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Postoperative infections associated with microvascular free flaps in head and neck reconstruction: Analysis of risk factors and results with a standardized prophylaxis protocol

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Summary Currently, large defects of the head and neck regions are mainly reconstructed using microvascular free flap. Postoperative infections, including surgical site infections (SSIs) and medical postoperative infections (MPI), are important causes of morbidity and worsening of surgical outcomes. The authors aimed to analyze the results obtained using a standardized prophylaxis protocol in a series of 100 consecutive patients who underwent microvascular reconstruction surgery between 2016 and 2021 at a single institution, to identify the risk factors, which could be overcome, to minimize the incidence of infectious complications. In this study, 24 patients developed infectious complications. Higher American Society of Anesthesiologists (ASA) score was statistically associated with higher risk of infectious complications ($p = 0.01$), need for postoperative transfusions ($p = 0.01$), and higher T and N stage ($p = 0.03$ and $p = 0.02$, respectively) in patients with cancer. We also found a correlation between the increase in surgery duration, hospitalization, and intensive care unit (ICU) stay with higher risk of infection ($p = 0.03$, $p = 0.01$, and $p = 0.001$, respectively). Nine patients reported partial or total flap necrosis and in this group of patients, a higher incidence of infectious complication was recorded ($p = 0.001$). Our experience shows that SSIs and MPIs affect the global and surgical outcomes of patients and both their incidences can be reduced by correcting potential risk factors preoperatively (e.g., anemia), intraoperatively (amount of

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blood loss and duration of surgery), and postoperatively (duration of hospitalization and ICU stay and early elimination of potential sources of infection).

Large defects of the head and neck regions secondary to resection of advanced tumors or those caused by severe facial trauma or malformations, often result in swallowing and phonation dysfunctions and cosmetic disorders.[1,2] Microvascular free-flap surgery enables reconstruction of these defects to improve functional and aesthetic outcomes, but the duration and complexity of surgery are significantly increased. In particular, when the reconstruction is performed contextually to a tumor resection, the patient is often exposed to additional risk factors for infections with longer duration of the procedure, neoadjuvant radio- or chemotherapy, high T stage, neck dissection, and heavy blood loss and consequent need for blood transfusions.[1] Moreover, the risks associated with pre-existing conditions or comorbidities have to be considered.

For these reasons, postoperative infections, including surgical site infections (SSIs) and medical postoperative infections (MPIs), are crucial contributors to morbidity and worsening of surgical outcomes in patients undergoing major head and neck microvascular reconstructive surgery.

Postoperative SSIs are common postoperative complications since their incidence is reported in the range of 3-41% in clean-contaminated head and neck surgery.[1,2] Therefore, their risk factors, epidemiology, microbiology, and outcomes are well described.[3,4]

However, few studies describe the incidence and risk factors associated with MPIs after microsurgical reconstruction of the head and neck regions.[4]

The aim of this study was to report the experiences gained from head and neck reconstruction using free flaps during a 5-year period in the Maxillo-Facial Surgery Division of the Turin University, Italy.

Through the analysis of their experience and comparison of the data present in the literature, the authors aimed to analyze the risk factors and results obtained using a standardized prophylaxis protocol intended to minimize the incidence of infectious complications and to reduce the impact of variables related to patient characteristics.

Materials and method

Study design and sample

The authors performed a retrospective review of patients who underwent surgical reconstruction for head and neck defects between December 2016 and December 2021 at the Division of Maxillofacial Surgery, Città della Salute e della Scienza University Hospital of Turin, Italy.

Inclusion criteria were as follows: (1) age over 18 years at the time of surgery; (2) microvascular free tissue transfer surgery for the reconstruction of head and neck defects; (3) availability of complete preoperative and postoperative medical, surgical, and pathological records.

Exclusion criteria were as follows: (1) infections already active at the time of surgery; (2) antibiotic therapy started at least one week prior to surgery; (3) incomplete surgical or clinical records.

