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Journal
Head & Neck, 40(2)

ISSN
1043-3074

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Publication Date
2018-02-01

DOI
10.1002/hed.24988

Peer reviewed

HHS Public Access

Author manuscript

Head Neck. Author manuscript; available in PMC 2019 April 30.

Published in final edited form as:

Head Neck. 2018 February ; 40(2): 417–427. doi:10.1002/hed.24988.

Antibiotic Prophylaxis in Clean-Contaminated Head and Neck Cases with Microvascular Free Flap Reconstruction: A Systematic Review and Meta-Analysis

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Abstract

Background: Optimal antibiotic prophylaxis duration in head and neck clean-contaminated free-flap (HNCCFF) cases is unknown.

Methods: Systematic review/meta-analysis conducted using Pubmed/MEDLINE, Cochrane Library, Web-of-Science, and Scopus.

Results: Of the 3755 searched articles, five articles were included for a total of 861 patients. The recipient surgical site infection (rSSI) risk was significantly higher in patients receiving prophylactic antibiotics for ≤24hrs compared to >24hrs (RR=1.56; 95%CI 1.13–2.14). In the post-hoc multivariate analysis based on available individual-level data on 697 patients from three studies, risk of SSI for ≤24hrs vs. >24hrs was not significant after adjusting for antibiotic type (RR=1.09; 95%CI 0.78–1.55). When compared to ampicillin-sulbactam, patients who received clindamycin prophylaxis had an increased likelihood of rSSI (RR=2.85, 95%CI 1.95–4.17).

Conclusions: Less than or equal to 24hrs antibiotic prophylaxis in HNCCFF is likely sufficient but a strong conclusion remains elusive. Clindamycin prophylaxis increases risk of rSSI. Further prospective trials are necessary to clarify.

Keywords

free flaps; microvascular surgery; clean-contaminated; prophylactic antibiotics; surgical site infection

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Presented at the American Head and Neck Society Meeting in Seattle, WA 2016; first place award in Microvascular/Reconstruction at the AHNS conference

Disclosures: The authors have no conflicts of interest to report

Introduction:

The need for antibiotic prophylaxis in head and neck cases has been well established in the literature.[1–5] A series of studies in the 1980s through the 2000s examined antibiotic prophylaxis in a variety of clean–contaminated head and neck procedures and suggested that (1) antibiotic prophylaxis reduced the risk of surgical site infections (SSI)[3–7] (2) prolonged prophylactic antibiotics do not generally result in reduced SSI[8–13] and (3) beta-lactam antibiotics are appropriate first-line agents, with clindamycin reserved for patients with beta-lactam allergies[3–5,7,14–17].

As a result of these studies, the Center for Disease Control (CDC) guidelines recommend that patients undergoing clean-contaminated head and neck surgery receive no further antibiotics after the incision is closed.[18] In 2003, the Surgical Care Improvement Project (SCIP) was introduced in a multiorganizational effort to improve surgical outcomes and reduce the incidence of SSI. The three main SSI related SCIP objectives include: (1) initiation of prophylactic antibiotics within one hour of surgical incision (within two hours for vancomycin or fluoroquinolones); (2) appropriate use of prophylactic antibiotics; and (3) cessation of prophylactic antibiotics within 24 hours of the surgical end time.[19] These guidelines, along with those by the American Society of Health-Systems Pharmacists (ASHP), recommend use of perioperative antibiotics for head and neck surgical procedures; however, maintaining antibiotics beyond 24 hours is not recommended.[19] Recommended agents for clean-contaminated cases include cefazolin or cefuroxime plus metronidazole, ampicillin-sulbactam, or, in cases of penicillin allergy, single agent clindamycin.[19]

The use of microvascular free tissue transfer has allowed complex head and neck defects to be reconstructed reliably with an overall flap survival rate of 95% or greater.[20–23] However, flap reconstruction is a significant independent risk factor for recipient SSI (rSSI) in clean-contaminated head and neck operations.[12,24–27] Though SSI is detrimental in any head and neck case, rSSI can be even more devastating in cases of free flap reconstruction due to the risks of flap failure, resultant prolonged hospitalization, oro- or pharyngocutaneous fistula, and need for additional surgery.[28,29] Despite recommendations from the CDC[18], SCIP[19], and ASHP[19] recommending against administration of prophylactic antibiotic therapy beyond 24 hours, postoperative antibiotics are often maintained in patients at the clinician's discretion[30], with many clinicians administering >24 hours of prophylactic antibiotics in cases of flap reconstruction. There is likely little agreement on antibiotic prophylaxis in this population due to the lack of explicit recommendations given for head and neck clean contaminated free flap (HNCCFF) cases.

