Surgical Site Infections in Patients Receiving Osteomyocutaneous Free Flaps to the Head and Neck. Does Choice of Antibiotic Prophylaxis Matter?

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Purpose: The most appropriate prophylactic antibiotic for clean-and-contaminated head and neck osteomyocutaneous free flap (OFF) tissue transfer procedures is unclear. The purpose of this study was to determine whether the choice of perioperative antibiotic was related to recipient surgical site infection (SSI) in patients receiving an OFF to the head and neck.

Materials and Methods: This retrospective cohort study evaluated SSI in relation to the perioperative antibiotic received from July 2010 through October 2013 at a tertiary care medical center. Minimum follow-up was 6 months. SSI was defined by the Centers for Disease Control and Prevention wound infection criteria. Perioperative antibiotic selected, duration of use, OFF performed, medical comorbidities, and SSIs were recorded and analyzed.

Results: One hundred two patients (64 men, 38 women) met the inclusion criteria. Forty patients developed an SSI. Analysis of variance showed that age ($P = .64$), gender ($P = .97$), use of alcohol ($P = .87$), final pathology ($P = .3$), cardiovascular disease ($P = .33$), and diabetes mellitus or immune dysfunction ($P = .95$) did not have a significant association with the development of a postoperative wound infection. On univariate analysis, non–head and neck primary malignancies showed a significant risk for SSI ($P = .03$), with previous head and neck surgery ($P = .05$) and oral tobacco use ($P = .06$) having trends for increased risk of SSI. Clindamycin antibiotic was strongly associated with the development of an SSI, with 50% of that cohort developing a recipient SSI (odds ratio = 7.0; $P < .002$), regardless of duration of use. The rate of development of a recipient SSI with cefazolin was 25% and that with ampicillin plus sulbactam was 19%.

Conclusion: A statistically relevant number of patients who developed a recipient SSI received clindamycin as perioperative antibiotic prophylaxis. An antibiotic regime other than clindamycin should be considered in patients with an allergy to penicillin or cephalosporin who are undergoing an OFF procedure to the head and neck.

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An inevitable consequence of surgery is that a certain proportion of patients will develop a surgical site infection (SSI) despite the maintenance of good aseptic surgical technique. Important risk factors reported for SSIs in the head and neck include the need for free tissue transfer, prolonged surgery, a contaminated surgical site, hypoalbuminemia, tobacco and alcohol consumption, post-laryngectomy tracheostoma, prior radiotherapy or chemotherapy, and the use of clindamycin prophylaxis.[1-7] Surgical wounds have been classified into 4 broad categories in ascending order of risk of SSI as clean wounds, clean-and-contaminated wounds, contaminated wounds, and dirty wounds.[8] Patients who receive an osteomyocutaneous free flap (OFF) to the head and neck, with few exceptions, are in the clean-and-contaminated category. These patients are reported to have an SSI rate of 13 to 50%, and these composite flaps are believed to be at greater risk of the development of infection and failure compared with soft tissue–only flaps.[9,10] Without antibiotic prophylaxis, the SSI rate can be considerably higher in clean-and-contaminated head and neck procedures, as reported by Becker and Parell[11] in a double-blinded placebo-controlled trial. This study reported strong evidence for the role of antibiotic prophylaxis, with 87% in the placebo arm developing an SSI compared with 38% in the cefazolin antibiotic arm. The consequences of a wound infection can vary from a trivial complication necessitating the application of the basic principles of wound care management to mortality. OFFs are commonly used to reconstruct serious postablative defects. In this population, the infection might not only affect the survival of the free tissue transfer but also delay the patient receiving any indicated adjuvant therapy such as radiation treatment, which can affect long-term survival.[12]

