Infectious Complications of Expanded Endoscopic Transsphenoidal Surgery: A Retrospective Cohort Analysis of 100 Cases

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Abstract

Objective To identify perioperative factors that may predict postoperative cerebrospinal fluid (CSF) leak and meningitis following expanded endoscopic transsphenoidal surgery (EETS).

Study Design This is a retrospective study. This study was set at the Cedars-Sinai Medical Center, Los Angeles. A total of 78 patients who underwent EETS between January 2007 and November 2018 were participated. The main outcome measures were CSF leak and meningitis.

Results A total of 78 patients underwent a total of 100 EETS procedures; 17.9 and 10.3% of patients developed postoperative CSF leaks and meningitis, respectively. Out of eight, three patients with meningitis did not develop an observable CSF leak. The risk of developing meningitis in patients with a CSF leak was significantly higher than those without a leak, with an odds ratio (OR) of 11.48 (95% confidence interval, 2.33–56.47; $p=0.004$). Pituicytomas were significantly associated with meningitis compared with other pathologies. No other patient-specific factors were identified as risks for leak or meningitis, including method of skull base repair, sex, tumor volume, or body mass index, although there was a strong trend toward reduced CSF leak rates in patient with nasoseptal flaps used for skull base repair, compared with those without (9.5 vs. 25%). CSF protein was consistently elevated on the first CSF values obtained when meningitis was suspected.

Conclusion CSF leak and meningitis are common complications of expanded endonasal surgery. No statistically significant risk factors for developing a postoperative leak other than the pathology of pituitaryoma were identified, including method of skull base repair, although the use of a vascularized nasoseptal flap did trend toward a reduced CSF leak rate. CSF protein is the most sensitive marker for the presumptive diagnosis and timely treatment of meningitis.

Keywords

- complication
- CSF leak
- expanded endoscopic transsphenoidal
- infection
- meningitis

Introduction

The panoramic visibility and image quality available with modern endoscopes, combined with increased mobility of a binasal technique and improved instrumentation designed for

endonasal surgeries, have increased the popularity of expanded endoscopic transsphenoidal surgery (EETS). Expanded approaches using transplanum, transclival, transthyoid, and other corridors to the brain and its related skull base structures facilitate the resection of intradural, intracranial

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tumors in the anterior skull base.¹ Additionally, these methods have also been used for clipping of cerebral aneurysms and treating pathologies other than tumors.^{2,3} EETS provides direct access to the subarachnoid intracranial space and cerebrospinal fluid (CSF) pathways, often intentionally creating very large skull base defects and CSF leaks. Therefore, the rate of CSF leak after expanded methods is significantly higher than the rate during endoscopic approaches in which the arachnoid space is not intentionally violated.^{4–6}

A major risk factor for developing meningitis following EETS is the presence of a postoperative CSF leak.^{4,7,8} The consequences from meningitis can be life-threatening⁹ and carries risks of both long-term physiological and cognitive impairments^{10–12}; therefore, it is crucial to identify clinical features that may predispose patients to postoperative infections. A few studies inconsistently report preoperative risk factors that are associated with postoperative meningitis, such as diabetes mellitus and intraventricular extension of the tumor.^{13–15} Here, we analyze patients from a single institution undergoing expanded endonasal surgeries for many pathologies, in an effort to identify perioperative factors that may predispose patients to CSF leakage and meningitis.

Methods

Patient Selection and Demographics

We performed a retrospective chart review of patients undergoing EETS by a single neurosurgeon (A.N.M.) from January 2007 to November 2018. The study was approved by the Institutional Review Board of Cedars Sinai Medical Center (IRB #56899) and did not require patient consent. We employ the term EETS to cover all procedures in which a skull base corridor other than just the sella turcica was opened, including the planum sphenoidale, tuberculum sella, clivus, or palate. All patients underwent EETS where the arachnoid space was intentionally opened in at least one corridor. Our general surgical methods have been previously described. Endoscopic procedures performed for other purposes, such as the removal of masses without planned arachnoid opening (e.g., pituitary adenoma or Rathke's cleft cyst with an intact diaphragm sella, chordoma with no transdural extension), repairing a preexisting CSF leak or encephalocele, or only obtaining a biopsy, were excluded from the study. Patients for which only the transsphenoidal corridor was used or where the dura was not intentionally opened were excluded from further analysis. We focused exclusively on cases where intradural and intraarachnoid dissections were performed.

