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Antibiotic Prophylaxis in Oral Cancer Surgery: A Critical Narrative Review of Current Evidence and Clinical Considerations

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Abstract
Background: Surgical-site infection (SSI) after oral cancer surgery can disrupt wound healing and reconstruction, prolong hospital stay, and delay adjuvant treatment. Choosing an antibiotic and deciding how long to continue it are related but separate decisions.
Objective: To review evidence on antibiotic selection and duration in oral cancer surgery, drawing on the wider head and neck literature where studies specific to oral cancer are limited, with particular attention to free-flap reconstruction.
Methods: This critical narrative review draws on relevant PubMed records, PubMed Central full texts, publicly accessible scholarly indexes, publisher records and reference lists of key reviews. It provides a focused clinical synthesis rather than an exhaustive systematic review.
Results: Reviews of clean-contaminated head and neck surgery generally support selected beta-lactam regimens with appropriate oral-flora coverage over clindamycin alone. Randomised trials have not consistently shown fewer SSIs when prophylaxis is extended from one day to three or five days. Evidence in free-flap reconstruction is less settled: an earlier meta-analysis found that the association between shorter prophylaxis and SSI weakened after adjustment for antibiotic type; a cohort of osteocutaneous free flaps found no significant advantage with courses longer than 72 hours; and available observational evidence remains limited and difficult to interpret because antibiotic choice, duration and baseline surgical risk may be confounded. Oral-cancer studies also identify reconstruction, mandibulectomy, prolonged surgery, transfusion and metabolic or nutritional factors as correlates of SSI. An Indian cohort found substantial Gram-negative involvement among cultured infections, highlighting the value of local microbiology when treating established infection. A meta-analysis comparing clindamycin with ampicillin–sulbactam was retracted and was not used to draw conclusions.
Conclusion: The evidence favours careful antibiotic selection, timely administration and appropriate intraoperative redosing over routine extension of prophylaxis for several postoperative days. For complex free-flap and osteocutaneous reconstruction, the evidence remains uncertain; decisions should reflect the procedure, patient risk, local microbiology and antimicrobial-stewardship principles.
Keywords: *oral cancer; head and neck cancer; antibiotic prophylaxis; surgical-site infection; duration; free-flap reconstruction; antimicrobial stewardship; narrative review.*

I. Introduction

Oral cavity and many head and neck cancer operations pass through a colonised mucosal field and are therefore commonly classified as clean-contaminated. The microbial burden is mixed, and infection can lead to wound breakdown, fistula, plate exposure, donor-site complications, reoperation and a longer hospital stay. In cancer care, these complications can also delay recovery and adjuvant treatment[1–4].

In practice, antibiotic prophylaxis is often discussed mainly in terms of how many postoperative days to prescribe. That can obscure three separate decisions: which agent and spectrum to use, when to administer and redose it, and when to stop after surgery. A longer course cannot compensate for inadequate coverage, administration too late, or missed intraoperative redosing.

The evidence includes older randomised trials, systematic reviews that draw on some of the same primary studies, retrospective cohorts and newer work focused on free-flap reconstruction. This review brings

those findings together while distinguishing direct evidence from observational associations and avoiding claims of exhaustive systematic-review coverage.

II. Review approach and scope

A focused narrative search was undertaken to identify relevant evidence on antibiotic selection and duration in oral cancer and related head and neck surgery. Sources included PubMed-indexed records, PubMed Central full texts, publicly accessible scholarly discovery sources, publisher records and reference lists of key reviews. Search terms combined oral cancer and head and neck surgery with antibiotic prophylaxis, surgical-site infection, duration, free-flap reconstruction and antimicrobial stewardship. The aim was to provide a clinically useful synthesis rather than an exhaustive systematic evidence map.

The review focuses on adult oral cavity and head and neck cancer surgery. Evidence from clean-contaminated mucosal procedures is discussed separately from evidence in microvascular free-flap and osteocutaneous reconstruction. General SSI guidelines are used as background principles, not as substitutes for procedure-specific evidence. Studies treating established infection rather than preventing SSI are outside the primary scope.

III. Regimen selection

The 2020 systematic review by Vander Poorten and colleagues included 39 studies of clean-contaminated head and neck surgery[2]. It reported that cefazolin, ampicillin–sulbactam and amoxicillin–clavulanate performed favourably relative to placebo or less effective alternatives in the included evidence, while benzylpenicillin and clindamycin were less effective in several comparisons. The review also reported a higher infection odds with clindamycin than ampicillin–sulbactam (OR 2.73, 95% CI 1.50–4.97); this is the published review estimate, not a new analysis in the present paper. Differences in surgical populations, regimens and study methods limit direct translation of that pooled estimate to every institution.