One of the goals of the Surgical Care Improvement Project is a decrease in postoperative wound infections through the administration of appropriate perioperative antibiotics.[13,14] Even with appropriate antibiotic prophylaxis, the infection rate of clean-and-contaminated head and neck surgical procedures remains high.[15] A multitude of antibiotic regimes have been proposed for the prophylaxis of head and neck surgical procedures, with the ultimate choice often determined by hospital policy or surgeon preference. Variables that need to be considered in the selection of an appropriate antibiotic include its spectrum of activity, safety, tolerability, and cost.[16] The β-lactam antibiotics are generally first choice for surgical prophylaxis in head and neck procedures, with clindamycin being reserved for those with an allergy to this group of antimicrobials. Once an appropriate antibiotic is selected, the duration of use has to be defined. Current evidence suggests no evidence in continuing beyond 24 hours postoperatively.[17] The purpose of this study was to investigate a patient population who received an OFF to reconstruct a head and neck defect and to determine whether there was any statistical difference in SSI depending on the perioperative antibiotic used. The authors hypothesized that patients receiving a non–β-lactamase antibiotic would have a higher rate of SSI.

Materials and Methods

A retrospective cohort study of patients who received an OFF to the head and neck from July 2010 through October 2013 at a single institute was designed. This study was approved by the institutional review board for ethical human research at the University of Maryland (Baltimore, MD). Data collected included demographics, patient comorbidities, pathologic condition requiring surgery, perioperative antibiotics chosen and duration of use, any SSI recorded, culture data, and treatment of any SSI. Inclusion criteria were patients who received an OFF during the defined dates and were followed up within 30 days of the surgical procedure. Exclusion criteria were incomplete records or those with inadequate follow-up. Data were recorded in a password-protected Excel database (Microsoft, Redmond, WA). Fisher exact test and analysis of variance (ANOVA) were calculated with the Statistics Toolbox in MatLab (Natick, MA) for statistical analysis.

The outcome variable was SSI. There is no unanimous definition of an SSI in the literature, but for this study the authors adopted the Centers for Disease Control and Prevention criteria for defining wound infection.[18] These criteria divide wound infection into superficial (defined as occurring within 30 days postoperatively and including purulent drainage from the skin or subcutaneous tissues of the incision, a spontaneously dehisced or incision opened by the surgeon because of infection, organisms isolated from an aseptically obtained culture, or a superficial SSI diagnosis by the surgeon) and deep (defined as occurring within 90 days postoperatively and including purulent drainage from tissue deep to the subcutaneous tissues, a spontaneously dehisced wound, or an abscess formation). Retrospectively differentiating superficial from deep is difficult. As a result, any patient who met either definition was included as a subject who developed an SSI (without further subclassification into superficial or deep SSI). The predictor variable used for this study was the perioperative antibiotic administered.

To ascertain the contribution of various comorbidities to SSI, the authors used a stepwise multiple regression analysis. The variables used were classified as follows in a binary fashion: *1)* current alcohol use, *2)* current tobacco use, *3)* presence of cardiovascular risk factors, *4)* systemic illnesses other than cardiovascular diseases, *5)* history of other primary malignancies, and *6)* history of head and neck surgery. A forward stepwise regression model was subsequently created from variables with a statistically significant contribution based on a threshold ($P < .05$) to enter the initial fitted model. The regression coefficients and the equation were derived. In all statistical comparisons, significance was set at a P value less than .05. Kruskal-Wallis ANOVA was used to compare unequal sample sizes for each variable and logistic regression analysis was only used for variables found to be statistically relevant on univariate analysis, because it would otherwise result in high probability of type II error (incorrect acceptance of the null hypothesis) and risk of overfitting.

Results

One hundred four patients had an OFF to the head and neck during the study period. Two patients had incomplete data; therefore, 102 patients met the study criteria. The mean age of patients was 55.8 years (range, 18 to 82 yr) and men predominated (n = 64; 63%). Squamous cell carcinoma (n = 42) was the most common pathology and the fibula OFF (n = 83) was the most common donor flap selected for reconstruction (Table 1). Ampicillin plus sulbactam was the most common antibiotic chosen for perioperative prophylaxis (n = 58). Nutrition through a nasogastric feeding tube or G-tube was uniformly used perioperatively. Oral feeding was not initiated until at least postoperative day 5, once the patient safely passed a swallowing test and the oral wound appeared clinically intact without any dehiscence.

