

## Cephazolin and metronidazole prophylaxis in head and neck surgery

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### Abstract

A seven-day course of cephazolin and metronidazole chemoprophylaxis for clean-contaminated head and neck oncological procedures is compared to results with previously published antibiotic regimens. Aetiological factors associated with increased rates of wound complications are analyzed. Retrospective analysis of procedures over a six-year period was performed. The overall wound complication rate was 28.1 per cent, comparing favourably with previously published results. A major fistula was the most common complication with a rate of 9.2 per cent. Factors statistically associated with increased rates of wound complications included: radical neck dissection, extended surgical procedures requiring flap reconstruction, previous tracheotomy, and race. This is the largest single institutional study to show that a seven-day course of cephazolin and metronidazole is an effective chemoprophylactic regimen in head and neck surgery.

**Key words:** Antibiotics; Wound infection; Surgery; Head and neck neoplasms

### Introduction

A wound which enters the aerodigestive tract through the skin is contaminated. When created surgically, the wound is considered to be clean-contaminated. Contaminated and clean-contaminated wounds require antibiotic prophylaxis to reduce the rate of infectious post-operative complications (Johnson *et al.*, 1984). Various prophylactic antibiotic regimens for major head and neck oncological procedures have been investigated, and many differing conclusions have been reached regarding optimal choice and duration of chemotherapeutic prophylaxis. (Becker and Parell, 1979; Goode *et al.*, 1979; Becker, 1981; Suarez *et al.*, 1981; Brand *et al.*, 1982; Fee *et al.*, 1984; Johnson *et al.*, 1984; Panosetti *et al.*, 1987; Johnson and Yu, 1988; Robbins *et al.*, 1988; Saginur *et al.*, 1988; Friberg and Lundberg, 1990; Sawyer *et al.*, 1990). In all cases, the use of prophylactic antibiotic therapy has been shown to reduce the incidence of post-operative infection related wound complications, and has become the standard of care in clean-contaminated head and neck surgical procedures.

Ninety-six per cent of infections in clean-contaminated head and neck procedures have been found to have a polymicrobial aetiology (Johnson *et al.*, 1986). Ninety-one per cent of cultures have shown aerobic pathogens with *Staphylococcus aureus* and  $\beta$ -haemolytic *Streptococcus* spp. being the most common

isolates. Seventy-four per cent of cultures have isolated anaerobic pathogens with *Bacteroides* species being the most common. Several studies have demonstrated that Gram negative organisms are not important aetiological agents in head and neck infections following oncological procedures; however, some controversy still exists regarding their role in these cases. (Goode *et al.*, 1979; Johnson and Yu, 1988).

Based on the previous observations, we have chosen a prophylactic regimen of cephazolin and metronidazole in all cases involving clean-contaminated head and neck surgical wounds. Patients received a standard seven-day course of cephazolin 1.0 g intravenously every eight hours and metronidazole 500 mg i.v. or per nasogastric tube every six hours, with the first doses given on induction of anaesthesia. An initial study demonstrating the efficacy of a seven-day *versus* a two-day course of cephazolin and metronidazole for head and neck prophylaxis has been previously published from our institution. Based on a clinical trial of 50 patients, the study showed a statistically significant advantage for the seven-day course. (Sawyer *et al.*, 1990). The experimental rationale for the prolonged use of these antibiotics is discussed in that article. We now review our extended experience with this regimen. We report here all complications of infection and

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Presented at the Middle Section Meeting of the Triological Society, Omaha, NE, 22 January 1995.  
Accepted for publication: 9 May 1997.

factors associated with these complications, and compare our results with those of other regimens previously reported in the literature.

### Materials and methods

The records for 249 cases of clean-contaminated head and neck oncological procedures were reviewed for the period beginning in January 1987 and ending in June 1994. All procedures were performed at University Hospitals of Cleveland and the Wade Park Veterans Administration Medical Center. All patients received at least a seven-day course of cephazolin and metronidazole.

Information obtained from the hospital records included demographical data, tumour staging information, modes of prior treatment, nutritional and laboratory data, type and duration of surgical procedures, types of wound complications, length of hospital stay, and time to resumption of an oral diet, if applicable.

The data regarding wound healing and wound complications were classified according to recorded observations by the surgical team. Major fistulae and tissue necrosis were identified by the need for packing, dressing changes or surgical repair. A minor fistula was defined as either the appearance of a small dehiscence in the wound with saliva present which allowed only a cotton tip applicator to pass, or identification of a sinus tract on barium swallow, resolving without packing or surgical repair in less than one week. Cellulitis was identified by persistent erythema and induration of the wound without purulent discharge. Abscess was classified as a wound with drainage of frank pus, requiring opening of the wound and packing for resolution.

Chi-square and Fisher's Exact Tests were used to evaluate for statistical differences in categorical data and Student *t*-tests for continuous outcome data. Multivariate logistic regression was used to study the simultaneous and independent effects of predictor variables for wound complications. Backward selection was used for final model building. *P*-values less than 0.05 were considered statistically significant, and 95 per cent confidence intervals are shown for percentages and odds ratios.

