**Neurosurgery**

In Reply: Systematic Antimicrobial Prophylaxis and Antimicrobial-Coated External Ventricular Drain Catheters for Preventing Ventriculostomy-Related Infections: A Meta-Analysis of 5242 Cases

--Manuscript Draft--

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</table>
| Corresponding Author: | Isaac Yang, MD  
University of California, Los Angeles  
Los Angeles, CA UNITED STATES |
| Order of Authors:  | John P. Sheppard, MS  
Courtney Duong, BS  
Carlito Lagman, MD  
Kunal Patel, MD  
Matthew Z. Sun, MD  
Giyarpuram Prashant, MD  
Isaac Yang, MD |
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Isaac Yang, MD
Associate Professor
Department of Neurosurgery
Department of Radiation Oncology
Department of Head and Neck Surgery Jonsson Comprehensive Cancer Center
Ronald Reagan UCLA Medical Center David Geffen School of Medicine, University of California, Los Angeles

Nelson M. Oyesiku, MD, PhD, FACS
Editor-in-Chief
Neurosurgery

Dear Dr. Oyesiku,

On behalf of the authors, I would like to thank you for the opportunity to submit this response regarding our manuscript, “Systematic Antimicrobial Prophylaxis and Antimicrobial-Coated External Ventricular Drain Catheters for Preventing Ventriculostomy-Related Infections: A Meta-Analysis of 5242 Cases”. We have carefully read through and addressed all the points brought to our attention in the letter to the editor.

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I, Isaac Yang, would like to personally thank you in advance allowing us to provide a response to the letter to the editor. We hope that we have addressed all points thoroughly and look forward to hearing back from your editorial office.

Sincerely,

Isaac Yang, MD
In Reply: Systematic Antimicrobial Prophylaxis and Antimicrobial-Coated External Ventricular Drain Catheters for Preventing Ventriculostomy-Related Infections: A Meta-Analysis of 5242 Cases

John P. Sheppard, MS¹, Courtney Duong, BS¹, Carlito Lagman, MD¹, Kunal Patel, MD¹, Matthew Z. Sun, MD¹, Giyarpuram Prashant, MD¹, Isaac Yang, MD¹

¹Department of Neurosurgery, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California

Correspondence
Isaac Yang, MD
Associate Professor
Department of Neurosurgery
Ronald Reagan UCLA Medical Center
757 Westwood Plaza, Los Angeles, CA, United States 90095
Harbor-UCLA Medical Center
1000 W Carson St, Torrance, CA, United States 90509
Tel.: (310) 267-2621
Fax: (310) 825-9384
E-mail: iyang@mednet.ucla.edu

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To the Editor:

We appreciate the recent letter regarding our recent article. This letter points out an issue in our reporting of ventriculostomy-related infection (VRI) outcomes observed in the prospective study by Murphy et al. Namely, Murphy et al. found no difference in the incidence of ventriculitis between patients receiving systemic antibiotic prophylaxis relative to peri-procedural systemic prophylaxis alone in the setting of EVD placement with antibiotic-coated EVD catheters (ac-EVD).

The authors responding to our article correctly point out that the data reported in Figure 1A of our original article was mistaken, and we are greatly appreciative that this issue was brought to our attention. Indeed, the VRI incidence data for Murphy et al. reported in our original paper were mistaken in that the treatment and control arms were erroneously switched. Additionally, the numbers reported in Figure 1A for the study in question correspond to reported cases of nosocomial infections (i.e., ventilator-associated pneumonia or bloodstream infection), and do not reflect incidence of ventriculitis. As such, these data did not meet our criteria for study inclusion and should not have been included in our meta-analysis.