Forty patients had a documented SSI (Table 2). Twenty-nine patients developed a recipient SSI and 14 patients developed a donor SSI (3 patients had recipient and donor SSIs). All SSIs were documented within 30 days of the procedure. In those with a recipient SSI, 20 of 29 patients' cultures grew microbes (Fig 1). Most infections were of mixed flora, with gram-positive cocci and gram-negative rods being the most commonly speciated. Incidences of SSI by type of antibiotic were 28, 44, and 64% for ampicillin plus sulbactam, cefazolin, and clindamycin, respectively. Subsequent analysis showed that perioperative antibiotic selected was the only statistically relevant modifiable factor associated with the development of an SSI (Table 3). Fourteen of 22 patients who received clindamycin antibiotic developed an SSI; of these SSIs, 11 (50%) occurred at the recipient site. The calculated odds ratio (OR) meaningfully showed a 7 times risk of infection with the use of clindamycin compared with ampicillin plus sulbactam ($P = .002$). On univariate analysis, secondary risk factors for increased SSI included patients with other primary malignancies ($P = .03$). No other risk factors were identified, including type of bone flap selected, pathology, anatomic location, age, gender, and medical comorbidities. Nonsignificant trends for previous head and neck surgery ($P = .05$) and oral tobacco use ($P = .06$) were identified. Subsequent post hoc testing with logistic regression analysis of these secondary risk factors calculated a slightly increased OR risk for previous head and neck surgery (OR = 1.7; confidence interval [CI], 0.15-3.6; $P = .04$) and tobacco use (OR = 1.73; CI, 0.5-3.1; $P = .008$). Interestingly history of other malignancy had a minimally increased nonsignificant OR risk of infection (OR = 1.1; CI, −4.5 to 0.9; $P = .08$). Tracheostomy was performed in 92 patients and there was no statistical difference in SSI compared with those not receiving a tracheostomy ($P = .31$).

Two OFFs failed, 1 of which was associated with a recipient SSI, for an overall success rate of 98%. Antibiotic-related *Clostridium difficile* infection occurred in 7 patients who received a β-lactam antibiotic (ampicillin plus sulbactam, n = 7; cefazolin, n = 2). Patients with a recipient SSI were found to have prolonged length of hospital stay with an average increase of 2 days ($P = .25$). Although patients remained an average of 4 days longer on clindamycin (16.2 days) antibiotic compared with ampicillin plus sulbactam (12.3 days), there was no significant difference identified ($P = .339$).

Discussion

This retrospective study analyzed patients seen at a tertiary care center who received an OFF to reconstruct a head and neck defect to determine whether there was any statistical difference in SSI depending on the perioperative antibiotic used. The hypothesis that patients receiving a non–β-lactamase antibiotic would have a higher rate of SSI was found to be correct based on the results. Overall, 28.4% of patients in the present study had a recipient SSI, which is within the previously reported range. Patients receiving clindamycin had a statistically significant higher rate of SSI compared with a β-lactamase antibiotic, with a calculated OR of 7 times increased risk of developing an SSI ($P = .002$). There are numerous factors that can increase the risk of SSI in clean-and-contaminated head and neck surgeries. The dynamic movement of the oropharyngeal musculature during respiration, cough reflex, and swallowing and dead space after tumor ablation (despite free flap reconstruction) can result in wound dehiscence, thereby allowing secretions and oral microbes access to the head and neck surgical wound.[19] Attention to careful approximation of the OFF to the native head and neck tissue minimizes leaking of upper respiratory tract secretions into the neck,

