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Considerations for antibiotic prophylaxis in head and neck cancer surgery

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ABSTRACT

Peri/post-operative antibiotic prophylaxis (POABP) has become standard practice for preventing surgical site infections (SSI) in head and neck cancer patients undergoing microvascular reconstruction, but few data exist on optimal POABP regimens. Current surgical prophylaxis guideline recommendations fail to account for the complexity of microvascular reconstruction relative to other head and neck procedures, specifically regarding wound classification and antibiotic duration. Selection of POABP spectrum is also controversial, and must balance the choice between too narrow, risking subsequent infection, or too broad, and possible unwanted effects (e.g. antibiotic resistance, *Clostridium difficile*-associated diarrhea). POABP regimens should retain activity against bacteria expected to colonize the upper respiratory/salivary tracts, which include Gram-positive organisms and facultative anaerobes. However, Gram-negative bacilli also contribute to SSI in this setting. POABP doses should be optimized in order to achieve therapeutic tissue concentrations at the surgical site. Antibiotics targeted towards methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa* are not warranted for all patients. Prolonged POABP durations have shown no differences in SSI when compared to short POABP durations, but prolonged durations provide unnecessarily antibiotic exposure and risk for adverse effects. Given the lack of standardization behind antibiotic POABP in this setting and the potential for poor patient outcomes, this practice necessitates an additional focus of surgeons and antimicrobial stewardship programs. The purpose of this review is to provide an overview of POABP evidence and discuss pertinent clinical implications of appropriate use.

Introduction

The incidence of surgical site infections (SSI) in head and neck cancer patients undergoing microvascular free-tissue transfer remains high, despite routine peri/post-operative antibiotic prophylaxis (POABP) [1,2]. While surgical excision and use of free flaps has become mainstay treatment in complex head and neck cancers, the technical components of surgery (e.g. tumor resection, neck dissection, flap harvest and revascularization) contribute to multiple wounds with diverse microbial flora at high risk for SSI [1,3]. SSI in this setting add to significant patient morbidity and can include flap failure, fistula development, functional or cosmetic abnormalities, and death [4,5]. SSI also contribute to elevated healthcare expenditure from prolonged patient hospitalizations, thus potentiating additional complications (e.g. post-operative pneumonia, deep-vein thrombosis) that can delay post-surgical chemo- or radiotherapy [6]. Discrepancies in optimal POABP regimens and wound classifications, in addition to difficult infectious risk assessment, are obstacles in the determination of appropriate antibiotic management and the long-term outcomes of head and neck cancer patients who receive free-tissue transfer.

Ketcham et al. were first to describe decreased SSI when using perioperative chloramphenicol in head and neck cancer patients after extensive surgical reconstruction [7]. Subsequent literature has supported POABP use in head and neck cancer surgery [8–11], but few sufficiently describe best practices regarding spectrum and duration. The majority of published data are limited by comparisons of heterogeneous or obsolete antibiotic regimens, nonstandard wound or SSI endpoint definitions, and small patient samples. Furthermore, many studies were not designed to determine appropriate antibiotic spectrum or durations, or were performed without present-day advancements in surgical technique. These concerns ultimately make study results difficult to extrapolate to the general population. A summary of studies

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Table 1
Comparative studies of antibiotic prophylaxis after head and neck surgery, 1983–2017.

