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Perioperative Antibiotic Use in Endoscopic Endonasal Skull Base Surgery

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Abstract

Introduction Improved evidence-based guidelines on the optimal type and duration of antibiotics for patients undergoing endoscopic endonasal transsphenoidal surgery (EETS) are needed. We analyze the infectious complications among a large cohort of EETS patients undergoing a standardized regimen of cefazolin for 24 hours, followed by cephalexin for 7 days after surgery (clindamycin if penicillin/cephalosporin allergic).
Methods A retrospective review of 132 EETS patients from 2018 to 2020 was conducted. Patient, tumor, and surgical characteristics were collected, along with infection rates. Multivariate logistic regression determined the variable(s) independently associated with infectious outcomes.
Results Nearly all patients (99%) received postoperative antibiotics with 78% receiving cefazolin, 17% receiving cephalexin, 3% receiving clindamycin, and 2% receiving other antibiotics. Fifty-three patients (40%) had an intraoperative cerebrospinal fluid (CSF) leak, and three patients (2%) developed a postoperative CSF leak requiring surgical repair. Within 30 days, no patients developed meningitis. Five patients (4%) developed sinusitis, two patients (3%) developed pneumonia, and one patient (1%) developed cellulitis at a peripheral intravenous line. Two patients (2%) developed an allergy to cephalexin, requiring conservative management. After adjustment for comorbidities and operative factors, presence of postoperative infectious complications was independently associated with increased LOS ($\beta = 3.7$ days; $p = 0.001$).
Conclusion Compared with reported findings in the literature, we report low rates of infectious complications and antibiotic intolerance, despite presence of a heavy burden of comorbidities and high intraoperative CSF leak rates among our cohort. These findings support our standardized 7-day perioperative antibiotic regimen.

Keywords
- antibiotic regimen
- anterior skull base surgery
- pituitary surgery
- postoperative infection
- transsphenoidal surgery

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Introduction

Endoscopic endonasal transsphenoidal surgery (EETS) is generally safe and associated with low morbidity and mortality rates.[1–3] However, the approach requires the surgeon to create a clean-contaminated incision through the nasal cavity which places patients at higher risk for infections. In addition, cerebrospinal fluid (CSF) leak is a significant complication of EETS that has been shown to further increased risk for meningitis.[1,4–6] Effective prophylactic antibiotic regimens are important in minimizing postoperative infections, especially meningitis and sinusitis.[7,8] However, there is still a lack of evidence-based clinical guidelines regarding which regimens should be administered prophylactically in EETS patients.[7–10]

While several systematic reviews have attempted to establish guidelines to address this, there is a lack of consensus.[8,9,11,12] Moldovan et al found a preference for cephalosporins as short-term prophylaxis across most studies, specifically <24 hours or between 24 and 48 hours after surgery, especially for those with comorbidities such as diabetes mellitus, smoking history, and respiratory disease.[8] Rates of infection among patients given cephalosporins for short-term prophylaxis ranged from 0.0 to 0.6% for meningitis and 0.0 to 10.2% for sinusitis.[8,11,13,14] They concluded that more studies were necessary to create evidence-based guidelines.[8] Patel et al found that rates of meningitis following EETS ranged broadly from 1.4 to 25%, depending on factors related to surgical history and the occurrence of intraoperative CSF leaks.[9] They concluded that perioperative antibiotic prophylaxis for clean-contaminated surgery (defined as skull base surgery with sinonasal mucosa involvement) was indicated both intraoperatively and postoperatively for a 24-hour time frame. Like other studies, this study also acknowledged the limited current literature regarding antibiotic regimens.[9]

In this study, we retrospectively evaluated the effectiveness of our prophylactic antibiotic regimen among 132 patients undergoing EETS. This represents one of the largest cohorts of patients receiving cephalosporin (cefazolin/cephalexin) prophylaxis alone, rather than multiple concurrent antibiotics or mixed cohorts with different antibiotic regimens. We aimed to identify the rates of infectious complications, including the incidences of sinusitis and meningitis, as well as the patient, tumor, and surgical factors associated with higher risk for these complications. Secondary outcomes included other complications, such as events of antibiotic intolerance and hospital length of stay (LOS).