Iocca and colleagues' 2022 systematic review and Bayesian network meta-analysis similarly concluded that penicillin- and cephalosporin-based regimens generally performed well and that longer courses did not show a consistent advantage[4]. Network comparisons rely on assumptions that studies are sufficiently comparable; indirect estimates should not be read as definitive head-to-head trials. The article has a published erratum, which should be consulted when interpreting it.

Clindamycin is often selected for patients labelled penicillin-allergic, but that label should be characterised rather than accepted uncritically [4,10]. Where feasible, clarify the reaction phenotype and distinguish intolerance from immediate hypersensitivity or severe delayed reactions. An alternative regimen should provide suitable coverage for the operative flora and reflect local resistance patterns. The increased SSI reported in a retrospective free-tissue-transfer cohort associated with clindamycin use reinforces the need to avoid treating clindamycin as an automatically equivalent substitute; observational findings, however, can be confounded by allergy status, comorbidity and institutional practice. The 2023 meta-analysis comparing clindamycin with ampicillin–sulbactam was retracted in 2025 and should not be used to support comparative efficacy claims [12,13].

In practice, regimen choice should reflect the procedure, expected flora, allergy history, local susceptibility patterns and institutional guidance. The available evidence does not justify one universal regimen for every operation or centre.

IV. Duration: what the randomised evidence shows

Two randomised trials by Righi and colleagues compared one-day with three-day clindamycin–cefonicid prophylaxis[6,7]. In the 1995 study, which excluded patients considered high risk because of pedicled or microvascular flap reconstruction, wound infection occurred in 1 of 62 patients in the one-day group and 3 of 64 in the three-day group. In the 1996 trial, infection occurred in 2 of 81 patients receiving one day and 3 of 81 receiving three days. Neither trial demonstrated a benefit from the longer schedule. These trials are clinically relevant to clean-contaminated cancer surgery without complex flap reconstruction, but their older regimens and practice context limit present-day generalisability.

Johnson and colleagues conducted a multicentre randomised double-blind study in high-risk head and neck surgery requiring myocutaneous flap reconstruction[8]. With cefoperazone, wound infection occurred in 10 of 53 patients assigned to 24 hours and 14 of 56 assigned to 120 hours; the difference was not statistically significant. The authors concluded that extending administration beyond 24 hours did not confer a demonstrated benefit in that population.

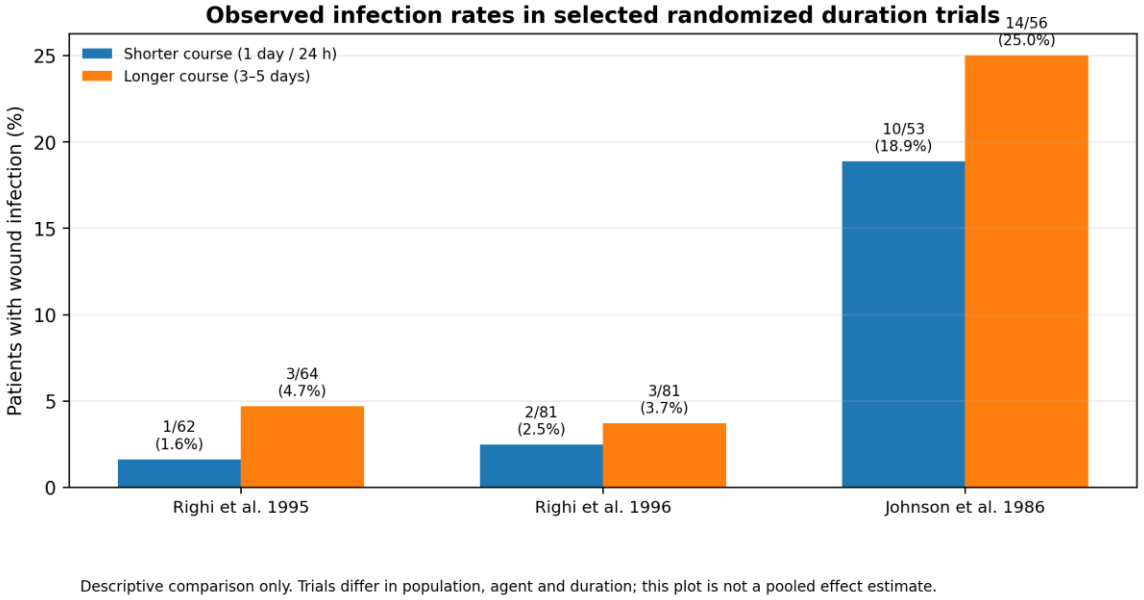
A large retrospective multi-institution analysis of 8,836 discharge records adds an important qualification[9]. Compared with ampicillin–sulbactam given on the day of surgery only, administration on the day of surgery and the first postoperative day was associated with lower SSI odds (OR 0.28, 95% CI 0.13–0.61); this association was not observed with clindamycin. Because the study was retrospective and compared agent–

