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Prophylactic antibiotics in head and neck free flap surgery: A novel protocol put to the test

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ABSTRACT

Objective: Recent evidence supports the use of ampicillin-sulbactam as a favored choice for antibiotic prophylaxis following head and neck free flap reconstructive surgery. However, there is a paucity of evidence guiding the optimal duration of antibiotic prophylaxis. The aim of this study is to compare the infection rates of short courses of ampicillin-sulbactam versus extended courses of various antibiotics in head and neck free flap reconstructive surgery.

Methods: This is a retrospective cohort study conducted from 2012 to 2017 at a tertiary academic center on 266 consecutive patients undergoing head and neck surgery with free flap reconstruction. The primary outcome measure was the rate of any infection within 30 days of surgery.

Results: There were 149 patients who received antibiotic prophylaxis for an extended duration of at least seven days. 117 patients received a short course of antibiotics defined as 24 h for non-radiated patients and 72 h for radiated patients. Postoperative infections occurred in 45.9% of patients, of which 92.6% occurred at surgical sites. There was no significant difference in terms of postoperative infection rate between patients receiving an extended duration of antibiotics versus a short duration ($p = 0.80$). This held true for subgroups of surgical site infections ($p = 0.38$) and distant infections ($p = 0.59$ for pneumonia and $p = 0.76$ for UTI). Risk factors for infections were identified as hypothyroidism ($p = 0.047$) and clean contaminated wound classification ($p = 0.0002$).

Conclusion: Shorter duration of ampicillin-sulbactam prophylaxis in free flap reconstruction of head and neck defects does not negatively affect postoperative infection rates.

Level of evidence: Level 2b.

1. Introduction

Extensive discussion has been devoted to the prevention of infections following free flap reconstruction after head and neck oncologic surgery. The development of a surgical site infection (SSI) following free tissue transfer can risk flap viability and lead to extensive hospital stays, development of mucocutaneous fistulas, and wound breakdown. The benefit of prophylactic antibiotics has been established by numerous studies, with SSI rates reaching 80% in patients that did not receive antibiotic prophylaxis [1,2]. The duration of antibiotic prophylaxis has been a subject of controversy, being dependent on institution and surgeon preference. Regarding head and neck procedures, several studies have demonstrated that antibiotic therapy beyond a 24-h regimen is unlikely to offer an advantage [3–6]. A recent meta-analysis regarding all head and neck procedures also demonstrated a lack of benefit in five days of antibiotic prophylaxis versus one day [7].

Abbreviations: SSI, surgical site infection; ORN, osteoradionecrosis; CCI, Charleson Comorbidity Index; LOS, length of stay; BMI, body mass index; SNF, skilled nursing facility; LTACH, long term acute care hospital; UTI, urinary tract infection; PNA, pneumonia; C.Diff, *Clostridium difficile*; PCR, polymerase chain reaction; ICU, intensive care unit; IV, intravenous; ID, infectious diseases; OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease

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However, the evidence remains conflicted as another recent meta-analysis on patients specifically receiving free flaps showed a higher infection rate in patients receiving 24 h or less of prophylactic antibiotics [8]. Considerable research has been dedicated to the role of antibiotic use in the development of antibiotic resistant infections [8], and surgeons are compelled to assume a responsibility to minimize antibiotic use whenever it is safe to do so.

Comparatively few studies have been performed specifically examining patients who have undergone free flap reconstruction after head and neck ablative surgery. As complications after free flap reconstruction can be disastrous, many reconstructive surgeons have been tentative to adopt short-course antibiotic prophylaxis for this patient set. While recent evidence has shown improved outcomes with short courses of ampicillin-sulbactam [9], no standardized protocol exists for this patient population. A number of factors in this cohort are proposed to lead to higher risk of infection, including longer duration of surgery, relatively higher incidence of preoperative radiation, longer hospital stays, more advanced cancer, and medical comorbidities [10]. Thus, many head and neck surgical oncologists continue to argue for optimal antibiotic prophylaxis.

The purpose of this study is to introduce a novel post-operative antibiotic prophylaxis protocol for head and neck – free flap surgery. The protocol in our study utilizes uniform antibiotic choices in a shortened course and was implemented in a prospective fashion. This approach is compared to a historical cohort of patients receiving prolonged courses of antibiotics. The aim is to compare infection rates and outcomes between the two groups.

2. Methods

The University of Florida Institutional Review Board (IRB201700498) granted research ethics approval. This study was conducted at a tertiary care academic referral center.

2.1. Setting and study design

Data was collected from inpatient and outpatient records of the Head and Neck Surgery Team at the University of Florida/Shands Hospital. The design was a retrospective cohort study with data collected from July 1, 2012 to January 1, 2017.

2.2. Patient selection

All patients ≥ 18 years old who underwent head and neck cancer surgery with free flap reconstruction or free flap reconstruction for osteoradionecrosis (ORN) resection over the course of the study period were included. The only exclusion criterion was the presence of active infection at the time of surgery.