Source	Design	POABP spectrum or antibiotic duration	SSI outcomes	*P*
Piccart et al., 1983$_a$ [10]	RCT	Ticarcillin (n = 56) v. carbenicillin (n = 51)	11% vs. 8%	0.85
Piccart et al., 1983$_b$ [10]	RCT	Carbenicillin, 1 d (n = 72) v. 4 d (n = 68)	14% v. 10%	0.52
Piccart et al., 1983$_c$ [10]	RCT	Clindamycin, 4 d (n = 37) v. clindamycin + netilmicin, 4 d (n = 43)	16% v. 9%	0.58
Fee et al., 1984 [64]	RCT	Moxalactam, 1 d (n = 16) v. 2 d (n = 15)	0% v. 6.7%	NS
Johnson et al., 1986 [60]	RCT	Cefoperazone, 1 d (n = 53) v. 5 d (n = 56)	18.9% v. 25%	> 0.05
Johnson et al., 1988$_a$ [49]	RCT	Clindamycin, 1 d (n = 52) v. clindamycin + gentamycin, 1 d (n = 81)	3.4% v. 3.4%	NS
Johnson et al., 1988$_b$ [49]	RCT	Cefoperazone, 1 d (n = 39) v. cefotaxmine, 1 d (n = 32), v. placebo, 1 d (n = 9)	10% v. 9.4%. v 78%	N/A
Johnson et al., 1988$_c$ [49]	RCT	Cefazolin (n = 59) v. moxalactam (n = 59)	8.5% v. 3.4%	> 0.05
Gerard et al., 1988 [77]	RCT	Ticarcillin/clavulanic acid (n = 58) v. clindamycin + amikacin (n = 55), peri-operative only	36% v. 10%	< 0.05
Robbins et al., 1988 [44]	RCT	Cefazolin + metronidazole (n = 158) v. cefazolin (n = 172)	9.5% v. 18.6%	0.03
Phan et al., 1992 [78]	RCT	Clindamycin + amikacin (n = 43) v. ampicillin/sulbactam (n = 42)	21% v. 33%	0.19
Weber et al., 1992 [48]	RCT	Ampicillin/sulbactam (n = 105) v. clindamycin (n = 107)	13.3% v. 27.1%	0.02
Mustafa et al., 1993 [61]	RCT	Cefotaxime, 1 d (n = 30) v. 7 d (n = 30)	13% v. 10%	> 0.05
Righi et al., 1996 [62]	RCT	Clindamycin + cefonicid, 1 d (n = 81) v. 3 d (n = 81)	2.5% v. 3.7%	NS
Rodrigo et al., 1997 [46]	RCT	Amoxicillin/clavulanate (n = 57) v. clindamycin + gentamicin (n = 52) v. cefazolin (n = 50), peri-operative only	22.8% v. 21.2% v. 26%	0.8
Bhathena et al., 1998 [66]	RCT	Cefoperazone, 1 d (n = 28), v. cefotaxime, 5 d (n = 22)	7.1% v. 9.8%	NS
Coskun et al. 2000 [50]	OBS	Cefazolin + tobramycin, 7 d (n = 90) v. clindamycin, 1 d (n = 117)	30% v. 28%	0.777
Carroll et al., 2003 [67]	RCT	Clindamycin, 1 d (n = 35) v. 3 d (n = 39)	11% v. 10%	0.99
Skitarelic et al., 2007 [47]	RCT	Cefazolin, (n = 92) v. amoxicillin/clauvulanate (n = 97), peri-operative only	24% v. 21%	> 0.05
Liu et al., 2008 [34]	RCT	Clindamycin, 1 d (n = 26) v. 3 d (n = 27)	30.7% v. 18.5%	0.473
Lotfi et al., 2008 [24]	RCT	Multiple combinations ≤ 2 d (n = 187) v. > 2 d (n = 71)	34.9% v. 49.3%	0.032
Sepher et al., 2009 [25]	OBS	Cefazolin + metronidazole ≤4 d (n = 202) v. > 5 d (n = 205)	7% v. 13%	0.06
Mitchell et al., 2015 [53]	OBS	Multiple combinations, ≤1 d (n = 96) v. > 1 d (n = 331)	57% v. 42%	0.16
Mucke et al., 2015 [79]	OBS	Ampicillin/sulbactam (n = 88) v. penicillin, (n = 262), cefuroxime v. control, all for 10 d	19.3% v. 27% v. 25.9%	0.018
Pool et al., 2016 [51]	OBS	Clindamycin-containing regimens (n = 41) v. non-clindamycin-containing regimens (n = 225), all peri-operative only	26.8% v. 8.4%	0.001
Khariwala et al., 2016 [65]	OBS	Multiple combinations, ≤2 d (n = 64) v. > 2 d (n = 85)	23.4% v. 21.2%	0.74
Wagner et al., 2016 [2]	OBS	Multiple combinations without GN POABP (n = 15) v. multiple combinations with GN POABP (n = 102), durations varied	60% v. 27%	< 0.05
Cohen et al., 2016$_a$ [63]	OBS	Cefazolin + metronidazole, ≤2 d (n = 14) v. > 2 d (n = 44)	28.6% v. 15.9%	0.44
Cohen et al., 2016$_b$ [63]	OBS	Multiple combinations, ≤2 d (n = 28) v. > 2 d (n = 72)	35.7% v. 18.1%	0.07
Langerman et al., 2015$_a$ [36]	OBS	Ampicillin/sulbactam or cefazolin + metronidazole (n = 863) vs. clindamycin, (n = 287)	5.1% v. 17.4%; OR, 3.87; 95%CI, 2.31–6.49	NA
Langerman et al., 2015$_b$ [36]	OBS	Ampicillin/sulbactam or cefazolin + metronidazole (n = 863) vs. clindamycin + other combinations (n = 166)	5.1% v. 11.4%; OR, 6.45; 95%CI, 2.0–20.8	NA
Langerman et al., 2016 [62]	OBS	Ampicillin/sulbactam DOS v. DOS + 1 day	OR, 0.28; 95%CI, 0.13–0.61	0.01
Murphy et al., 2017 [52]	OBS	Clindamycin, (n = 22) v. multiple combinations (n = 80), durations varied	64% v. 33%	0.002
Bartella et al., 2017 [1]	RCT	Ampicillin/sulbactam, peri-operative (n = 25) v. 5 d (n = 25)	36% v. 4%	0.011