The study was conducted in compliance with the principles of the Declaration of Helsinki. Informed consent was obtained from every patient.

Data collection

Clinical charts, surgical, and pathological reports were reviewed

The following data were recorded: demographics, risk factors, and comorbidities, prior chemotherapy and/or radiation to the head and neck regions, histology, surgery duration, surgical resection type, reconstruction type, perioperative antibiotic and steroid therapy, surgical outcome (flap loss or partial necrosis), total duration of admission and intensive care unit (ICU) stay. We also recorded data from patients with malignant cancer including tumor staging according to the 8th American Joint Committee on Cancer - Tumor, Nodes, Metastasis classification,[5] eventual neoadjuvant therapies, and execution and type of laterocervical dissection.

The following variables were considered as risk factors: ASA score, smoking, and habitual alcohol consumption. Diabetes, hypertension, Chronic obstructive pulmonary disease dyslipidemia, and obesity (BMI > 30) were noted as debilitating comorbidities. Operative variables included surgery duration, tracheostomy, flap type, and neck dissection. The necessity for intra and/or postoperative blood transfusions was also noted as a potential risk factor.

Postoperative infectious complications were recorded as SSI and MPI. SSIs were defined according to Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network guidelines.[6,7]

MPIs included pneumonia and respiratory infections, urinary tract infections (UTIs), and bloodstream infections (BSIs).[4] UTI and BSI were defined according to the CDC criteria.[8,9] Pneumonia and respiratory infections were defined by the presence of new lung infiltrate and the clinical evidence that the infiltrate is of an infectious origin with symptoms including onset of fever, purulent sputum, leukocytosis, and decline in oxygenation, according to the American Thoracic Society and Infectious Diseases Society of America guidelines.[10]

All data on infectious complications were collected after crosschecking the medical charts of the patients and reports of all the microbiological tests performed on patients hospitalized in the Maxillo-Facial division.

Protocol for prevention of postoperative infections

In cases where a neoadjuvant therapy was necessary, surgery was performed after recovery from side effects that could increase the risk of infectious complications such as myelosuppression.

At hospital admission, personal and oral hygiene of the patients were checked. Trichotomy and a peripherally inserted central catheter (PICC) positioning were performed the day before surgery.

The institutional recommendations for antibiotic usage for perioperative prophylaxis in clean-contaminated head and neck surgeries during the analyzed period suggested amoxicillin-clavulanate as the first-line therapeutic agent; clarithromycin or ciprofloxacin was usually administered to patients with penicillin allergy.

All the patients were administered prophylactic intravenous antibiotics 1 h before incision and the antibiotics were re-administered intraoperatively based on the posology of the antibiotic used.

The surgical fields, including the face, oral cavity, neck, chest, and flap donor site, were prepped with povidone-iodine solution before the commencement of surgery.

All the procedures were performed by the same equipe consisting of 2 surgeons.

At the end of the procedure, low-pressure suction drains were inserted to prevent subcutaneous hematoma, exudates, and dead spaces in the neck and donor site.

All the patients were managed in an ICU for at least one day after surgery. Unless the cases presented with specific intraoperative complications, the patients were awakened and mechanical ventilation was interrupted in the operating room immediately after the surgical procedure ended.

Postoperative steroid therapy was administrated to patients who had undergone surgery before December 2020; since January 2021, no steroid therapy was administrated except in cases showing massive soft tissue edema. When tracheostomy was performed, the tracheal cannula was removed early in the first few days after surgery. Patients received red blood cell transfusion if their hemoglobin level was below 9 mg/dL.[11]

Drainage collection bags were changed every day until removal. Urinary catheter was removed when the patients were mobilized, usually on the third or fourth postoperative day. Sutures were removed 7-10 days after surgery. The patients were discharged with the PICC which was not removed until the histological report was available, to be eventually used for adjuvant chemotherapy.