Patient demographics including age, sex, and body mass index (BMI) at the time of the surgery, history of prior surgeries or radiotherapy, length of hospitalization, and cases requiring repeat surgeries were extracted from the medical records.

Skull Base Repair Technique

As the primary variables of interest in this series were CSF leak rates and meningitis, we evaluated the method of skull

base repair and use of lumbar drainage by reviewing operative notes and clinical progress notes. Our general technique is as follows: Briefly, fat is harvested from the right lower quadrant of the abdomen and used to fill the skull base defect as a plug. This is then covered with a layer of either anterior rectus fascia (harvested at the same site as the fat graft), or a biological allograft, such as bovine pericardium or bovine small intestinal mucosa as an inlay tucked under the dura. A second piece of allograft or fascia is then placed as an overlay covering the entire defect and held in place with a piece of polyethylene transsphenoidal implant (Medpor, Stryker) as a gasket seal,¹⁷ followed by fibrin glue (Tisseel, Baxter). This is then covered with small pieces of gel foam and NasoPore (Stryker) as a buttress. Starting in 2011 (last 49 cases), we have also placed a large vascularized nasoseptal flap over the skull base defect after completing the layered gasket seal closure, with fibrin glue applied over the flap rather than over the nonvascularized portion of the repair. The method of nasoseptal flap harvest and repair follows closely the method described by Hadad et al.¹⁸

Use of Lumbar Drainage

A lumbar subarachnoid drain is placed in every patient at the time of surgery. After completion of surgery, the drain is generally kept open at a rate of 5 mL per hour for 2 days and then clamped. The patient is observed the next day to assess for active CSF rhinorrhea. If no CSF leak is detected, the drain is removed. If a CSF leak is suspected, the drain is reopened for another 2 to 3 days, then rechallenged. If a leak persists, the patient is then taken for repair of the leak. Lumbar drains were clamped earlier than 2 days if there was evidence of a significant pneumocephalus on postoperative imaging, or if the drainage resulted in severe headaches. If a drain stopped working although there was no evidence of leak, the drain was generally not replaced.

Antibiotics

All patients received cefazolin (1–2 g) intravenously prior to the start of the procedure, and cefuroxime was continued in the postoperative period until the lumbar drain was removed. In patients who were allergic to cephalosporins, an alternate antibiotic with gram-positive coverage was employed. One patient received clindamycin, one received a fluoroquinolone, and one received ceftriaxone.

Surgical Variables

Each case was subcategorized by the additional approaches and skull base corridors that were employed. The method used to repair the skull base defect created by the surgical approach was documented by reviewing operative reports. The length of the operations was recorded in minutes from the time of incision to the time of closure.

Tumor Characteristics

Tumor type was determined by the review of the pathology reports. Approximate preoperative tumor volume was determined using the ABC/2 method,¹⁹ using the immediate preoperative magnetic resonance imaging scans.

Postoperative CSF Leak and Infection

We recorded any instances of postoperative CSF leaks. We identified all cases of meningitis based on abnormal CSF laboratory results or clinical suspicion based on signs of meningeal irritation, altered mentation, or similar suspicious findings. Not all cases of suspected meningitis were confirmed with verified CSF microbiology, but CSF glucose, protein, and cell count supported the diagnosis. We detailed the CSF values of the patients who developed meningitis. CSF glucose, protein, red blood cell (RBC) count, white blood cell (WBC) count, polymorphonuclear (PMN) cell count, lymphocyte count, and monocyte count were recorded by the first lumbar puncture or the sample from an indwelling lumbar drain taken after meningitis was suspected. Any identified microorganisms in CSF cultures were also noted. We included one patient whose CSF culture was negative, but an endonasal deep biopsy culture identified an organism. Outcomes and sequelae of meningitis following treatment were also tabulated.