Materials and Methods

A retrospective review of consecutive adult patients (≥18 years old) undergoing EETS by one senior rhinologist (M.B.W.) and one senior neurosurgeon (M.B.) from July 2018 to July 2020 was performed. Patient, tumor, and surgical characteristics were collected, along with postoperative infection rates and LOS. Patient factors included sex, age, ethnicity, body mass index, preoperative antibiotic use, and comorbidities. Exclusion criteria included patients under 18 years of age and preoperative antibiotic use. Tumor characteristics included pathology, size, and location. Tumor size was reported as the largest dimension (cm) on preoperative magnetic resonance imaging (MRI). Tumor location was categorized by the degree of extension into nearby structures: sella alone; with suprasellar extension; with cavernous sinus(es) extension; or with severe extension, defined as tumor extension into more than three sites.

Surgical factors included presence and grade of intraoperative CSF leak, type of sellar reconstruction, type of nasal packing, primary or revision status, and duration of surgery. Intraoperative CSF leak was categorized into the following grades: grade 0, no leak; grade 1, small “weeping” CSF leak, without obvious or with small diaphragmatic defect; grade 2, moderate CSF leak, with obvious diaphragmatic defect; or grade 3, large diaphragmatic and/or dural defect, as has been previously described.[15] Type of sellar reconstruction included a combination of septal mucosal graft, nasoseptal flap, abdominal fat graft, turbinate graft/flap, and/or rigid fixation. Rigid fixation included sellar reconstruction with use of KLS Martin Resorb-X 1.0-mm double-Y extra plate (Tuttlingen, Germany) or septal bone. Nasal packing included none, NasoPore (Stryker, Kalamazoo, Michigan, United States), or Doyle Open Lumen Splints (Boston Medical Products, Shrewsbury, Massachusetts, United States). Postoperative factors were also obtained, including presence of a postoperative CSF leak, LOS, and incidence of infection up to 30 days after the operation. Furthermore, information about perioperative antibiotics, as well as discharge medications, was recorded.

Utilizing Stata16 statistical software (StataCorp LLC, College Station, Texas, United States), continuous and binary variables were compared using the Wald and Pearson χ^2 tests, respectively, and one-way analysis of variance (ANOVA) testing was performed for categorical (>2) variables. Univariate and multivariate logistic regression analyses were performed to investigate independent risk factors associated with postoperative infectious outcomes. Statistical significance was defined as an $\alpha < 0.05$. β represented the degree of change in the outcome variable for every 1-unit of change in the predictor variable. This study was approved by the University of California, Los Angeles Institutional Review Board (IRB no.: 13–000154).

Results

A total of 132 patients underwent EETS for tumor resection. Mean age was 46 years (standard deviation [SD] ± 16). Patient demographics and clinical characteristics are listed in ►Table 1. Our patient cohort included notable presence of comorbidities, including body mass index ≥30 (43%), diabetes mellitus (22%), and immunosuppression (11%). Of note, 23% of patients had a smoking history of which 6% were current smokers.

Nearly all patients (99%) received intraoperative antibiotics, with the majority receiving cefazolin (95%) and 4% receiving clindamycin. Operations lasted an average of

Table 1 Patient demographics and clinical characteristics

Total cohort	$n = 132$	%
Mean age (y) ± SD	46 ± 16	
Female	70	53
Race		
Caucasian	58	44
African American	25	19
Hispanic	7	5.3
Middle Eastern	2	1.5
Asian	23	17
Refused/other	17	13
Average BMI ± SD	30 ± 6.7	
Preoperative steroid use	23	17
Prior sinus surgery or rhinoplasty	28	21
History of radiation therapy	1	1
History of smoking	30	23
Current smoker	8	6
Prior smoker	22	17
History of alcohol use	24	18
Comorbidities		
Obstructive sleep apnea	31	23
Diabetes mellitus	29	22
Obesity	57	43
History of lung disease[a]	9	7
Immunosuppression[b]	14	11
Depression	28	21
Anxiety	26	20
History of allergies	58	44

Abbreviations: BMI, body mass index; SD, standard deviation.
[a]Includes emphysema, chronic bronchitis, and asthma.
[b]Includes chronic steroid use, chronic immunosuppressants, organ transplant, HIV/AIDS, and dialysis.