The Murphy et al. study reported an incidence density of 0.54 ventriculitis cases per 1000 catheter days for ac-EVD + peri-procedural systemic antibiotics, and 1.35 ventriculitis cases per 1000 catheter days for ac-EVD + extended systemic antibiotics (P = 0.26). These results were in contrast to three other studies included in our meta-analysis, which collectively yielded a significant reduction in VRI incidence with ac-EVD + extended systemic prophylaxis versus ac-EVD + peri-procedural prophylaxis alone. However, regarding the ventriculitis incidence data reported by Murphy et al., the only reported data we could corroborate was reported in terms of incidence density as above. In terms of the raw number of ventriculitis cases, 8 total cases were reported among the 866 patients spanning both study arms. Murphy et al. reported a ventriculitis rate of 1.1% among 410 patients receiving ac-EVD + extended systemic antibiotics, and 0.4% among 135 patients receiving ac-EVD + peri-procedural systemic antibiotics. Our meta-analysis requires binomial data consisting of integer numbers of ventriculitis cases and total patients for each study arm. We were unable to calculate integer numbers of cases from the total number of
patients in either study arm that would yield the reported ventriculitis rates (1.1% and 0.4%), and
as such were unable to include ventriculitis outcomes from this study in the revised analysis we
provide below.

To assess the impact of the above on our published meta-analysis, we report corrected data
showing the core meta-analytic results after exclusion of the ineligible data from the Murphy et
al. study. Figure 1 demonstrates that after exclusion of the Murphy et al. study, the relative risk
remains significantly in favor of extended systemic prophylaxis using either a fixed- or random-
effects model for the remaining studies. Figure 2 displays corrected funnel plots for the
corrected set of studies. As before, assessment for study bias using Egger’s test was insignificant
for studies of extended systemic prophylaxis, or for the pooled set of reviewed studies. Figure 3
and Tables 1-2 provide updated results from our mixed effects analysis comparing absolute rates
of VRI observed for each intervention strategy after exclusion of the Murphy et al. data.

A comparable pattern of results was observed for our cost analysis, which yielded estimated net
costs per patient of $6,930 for no prophylaxis, $2,918 for peri-procedural IV prophylaxis, $2,536
for extended IV prophylaxis, $1,818 for ac-EVD + peri-procedural IV prophylaxis, and $1,136
for ac-EVD + extended IV prophylaxis. Relative to no prophylaxis, this translated to estimated
cost savings per patient of $4,012 for peri-procedural IV prophylaxis, $4,394 for extended IV
prophylaxis, $5,112 for ac-EVD + peri-procedural IV prophylaxis, and $5,794 for ac-EVD +
extended IV prophylaxis. The underlying assumptions for this cost analysis are described in our
original paper.

To the authors’ point, the one consequential difference in our corrected results, as compared to
our original published study, concerns the absolute pooled VRI rates obtained for each
intervention category. In the corrected analysis, we no longer observe a significant reduction in
VRI rates with extended systemic antibiotics alone as monotherapy versus peri-procedural
antibiotics alone as monotherapy (Figure 3, Table 2). However, even after exclusion of the data
in question, the lowest VRI rates estimated in our meta-analysis were still observed with dual
therapy of ac-EVD + extended systemic antibiotics, and VRI rates observed with dual therapy
continued to be significantly lower than all other intervention categories, including ac-EVD ± peri-procedural systemic antibiotics.

In summary, the core findings of our meta-analysis were unaffected by the numbers we originally reported for the Murphy et al. study. On the whole, evidence from the literature does support efficacy of using systemic antibiotics or ac-EVDs to lower risk of ventriculitis in the setting of EVD placement. Again, to the authors’ point, the question of whether extended systemic antibiotics confer a clinically significant advantage over peri-procedural prophylaxis remains unclear, and more research is needed. Our corrected data demonstrate no additional benefit in pooled outcomes for extended systemic antibiotic monotherapy compared to peri-procedural systemic antibiotic monotherapy, while dual therapy with ac-EVD + extended systemic antibiotics remained significantly favorable compared to ac-EVD use without extended systemic antibiotics. An important caveat to this finding is that the ventriculitis outcomes from the Murphy et al. study argue against additional benefit of extended IV antibiotics in the setting of ac-EVD use, but these data were not amenable to our analysis because we were unable to derive the number of ventriculitis cases in each study arm. Moreover, our study does not consider important disadvantages of IV antibiotic administration, including adverse drug events, increased risk of nosocomial infections (e.g., C diff colitis), and risk of selection for antimicrobial-resistant organisms, among other risks.