Statistical Analysis

We analyzed all variables with respect to two primary end points: (1) development of a postoperative CSF leak and (2) a diagnosis of meningitis. We grouped patients based on whether they met one, both, or none of the two end points. Dichotomous variables were analyzed using the Fisher's exact test, and continuous variables were analyzed using Mann-Whitney's *U*-test. For multivariate analyses with $m \times n$ contingency tables, a post hoc analysis was performed to look for significant differences between each variable. Statistical significance was determined at a *p*-value less than 0.05, with adjustment using the Bonferroni correction for multivariate analyses. Patients' age and BMI were further stratified to male and female cohorts to look for differences in the end points.

Results

Patient Demographics and Overall Outcome

A total of 78 patients underwent 100 endoscopic transsphenoidal surgeries (►Table 1). Ninety-eight surgeries were performed for tumor resection, and two surgeries were performed for clipping of a superior cerebellar artery aneurysm. Fourteen (17.9%) patients experienced postoperative CSF leaks, and eight patients (10.3%) were diagnosed with postoperative meningitis. Among the patients with CSF leaks, five patients (6.4% out of 78 total patients) were also subsequently diagnosed with meningitis. The risk of developing meningitis in the presence of a CSF leak was significantly higher than in patients without a leak, with an odds ratio (OR) of 11.48 (95% confidence interval [CI], 2.33–56.47; $p = 0.004$). There were no significant differences appreciated between the noninfected and the infected groups regarding the time of onset or the duration of the CSF leak ($p = 0.415$ and 0.392 , respectively) (►Table 2).

Prior Surgical History and Repeat Surgeries

Twenty-one patients had a previous history of treatment of the lesion at an outside institution before undergoing EETS at our institution (►Table 3). We analyzed only the results from surgeries performed at our center, focusing on the results of a

Table 1 Patient demographics

Total no. of patients	78
Sex	
Male	34
Female	44
Age (mean $\pm$ SD)	54.2 $\pm$ 15.8
BMI (mean $\pm$ SD)	28.1 $\pm$ 6.5
Total no. of surgeries	100
Surgical approaches	
Transplanum	80
Transpalatal	1
Transclival	17
Transethmoidal	4
Total no. of tumors	98
Pituitary adenoma	28
Gonadotroph	8
Somatotroph	4
Prolactin	2
Nonfunctioning/other	14
Craniopharyngioma	21
Adamantinomatous	17
Papillary	4
Meningioma	13
Grade I	12
Grade II	1
Other	16

Abbreviations: BMI, body mass index; SD, standard deviation.

Table 2 Days from surgery to the onset of cerebrospinal fluid leak, and the duration of the cerebrospinal fluid leak in days

	Onset (d)	Duration (d)
Total	8.0 $\pm$ 7.6	5.6 $\pm$ 4.9
Noninfected	6.1 $\pm$ 4.7	4.6 $\pm$ 4.0
Infected	11.4 $\pm$ 11.1	7.4 $\pm$ 6.2

single institution and neurosurgeon. Twenty-four patients who underwent EETS at our institution required at least one additional operation for the same lesion, nine of whom underwent another EETS. Only one patient, who did not develop any postoperative complications, had chronic rhinosinusitis at the time of surgery. The chance of developing a CSF leak or meningitis after EETS was not altered by a history of prior surgery or radiotherapy. Similarly, an increased rate of CSF leak or infection was not noted following repeat surgery for the same lesion.

Age, Sex, and BMI

There were no significant differences in age or BMI among the patients who developed CSF leaks or meningitis (►Table 4). The cohort was further stratified to male and female patients.

Table 3 Summary of surgical treatments

	Total patients	CSF leak (%)	Infection (%)
Patients with previous treatment (other institution) ^a	21	2 (10)	1 (5)
Endoscopic surgery	1	0	0
Endoscopic surgery and radiation	1	0	0
Craniotomy	9	0	0
Craniotomy and radiation	2	1	0
Multiple endoscopic surgeries	2	0	0
Multiple endoscopic surgeries and radiation	1	1	0
Multiple craniotomies	4	0	0
Multiple craniotomies and radiation	1	0	1
Repeat operations needed (at Cedars-Sinai) ^b	24	2 (8)	1 (4)
Endoscopic surgery	9	0	1
Craniotomy	7	0	0
Both craniotomy and/or endoscopic surgery	8	2	0

Abbreviation: CSF, cerebrospinal fluid.

^aPrior to treatment at Cedars-Sinai.