Table 2 Tumor and surgical factors

Total cohort	$n = 132$	%
Average tumor size (cm) ± SD[a]	1.8 ± 1.1	
Pathology		
Pituitary adenoma	105	80
Rathke's cleft cyst	17	13
Meningioma	3	2.3
Chordoma	1	0.8
Craniopharyngioma	3	2.3
Suprasellar cyst	1	0.8
Chondrosarcoma	1	0.8
Glioma	1	0.8
Tumor location		
Sella	67	51
Suprasellar extension	29	22
Cavernous sinus extension	23	17
Severe extension[b]	12	9
Clival	1	1
Average duration of surgery (h) ± SD	2.7 ± 1.1	
Surgery longer than 3 hours	22	17
Revision surgery	20	19
Concurrent septoplasty	12	11
Concurrent endoscopic sinus surgery	6	6
Intraoperative CSF leak	53	40
Grade 1	30	23
Grade 2	13	10
Grade 3	10	8

Abbreviations: CSF, cerebrospinal fluid; SD, standard deviation.
[a]Tumor size was reported as the largest dimension (cm) on preoperative magnetic resonance imaging.
[b]Defined as tumor extension into more than three sites or extension into either middle cranial fossa, posterior cranial fossa, or petrous apex.

2.7 hours (SD ± 1.0). Most patients had pituitary adenomas (80%) and underwent primary surgery (81%). The average tumor size was 1.77 cm (SD ± 1.10), and most tumors (51%) did not have extension out of the sella. Tumor size was defined as the largest dimension on preoperative MRI. Complex expanded endonasal cases tended to involve larger tumors, and included a chordoma (3.0 cm), chondrosarcoma (2.7 cm), glioma (2.0 cm), suprasellar cyst (1.5 cm), and three craniopharyngiomas (5.1, 2.0, and 1.3 cm). Ten pituitary adenomas with severe cavernous sinus invasion averaged 3.3 cm and ranged from 1.8 to 5.5 cm, while the single pituitary adenoma with clival invasion was 3.0 cm.

Fifty-three patients (40%) experienced an intraoperative CSF leak, with 8% having a grade-3 leak. Tumor and surgical factors are presented in ►**Table 2** and repair techniques are reported in ►**Table 3**. Following EETS, all patients were admitted to the hospital for routine postoperative monitoring. LOS averaged 2.5 days (SD ± 2.1). Nearly all patients (99%) received inpatient postoperative antibiotics for 24 hours with 78% receiving cefazolin, 17% receiving cephalexin, 3% receiving clindamycin, and 2% receiving other antibiotics, followed by a 6-day course of oral antibiotics which most commonly was cephalexin (86%; ►**Table 4**). Three patients (2.3%) developed a postoperative CSF leak requiring return to the operating room for repair. Three patients (2%) developed a postoperative CSF leak that responded conservatively with placement of a lumbar drain. No patients developed meningitis, sinusitis, or *Clostridium difficile* diarrhea during hospitalization. Two patients (2%) developed pneumonia. One patient developed postoperative epistaxis with aspiration of blood, requiring reintubation for hypoxic respiratory failure, and later developed pneumonia. The other patient developed aspiration pneumonia within 1 day postoperatively, requiring high-flow oxygen and

Table 3 Repair techniques

Total cohort	$n = 132$	%
Type of sellar reconstruction		
Septal mucosal graft	77	58
Nasoseptal flap	51	39
Abdominal fat graft	22	17
Turbinate flap/graft	4	3
Rigid fixation[a]	14	11
Other repair parameters		
Nasal trumpet	35	27
Synthetic material use[b]	51	39
Nasal packing[c]		
None	1	1
Bilateral nasopore	98	74
Bilateral nasopore with coude	27	20
Coude catheter only	3	2
Bilateral silastic stents and bilateral nasopore	1	1
Bilateral silastic stents with coulde and bilateral nasopore	2	2

[a]Rigid fixation included sellar reconstruction with use of KLS Martin Resorb-X 1.0 mm double-Y extra plate (Tuttlingen, Germany) or septal bone.
[b]Synthetic materials included DuraMatrix, DuraGen, resorbable plate, BioDesign, and Propel.
[c]Nasal packing included none, NasoPore (Stryker, Kalamazoo, Michigan, United States), or Doyle Open Lumen Splints (Boston Medical Products, Shrewsbury, Massachusetts, United States).

