SURGICAL INFECTIONS
Volume 17, Number 1, 2016

DOI: 10.1089/sur.2015.131

Antibiotic Use after Free Tissue Reconstruction of Head and Neck Defects: Short Course vs. Long Course

Samir S. Khariwala,[1] Bin Le,[1] Brendan H.G. Pierce,[1] Rachel Isaksson Vogel,[2] and Jeffrey G. Chipman[3]

Abstract

Background: Free tissue reconstruction has become the standard of care for most major defects in the head and neck. Surgical site infection (SSI) can lead to vessel thrombosis and eventual flap loss. The use of antibiotics after free tissue reconstruction has not been studied in the current environment of heightened bacterial antibiotic resistance. We compared the use of short-term and longer-term antibiotics in a series of patients receiving free tissue reconstructions.

Methods: A retrospective review was performed of 147 patients receiving 149 free flaps who were treated with either short-course (≤2 d; n = 149 [43%]) or long-course (>2 d; n = 85 [57%])) post-operative antibiotics from 2009 to 2014. The outcomes examined were infection, return to the operating room, length of hospital stay, and patient death up to six weeks post-surgery. In addition, risk factors associated with SSI were explored.

Results: Surgical site infection, flap dehiscence, flap loss, and length of stay were not different in the two groups. However, those receiving long-course antibiotics had a significantly higher rate of pneumonia (24.7% vs. 10.9%; p = 0.03), although they had a lower rate of urinary tract infection (0.0% vs 9.4%, respectively; p = 0.01). Body mass index remained a statistically significant risk factor in the multivariable analysis (p = 0.005).

Conclusion: Prolonged antibiotic use after free flap reconstruction of head and neck defects does not appear to prevent SSI better than short-course treatment in this population. Moreover, long-course antibiotic use was associated with a higher risk of pneumonia.

Since the first successful use of free tissue to reconstruct the oral cavity in 1976 [1], free flap reconstruction after head/neck oncologic surgery has gained popularity steadily over the past four decades. Free tissue reconstruction is now the standard of care for head and neck defects. Compared with local flap and regional flaps, free tissue offers clear advantages, including a robust blood supply, multiple potential donor sites, and the possibility of a large supply of tissue [2]. These advantages, together with the improvement in surgical techniques and instrumentation, has pushed success rates to greater than 95% [2–6], making free flap reconstruction the first choice in addressing defects in the head and neck.

Nevertheless, the complications associated with free flap reconstruction can be devastating [6–8]. Surgical site infection (SSI), one of the most common complications, may lead to vessel thrombosis and, eventually, to flap loss [6]. Moreover, reconstruction with free flaps is a significant risk factor for SSI in clean-contaminated head and neck operations [9–11]. Therefore, there has been great interest in determining the optimal regimen for antibiotic prophylaxis in the peri-operative period.

A series of studies in the 1980s and 1990s examined antibiotic prophylaxis in a variety of clean–contaminated head and neck procedures. These data suggest that: (1) Antibiotic prophylaxis reduced infection rates [12–14]; (2) beta-lactam antibiotics are appropriate first-line agents, with clindamycin reserved for patients with beta-lactam allergies [12–19]; and (3) prolonged courses of antibiotics do not generally result in greater reduction of infection rates. [5,20–22]. However, all these studies either excluded patients receiving free flaps or had only a small number of patients having free flaps. One study the addressed this issue more than 10 years ago showed no difference between short- and long-course antibiotic use [23]. Still, a recent survey of free tissue surgeons suggested that antibiotics are being used at greater rates than previously [24].

[1]Department of Otolaryngology-Head and Neck Surgery, [2]Masonic Cancer Center, Biostatistics and Bioinformatics Core, [3]Department of Surgery, University of Minnesota, Minneapolis, Minnesota.