2.3. Data collection

Patients were identified though a departmental registry. A retrospective chart review was then performed to obtain data: socioeconomic factors, smoking and alcohol consumption, previous cancer treatment, TNM staging, Charlson Comorbidity Index (CCI), perioperative details, discharge location, hospital length of stay (LOS), antibiotic regimens, SSI, distant infections, as well as antibiotic complications. A CCI cut-off of 4 was used based on previous studies showing this cut-off to be significant in terms of mortality difference [11]. Malnutrition was defined as an unexplained weight loss > 10% in the months prior to surgery, a pre-operative albumin < 3.5 g/dL, or body mass index (BMI) < 18.5. Chronic kidney disease was defined as a glomerular filtration rate < 60 mL per minute. Chronic liver disease was determined based on the patient carrying a diagnosis of cirrhosis made by their primary care provider or medical specialist. Hypothyroidism was determined based on thyroid labs drawn preoperatively. Gender and race were self-reported. Pathologic diagnosis was classified as benign or malignant. Oncologic staging was divided into early stages (stage 0-II) or late stages (stage III-IV). Discharge locations included home or a facility (e.g. skilled nursing facility [SNF], inpatient rehabilitation, long term acute care hospital [LTACH]).

Electronic medical records were examined to determine outcomes spanning 30 days from the day of surgery. The possibility of infection at distant and surgical sites was assessed twice daily during team rounds as an inpatient, and at every outpatient appointment. All progress notes had a mandatory assessment for infections and stated whether an infection was present or not, current treatment of infection, and plan for treatment. SSI were noted based on a combination of erythema/tenderness at the surgical site, wound drainage, fever, and leukocytosis. If purulent fluid was expressed from a wound, it was swabbed and sent for cultures. The presence of a urinary tract infection (UTI) was based on either frank pyuria or positive urine culture. Ordering of the urine culture was prompted by two of the following symptoms: fever of unknown origin, suprapubic tenderness, dysuria, or urinary urgency. The presence of pneumonia (PNA) was based on chest radiographs or bronchoscopy with bronchioalveolar lavage, the ordering of which was prompted by fever of unknown origin, leukocytosis of unknown origin, or symptoms including cough, tachypnea, or shortness of breath. Other infections such as meningitis were determined clinically as they were identified.

We also analyzed antibiotic complications, namely *Clostridium difficile* (C. diff) infections. These infections were diagnosed with either enzyme immunoassay or polymerase chain reaction (PCR) at the discretion of the intensive care unit (ICU) team. The ordering of these tests was prompted by diarrhea and/or leukocytosis of unknown origin. We did not collect data regarding antibiotic resistance rates in our surgical unit.

2.4. Study groups

The study cohort was separated into two groups: extended antibiotic duration, and shortened antibiotic duration. In the former group, the length of antibiotic administration was 7–14 days. This group exclusively encompassed the time from July 1, 2012 to June 30, 2015. The duration and choice of antibiotics was based on surgeon preference on a case-by-case basis. In general, radiated patients in this cohort received 14 days of antibiotics, and non-radiated patients received 7 days. A small number of patients with osteoradionecrosis (ORN) of the mandible received 12 weeks of IV antibiotics. The choices of antibiotics included ampicillin-sulbactam, combination of ciprofloxacin and clindamycin, combination of cefazolin and metronidazole, or a combination of vancomycin and piperacillin-tazobactam. The choice of antibiotic was dependent on surgeon preference, history of antibiotic resistant infections, and infectious disease team recommendations.

In early 2015, the surgical ICU analyzed distant infection rates, SSI rates, and pathogens found in cultures. Antibiotic resistance rates were used to form antibiograms to formulate future antibiotic prophylaxis protocols. The head and neck surgical oncology protocol was developed between the head and neck surgeons (PTD, RS) and the surgical ICU infectious disease leader (KC). The best available evidence for antibiotic choice and duration was applied and combined with institutional data and experience. The protocol was implemented on July 1, 2015 and has been consistently used in all head and neck surgical oncology – free flap patients since then.

In the shortened duration arm, patients received antibiotic prophylaxis based on membership to one of three groups, assuming no known drug sensitivity to penicillin:

1. Non-radiated: 24 h of intravenous (IV) ampicillin-sulbactam.
2. Radiated: 72 h of IV ampicillin-sulbactam.
3. ORN: 7 days of IV ampicillin-sulbactam with an automatic consultation to infectious diseases (ID). The ID team then determined

further antibiotic treatment based on culture results of the necrotic bone.

Ampicillin-sulbactam was the choice of antibiotic for all patients without a penicillin allergy based on recent evidence [9,12]. Patients with true penicillin allergies (history of angioedema or anaphylaxis with a penicillin-based antibiotic) received IV metronidazole and IV levofloxacin. This combination was chosen based on hospital antibiograms and resistant rates of pathogens found in distant infections and SSI in 2014.

All patients in both the extended and shortened duration arms received one preoperative dose of IV antibiotics (the same type of antibiotic they received postoperatively) within 1 h of incision. All patients received oral care with chlorhexidine 0.12% solution four times per day. Neck incisions were cleansed with normal saline followed by an application of bacitracin ointment three times per day.