Table 4 Antibiotic use

Total cohort	$n = 132$	%
Intraoperative antibiotics		
Cefazolin	125	95
Clindamycin	5	4
None	1	1
Postoperative antibiotics		
Cefazolin[a]	103	78
Cephalexin[b]	22	17
Clindamycin[c]	4	3
Other	2	2
None	1	1
Discharge antibiotics		
Cephalexin[b]	113	86
Clindamycin[d]	8	6
Amoxicillin–clavulanate	3	2
None	8	6

[a]1 g every 8 hours.
[b]500 mg four times a day.
[c]450 mg three times a day.
[d]300 mg three times a day.

treatment with amoxicillin–clavulanate. Three patients (2%) developed urinary tract infections, while one patient (1%) developed cellulitis at a peripheral intravenous line. All of these patients improved after changing their initial antibiotic regimens. One patient (1%) developed an allergy to cephalexin during hospitalization, requiring conservative management with antihistamines (►**Table 5**).

Upon discharge, most patients were given antibiotics (95%) to complete a total 7-day course. These included cephalexin (86%), clindamycin (6%), or amoxicillin–clavulanate (3%). The most common reason a patient did not receive discharge antibiotics was due to LOS > 7 days. On average, patients had their first follow-up appointment 19 days (SD ± 35) after surgery and their second follow-up appointment 63 days (SD ± 55) after surgery. After discharge, no patients developed meningitis. Five patients (4%) developed sinusitis, requiring an additional round of antibiotics (amoxicillin–clavulanate or trimethoprim/sulfamethoxazole), and later recovered. Diagnosis was made based on the presence of mucopurulent drainage found in the sinus cavities and/or increased crusting. Of these five patients, two patients were diagnosed with sinusitis at outside facilities, so diagnostic criteria were unspecified. Another patient (1%) reported an allergy to cephalexin after discharge which improved after taking antihistamines.

Table 5 Postoperative outcomes

Total cohort	$n = 132$	%
Average length of hospital stay (d) ± SD	2.5 ± 2.1	
During hospitalization		
Postoperative CSF leak	3	2
Altered mental status	0	0
Development of allergy to antibiotics	1	1
Pneumonia	2	2
Cellulitis	1	1
Urinary tract infection	3	2
After discharge		
Average follow-up (d) for first Postoperative clinic visit ± SD	19 ± 35	
Meningitis	0	0
Sinusitis	5	4
Development of allergy to antibiotics	1	1

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

On univariate analysis alone, factors associated with postoperative infectious complications during hospitalization included revision surgery ($p = 0.001$), concurrent endoscopic sinus surgery ($p = 0.001$), rigid fixation ($p = 0.013$), and usage of a nasal trumpet ($p = 0.003$). Factors associated with infectious complications after discharge included depression ($p = 0.001$) and use of a turbinate flap ($p < 0.001$). On multivariate analysis, no patient-, tumor-, or surgical-related factors were significantly associated with infectious complications. This included any associations between repair techniques, grades of CSF leaks, and rates of sinusitis. After adjustment for patient characteristics, comorbidities, and operative factors, presence of postoperative infectious complications was independently associated with increased LOS ($\beta = 3.7$ days; $p = 0.001$).

Discussion

There remains a lack of consensus on the use of perioperative antibiotics in both endoscopic sinus and skull base surgery. Although current evidence does not support the use of routine prophylactic antibiotic use for endoscopic sinus surgery, but may support its use in skull base surgery,[9] there is wide variation among surgeons' actual practices, as found in surveys among members of the American Rhinologic Society and the North American Skull Base Society.[16,17]

The present study seeks to expand current understanding of infectious outcomes following EETS by characterizing the effectiveness of perioperative antibiotics and the risk factors for infectious outcomes postoperatively. We report low rates of infectious complications and antibiotic intolerance within a robust cohort of 132 patients, despite presence of a heavy burden of comorbidities, and high rates of intraoperative CSF leaks. Compared with other studies, our patients had a greater than four-fold rate of diabetes mellitus (22.0 vs. 5.2%) and more than twice the rate of smoking (22.7 vs. 7.6%).[8,18] Furthermore, while these comorbidities have been associated with increased rates of postoperative infection, especially meningitis, we report no cases of meningitis among our cohort and a low rate of sinusitis (4%) which all resolved with an additional short-term course of antibiotics.[8,18,19] Similarly, while we did have a higher incidence of intraoperative CSF leak compared with other studies (40.2 vs. 32.8%) due to inclusion of nonpituitary pathologies with expected intraoperative leaks, this was not associated with increased inpatient or postdischarge infectious complications up to 30 days after surgery ($p = 0.896$), as it has shown to be in other studies.[8,18–20] These findings support our standardized perioperative antibiotic regimen: cefazolin for 24 hours, followed by cephalexin for 6 days after surgery (clindamycin if penicillin/cephalosporin allergic).

