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"Risk factors for surgical site infection in free-flap reconstructive surgery for head and neck cancer: a retrospective Australian cohort study."

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Brief Running Title: Surgical Infections in Head and Neck Free Flaps.

Key words: surgical site infection, antibiotic prophylaxis, free-flap, head and neck cancer, risk factors

Abstract

Background:

Surgical site infections (SSI) are common complications of free-flap reconstruction for head and neck cancer defects. This study aimed to identify risk factors for SSI following a significant change in local antibiotic prophylaxis practice.

Methods:

A retrospective cohort study was conducted of 325 patients receiving free-flap reconstruction for head and neck cancer defects at a tertiary hospital in Melbourne, Australia between 2013 and 2019. Charts were queried for recipient SSI (primary outcome), donor SSI, other infections, antibiotic use, hospital length of stay, and mortality.

Results:

Risk factors for SSI included female gender, T-classification, hardware insertion, clindamycin prophylaxis, and operative duration. There was a trend towards increased SSI with shorter ≤24-hour prophylaxis (OR = 0.43).

Conclusion:

Antibiotic duration and type were associated with SSI. Complexity of surgery, T-classification, hardware use and operative duration were also independently associated with SSI. A prospective trial is indicated to elicit optimal prophylactic antibiotic duration.

1 | Introduction

Head and neck cancers affect 600,000 to 700,000 new patients worldwide every year[1], with approximately 4000 cases occurring in Australia[2]. The majority of these cancers are squamous cell carcinomas (SCCs) with relatively poor survival (approximately 50%) due to a high risk of loco-regional recurrence[3].

Free flap reconstruction is considered the standard of care for head and neck reconstruction[4,5] with success exceeding 95%[4,6-8]. Failed transfer is associated with significant morbidity and financial cost[9], partly as it can lead to exposure of the carotid arteries and other vital structures, and may require a second free flap transfer[10]. The vascular compromise that precedes free flap failure can occur in the context of surgical site infections (SSI)[5,9,11] at the recipient flap site. Recipient SSIs also independently increase hospital length of stay, unplanned return to theatre, and oro-cutaneous fistula formation[6].

Most head and neck reconstructions are considered clean-contaminated as they breach the aerodigestive tract (under controlled conditions), contaminating the site with oral flora & oropharyngeal secretions[12] and increasing risk of SSI[13]. While some head and neck SSIs are due to single pathogens such as *Pseudomonas aeruginosa*, the majority are polymicrobial[14]. Optimal use of antibiotic prophylaxis could significantly reduce SSI rates, particularly as without prophylaxis, SSI rates have been reported as high as 87%[15].

Historically, the duration of surgical prophylaxis was neither standardised nor evidence-based, rather chosen at the discretion of individual surgeons. As a result, antibiotic prophylaxis was commonly used until drain tubes were removed[16], leading to coverage in excess of 7 days[17]. However, recent reviews have shown that most surgical infections can be prevented with short courses of intravenous (IV) antibiotics, from a single peri-operative dose up to 24 hours post-operatively[6,14,18,19]. This would lead to reduced costs, reduced development of resistant organisms such as methicillin-resistant *Staphylococcus*

aureus (MRSA)[20] and *Candida auris*[21], and reduced antibiotic-associated complications such as *Clostridium difficile* infection[20].

In late 2017, an education campaign was undertaken in the Plastic & Reconstructive Surgery department of the Royal Melbourne Hospital (RMH) (Melbourne, Australia) to encourage the uptake of changes to local guidelines towards 24-hour prophylaxis. As there are limited quantitative studies of antibiotic prophylaxis duration in head and neck surgery, a retrospective review was conducted. 325 head and neck free flap cases (Jan 2013 – Feb 2019) at RMH were reviewed with the following aims:

1. To identify SSI risk factors (pre-operative, operative, and post-operative).
2. To identify if SSI was associated with antibiotic prophylaxis type and duration.

2 | Materials and Methods

2.1 | Study population

This retrospective cohort study was approved by the RMH Human Research Ethics Committee (HREC) (project number QA2019019). The RMH Plastic and Reconstructive Surgery Register (a handwritten database of all planned operations) was screened by three researchers (PG, JD & NT) for cases occurring between Jan 1st 2013 and Feb 19th 2019 (**Figure 1**), for operative indication (head and neck tumour) and operative details (resection with free flap reconstruction). Of 10,042 cases, 404 cases were identified for review.

Formal review and data collection were conducted using records from The Royal Melbourne Hospital's (RMH) Health Information Services. Patients were excluded with the following criteria: clean (n=49) or dirty (n=2) operative field (using the operative report as per CDC criteria[12]), secondary reconstruction (n=25) and incomplete records (n=5). Of the remaining cases, minimal data fields were incomplete; the number of cases missing from each variable is described in **Tables 1** and **3** as "NA".

Data was abstracted from patient records using hard copy and electronic records as available. For all cases, the pre-admission summary, operative and anaesthetic reports, and medication charts were reviewed. Demographics were collected from the pre-admission summary and included age at surgery, body mass index (BMI), American Society of Anaesthesiologists (ASA) class, tobacco use, diabetes mellitus, cardiovascular risk factors, and previous radiotherapy. Discharge summaries were reviewed for tumour type and *AJCC* T/N/M classification[22], hospital length of stay, and to screen for outcomes such as infections and returns to theatre. Operative reports were reviewed for operative duration and details (including resection site, neck dissection, flap type, and hardware insertion), as well as returns to theatre.

Intra-operative antibiotics were recorded from anaesthetic charts, while inpatient medication charts were used to identify antibiotic use within 30 days (type, duration, dose, route and frequency), as well as topical antibiotic (e.g. chloramphenicol ointment) and nystatin use. Finally, all progress notes were reviewed to identify the date of tracheostomy decannulation, first oral intake, recipient site drain tube removal, and any recorded infections or flap failures.