The reporting of ventriculitis outcomes as incidence density by Murphy et al. also emphasizes the fact that risk of ventriculitis increases with duration of EVD placement. Although several studies only report on overall incidence of ventriculitis cases, considering the duration of catheter insertion will be important in future research to compare literature outcomes under different intervention studies. VRI prophylactic strategies may have different cost-benefit tradeoffs depending upon the anticipated duration of EVD placement. Aside from these issues, many other aspects of EVD management affect ventriculitis risk and were not considered in our study, including antibiotic regimens, indication and setting of EVD placement, study design, sterile and CSF surveillance protocols, protocols regarding EVD catheter exchange (or not), and other factors. We view our study as a first attempt at a general picture of ventriculitis incidence under different broad intervention strategies. More fully delineating best practices to minimize the risk
of VRI will require extensive future effort. We deeply appreciate the authors’ interest in our study and thank them for pointing out this mistake in our results as originally published.
REFERENCES


FIGURE LEGEND

**Figure 1.** Corrected forest plot summarizing VRI incidence and risk ratios in reviewed studies of extended systemic antimicrobial prophylaxis.

**Figure 2.** Corrected funnel plots assessing bias in reviewed studies of A, extended IV therapy, and B, all reviewed studies combined. Dotted oblique lines denote 95% confidence boundaries of study variation expected by chance assuming random sampling of patients from a population with a fixed population-level treatment effect. Systematic deviation of points either above or below the expected aggregate risk ratio suggests the presence of systematic bias. T-statistics and P-values indicate results of Egger’s tests for funnel plot asymmetry.

**Figure 3.** Corrected comparison of VRI incidence rates in pooled cohorts grouped by type of prophylactic strategy. Expected incidence rates and confidence intervals were determined via random effects analysis using a general linear mixed model and logistic regression. Error bars indicate 95% confidence intervals. n.s., not significant; * P < .05; ** P < .001. P-values reflect FDR-corrected significance levels for post-hoc contrasts computed using Tukey’s Honestly Significant Difference test.
Table 1. Corrected Ventriculostomy Related Infection (VRI) Incidence by Intervention Strategy Observed in Mixed Effects Analysis Using General Linear Mixed Models and Logistic Regression

Table 2. Corrected Pair-Wise Treatment Effect Contrasts of Intervention Strategies Between Pooled Cohorts Using Mixed Effects General Linear Mixed Models
<table>
<thead>
<tr>
<th>Route</th>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>VRIs</td>
<td>Pts</td>
<td>VRIs</td>
<td>95% CI</td>
</tr>
<tr>
<td>IV</td>
<td>Wyler (1972)</td>
<td>4</td>
<td>44</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Blomstedt (1985)</td>
<td>1</td>
<td>25</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Stenager (1986)</td>
<td>1</td>
<td>10</td>
<td>14</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Poon (1998)</td>
<td>3</td>
<td>115</td>
<td>12</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td>Alleyne (2000)</td>
<td>8</td>
<td>209</td>
<td>4</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>403</strong></td>
<td></td>
<td></td>
<td><strong>342</strong></td>
</tr>
</tbody>
</table>

Random effects model

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0\%$, $p = 0.53$

<table>
<thead>
<tr>
<th>Route</th>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IT</td>
<td>Fu (2017)</td>
<td>3</td>
<td>97</td>
<td>18</td>
<td>140</td>
<td>0.24 [0.07; 0.79]</td>
</tr>
</tbody>
</table>

Treatment favored
Extended IV prophylaxis studies

$t(3) = 0.62$

$P = .58$
Figure 3

The graph shows the VRI rate (%) for different prophylaxis methods:

- **no prophylaxis**
- **peri-op IV**
- **extended IV**
- **ac-EVD ± peri-op IV**
- **ac-EVD + extended IV**

The bars with error bars indicate the variability in the VRI rate for each group. Significant differences are indicated by asterisks:

- * indicates a significant difference.
- *** indicates a highly significant difference.