^bSurgery not related to index case, repair of CSF leak, or infection.

Female patients who experienced a CSF leak were significantly older (65.3 ± 14.4 years) than those who did not (51.5 ± 16.1 years) ($p = 0.049$), but no differences in BMI were identified with respect to CSF leaks. No differences in age or BMI were found in males with respect to CSF leaks and meningitis. Both male and female patient groups who developed a CSF leak were more likely to develop meningitis than those who did not have a leak, with an OR of 9.0 (95% CI, 1.2–71.9; $p = 0.038$) and OR of 14.8 (95% CI, 1.1–194.5 $p = 0.040$), respectively.

Tumor Characteristics and Surgical Factors

Of the 98 tumors that underwent EETS, the primary pathology was pituitary adenoma (35%), craniopharyngiomas (27%), and meningioma (16%) (► **Table 1**). Other lesions (22%) included arachnoid cyst (one), chondrosarcoma (one), chordoma

(three), esthesioneuroblastoma (one), germinoma (one), granular cell tumor (one), hemangioblastoma (one), malignant epitheloid hemangioendothelioma (one), pituitaryoma (two), Rathke's cleft cyst (two), and sinonasal undifferentiated carcinoma (one). There was a total of 100 operations.

We evaluated tumor histology, tumor volume, surgical approach, method of skull base reconstruction, the length of the operation, and the length of hospital stay to identify potential risk factors for either CSF leak, infection, or both (► **Table 5**). Tumor histology was a significant predictor for developing meningitis ($p = 0.008$). Post hoc analysis revealed that pituitaryomas were significantly associated with infection when compared with meningiomas ($p = 0.01$), craniopharyngiomas ($p = 0.04$), and pituitary adenomas ($p = 0.01$).

No significant differences were related to tumor volume, type of surgical approach and reconstruction, and the duration of the operation.

Although not statistically significant, CSF leak rate in patients without a nasoseptal flap trended higher 25% (10/40 cases), whereas the rate was 9.5% (4/42 cases) in patients with a vascularized flap ($p = 0.152$). Interestingly, there was a slightly higher rate of meningitis in patients with a nasoseptal flap repair (15%) compared with those without (6%). Overall, the chances of developing both a leak and meningitis were similar, regardless of whether a nasoseptal flap was employed or not (8% without vs. 5% with flap). None of these differences between the groups was statistically significant.

Patients were hospitalized significantly longer when they developed a CSF leak (19.2 vs. 9.2 days, $p = 0.002$), meningitis (25.8 vs. 9.1 days; $p = 0.026$), or both (22.0 vs. 8.2 days; $p = 0.028$).

Cases of Meningitis

► **Table 6** lists the initial CSF values for each of the eight meningitis cases. The median and the range of all cases were: glucose 10.5 (range: 15–157), protein 153 (range: 26–682), RBC 455 (range: 0–410,000), WBC 197 (range: 1–1,789), PMN 60.5 (range: 0–86), lymphocytes count 12 (range: 1–67), and monocyte count 7 (range: 0–34). Out of the eight patients, five had abnormal glucose, and seven had abnormal protein levels. Five out of six patients had abnormal WBC levels. Most CSF cultures did not grow any organisms within 3 days; however, three patients had at least one positive culture. Identified organisms included *Enterococcus*, vancomycin-resistant *Enterococcus* (VRE) *faecium*, VRE *faecalis*, *Candida*

Table 4 Rate of cerebrospinal fluid leak, infection, and both stratified by age, sex, and body mass index

	All patients	CSF leak		Infection		Both	
		No leak	Leak	No infection	Infection	None	Leak + infection
No. of patients (%)	78	64 (82)	14 (18)	70 (90)	8 (10)	61 (78)	5 (6)
Age (mean $\pm$ SD)	54.2 $\pm$ 15.8	53.2 $\pm$ 15.4	58.5 $\pm$ 15.4	54.6 $\pm$ 15.1	50.8 $\pm$ 21.8	53.4 $\pm$ 15.1	52 $\pm$ 22.8
Male (%)	34	27 (79)	7 (21)	32 (94)	2 (6)	25 (74)	3 (9)
Female (%)	44	37 (81)	7 (19)	41 (93)	3 (7)	36 (82)	2 (5)
BMI (mean $\pm$ SD)	28.1 $\pm$ 6.5	27.5 $\pm$ 5.9	30.6 $\pm$ 8.7	27.7 $\pm$ 5.8	31.5 $\pm$ 11.0	27.5 $\pm$ 6.0	34.0 $\pm$ 13.0

Abbreviations: CSF, cerebrospinal fluid; SD, standard deviation.

