Original Article

Antibiotic Use in Patients Undergoing Complex Clean-Contaminated Head and Neck Surgery: A Prospective Study

Pierre Mestrallet[1], Antoine Yanni[1], Alain Roman[2], Alexandra Rodriguez[3], Cyril Bouland[1], Rokneddine Javadian,[1] Deborah Konopnicki[4], Didier Dequanter[1,3]

Departments of [1]Stomatology-Maxillofacial Surgery, [2]Intensive Care, [3]Otolaryngolology-Head & Neck Surgery, and [4]Infectious Diseases, CHU Saint Pierre, Université Libre de Bruxelles (ULB), Brussels, Belgium

Pierre Mestrallet and Antoine Yanni contributed equally to this work and should be regarded as joint first authors.

Deborah Konopnicki and Didier Dequanter contributed equally to this work and should be regarded as joint senior authors.

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ABSTRACT

Aims and Objectives: Oncological surgery of the upper aerodigestive tract is a complex procedure and often includes neck dissection and flap reconstruction. It can be complicated by severe surgical site infection (SSI) leading to flap necrosis, delayed wound healing, and increasing mortality and morbidity. The purpose of this study is to perform a systematic descriptive analysis and to evaluate the effect of our adapted antibiotic regimen strategy on postoperative outcomes. **Materials and Methods:** A prospective cohort analysis of 47 patients undergoing major clean-contaminated head and neck surgery was conducted at the Cervicomaxillofacial Surgery Department (Saint-Pierre Hospital), between 2019 and 2022. The patients were divided into two groups: group I, which received a short-term postoperative antibiotic regimen for 24 h, and group II, which received a more extended postoperative antibiotic course for more than 24 h. Antibioprophylaxy amoxicillin and clavulanate were administered intravenously 30–60 min before making the incision. The antibiotic regimen was continued after surgery. The prognostic significance of the antibiotic regimen on postoperative outcomes, including clinical signs of infection and biological markers such as white blood cells count, and C-reactive protein levels was evaluated using univariate analysis. **Results:** Eighteen patients developed SSIs. All of these infections were grade 2 and were treated with antibiotics. After univariate analysis, only a history of hypothyroidism seems to be a predictor of SSI (P = 0.038). No significant difference was found in terms of onset and hospital stay when we compared the patients who received antibiotics for 24 h or more. Moreover, the rate of multidrug-resistant bacteria was not different in both groups. **Conclusions:** Our results suggest that postoperative antibiotics for more than 24 h do not confer benefit in terms of SSI. Oncological patients undergoing complex clean-contaminated head and neck surgery are often suffering from infectious complications and, despite the absence of guidelines, practicians should consider these findings in their decision-making.

Keywords: *Antibiotic, head, neck, oncology, prophylactic, surgery*

Introduction

Oncological surgery of the upper aerodigestive tract is often a complex multistep procedure that includes major tumor resections, extensive bilateral neck dissection, and mostly vascularized tissue

Address for correspondence: Prof. Didier Dequanter, Department of Stomatology-Maxillofacial Surgery, CHU-Saint-Pierre, Université Libre de Bruxelles (ULB), 322 rue Haute, 1000 Brussels, Belgium.
E-mail: didier.dequanter@stpierre-bru.be

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reconstruction.[1-3] Surgery requires disrupting the mucosal lining of the upper digestive tract, increasing the bacterial contamination of the surgical site.[4] Infections, reported with a rate varying from 4% to 46% are serious complications that can result in delayed wound healing, fistula formation, and compromised tissue reconstruction increasing morbidity and mortality, resulting in increased hospital stay and healthcare costs.[5-14] Furthermore, surgical site infection (SSI) has the effect of delaying the adjuvant treatment, compromising the patient's prognosis.