One possible reason for the increased use of peri-operative antibiotics after free tissue reconstruction is concern about the higher rates of antibiotic-resistant bacterial infections documented over the last 10–15 years. Given the lack of consensus and the paucity of recent data in an environment of antibiotic resistance, we reviewed the antibiotic usage and clinical outcomes at our institution to examine the effect of antibiotic prophylaxis duration after free tissue reconstruction in the head and neck.

Patients and Methods

The medical charts of patients who underwent free flap reconstruction in the Department of Otolaryngology Head and Neck Surgery, University of Minnesota Medical Center, from May 2009 to February 2014 were reviewed after approval from the University of Minnesota Institutional Review Board. The exclusion criteria were: (1) Active infection pre-operatively or intra-operatively; (2) receipt of antibiotics within one week prior to surgery; (3) inadequate documentation of peri-operative medications; and (4) flap failure intra-operatively. Patient demographic and disease characteristics, including age, gender, body mass index (BMI), tobacco use, diabetes mellitus status, disease type, disease site, cancer stage, history of chemotherapy, and history of radiation were recorded. Intra-operative and post-operative variables, including flap types, hardware usage, tracheostomy/laryngectomy (either pre-existing or as a part of the operation), surgery length, transfusions, and post-operative antibiotic regimen, were recorded. Patient outcomes, including infection (SSI, pneumonia, urinary tract infection [UTI] and others), return to the operating room (OR), hospital length of stay (LOS), and patient death were reviewed up to six wks post-operatively.

Patient demographic and clinical data were summarized, and associations with antibiotic course length (short: ≤2 d, long: >2 d) and any SSI were assessed using the χ^2 and Fisher exact tests for categorical data and t-tests and Wilcoxon rank sum tests for continuous data as appropriate. In addition, the risk of any SSI was assessed using a multivariable logistic regression model, adjusting for variables with $p < 0.10$ in the univariate analyses, including history of chemotherapy, history of radiation, use of penicillins, use of clindamycin, and BMI. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented. As this was an exploratory analysis, p values were not adjusted for multiple comparisons. Analyses were performed using SAS version 9.3 (Cary, NC), and p values <0.05 were considered statistically significant.

Results

A total of 149 free tissue transfers in 147 patients were conducted during the study period and eligible for inclusion in this study. Two patients received a second free flap reconstruction in a separate operation. Most patients were male (65.8%), and the mean age was 59.4 ± 14.7 (standard deviation) years (range 16–87 y). The indications for surgery were malignant tumor (133 cases [89%], with 123 squamous-cell carcinomas), benign tumor (seven cases [5%], with 5 ameloblastomas), and non-tumor (9 case [6%], with four cases of osteoradionecrosis). The free flap types used were radial forearm (49%), fibular (28%), anterolateral thigh (14%), latissimus dorsi (3%), scapular (2%), rectus abdominis (2%), and multiple (2%). A total of 126 cases involved the oral cavity, larynx, or pharynx; 12 cases involved craniofacial structures; seven cases involved both the oral cavity and craniofacial structures; and four cases involved the scalp. All patients received intra-operative antibiotics with either a single drug or a combination of cefazolin, ampicillin/sulbactam, clindamycin, or metronidazole. The post-operative antibiotics used were ampicillin/sulbactam (69%), clindamycin (17%), and others (14%), including multiple and no antibiotics. The overall recipient-site SSI rate was 16.8%, and the donor-site SSI rate was 5.4%, with a total SSI rate of 22.2%. One patient had both recipient and donor site SSI.