Table 5 Tumor characteristics and surgical factors

	Total	CSF leak		P	Infection		P	Both		P
		No leak (%)	Leak (%)		No infection (%)	Infection (%)		None (%)	Leak + infection (%)	
No. of tumors	98	84	14		89	9		80	5	
Tumor volume (cm ³)										
Mean ± SD	10.89 ± 15.31	10.70 ± 15.72	12.03 ± 12.96	0.478	11.02 ± 15.84	9.57 ± 8.92	0.529	10.84 ± 16.08	10.88 ± 11.79	0.582
Tumor histology										
Pituitary adenoma	28	22 (79)	6 (21)	0.999	26 (93)	2 (7)	0.008	22 (79)	2 (7)	0.565
Craniopharyngioma	21	16 (76)	5 (24)		18 (86)	3 (14)		15 (53)	2 (10)	
Meningioma	13	11 (85)	2 (15)		13 (100)	0		11 (85)	0	
Pituicytoma	2	1 (50)	1 (50)		0	2 (100)		0	1(50)	
Granular cell tumor	1	1 (100)	0		0	1 (100)		0	0	
Surgical approach										
Transplanum	80	67 (84)	13 (16)	0.176	71 (89)	9 (11)	0.999	63 (79)	5 (6)	0.999
Transpalatal	1	0	1 (100)		1 (100)	0		0	0	
Transclival	17	17 (100)	0		17 (100)	0		17 (100)	0	
Transethmoidal	4	4 (100)	0		4 (100)	0		4 (100)	0	
Multilayer repair										
Without NSF	50	40 (75)	10 (25)	0.152	47 (94)	3 (6)	0.304	40 (92)	3 (8)	0.999
With NSF	46	42 (90)	4 (10)		40 (85)	6 (15)		38 (95)	2 (5)	
Operation time (min)										
Mean ± SD	178 ± 71	175 ± 74	182 ± 59	0.638	175 ± 75	180 ± 33	0.549	174 ± 76	176 ± 34	0.779
Length of stay (d)										
Mean ± SD	10.7 ± 16.7	9.2 ± 15.4	19.2 ± 21.3	0.002	9.1 ± 13.3	25.8 ± 33.8	0.026	8.2 ± 12.0	22.0 ± 24.0	0.028

Abbreviations: CSF, cerebrospinal fluid leak; SD, standard deviation.

Note: P indicates the p-value of the differences among tumor histology, surgical approach, type of reconstruction, duration of surgery, and duration of hospital stay. Bolded values represent significance when $p < 0.05$.

Table 6 The first cerebrospinal fluid laboratory values for all eight cases of meningitis

Cerebrospinal fluid laboratory values									
Reference ranges		45–80 mg/dL	15–45 mg/dL	0–25/μL	0–5/μL				
Patient (n = 8)	POD	Glucose	Protein	RBC	WBC	PMNs	Lymph	Monocytes	Identified organisms
1	36	23	149	12,900	120	86	2	2	VRE <i>faecium</i> and <i>Candida albicans</i>
2	4	157	46	410,000	1,100	82	14	2	<i>Candida albicans</i> , VRE <i>faecalis</i>
3	3	58	65	3	1	0	1	0	<i>Pseudomonas</i> (×4)
4	13	37	682	180,000	900	n/a	n/a	n/a	None
5	8	18	309	455	1,789	52	14	34	None
6	16	15	248	n/a	n/a	n/a	n/a	n/a	None
7	6	34	157	340	197	69	10	21	None
8	78	65	26	0	2	0	67	12	<i>Enterococcus</i>

Abbreviations: Lymph, lymphocytes; n/a, values not obtained; PMN, polymorphonuclear cells; POD, postoperative day, the number of days since surgery when CSF values were obtained; RBC, red blood cells; VRE, vancomycin-resistant *Enterococcus*; WBC, white blood cells.

albicans, and *Pseudomonas*. We included one patient whose CSF culture was negative, but the endonasal deep biopsy culture grew *Enterococcus* species. All cases of meningitis were resolved with the appropriate antibiotic regimen, although intrathecal antibiotics were required in addition to intravenous antibiotics in two cases.