The aim of our study was thus to 1) systematically review the literature regarding use of prophylactic antibiotics in patients undergoing microvascular free-flap reconstruction for clean-contaminated head and neck defects, 2) perform a meta-analysis of eligible studies to compare short duration versus prolonged prophylactic antibiotics as a means of reducing postoperative SSI. We secondarily performed an exploratory post-hoc analysis to determine if antibiotic type or duration plays a role in rSSI or donor site SSI (dSSI) risk, risk of dehiscence/fistula, distant infections (pneumonia or UTI), methicillin-resistant staphylococcus aureus, and *Clostridium difficile* infections.

Methods/Literature Search:

This study was exempt from review by our institutional review board as this was a systematic review and meta-analysis of publically available articles. Throughout the study, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was followed.

Search Strategy

Two authors (YH and PT) independently reviewed the literature for studies presenting data on antibiotic prophylaxis in HNCCFF cases. The search was initiated on March 9, 2016, with an update through December 1, 2016 in Pubmed/MEDLINE, Scopus, The Cochrane Library, and Web of Science from the inception of each database. The detailed search strategy performed is shown in Supplementary Table 1. Finally, we examined the reference lists of all relevant publications to locate additional studies meeting our eligibility criteria.

Study Selection and Data Extraction

Inclusion and exclusion criteria is demonstrated in Table 1. The search method and results of the search is shown in Figure 1. The authors of all manuscripts meeting these criteria were contacted three times in an effort to obtain their raw data. If there was no response, the raw data was not available, or the information in the manuscript was insufficient for analysis, the study was excluded. If the data reported in the manuscript was sufficient for analysis, the study was still included, regardless of author response. The Cochrane CFGD November 2004 study selection, quality assessment, and data extraction form was used to assess study quality and extract the pertinent data from each manuscript that met inclusion criteria. Ultimately, five studies were appropriate for inclusion.[31–35] From the identified studies, we extracted relevant clinical information regarding the number of patients receiving short term (≤24 hours) prophylactic antibiotics, the number of patients receiving long term (>24 hours) prophylactic antibiotics, and the risk of rSSI. For studies reporting secondary endpoints of interest in the obtained raw data, we also extracted information of antibiotic type, rates of distant infections (urinary tract infections [UTI] or pneumonia), rates of methicillin-resistant staphylococcus aureus (MRSA) infections, and rates of *Clostridium difficile* (*C. diff*) gastrointestinal infections in the groups of patients receiving ≤ 24 hours and > 24 hours of prophylactic antibiotics.

Statistics

The null hypothesis for this study is that prolonged (> 24 hours) prophylactic antibiotic administration has no effect on the risk of rSSI in HNCCFF cases. A meta-analysis was used to examine this hypothesis based on five published studies[31–35] meeting inclusion/exclusion criteria. For each study, the relative risk (RR) and 95% confidence interval (CI) were calculated, where RR refers to rSSI risk in short term group relative to rSSI risk in long term group. A p-value of < 0.05 was considered statistically significant. Mantel-Haenszel methods under the fixed-effect model were designated as the primary analysis and the random-effect model as a secondary analysis.[36] Tests for heterogeneity of RRs were conducted based on the Chi-square (χ^2) test (Woolf method) to assess variation of effect across studies.[37,38] The primary comparison measured the risks of rSSI in patients receiving

≤24 hours of prophylactic antibiotics compared >24 hours. Secondary comparisons, planned *a priori*, were also performed to compare the risks of rSSI when excluding those receiving greater than seven days of antibiotics and when comparing groups receiving ≤48 hours of prophylactic antibiotics compared to >48 hours. We chose to perform a secondary analysis excluding those receiving greater than seven days of antibiotics, as this population was thought to potentially be receiving continued therapy for a suspected rSSI not otherwise documented (i.e, in response to leukocytosis or clinical signs not meeting criteria for a rSSI).

Given the results of the primary meta-analysis which differed from our study's null hypothesis, we further sought to correct for antibiotic type and determine if there continued to be an effect on antibiotic prophylaxis duration on rSSI. Antibiotic type was chosen as a variable because it has been previously shown in multiple studies, including that of the largest study in our meta-analysis[33], to affect the risk of rSSI. We also further wished to determine in this post-hoc analysis whether antibiotic duration can affect further post-surgical outcomes, including risk of dSSI, distant infections (UTI or pneumonia), dehiscence/fistula, C. *diff*, and MRSA. Post-hoc analyses were performed on a subset of three studies[32,33,35] in which individual-level data was available from the original authors to determine the impact of antibiotic type on the risk of rSSI in the short (≤24 hours) vs. long duration (>24 hours) prophylactic antibiotic groups. Mixed effect logistic regression model with a study random effect (to account for correlation within study) was used to assess the association between rSSI and antibiotic type, duration (≤24 hours vs. >24 hours) as adjusting covariate. Effect modification of antibiotic type was also examined by adding the interaction term of antibiotic type and duration. Similarly, post-hoc analyses of secondary outcomes, included dSSI, distant infections and dehiscence/fistula. Statistical analyses were performed using SAS version 9.4 (Cary, North Carolina) and the R software package "metaphor" (Vienna, Austria 2013).