2.5. Outcome measures

The primary outcome measure was the presence of any infection within 30 days of surgery. Secondary outcomes included rates of infections occurring as an inpatient versus outpatient, as well as rates of infection at each distant and surgical site. Infection rates were also determined for radiated patients separately. Lastly, the risk factors for the various categories of infections were determined in a multivariate analysis.

2.6. Statistical analysis

Statistical analysis was conducted with SPSS 23.0 software package (SPSS Inc., Chicago, IL). Patients and variables were characterized by standard descriptive statistics. Continuous variables were compared using a *t*-test, and categorical variables with a Chi-squared test or Fisher's exact test where appropriate. All variables were analyzed with multivariate logistic regression analysis to identify predictors of infection types. A level of statistical significance was set as $p \leq 0.05$.

3. Results

266 consecutive free flap surgeries were performed which met study criteria. No patients met exclusion criteria. 149 flaps belonged to the extended antibiotic group and were performed prior to July 1, 2015. The number in the shortened antibiotic arm totaled 117. Regarding the choice of antibiotic in the extended group, 27.5% received clindamycin/ciprofloxacin, 14.1% received cefazolin/metronidazole, 36.2% received ampicillin-sulbactam, and 6.0% received vancomycin/piperacillin-tazobactam. The remainder received various other combinations of the above antibiotics. There were three patients in this cohort with ORN who received 12 weeks of IV antibiotics. Other than these three patients, the average number of days of antibiotics received in this cohort was 7.8. In the shortened antibiotic group, all received ampicillin-sulbactam other than the 12.1% of patients who were penicillin allergic who received levofloxacin/metronidazole. There were three patients with ORN in this group who received 6 weeks of IV antibiotics. Other than these three patients, they all received either one or three days of antibiotics dependent on radiation status.

Table 1 details patient demographics of the two groups. There were no significant differences in terms of age, race, sex, marital status, or insurance status between the two groups. Table 2 details medical comorbidities. Most comorbidities included in the study showed no significant difference between groups, although the CCI showed an increased presence of medical comorbidities in the extended antibiotic group. Table 3 specifies pathology and surgical details. There were no major differences in terms of stage of cancer, type of flap, or wound classification (clean vs clean contaminated). However, the extended antibiotic patients had longer operative times and more blood loss during the cases Table 4 shows that the short course of antibiotics had a shorter length of stay with fewer patients discharged home..

Table 1
Patient demographics by group.

Demographic	Prolonged course of ABX	Short course of ABX	p-Value
Number of patients	149 (56)	117 (44)	–
Males	107 (72)	84 (72)	0.99
Mean age (y)	60.7	61.7	0.69
Age > 55y	99 (52)	90 (48)	0.08
Insurance			
Self-pay/Medicaid	47 (32)	29 (25)	0.27
Medicare/private	102 (69)	88 (75)	
Race			
Not-Caucasian	21 (14)	17 (15)	0.99
Caucasian	128 (86)	100 (85)	
Marital status			
Not-married	72 (48)	45 (39)	0.14
Married	77 (52)	72 (61)	

Abbreviations: ABX, antibiotics; n, number; y, years.
Note: results reports as number (%) unless stated otherwise.

A total of 122 of patients (45.9%) developed either SSI or distant infections during a 30-day postoperative period. Table 5 details the infection rates between the two groups. Overall, there was no significant difference in infection rates between the two antibiotic prophylaxis groups ($p = 0.80$). This held true for subgroups of SSI ($p = 0.38$), distant infections ($p = 0.59$ for pneumonia and $p = 0.76$ for UTI), and timing of infection (inpatient versus outpatient, $p = 0.59$). The mucocutaneous fistula rates were also similar ($p = 0.76$). For radiated patients, there was also no significant difference in infection rates between the two antibiotic groups ($p = 0.34$). This held true for all infection subgroups and is detailed in Table 6.

Table 7 shows the association of each independent variable with infection rates by multivariate analysis using logistic regression with each independent variable included in this study. Hypothyroidism (odds ratio [OR] 2.4; 95% CI 1.0–5.5, $p = 0.47$), clean contaminated wound class (OR 7.7, CI 0.4–13.8, $p = 0.0002$), and LOS over 10 days (OR 2.1, CI 1.1–3.9, $p = 0.02$) were significantly associated with a higher risk of infections. Regarding the subgroup of SSI, COPD was associated with a higher risk of infections (OR 2.2, CI 1.0–4.6, $p = 0.048$). Relating to distant infections, PVD (OR 21.1, CI 2.8–156.7, $p = 0.003$) and smoking (OR 5.1, CI 1.6–16.6, $p = 0.007$) were associated with an increased risk. Table 8 shows a multivariate analysis of each independent variable and their relation to outpatient infection and inpatient infection subgroups.

4. Discussion

The original impetus behind the alteration of antibiotic prophylaxis at the University of Florida was related to the development of antibiotic-resistant infections. Prior to July 1, 2015, the durations of antibiotic prophylaxis for free flap cases were 7 to 14 days. A high rate of antibiotic-resistant infections in the surgical ICU, shared with several other surgical services, prompted the head and neck surgery team to develop a new perioperative antibiotic approach. It was at this time that all patients' antibiotic duration was shortened to 24 h for non-radiated patients and 72 h for radiated patients. ORN patients were kept on longer durations of antibiotics if bone cultures were positive representing potential osteomyelitis.