Discussion

The reported rate of CSF leak and meningitis following EETS ranges from ~0 to 21% and 0 to 10%, respectively.^{4,6,20–30} Consistent with this observation, our study found CSF leaks in 17.9% and meningitis in 10.3% of our patients. Our rate of meningitis fell in the higher range, which we suspect was due to our more inclusive definition of meningitis compared with other studies, as well as limiting our analysis only to cases with intentional larger violations of the arachnoid. For example, Gondim et al defined meningitis in patients who underwent routine pituitary surgery with a confirmed CSF culture,³¹ while other studies included patients with clinical symptoms⁶ or with an abnormal CSF examination,³² similar to our criterion.

The most important factor for developing meningitis in our cohort was the presence of a postoperative CSF leak, which is consistently reported in the literature.^{4,7,33,34} Kono et al⁷ described a series of 1,000 endoscopic surgeries in which CSF leak, which occurred in 14% of cases, was the strongest risk factor for developing a subsequent meningitis with an OR of 12.99 (95% CI, 4.24–39.82; $p < 0.001$). Interestingly, they concluded that the expanded approach was not a risk factor for meningitis. In a systematic review by Lai et al,⁴ of 2,005 patients who underwent expanded EETS, CSF leaks were again reported to be a strong risk factor for developing meningitis, with an OR of 91.99 (95% CI, 11.72–721.88; $p < 0.01$). Four of our EETS cases developed meningitis without a CSF leak; however, we postulate that these cases may have had CSF leaks that were not clinically detected because of our routine use of a lumbar drain after EETS.

Preoperative Risk Factors

We found no significant differences in age or BMI among the patients who developed a CSF leak or meningitis. Lobatto et al¹³ performed a systematic analysis of 23 articles with 5,491 patients who underwent endoscopic surgery. Younger age, female sex, and higher BMI were noted to be risk factors for developing a postoperative CSF leak. CSF leaks were found to be more prevalent in the older age group.⁶ Of the five studies that assessed sex, two studies with overlapping patient populations demonstrated that female patients had a significantly higher rate of CSF leaks. Although we did not observe a difference between sexes, female patients who developed a CSF leak were significantly older than female patients who did not develop a leak.

In some reports, preoperative BMI has been shown to be a risk factor for CSF leak after endoscopic surgery. Furthermore, preoperative BMI has been reported as a risk factor for meningitis.⁶ Although not statistically significant, we noted that BMI trended higher in patients who were diagnosed with CSF leak (mean $\pm$ standard deviation: 30.6 ± 8.7), men-

ingitis (31.5 ± 11.0), or both (34.0 ± 13.0) than their counterparts (27.5 ± 5.9 , 27.7 ± 5.8 , and 27.5 ± 6.0 , respectively).

Tumor Characteristics

Lobatto et al¹³ also reported that only one out of five series in their review demonstrated an association between tumor size and CSF leaks.^{35–40} In our cohort of patients, tumor volume was not found to be a significant predictor of CSF leaks or meningitis, although the tumor volume of the patients with CSF leaks trended higher (12.03 ± 12.96 mL) than patients who did not develop a CSF leak (10.7 ± 15.7 mL).

Meningitis occurred in two patients with pituitaryoma. Although limited by the rarity of the tumor histology, we found statistical significance when comparing pituitaryoma to other more common tumors, such as meningiomas, cranio-pharyngiomas, and pituitary adenomas. Pituitaryomas are rare benign tumors, with only 117 cases in literature reported by a systematic review, 13 of which were treated with EETS.^{41,42} Pituitaryomas are known to be hypervascular, which can increase operative difficulties because of the risk of bleeding.^{43–45} Given that more complex endoscopic surgeries have been shown to be associated with meningitis,⁷ we speculate that these lesions may be more prone to infection.