Table 1. STUDY VARIABLES AND PERIOPERATIVE ANTIBIOTIC PROPHYLAXIS GIVEN

	Ampicillin + Sulbactam	Clindamycin	Cefazolin	Others*	*P* Value
Sample size (N = 102)	58	22	16	6	N/A
Age (yr)	53.9 ± 15.9	57.1 ± 17.4	61.3 ± 15.1	54.5 ± 16.6	.42
Gender					
Men	40	13	8	3	.11
Women	18	9	8	3	
Race					.67
Caucasian	14	4	3	3	
African American	40	18	12	3	
Asian	4	0	1	0	
Others	0	0	0	0	
Flap selection					.38
Fibula	49	16	13	5	
DCIA	5	4	3	1	
CSA	4	2	0	0	
Anatomic location					.10
Maxilla	11	3	15	6	
Mandible	44	19	1	0	
Others	3	0	0	0	
Pathology					.09
SCC	19	10	13	0	
Ameloblastoma	15	3	0	1	
Osteoradionecrosis	7	2	2	2	
Other	17	7	1	3	
Smoking status					.57
Nonsmoker	32	14	5	4	
Smoker	26	8	11	2	
Alcohol use					.56
No alcohol	30	14	5	3	
Alcohol	28	8	11	3	
Tracheostomy performed					.31
No tracheostomy	4	4	0	2	
Tracheostomy	54	18	16	4	
Pre-existing comorbidities					
No cardiovascular disease or PVD	29	12	7	2	.61
Cardiovascular disease or PVD	29	10	9	4	
No DM or immune dysfunction†	52	20	12	5	.26
DM or immune dysfunction	6	2	14	1	
No history of other malignancy	49	18	15	5	.67
History of other malignancy	9	4	1	1	
No history of head and neck surgery	44	15	13	4	.83
History of head and neck surgery	14	7	3	2	
Hospital LOS (days)	12.3 ± 6.9	16.2 ± 13.7	13.6 ± 5.4	14.7 ± 9.0	.339

Abbreviations: CSA, circumflex scapular artery; DCIA, deep circumflex iliac artery flap; DM, diabetes mellitus; LOS, length of stay; N/A, not applicable; PVD, peripheral vascular disease; SCC, squamous cell carcinoma.

* Includes vancomycin plus clindamycin (n = 3); vancomycin, piperacillin, plus tazobactam (n = 1); piperacillin plus tazobactam (n = 1); and daptomycin (n = 1).

† Immune dysfunction includes any autoimmune disease, long-term steroid use, or immunosuppression.

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which has been emphasized as important in lowering the risk of head and neck SSI.[20] Furthermore, the ischemia that inevitably results with free tissue transfer and the prolonged nature of the surgery are contributing factors to head and neck SSI in microvascular reconstructive procedures.[21]

Perioperative antibiotic prophylaxis with clindamycin was found to be the only statistically relevant factor associated with the development of a head and neck SSI. Its duration of use did not affect the likelihood of not developing an infection. Clindamycin antibiotic prophylaxis with head and neck oncologic

Table 2. RELATION OF STUDY VARIABLES AND DEVELOPMENT OF SSI

	SSI	No SSI	*P* Value
Sample size (N = 102)	40	62	N/A
Age (yr)	56.8 ± 16.4	55.2 ± 16.4	.64
Gender			.97
Men	25	39	
Women	14	23	
Race			.19
Caucasian	12	12	
African American	26	47	
Asian	2	3	
Flap selection			.75
Fibula	34	49	
DCIA	3	6	
CSA	3	7	
Anatomic location			.16
Maxilla	4	10	
Mandible	36	48	
Other	0	4	
Pathology			.3
SCC	19	23	
Ameloblastoma	6	13	
Osteoradionecrosis	7	6	
Other	8	20	
Tobacco use			.06
No tobacco	17	38	
Tobacco	23	24	
Alcohol use			.87
No alcohol	20	32	
Alcohol use	20	30	
Tracheostomy performed			.16
No tracheostomy	6	4	
Tracheostomy	34	58	
Comorbidities			
No cardiovascular disease or PVD	22	28	.33
Cardiovascular disease or PVD	18	34	
No DM or immune dysfunction*	35	54	.95
DM or immune dysfunction	5	18	
No history of other malignancy	38	49	.03
History of other malignancy	2	13	
No history of head and neck surgery	34	42	.05
History of head and neck surgery	6	20	
Hospital LOS (days)	14.7 ± 9.8	12.7 ± 8.0	.25