The ideal type of antibiotic has likely been narrowed by recent studies showing the drawbacks of the traditionally used bacteriostatic clindamycin. One study showed clindamycin associated with a four-fold increase in rate of SSI [12]. In 2015, Mitchell et al. retrospectively compared short versus long duration of antibiotic prophylaxis for free flap reconstruction [9]. The choice of antibiotic did affect infection rates in their study. Ampicillin-sulbactam, a bactericidal drug, was

Table 2
Medical comorbidities by group.

Variable	Prolonged course of ABX	Short course of ABX	p-Value
Age-adjusted CCI			
< 4	88 (59)	52 (44)	**0.02**
≥4	61 (41)	65 (56)	
Smoking (mean pyh)			
Smoking			
< 30 pyh	92 (62)	65 (56)	0.32
≥30pyh	57 (38)	52 (44)	
Alcohol use			
Not daily	121 (81)	90 (77)	0.45
Daily	28 (19)	27 (23)	
Thyroid status			
Not hypothyroid	127 (85)	102 (87)	0.72
Hypothyroid	22 (15)	15 (13)	
DM2			
No DM2	132 (89)	99 (85)	0.37
DM2	17 (11)	18 (15)	
HTN			
No HTN	67 (45)	59 (50)	0.39
HTN	82 (55)	58 (50)	
CAD			
No CAD	123 (83)	97 (83)	0.99
CAD	26 (17)	20 (17)	
PVD			
No PVD	144 (97)	110 (94)	0.38
PVD	5 (3)	7 (6)	
CVA			
No CVA	144 (96)	102 (87)	**0.005**
CVA	5 (4)	15 (13)	
COPD			
No COPD	127 (85)	84 (72)	**0.009**
COPD	22 (15)	33 (28)	
CRF			
No CRF	146 (98)	112 (96)	0.31
CRF	3 (2)	5 (4)	
CLD			
No CLD	143 (96)	108 (92)	0.28
CLD	6 (4)	9 (8)	
Obesity			
No obesity	132 (89)	100 (85)	0.47
Obesity	17 (11)	17 (15)	
Malnutrition			
No malnutrition	139 (93)	96 (82)	**0.006**
Malnutrition	10 (7)	21 (18)	
History of RT			
No previous RT	102 (69)	89 (76)	0.22
Previous RT	47 (31)	28 (24)	
History of CRT			
No previous CRT	128 (86)	98 (84)	0.73
Previous CRT	21 (14)	19 (16)	

Abbreviations: ABX, antibiotics; n, number; CCI, Charleson Comorbidity Index score; pyh, pack-year history; DM2, diabetes mellitus type 2; HTN, hypertension; CAD, coronary artery disease; PVD, peripheral vascular disease; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CLD, chronic liver disease; RT, radiation therapy (external beam); CRT, chemo-radiation therapy.
Note: results reports as number (%) unless stated otherwise.
Bold denotes statistical significance (i.e. $p < 0.05$)

Table 3
Pathology and surgical details by group.

Variable	Prolonged course of ABX	Short course of ABX	p-Value
Pathology n(%)			
Benign	12 (8)	3 (3)	0.06
Malignant	136 (92)	114 (97)	
Cancer stage n(%)			
Stage 0–II	50 (37)	34 (31)	0.32
Stage III–IV	84 (63)	76 (69)	
Wound classification			
Clean	18 (12)	12 (10)	0.70
Clean contaminated	131 (88)	105 (90)	
Flap n(%)			
Soft tissue	113 (76)	77 (66)	0.08
Osteocutaneous	36 (24)	40 (34)	
Mean or time (h)	11.2	9.7	**0.00001**
OR time			
≤8 h	11 (7)	34 (29)	**0.00007**
> 8 h	138 (93)	83 (71)	
Mean EBL (mL)	443	364	**0.03**
EBL			
≤300 mL	78 (52)	89 (76)	**0.0001**
> 300 mL	71 (48)	28 (23)	

Abbreviations: ABX, antibiotics; n, number; OR, operating room; h, hours; EBL, estimated blood loss; mL, milliliters.
Note: results reports as number (%) unless stated otherwise.
Bold denotes statistical significance (i.e. $p < 0.05$)

Table 4
Hospital stay and discharge details.

Variable	Prolonged course of ABX	Short course of ABX	p-Value
Mean LOS	8.4	6.6	**< 0.001**
LOS			**< 0.001**
< 10 days	44 (29)	70 (60)	
> 10 days	105 (71)	47 (40)	
Disposition			**0.04**
Home	108 (73)	70 (60)	
Facility			
SNF	30 (20)	26 (22)	
LTACH	4 (3)	10 (9)	
Inpatient rehab	7 (5)	11 (9)	

Abbreviations: ABX, antibiotics; LOS, length of stay; SNF, skilled nursing facility; LTACH, long term acute care hospital; rehab, rehabilitation facility.
Note: results reports as number (%) unless stated otherwise.
Bold denotes statistical significance (i.e. $p < 0.05$)

associated with a lower risk of postoperative infections. This is the first study to specifically examine the ideal duration of ampicillin-sulbactam administration following free flap reconstruction. The rates of penicillin allergy have been reported to be 11.5% in the literature [13]. Given this relatively high rate, the protocol was devised with an option for these penicillin-allergic patients. The infectious diseases service at the University of Florida formulated an antibiogram which showed low resistance rates to and similar coverage of gram negatives, gram positives, and anaerobes with levofloxacin and metronidazole compared to ampicillin-sulbactam.