N = number of study participants; RCT = randomized controlled trial; OBS = observational; d = days; NS = not significant; N/A = not available; GN POABP = Gram-negative peri/post operative antibiotic prophylaxis; DOS = day of surgery; OR = odds ration; 95%CI = ninety-five percent confidence interval; NA = not available.

examining relevant antibiotic prophylaxis comparisons in head and neck cancer patients is described in Table 1.

Additional issues surround the potential for free-tissue wound misclassification and the subsequent impact on antibiotic prophylaxis trends. Surgical infection prophylaxis guideline recommendations fail to account for the complexity of wounds secondary to excising fungating tumors and free-tissue transfer relative to other head and neck surgeries [12–15]. This may contribute to discordance in national antibiotic prophylaxis prescribing habits, irrespective of guideline recommendations [16]. Further, limited data are available regarding risk factors for SSI with multi-drug resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*. This proves difficult for clinicians to guide informed therapeutic decisions and prevent potential antibiotic overexposure, which can ultimately lead to antibiotic resistance and other severe antimicrobial-related adverse effects [17].

This focused review provides updated information regarding evidence-based POABP use in head and neck cancer microvascular reconstruction. This includes SSI microbiology, POABP selection, dosing, and duration considerations, and challenges presented in the context of antimicrobial stewardship.

Literature search strategy

The following Medical Subject Headings terms were used to identify literature associated with this topic: “antibiotic prophylaxis”, “head and neck neoplasms”, “head and neck cancer”, “cancer of head and neck”, “cancer of the head and neck”, “free tissue flaps”, “free flap, microsurgical”. Subsequent broad key terms were searched using the PubMed database: “antibiotic prophylaxis head neck cancer”, “antimicrobial prophylaxis head neck cancer surgery”, “antibiotic prophylaxis free flap”. Other key terms were used according to each specific subsection of the review. The content and selection of articles included English language peer-reviewed literature derived from human studies, and included selections from 1962 until 2017. Case reports and case series were evaluated based on criteria supported in the literature and if they included at least 20 patients [18]. In the event of multiple and numerous publications identified from literature searches, priority was given to higher quality or more recently published articles in order to stay within publication reference limitations. Summative recommendations regarding POABP were made with the following designations based on the highest level of existing evidence: high, medium, and low.

Epidemiology of surgical site infections

Surgical site infections are the most common complication after extensive surgical resection of the head and neck, and occur in 13–51% of cases [2,19–23]. SSI are formally defined as infections of the incision, organ, or space that occur after a surgical procedure [12]. While risk