Abbreviations: CSA, circumflex scapular artery; DCIA, deep circumflex iliac artery flap; DM, diabetes mellitus; LOS, length of stay; N/A, not applicable; PVD, peripheral vascular disease; SCC, squamous cell carcinoma; SSI, surgical site infection.

* Immune dysfunction includes any autoimmune disease, long-term steroid use, or immunosuppression.

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surgery has been frequently associated with a higher rate of postoperative SSI.[22-25] The exact reason behind this is unknown but the development of resistance to clindamycin by microbes of the upper respiratory tract and the inability of clindamycin to have activity against gram-negative aerobes have been cited.[16,23,26,27] The merit of clindamycin as an appropriate prophylactic antibiotic, when a β-lactam cannot be used, for head and neck clean-and-contaminated procedures requiring an OFF must be questioned. The economic and personal cost of a recipient SSI might justify sensitivity testing of β-lactams in those with a documented allergy to confirm or refute the veracity of the documented allergy. Alternatively, the cost implications of using a carbapenem or monobactam antibiotic in those with a

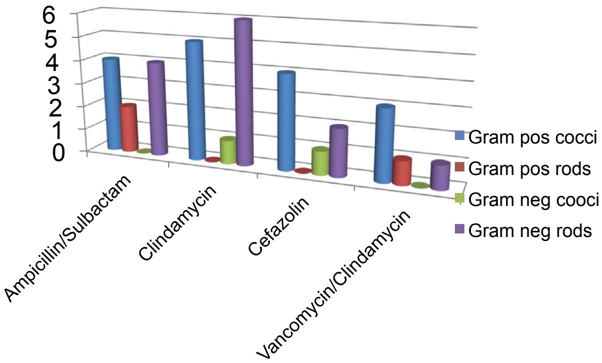

FIGURE 1. Recipient site infections and micro-organisms cultured.

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documented β-lactam allergy could be offset by the savings gained in a potentially lower SSI rate. The study center is using a strategy of a combination of cefazolin and metronidazole as antibiotic prophylaxis for clean-and-contaminated head and neck procedures. This regime has advantages of being cost effective and providing prophylaxis against most head and neck flora. It also can be used in those with a documented penicillin allergy, so long as the allergic reaction was not anaphylaxis, because the 10% crossover allergic reaction between cephalosporins and penicillins relates to those who had an anaphylactic reaction. The effect of this regime on SSI in clean-and-contaminated head and neck procedures will be reported at a future date. It is the authors' opinion that consideration should be given to the use of a combination of the bactericidal antibiotics vancomycin and metronidazole or a fourth-generation fluoroquinolone (ie, moxifloxacin) for perioperative prophylaxis in patients receiving an OFF to the head and neck with a history of anaphylaxis to a β-lactam as opposed to clindamycin. The 2 therapeutic regimens will cover against oral and respiratory flora (gram-positive and anaerobic flora), and moxifloxacin offers the advantage of a monotherapy prophylaxis with added coverage against gram-negative bacteria.