Actually, many high-risk factors for infective complications based on cancer stage, tumor size, nutritional status, comorbid factors, type of surgery, and extent of reconstruction have been described and must be considered to assess the risk of infectious complications.[1-3]

Nowadays, the choice of prophylactic antibiotic therapy is generally a first- or second-generation beta-lactamase as the first line to cover Gram-positive and some Gram-negative organisms (*Escherichia coli*, *Klebsiella*, and *Proteus*).[13] The systematic review and meta-analysis published by Vander Poorten *et al.*[5] confirmed that this regimen of antibiotics was associated with the highest prevention rate of SSI.

Regarding the duration of the treatment reported in the literature, the authors suggest that antibiotic treatment for more than 48 h did not significantly reduce wound infections.[13-15] However, nowadays, there is no consensus on antibiotic regimen duration.

Historically, prolonged antibiotic prophylaxis associated with intravenous amoxicillin 1 g and clavulanate 200 mg, four times a day, was given for 5 days to patients undergoing flap reconstruction. In 2017, new Belgian national guidelines on surgical antibiotic prophylaxis were published recommending prophylaxis for 24 h maximum.[16] In 2019, a literature review was performed by our department in collaboration with the antibiotic stewardship team of our hospital, which led to the change in this procedure and to shorten the antibiotic prophylaxis from 5 days to a duration of 24 h maximum.

Because major complex oncological head and neck surgery with flap reconstruction can be complicated by severe SSI, including flap necrosis, we have performed a prospective analysis of intensive care patients who have undergone oncological surgery of the upper aerodigestive tract to evaluate the impact of our new strategy on SSI and the antibiotic-related side effects. Knowing that the results reached no consensus, the purpose of this study is to describe the infectious complications and to identify the risk factors most commonly associated.

Materials and Methods

Study population

This prospective study was conducted within the Cervico Maxillofacial Surgery Department. The study was approved by the Local Ethics Committee at CHU Saint-Pierre, Brussels, with reference O.M. 007. Clinical data of oncological patients were analyzed prospectively. Patients treated surgically for head and neck cancer between December 2019 and April 2022 were identified. Patients were included if they were over 18 and undergoing major clean-contaminated head and neck surgery as defined by the centers for disease control ands prevention (CDC), either with or without tissue transfer (pedicled or free flaps).[17] After a comprehensive assessment of these criteria, a total of 47 patients were enrolled in the investigation.

Surgical approach

An oral cavity swab was done preoperatively. On the day of the surgery, all patients underwent a manual brushing of dentition followed by routine antisepsis using povidone-iodine. During the surgery, primary-site resection was combined with neck dissection, making the oral cavity and the cervical wound communicate. All reconstructive procedures were carried out after tumor resection, and, as a prophylactic approach, patients received a combination of amoxicillin and clavulanate intravenously (1 g and 200 mg, respectively) four times a day, starting from 30 to 60 min before incision and continuing after surgery. Postoperative prophylaxis ranged from a brief 24-h period to a prolonged antibiotic course for more than 24 h.

Clinical characteristics

Patients were monitored closely for signs of infection until discharge. The characteristics of patients such as gender, age, high alcohol consumption (defined as more than two drinks per day for females and more than three drinks per day for males), high tobacco use (defined as more than 20 pack-year), tumor site, the TNM classification of malignant tumors (TNM) stage, preoperative body mass index (BMI), and American Society of Anesthesiologists (ASA) physical assessment were recorded. The eighth American Joint Committee on Cancer staging manual was used to determine the clinical tumor staging.

In our study, the presence of diabetes mellitus defined as a preoperative diagnosis of borderline or more severe diabetes mellitus (HbA1c > 7%) was considered

a risk factor comorbidity. Moreover, anemia defined as a hemoglobin concentration below 8.5 g/dL and hypoalbuminemia determined by serum albumin level below 4.0 mg/dL were considered in our analysis.

Previous treatments, including previous radiotherapy (defined as a radiation dose of 50 Gy or more to the cervical field), concomitant radiochemotherapy, and neoadjuvant chemotherapy, were reported. Examined perioperative factors included wound contamination level (dirty wound class or clean-contaminated), type of surgery, reconstructive procedures, and duration of operation were analyzed.