Furthermore, we report one of the largest cohorts of EETS patients receiving cephalosporin (cefazolin/cephalexin) prophylaxis alone, rather than multiple concurrent antibiotics or mixed cohorts with different antibiotic regimens. Analyzing the bacterial flora in the nasal cavity and sphenoid sinus in EETS patients, Shibao et al reported that 96.8% of bacterial isolates in the nasal cavity and 80% in the sphenoid sinus were sensitive to cephalosporins.[21] Orlando et al reviewed a cohort of 170 patients who primarily (>90%) received a third-generation cephalosporin plus an aminoglycoside for an average of 3 days, and reported a 0.6% rate of meningitis, and 0.6% rate of sinusitis within 30 days postoperatively.[13] Our regimen of a cephalosporin alone for 7 days avoids the toxicities related to aminoglycosides (nephrotoxicity, ototoxicity, etc.), while also preventing postoperative meningitis, a potentially devastating outcome of EETS; while our cohort had a higher risk for developing postoperative sinusitis (4%), all patients recovered with oral antibiotics. Brown et al reported a cohort of 79 patients receiving cefazolin for 24 to 48 hours with a 0% meningitis rate and 2.2% sinusitis rate within 30 days.[14] Similarly, Somma et al described a cohort of 97 patients undergoing cefazolin for <24 hours and reported no rates of meningitis or sinusitis within the same time period.[22] This may imply that we may be giving antibiotics for too long after surgery. However, Brown et al did not provide any information related to patient comorbidities, and Somma et al excluded patients with comorbidities, including those with a smoking history, respiratory disease, and diabetes. Our cohort exhibited a heavy burden of these comorbidities which have been shown in the literature to be associated with higher risk for development of infection,[8,18,22] arguing that our longer duration of antibiotic prophylaxis may have been warranted. Little and White evaluated a cohort of 442 transsphenoidal surgery patients receiving intravenous cefuroxime <24 hours and reported no cases of bacterial meningitis.[23] However, this study did not report rates of sinusitis and excluded all patients with a lumbar drain, while we retained these patients.[23] Ceraudo et al also reported a promising ultrashort antibiotic regimen of a single dose of antibiotics at anesthesia induction (with a second dose added for surgeries longer than 3 hours) based on nasal swab-related antibiotic protocols in a cohort of 120 patients.[24] However, when comparing the 60 patients undergoing this procedure to the 60 controls, the rates of meningitis and sinusitis during and after hospitalization were not statistically significant. Furthermore, Ceraudo et al described the need for a rectal swab and possible additional antibiotics for patients with risk factors, including previous hospitalizations and comorbidities, such as diabetes and chronic obstructive pulmonary disease, which only made up 7.2% of their experimental cohort. Since our cohort exhibits much higher rates of these risk factors, the application of this complex multitiered system of multiple swabs and multiple antibiotics, for no clear additional benefit in terms of infectious rates, does not seem necessary. Furthermore, while a review by Patel et al additionally supported antibiotic use for <24 hours in skull base surgery, a more recent review by Jin et al reported higher rates of meningitis and bacteremia (1.8%), and even death from infection (0.4%), among 3,242 patients treated with antibiotic prophylaxis for a total duration of 48 hours after surgery.[9,18] This may support the use of antibiotic prophylaxis for a longer duration after surgery.