duration combinations, it cannot establish that extending duration alone caused the reduction. It reinforces the need to interpret duration together with antibiotic choice rather than treating duration as an isolated exposure.

Vila and colleagues' 2017 systematic review pooled four randomised trials (340 patients) comparing one day with five days of prophylaxis and reported RR 0.98 (95% CI 0.58–1.61; I^2=0%)[1]. This estimate is compatible with clinically meaningful benefit or harm and should not be interpreted as proof of equivalence. The important inference is that the included trials did not demonstrate that five days reduced wound infection compared with one day.

Overall, the trials do not establish that every patient should receive exactly 24 hours of prophylaxis, and they do not prove that duration never matters. They do, however, provide little support for routinely extending prophylaxis to three or five days in standard clean-contaminated cases without a specific indication. Prophylaxis should also be distinguished from therapeutic antibiotics for established infection, gross contamination or a postoperative complication. Figure 1 summarises event rates from selected duration trials.

Figure 1. Infection rates in selected randomised prophylaxis-duration trials



Note: Event counts are shown as reported in the individual trials. The studies are clinically heterogeneous; the figure is descriptive and does not imply a pooled treatment effect.

V. Free-flap and osteocutaneous reconstruction: a distinct evidence problem

Microvascular reconstruction differs from less complex procedures because operative duration, tissue transfer, tracheostomy, hardware, large dead spaces, prior radiotherapy, malnutrition, anaemia and comorbidity may increase baseline risk. These factors can also influence clinicians' decisions to prescribe longer courses, creating confounding by indication in observational comparisons.

Haidar and colleagues' 2018 systematic review and meta-analysis focused on clean-contaminated head and neck surgery with microvascular free-flap reconstruction[3]. The review reported a higher SSI risk in patients receiving 24 hours or less compared with longer prophylaxis in an unadjusted comparison (RR 1.56, 95% CI 1.13–2.14). However, the association attenuated after accounting for antibiotic type (adjusted estimate 1.09, 95% CI 0.78–1.55). This is a key caution: duration and agent may be entangled, and a crude association does not establish that extra postoperative days themselves prevent infection.

Chacko and colleagues' 2025 single-centre retrospective cohort examined 198 patients undergoing head and neck reconstruction with osteocutaneous free flaps and hardware[11]. SSI within 30 days occurred in 39% of the 24–72-hour group and 33% of the group receiving more than 72 hours (p=0.460); hardware exposure at six months was 5% in each group. The study did not show a significant benefit from the longer course. It does not prove the strategies are equivalent, and residual confounding remains possible.

Evidence in the available literature remains mixed in complex reconstruction. Haidar and colleagues found that an apparent association between shorter prophylaxis and SSI weakened after adjustment for antibiotic type, while the 2025 osteocutaneous free-flap cohort did not demonstrate a significant advantage for courses longer than 72 hours. These findings support individualised, procedure-specific protocols rather than a universal duration rule.

The evidence does not support a blanket rule either to extend antibiotics for every free-flap patient or to dismiss duration as irrelevant. Findings remain inconsistent and are vulnerable to confounding. Local protocols for complex reconstruction should specify the agent, timing, intraoperative redosing and stop point, as well as when a suspected infection should be treated as a therapeutic problem. Local microbiology and antimicrobial-stewardship review are especially important in previously irradiated patients, osteoradionecrosis and cases involving hardware. Key studies are summarised in Table 1.