In addition to the patient-specific measures, the authors' institution has a protocol for sanitizing the operation theater that consists of daily sanitization of all surfaces up to 2 m from the floor and a monthly deep disinfection protocol extended to the hard to reach surfaces.

Statistical analysis

The Chi-square test for categorical variables was used to compare the association between potential risk factors and incidence of infectious complications. For continuous data, Shapiro-Wilk normality test was performed to check if the variables followed a normal distribution. For normally distributed variables, Student's t-test was performed; and when the distribution departed significantly from normality, Mann-Whitney test was used. A value of $p < 0.05$ was considered significant. Analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

A total 298 reconstructive surgeries of the head and neck regions were identified. Among the 110 patients who underwent microvascular reconstruction, 10 patients were excluded because they did not meet other inclusion criteria. One hundred patients were included in the study 52 were male and 48 were female. The mean age was 62.3 years (range, 20-85 years; median, 63 years).

The majority of cases (75 patients—75%) underwent surgery for malignant tumor resection, the incidence of infectious complications was not significantly higher in this group of patients compared to that of patients affected by a benign pathology or requiring a secondary reconstruction (25 patients—25%) ($p = 0.1$; Table 1).

Infectious complications occurred in 24 patients (24%), Table 2 summarizes their sites and pathogens. Local infections were observed in 9 cases, systemic complications in 10 cases, while 5 patients had both local and systemic infections.

Table 3 summarizes the statistical correlations between patients characteristics, pathology, surgery, and infection rates.

There were 39 patients (39%) with at least one risk factor between smoking habits and alcohol consumption; furthermore, 55 patients (55%) were affected by one or more debilitating comorbidities, 19 patients had previous radiotherapy in the head and neck regions and 10 patients had previous chemotherapy (considering the five years preceding surgery): in 8 of these cases, the patients were affected by relapse of a previous tumor, while in 2 cases, chemotherapy was administered as neoadjuvant treatment. None of the characteristics mentioned above was associated with a higher risk of infection (Table 3).

Table 1 Summary of histopathologic characteristics of the disease.

Etiology	Total Patients *N* = 100	No. of Patients with Infections *N* (%)
Malignant disease	75	20 (26.7)
Squamous cell carcinoma	64 (85.3%; *n* = 75)	17 (26.6)
Other tumors	11 (14.7%; *n* = 75)	3 (27.3)
Ameloblastoma	10	3
Tumor resection sequelae	4	0
Trauma sequelae	2	1
Atrophy	3	0
Osteonecrosis sequelae	5	0
Osteomyelitis sequelae	1	0

Table 2 Summary of sites, characteristics, and pathogens of the reported infections.

Infection	Total Patients $N = 100$	Main Pathogen
Surgical site infections	14	*Klebsiella P.*, *S. Aureus*, *S. Costellatus* (28.6% each)
Tracheostomy	2	
Recipient site	12	
Medical postoperative infections	15	*Klebsiella* (28.6%), *Enterobacter aerogenes* (21.4%), *S. Costellatus* (14.3%)
Airway	9	
Sepsis	6	
UTI	1	*E. Coli*

Abbreviations. UTI: urinary tract infection.

A higher ASA score was found to be associated with a higher risk of infection (p = 0.01; Table 3).

In 5 cases the procedure was classified as "clean," since the oral cavity was not involved. The flap donor sites were fibula (45 cases), antero-lateral thigh flap (25 cases), latissimus dorsi (16 cases), radial forearm (12 cases), and iliac crest flap (2 cases); no statistical difference in the rate of infection between different donor sites was found (p = 0.4; Table 3). A titanium reconstruction plate was used in 47 patients. Tracheostomy was performed in 82 cases (82%), while neck dissection was necessary in 68 of the 76 patients (89.5%, 57 unilateral, and 11 bilateral dissections) with malignant oncologic diseases. No statistical association was found between the above mentioned factors and infective complications.

The average duration of surgery was 8.7 h (range, 5–15 h): longer operative times were found to increase the risk of infection (p = 0.03; Table 3). Intraoperative blood transfusion was necessary in 43 patients and did not influence the incidence of infections (p = 0.2; Table 3).