2.2 | Surgical Site Infections

The CDC criteria[12] were used to define SSI as one of the following events, occurring within 30 days of surgery:

1. Purulent drainage.
2. Spontaneous deep incision dehiscence (or deliberate wound re-opening in the context of fever (>38ºC), localised pain or tenderness).
3. Abscess (on examination, during re-operation, on histopathology, or radiology).
4. Diagnosis of SSI by a surgeon or physician.

Progress notes, operative reports, discharge summaries, radiology (Fuji Synapse) and microbiology (AusCare and Clinical Integration System (CIS)) results services were each reviewed for records of purulent drainage, incisional dehiscence, abscess formation (CT or ultrasound), microbiological cultures,

and pre-operative albumin levels. Serous or salivary collections (on imaging) that were not diagnosed as an infection and did not have other features of infection were not included as infections. If a patient was newly charted IV antibiotics (or had their prophylactic antibiotics altered) for the indication of "neck collection" or similar (excluding non-infective sialocoeles and haematomas), this was recorded as a deep SSI.

The primary outcome was the occurrence of SSIs at the recipient site within 30 days of the reconstruction. Secondary outcomes were deep SSIs of the donor site, flap failure (complete necrosis of the flap), other infections (pneumonia, urinary tract infection (UTI), *Clostridium difficile* infection, sepsis), mortality and returns to theatre.

Antibiotic prophylaxis was defined as any intra-operative intravenous antibiotics (per the anaesthetic chart), in combination with intravenous or oral antibiotics (from the medication chart), continued directly post-operatively in the absence of any recorded signs, symptoms or diagnosis of infection. Prophylaxis duration was clearly recorded in the majority of patients' drug charts. If alternative or additional antibiotics were charted during the course of prophylaxis, the duration of prophylaxis was recorded as up until that change.

2.3 | Statistical analysis

Risk factors for SSI (including antibiotic duration) were assessed using the Chi^2 test for categorical data, and the student's T test and Mann-Whitney U test for continuous data. Variable correlations were assessed using regression analysis. Multivariate analysis was undertaken using binomial logistic regression models; variables were excluded from the analysis using backward exclusion with a selection criterion of $p < 0.157$[23]. Odds ratios and 95% confidence intervals are presented. Statistical analyses were performed using Jamovi version 1.6.15[24], with p values < 0.05 considered statistically significant. Results were verified by an independent statistician (LB) at the Melbourne EpiCentre (RMH).

3 | Results

3.1 | Patient characteristics (Table 1)

The majority of the 325 included cases were indicated for resection of malignant tumours (n=307, 94.5%), of which most had the pathological diagnosis of squamous cell carcinomas (n=275, 84.6%). Tumours were most commonly resected from the oral cavity (including the tongue) (n=277, 85.2%) and 74.9% (n=243) had bony resection as part of their operation.

Patients consisted of 196 men (60.3%) and 129 women (39.7%) with an average age of 60.4 (range 17–94) years. T classification was predominantly T2 or greater (n=187, 81.7%), with 43.2 % of patients (n=99) having T4 tumours resected. ASA class was most commonly II-III (n=267, 88.5%), with the remainder of patients either ASA I or IV (no patients were ASA class V). Sixty-one patients were current smokers (19.6%) and a further 98 patients were former smokers (31.1%). Forty patients (12.3%) had either type 1 or type 2 diabetes mellitus (DM), and 156 patients (48.0%) had either hypertension or hypercholesterolaemia. The mean BMI was 27.1 (SD: 6.0) and the mean pre-operative albumin level was 37.9 (SD: 5.5; reference range: 35-50).

A tracheostomy was inserted as part of the operative procedure in 92.6% (n=301), which was removed after a mean 11.8 days (SD: 5.6). Patients were kept nil-by-mouth for a mean 13.6 days (SD: 8.0) and had at least one drain tube at the recipient site for mean 12.7 days (SD: 5.5).

The mean operation duration was 624 minutes (SD: 121). Neck dissection was performed in 283 cases, unilaterally in 223 cases (68.6%) and bilaterally in 60 cases (18.5%). All cases included microvascular free flap reconstruction, of which the majority were soft tissue (e.g. fasciocutaneous) flaps, in particular the anterolateral thigh (ALT; n=124, 38.2%) or radial forearm (n=93, 28.6%) flaps. Bony (e.g. osseocutaneous) flaps were used in 97 cases (29.8%), most commonly for reconstruction of mandibular or maxillary defects. For these flaps, the fibula (free fibular flap; n=79, 24.3%) and iliac crest (DCIA flap;

n=20, 6.2%) were the most common sites of bone tissue harvest. In 115 cases (35.4%), hardware was inserted as part of the reconstruction.

The majority of patients received cephazolin-based prophylaxis. 87 patients received IV cephazolin (27.0%) with or without a step-down to oral antibiotics, and 218 patients received IV cephazolin in combination with metronidazole (67.7%), with or without step-down prophylaxis. Other antibiotics used were vancomycin (n=3, 0.9%), clindamycin (n=7, 2.2%), cephazolin, metronidazole, and ceftriaxone (n=2, 0.6%), tazocin and metronidazole (n=1, 0.3%), cephazolin, metronidazole, and teicoplanin (n=1, 0.3%), cephazolin and gentamicin (n=1, 0.3%), and lincomycin (n=1, 0.3%).

The mean duration of antibiotic prophylaxis was 7.6 days (SD: 5.8). 268 patients (83.2%) received >24-hour prophylaxis and 54 (16.8%) received ≤24-hour prophylaxis. 56 patients (17.3%) were prescribed topical antibiotic ointment to the head or neck wound as part of their prophylaxis, which was with chloramphenicol ointment (17.0%) in all but one case (tobramycin ointment, 0.3%). 101 patients (31.2%) were prescribed oral nystatin as part of their care.

3.2 | Surgical Site Infections

66 patients (20.3%) developed a recipient SSI according to the CDC criteria. Of these, 65 had swabs taken for microbiological culture. Of the total 147 isolates, the commonest species were *Streptoccocus* spp. (n=31), *Staphylococcus* spp. (n=29) including MRSA (n=4), Gram-negative bacilli (n=23), *Enterococcus* spp. (n=7), *Neisseria* spp. (n=3) and *Pseudomonas aeruginosa* (n=3). Additionally, *Candida albicans* was grown from 11 patient samples of recipient SSIs. 5 isolates had no growth.