Table 1. Demographic and Disease Characteristics by Antibiotic Use after Surgery

Characteristic	*Short Course (<2 days)* n = *64* n (*%*)	*Long Course (>2 days)* n = *85* n (*%*)	p
Gender			0.70
Male	41 (64.1)	57 (67.1)	
Female	23 (35.9)	28 (32.9)	
Tobacco use			0.34
Never	16 (25.0)	14 (16.5)	
Former	28 (43.8)	46 (54.1)	
Current	20 (31.3)	25 (29.4)	
Diabetes	6 (9.4)	17 (20.0)	0.08
Disease site			0.22
Oral cavity/ larynx/pharynx	57 (89.1)	69 (81.2)	
Craniofacial	2 (3.1)	10 (11.8)	
Craniofacial and oral cavity	3 (4.7)	4 (4.7)	
Scalp	2 (3.1)	2 (2.4)	
Disease type			0.06
Benign	3 (4.7)	13 (15.3)	
Malignant	61 (95.3)	72 (84.7)	
Disease stage (if cancer)			0.45
I	1 (1.6)	3 (3.5)	
II	5 (7.8)	6 (7.1)	
III	10 (15.6)	6 (7.1)	
IV	32 (50.0)	31 (36.5)	
Recurrent	11 (17.2)	21 (24.7)	
Unknown	2 (3.1)	5 (5.9)	
History of chemotherapy	10 (15.6)	17 (20.0)	0.49
History of radiation	17 (26.6)	33 (38.8)	0.12
Year of surgery			0.001
2009–2010	15 (23.4)	34 (40.0)	
2011–2012	23 (35.9)	39 (45.9)	
2013–2014	26 (40.6)	12 (14.1)	
	n *(Mean [SD])*	n *(Mean [SD])*	p
Age at surgery (years)	64 (59.9 [14.2])	85 (59.0 [15.1])	0.69
Body mass index (kg/m^2)	64 (26.2 [6.1])	85 (26.6 [6.6])	0.70
Pre-operative hemoglobin	55 (13.3 [1.9])	75 (12.9 [1.8])	0.26

SD = standard deviation.

Table 2. Intra-Operative and Post-Operative Features by Antibiotic Use after Surgery

Characteristic	*Short course (<2 d)* n = *64* n (%)	*Long course (>2 d)* n = *85* n (%)	p
Flap type			0.32
Radial forearm	27 (42.2)	46 (54.1)	
Fibular	19 (29.7)	23 (27.1)	
ALT	13 (20.3)	8 (9.4)	
Scapular	2 (3.1)	2 (2.4)	
Rectus abdominis	2 (3.1)	1 (1.2)	
Latissimus dorsi	1 (1.6)	3 (3.5)	
Multiple	0	2 (2.4)	
Hardware	39 (60.9)	48 (56.5)	0.58
Tracheostomy/ laryngectomy	55 (85.9)	63 (74.1)	0.08
Transfusion	39 (60.9)	60 (70.6)	0.74
Steroids	2 (3.1)	1 (1.2)	0.58
Antibiotics			
Cephalosporins	2 (3.1)	8 (9.4)	0.19
Penicillins	49 (76.6)	58 (68.2)	0.26
Quinolones	0	4 (4.7)	0.14
Clindamycin	8 (12.5)	17 (20.0)	0.23
	n *(Median [Range])*	n *(Median [Range])*	p
Length of surgery (h)	60 (11.8 [8.5–15.8])	66 (11.6 [2.5–22.6])	0.62
Total amount units transfused (OR + post OP)	64 (2.0 [0–16])	85 (2.0 [0–13])	0.52

ALT = anterolateral thigh; OR = operating room; OP = operation.

Of the 149 cases, 64 (43.0%) received short-course post-operative antibiotic prophylaxis, and 85 (57.0%) received long-course prophylaxis (Table 1). When comparing those who received short- vs. long-course prophylaxis, there were no statistically significant differences in age, gender, BMI, tobacco use, diabetes mellitus status, disease type, disease site, cancer stage, history of chemotherapy, or history of radiation therapy. There was, however, a greater proportion of patients who received short-course antibiotic prophylaxis in years 2013–2014 (68.4%) compared with years 2011–2012 (37.1%) as well as years 2009–2010 (30.6%; p = 0.001). This difference reflected the transition over time to preference for shorter antibiotic prophylaxis regimens in our institution.