Results:

Results of Systematic Review

The sequence of review and exclusion of studies is summarized in the flowchart shown in Figure 1. The initial search yielded 3127 articles. The subsequent review of reference lists of these yielded an additional 628 articles for a total pool of 3755 articles reviewed. The results of our electronic literature search and cross-referencing yielded three retrospective studies (level III of evidence),[33–35] one prospective cohort study (level III of evidence)[32], and one randomized controlled clinical trial (level II of evidence)[31], for a total of 5 studies meeting inclusion criteria with sufficient available data to proceed with a meta-analysis [Table 2]. Four of the studies[32–35] required the raw data for inclusion in the meta-analysis, while one study[31] did not have available raw data but had sufficient data within the manuscript for inclusion. Three of those four studies had information available for a post-hoc analysis with individual-level data available, which included additional information about antibiotic type and risk of dSSI, distant infections, dehiscence/fistula, C. diff, and MRSA.

Primary Analysis of Short vs. Long Term Antibiotics on Risk of rSSI

The overall percentage of rSSI ranged from 6.6% to 22.1%. The results of the random and fixed effects model of the meta-analysis performed on the five included studies regarding the four utilized definitions of short-term and long-term antibiotic prophylaxis is demonstrated in Table 3. The risk of rSSI was significantly higher in short term group (≤ 24 h) compared to long term group antibiotic prophylaxis use (> 24 h) in the fixed effect model: RR: 1.56 (95% CI: 1.13–2.14), with minimal heterogeneity in the results ($\chi^2 = 1.62$; p=0.8059; Table 4). The sensitivity analysis of rSSI risk based on the random effect model showed a similar result (RR: 1.60, 95% CI: 1.17–2.20); see Table 3. Other analyses which examined antibiotic prophylaxis use durations yielded a similar conclusion that risk of rSSI is lower with longer duration of antibiotic prophylaxis use, even when examining short term prophylaxis as ≤48 hours or when excluding patients who had greater than seven days of antibiotic prophylaxis (Figure 2, Table 3). There was similarly no significant evidence of heterogeneity across studies (Table 4).

Post-hoc Analysis Evaluating Effect of Antibiotic Type on rSSI

Given the findings of a statistically significant reduction in rSSI among those receiving prolonged antibiotic therapy which differed from our null hypothesis, we performed a post-hoc multivariate analysis to determine whether antibiotic type was associated with rSSI, dSSI, distant infections, dehiscence/fistula, MRSA, and *C. diff* infections. Individual-level data was required for this analysis and was available and obtained from the authors of 3 studies.[32,33,35] A total of 697 patients from these were included. Antibiotics were characterized into three groups: 1) ampicillin/sulbactam (69.2%), 2) clindamycin (24.3%), and 3) others (6.6%), which included clindamycin/levofloxacin, clindamycin/vancomycin, levofloxacin, vancomycin, cefazolin, Ampicillin-sulbactam/clindamycin, clindamycin/cefazolin, levofloxacin/metronidazole, cefepime/metronidazole, ampicillin-sulbactam/piperacillin and tazobactam, piperacillin and tazobactam, ampicillin-sulbactam/ciprofloxacin, ciprofloxacin/metrondiazole, ampicillin-sulbactam/metronidazole, vancomycin/piperacillin and tazobactam, or clindamycin/levofloxacin/vancomycin/fluconazole. No individual antibiotic group within the “others” category contained a sufficient number of patients to be analyzed separately and were thus grouped together.

The overall percentage of rSSI in this population was 16.9%. As shown in Table 5, mixed effect logistic regression model demonstrated no statistically significant difference in rSSI when comparing ≤ 24 hours to >24 hours of prophylactic antibiotics after accounting for antibiotic type (RR = 1.09, 95% CI 0.78 – 1.55, p = 0.6082). When compared to ampicillin-sulbactam, patients who received clindamycin prophylaxis had an increased likelihood of rSSI (RR = 2.85, 95% CI 1.95–4.17, p < 0.0001).