Patients with SSI (**Table 1**) were significantly more likely to require a return to theatre ($p < 0.001$) and to have a complete free flap failure ($p = 0.016$). There was no significant difference in mortality, although only 1 death was recorded.

3.3 | SSI Risk Factors

Univariate (**Table 1**) and multivariate (**Table 2**) analysis revealed several significant risk factors. On univariate analysis of categorical variables, significant increases in SSI were found for female gender ($p = 0.028$), higher T classification (T2 to T4 compared to T1; $p = 0.033$), bony flap use ($p < 0.001$), hardware insertion ($p < 0.001$) and clindamycin-based prophylaxis ($p = 0.004$). Hardware insertion and bony flap use were highly associated variables ($p < 0.001$) on Chi^2 analysis. There were no differences between fasciocutaneous flap types (RFFF, ALT, other) ($p = 0.626$).

Analysis of continuous variables found operative duration ($p = 0.004$), days with a tracheostomy in situ ($p < 0.001$), days nil-by-mouth ($p = 0.022$) and days with a recipient site drain tube in situ ($p < 0.001$) to be significant risk factors for SSI development. However, these variables were each highly correlated with each other ($p < 0.001$). Multivariate analysis showed that bony flap use ($p = 0.014$), prophylaxis type ($p = 0.026$), and days with a recipient drain tube ($p = 0.002$) were significant risk factors. Patient comorbidities (including age, BMI, diabetes, tobacco use, ASA class, cardiovascular risk, pre-operative albumin) were not significant risk factors, nor was the site of resection (soft tissue or bony). Further, topical antibiotic use was not found to affect SSI outcomes.

3.4 | Prophylaxis Duration

Patients given ≤24-hour antibiotic prophylaxis had comparable characteristics to those given longer prophylaxis (**Table 3**). There were non-significant differences in all demographics. There was a trend towards patients receiving >24-hour prophylactic antibiotics having had benign tumour resection (p = 0.050).

The effect of prophylaxis duration on SSI rates was analysed using two methods. Analysis of duration as a continuous variable found that reduced duration was a significant risk factor for infection (p = 0.004). This was also significant on multivariate analysis (**Table 2**) (p = 0.030; OR 0.94). Secondly, duration was categorised into short (≤24 hour) and long-duration (>24-hour) groups. Shorter prophylaxis was approximately two times more likely to be associated with SSI (p = 0.008, OR 0.43; 95% CI = 0.22 – 0.81). Further sensitivity analysis was undertaken using 48-hour and 72-hour cut-offs. At a 48-hour cut-off, short prophylaxis was also approximately twice as likely to be associated with SSI (p = 0.029, OR 0.53; 95% CI = 0.30 – 0.94). There was no significant difference in recipient SSI rates at a 72-hour cut-off (p = 0.078).

Due to the potential confounding effect of tumour stage and type (benign or malignant) on infection rates, analysis was also undertaken with benign and T-1 malignant tumours excluded. Short prophylaxis was similarly associated with SSI (p = 0.011, OR 0.42 (95% CI = 0.22 – 0.83)). Analysis of the effect of prophylaxis duration on secondary outcomes revealed similar results (**Table 4**). Short prophylaxis was associated with significantly higher rates of recipient SSI (p = 0.008). Prophylaxis duration was not associated with donor site infections (p = 0.112). When combined with donor SSIs, short course prophylaxis was approximately 2-3 times more likely to be associated with infection (p = 0.002, OR = 0.38). This increase was also reflected by returns to theatre for infection (p = 0.001), rates of sepsis (p = 0.046) and a trend towards increased mortality. Longer prophylaxis was not associated with an increase in antibiotic-associated infections including *C. difficile* (p = 0.336) but was associated with reduced urinary tract infections (p = 0.011).

4 | Discussion

4.1 | SSI Risk Factors

A review of literature found diabetes mellitus[7,8,25-28], younger age[8,27,29], hypertension[8,27,30], and pre-operative radiotherapy[25,29,31] to be statistically significant patient (demographic) risk factors. Identifying patients at high risk of infection could theoretically be used to alter perioperative management to reduce SSIs. However, none of these factors were significant in our study. As the majority of patients were of similar age (60.4 ± 14.6), were not diabetic (87.7%), nor exposed to pre-operative radiotherapy (91.7%), the study may have been underpowered for these variables. Female gender was a significant factor in this study. This factor was significantly associated with smoking ($p < 0.001$), a potential confounding factor, but not with any other measured variables, warranting further investigation.

Karakida et al.[32] found T classification to be the most significant disease-related SSI risk factor in head and neck surgery, suggesting it is a marker for resection size, surgical invasiveness, and likelihood of dead-space occurrence after reconstruction (which itself predisposes to SSI)[12]. Indeed, T classification 2-4 was a significant risk factor in our study. To mitigate the potential bias of T classification on our data, secondary analysis with T1 tumours excluded was undertaken, however this did not significantly affect the results.

Operative duration[33,34] is also commonly found to be a risk factor for SSI, reflected in our study ($p = 0.004$). It is likely a surrogate for the procedural complexity[33] but may also be an independent risk factor due to the prolonged duration of wound exposure to circulating microbes in the operating theatre. Bony (e.g. osseocutaneous) flaps were also a significant SSI risk factor ($p < 0.001$), although were correlated with operative duration and with hardware use ($p < 0.001$) that can act as a nidus of infection[35], and was itself a significant risk factor for SSI ($p < 0.001$).

4.2 | Prophylaxis type

In terms of prophylaxis type, current Australian guidelines (recommending cephazolin-metronidazole) seem effective for preventing the majority of SSI. Many Gram-negative bacilli were cultured in this study, suggesting that alternative regimens such as ampicillin-sulbactam (favoured by US guidelines[15]) should be compared with prospective data, and indicates the importance of tailoring antimicrobials to any cultured pathogens' susceptibilities.