Peri-operative variables, including flap type, hardware use, presence of a tracheostomy or laryngectomy, transfusion, use of steroids, length of surgery, and post-operative antibiotic choice, were not statistically significantly different in the two groups (Table 2). In addition, clinical outcomes, including SSI, tracheitis, flap dehiscence rate, flap loss rate, and hospital LOS were not statistically significantly different in the two groups (Table 3). There were, however, statistically significant differences between the groups in the rates of pneumonia and UTI. In particular, the long-course antibiotic

Table 3. Surgery Outcomes by Antibiotic

Characteristic	*Short course (<2 d)* n = *64* n (%)	*Long course (>2 d)* n = *85* n (%)	p
Recipient site infection	10 (15.6)	15 (17.7)	0.74
Donor site infection	4 (6.3)	4 (4.7)	0.73
Any site infection	15 (23.4)	18 (21.2)	0.74
Pneumonia	7 (10.9)	21 (24.7)	0.03
Tracheitis	3 (4.7)	0	0.08
Urinary tract infection	6 (9.4)	0	0.01
Return to operating room	19 (29.7)	38 (44.7)	0.06
Flap dehiscence	11 (17.2)	22 (25.9)	0.21
Total flap loss	1 (1.6)	2 (2.4)	1.00
	n *Median (Range)*	n *Median (Range)*	p
Hospital stay (d)[a]	63 (11.0 [6–29])	85 (10.0 [6–47])	0.83

[a]Excludes one patient who died in hospital (day 13).

Table 4. Patient Demographic and Disease Characteristics by Surgical Site Infection (SSI)

Characteristic	*Any SSI* n = *33* n (%)	*No SSI* n = *116* n (%)	p
Gender			0.12
Male	18 (54.5)	80 (69.0)	
Female	15 (45.5)	36 (31.0)	
Tobacco use			0.22
Never	7 (21.2)	23 (19.8)	
Former	20 (60.6)	54 (46.6)	
Current	6 (18.2)	39 (33.6)	
Diabetes mellitus	7 (21.2)	16 (13.8)	0.30
Disease site			0.15
Oral cavity	22 (66.7)	92 (79.3)	
Larynx	2 (6.1)	5 (4.3)	
Pharynx	7 (21.2)	9 (7.8)	
Other	2 (6.1)	10 (8.6)	
Disease type			1.00
Benign	3 (9.1)	13 (11.2)	
Malignant	30 (90.9)	103 (88.8)	
Disease stage (if cancer)			0.90
I	0	4 (3.4)	
II	2 (6.1)	9 (7.8)	
III	3 (9.1)	13 (11.2)	
IV	16 (48.5)	47 (40.5)	
Recurrent	6 (18.2)	26 (22.4)	
Unknown	3 (9.1)	4 (3.4)	
History of chemotherapy	11 (33.3)	16 (13.8)	0.01
History of radiation	17 (51.5)	33 (28.5)	0.01
Year of surgery			0.49
2009–2010	13 (39.4)	36 (31.0)	
2011–2012	14 (42.4)	48 (41.4)	
2013–2014	6 (18.2)	32 (27.6)	
	n *(Mean [SD])*	n *(Mean [SD])*	p
Age at surgery (years)	33 (57.8 [15.5])	116 (59.8 [14.5])	0.48
Body mass index (kg/m^2)	33 (28.3 [6.5])	116 (25.9 [6.2])	0.05
Pre-operative hemoglobin	30 (12.7 [1.9)]	100 (13.2 [1.8])	0.23

Table 5. Intra-Operative and Post-Operative Characteristics by Surgical Site Infection (SSI)