### Results

The patients' mean age at the time of operative procedure was 61 years. There were 180 male patients and 69 female patients. Whites comprised 187 of the 249 patients, while blacks and other races

TABLE I  
OPERATIVE PROCEDURES

Primary procedures	Adjuvant procedures	
Total laryngectomy	92	Neck dissection 157
Composite resection	90	Flap reconstruction 72
Partial laryngectomy	36	Previous tracheotomy 34
Laryngopharyngectomy	28	Primary speech fistula 15
Pharyngoesophagectomy	3	

TABLE II  
CANCER SITES AND STAGING

Site of primary	Stage of disease	
Larynx	124	Stage I 24
Oral cavity	69	Stage II 54
Oral pharynx	34	Stage III 49
Hypopharynx	18	Stage IV 122
Thyroid	4	

comprised 62. The difference in mean age between white (61.9 years) and non-white (58.2 years) patients was statistically significant ( $p = 0.02$ ).

The primary and adjuvant procedures performed are listed in Table I. The sites and stages of disease are depicted in Table II.

Table III lists the number and types of wound complications encountered. The overall complication rate was 28.1 per cent, 70 out of 249, (95 per cent confidence level 22.6, 34.1). Major fistulae were seen in 9.2 per cent of cases and minor fistulae in 3.6 per cent. Demographic variables of sex, age, diabetes mellitus, the site of the primary tumour, and the use of pre-operative chemotherapy had no impact on rates of complication.

Table IV, A and B, lists the factors identified as having a statistically significant association with an increased rate of post-operative wound complications. Analysis was performed by univariate and multivariate logistic regression.

With univariate analysis the following had a significant association with the development of a wound complication: stage IV disease, myocutaneous flap use in reconstruction, radical neck dissection, prolonged surgical procedure, previous tracheotomy, recurrent tumour, low pre-operative haematocrit, weight loss, prior radiation therapy, and pharyngectomy or composite resection. Multivariate logistic regression analysis, however, only showed a significant association with the development of a wound complication with the following: radical neck dissection, myocutaneous flap use in reconstruction, previous tracheotomy and in whites undergoing surgery.

Patients experiencing non-wound related complications such as urinary tract infections and pneumonia had no differences in rate of wound complications. There was no drug toxicity to the agents observed, and no incidence of *C. difficile* colitis.

Excluding the patients staying in the hospital for post-operative radiotherapy, the average length of hospital stay was 15 days. Patients resumed an oral

TABLE III  
WOUND COMPLICATIONS

	Number	Per cent	95% Confidence interval
Major fistula	23	9.2	(5.9, 13.5)
Tissue necrosis	18	7.2	(4.3, 11.2)
Cellulitis	18	7.2	(4.3, 11.2)
Minor fistula	9	3.6	(1.7, 6.8)
Abscess	2	0.8	(0.1, 2.9)
None	179	71.9	(65.9, 77.4)

**TABLE IVA**  
FACTORS ASSOCIATED WITH INCREASED WOUND COMPLICATIONS BY UNIVARIATE ANALYSIS

Stage IV disease	$p = 0.0003$
Myocutaneous flap reconstruction	$p = 0.0001$
Neck dissection	$p = 0.002$
Prolonged surgical procedure	$p = 0.002$
Previous tracheotomy	$p = 0.008$
Tumour recurrence	$p = 0.02$
Low pre-operative hematocrit	$p = 0.03$
Weight loss	$p = 0.03$
Prior radiation treatment	$p = 0.04$
Pharyngectomy or composite resection	$p = 0.05$

**TABLE IVB**  
FACTORS ASSOCIATED WITH INCREASED WOUND COMPLICATIONS MULTIPLE LOGISTIC REGRESSION RESULTS USING BACKWARD ELIMINATION

Variable	Odds ratio	95% Confidence interval	$p$ -value
Neck dissection radical	3.96	(0.84, 8.53)	0.0004
Myocutaneous flap reconstruction	2.80	(1.42, 5.3)	0.003
Previous tracheotomy	3.04	(1.26-7.31)	0.01
Race black vs. white	0.41	(0.19, 0.91)	0.03

diet on the mean post-operative day 11.0. Patients who experienced post-operative wound complications had a hospital stay prolonged by 3.2 days and oral feeds delayed by 3.9 days, both differences being statistically significant ( $p = 0.001$ ). Seventeen of the 23 patients with major fistula did not resume oral diets prior to hospital discharge, and 12 of the 23 with fistula had hospital stays in excess of 30 days.