For patients with penicillin allergy, clindamycin-based prophylaxis was inferior, consistent with meta-analyses by Haidar et al.[6] and Chiesa-Estomba et al.[36], and with recent updates to the Australian therapeutic guidelines (recommending that clindamycin now be combined with gentamicin)[37]. Additionally, topical antimicrobials were not beneficial for SSI prophylaxis, consistent with a recent systematic review by the CDC[38].

4.3 | Prophylaxis duration

Australian guidelines[37] suggest that 24-hour prophylaxis may be superior to single-dose prophylaxis in specifically high-risk operations (e.g. reconstructive surgery for malignancy in general). However, there is no current guideline for free-flap head and neck surgery prophylaxis, and the guidelines do not recommend >24-hour prophylaxis. In literature, a meta-analysis by Chiesa-Estomba et al.[36] recommends up to 48-hour prophylaxis. Other reviews recommend up to 5-day coverage[20] while the optimal duration remains unclear. Indeed, many individual studies found significantly lower SSI rates with extended prophylaxis[33,34,39-41], suggesting that ≤24-hour courses may be inadequate. Overall, our study also suggests that short-course antibiotic prophylaxis may be inadequate in head and neck free-flap surgery. As there was no statistically significant difference in SSI rates using a 72-hour cut-off, this could be a viable recommendation.

4.4 | Limitations

The strength of this study is the large population of similar patients. There are several limitations. The data was limited by the quality of the hand-written records. The operations were performed by multiple surgeons, so individual surgical practice may not have been consistent. Furthermore, given the Australian patient cohort, the generalisability to cohorts in other countries is unclear.

In terms of confounding factors, retrospective determination of prophylaxis duration in patients with mild infectious features was difficult, partly due to the subjective nature of the CDC criteria. However, no alternative criteria are widely used. These cases may have had prolonged prophylaxis for features not classified as SSI. There was also a trend towards increasingly complex surgery, with higher proportions of malignant tumours of higher T classification in the short prophylaxis group. However, exclusion of benign and T1 cases did not significantly affect the overall rates of SSI. Additionally, there was a trend towards cephazolin-metronidazole prophylaxis (rather than cephazolin monotherapy) in the short duration group, although this should skew the benefit towards shorter prophylaxis.

Ultimately, prospective data is required. Sample size calculations[42,43] for a study with 80% power, alpha = 0.05 and enrolment ratio of 1:1 were calculated using the approximate SSI rates identified in our study. Comparison of 24-hour and 72-hour prophylaxis yields an approximate size of 300 to 350 participants. This would be achieved over several years at our institution, or in one year as a multi-centre trial.

5 | Conclusion

Overall, this research does not support shorter antibiotic prophylaxis (≤24-hour) for head and neck free flap cancer surgery, suggesting 72-hour prophylaxis with cefazolin-metronidazole may be an adequate compromise. Given the limitations of this retrospective study and of current literature, a prospective randomised-controlled trial comparing 24-hour prophylaxis with extended courses (e.g. 72-hour) is warranted.

References

1. Fitzmaurice C, Allen C, Barber RM et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A systematic analysis for the global burden of disease study. *JAMA Oncology*. 2017;3(4):524-48.

2. Australian Institute of Health and Welfare. *Head and neck cancers in Australia. Cancer series no. 83. Cat. No. CAN 80*. Canberra: AIHW; 2014.

3. Pang L, Jeannon JP, Simo R. Minimizing complications in salvage head and neck oncological surgery following radiotherapy and chemo-radiotherapy. *Curr Opin Otolaryngol Head Neck Surg*. 2011;19(2):125-31.

4. Wong CH, Wei FC. Microsurgical free flap in head and neck reconstruction. *Head Neck*. 2010;32(9):1236-45.

5. Cloke DJ, Green JE, Khan AL, Hodgkinson PD, McLean NR. Factors influencing the development of wound infection following free-flap reconstruction for intra-oral cancer. *Br J Plast Surg*. 2004;57(6):556-60.

6. Haidar YM, Tripathi PB, Tjoa T et al. Antibiotic prophylaxis in clean-contaminated head and neck cases with microvascular free flap reconstruction: A systematic review and meta-analysis. *Head Neck*. 2018;40(2):417-27.

7. Pool C, Kass J, Spivack J et al. Increased Surgical Site Infection Rates following Clindamycin Use in Head and Neck Free Tissue Transfer. *Otolaryngol Head Neck Surg*. 2016;154(2):272-8.

8. Khariwala SS, Le B, Pierce BH, Vogel RI, Chipman JG. Antibiotic Use after Free Tissue Reconstruction of Head and Neck Defects: Short Course vs. Long Course. *Surg Infect*. 2016;17(1):100-5.

9. Saunders S, Reese S, Lam J, Wulu J, Jalisi S, Ezzat W. Extended use of perioperative antibiotics in head and neck microvascular reconstruction. *Am J Otolaryngol*. 2017;38(2):204-7.

10. Wei F-C, Demirkan F, Chen H-C et al. The outcome of failed free flaps in head and neck and extremity reconstruction: What is next in the reconstructive ladder? *Plast Reconstr Surg*. 2001;108(5):1161-2.

11. Kinzinger MR, Bewley AF. Perioperative care of head and neck free flap patients. *Curr Opin Otolaryngol Head Neck Surg*. 2017;25(5):405-10.

12. Mangram AJ, Hora TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. *Infect Control Hosp Epidemiol*. 1999;20(4):250.

13. 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(3):242-8.

14. Bratzler DW, Dellinger EP, Olsen KM et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm*. 2013;70(3):195-283.

15. Becker GD, Parell GJ. Cefazolin prophylaxis in head and neck cancer surgery. *Ann Otol Rhinol Laryngol*. 1979;88(2 Pt 1):183-6.

16. Allegranzi B, Zayed B, Bischoff P et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: An evidence-based global perspective. *Lancet Infect Dis*. 2016;16(12):e288-e303.

17. Girod DA, McCulloch TM, Tsue TT, Weymuller EA Jr. Risk factors for complications in clean-contaminated head and neck surgical procedures. *Head Neck*. 1995;17(1):7-13.

