Extraventricular drain infection


Cerebral spinal fluid drainage is a common and fundamental neurosurgical procedure for the monitoring and relief of intracranial pressure, and CSF drainage–related meningitis is a troublesome complication in neurosurgical intensive care. The true source of infection could be related to the surgical procedure or it could be a urinary tract infection secondary to catheter insertion, a central venous pressure catheter infection, or bacteria within the bloodstream. Hetem et al. reported on a total of 139 patients with positive results on CSF-drain cultures. In their series, 72 patients (52%) developed secondary meningitis. The clinical presentation of secondary meningitis was associated with the use of ventricular drains (OR 3.4 vs lumbar drains, 95% CI 1.7–6.8), patient age less than 18 years (OR 4.7, 95% CI 1.3–17.3), and culture results positive for Staphylococcus aureus (OR 3.1 vs other microorganisms, 95% CI 1.2–8.5). In 32 patients (44% of those with secondary meningitis) meningitis was diagnosed 24 hours or more after CSF drain removal; in 13 patients (18%) the diagnosis was made after 48 hours or more. The finding of S. aureus in CSF-drain cultures was strongly associated with development of secondary meningitis. These results are not surprising.

There are some limitations in this retrospective study. First, standard care with respect to external ventricular drainage (EVD) varies among neurosurgical training centers. In addition, the procedures for drainage tip harvest for culture in the authors’ institution were not well addressed. Therefore, the chance of positive colonization leading to subsequent secondary meningitis might differ substantially among institutions. Second, the duration of EVD has been associated with the incidence of meningitis, although there is some debate on this issue. Leung et al. reported that the lengthened subcutaneous tunnelling technique did not influence the infection risk in their institution. Scheithauer et al. found that the presence of intraventricular blood and previous trauma were significant risk factors predisposing to secondary meningitis; furthermore, length of stay was significantly longer in patients with meningitis. However, their findings with regard to the most prevalent pathogen differed from those of Hetem et al. In the study by Scheithauer et al., coagulase-negative staphylococci were the main pathogens (56%) leading to meningitis, followed by S. aureus (25%).

Because the study by Hetem et al. is basically a single-center investigation, the findings should be interpreted with great caution and with the understanding that individual institutions may have unique patterns and risks of drainage-related infection. In spite of these limitations, the study demonstrated a high incidence of secondary meningitis (52%) in patients with positive CSF-drain cultures. This study does draw attention to the optimal care of patients being treated with EVD, such as taking great precautions against the development of secondary meningitis in patients with CSF drain tip cultures positive for S. aureus. Empiric antibiotic therapy should be promptly considered prior to development of secondary meningitis. Finally, further prospective studies are needed to investigate the possible risk factors for drainage catheter–related secondary meningitis.

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Disclaimer
The authors report no conflict of interest.

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Response: The letter by Lin et al. was greatly appreciated. The authors emphasize a couple of important limitations of our study, inherent to its retrospective nature and to the differences in the standard care of external CSF drainage systems among different neurosurgical centers. Indeed, differences in the care of CSF drains will influence their colonization and, subsequently, the development of secondary meningitis. Furthermore, the indications for drain tip culture—that is, culturing on a routine basis or only when signs or symptoms of infection are present—may select for subgroups of patients and possibly bias outcomes.

From a microbiological point of view, any procedure that minimizes contamination at removal and secures rapid processing of the drain tip should yield a reliable and reproducible culture result. Centers in which the patient’s skin is not disinfected around the drain entry site may have more nonspecific positive results on drain tip cultures; on the other hand, cultures may remain falsely neg-
ative when drains are not processed in the microbiology laboratory within a couple of hours. These issues should be taken into consideration, as should the fact that differences in patient populations and pathogens may exist between centers. However, we do not believe the pathogens isolated in our study to be outliers; as in most studies, coagulase-negative staphylococci were the most frequent pathogens (46% of secondary meningitis cases), followed by *S. aureus* and Gram-negative bacteria. Whether differences between centers influence the predictive value of CSF-drain cultures remains to be determined, and we, therefore, fully agree with Lin et al. that larger prospective studies on the subject are warranted.

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**Temozolomide and pituitary adenoma**


Temozolomide is FDA approved for the treatment of high-grade gliomas. The application of temozolomide to treat aggressive pituitary neoplasms has been reported in several case reports,1–3 igniting hope in the multimodality management of pituitary adenomas. Sheehan et al.4 reported on the effect of temozolomide in 2 rat-derived pituitary adenoma cell lines, MMQ and GH3, and 1 mouse-derived pituitary adenoma cell line. They found that temozolomide exhibited significant inhibition of proliferation through the mechanism of apoptosis, as shown on TUNEL. Moreover, using an ELISA of the supernatant, they found that temozolomide suppressed prolactin secretion.

There is one minor concern about their prolactin assay. Although Sheehan and colleagues4 showed that the temozolomide has a suppressive effect on proliferation, they did not mention the cell counts at the harvesting of the supernatant for ELISA. Without standardizing the cell counts, more pituitary adenoma cells would certainly secrete higher concentration of prolactin in cells exposed to medium without temozolomide. In other words, it would lead to an interpretation that temozolomide suppresses the proliferation of adenoma cells, but the effect of temozolomide on inhibiting prolactin secretion would be uncertain. We believe the prolactin level from the assay needs to be divided by the number of cells present at the time of the assay measurement. Therefore, to draw a final conclusion, this experiment still needs to be standardized with the cell counts at the time of supernatant harvesting.

Despite of this minor concern, the study demonstrated solid evidence of temozolomide’s tumor suppressive effect on 3 adenoma cell lines. One of the mechanisms was temozolomide-induced suppression through induction of apoptosis. The findings provide us with another chance for the clinical application of temozolomide in the therapy of aggressive pituitary adenomas. Further identifying the role of temozolomide in human-derived pituitary adenoma cells and in vivo orthotopic pituitary adenoma model will help clarify the effect of temozolomide on human aggressive pituitary adenomas.

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The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**References**


**Response:** I appreciate the kind words of Dr. Hueng and colleagues regarding the recent article, “Temozolomide-induced inhibition of pituitary adenoma cells.” The study demonstrates the efficacy of temozolomide in aggressive pituitary adenoma cell lines. There are certainly a number of limitations to the study, as outlined in the Discussion section of the article. Nevertheless, it is clear that temozolomide and other medical approaches currently under development have great potential for treating aggressive pituitary adenomas.

Antisecretory medications, such as bromocriptine and cabergoline, can be used to reduce the number and size of cells in a pituitary adenoma and to reduce the prolactin secretion.1,8 At times, the decrease in adenoma size does not directly correlate with the reduction or cessation of hormonal overproduction.1,6,8 As such, we chose to design and depict the prolactin output over time in a fashion that would be more representative of a response seen in a patient with prolactinoma if he/she were given temozolomide. A fixed volume of cells was present at the start, and temozolomide would have various effects over time on the tumor cells. One of these effects was to reduce prolactin output compared with an equivalent starting number of cells not treated with temozolomide. When a patient with a functioning adenoma receives medical manage-