Characteristic	*Any SSI* n = *33* n (*%*)	*No SSI* n = *116* n (*%*)	p
Flap type			0.65
Radial forearm	15 (45.5)	58 (50.0)	
Fibular	10 (30.3)	32 (27.6)	
ALT	6 (18.2)	15 (12.9)	
Scapular	0	4 (3.5)	
Rectus abdominis	1 (3.0)	2 (1.7)	
Latissimus dorsi	0	4 (3.5)	
Multiple	1 (3.0)	1 (0.9)	
Hardware	20 (60.6)	67 (57.8)	0.77
Tracheostomy/ laryngectomy	27 (81.8)	91 (78.5)	0.67
Transfusion	25 (75.8)	74 (63.8)	0.45
Steroids	1 (3.0)	2 (1.7)	0.53
Antibiotic			
Cephalosporins	2 (6.1)	8 (6.9)	1.00
Penicillins	19 (57.6)	88 (75.9)	0.04
Quinolones	2 (6.1)	2 (1.7)	0.21
Clindamycin	10 (30.3)	15 (12.9)	0.02
	n (*Median [Range]*)	n (*Median [Range]*)	p
Length of surgery (h)	27 (12.3 [8.6–15.4])	99 (11.6 [2.5–22.6])	0.18
Total amount transfused (OR + post OP)	33 (2.0 [0–13])	116 (2.0 [0–16])	0.70

OP = operation.

Table 6. Surgery Outcomes by Surgical Site Infection (SSI)

Characteristic	*Any SSI* n = *33* n (*%*)	*No SSI* n = *116* n (*%*)	p
Return to operating room	25 (75.8)	32 (27.6)	<0.0001
Flap dehiscence	14 (42.4)	19 (16.4)	0.001
Total flap loss	2 (6.1)	1 (0.9)	0.12
	n (*Median [Range]*)	n (*Median [Range]*)	p
Hospital stay (d)[a]	32 (13.5 [7–47])	116 (10.0 [6–47])	0.01

[a]Excludes one patient who died in hospital (day 13).

prophylaxis group had a significantly higher rate of pneumonia than the short-course group (24.7% vs. 10.9%; p = 0.03), but a lower rate of UTI (0 vs. 9.4%; p = 0.01).

Several patient baseline characteristics were identified as risk factors for SSI of any type, including higher BMI (p = 0.05), history of chemotherapy (p = 0.01), and history of radiation (p = 0.01; Table 4). In addition, use of penicillins was associated with a lower rate of SSI (p = 0.04), whereas use of clindamycin was associated with a higher rate (p = 0.02) compared with those not given those antibiotics (Table 5). No other demographic, clinical, or peri-operative variables were associated significantly with SSI. When looking at these identified risk factors (BMI, history of chemotherapy, history of radiation, use of penicillins, and use of clindamycin) simultaneously in a multivariable model, higher BMI remained a significant risk factor (OR 1.63; 95% CI 1.16–2.29; p = 0.01). All other risk factors had p values >0.05 in the multivariable model, although a history of radiation was borderline significant (OR 2.82; 95% CI 0.84–9.14; p = 0.08). Finally, patients with any SSI were significantly more likely to return to the OR (p < 0.0001) or experience flap dehiscence (p = 0.001) and required a longer LOS (p = 0.01) than patients without an SSI (Table 6).

Discussion

Microvascular free-tissue reconstruction has become the mainstay of head and neck reconstructive surgery in the past four decades. However, there is still a high degree of variability in the implementation of peri-operative antibiotic prophylaxis. Given the greater risk of SSI in free flap reconstructions [9–11] and the potential highly morbid consequences of infection, many clinicians use antibiotics in an effort to prevent complications. Still, data attesting to the value of this practice are lacking. Our study showed that prolonged post-operative prophylactic antibiotic administration (>2 d) did not reduce the SSI rate significantly in free-flap reconstruction of head and neck defects.