Antibiotic prophylaxis with amoxicillin-clavulanate was administered in 58 patients (58%), while 34 patients received piperacillin-tazobactam (34%). Eight patients who reported penicillin allergy received other antibiotics (e.g., clarithromycin or ciprofloxacin). Univariate analysis showed no statistically significant differences between the antibiotic prophylaxis schemes (p = 0.15). Postoperative steroid therapy was administered in 60 patients (60%) on an average for 7.2 postoperative days (range, 1–21 days). The administration of steroids and its duration did not appear to influence the incidence of infections (p = 0.8 and p = 0.5, respectively).

In 62 cases, blood transfusion was required postoperatively and resulted in increased risk of infection (p = 0.01); 18 of these patients underwent reconstruction using Antero Lateral Thigh flap, 28 using fibula flap, 7 using radial forearm flap, 8 latissimus dorsi flap, and 1 iliac crest flap; and more than a half of them (56.5%) were affected by malignant disease with advanced local extension (≥T3).

Considering the oncologic group of patients, 72.4% were affected mainly by T3-T4 stage tumors, whereas 51.5% (35 of the 68 cases) had N0 neck on which neck dissection was performed. Patients with advanced tumors (T3-4 or N ≥ 2a) were at a higher risk of infection (p = 0.03 or p = 0.02, respectively; Table 3).

The length of stay in ICU was on average 3.2 days (range, 1-40 days), with three extreme values of 14, 20, and 40 days in patients with multiple complications; on excluding these 3 patients, the mean ICU stay was 2.6 days (range, 1-9 days). The mean hospitalization time was of 28.4 days (range, 7–175 days) with three extreme values of 96, 105, and 175 days in patients with multiple complications. Mann-Whitman U test revealed that both ICU and total hospitalization time were found to be associated with higher incidences of infectious complications ($p < 0.05$; Table 4).

In 9 cases, a partial or total flap necrosis occurred; this complication was found to be more frequent, statistically, in patients with infectious complications (p = 0.001; Table 3).

Discussion

Postoperative infections are important causes of morbidity following major head and neck free-flap reconstruction. Multiple studies indicate that the rate of SSI when performing microvascular reconstruction of the head and neck regions varies in the range of 9.8-50%[11-22] and principal risk factors reported in literature include higher T classification, lymph node dissemination, bony flap insertion, operative duration, days with a tracheostomy in situ, and days with a recipient site drain tube in situ.[1] Per the CDC guidelines, patient characteristics associated with an increased risk of infectious complications include age, nutritional status, and diabetes.[6]

Although very few studies report the comprehensive incidence of MPI in the head and neck free-flap population (e.g., Tjoa et al.[4]—14%),[15] some studies have reported the incidence of each MPI (pneumonia, bacteremia/sepsis, septic shock, and urinary tract infection [UTI]; Table 5).[4,16-22]

The present study aimed to report the incidence of both SSIs and MPIs in a population of 100 patients who underwent head and neck free-flap reconstruction surgeries and to describe the comorbidities and possible risk factors that can influence their incidence.

Table 5 lists major studies that have reported the incidence of both SSI and at least one MPI in the head and neck free-flap population.

The present study found that MPIs occurred in 15% of patients and SSIs in 14% of patients. Pneumonia was the major MPI and occurred in 9% of patients, postoperatively; this is consistent with the incidences reported in literature (range 4.5–18.8%; Table 5).[16-23]

Table 3 Relationships between patient, pathology, and surgery-related characteristics and risk of infection.