Surgical Factors

We did not identify a significant difference in the rate of CSF leaks depending on the type of additional surgical corridor used for the lesion. Pagliano et al³² reported higher CSF leaks in the transtubaric approach (8.3%) when compared with the standard endoscopic approach (1%). Of note, the grading of CSF leaks from transsphenoidal surgery and the related risks of postoperative leaks is in line with these observations as well.⁴⁶ Furthermore, we also did not note a difference in operation time in patients with CSF leaks or meningitis, although one study did note this association.³³

As the techniques for skull base reconstructions have evolved, the incidence of CSF leaks and meningitis has decreased.^{4,7,47,48} Multilayered reconstruction techniques and the use of vascularized tissue flaps have been shown to decrease the risk of meningitis.^{7,47,48} Interestingly, the type of reconstruction we used did not impact the rates of CSF leak or meningitis in our series. Since we use lumbar drains in all of our patients, we were unable to discern any relationship between their use and the risk of leak or infection. However, a recent well-performed randomized clinical trial found that the use of lumbar drains can reduce incidence of postoperative CSF leak significantly.⁴⁹ One potential downside of lumbar drainage is that it may prove to be an additional source for meningitis. Nonetheless, based on overall trends and many other reports, we advocate for the use of multilayered closures including a vascularized tissue flap, and short-term use of lumbar drainage as means to reduce the rate of CSF leak and infection following expanded approaches.

CSF Studies

Of the eight patients diagnosed with meningitis, we reported the first CSF studies that were obtained immediately after meningitis was suspected. Many of these patients had CSF

glucose, protein, and WBC values highly suggestive of meningitis, even with negative cultures. The most consistently abnormal marker of the first set of CSF values seemed to be the protein levels (seven out of eight patients) and WBC (five out of six patients). Fouad et al reported that among the CSF values, the level of protein had the highest accuracy (78%), sensitivity (88%), and specificity (72%) in patients with acute bacterial meningitis.⁵⁰ Serum procalcitonin levels and CSF lactate also have been reported to be reliable for the diagnosis of meningitis.^{50–52}

Pagliano et al³² defined meningitis after EETS identical to our criterion and identified *Streptococcus*, *Staphylococcus*, and *Haemophilus* species. Out of the 28 cases in the review, only one case each of *Candida albicans* and *Enterococcus* species were reported. *Candida* was identified in two of our patients, and *Enterococcus* in one. We also identified one patient with a CSF culture growing *Pseudomonas*. To our knowledge, this is the first case of meningitis with culture-proven *Pseudomonas* after EETS. All of our cases of meningitis were resolved with antibiotics, with extended intrathecal antibiotics required for the patient with *Pseudomonas* meningitis.

Costs of Care

Asemota et al⁵³ assessed the health care costs for transsphenoidal surgery and its related complications. They indicated a 50% increase in costs for patients with complications compared with those without. In light of the markedly extended hospital stays seen in patients with leaks or meningitis, it is reasonable to assume these costs represent a significant economic burden. These costs highlight the importance of identifying risk factors for CSF leak and meningitis to also contribute to the cost-containment efforts. Somma et al⁵⁴ have proposed a chemoprophylaxis regimen for reducing meningitis during EETS. Further studies will be needed to confirm and expand the utility of such regimen.

Limitations

In addition to an inherent bias in retrospective study designs, our analysis of tumor histology was limited by the infrequent number of cases with pituitaryomas and meningitis. However, our findings suggest a possible association of tumor histology and meningitis, which we hypothesize may be due to the vascularity of pituitaryomas. Therefore, future studies will focus on analyzing the outcomes with respect to objective measurements of tumor vascularity, such as intraoperative blood loss.

Conclusion

Postoperative CSF leak is the greatest risk factor for subsequent development of meningitis. An increase in CSF protein levels is the most helpful laboratory indicator for a presumptive diagnosis of meningitis. Skull base corridor, type of repair, age, BMI, or tumor volume do not significantly change the rate of leak or infection, although pituitaryoma as a surgical pathology may be a relative risk factor, and there is a trend toward reduced leak in patients with vascularized

nasoseptal flaps. Vigilant monitoring for early signs of meningitis, especially in patients with postoperative leaks, and rapid treatment in suspected patients serves to reduce both the overall morbidity and medical costs.

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Conflict of Interest

None.

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