Our study identified a history of chemotherapy, radiation therapy, and obesity as significant risk factors for SSI. However, the validity of these risk factors is controversial in the current literature [7,25–27]. Our study also demonstrated a significantly lower rate of SSI in patients treated with penicillins and a significantly higher rate of SSI in patients treated with clindamycin. This result is consistent with the data in the literature, which suggest that clindamycin monotherapy is a significant risk factor for recipient site infection [28]. In addition, a prolonged prophylactic antibiotic course was associated with a greater risk of adverse outcomes such as acquired antimicrobial resistance, *Clostridium difficile* infection, medication toxicity, etc. [29]. Although we did not collect data regarding antimicrobial resistance in our study, one patient who received short-course ampicillin/sulbactam developed a *C. difficile* infection.

Interestingly, our study demonstrated a significantly higher rate of pneumonia in the long-course group (24.7%) than the short-course group (10.9%). The most common pathogens isolated from bronchial cultures were *Enterobacter* and *Escherichia coli*. Another report found that trauma patients given prolonged (>48 h) prophylactic antibiotics were more likely to develop pneumonia with resistant or gram-negative bacteria [30]. Moreover, prolonged antibiotic regimens may alter the normal flora and phenotypes even without the selection of resistant organisms, potentially inducing normal flora to become pathogenic [31].

Current recommendations on the choice and duration of prophylactic antibiotics are based on studies excluding patients undergoing free-flap reconstruction or including only a small number of such cases. Even with the recommended prophylactic antibiotic duration of less than 24–48 h in these

studies, many surgeons hesitate to adhere to short-course prophylactic antibiotics. Although our study did show a significant association of SSI with flap dehiscence and longer hospital stay, it did not associate prolonged antibiotic prophylaxis with reduced SSIs.

Carroll et al. studied the use of clindamycin after free tissue reconstruction by comparing a 1-d with a 5-d course [32]. Their study did not find a difference in outcomes in the two groups. However, as stated above, clindamycin monotherapy has been associated with a greater risk of infection. One motivation for performing our study was concern that higher rates of antibiotic resistance over the last 10 years might render prior data (i.e., Carroll et al. [32]) invalid. Yet, regarding length of therapy, our results are consistent with theirs in that no difference was found between those receiving short- or long-course antibiotics. Another, albeit smaller, study that compared antibiotic use <48 h vs. >48 h in oropharyngeal reconstructions found that clindamycin use, advanced age, and long durations of surgery were all associated with recipient site infection [28]. However, duration of therapy (<48 vs >48 h) was not a predictor of recipient site infection.

Interestingly, the conclusion that a prolonged prophylactic antibiotic course does not further reduce the SSI rate also holds true almost universally across all surgical specialties, including neurosurgery, cardiothoracic surgery, orthopedic surgery, gastroduodenal surgery, and colorectal surgery [33]. The initiation of appropriate prophylactic antibiotics prior to the surgical incision and the maintenance of serum antibiotic concentrations in the therapeutic range during the procedure appear to be more important than the duration of post-operative antibiotics [33].

The only observed benefit for long-course antibiotic prophylaxis in our study was a lower incidence of UTI. This could be explained by the positive effect of antibiotics in patients who required short-term urinary catheterization. A recent meta-analysis showed that antibiotic use at the time of urinary catheter removal carried an absolute reduction in the risk of UTI by 5.8% [34]. In our study, all patients remained on ventilation with deep sedation post-operatively to protect the delicate microvascular anastomosis. Therefore, all patients required short-term urinary catheterization. Although the timing of urinary catheter removal was not assessed in this study, patients with long-course prophylactic antibiotic were more likely to have an antibiotic at a therapeutic concentration when the catheter was removed.

The strength of our study is the inclusion of a relatively large population of patients treated at a single institution. The limitations include those inherent in a retrospective study. We were reliant on the electronic medical records and therefore limited by the quality of documentation. An example of this inadequacy relates to the nutritional status of the subjects. Although we intended to include this variable in the analysis, more than half of the subjects had missing data, and thus, we were unable to study this variable. Additional limitations relate to difficulties in addressing changes or practice patterns concerning glycemic control, resuscitation strategies, transfusion practices, and the placement of central lines or bladder catheters or both. In addition, the operations discussed in this study were performed by seven tumor ablation surgeons and four microvascular reconstruction surgeons. Therefore, surgical practices and decision making may not have been consistent.