18. Vila PM, Zenga J, Jackson RS. Antibiotic Prophylaxis in Clean-Contaminated Head and Neck Surgery: A Systematic Review and Meta-analysis. *Otolaryngol Head Neck Surg*. 2019;157(4):580-8.

19. Balamohan SM, Sawhney R, Lang DM et al. Prophylactic antibiotics in head and neck free flap surgery: A novel protocol put to the test. *Am J Otolaryngol*. 2019;40(6):102276.

20. Veve MP, Davis SL, Williams AM, McKinnon JE, Ghanem TA. Considerations for antibiotic prophylaxis in head and neck cancer surgery. *Oral Oncol*. 2017;74:181-7.

21. Forsberg K, Woodworth K, Walters M et al. Candida auris: The recent emergence of a multidrug-resistant fungal pathogen. *Med Mycol*. 2019;57(1):1-12.

22. Amin MB, Edge SB, Greene FL et al, eds. *AJCC Cancer Staging Manual*. 8th ed. Springer; 2017.

23. Heinze G, Wallisch C, Dunkler D. Variable selection - A review and recommendations for the practicing statistician. *Biom J*. 2018(3):431.

24. The jamovi project: jamovi (Version 1.6.15). 2021. Available at: https://www.jamovi.org. Accessed February 23, 2021.

25. Nuara MJ, Sauder CL, Alam DS. Prospective analysis of outcomes and complications of 300 consecutive microvascular reconstructions. *Arch Facial Plast Surg*. 2009;11(4):235-9.

26. Avery CM, Ameerally P, Castling B, Swann RA. Infection of surgical wounds in the maxillofacial region and free flap donor sites with methicillin-resistant Staphylococcus aureus. *Br J Oral Maxillofac Surg*. 2006;44(3):217-21.

27. Fischer JP, Sieber B, Nelson JA et al. A 15-year experience of complex scalp reconstruction using free tissue transfer-analysis of risk factors for complications. *J Reconstr Microsurg*. 2013;29(2):89-97.

28. Khan MN, Russo J, Spivack J et al. Association of body mass index with infectious complications in free tissue transfer for head and neck reconstructive surgery. *JAMA Otolaryngol Head Neck Surg*. 2017;143(6):574-9.

29. Yarlagadda BB, Deschler DG, Rich DL et al. Head and neck free flap surgical site infections in the era of the Surgical Care Improvement Project. *Head Neck*. 2016;38 Suppl 1:E392-8.

30. Simpson KH, Murphy PG, Hopkins PM, Batchelor AG. Prediction of outcomes in 150 patients having microvascular free tissue transfers to the head and neck. *Br J Plast Surg*. 1996;49(5):267-73.

31. Usubuchi M, Matsuura K, Goto T et al. Professional oral health care at general dental clinic reduces postoperative complications of head and neck free-flap reconstruction surgery. *J Cancer*. 2019;10(1):205-10.

32. Karakida K, Aoki T, Ota Y 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(5):334-9.

33. McMahon JD, MacIver C, Smith M et al. Postoperative complications after major head and neck surgery with free flap repair-prevalence, patterns, and determinants: a prospective cohort study. *Br J Oral Maxillofac Surg*. 2013:689-695.

34. Langerman A, Thisted R, Hohmann S, Howell M. Antibiotic and duration of perioperative prophylaxis predicts surgical site infection in head and neck surgery. *Otolaryngol Head Neck Surg.* 2016:1054-63.

35. Yao CM, Ziai H, Tsang G et al. Surgical site infections following oral cavity cancer resection and reconstruction is a risk factor for plate exposure. *Otolaryngol Head Neck Surg*. 2017;46(1):30.

36. Chiesa-Estomba CM, Lechien JR, Fakhry N et al. Systematic review of international guidelines for perioperative antibiotic prophylaxis in Head & Neck Surgery. *Head Neck*. 2019;41(9):3434-56.

37. eTG complete. Surgical antibiotic prophylaxis for specific procedures: Surgical prophylaxis for head and neck surgery. 2019. Available at: www.tg.org.au. Accessed February 23, 2021.

38. Berrios-Torres SI, Umscheid CA, Bratzler DW et al. Centers for Disease Control and Prevention guideline for the prevention of surgical site infection, 2017. *JAMA Surgery*. 2017;152(8):784-91.

39. Bartella AK, Kamal M, Teichmann J et al. Prospective comparison of perioperative antibiotic management protocols in oncological head and neck surgery. *J Craniomaxillofac Surg*. 2017;45(7):1078-82.

40. Mitchell RM, Mendez E, Schmitt NC, Bhrany AD, Futran ND. Antibiotic prophylaxis in patients undergoing head and neck free flap reconstruction. *JAMA Otolaryngol Head Neck Surg*. 2015;141(12):1096-103.

41. Sawyer R, Cozzi L, Rosenthal DI, Maniglia AJ. Metronidazole in head and neck surgery - the effect of lengthened prophylaxis. *Otolaryngol Head Neck Surg*. 1990;103(6):1009-11.

42. Rosner B. *Fundamentals of biostatistics: Seventh edition*. Boston, Mass: Brooks/Cole; 2011.

43. Jones SR, Carley S, Harrison M. An introduction to power and sample size calculation. *Emerg Med J*. 2003;20:453-458.