Carroll et al. prospectively compared one day versus five days antibiotic prophylaxis in free flap cases and found no significant differences in SSI between the two groups [14]. However, their group solely utilized clindamycin which, as previously mentioned, is suboptimal in prophylaxis. Mitchell et al. also analyzed short versus longer duration of antibiotic prophylaxis (24 h versus longer than 24 h) in free flap patients and found no significant difference in overall infection rates between the two groups [9]. However, they did find that a longer duration of antibiotics improved infection rates in the SSI subgroup. Another recent study found that less than two days of antibiotics is equivalent to more than two days of antibiotic prophylaxis in free flap cases[B]. Their study utilizes clindamycin in both groups and contains relatively smaller patient cohorts. As previously stated, one motivation for our study was to analyze a specific protocol which excludes clindamycin. Our study finds that duration of ampicillin-sulbactam prophylaxis does not influence infection rates as a whole, and this held true for all infection subgroups ($p > 0.05$).

Given inconsistencies in the literature related to RT and whether it increases the rate of surgical complications [15–18], it was sought to analyze this potential risk factor. Girod et al. analyzed over 30 preoperative and perioperative risk factors for infections in clean contaminated head and neck cases. The only factor to significantly increase wound infections in their study was prior radiotherapy [15]. There are

Table 5
Infections and complications.

Variable	Prolonged course of ABX	Short course of ABX	p-Value
Any site infection	67 (45)	55 (47)	0.80
SSI	54 (36)	49 (42)	0.38
Flap/reconstructive site	25 (17)	26 (22)	0.35
Flap donor site	12 (8)	17 (15)	0.12
Neck infection	28 (19)	21 (18)	0.88
Fistula	7 (5)	4 (3)	0.76
Distant infection			
PNA	7 (5)	8 (7)	0.59
UTI	7 (5)	4 (3)	0.76
Meningitis	1 (1)	0 (0)	0.99
Infection timing			0.59
Inpatient	30 (44)	22 (39)	
Outpatient	38 (56)	35 (61)	
Mean time to first infection (d)	11.8	12.4	0.86
SSI	12.8	13.6	0.99
Distant infection	10.8	11.1	0.14
Complications from ABX			**0.046**
C.Diff	1 (1)	7 (6)	
AKI	1 (0)	0 (0)	
Outpatient infections			0.14
At home	37 (59)	25 (44)	
At a facility	26 (41)	32 (56)	

Abbreviations: ABX, antibiotics; SSI, surgical site infection; PNA, pneumonia; UTI, urinary tract infection; d, days; C.Diff, clostridium difficile infection; AKI, acute kidney injury.
Note: results reports as number (%) unless stated otherwise.
Bold denotes statistical significance (i.e. $p < 0.05$)

Table 6
Infections and complications in-patients with a history of RT.

Variable	Prolonged course of ABX	Short course of ABX	p-Value
Any site infection	23 (49)	10 (64)	0.34
SSI			
Flap/reconstructive site	11 (24)	7 (25)	0.99
Flap donor site	3 (6)	3 (11)	0.67
Neck infection	12 (26)	6 (21)	0.78
Fistula	4 (5)	0 (0)	0.29
Distant infection			
PNA	5 (11)	1 (1)	0.40
UTI	1 (2)	1 (4)	0.99
Meningitis	1 (2)	1 (4)	0.99
Infection timing			
Inpatient	13 (28)	5 (18)	0.41
Outpatient	10 (21)	7 (25)	
Mean time to first infection (days)			
SSI	10.8	10.4	0.12
Distant Infection	14.0	10.0	0.19
Complications from ABX			0.99
C.Diff	1 (2)	1 (4)	
AKI	1 (2)	0 (0)	
Outpatient infections			0.50
At home	3 (43)	3 (43)	
At a facility	4 (57)	4 (57)	

Abbreviations: ABX, antibiotics; SSI, surgical site infection; PNA, pneumonia; UTI, urinary tract infection; d, days; C.Diff, clostridium difficile infection; AKI, acute kidney injury.
Note: results report as number (%) unless stated otherwise.

conflicting studies regarding this subject, with some finding prior history of radiation to increase infection rates and others to find no correlation [16–18]. Based on the best available literature it was decided that radiated patients would receive an intermediate duration of antibiotics of 72 h. Within the subset of radiated patients, there was no significant difference in infection rates in this study whether the patients were in the extended antibiotics arm or the shortened antibiotics arm ($p > 0.05$). This shows that 72 h of prophylaxis may be effective as ≥7 days. However, patients previously treated with RT had a 2.6-fold increased risk of outpatient SSI ($p = 0.04$) compare to non-radiated patients, regardless of days of antibiotic prophylaxis. This may be due to increased wound dehiscence and prolonged wound healing in these patients [19,20], which may introduce increased portals for pathogens to enter.