Conclusion

Prolonged post-operative antibiotic prophylaxis in free flap reconstruction of head and neck defects does not appear to provide additional reduction of SSI risk. Moreover, long-course antibiotic prophylaxis was associated with a higher rate of pneumonia and potentially additional adverse effects such as medication toxicity and microbial resistance. Given the minimal benefit relative to the potential risk, we recommend against the use of antibiotic prophylaxis for greater than 24 h in free flap reconstruction of head and neck defects, while recognizing that a randomized trial would be required to address this issue definitively.

Author Disclosure Statement

No competing financial interests exist.

References

1. Panje WR, Bardach J, Krause CJ. Reconstruction of the oral cavity with a free flap. Plast Reconstr Surg 1976;58:415–418.
2. Rinaldo A, Shaha AR, Wei WI, et al. Microvascular free flaps: A major advance in head and neck reconstruction. Acta Oto-Laryngol 2002;122:779–784.
3. Khouri RK. Free flap surgery: The second decade. Clin Plast Surg 1992;19:757–761.
4. Disa JJ, Pusic AL, Hidalgo DH, Cordeiro PG. Simplifying microvascular head and neck reconstruction: A rational approach to donor site selection. Ann Plast Surg 2001;47: 385–389.
5. Bozec A, Poissonet G, Chamorey E, et al. Radical ablative surgery and radial forearm free flap (RFFF) reconstruction for patients with oral or oropharyngeal cancer: Post-operative outcomes and oncologic and functional results. Acta Oto-Laryngol 2009;129:681–687.
6. Genden EM, Rinaldo A, Suárez C, et al. Complications of free flap transfers for head and neck reconstruction following cancer resection. Oral Oncol 2004;40:979–984.
7. Kruse AL, Luebbers HT, Gratz KW, Obwegeser JA. Factors influencing survival of free-flap in reconstruction for cancer of the head and neck: A literature review. Microsurgery 2010;30:242–248.
8. Singh B, Cordeiro PG, Santamaria E, et al. Factors associated with complications in microvascular reconstruction of head and neck defects. Plast Reconstr Surg 1999;103: 403–411.
9. Lotfi CJ, Cavalcani Rde C, Costa e Silva AM, et al. Risk factors for surgical-site infections in head and neck cancer surgery. Otolaryngol Head Neck Surg 2008;138:74–80.
10. Liu SA, Tung KC, Shiao JY, Chiu YT. Preliminary report of associated factors in wound infection after major head and neck neoplasm operation: Does the duration of prophylactic antibiotic matter? J Laryngol Otol 2008;122:403–408.
11. Strauss M, Saccogna PW, Allphin AL. Cephazolin and metronidazole prophylaxis in head and neck surgery. J Laryngol Otol 1997;111:631–634.
12. Becker GD, Parell GJ. Cefazolin prophylaxis in head and neck cancer surgery. Ann Otol Rhinol Laryngol 1979;88: 183–186.
13. Johnson JT, Yu VL, Myers EN, et al. Efficacy of two third-generation cephalosporins in prophylaxis for head and neck surgery. Arch Otolaryngol 1984;110:224–227.
14. Saginur R, Odell PF, Poliquin JF. Antibiotic prophylaxis in head and neck cancer surgery. J Otolaryngol 1988;17:78–80.