Figure 1: Case selection process

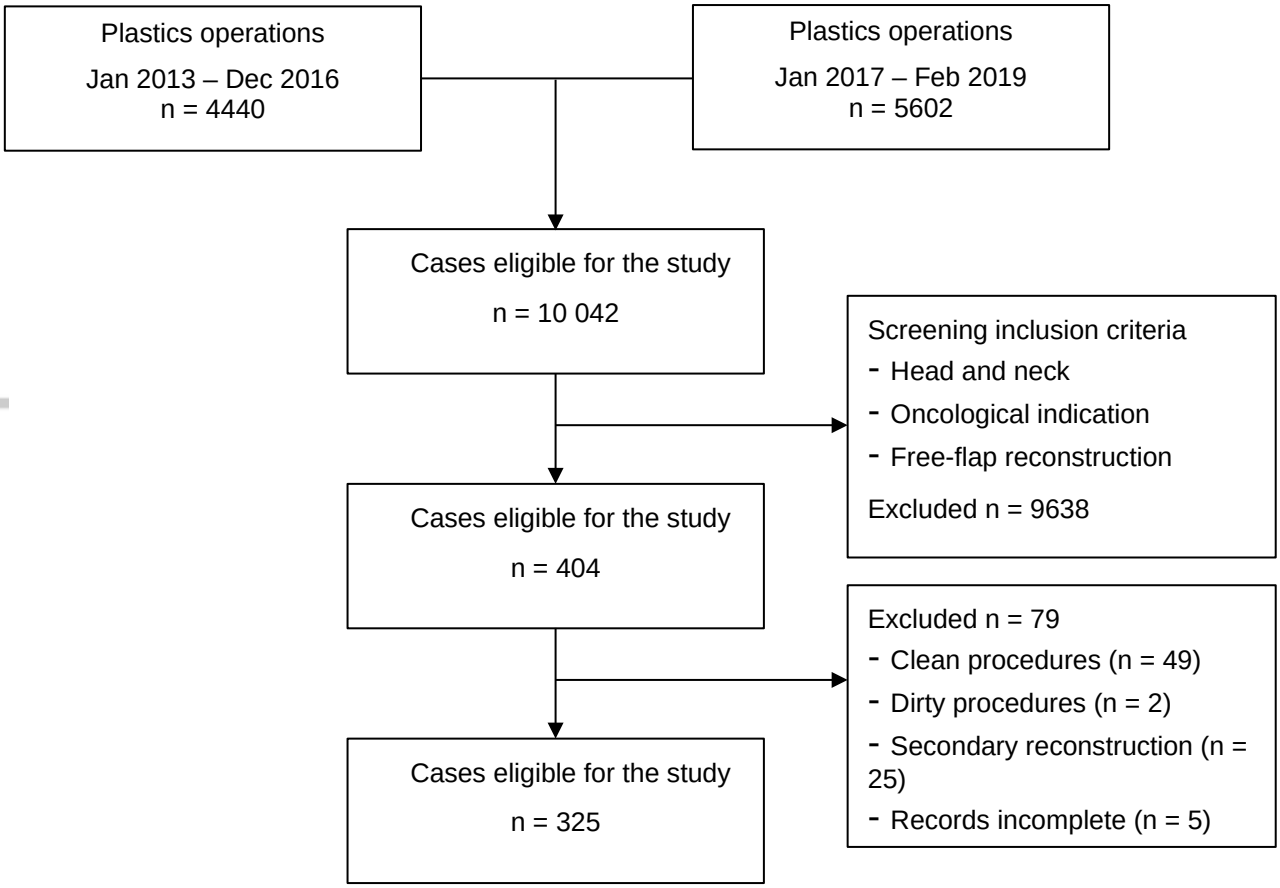

Table 1: Characteristics of Head and Neck Free Flap Patients and Risk of Recipient SSI

Characteristic		Total n = 325 n (%)	Recipient SSI n = 66 (20.3%) n (% of characteristic)	No SSI n = 259 (79.7%) n (% of characteristic)	p value (Chi^2)
Gender	Male	196 (60.3)	32 (16.3)	164 (83.7)	**0.028**
	Female	129 (39.7)	34 (26.4)	95 (73.6)	
ASA class	1	30 (9.2)	7 (23.3)	23 (76.7)	0.629
	2	127 (39.1)	24 (18.9)	103 (81.1)	
	3	140 (43.1)	32 (22.9)	108 (77.1)	
	4	5 (1.5)	2 (40.0)	3 (60.0)	
	5	0 (0)	0 (0)	0 (0)	
	NA	23	1	22	
Tobacco use	Never	156 (48.0)	37 (23.7)	119 (76.3)	0.406
	Former	98 (30.2)	17 (17.3)	81 (82.7)	
	Current	61 (18.8)	11 (18.0)	50 (72.0)	
	NA	10	1	9	
Diabetes	Yes	40 (12.3)	8 (20.0)	32 (80.0)	0.959
	No	285 (87.7)	58 (20.3)	227 (87.7)	
Other CV risk factors					0.840
Hypertension		58 (17.8)	10 (17.2)	48 (82.8)	
Hypercholesterolaemia		19 (5.8)	3 (15.8)	16 (84.2)	
Hypertension and hypercholesterolaemia		79 (24.3)	16 (20.3)	63 (79.7)	
Prior radiotherapy to recipient site	Yes	21 (6.5)	6 (28.6)	15 (71.4)	0.314
	No	298 (91.7)	58 (19.5)	240 (80.5)	
	NA	6	2	4	
Disease type	Malignant	307 (94.5)	63 (20.5)	244 (79.5)	0.693
	Benign	18 (5.5)	3 (16.7)	15 (83.3)	
Tumour classification	I	42 (12.9)	3 (7.1)	39 (92.9)	0.120
	II	64 (19.7)	11 (17.2)	53 (82.8)	
	III	24 (7.4)	5 (20.8)	19 (79.2)	
	IV	99 (30.5)	24 (24.2)	75 (75.8)	
Tumour classification (T I vs T II-IV)	I	42 (12.9)	3 (7.1)	39 (92.9)	**0.033**
	II-IV	187 (57.5)	40 (21.4)	147 (78.6)	
	NA	96	23	73	
Soft tissue resection					0.274
Oral cavity		277 (85.2)	56 (20.2)	221 (79.8)	
Larynx or pharynx		18 (5.5)	4 (22.2)	14 (77.8)	
Oral cavity & larynx or pharynx		21 (6.5)	2 (9.5)	19 (90.5)	
Oral cavity & nasal		6 (1.8)	3 (50.0)	3 (50.0)	
Nasal		3 (0.9)	1 (33.3)	2 (66.7)	
Bony resection					0.132
Nil (soft tissue only)		82 (25.2)	12 (14.6)	70 (85.4)	
Mandible (± other)		146 (44.9)	34 (23.3)	112 (76.7)	
Maxilla (± other)		39 (12.0)	6 (15.4)	33 (84.6)	
Mandible and maxilla		55 (16.9)	12 (21.8)	43 (78.2)	
Other		3 (0.9)	2 (66.7)	1 (33.3)	
Neck dissection	Unilateral	42 (12.9)	8 (19.0)	34 (81.0)	0.971
	Bilateral	223 (68.6)	46 (20.6)	177 (79.4)	
	Nil	60 (18.5)	12 (20.0)	48 (80.0)	
Flap type	Bony flap	97 (29.8)	31 (32.0)	66 (68.0)	**<0.001**
	Soft tissue flap	228 (70.2)	35 (15.4)	193 (84.6)	
Hardware insertion	Yes	115 (35.4)	37 (32.2)	78 (67.8)	**<0.001**
	No	210 (64.6)	29 (13.8)	181 (86.2)	
Topical antibiotic use	Yes	56 (17.2)	8 (14.3)	48 (85.7)	0.214
	No	269 (82.8)	58 ()	211 ()	
	NA	1	0	1	
Nystatin use	Yes	101 (31.1)	20 (19.8)	81 (80.2)	0.864
	No	224 (68.8)			
	NA	1	0	1	