Preoperative hypothyroidism was a factor independently associated with increased risk of infections. These findings combined with other studies showing the detrimental effect of hypothyroidism on complication rates [9,21] may support the routine screening of all patients for thyroid function along with their preoperative lab tests. COPD was found to increase outpatient infections 2.2–12.1-fold ($p \leq 0.05$). Because most patients with COPD are exposed to tobacco smoke [22], it may be deduced that once discharged from the hospital they may be exposed to more tobacco smoke, which is known to inhibit wound healing and lead to increased infections [23,24]. Another factor which was independently associated with infections was clean contaminated wound status, which is consistent with other studies [25] and typically encompasses mucosal defects [26,27]. A greater LOS was also associated with a higher infection rate. This is possibly a reflection of infections developing with increased exposure to pathogens in a hospital environment. Higher LOS was also independently associated with higher rates of outpatient SSIs ($p < 0.05$), which may also reflect increased hospital acquired infections.

There were three ORN patients in both the extended and shortened antibiotic groups. Although these patients formerly were kept on 12 weeks of IV antibiotics per the infectious disease service, this was shortened to 6 weeks of antibiotics in the recent cohort again as dictated by the infectious disease service. Moreover, they only received the full 6 weeks if intraoperative bone cultures were positive as this potentially signified chronic osteomyelitis. Although total numbers of ORN patients are too low to draw meaningful conclusions in this study, analysis did not reveal any differences in outcomes between the extended and shortened antibiotic groups in terms of postoperative wound infections ($p = 0.41$).

A limitation to this study relates to the progression in skill level of the surgeons. The three primary surgeons are trained in head and neck microvascular reconstruction. A notable finding in the study shows that the operative time as well as estimated blood loss is significantly lower in the shortened antibiotic group compared to the extended antibiotic group. This could represent an increase in surgical efficiency due to relatively more experienced surgeons. However, analysis showed that neither operative time nor estimated blood loss were associated with infection rates. Another limitation of this study is the inherent difficulty in detecting early postoperative infections. The diagnosis of infection was dependent on subjective clinical assessment, which may have varied between providers.

A paradoxical finding in this study is the seven C. diff cases in the shortened antibiotic group and only one case in the extended antibiotic group. All these cases are presumed to result from the 1–3 days of antibiotic prophylaxis as none received another course of antibiotics during their hospitalization. One potential explanation relates to changes in the way our ICU has tested for C. diff. The testing methodology has changed from enzyme immunoassay to Cepheid GeneXpert PCR, which is extremely sensitive. Patients found to have C diff with this technique may merely represent colonization. Our internal data show false positive diagnosis in up to 30% of cases. Our surgical ICU, shared with other services, has also had an increase in the number of patients found to have C diff over the last 2 years.

5. Conclusion

A shortened duration of antibiotic prophylaxis is not shown to increase SSI or distant infection rates. These findings underscore the importance of avoiding antibiotic overuse to improve antibiotic

Table 7
Multivariate analysis of variables predicative of infections at all time periods.