Variable		No. of Patients ($N = 100$)	Infectious Complications n (%)	p-value*
Gender	M	52	10 (19.2)	0.2
	F	48	14 (29.2)	
Smoking habits	Yes	36	10 (27.8)	0.5
	No	64	14 (21.9)	
Habitual alcohol consumption	Yes	14	6 (42.85)	0.07
	No	86	18 (20.9)	
Obesity (BMI > 30)	Yes	12	2 (16.7)	0.5
	No	88	12 (13.6)	
Hypertension	Yes	36	11 (30.5)	0.2
	No	64	13 (20.3)	
Diabetes	Yes	15	1 (6.7)	0.08
	No	85	23 (27.05)	
COPD	Yes	7	3 (42.85)	0.2
	No	93	21(22.6)	
Dyslipidemia	Yes	23	5 (21.7)	0.8
	No	77	19 (24.7)	
ASA score	1-2	59	9 (15.25)	0.01
	3	41	15 (36.6)	
Previous CT	Yes	10	2 (20)	0.75
	No	90	22 (22.4)	
Previous head and neck RT	Yes	19	2 (10.5)	0.1
	No	81	22 (27.2)	
Malignant disease	Yes	76	21 (26.7)	0.1
	No	24	3 (12.5)	
Neck dissection	Yes	68	19 (27.6)	0.2
	No	32	5 (15.6)	
Type of surgery	Clean	5	1 (20)	0.8
Clean-contaminated		95	23 (24.2)	
Donor site	ALT	25	8 (32)	0.4
	Fibula	45	7 (15.5)	
	Radial forearm	12	4 (33.3)	
	Latissimus dorsi	16	4 (25)	
	Iliac crest	2	1 (50)	
Tracheostomy	Yes	82	21 (25.6)	0.4
	No	18	3 (16.7)	
Antibiotic prophylaxis	Amoxicillin-clavulanate	58	16 (27.6)	0.15
	Piperacillin-tazobactam	34	5 (14.7)	
	Other antibiotics	8	3 (37.5)	
Steroid postoperative therapy	Yes	60	15 (25)	0.8
	No	40	9 (22.5)	
Intraoperative blood transfusion	Yes	43	13 (30.2)	0.2
	No	57	11 (19.3)	
Postoperative blood transfusion	Yes	62	20 (32.25)	0.01
	No	38	4 (10.5)	
Flap necrosis	Yes	9	6 (66.7)	0.002
	No	81	18 (22.1)	
T stage ($N = 76$)	T1-T2	21	2 (9.5)	0.03
	T3-T4	55	19 (34.5)	
N stage ($N = 68$)	N0-N1	40	7 (17.5)	0.02
	N2-N3	28	12 (42.85)	

Abbreviations. ALT: Antero Lateral Thigh; BMI: body max index; COPD: chronic obstructive pulmonary disease; ASA: American Society of Anesthesiologists; CT: chemotherapy; RT: radiotherapy.
Underline values indicate that the correlation between the variable and the risk of infection has reached statistical significance.
* Chi-square test was conducted

Table 4 Characteristics of patient, pathology, and surgery and risk of infection - continuous data.

Variable	Overall Average	Patients with Infections (average)	Patients without Infection (average)	p-value
Age (years)	62.3 ± 14.1	60.1 ± 14.4	63 ± 14	0.18[a]
Duration of surgery (hours)	8.7 ± 2.2	9.4 ± 2.2	8.5 ± 2.1	0.03[a]
Duration of admission (days)	28.4	54.2	20.3	< 0.01[b]
ICU stay (days)	3.2	6	2.4	0.001[b]
Steroid therapy (days)	7.2	7.6	7.1	0.5[b]

Underline values indicate that the correlation between the variable and the risk of infection has reached statistical significance.
[a] Normally distributed variables: Student's t-test was performed.
[b] Variables with non normal distribution: Mann-Whitney U test was performed.

Table 5 Reports of postoperative SSIs and at least one MPI in patients who received major head and neck flap reconstruction.

