No additional protection against ventriculitis with prolonged systemic antibiotic prophylaxis for patients treated with antibiotic-coated external ventricular drains

Rory K. J. Murphy, MD,1 Betty Liu, BA,2 Abhinav Srinath,2 Matthew R. Reynolds, MD, PhD,1 Jingxia Liu, PhD,3 Martha C. Craighead, MBA, RN, CIC,4 Bernard C. Camins, MD, MSCR,4 Rajat Dhar, MD, FRCPC,6 Terrance T. Kummer, MD, PhD,6 and Gregory J. Zipfel, MD1,6

Departments of 1Neurological Surgery and 4Neurology, and 4Division of Infectious Diseases, Department of Internal Medicine, Washington University School of Medicine; 3Division of Biostatistics, Washington University; and 4Infection Prevention, Barnes-Jewish Hospital Infection Prevention, St. Louis, Missouri

OBJECT External ventricular drains (EVDs) are commonly used for CSF diversion but pose a risk of ventriculitis, with rates varying in frequency from 2% to 45%. Results of studies examining the utility of prolonged systemic antibiotic therapy for the prevention of EVD-related infection have been contradictory, and no study to date has examined whether this approach confers additional benefit in preventing ventriculitis when used in conjunction with antibiotic-coated EVDs (ac-EVDs).

METHODS A prospective performance analysis was conducted over 4 years to examine the impact of discontinuing systemic antibiotic prophylaxis after insertion of an ac-EVD on rates of catheter-related ventriculitis. Ventriculitis and other nosocomial infections were ascertained by a qualified infection disease nurse using definitions based on published standards from the Centers for Disease Control and Prevention, comparing the period when patients received systemic antibiotic therapy for the duration of EVD treatment (Period 1) compared with only for the peri-insertion period (Period 2). Costs were analyzed and compared across the 2 time periods.

RESULTS Over the 4-year study period, 866 patients were treated with ac-EVDs for a total of 7016 catheter days. There were 8 cases of ventriculitis, for an overall incidence of 0.92%. Rates of ventriculitis did not differ significantly between Period 1 and Period 2 (1.1% vs 0.4%, p = 0.22). The rate of nosocomial infections, however, was significantly higher in Period 1 (2.0% vs 0.0% in Period 2, p = 0.026). Cost savings of $162,516 were realized in Period 2 due to decreased drug costs and savings associated with the reduction in nosocomial infections.

CONCLUSIONS Prolonged systemic antibiotic therapy following placement of ac-EVDs does not seem to reduce the incidence of catheter-related ventriculitis and was associated with a higher rate of nosocomial infections and increased cost.

http://thejns.org/doi/abs/10.3171/2014.9.JNS132882

KEY WORDS external ventricular drains; antibiotics; ventriculitis; infection
prolonged systemic IV antibiotic therapy until removal of the EVD and/or use of antibiotic-coated EVD catheters (ac-EVD catheters). In a previous study, we showed that perioperative administration of antibiotics along with use of ac-EVD catheters decreased the incidence of CSF infection as compared with use of neither perioperative antibiotics nor ac-EVD; however, this study did not address the issue of prolonged systemic antibiotics. Perioperative systemic antibiotic therapy is widely regarded to be beneficial, but the evidence for prolonged systemic antibiotic therapy is less clear. To date, 3 cohort studies and 2 randomized controlled trials have examined the issue of whether prolonged systemic antibiotic prophylaxis following EVD placement reduces the rate of ventriculitis—the results of which are conflicting. Two cohort studies and 1 randomized controlled trial suggest prolonged systemic antibiotic prophylaxis after EVD placement does not reduce the rate of ventriculitis, while 1 cohort study and 1 randomized controlled trial suggest prolonged systemic antibiotic prophylaxis after EVD placement does reduce the rate of ventriculitis. Importantly, none of these studies were performed in patients who were treated with ac-EVDs. Only one of these studies assessed the issue of cost.

Due to these discrepancies and out of concern for the promotion of drug-resistant nosocomial infections, we discontinued the use of prolonged systemic antibiotic therapy following ac-EVD placement in May 2012. This change in practice, along with our prospective recording of infection data, provided a unique opportunity to evaluate whether prolonged antibiotic administration confers additional benefit beyond the use of ac-EVDs alone in the prophylaxis of EVD-associated ventriculitis.