The duration to continue perioperative antibiotics is not established. Langerman et al[28] reported that prolonging ampicillin plus sulbactam beyond the day of surgery might have a protective effect against the development of a head and neck SSI in clean-and-contaminated procedures in contrast to clindamycin, which showed an increased risk of SSI with prolonged use.[28] The current opinion is a short duration no longer than 24 hours of prophylactic antibiotics for clean-and-contaminated head and neck surgical procedures, which are supported by the present results.[4,29] Vigilant monitoring for an SSI should take place thereafter with appropriate surgical and medical treatment for any SSI that develops and should be considered the standard of care. Potential implications for prolonged antibiotic use include the development of antibiotic-associated diarrhea. No patient receiving clindamycin in the present study developed *C difficile* diarrhea, whereas 7 patients receiving a β-lactam developed *C difficile* diarrhea. The study design and the numbers involved mean this finding is merely observational and no comment on its true relevance can be made.

The retrospective nature of this study is a weakness. Twenty of the 29 patients with a documented recipient SSI had microbiology data to strongly support the SSI. Donor SSI was documented in the medical record based on clinical examination of the surgeon and none of these patients had supporting microbiological data. This must be acknowledged when interpreting the donor SSI in this study. Statistical analysis used in the present study was able to identify primary malignancies ($P = .03$) as a potential risk factor for SSI, but the retrospective nature of the study and the relatively small sample affect the generalization of these results. Although not statistically significant, oral tobacco use ($P = .06$) and previous head and neck surgery ($P = .05$) were identified as possible risk factors in the development of SSI. Tobacco use can increase

Table 3. RISK OF SSI COMPARED WITH TYPE OF PROPHYLACTIC ANTIBIOTIC SELECTION

Antibiotic	SSI (n = 40)*	No SSI (n = 62)	*P* Value	2.5% CI	97.5% CI	Odds Ratio
Ampicillin + sulbactam	16 (28%)	42 (72%)	N/A	N/A	N/A	1
Clindamycin	14 (64%)	8 (36%)	.002	2.1	26.5	7.0
Cefazolin	7 (44%)	9 (56%)	.73	0.3	4.8	1.2
Other†	3 (50%)	3 (50%)	.13	0.6	36.1	4.6

Abbreviations: CI, confidence interval; N/A, not applicable; SSI, surgical site infection.

* Three patients had recipient and donor site infections (ampicillin + sulbactam group, n = 2; clindamycin group, n = 1).

† Includes vancomycin plus clindamycin (n = 3); vancomycin, piperacillin, plus tazobactam (n = 1); piperacillin plus tazobactam (n = 1); and daptomycin (n = 1). No meaningful statistical information can be interpreted for this category (included for overall study power and completeness of data).

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the risk of wound breakdown by direct thermal injury or local tissue vascular injury allowing for salivary leak and subsequent infection. In the recent series by Mitchell et al,[22] tobacco use and clindamycin antibiotic were identified as risk factors for markedly increasing the risk of an SSI. Previous head and neck surgery further adds complexity, with increased operative time to access a previously scarred and vessel-depleted neck possibly increasing the risk of infection and failure.[22,25] The current literature suggests that immune dysfunction resulting from prior cancer diagnosis and treatment protocols (ie, chemotherapy regimens or radiation- or medication-induced jaw necrosis) could contribute to an increased risk of SSI.[30] Further prospective studies are necessary to validate these observations.

The addition of vancomycin to clindamycin as an antibiotic prophylaxis regime did not lower the SSI rate. The 3 patients who received this combination were under the care of an infectious disease specialist. Although there was no clinical evidence of an active infectious process at the time of the surgical procedure, the possibility of a clinically undetectable latent infection cannot be excluded. Because the number of patients receiving this combination antibiotic prophylaxis was very small, only observational information can be reported without any meaningful statistical analysis.

The present study represents one of the largest series to investigate SSIs and antibiotic prophylaxis in patients exclusively undergoing vascularized OFF tissue transfer for maxillofacial reconstruction. A statistically relevant number of patients who received clindamycin antibiotic prophylaxis for OFF transfer to the head and neck developed an SSI. An alternative antibiotic should be considered in patients with a history of anaphylaxis to β-lactamase antibiotics who are undergoing an OFF reconstruction to the head and neck.

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