Additional perioperative variables recorded were the duration of perioperative antibiotic administration and the length of postoperative hospital stay following the surgery. Furthermore, the outcomes of bacterial cultures derived from infected fields were also examined.

According to the guidelines of the United States Centers for Disease Control and Prevention, the presence of purulent drainage from the incision or dehiscence or opening of the incision with signs or symptoms of infection, or organisms isolated from a culture of fluid from the incision defined an SSI.[17] The Clavien and Dindo classification was used to define the severity of the infective complications.[18] In the case of SSI, wound cultures were obtained from the infected site from swabs or excised tissue for aerobic and anaerobic cultures. Routine antibiotic susceptibility testing was performed for every pathogen isolated.

Statistical analysis

Descriptive statistics are summarized using numbers and percentages. The Shapiro–Wilk test was used to detect significant deviation from normality when continuous variables were used. To evaluate the difference in the duration of hospital stay between the two groups (<24 h and >24 h of prophylactic antibiotherapy), a Student *t* test was performed. To evaluate the difference between the two groups (infection and no infection), the Chi-square test or Fisher's exact test was performed as appropriate. The unequal distribution of participants in each group was considered in statistical analysis. Statistical tests were carried out using the IBM SPSS Statistics software (Chicago, United States). All reported *P* values are two-tailed and considered significant when less than 0.05.

Results

Patient characteristics

In our study, 47 patients underwent major oncological surgery of the upper aerodigestive tract. The age ranged from 20 to 89 years with an average of 63 years. Of the 47 patients, 36 (76.6%) were male and 11 (23.4%) were female. Thirty-five patients (74.5%) reported smoking habits. The majority of tumor locations included the oral cavity (n = 21) and the larynx and/or the hypopharynx (n = 15). Most of the patients (81%) presented with advanced stage (stages III–IV) head and neck cancers. BMI was more than 30 in 4 cases, between 25 and 30 in 3 cases, between 18.5 and 25 in 19 cases, and less than 18.5 in 9 cases. The most frequent ASA score was 3, accounting for 51.1%. There were 11 patients with debilitating comorbidities such as diabetes mellitus and/or hypothyroidism. Preoperatively, hypoalbuminemia was diagnosed in six cases.

Regarding the previous treatments, four patients had undergone radiotherapy, and two patients were treated with chemotherapy. Five of them had oncological recurrence, leading to the decision of surgical treatment.

In terms of the surgical procedure, reconstructive procedures involved free flaps in 11 cases, and a pedicled flap in 21 cases. Neck dissection was performed in 40 cases. The pathological diagnosis in the majority of cases was squamous cell carcinoma, accounting for 97% of the cases.

The patient characteristics are listed in Table 1.

Infectious outcomes

Thirty-two patients received 24-h antibiotic therapy, whereas 15 patients received antibiotic therapy for more than 24 h. SSI occurred in 18 cases, resulting in an infection rate of 38%. The onset of infection ranged from 4 to 20 days after surgery, with an average onset time of 9.3 days. According to the Clavien and Dindo classification, all of these infections were grade 2 and were treated with antibiotic therapy. The three commonest species were *Enterobacter cloacae* (34%), *Escherichia coli* (28%), and *Streptococcus viridans* (28%). A total of 12 cases were diagnosed with general infective complications, comprising eight case of pulmonary infections and four cases of urinary tract infections.

A thorough statistical analysis suggests that SSI was not significantly correlated to active smoking, diabetes, hypoalbuminemia, ASA score, TNM stage, history of previous treatment, tracheotomy, neck dissection, or the type of reconstruction. Only a history of hypothyroidism seems to be a predictor of SSI (P = 0.038) [Table 2].