Post-hoc Analysis of Secondary Outcomes

As seen in Table 5, the overall percentage of dSSI in this population of 697 patients was 10.6%, dehiscence/fistula was 17.9%, distant infection (pneumonia or UTI) was 17.9%, MRSA was 6.2%, and *C. diff* was 1.6%. Due to the low prevalence of *C. diff*, further analysis of this outcome based on antibiotic type and duration was not performed. There was no association between antibiotic duration and development of dSSI, dehiscence/fistula, or

distant infections (pneumonia or UTI). However, when compared to ampicillin-sulbactam, patients who received clindamycin prophylaxis had an increased risk of dehiscence/fistula (RR = 2.51, 95% CI 1.86 – 3.39, p < 0.0001), distant infections (RR = 2.20, 95% CI 1.52 – 3.17, p < 0.0001), and MRSA infections (RR=2.13, 95% CI 1.16–3.91, p=0.0154). On the contrary, patients on clindamycin prophylaxis demonstrated lower risk of dSSI (RR = 0.39, 95% CI 0.19 – 0.77, p = 0.0069). We also examined the sensitivity of the results when excluding the "other" antibiotic category. The sensitivity analysis results were similar and consistent to that with all antibiotic categories (Supplementary Table 2).

Discussion:

While the meta-analysis of the five initial studies found a lower risk of rSSI with prolonged antibiotic administration, this effect appears to have been modified by antibiotic type when individual level data is included. Patients undergoing microvascular free flap reconstruction of clean-contaminated defects present a unique challenge not encountered during routine clean-contaminated cases. Many studies have demonstrated an increased risk of wound infections with flap reconstruction,[12,24–27] most of which demonstrated an infection risk approximately 2.2–2.8 times higher than other clean contaminated oncologic cases.[24,25,27] Proposed reasons for this increased risk for rSSI in this patient population include increased contamination of the recipient site with salivary and respiratory secretions, theoretically decreased vascularity of the donor tissue at the new recipient site, and potentially increased postoperative soft-tissue dead space.[12,24–27,39] The inherent risk factors of this patient population and this surgery can also contribute to an increased risk of SSI.[39] These risk factors include a higher patient American Society of Anesthesiologist's (ASA) score, increased duration of surgery, increased tendency for intraoperative blood loss, and increased preoperative T classification which can increase surgical invasiveness and postoperative soft tissue dead space.[39] Most clinicians agree that antibiotic prophylaxis should be administered perioperatively in HNCCFF cases, with studies demonstrating a significantly increased risk of SSI when prophylactic antibiotics are not administered.[40] However, there is a lack of clinician agreement on the optimal duration of antibiotic prophylaxis in these cases. While our initial meta-analysis revealed a difference in risk of rSSI based upon duration of antibiotic usage, this difference was no longer significant when type of antibiotic utilized was evaluated in multivariate analysis performed on raw data from the three largest studies. In this multivariate analysis, there was no difference in the risk of rSSI, dSSI, dehiscence/fistula, distant infections (pneumonia or UTI), or MRSA infections when antibiotics are administered for >24 hours compared to ≤ 24 hours. While a strong conclusion regarding optimal duration of antibiotic prophylaxis in HNCCFF cases remains elusive, the results of this analysis suggest that ≤24 hours of appropriately chosen antibiotic prophylaxis is likely sufficient in HNCCFF cases, especially when considering the risk of prolonged antibiotic administration.

Perioperative antibiotic regimens aim to provide adequate coverage of common oral flora, including Streptococci, Staphylococci, Bacteriodies, Peptostreptococcus, Prevotella, and Fusobacterium species and Enterobacteriaceae.[19,41] The ASHP guidelines advocate the use of prophylactic cefazolin with metronidazole, cefuroxime with metronidazole, or ampicillin-sulbactam for oncologic clean-contaminated head and neck surgery. The guidelines also

suggest the use of clindamycin in patients with a beta-lactam allergy.[19] At present, according to ASHP guidelines, any one of these regimens are considered adequate perioperative therapy in the prevention of SSI in clean-contaminated head and neck cases. In our analysis, clindamycin carried a 2.85 times increased risk of rSSI and 2.51 times increased risk of dehiscence/fistula when compared to ampicillin-sulbactam. Interestingly, a protective effect on dSSI was seen with clindamycin administration, which we could not fully explain. While clindamycin should have adequate gram-positive coverage at the donor site, we would not expect this coverage to be better than ampicillin-sulbactam and thus the reason behind this statistical result is unclear. However, given the increased risk of rSSI with clindamycin prophylaxis, the authors of this study would suggest a modification to the ASHP guidelines such that additional gram negative coverage is administered in HNCCFF cases in patients with beta-lactam allergy.