Table 1. Selected evidence most relevant to regimen and duration

Evidence source	Population / design	Main finding	How to interpret it
Vila et al., 2017 [1]	Systematic review; 4 RCTs, 340 patients in pooled duration comparison	1 day vs 5 days: RR 0.98 (95% CI 0.58–1.61), I^2=0%	No demonstrated benefit from 5 days; wide CI does not establish equivalence.
Vander Poorten et al., 2020 [2]	Systematic review; 39 studies in clean-contaminated head and neck surgery	Reported favourable results for selected beta-lactam regimens; >48 h did not further reduce infection in duration comparisons	Heterogeneity and differences between studies limit one-size-fits-all inference.
Haidar et al., 2018 [3]	Systematic review/meta-analysis; microvascular free-flap reconstruction	≤24 h vs >24 h: unadjusted RR 1.56 (95% CI 1.13–2.14); adjusted estimate 1.09 (95% CI 0.78–1.55)	Adjustment for antibiotic type attenuated the association; duration may be confounded by agent.
Iocca et al., 2022 [4]	Systematic review and Bayesian network meta-analysis; 20 studies	Concluded that penicillins/cephalosporins generally performed well; no consistent advantage for longer courses	Network estimates are indirect; consult published erratum.
Chacko et al., 2025 [11]	Retrospective cohort; 198 osteocutaneous free flaps with hardware	SSI: 39% with 24–72 h vs 33% with >72 h (p=0.460); hardware exposure 5% in both groups	No statistically significant advantage observed with >72 h; not proof of equivalence.
Hu et al., 2023 / retraction 2025 12,13	Meta-analysis comparing clindamycin and ampicillin–sulbactam	Retracted in 2025 following compromised peer review	Exclude from evidence synthesis and conclusions.
Chen et al., 2025 [16]	Systematic review; 9 observational studies, 4,360 oral cancer patients	SSI incidence 22.22%; associations included flap reconstruction OR 4.50, mandibulectomy OR 4.35 and diabetes OR 3.67	Risk-factor associations do not establish that longer prophylaxis reduces SSI; case mix and definitions differ.
Balagopal et al., 2022 [17]	Prospective observational study; 1,431 oral cavity cancer operations in India	SSI 118/1,431 (8%); among cultured infections, 122 isolates; 41.6% polymicrobial; Gram-negative isolates 70.5%	Microbiology of established infection is not a comparative prophylaxis study; local surveillance informs empiric treatment.
Kohli et al., 2022 [18]	Indian single-centre protocol study; 200 clean-contaminated HNSCC operations	SSI rate 12%; protocol feasible in 70%; reconstruction associated with deviation	Supports feasibility and stewardship implementation, not superiority over another regimen.
Langerman et al., 2016 [9]	Retrospective multi-institution analysis; 8,836 discharge records	Day-of-surgery plus first postoperative day ampicillin–sulbactam was associated with lower SSI odds than day-of-surgery-only ampicillin–sulbactam (OR 0.28, 95% CI 0.13–0.61); no similar association for clindamycin	Observational comparison of agent–duration combinations; cannot isolate a causal effect of duration alone.

VI. Oral-cancer-specific risk and the importance of local microbiology

Antibiotic choice cannot be separated entirely from the patients and operations to which it is applied. A 2025 systematic review of nine observational studies involving 4,360 patients with oral cancer estimated an overall SSI incidence of 22.22%. The pooled associations were strongest for flap reconstruction (OR 4.50, 95% CI 2.13–9.50), mandibulectomy (OR 4.35, 95% CI 2.39–7.04), diabetes (OR 3.67, 95% CI 2.13–6.33), perioperative transfusion (OR 3.04, 95% CI 2.11–4.37), oral–neck communication (OR 3.88, 95% CI 2.04–7.36), and longer operative time (OR 2.18, 95% CI 1.22–3.90)[16]. These are risk-factor associations, not evidence that extending prophylaxis will neutralise the risks. The review also reported an association involving postoperative serum albumin; because albumin measured after surgery may reflect illness severity or postoperative events, it should not be interpreted straightforwardly as a preoperative causal risk factor. The principal reported associations are illustrated in Figure 2.