Previous study	No of Free Flaps	Surgical Site Infection	Pneumonia	Bacteremia or Sepsis	Septic shock	UTI
Carniol et al.[16]	1204	13.95%	6.6%	3.7%	0.9%	1.2%
Kordahi et al.[17]	534	13.1%	7.1%	4.3%	0.6%	2.0%
Drinane et al.[18]	2322	9.8%	4.5%	3.6%	0.8%	1.2%
Ligh et al.[19]	855	13.6%	6.3%	4.1%	0.5%	1.8%
Khariwala et al.[20]	149	22.1%	18.8%	4%	N/A	N/A
Balamohan et al.[21]	266	42.5%	5.6%	N/A	N/A	4.1
Eskander[22]	515	11.65%	7.4%	N/A	N/A	N/A
Tjoa et al.[4]	540	10%	11.7%	0.7%	N/A	1.9%
Present study	100	14%	9%	6%	0%	1%

Abbreviation. MPI: medical postoperative infections; SSI: surgical site infection; UTI: Urinary tract infection

In our study, the incidence of BSI was 6%, which is higher than most single center and large database studies (range, 0.7-4.3%). Although BSI was not reported in two out of four single center studies considered, we did not record any case of septic shock, which occurred with an incidence in the range of 0.5-0.9% in other studies.

The incidence of UTI was 1%, which was lower than the incidence reported in all single centers and large databases in other studies.

In this study, the incidence of SSIs was of 14%, which was within the range of 3-41% reported in literature in clean-contaminated surgery of the head and neck regions[1] and a range of 9.8-50% was reported for microvascular reconstruction surgeries.

However, few studies report the incidence of SSI without antibiotic prophylaxis (range, 78-87%).[24,25]

In the present study, univariate analysis showed a statistical correlation with a high ASA score. On the contrary, no significant relationships were found between SSI and sex, age, BMI, debilitating comorbidities, smoking, and alcohol consumption.

Regarding specific disease characteristics, T and N stages showed a statistically significant influence on the incidence of infections. When the defects requiring resection become larger and more complex, the duration of surgery and exposure of the surgical field increases.[1]

According to literature, longer duration of surgery was significantly associated with a higher rate of infection.[1]

Regarding the perioperative antibiotic management in patients in the present study, no difference was found between the antibiotic prophylaxis schemes. From the current literature, it is evident that antibiotic prophylaxis is an important protective factor in reducing SSI incidence, despite controversies on which antibiotic is the gold standard for prophylaxis, especially when cancer surgery is considered. A recent meta-analysis by Iocca et al.[26] indicated that penicillins and cephalosporins as the best choice for antibiotic prophylaxis and that a longer course (> 48/72 h) is not advantageous when compared to a shorter course (< 48 h).[27]

Steroids, likewise, did not appear to influence the rate of infection. Complex surgeries often cause major blood loss and multiple blood transfusions may be required,[1] which could lead to higher risk of complications. The results of the present study confirmed the above mentioned statement. The observed results indicate that an adequate preoperative management of patient's blood allows the surgery to be carried out under the best possible conditions to reduce postoperative blood transfusion.

Despite this study showing a correlation between risk of infectious complications and duration of hospital and ICU stay, larger studies that include a multivariate analysis of these factors are needed; as one of the consequences, the duration of recovery could indicate an increased risk of infectious complications and higher incidence of flap failures.

Conclusion

Our experience shows that SSIs affect the global and surgical outcomes of the patient to the same extent as MPIs and both their incidences can be reduced with accurate pre- and postoperative management of the patient. This includes protocols for adequate disinfection of the patients and the operating room, correct administration of antibiotic prophylaxis, correction of potential risk factors such as anemia, and reduction in the duration of ICU and total hospital stay, along with the removal of potential sources of infection (such as central cenous catheter and tracheostomy) at the earliest. We believe that one limitation of this study, given the retrospective nature of the study, was that we could not analyze the role of preoperative nutritional status of the patients. Further prospective studies will be needed to underline the role of this additional preoperative variable.

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Ethical approval

This study was approved by the local Ethical Committee and the need for ethical approval was waived considering the retrospective nature of the study.

Declaration of Competing Interest

All authors have nothing to declare.

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