Previous studies have similarly suggested an increased risk of rSSI with prophylactic clindamycin compared to ampicillin-sulbactam in clean-contaminated head and neck cases[15,29,33,35,42–45], although this association was not demonstrated in all studies.[16] SSIs in head and neck clean contaminated cases are often polymicrobial[46] and can include gram negative aerobic bacteria (e.g. Escherichia coli, Klebsiella pneumoniae, or Pseudomonas aeruginosa) for which clindamycin does not offer coverage.[47] Furthermore, elevated or increasing clindamycin resistance of methicillin-resistant and methicillin sensitive Staphylococcus aureus (40%−45%)[48] and Bacteroides (34%−47%)[49] has been reported. Lastly, patients with head and neck squamous cell carcinoma of the upper aerodigestive tract, which comprise a large subset of the population requiring microvascular reconstruction, harbor increased levels of intra-oral gram-negative bacteria[50], suggesting that they may require broader prophylaxis, for which clindamycin is not sufficient.

While ampicillin-sulbactam is the most common choice of antibiotic for prophylaxis in HNCCFF cases, clindamycin alone continues to be used among clinicians. Clindamycin is typically used by clinicians in cases of penicillin allergy. However, a true penicillin allergy is present in only 10% of the population who report an allergy.[51] Thus, in 90% of patients reporting an allergy, a beta-lactam antibiotic can likely be safely administered. Allergy confirmation or desensitization in patients with a possible beta-lactam allergy can be performed but may be unrealistic depending on the circumstances. At the very least, given the increased risk of rSSI with clindamycin prophylaxis demonstrated in this meta-analysis and several other studies, administration of an additional antibiotic with increased gram-negative coverage should be considered in penicillin allergic patients.

Based on the available literature, including the data available from this systematic review and meta-analysis, we would suggest that ≤ 24 hours of appropriately chosen antibiotic prophylaxis is likely sufficient in HNCCFF cases. However, the finding of the meta-analysis on five includable studies that > 24 hours of antibiotic administration offered a protective effect against rSSI is difficult to completely ignore. Future studies into duration of antibiotic prophylaxis in these higher risk cases may ultimately demonstrate a protective effect of prolonged antibiotic administration. However, at this point, all available data would suggest that the patient population receiving free flap reconstruction of head and neck clean contaminated defects should receive similar duration antibiotic prophylaxis (≤ 24 hours) as

other clean contaminated head and neck cases, despite the increased risk factors for infection seen in this patient population. This study was able to demonstrate with greater certainty that clindamycin as single drug therapy is associated with an increased risk of rSSI, dehiscence/fistula, MRSA, and distant infections when compared to ampicillin-sulbactam. Thus, the authors of this study would suggest that clindamycin antibiotic prophylaxis is inadequate in HNCCFF cases.

As with many systematic reviews and meta-analyses, we are limited by the available data of the current literature and unable to testify to the quality of the data obtained. Our data rests on individual case-control or retrospective case series with small sample sizes. In addition, inherent to all systematic reviews is the limitation that includable studies could be missed, despite authors' best efforts to be thorough and comprehensive. The evaluation of the risk of SSI with the use of prophylactic antibiotics is best addressed with prospective randomized clinical trials.

In addition, many studies in the current literature do not use a uniform definition of SSI. The CDC defines SSI as an infection occurring within 30 days of surgery and including at least 1 of the following: (1) purulent drainage from the incision; (2) an incision that spontaneously dehisces or is deliberately opened by a surgeon and is culture positive or not cultured and the patient has clinical signs of infection (fever and/or localized pain or tenderness); (3) an abscess or other evidence of infection involving the deep tissue that is detected on gross, anatomic, or histopathologic examination or imaging; or (4) diagnosis of SSI made by the surgeon.[52] All but one study in our meta-analysis used this definition for SSI.[31] Furthermore, we must assume that antibiotics were given on time and dosed appropriately to achieve therapeutic steady-state concentrations.[34]

Additionally, this type of analysis precluded our ability to adjust for preoperative risk factors that can affect the rates of SSI, such as body mass index, diabetes mellitus, tracheotomy, length of surgery, or history of radiation. This lack of uniformity makes it difficult to standardize the risk of SSI in head and neck clean contaminated cases, especially when subjectivity and variability may exist with respect to the surgeon's ability to definitely identify and document an SSI.