Antibiotic choice					**0.034**
Cephazolin (± oral)		87 (26.8)	13 (14.9)	74 (85.1)	
Cephazolin-metronidazole (± oral)		218 (67.1)	48 (22.0)	171 (78.0)	
Vancomycin-based prophylaxis		3 (0.9)	0 (0)	3 (100)	
Clindamycin-based prophylaxis		7 (2.2)	4 (57.1)	3 (42.9)	
Other		7 (2.2)	3 (42.9)	4 (57.1)	
NA		3	0	3	
Simplified antibiotic choice					**0.046**
Cephazolin (± oral)		87 (26.8)	13 (14.9)	74 (85.1)	
Cephazolin-metronidazole (± oral)		218 (67.1)	46 (21.1)	172 (78.9)	
Other		17 (5.2)	7 (41.2)	10 (58.8)	
NA		3	0	3	
Duration	≤24-hour	54 (16.6)	18 (33.3)	36 (66.7)	**0.008**
	vs. >24-hour	271 (83.4)	48 (17.7)	223 (82.3)	
	≤48-hour	89 (27.4)	25 (28.1)	64 (71.9)	**0.029**
	vs. >48-hour	236 (72.6)	41 (17.4)	195 (82.6)	
	≤72-hour	109 (33.5)	28 (25.7)	81 (31.5)	0.078
	vs. >72-hour	216 (66.5)	38 (16.8)	178 (83.2)	
	NA	3	1	2	
Continuous variables		n (Mean [SD])	n (Mean [SD])	n (Mean [SD])	p (t-test)
Age at surgery (years)		325 (60.4 [14.6])	66 (59.5 [15.3])	259 (60.6 [14.5])	0.594
Body mass index (kg/m^2)		324 (27.1 [6.0])	65 (26.6 [4.8])	259 (27.2 [6.3])	0.476
Pre-op albumin		212 (37.9 [5.5])	47 (37.3 [7.9])	165 (38.0 [4.6])	0.486^
Operation duration (minutes)		321 (624 [121])	65 (662.3 [122.7])	256 (613.8 [118.8])	**0.004**
Days with tracheostomy in situ		295 (11.8 [5.6])	60 (14.2 [6.1])	235 (11.2 [5.4])	**<0.001^**
Days nil by mouth		288 (13.6 [8.0])	53 (15.8 [8.7])	235 (13.2 [7.8])	**0.022^**
Days with recipient drain tube in situ		301 (12.7 [5.5])	56 (15.5 [6.7])	245 (12.1 [5.0])	**<0.001^**
Duration of antibiotic prophylaxis (days)		322 (7.6 [5.8])	65 (5.8 [4.8])	257 (8.1 [5.9])	**0.004**
Infection-related outcomes		n (%)	n (% of total)	n (% of total)	
Flap failure (up to 12 months post-op)		7 (2.2)	4 (6.2)	3 (1.2)	**0.016**
Sepsis		10 (3.1)	4 (6.1)	6 (2.3)	0.116
Mortality		1 (0.3)	0 (0)	1 (0.3)	0.613
Return to theatre for any reason		123 (37.8)	53 (80.3)	70 (27.0)	**<0.001**

^ = Levene's test was significant ($p < 0.05$), so the Mann-Whitney U test was used (otherwise, the student's T test was used)

Table 2: Multivariate Logistic Regression of Risk Factors for Developing Recipient SSI following Head and Neck Free Flap Reconstruction

Characteristic	Multivariate regression	
	P value	OR (95% CI)
Sex	0.050	1.89 (0.99, 3.57)
Flap type	**0.014**	2.25 (1.17, 4.29)
Antibiotic choice	**0.026**	1.54 (1.05, 2.26)
Days with recipient drain tube in situ	**0.002**	1.09 (1.03, 1.15)
Duration of antibiotic prophylaxis (days)	**0.030**	0.94 (0.88, 0.99)

Table 3: Characteristics of Head and Neck Free Flap Patients by Prophylaxis Duration