In our study, we found no significant difference in terms of SSI and hospital stay when we compared the patients who received antibiotics for 24 h or more [Figure 1], and the statistical power of this result is 83%. Moreover,

Table 1: Patient characteristics

Variable	*n* (%)
Total number of patients	47 (100)
Gender	
Male	36 (76.6)
Female	11 (23.4)
Current tobacco use	
Yes	33 (70.2)
No	14 (29.8)
ASA	
ASA 1, 2	22 (46.8)
ASA 3, 4	25 (53.2)
Albumin level	
<40	35 (74.5)
>40	11 (23.4)
-	1 (2.1)
Diabete	
Yes	5 (10.6)
No	42 (89.4)
Hypothyroidy	
Yes	6 (12.8)
No	41 (87.2)
Previous radiotherapy	
Yes	4 (8.5)
No	43 (91.5)
Previous chemotherapy	
Yes	2 (4.3)
No	45 (95.7)
T status	
T1, T2	12 (25.5)
T3, T4	31 (66)
-	4 (8.5)
N status	
N0, 1	32 (68.1)
N2, 3	11 (23.4)
-	4 (8.5)
Tracheotomy	
Yes	36 (76.6)
No	11 (23.4)
Reconstruction type	
Primary closure	8 (17)
Pedicle flap	28 (59.6)
Free flap	11 (23.4)
Neck dissection	
Yes	40 (85.1)
No	7 (14.9)
Corticosteroid treatment	
Yes	2 (4.3)
No	45 (95.7)
Postoperative antibiotics	
Amoxicillin-clavulanate	43 (91.5)
Other	4 (8.5)
Post-operative antibiotics duration	
1 day	32 (68)
>1 day	15 (32)
Local site infection	
Yes	18 (38.3)
No	29 (61.7)

the rate of multidrug-resistant bacteria (including methicillin-resistant *S. aureus* and methicillin-resistant *S. epidermis*) among the 47 patients was 21%. Again, the rate was not different between these two groups of patients. *Clostridium difficile* colitis was observed in two patients receiving antibiotics.

Discussion

SSI is a frequent postoperative complication after head and neck surgery. The incidence of SSIs in patients undergoing head and neck surgery varies between 3% and 41%.[1,2] In our report, 38% of the patients who underwent a major complex oncological head and neck surgery developed SSI. The severity of SSI can range from mild, requiring local wound care and antibiotics to severe, requiring operations and possibly leading to death.[3] In our study, according to the Clavien and Dido classification, the majority of infective complications were classified as grade II, only requiring antibiotics.

According to the CDC guidelines, the patient characteristics considered a risk factor of SSI are age, nutritional status, and diabetes.[17] In this study, the univariate analysis did not confirm the previous reports. Moreover, a higher ASA score was not associated with a higher incidence of SSI. Furthermore, BMI and smoking were not determined as risk factors in our study. However, patients with hypothyroidism have a higher incidence of SSI. This has been observed in other studies reported in the literature.[8-20]

Regarding the tumor itself, the incidence of SSI was not associated with the size of the tumor. Moreover, the N status did not seem to be a predictor of SSI. In contrast to our results, Kohli *et al*.[6] demonstrated a statistical difference between the incidence of SSI and the size of the tumor resection even if this was not influenced by the N status.

In our study, according to the surgery, nor the tracheotomy, nor the type of the reconstruction, and nor the operative time was associated with a higher risk of infectious complications. Our results are different from those reported for the use of flaps since Kohli *et al*.[6] demonstrated the opposite in their study. Concerning the operating time, Kohli *et al*.[6] demonstrated the significant relation between the operating time and the rate of infection by integrating the National Nosocomial Infection Surveillance System, a useful tool for predicting postoperative infections.