Conclusion:

While a strong conclusion regarding optimal duration of antibiotic prophylaxis in HNCCFF cases remains elusive, the results of this analysis suggest that ≤24 hours of appropriately chosen antibiotic prophylaxis is likely sufficient in HNCCFF cases, especially when considering the risk of prolonged antibiotic administration. In this analysis, clindamycin prophylaxis was noted to be inadequate when compared to ampicillin-sulbactam in HNCCFF cases. Prospective randomized clinical trials that are adequately powered to examine the duration and type of antibiotic prophylaxis are needed to better clarify the question of optimal duration of antibiotic prophylaxis in clean-contaminated head and neck microvascular cases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was partially supported by grant UL1 TR001414 from the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), through the Biostatistics, Epidemiology and Research Design Unit. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Funding: None

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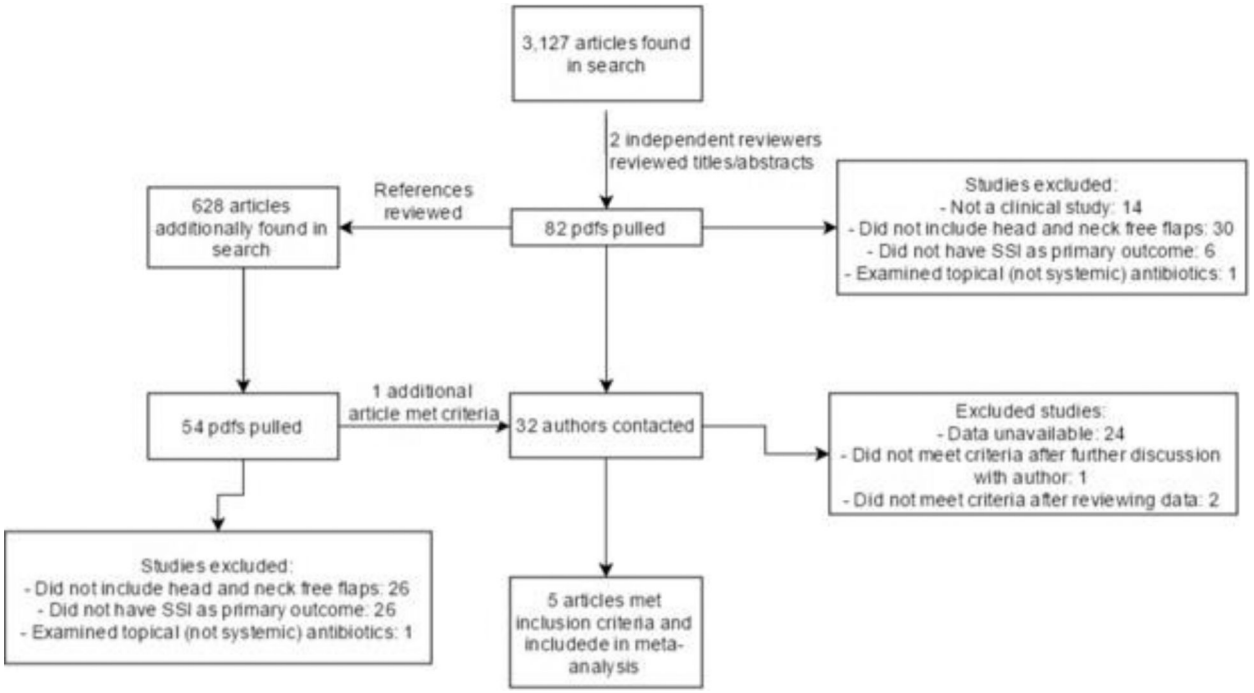

Figure 1:
Flow diagram of study inclusion process for the meta-analysis.