**Discussion**

Our overall wound complication rate of 28.1 per cent is comparable to results reported previously for chemoprophylaxis in head and neck oncological surgery, but greater than the 20 per cent rate reported by Sawyer *et al.* for the initial 25 patients studied using this seven-day regimen. (Sawyer *et al.*, 1990). Saginur reported a 33 per cent incidence of wound complications with Mandol, while Mandell-Brown reported an identical rate for cephalosporin alone. (Mandell-Brown *et al.*, 1984; Saginur *et al.*, 1988). Friberg, using benzylpenicillin and tinidazole, showed complication rates up to 75 per cent when all minor wound changes were reported (Friberg and Lundberg, 1990). Robbins reported an overall 9.5 per cent rate of wound infection using cephalosporin and metronidazole, but he included some clean cases in his study group, while reporting complications up to 33 per cent with contaminated cases (Robbins *et*

**TABLE V**  
ANTIBIOTIC COSTS

Cephalosporin (1 g)	\$17.74
Metronidazole (500 mg)	16.61
Gentamicin (80 mg)	17.02
Clindamycin (600 mg)	28.20
Benzylpenicillin (2 million units)	27.41

*al.*, 1988). Johnson reported rates of infection as low as seven per cent and four per cent with short- and long-term courses of clindamycin and gentamicin respectively, but generally included only fistulae and purulent wounds in his report (Johnson *et al.*, 1984). Therefore, overall infection rates vary as do the criteria for reporting complications of infection, the populations studied, and procedures evaluated.

We confirmed that use of myocutaneous flaps are associated with increased post-operative complications. We showed a 47 per cent wound complication rate for flap reconstruction, while Johnson reported a 37 per cent wound complication rate for these patients (Johnson *et al.*, 1984). We report on 72 flap reconstructions or 28 per cent of our population, while Johnson reported on 19 cases, representing 17 per cent of his population. In a multi-institutional study comparing one day versus five days cefoperazone for 109 high-risk flap reconstruction patients, Johnson showed no improvement with extended therapy with complications rates of 19 and 25 per cent respectively (Johnson *et al.*, 1986). Cole, in an extensive review of possible predictive factors for patients developing post-operative wound infections in head and neck surgery, found only tumour stage, nodal stage and duration of surgery to be statistically associated with increased infection rate (Cole *et al.*, 1987).

It is not clear why there is a decreased complication rate in our black population. The evaluation was controlled for by multivariate analysis. There is no previous study citing such a difference.

We demonstrated increased length of hospital stay with post-operative wound complications, confirming Mandell-Brown's findings (Mandell-Brown *et al.*, 1984). We also demonstrated delay in oral feedings, further emphasizing the increased cost of care for patients with post-operative wound complications.

The per dosage costs of the various antimicrobial agents at University Hospitals in-patient pharmacy are depicted in Table V. Overall the cost of our seven-day course of cephalosporin and metronidazole is roughly \$840, excluding nursing administration costs. A five-day course of gentamicin and clindamycin costs approximately \$680. Costs of administration are assumed to be similar for each agent, although any serum drug level monitoring for gentamicin would increase costs. Obviously, one- to two-day courses of either of these regimens are significantly less costly. However, the costs of continuing therapy in the event of a wound complication must be considered.

The constellation of factors shown to be associated with increased rate of wound complications can be grouped together in theory based on an advanced stage of disease requiring radical neck dissection and flap reconstruction. Our review shows that the cephalosporin and metronidazole chemoprophylaxis regimen is quite effective for less extensive operative procedures and less debilitated patients. We cannot comment, however, on whether the increased rate of wound complications in the high risk subset of patients could be affected by a different choice of

antibiotics, more intensive pre-operative rehabilitation, or some other means of intervention. However, it appears this regimen is as effective as other antibiotic prophylaxis regimens currently used and on which reports are available in the literature.

### Conclusion

We report our long-term experience with a seven-day course of cephazolin and metronidazole chemoprophylaxis in major clean-contaminated head and neck oncological procedures. To date this is the largest single institution study reporting on the prophylactic use of these antibiotics in such cases. This regimen is comparable or superior to others reported in the literature for controlling the rate of post-operative wound complications, but the complication rate is slightly higher in this updated experience than in the initial 25 patient study of this regimen. We conclude that this particular regimen is effective in preventing wound complications associated with clean-contaminated head and neck procedures, but that certain factors may place the patient at increased risk for wound complications, despite the effectiveness of the antibiotic prophylaxis regimen. These factors include: radical neck dissection, myocutaneous flap reconstructive procedures, previous tracheotomy, and race. In such patients it appears that other methods of prevention need to be investigated in an effort to reduce wound complication rates. These alternatives may involve nutritional intervention, addition of a third antimicrobial agent, possibly an aminoglycoside, or other as yet unknown intervention. Clearly, further study is indicated.

### Acknowledgments

We would like to acknowledge all members of the residency staff and faculty of the Department of Otolaryngology-Head and Neck Surgery of the Case Western Reserve University School of Medicine who participated in the care of these patients.

We would also like to express our appreciation to Steven J. Bowlin, D.O., PhD., Case Western Reserve University School of Medicine, for assistance in statistical analysis.

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