**Methods**

**Study Design**

A prospective performance analysis was conducted to examine the impact of discontinuing the use of prolonged antibiotic prophylaxis after insertion of an EVD on rates of catheter-related ventriculitis. The study was approved by the Washington University ethics committee. All patients who underwent intraventricular catheterization and were admitted to our 20-bed neurology-neurosurgical intensive care unit (NNICU) at Barnes-Jewish Hospital St. Louis, an academic, tertiary care center, were included in our study. Patients presenting with ventriculitis or a shunt infection were excluded. We included cases from January 2009 (when our management of intraventricular catheters was standardized) to June 2013. After May 2012, we no longer administered prolonged systemic antibiotic prophylaxis following placement of an EVD. Perioperative administration of antibiotics at the time of EVD insertion was continued (duration ≤ 24 hours).

**Data Sources/Measurements**

Microbiological culture data were prospectively identified from a centralized laboratory system utilizing Germ-Watcher (Washington University St. Louis), an automated surveillance tool that monitors data and identifies those cultures that represent infection and reports them to the infectious disease team. A specially trained infectious diseases nurse evaluated all patients with an EVD in place daily and recorded data.

We defined ventriculitis based on published standards from the Centers for Disease Control and Prevention (CDC)—1) the presence of organisms in CSF cultures or 2) the presence of fever (temperature > 38°C), headache, stiff neck, meningeal signs, cranial nerve signs, or irritability with at least one of the following: increased CSF white blood cell count, elevated CSF protein level, or decreased CSF glucose level; organisms seen with Gram staining of CSF sample; organisms cultured from blood; a positive non-culture diagnostic laboratory test of CSF, blood, or urine; and a diagnostic single-antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen.

The calculation of institutional savings after discontinuation of prolonged systemic antibiotic prophylaxis was based on the number of patient days per year that EVD catheters were in place. The average cost to the hospital pharmacy for a 1.5-g dose of cefazolin is $1.50; assuming that 3 doses are administered per day, the average cost for routine prophylactic antibiotic therapy is $4.50 per patient per 24 hours. Bloodstream infection (BSI) and ventilator-associated pneumonia (VAP) cost analyses for our health care organization have been previously delineated.

For statistical analyses, we compared 2 groups using generalized Fisher exact tests for categorical variables and 2-tailed Student t-tests for continuous variables that were approximately normally distributed. The level of statistical significance was set at p < 0.05.

**EVD Protocol**

Since January 2009, standard protocols have been used for the management of EVDs. Our protocol for EVD insertion includes hair clipping, use of Betadine scrub, maximal barrier precautions (i.e., use of cap, mask, sterile gown, and sterile gloves), and administration of perioperative antibiotics. Patients received 1–2 g of IV cefazolin prior to placement of the EVD, followed by 1 g IV every 8 hours for 24 hours. Patients allergic to cefazolin were given 1 g of IV vancomycin prior to placement of the EVD, followed by 1 g IV every 12 hours for 24 hours. Codman Bactiseal EVD catheters (impregnated with 0.15% clindamycin and 0.054% rifampicin, DePuy Synthes) were used. Both the inner lumen and the exterior catheter wall are supplied up to 28 days with antibiotic concentrations that protect against colonization with gram-positive bacteria.

The majority of EVDs were inserted at the bedside in the NNICU, with a minority placed in the operating room. Our protocol for post–EVD placement dressing care consists of 3 components: use of sterile gauze dressing to cover the EVD site, with adhesive tape to secure borders; routine changing of the EVD site dressing every 48 hours by trained NNICU nurses; and comprehensive documentation of gauze-dressing changes. CSF samples were drawn if the patient had a fever (temperature > 38.5°C) or demonstrated alteration of neurological status with no other apparent cause. Routine cultures of CSF were not performed based on published evidence that demonstrates this practice confers no clinical value.
were replaced at the bedside under the above-described protocol only if EVD malfunction or CSF infection developed. Before May 2012 (Period 1), patients who underwent EVD placement received systemic antibiotics for infection prophylaxis as long as the catheter was in place. For most patients, 1 g IV cefazolin was administered for prophylaxis every 8 hours until the catheter was removed. For those allergic to penicillin, 1 g IV vancomycin was administered for prophylaxis every 12 hours until the catheter was removed. In May 2012, this practice was discontinued. Subsequently (Period 2), patients only received perioperative systemic antibiotics (i.e., antibiotics were administered prior to EVD placement, continued for 24 hours or less, and then discontinued).