Our research did not manage to find any significant association between a previous history of radiotherapy and SSI. Adverse effects of radiotherapy, particularly with radiation doses of more than 60 Gy, are demonstrated on different types of infections.[2]

Table 2: Predictors for local site infection, univariate analysis

Variable	Groups, *n* (%)—M (range)		OR (95% CI)	*P* value
	Infection	No infection		
Gender				
Female	2	9	0.278 (0.052–1.472)	NS
Male	16	20	Ref.	
Current tobacco use				
Yes	12	21	0.762 (0.213–2.724)	NS
No	6	8	Ref.	
Diabete				
Yes	3	2	2.7 (0.405–18)	NS
No	15	27	Ref.	
ASA				
1, 2	6	16	0.4063 (0.12 – 1.38)	NS
3, 4	12	13	Ref.	
BMI				
<25	9	18	0.61 (0.19–2.01)	NS
≥25	9	11	Ref.	
Albuminemia				
<32	4	12	0.36 (0.093–1.37)	NS
≥32	14	15	Ref.	
Hypothyroidy				
Yes	5	1	10.769 (1.14–101.721)	0.038
No	13	28	Ref.	
Previous radiotherapy				
Yes	4	0	18.31 (0.922–363.62)	NS
No	14	29	Ref.	
Previous chemotherapy				
Yes	1	1	1.65 (0.097–28.094)	NS
No	17	28	Ref.	
T status				
T1, T2	4	8	0.79 (0.195–3.214)	NS
T3, T4	12	19	Ref.	
N status				
N0, 1	10	22	0.379 (0.093–1.54)	NS
N2, 3	6	5	Ref.	
Tracheotomy				
Yes	16	20	3.6 (0.68–19.071)	NS
No	2	9	Ref.	
Reconstruction type				
Pedicle flap	9	19	0.47 (0.096–2.34)	NS
Free flap	5	6	1.2 (0.194–7.44)	
Primary closure	4	4	Ref.	
Neck dissection				
Yes	17	23	4.43 (0.49–40.34)	NS
No	1	6	Ref.	
Postoperative antibiotics				
Amoxicillin-clavulanate	15	28	0.179 (0.017–1.87)	NS
Other	3	1	Ref.	
Postoperative antibiotics duration				
1 day	12	20	0.9 (0.256–3.162)	NS
>1 day	6	9	Ref.	
Corticosteroids				
Yes	1	1	0.647 (0.096–28.1)	NS
No	17	28	Ref.	

CI = confidence interval, NS = nonsignificant, OR = odds ratio

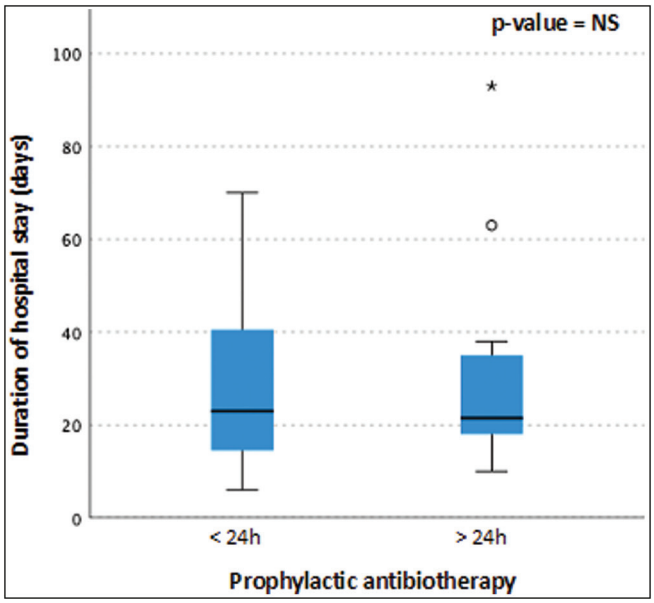

Figure 1: Box Plot—duration of hospital stay and duration of prophylactic antibiotherapy

However, in our cohort, the irradiated patients presented a higher rate of postoperative infection but that not reached statistical significance. This result must be interpreted with caution since only four patients previously had radiotherapy. However, preoperative radiotherapy seems not increase the risk of SSI.[2-4] Other studies do suggest a positive association between preoperative radiotherapy and SSI development.[21,22]

But, because the majority of published information regarding SSI development in patients with head and neck cancer has combined different surgical procedures with multiple surgical classifications, extrapolating risk factors and antimicrobial recommendations is challenging.