Patient variable	Any infection		SSI		Distant infection	
	p value	Odds ratio [95% CI]	p value	Odds ratio [95% CI]	p value	Odds ratio [95% CI]
Age						
≤55 yrs	0.57	1 [Ref]	0.72	1 [Ref]	0.61	1 [Ref]
> 55 yrs		0.82 [0.4–1.6]		0.9 [0.4–1.7]		1.5 [0.4–6.6]
DM2						
No	0.97	1 [Ref]	0.91	1 [Ref]	0.42	1 [Ref]
Yes		1.0 [0.4–2.3]		0.9 [0.4–2.2]		2.1 [0.5–9.8]
PVD						
No	0.21	1 [Ref]	0.62	1 [Ref]	**0.003**	1 [Ref]
Yes		2.5 [0.6–10.7]		0.7 [0.8–2.6]		**21.1 [2.8–156.7]**
COPD						
No	0.20	1 [Ref]	**0.048**	1 [Ref]	**0.01**	1 [Ref]
Yes		1.7 [0.8–3.6]		**2.2 [1.0–4.6]**		**12.1 [0.9–22.2]**
CRF						
No	0.34	1 [Ref]	0.41	1 [Ref]	0.99	1 [Ref]
Yes		0.4 [0.1–2.3]		0.5 [1–2.7]		–
Hypothyroid						
No	**0.047**	1 [Ref]	0.11	1 [Ref]	0.65	1 [Ref]
Yes		**2.4 [1.0–5.5]**		1.9 [0.8–4.3]		1.3 [0.2–9.5]
Malnutrition						
No	0.61	1 [Ref]	0.72	1 [Ref]	0.78	1 [Ref]
Yes				0.9 [0.3–2.1]		1.4 [−0.2–9.5]
CCI						
No	0.99	1 [Ref]	0.91	1 [Ref]	0.63	1 [Ref]
Yes		1.0 [0.5–2.0]		1.1 [0.5–2.1]		0.7[0.2–2.7]
Hx of RT						
No	0.52	1 [Ref]	0.90	1 [Ref]	0.69	1 [Ref]
Yes		0.8 [0.4–1.6]		1.0 [0.5–1.9]		0.8 [0.2–3.1]
Smoker						
≤30 pyh	0.86	1 [Ref]	0.61	1 [Ref]	**0.007**	1 [Ref]
> 30 pyh		0.9 [0.5–1.7]		0.9 [0.5–1.5]		**5.1 [1.6–16.6]**
Daily EtOH						
No	0.78	1 [Ref]	0.42	1 [Ref]	0.91	1 [Ref]
Yes		0.9 [0.5–1.8]		0.8 [0.4–1.5]		0.9 [0.3–3.8]
Wound class						
Clean	**0.0002**	1 [Ref]	**0.05**	1 [Ref]	**0.01**	1 [Ref]
Clean contaminated		**7.7 [0.4–13.8]**		**2.6 [0.2–10.1]**		**8.6 [0.02–16.5]**
cT class						
T1/T2	0.75	1 [Ref]	0.6	1 [Ref]	0.99	1 [Ref]
T3/T4		1.0		0.8 [0.01–8.1]		2.5 [0.04–8.9]
Flap type						
Soft tissue	0.89	1 [Ref]	0.7	1 [Ref]	0.8	1 [Ref]
Bone containing		1.0 [0.5–2.1]		1.2 [0.6–2.4]		1.2 [0.3–5.0]
OR time						
≤8 h	0.10	1 [Ref]	0.2	1 [Ref]	0.9	1 [Ref]
> 8 h		0.5 [0.2–1.1]		0.6 [0.3–1.3]		1.1 [0.2–5.7]
EBL						
≤300 mL	0.61	1 [Ref]	0.4	1 [Ref]	0.3	1 [Ref]
> 300 mL		0.85 [0.4–1.6]		0.8 [0.4–1.5]		2.0 [0.5–7.4]
Transfusion						
No	0.78	1 [Ref]	0.9	1 [Ref]	0.2	1 [Ref]
Yes		0.9 [0.5–1.8]		0.9 [0.5–1.9]		2.4 [0.6–9.4]
LOS						
≤10 d	**0.02**	1 [Ref]	0.4	1 [Ref]	**0.02**	1 [Ref]
> 10 d		**2.1 [1.1–3.9]**		1.3 [0.7–2.4]		**16.8 [2.9–98.8]**
ABX plan						
Long course	0.97	1 [Ref]	0.9	1 [Ref]	0.09	1 [Ref]
Short course		1.0 [0.5–1.9]		0.9 [0.5–1.8]		3 [0.9–10.7]

Abbreviations: ABX, antibiotics; CI, confidence interval; yrs., years; Ref, reference value; n, number; CCI, Charleson Comorbidity Index score; pyh, pack-year history; DM2, diabetes mellitus type 2; HTN, hypertension; CAD, coronary artery disease; PVD, peripheral vascular disease; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; RT, radiation therapy (external beam); cT Class, clinical tumor classification; OR, operating room; EBL, estimated blood loss; mL, milliliters; LOS, length of stay; d, days.
Bold denotes statistical significance (i.e. $p < 0.05$)

resistance rates in surgical care units.

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None.

Declaration competing interest

None.

Ethics approval

Prior to commencement of this study, IRB ethics approval was

Table 8
Multivariate analysis of variables predicative of infections at defined time periods.