Results

Participants

Period 1 refers to the time period during which patients received prolonged systemic antibiotics after EVD placement (> 24 hours) (January 2009–April 2012). Period 2 refers to the time period during which patients received only perioperative antibiotics (≤ 24 hours) after EVD placement (May 2012–June 2013). Four hundred ten patients treated during Period 1 and 135 patients treated during Period 2 qualified for inclusion in the study. Demographic and clinical characteristics for the patients treated during these 2 periods are shown in Table 1. The only statistically significant difference in the variables analyzed involved duration of EVD treatment; the median duration was 1 day longer for the patients treated during Period 1 (7 days vs 6 days for Period 2). The indications for EVD placement were similar, with no statistically significant difference (Table 2). Neither discharge outcomes nor rates of subsequent shunt placement differed significantly between Period 1 and Period 2 (Tables 3 and 4).

Infection Results

A total of 866 EVDs were placed during this 4-year study period, for a total of 7016 catheter days (Fig. 1). There were 8 cases of ventriculitis, for an overall incidence density of 1.1 infections per 1000 catheter days and a ventriculitis infection rate of 0.92% per catheter insertion. There was no statistically significant difference in the rates of ventriculitis between the 2 time periods, with an incidence density of 1.35 cases per 1000 catheter days in Period 1 and 0.54 per 1000 catheter days in Period 2 (p = 0.26; Table 5).

Of these 8 cases, 4 were due to gram-negative bacteria, 2 due to gram-positive bacteria, 1 due to a yeast species, and 1 was culture negative.

In contradistinction, a significantly higher rate of nosocomial infections (BSI and VAP) was noted in Period 1 compared with Period 2 (2.0% vs 0.0%, respectively; p = 0.0261). Specifically, 8 patients in Period 1 contracted a BSI and 5 contracted a VAP, while no patient in Period 2 contracted either (Table 6; Fig. 2). The incidence density of central line–related BSI (CLABSI) per 1000 central-line days was 2.7 cases for Period 1 and 0.9 for Period 2. The incidence density of VAP per 1000 ventilator days was 3 cases for Period 1 and 1.2 for Period 2.

Cost Results

During Period 1, 4824 doses of antibiotics were administered, resulting in a total of $7263 in drug costs not incurred during Period 2. In our health care organization, the cost per case of BSI is $11,97127 and the cost per case of VAP is $11,897.28 During Period 1, $95,768 of BSI-related costs and $59,485 of VAP-related costs were incurred. During Period 2, no BSI- or VAP-related costs were incurred. The total cost savings, therefore, were estimated at $162,516 in the period when no prophylactic systemic antibiotics were used.

Discussion

Our analysis shows that discontinuation of prolonged systemic antibiotic prophylaxis following ac-EVD placement was not associated with higher rates of ventriculitis.
and was associated with a significant reduction in nosocomial infections, including BSI and VAP. No patient with an ac-EVD contracted a BSI or VAP in Period 2, the period after cessation of prolonged antibiotic prophylaxis. Substantial cost savings related to cessation of prolonged antibiotic administration ($7263) and a reduction in nosocomial infections ($95,768 for BSI and $59,485 for VAP) were also realized. In total, these results argue against a policy of prolonged antibiotic prophylaxis in patients treated with ac-EVDs.