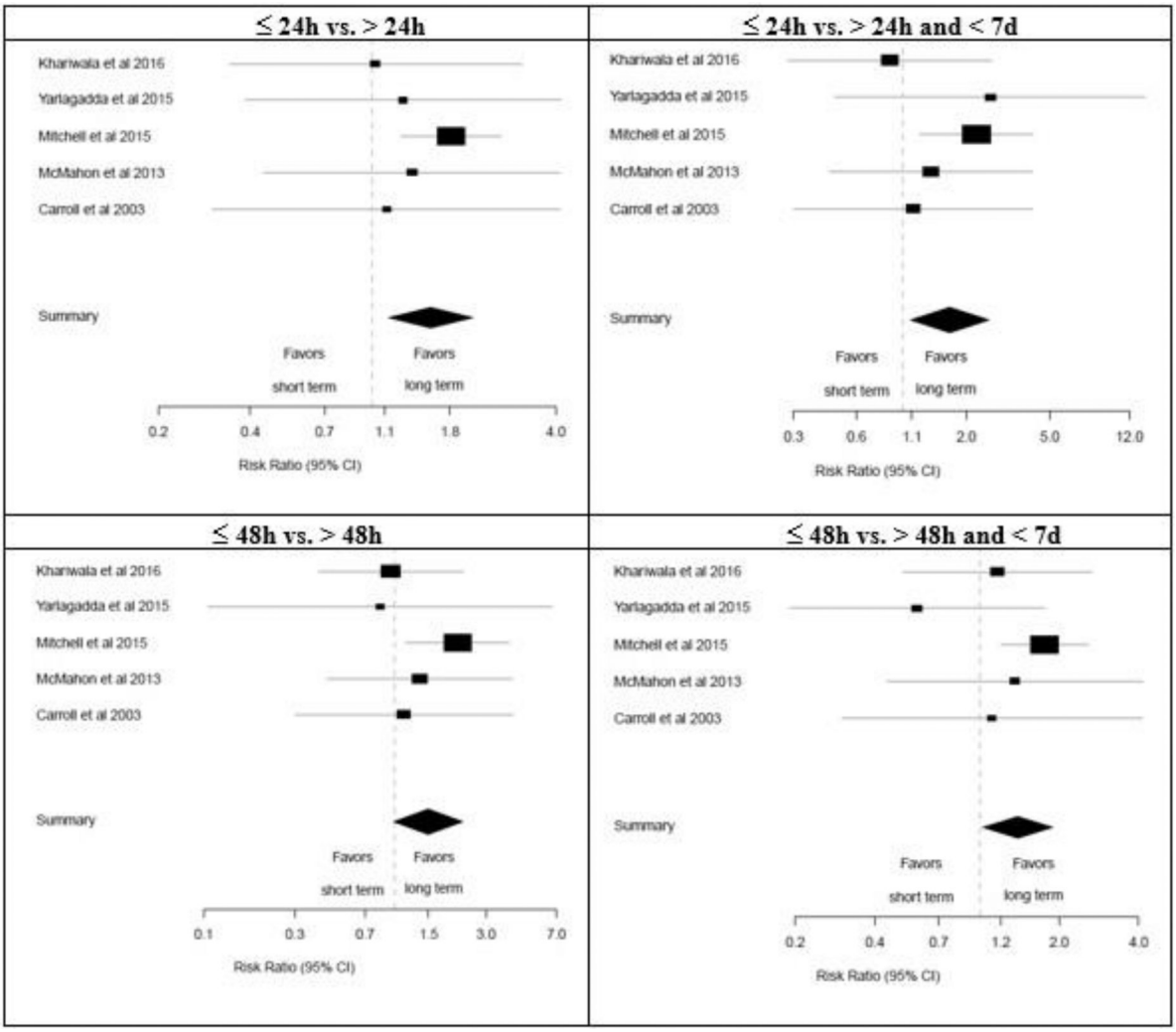

Figure 2:

Forrest plots showing results of the meta-analysis when comparing short duration vs long duration of antibiotic prophylaxis. (A) Comparison of ≤24 hours and >24 hours. (B) Comparison of ≤24 hours and >24 hours, excluding >7 days. (C) Comparison of ≤48 hours and >48 hours. (D) Comparison of ≤48 hours and >48 hours, excluding >7 days.

Table 1:

Inclusion and exclusion criteria for the meta-analysis

Inclusion Criteria	• Participants: patients undergoing free flap reconstruction in clean contaminated head and neck surgery. • Comparison: short term (< 24 or < 48 hours) vs long term prophylactic antibiotic administration • Outcomes: primary – recipient (neck or flap) SSI; secondary – dSSI, dehiscence/fistula, distant (UTI or pneumonia) infections, C. diff, or MRSA infections • Study design: published and unpublished studies (abstracts, case series, cohorts, or randomized clinical trials) • All languages were included
Exclusion Criteria	• Studies examining therapeutic antibiotics or antibiotics administered preoperatively • Animal studies • Case reports

Table 2:

Summary of articles in the systematic review

Author	Year	Study design	Sample Size	Antibiotic Type (Percent of population received in parentheses)	Duration of antibiotic administration (with number of patients and percent in parentheses)	SSI definition	Overall risk of rSSI
Khariwala et al	2016	Retrospective chart review	120	ampicillin-sulbactam (65%) Clindamycin (18.3%) Others (16.7%)	≤ 24 hours (n=16, 13.3%) 25–48 hours (n=20, 16.7%) 49–72 hours (n=15, 12.5%) 4–7 days (n=34, 28.3%) >7 days (n=35, 29.2%)	CDC criteria	17.5%
Yarlagadda et al	2015	Retrospective chart review	99	ampicillin-sulbactam (83.8%) Clindamycin (12.1%) Others (4.0%)	≤ 24 hours (n=19, 19.2%) 25–48 hours (n=24, 24.2%) 49–72 hours (=3, 3.0%) 4–7 days (n=6, 6.1%) >7 days (n=47, 47.5%)	CDC criteria	13.1%
Mitchell et al	2015	Retrospective cohort study	385	ampicillin-sulbactam (55.1%) Clindamycin (37.9%) Others (7.0%)	≤ 24 hours (n=91, 23.6%) 25–48 hours (n=2, 0.5%) 49–72 hours (n=2, 0.5%) 4–7 days (n=69, 17.9%) >7 days (n=221, 57.4%)	CDC criteria	22.1%
McMahon et al	2013	Prospective cohort study	183	ampicillin-sulbactam	24 hours (n=93, 48.4%) 5 days (n=99, 51.6%)	CDC criteria	6.6%
Carroll et al	2003	Prospective clinical trial	74	Clindamycin	24 hours (n=35, 47.3%) 5 days (n=39, 52.7%)	Erythema, edema, or purulence prior to discharge	10.8%

Table 3:

Relative risk of surgical site infections in short vs. long term antibiotic prophylaxis

Relative risk* (95% confidence interval)				
	≤ 24h vs. >24h	**≤ 24h vs. > 24h and <7d**	**≤ 48h vs. > 48h**	**≤ 48h vs. > 48h and < 7d**
Fixed effect model	1.56 (1.13, 2.14) P = 0.006	1.67 (1.08, 2.57) P = 0.020	1.49 (0.99, 2.27) P = 0.059	1.39 (1.03, 1.89) P = 0.033
Random effect model	1.60 (1.17, 2.20) P = 0.004	1.66 (1.07, 2.58) P = 0.023	1.48 (0.97, 2.26) P = 0.070	1.44 (1.05, 1.98) P = 0.023

*RR: Risk of SSI in short term vs. long term antibiotic prophylaxis use; P = P-value

Table 4:

Test for heterogeneity of treatment effect across studies

Test for heterogeneity χ^2 Statistic (P-value)				
	≤ 24h vs. >24h	**≤ 24h vs. > 24h and <7d**	**≤ 48h vs. > 48h**	**≤ 48h vs. > 48h and < 7d**
Fixed effect model	1.62 (0.8059)	2.98 (0.5614)	2.82 (0.5877)	4.19 (0.381)
Random effect model	1.59 (0.8111)	2.98 (0.5614)	2.82 (0.5881)	4.1 (0.3929)

Table 5:

Association of duration of antibiotic prophylaxis and antibiotic type with infection. ampicillin-sulbactam was set at the reference point (relative risk of 1) with clindamycin and "others" being compared to ampicillin-sulbactam (e.g., clindamycin carries a 2.85× increased risk of rSSI compared to ampicillin-sulbactam).

Outcome	Variable	Raw Incidence Rate	RR	95% CI		p-value
rSSI	Duration (≤ 24h vs. > 24h)	--	1.09	0.78	1.55	0.6082
	ampicillin-sulbactam	10.17%	--	--	--	--
	Clindamycin	34.91%	2.85	1.95	4.17	<0.0001
	Others	21.74%	1.84	0.98	3.44	0.0564
dSSI	Duration (≤ 24h vs. > 24h)	--	1.1	0.64	1.87	0.7283
	ampicillin-sulbactam	12.24%	--	--	--	--
	Clindamycin	5.92%	0.39	0.19	0.77	0.0069
	Others	10.87%	0.84	0.35	2.01	0.6934
Dehiscence/Fistula	Duration (≤ 24h vs. > 24h)	--	0.8	0.58	1.09	0.1531
	ampicillin-sulbactam	15.77%	--	--	--	--
	Clindamycin	40.83%	2.51	1.86	3.39	<0.0001
	Others	17.39%	0.98	0.5	1.91	0.9486
Distant Infection (PNA or UTI)	Duration (≤ 24h vs. > 24h)	--	1.07	0.76	1.51	0.7086
	ampicillin-sulbactam	13.69%	--	--	--	--
	Clindamycin	28.99%	2.2	1.52	3.17	<0.0001
	Others	21.74%	1.55	0.84	2.84	0.158
MRSA	Duration (≤ 24h vs. > 24h)	--	1.56	0.86	2.84	0.1429
	ampicillin-sulbactam	4.56%	--	--	--	--
	Clindamycin	10.65%	2.13	1.16	3.91	0.0154
	Others	6.52%	1.53	0.47	4.9	0.4786