In our study, wound infection was polymicrobial in origin. The three commonest species were *Enterobacter cloacae*, *Escherischia coli*, and *Streptococcus viridans*. The bacterial agents found in other reports were, for some of them, nosocomial infection pathogens, such as methicillin-resistant Staphylococcus aureus (MRSA), *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, or other enteric bacteria.[5,6] The rate of SSI due to *Staphylococcus aureus* was low.[23] In their study, Fiedler *et al.*[7] estimated that approximatively 30% of head and neck surgical patients are colonized with *Staphylococcus aureus* preoperatively, of whom a minority have MRSA. Therefore, the authors advocated the use of preoperative topical antimicrobial decolonization but had no effect on the incidence of SSI.

The use of an antibioprophylaxy has shown to be effective in the prevention of infection in head and neck cancer patients undergoing surgery. Compared with placebo, perioperative antibiotics significantly reduce the risk of SSI and are, therefore, routinely used.[5-15] The rate of the postoperative SSI depends on the dosage and the duration of the prophylaxis.[23] The ideal choice must provide a coverage for Gram-positive aerobes, Gram-negative aerobes, and anaerobes.[5-20,23]

In general, a first-generation cephalosporin like cefazolin is the drug of choice; equally effective are amoxicillin-clavulanate and ampicillin-sulbactam, independent of the need for flap reconstruction.[8-12] In our study, the prophylactic antimicrobial treatment used was a combination of 1 g of amoxicillin and 200 mg of clavunate, four times a day, intravenously, starting from 30 to 60 min before incision and continuing after surgery. In our study, our choice proved to be consistent because the three commonest species were *Enterobacter cloacae*, *Escherichia coli* and *Streptococcus viridans*, sensitive to the prescribed antibiotic therapy.

Multiple studies evaluated the difference in SSI rate between short- and long-term prophylaxis.[11-21,23] Many studies showed that no statistically significant reduction in the SSI rate could be found in patients receiving prophylaxis for more than 5 days, compared with 1 day postoperatively.[11-21,23] Similarly, one study could not demonstrate a beneficial effect in patients receiving prophylaxis for 3 days compared with 1 day.[22] A recent review by Haidar *et al.*[23] concluded that less than 24 h of appropriate prophylaxis is likely sufficient. In our study, no higher incidence of infections was observed by the patients that received prophylactic antibiotics during 24 h. In our study, no difference in the rate of resistant species was observed, regardless of the duration of the antibiotic therapy. Moreover, the administration of antibiotics can lead to side effects. In our study, only two cases of enterocolitis due to *Clostridium difficile* were observed.

Mostly, surgeons tend arbitrarily to prolong postoperative antibiotics in patients with increased risk of complications, for example, after pharyngolaryngectomy with flap reconstruction or after pelviglossomandibulectomy in irradiated region with free flap reconstruction, or in patients with other risk factors including diabetes, increased BMI.[10-13] Our findings argue otherwise, supported by a recent systematic review by Khariwala *et al.*[9] and the conclusions of a recent meta-analysis.[5-9] However, this prospective study had some minor limitations regarding the less number of patients included and the lack of randomization between the two groups of patients.

Conclusion

To conclude, our results suggest that postoperative antibiotics for more than 24h do not confer benefit in terms of SSI. However, thyroid disorders appear to be predictors of

postoperative infection and should be integrated into the treatment decision. Oncological patients undergoing complex clean-contaminated head and neck surgery are often suffering from infectious complications, and, despite the absence of guidelines, practicians should consider these findings in their decision-making. Further prospective studies are warranted to confirm this recommendation and to examine the safety and efficacy of even shorter perioperative antibiotic courses.

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Conflicts of interest

There are no conflicts of interest.

Authors contributions

Not applicable.

Ethical policy and Institutional Review board statement

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Patient declaration of consent

Not applicable.

Data availability statement

The data that support the funding of this study are available at the Department of Surgery CHU Saint-Pierre, Brussels, Belgium.

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