Several studies have examined the utility of prolonged systemic antibiotic prophylaxis in patients treated with EVDs, with conflicting results. Alleyne et al. performed a retrospective analysis of a cohort of 308 patients treated with standard EVDs (i.e., not antibiotic coated) and found no relationship between ventriculitis rates and prolonged systemic antibiotic administration (4% with prolonged antibiotics vs 4% without prolonged antibiotics). The authors calculated approximately $80,000 in savings per year related to direct drug costs. Stenager et al. performed a prospective analysis of a cohort of 87 patients treated with standard EVDs and found no relationship between ventriculitis rates and prolonged systemic antibiotic administration (10% with prolonged antibiotics vs 18% without prolonged antibiotics). In contradistinction, Wyler and Kelly performed a retrospective analysis of a cohort of 70 patients treated with standard EVDs and noted a significant reduction in nosocomial infections, including BSI and VAP. No patient with an ac-EVD contracted a BSI or VAP in Period 2, the period after cessation of prolonged antibiotic prophylaxis.

TABLE 3. Discharge disposition after treatment of primary pathology and removal of EVD or shunt placement

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Total</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home</td>
<td>100</td>
<td>24</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Rehab</td>
<td>174</td>
<td>59</td>
<td>233</td>
<td></td>
</tr>
<tr>
<td>Nursing</td>
<td>47</td>
<td>15</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>78</td>
<td>31</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>Hospice</td>
<td>4</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>LTAC</td>
<td>7</td>
<td>2</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>410</td>
<td>135</td>
<td>545</td>
<td>0.3522</td>
</tr>
</tbody>
</table>

LTAC = long-term acute care.
* Chi-square test.

They also reported a higher nosocomial infection rate in the perioperative antibiotic group compared with the prolonged antibiotic group (42% vs 20%, respectively; p = 0.002). A potential weakness of this study, however, is that EVD revision was routinely performed every 5 days—a practice that is now discouraged, as it is associated with an increased risk of infection. The results of the study therefore may not be applicable to current practice given that very few neurosurgeons electively revise EVDs. Finally, Sonabend et al. performed a meta-analysis of the aforementioned studies and found that prolonged antibiotic prophylaxis following standard EVD placement appears to provide significant protection against ventriculitis (RR 0.45, 95% CI 0.27–0.74).

Importantly, none of the above studies used ac-EVDs, which themselves have been shown to reduce the risk of ventriculitis by up to 50%. In fact, to date there is no evidence to suggest that prolonged systemic antibiotic therapy provides additional clinical or microbiological benefit when used in combination with ac-EVDs. The possibility that ac-EVDs may obviate the need for prolonged systemic antibiotic prophylaxis was first raised by the recent study of Wright et al. However, because their study examined patients treated with standard EVDs in comparison with those treated with ac-EVDs exclusively in the setting of prolonged systemic antibiotic administration, no definitive conclusions could be drawn. Our study, therefore, represents the first direct evidence that prolonged systemic antibiotic prophylaxis in patients treated with ac-EVDs may provide no additional protection against ventriculitis.

Our results show that prolonged systemic antibiotic administration is associated with a statistically significant increase in the rate of systemic nosocomial infections like VAP and BSI. This has important clinical ramifications, as the mortality rate associated with VAP is 10% and the mortality rate associated with BSI is as high as 26%. The reason for the reduction in nosocomial infections when prolonged systemic antibiotic administration was avoided is less clear. Our NNICU rates of VAP and BSI in patients without an EVD remained broadly similar throughout both time periods. One potential explanation stems from studies of a related clinical scenario that has been extensively investigated with prospective randomized trials—the use of central venous catheters. VAP and CLABSI are infections related to the development of biofilm on endotracheal tubes and catheter lines. Numerous studies have demonstrated that sub-minimum inhibitory concentrations (MICs) of a variety of chemically distinct antibiotics with different modes of action can significant-

TABLE 4. Analysis of the numbers of patients who required a shunt after EVD treatment

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period 1</td>
<td>81</td>
</tr>
<tr>
<td>Period 2</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>102</td>
</tr>
</tbody>
</table>

* Chi-square test.
ly induce biofilm formation in phylogenetically diverse gram-negative and gram-positive bacteria in vitro. To help prevent biofilm formation and reduce the development of antibiotic-resistant organisms in patients treated with central venous catheters, the CDC recommends use of antibiotic-coated catheters and avoidance of systemic antimicrobial prophylaxis. Extending this potential mechanism to our study, the prolonged administration of systemic antibiotics administered during Period 1 without MIC monitoring may have provoked the development of biofilms on endotracheal tubes and catheters resulting in the increased cases of VAP and BSI.