15. Johnson JT, Myers EN, Thearle PB, et al. Antimicrobial prophylaxis for contaminated head and neck surgery. Laryngoscope 1984;94:46–51.
16. Johnson JT, Wagner RL, Schuller DE, et al. Prophylactic antibiotics for head and neck surgery with flap reconstruction. Arch Otolaryngol Head Neck Surg 1992;118: 488–490.
17. Weber RS, Raad I, Frankenthaler R, et al. Ampicillin–sulbactam vs clindamycin in head and neck oncologic surgery: The need for gram-negative coverage. Arch Otolaryngol Head Neck Surg 1992;118:1159–1163.
18. Johnson JT, Kachman K, Wagner RL, Myers EN. Comparison of ampicillin/sulbactam versus clindamycin in the prevention of infection in patients undergoing head and neck surgery. Head Neck 1997;19:367–371.
19. Skitarelic N, Morovic M, Manestar D. Antibiotic prophylaxis in clean–contaminated head and neck oncological surgery. J Cranio-Maxillo-Facial Surg 2007;35:15–20.
20. Fee WE Jr, Glenn M, Handen C, Hopp ML. One day vs. two days of prophylactic antibiotics in patients undergoing major head and neck surgery. Laryngoscope 1984;94:612–614.
21. Johnson JT, Wagner RL, Schuller DE, et al. Antibiotic prophylaxis in high-risk head and neck surgery: One-day vs. five-day therapy. Otolaryngol Head Neck Surg 1986;95: 554–557.
22. Bhathena HM, Kavarana NM. Prophylactic antibiotics administration head and neck cancer surgery with major flap reconstruction: 1-Day cefoperazone versus 5-day cefotaxime. Acta Chirurg Plast 1998;40:36–40.
23. Carroll WR, Rosenstiel D, Fix JR, et al. Three-dose vs extended-course clindamycin prophylaxis for free-flap reconstruction of the head and neck. Arch Otolaryngol Head Neck Surg 2003;129:771–774.
24. Hauck RM, Nogan S. The use of prophylactic antibiotics in plastic surgery: Update in 2010. Ann Plast Surg 2013;70: 91–97.
25. Penel N, Lefabvre D, Fourier JC, et al. Risk factors for wound infection in head and neck cancer surgery: A prospective study. Head Neck 2001;23:447–455.
26. Cloke DJ, Green JE, Khan AL, et al. Factors influencing the development of wound infection following free-flap reconstruction for intra-oral cancer. Br J Plast Surg 2004; 57:556–560.
27. Karakida K, Aoki T, Yamazaki H, et al. Analysis of risk factors for surgical-site infections in 276 oral cancer surgeries with microvascular free-flap reconstructions at a single university hospital. J Infect Chemother 2010;16:334–339.
28. Cohen LE, Finnerly BM, Golas AR, et al. Perioperative antibiotics in the setting of oropharyngeal reconstruction: Less is more. Ann Plast Surg 2014. August 20. Epub ahead of print.
29. Bratzler DW, Houck PM, Surgical Infection Prevention Guideline Writers. Antimicrobial prophylaxis for surgery: An advisory statement from the National Surgical Infection Prevention Project. Am J Surg 2005;189:395–404.
30. Hoth JJ, Franklin CA, Stassen NW, et al. Prophylactic antibiotics adversely affect nosocomial pneumonia in trauma patients. J Trauma 2003;55:249–254.
31. Rafii F, Sutherland JB, Cerniglia CE. Effects of treatment with antimicrobial agents on the human colonic microflora. Ther Clin Risk Manage 2008;4:1343–1358.
32. Carroll WR, Rosenstiel D, Fix JR, et al. Three-dose vs extended-course clindamycin prophylaxis for free-flap reconstruction of the head and neck. Arch Otolaryngol Head Neck Surg 2003;129:771–774.
33. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013;70:195–283.
34. Marschall J, Carpenter CR, Fowler S, et al. Antibiotic prophylaxis for urinary tract infections after removal of urinary catheter: Meta-analysis. BMJ 2013;346:f3147.

Address correspondence to:
Dr. Samir S. Khariwala
MMC 396
420 Delaware Street
Minneapolis, MN 55455

E-mail: Khari001@umn.edu