	0.44–2.55	0.89
Recent shunt infection	2.16	0.72–6.49	0.17
Tracheostomy present	3.15	1.05–9.50	0.04†
GT present	2.82	1.33–5.96	0.007†
Bacitracin powder	0.12	0.04–0.41	0.0006†
Multivariate analysis of factors previously related to shunt infection			
Age (days)	1.00	1.00–1.00	0.91
Sex	0.71	0.28–1.79	0.46
Etiology of hydrocephalus	1.46	0.44–4.83	0.53
Operations within 90 days of life in a premature infant	0.98	0.07–13.6	0.99
Initial shunt operation	0.92	0.07–12.8	0.95
Antibiotic-impregnated catheters	1.01	0.30–3.38	0.98
Recent shunt infection	2.13	0.49–9.24	0.31
Operative time	1.02	1.00–1.03	0.041†
GT present	5.20	1.85–14.6	0.002†
Bacitracin powder	0.15	0.03–0.70	0.016†

* Based on factors with $p < 0.2$ in univariate analysis (Table 4).
† Statistically significant.

not correlate with shunt infection. We defined health insurance as "private" and "not private." Simon et al. showed an infection association in patients with public insurance, but our results failed to show any significant difference with regard to health insurance.[41]

There have been studies showing that the etiology of hydrocephalus correlated with infection. Specifically, spinal dysraphisms and posthemorrhagic hydrocephalus have previously been shown to increase infection risk.[13,34,50] Although that population represented roughly half of our study (47%; 255/539) the etiology of hydrocephalus was not shown to correlate with infection in our patient group. This finding is consistent with the majority of published literature.[7,11,21,36,41,47] Lastly, neuroendoscopy has been reported to increase infection rates,[26] but our study showed no difference in infection when endoscopy was used. However, endoscopy was used in only a small number of the procedures in our cohort (17%).

Of special significance is the lack of association between the use of antibiotic-impregnated catheters and infection in our study. This topic has been a source of great debate among neurosurgeons, and a plethora of medical literature has been published on this topic.[1,5,31,45,48,52] We found a borderline significant association ($p = 0.12$) between the use of antibiotic-impregnated catheters and a reduction in shunt infection in the univariate analysis. However, this correlation did not persist in the multivariate analysis. Based on our findings, we cannot make any association between infection prevention and the use of antibiotic-impregnated catheters. Of course, this analysis suffers from all the shortcomings of a retrospective study. The ongoing British prospective randomized trial investigating the use of antibiotic- and silver-impregnated catheters will shed more light on this topic in the coming years.[25]

It must be noted that we are merely comparing the results of the above studies with ours and do not claim superiority to other published findings. Other reported studies differ vastly with respect to design (retrospective vs prospective), patient population (pediatrics vs adults and children), procedure volume (< 100 to > 7000 procedures), the definition of shunt infection, length of follow-up, type of shunt placement, and the statistical methods used.

Strengths and Limitations of the Study

We chose to study the shunt infection rate for a single surgeon to reduce the effect of variations in surgical technique between surgeons as a factor in the analysis. While the surgeon in this study did change some practice patterns during the study period, he was considered experienced throughout the study period (7–19 years after residency),[9,41,47,50] he did not change his fundamental surgical techniques, and his overall referral sources and practice environment did not change appreciably during the study period. He also made an abrupt and complete change to use of bacitracin antibiotic powder at the conclusion of every shunt operation starting in 2008. Other surgeons at the hospital intermittently used antibiotic powder on some of their cases, particularly during the final year of the study, but they did not apply the technique uniformly. We were unable to include other surgeons' data in our analysis because documentation in the operative note and in the nursing notes with regard to the use of bacitracin powder was inconsistent and incomplete. When overall shunt infection rates for all surgeons at the hospital were analyzed, only

the surgeon in this report had a marked decline in shunt infection rate over the study period.

The strength of the conclusions that can be drawn from this study is also limited by the retrospective nature of the study. As a result, not all variables could be analyzed due to incomplete or unavailable documentation. Many of these undocumented factors are believed to have remained unchanged during the study period. The surgical team followed the same general protocol throughout the study period but there were no formal checks on compliance with a specific protocol during the study. Factors that have been previously associated with infection that were constant throughout our study were as follows: use of double gloves by all staff, opening hardware shortly before implantation, and irrigation of all wounds with bacitracin multiple times. The primary surgeon did not strictly adhere to the "no touch" technique, and he consistently used a traditional Hibiclens hand scrub, with the staff and residents using a variety of different hand preparation techniques. The timing and use of preoperative antibiotics could not be strictly documented, but it is believed that they were routinely administered in all patients during the time period because a formal oral confirmation protocol between the surgeon and the anesthesiologists was in place for the entire time period. Cefazolin was the first-line antibiotic, with clindamycin or vancomycin used if an allergy was reported.

Some other practice patterns did change during the study period, but they could not be evaluated because of a lack of reliable documentation. A preoperative bath was frequently performed throughout the study period but was more commonly performed in the past 3 years. A Betadine-based skin scrub was used to prepare the skin throughout the study period, but the attending surgeon tended to perform more of the skin preparations himself during the later part of the study. Finally, the use of antibiotic suture, previously associated with a significant reduction in shunt infection in a randomized prospective trial by Rozelle et al., could not be tracked in our patient group.[37] Antibiotic-coated suture was not available at the hospital until 2006, with its use variable initially and more consistent later in the study period.

While we studied a modest number of patients over a long time period in comparison with other published studies, a larger and more complete data set might provide different results. Furthermore, we analyzed 23 different covariates with 38 degrees of freedom in an attempt to comprehensively review risk factors that had been previously reported to be associated with shunt infection. With this many covariates and only 539 procedures, our study suffers from a lack of power. A much larger, multicenter trial would better evaluate these findings.

Analyzing a single surgeon's experience eliminates significant variability in surgical technique and patient selection noted in most retrospective studies, but it makes the results less generalizable. Bacitracin powder was used uniformly and exclusively in the later time period, which we believe is a significant strength because it minimizes selection bias and provides a good control population with that surgeon's technique and patient selection. However, other undocumented changes in practice patterns or surgical technique over time could also have contributed to the noticeable reduction in shunt infection.

Despite these strengths and limitations, we believe further study is warranted before the use of concentrated bacitracin powder in wounds during cranial shunt surgery can be strongly recommended. A prospective randomized trial could be reasonably performed due to the low cost, availability, and safety of bacitracin powder. A standardized protocol would need to be followed to eliminate variability in the numerous factors that affect shunt infection. In addition, the dose, route of application, and particular antibiotic to be studied would need to be determined and standardized.

Conclusions

This study suggests for the first time that the application of concentrated bacitracin powder to surgical wounds prior to closure during cranial shunt surgery may be associated with a reduction in cranial shunt infection. This initial finding warrants validation in a large prospective study before widespread application can be advocated.

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Disclosure

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Author Contributions

Conception and design: Tuite, Beckman. Acquisition of data: Beckman, Tetreault. Analysis and interpretation of data: Tuite, Beckman, Amankwah. Drafting the article: Beckman. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Tuite. Statistical analysis: Beckman, Amankwah. Administrative/technical/material support: Tuite, Beckman, Tetreault. Study supervision: Tuite.

Supplemental Information

Previous Presentation

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