There are a number of weaknesses or limitations in our study. It is not a randomized study. Also, our catheter infection rate is significantly lower (1.1 infections per 1000 catheter days) than that reported elsewhere in the literature. We believe bacterial colonization and local inoculation around the intraventricular catheter site likely predisposes a patient to intraventricular catheter–related ventriculitis. Thus, the aseptic insertion and care of an intraventricular catheter are essential to preventing infection. Our incidence of intraventricular catheter–related ventriculitis decreased by more than three-quarters after the implementation of the multiple interventions mentioned in the EVD protocol portion of the text. We hypothesize that the implementation of a standardized protocol for dressing an intraventricular catheter site, adapted from guidelines to prevent intravascular catheter–related bloodstream infections, was a key component in reducing the risk of intraventricular catheter–related ventriculitis. This may mean that our results are not generalizable; however, other authors have shown similar low rates of infection. Our low rates of ventriculitis could also raise the possibility that our study is not powered sufficiently to see a difference. We were also unable to analyze cases in which there was a break in the sterile collection device. Such patients may still benefit from prolonged administration of systemic antibiotics.

Conclusions

Discontinuation of routine prolonged systemic antibiotic prophylaxis had no significant impact on the incidence of intraventricular catheter–related ventriculitis when us-

**TABLE 5. Number of catheter days, catheters placed, ventriculitis incidence density, and rate of ventriculitis as a percentage**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Period 1 w/ IV Prophylactic ABx</th>
<th>Period 2 w/ IV Prophylactic ABx</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of catheter days</td>
<td>5176</td>
<td>1840</td>
<td></td>
</tr>
<tr>
<td>No. of catheters placed</td>
<td>640</td>
<td>226</td>
<td></td>
</tr>
<tr>
<td>Incidence density</td>
<td>1.35</td>
<td>0.54</td>
<td>0.2664</td>
</tr>
<tr>
<td>Rate of ventriculitis</td>
<td>1.1%</td>
<td>0.4%</td>
<td></td>
</tr>
</tbody>
</table>

ABx = antibiotic.
* Fisher exact test, 2-tailed.

**TABLE 6. Rates of BSI, VAP, and BSI and VAP combined for each period**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Period 1</th>
<th>Period 2</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSI (%)</td>
<td>8 (1.3)</td>
<td>0 (0)</td>
<td>0.12</td>
</tr>
<tr>
<td>VAP (%)</td>
<td>5 (0.8)</td>
<td>0 (0)</td>
<td>0.3378</td>
</tr>
<tr>
<td>BSI+VAP (%)</td>
<td>13 (2.0)</td>
<td>0 (0)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

* Fisher exact test, 2-tailed.
ing ac-EVDs and led to a statistically significant reduction in nosocomial infections. This practice led to substantial cost savings. These data suggest that patients treated with ac-EVDs may not require prolonged systemic antibiotic prophylaxis.

References


Author Contributions
Conception and design: Murphy, B Liu, Reynolds, Craighead. Acquisition of data: Murphy, B Liu, Srinath, Reynolds, Craighead. Analysis and interpretation of data: Zipfel, Murphy, B Liu, Reynolds, Craighead, Camins, Dhar. Drafting the article: Zipfel, Murphy, B Liu, Reynolds, Craighead, Camins. Critically revising the article: Zipfel, Murphy, B Liu, Craighead, Camins, Kummer. Reviewed submitted version of manuscript: Zipfel, Murphy, B Liu, Craighead, Camins. Statistically analyzing the article: Zipfel, Murphy, B Liu, Craighead, Camins, Kummer. Administrative/technical/material support: Zipfel, Murphy, Craighead, Camins, Kummer. Study supervision: Zipfel, Murphy, Kummer.

Correspondence
Gregory J. Zipfel, Department of Neurosurgery, Washington University School of Medicine, 660 S. Euclid Ave., Campus Box 8057, St. Louis, MO 63110. email: zipfelg@wustl.edu.