Characteristic	≤24hr prophylaxis n = 54	>24hr prophylaxis n = 268	p value (Chi^2)
	n (%)	n (%)	
Gender			0.158
Male	37 (68.5)	156 (58.2)	
Female	17 (31.5)	112 (41.8)	
ASA class			0.211
1	5 (10.4)	25 (9.9)	
2	15 (31.3)	112 (44.4)	
3	28 (58.3)	111 (43.7)	
4	0 (0)	5 (2.0)	
5	0 (0)	0 (0)	
NA	6	16	
Tobacco use			0.178
Never	20 (40.0)	135 (51.5)	
Former	21 (42.0)	76 (29.0)	
Current	9 (18.0)	51 (19.5)	
NA	4	6	
Diabetes	10 (18.5)	28 (10.4)	0.094
Other CV risk factors			0.631
Hypertension	11 (20.4)	47 (17.5)	
Hypercholesterolaemia	4 (7.4)	15 (5.6)	
Hypertension and hypercholesterolaemia	15 (27.8)	61 (22.8)	
Prior radiotherapy to recipient site	1 (1.9)	19 (7.2)	0.145
NA	1	5	
Disease type			0.050
Malignant	54 (100)	250 (93.3)	
Benign	0 (0)	18 (6.7)	
Tumour classification			0.424
I	4 (11.1)	38 (19.9)	
II	10 (27.8)	54 (28.3)	
III	6 (16.7)	18 (9.4)	
IV	16 (44.4)	81 (42.4)	
NA	18	77	
Tumour classification			0.213
I	4 (11.1)	38 (19.9)	
II-IV	32 (88.9)	153 (80.1)	
NA	18	77	
Soft tissue resection			0.944
Oral cavity	45 (83.3)	231 (86.2)	
Larynx or pharynx	3 (5.6)	13 (4.9)	
Oral cavity & larynx or pharynx	4 (7.4)	17 (6.3)	
Oral cavity & nasal	1 (1.9)	5 (1.9)	
Nasal	1 (1.9)		

Bony resection			0.887
Nil (soft tissue only)	13 (24.1)	67 (25.0)	
Mandible (± other)	25 (46.3)	120 (44.8)	
Maxilla (± other)	5 (9.3)	34 (12.7)	
Mandible and maxilla	10 (18.5)	45 (16.8)	
Other	1 (1.9)	2 (0.7)	
Neck dissection			0.121
Nil	3 (5.6)	39 (14.6)	
Unilateral	43 (79.6)	179 (66.8)	
Bilateral	8 (14.8)	50 (18.7)	
Flap type			0.573
Soft tissue flap	36 (66.7)	189 (70.5)	
Bony flap	18 (33.3)	79 (29.5)	
Hardware insertion	22 (40.7)	93 (34.7)	0.398
Topical antibiotic use (to surgical wound)	5 (9.3)	50 (18.7)	0.094
Nystatin use (oral)	12 (22.2)	89 (33.2)	0.112
Antibiotic choice			0.381
Cephazolin (± oral)	10 (18.5)	77 (28.8)	
Cephazolin-metronidazole (± oral)	41 (75.9)	177 (66.3)	
Vancomycin-based prophylaxis	0 (0)	3 (1.1)	
Clindamycin-based prophylaxis	1 (1.9)	6 (2.2)	
Other	2 (3.7)	4 (1.5)	
NA	0	1	
Simplified antibiotic choice			0.298
Cephazolin (± oral)	10 (18.5)	77 (28.8)	
Cephazolin-metronidazole (± oral)	41 (75.9)	177 (66.3)	
Other	3 (5.6)	13 (4.9)	
NA	0	1	
	n (Mean [SD])	*n* (Mean [SD])	p
Age at surgery (years)	54 (60.7 [14.5])	268 (60.2 [14.7])	0.820
Body mass index (kg/m^2)	54 (26.9 [4.9])	267 (27.1 [6.2])	0.792
Pre-op albumin	31 (38.7 [8.7])	178 (37.9 [4.6])	0.455^
Operation duration (minutes)	54 (612.1 [127.2])	265 (626.4 [119.3])	0.429
Days with tracheostomy in situ	50 (11.9 [6.1])	244 (11.7 [5.5])	0.821
Days nil by mouth	43 (14.5 [11.3])	243 (13.4 [7.2])	0.424
Days with recipient drain tube in situ	47 (13.8 [5.3])	251 (12.3 [5.3])	0.085
Duration of antibiotic prophylaxis (days)	54 (0.94 [0.23])	268 (9.0 [5.4])	**<0.001**^

^ = Levene's test was significant ($p < 0.05$), so the Mann-Whitney U test was used (otherwise, the student's T test was used)

Table 4: Secondary Outcomes by Prophylaxis Duration

Characteristic	≤24hr prophylaxis *n* (%)	>24hr prophylaxis *n* (%)	p value (Chi^2)	OR (95% CI)
Recipient site infection				
CDC Criteria	18/54 (33.3)	47/268 (17.5)	**0.008**	0.43 (0.22, 0.81)
Excluding benign & T1 cases	18/50 (36.0)	41/212 (19.3)	**0.011**	0.42 (0.22, 0.83)
Donor site infection				
CDC Criteria	3/54 (5.6)	5/268 (1.9)	0.112	0.32 (0.07, 1.40)
Excluding benign & T1 cases	2/50 (4.0)	5/212 (2.4)	0.517	0.58 (0.11, 3.08)
Any site infection				
CDC Criteria	21/54 (38.9)	52/268 (19.4)	**0.002**	0.38 (0.20, 0.71)
Excluding benign & T1 cases	20/50 (40.0)	46/212 (21.7)	**0.007**	0.42 (0.22, 0.80)
Other infection				
UTI	4/54 (7.4)	4/268 (1.5)	**0.011**	0.19 (0.05, 0.78)
C. difficile	0/54 (0)	4/268 (1.5)	0.366	0.37 (0.10, 34.9)
Sepsis	4/54 (7.4)	6/268 (2.2)	**0.046**	0.29 (0.08, 1.05)
Pneumonia	11/54 (20.4)	78/268 (29.1)	0.190	1.60 (0.79, 3.27)
Total	16/54 (29.6)	84/268 (31.3)	0.804	1.08 (0.57, 2.05)
Return to theatre				
For infection	18/54 (33.3)	40/268 (14.9)	**0.001**	0.35 (0.18, 0.68)
For another reason	11/54 (20.4)	71/268 (26.5)	0.346	1.41 (0.69, 2.88)
For any reason	24/54 (44.4)	99/268 (36.9)	0.300	0.73 (0.41, 1.32)
Mortality	1/54 (1.9)	0/268 (0)	**0.026**	0.07 (0.00, 1.65)
	n (Mean [SD])	*n* (Mean [SD])	p	
Hospital length of stay (days)	54 (19.5 [11.3])	268 (19.2 [8.9])	0.820	