The highest VRI rate is observed in the group with no prophylaxis.
Table 1. Corrected Ventriculostomy Related Infection (VRI) Incidence

<table>
<thead>
<tr>
<th>Prophylactic intervention</th>
<th>Total Pts</th>
<th>VRI cases</th>
<th>VRI incidence (%)</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>no prophylaxis</td>
<td>568</td>
<td>57</td>
<td>23.1 [13.0, 37.6]</td>
<td>-1.20 [-1.90, -0.51]</td>
</tr>
<tr>
<td>peri-op IV</td>
<td>662</td>
<td>62</td>
<td>9.6 [5.6, 15.9]</td>
<td>-2.25 [-2.83, -1.66]</td>
</tr>
<tr>
<td>extended IV</td>
<td>749</td>
<td>54</td>
<td>7.2 [4.1, 12.1]</td>
<td>-2.56 [-3.14, -1.98]</td>
</tr>
<tr>
<td>ac-EVD ± peri-op IV</td>
<td>1739</td>
<td>45</td>
<td>4.6 [2.5, 8.3]</td>
<td>-3.03 [-3.66, -2.40]</td>
</tr>
<tr>
<td>ac-EVD + extended IV</td>
<td>272</td>
<td>6</td>
<td>1.2 [0.5, 2.8]</td>
<td>-4.43 [-5.32, -3.55]</td>
</tr>
</tbody>
</table>

β, model coefficients for fixed treatment effects of each prophylactic intervention category. Brackets indicate 95% confidence intervals.
<table>
<thead>
<tr>
<th>Contrast</th>
<th>Estimate</th>
<th>Z-value</th>
<th>Adjusted p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(no prophylaxis) - (peri-op IV)</td>
<td>1.04</td>
<td>3.07</td>
<td>.003**</td>
</tr>
<tr>
<td>(no prophylaxis) - (extended IV)</td>
<td>1.36</td>
<td>3.82</td>
<td>.0003***</td>
</tr>
<tr>
<td>(no prophylaxis) - (ac-EVD ± peri-op IV)</td>
<td>1.83</td>
<td>6.61</td>
<td>3.7e-10***</td>
</tr>
<tr>
<td>(no prophylaxis) - (ac-EVD + extended IV)</td>
<td>3.23</td>
<td>5.68</td>
<td>6.9e-08***</td>
</tr>
<tr>
<td>(peri-op IV) - (extended IV)</td>
<td>0.31</td>
<td>1.06</td>
<td>.29</td>
</tr>
<tr>
<td>(peri-op IV) - (ac-EVD ± peri-op IV)</td>
<td>0.78</td>
<td>3.05</td>
<td>0.003**</td>
</tr>
<tr>
<td>(ac-EVD ± peri-op IV) - (extended IV)</td>
<td>0.47</td>
<td>1.45</td>
<td>.16</td>
</tr>
<tr>
<td>(peri-op IV) - (ac-EVD + extended IV)</td>
<td>2.18</td>
<td>4.12</td>
<td>9.6e-05***</td>
</tr>
<tr>
<td>(extended IV) – (ac-EVD + extended IV)</td>
<td>1.87</td>
<td>4.14</td>
<td>9.6e-05***</td>
</tr>
<tr>
<td>(ac-EVD ± peri-op IV) - (ac-EVD + extended IV)</td>
<td>1.40</td>
<td>2.57</td>
<td>.013*</td>
</tr>
</tbody>
</table>

*p<.05, **p<.01, ***p<.001. peri-op IV, IV prophylaxis for <24 post-operative hours. extended IV, IV prophylaxis for >24 hrs post-operative hours. ac-EVD, antibiotic-coated external ventricular drain. Estimates indicate estimated difference in model coefficients for fixed effects of each prophylactic intervention category.