Overall, our rates of infection are comparable to that of current literature. We report no cases of meningitis within 30 days postoperatively which has also been reported among multiple EETS cohorts with cephalosporin prophylaxis.[8] We also report a 4% rate of sinusitis infection within 30 days postoperatively which is comparable with other studies that utilize cephalosporin prophylaxis for similar cohorts.[8,11] These studies report rates of sinusitis infection that range from 2.2 to 10.2%.[11,14] Our rates of other infectious complications are also on par with similar studies that report them, such as Brown et al, which reported a 3% rate of urinary tract infection and 2% rate of aspiration pneumonia, as well as a 64% incidence of intraoperative CSF leak, within their cohort.[14]

Patients who developed sinusitis in our study had various risk factors that may have placed them at higher risk of infection. These included a heavy burden of comorbidities, including diabetes mellitus and history of radiation therapy or smoking, as well as various predisposing surgical factors, including use of rigid fixation, prior or concurrent endoscopic sinus surgery, intraoperative CSF leak, and extension of the tumor to the clivus. While none of these factors were significantly associated with higher risk for infectious complications in our cohort, many of these factors have been shown to increase infectious risk in other studies.[18,20,25] Milanese et al specifically linked intraoperative and postoperative CSF leaks with increased rates of meningitis among 2,032 patients, reporting 1.3% of patients with intraoperative CSF leaks and 10.14% of patients with postoperative CSF leaks suffering from meningitis.[20] Furthermore, this study employs a short-term intraoperative antibiotic prophylaxis regimen that was switched to an ultrashort (single dose) intraoperative antibiotic regimen. However, despite an even higher rate of intraoperative CSF leak (40 vs. 32.8%), we report no cases of meningitis, suggesting that our longer antibiotic prophylaxis regimen may be superior in preventing these rare but potentially fatal occurrences. In a large study (509 patients) encompassing 7 years, Conger et al rigorously analyzed approaches to skull base repair and their associations with CSF leaks and infections and showed that an intraoperative CSF leak nearly doubled the rates of meningitis (1.1 vs. 2.1%).[26] Furthermore, the rate of meningitis decreased in the latter portion of the study when a stricter antibiotic dosing protocol was implemented which included antibiotic prophylaxis (3 g ampicillin/sulbactam or clindamycin if penicillin or cephalosporin allergic) for 24 hours after surgery or until nasal packs were removed for patients with nasal packing (usually postoperative day 5). Finally, despite reporting 27% of cases as being complex extended approaches, Conger et al similarly reported that CSF leak grade and tumor type were not predictive of meningitis.[26] Moreover, our low incidence of outcome events (postoperative infections) likely precluded our ability to determine risk factors, including CSF leaks and types of repair, associated with infectious complications on multivariate logistic regression. Thus, the lack of significant association of several risk factors may simply be a function of a limited patient cohort.

Johans et al also reported a smaller patient cohort (39 patients), with no incidence of meningitis or postoperative CSF leaks, and a 10.2% rate of sinusitis, following a longer (average: 5–7 days) regimen of antibiotic prophylaxis.[11] Both the facts that the antibiotic regimen varied even among this small cohort of patients, as well as the fact that a survey conducted as part of the study revealed significant variations in prophylactic antibiotic protocols nationally, emphasize the need for a universal standard protocol. Our antibiotic regimen presents a straightforward and effective protocol that can be applied to all patients as a universal standard, after which fine-tuning with prospective studies can be effectively accomplished on a larger scale.

Strengths and Limitations

A strength of our study was that all patients were admitted routinely after surgery and followed up for at least 30 days. In addition, by maintaining the same two operating surgeons and hospital site with exposure to a set of bacterial flora, certain variables were controlled. The major limitations of our study include its retrospective nature. There were no controls, and all patients were provided with the same antibiotic regimen except for rare exceptions including allergies. Another limitation was that some patients were diagnosed with sinusitis at outside facilities which may have different guidelines regarding diagnoses. Despite these limitations, our study provides valuable data concerning the effectiveness of our antibiotic regimen and expands the available literature concerning postoperative infectious complications following EETS.

Conclusion

Compared with reported findings in the literature, we report low rates of infectious complications and antibiotic intolerance among 132 patients undergoing EETS, despite presence of a heavy burden of comorbidities and high intraoperative CSF leak rates among our cohort. These findings support our standardized 7-day perioperative antibiotic regimen of cefazolin for 24 hours, followed by cephalexin for 6 days after surgery (clindamycin if penicillin/cephalosporin allergic). This regimen is well tolerated with few adverse events and is effective in preventing significant postoperative infections.

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Conflict of Interest
None declared.

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