Patient variable	Inpatient infection		Outpatient infection		Outpatient SSI	
	p value	Odds ratio [95% CI]	p value	Odds ratio [95% CI]	p value	Odds ratio [95% CI]
Age						
≤55 yrs	**0.02**	1 [Ref]	**0.04**	1 [Ref]	0.37	1 [Ref]
> 55 yrs		**4.1 [1.3–13.1]**		**2.3 [0.2–9.5]**		0.67 [0.3–1.6]
DM2						
No	0.21	1 [Ref]	0.3	1 [Ref]	0.81	1 [Ref]
Yes		2.0 [0.7–5.8]		0.6 [0.2–1.6]		0.9 [0.3–5.4]
PVD						
No	0.73	1 [Ref]	0.38	1 [Ref]	0.89	1 [Ref]
Yes		1.3 [0.3–6.7]		1.9 [0.5–7.7]		1.1 [0.2–5.4]
COPD						
No	0.08	1 [Ref]	**0.005**	1 [Ref]	**0.02**	1 [Ref]
Yes		0.4 [0.1–1.1]		**3.5 [1.5–8.3]**		**3.1 [1.2–7.8]**
CRF						
No	0.5	1 [Ref]	0.44	1 [Ref]	0.50	1 [Ref]
Yes		0.4 [0.04–4.1]		0.4 [0.04–4.2]		0.4 [0.04–4.9]
Hypothyroid						
No	0.95	1 [Ref]	**0.02**	1 [Ref]	**0.01**	1 [Ref]
Yes		1.0 [0.3–3.2]		**2.9 [1.2–7.0]**		**3.4 [1.3–8.8]**
Malnutrition						
No	0.14	1 [Ref]	0.07	1 [Ref]	0.31	1 [Ref]
Yes		2.5 [0.8–8.4]		0.3 [0.09–1.1]		0.5 [0.1–1.9]
CCI						
No	0.48	1 [Ref]	0.42	1 [Ref]	0.32	1 [Ref]
Yes		1.4 [0.6–3.4]		0.7 [0.3–1.6]		0.5 [0.1–1.9]
Hx of RT						
No	0.59	1 [Ref]	0.13	1 [Ref]	**0.04**	1 [Ref]
Yes		1.3 [0.5–3.1]		0.5 [0.2–1.2]		**2.6 [0.2–11.7]**
Smoker						
≤30 pyh	0.91	1 [Ref]	0.95	1 [Ref]	0.31	1 [Ref]
> 30 pyh		1.0 [0.5–2.3]		1.0 [0.5–1.9]		0.7 [0.3–1.4]
Daily EtOH						
No	0.35	1 [Ref]	0.78	1 [Ref]	0.44	1 [Ref]
Yes		0.6 [0.2–1.7]		1.1 [0.5–2.5]		1.4 [0.6–3.2]
Wound class						
Clean	**0.04**	1 [Ref]	**0.008**	1 [Ref]	0.11	1 [Ref]
Clean contaminated		**0.2 [0.04–1.0]**		**0.2 [0.07–0.7]**		0.4 [0.1–1.3]
cT class						
T1/T2	0.97	1 [Ref]	0.96	1 [Ref]	0.65	1 [Ref]
T3/T4		1.0 [0.05–10.1]		1.0 [0.5–7.8]		1.1 [0.3–6.7]
Flap type						
Soft tissue	0.13	1 [Ref]	0.31	1 [Ref]	0.44	1 [Ref]
Bone containing		0.4 [0.2–1.3]		1.5 [0.7–3.4]		1.4 [0.6–3.5]
OR time						
≤8 h	0.47	1 [Ref]	0.20	1 [Ref]	0.28	1 [Ref]
> 8 h		0.7 [0.2–2.1]		0.6 [0.2–1.4]		0.6 [0.2–1.5]
EBL						
≤300 mL	0.96	1 [Ref]	0.49	1 [Ref]	0.19	1 [Ref]
> 300 mL		1.0 [0.4–2.4]		0.8 [0.4–1.6]		0.6 [0.3–1.3]
Transfusion						
No	0.25	1 [Ref]	0.18	1 [Ref]	0.65	1 [Ref]
Yes		1.7 [0.7–4.1]		0.6 [0.3–1.3]		0.8 [0.4–1.9]
LOS						
≤10 days	**0.05**	1 [Ref]	0.91	1 [Ref]	**0.02**	1 [Ref]
> 10 days		**2.6 [1.0–6.7]**		1.0 [0.5–2.2]		**0.4 [0.2–0.9]**
ABX plan						
Long course	0.79	1 [Ref]	0.9	1 [Ref]	0.40	1 [Ref]
Short course		0.9 [0.4–2.2]		1.0 [0.4–2.1]		0.7 [0.3–1.6]
DC location						
Home	NA	NA	0.87	1 [Ref]	0.36	1 [Ref]
Facility				1.1 [0.5–2.4]		1.5 [0.6–3.6]
Trach at DC						
No	0.08	1 [Ref]	0.95	1 [Ref]	0.26	1 [Ref]
Yes		2.3 [0.9–6.0]		1.0 [0.4–2.4]		1.8 [0.7–4.7]
GTube at DC						
No	**0.04**	1 [Ref]	0.31	1 [Ref]	0.08	1 [Ref]
Yes		**4.0 [1.0–15.0]**		0.7 [0.3–1.5]		0.5 [0.2–1.1]

Abbreviations: ABX, antibiotics; CI, confidence interval; yrs., years; Ref, reference value; n, number; CCI, Charleson Comorbidity Index score; pyh, pack-year history; DM2, diabetes mellitus type 2; HTN, hypertension; CAD, coronary artery disease; PVD, peripheral vascular disease; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; RT, radiation therapy (external beam); cT Class, clinical tumor classification; OR, operating room; EBL, estimated blood loss; mL, milliliters; LOS, length of stay; d, days; GTube, gastrostomy tube; trach, tracheostomy tube.
Bold denotes statistical significance (i.e. $p < 0.05$)

obtained.

Manuscript presentation

This study was presented as an oral presentation at the AHNS section of COSM on April 26, 2017 in San Diego, California.

Ethics approval and consent to participate

Prior to commencement of this study, IRB ethics approval was obtained from the University of Florida Institutional Review Board (IRB201700498). The need for consent was waived as the study was a retrospective review.

Consent for publication

Not applicable.

Availability of data and material

Data is stored on a locked computer the study institution. The IRB has not granted sharing rights to it at this time.

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None.

Authors' contributions

SB: study design, IRB, data collection, data interpretation, manuscript preparation.

RS: study design, IRB, data collection, data interpretation, manuscript review and editing.

DL, KC, VV, SB, LM: data collection, data interpretation, manuscript review and editing.

BB, PJA, PE: study design, data interpretation, manuscript review and editing.

PTD: study design, IRB, data collection, data interpretation, manuscript preparation and editing.

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