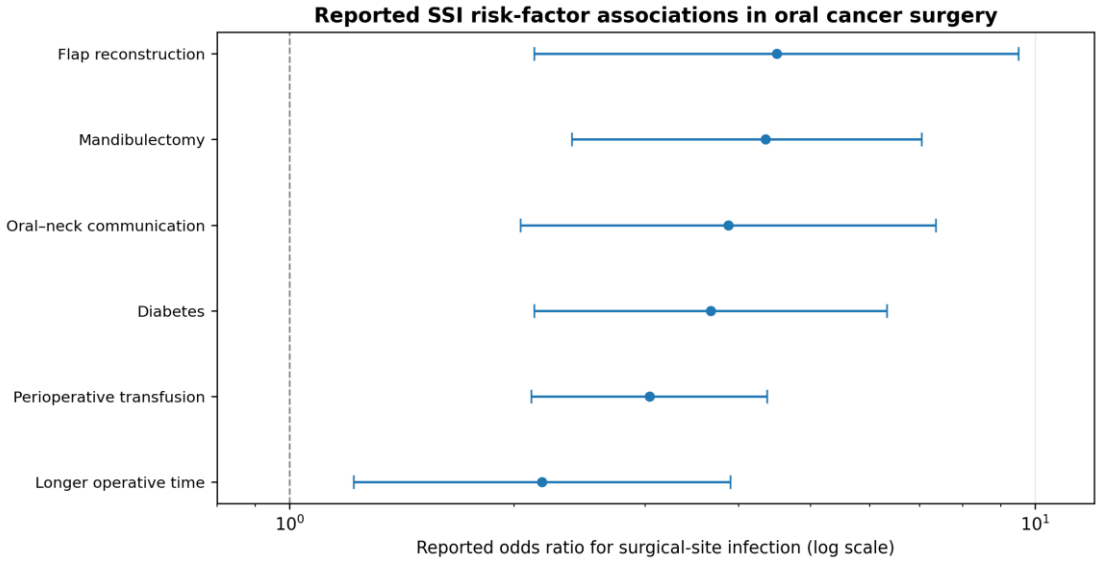
An Indian prospective observational study followed 1,431 patients undergoing oral-cavity cancer surgery and recorded SSI in 118 patients (8%). Among 72 infected patients with cultures, 122 isolates were recovered; 41.6% of cultured infections were polymicrobial, and Gram-negative isolates outnumbered Gram-

positive isolates (70.5% versus 27%)[17]. This cohort describes pathogens in established infection, not a randomised comparison of prophylactic regimens. It therefore cannot by itself justify routine broad-spectrum prophylaxis. Its practical lesson is narrower: local SSI surveillance and antibiograms matter, and treatment of a suspected postoperative infection should be guided by clinical assessment, cultures when appropriate, and source control rather than by blindly extending the original prophylactic agent. A 2025 retrospective study from Pakistan similarly reported that Gram-negative organisms predominated among SSIs after head and neck free-flap reconstruction, with multidrug resistance common among the cultured isolates[19]. Although this is not Indian data and its small cohort limits generalisation, it reinforces the need to separate prophylaxis policy from culture-directed treatment and to base local protocols on contemporary institutional surveillance. A 2025 retrospective study of head and neck reconstruction found no significant difference in SSI according to postoperative day of drain removal; oral cavity lesions and the prophylactic agent were associated with SSI, but the study was not designed to establish the optimal prophylaxis duration [20].

An Indian single-centre protocol study of 200 patients with clean-contaminated head and neck squamous-cell cancer surgery reported that a short perioperative regimen was feasible, with an SSI rate of 12%; reconstruction and age over 50 years were associated with deviation from the protocol[18]. Because the study was not a randomised comparison of alternative regimens and used a bundled protocol, it supports feasibility and stewardship implementation more than comparative efficacy. These Indian data are particularly relevant to practice in settings where antimicrobial resistance patterns and availability differ from those in the North American and European cohorts that dominate much of the literature.

A 2025 open-access review focused specifically on oncologic head and neck free-flap reconstruction proposed a procedure-stratified approach, suggesting 24–48 hours for soft-tissue reconstruction and up to 72 hours for bony reconstruction, while acknowledging the lack of robust validating trials 5. This is a reasoned proposal by the review authors, not a universally established guideline. It should be presented as such, particularly because other guidance recommends stopping prophylaxis at closure for clean and clean-contaminated procedures and because the available evidence remains inconsistent.

Figure 2. Reported risk-factor associations for SSI in oral cancer surgery



Note: Odds ratios and 95% confidence intervals are reproduced from the published systematic review by Chen et al. (2025); they are not recalculated here. Observational associations should not be interpreted as causal effects.

VII. General SSI guidance and stewardship

The CDC guideline for prevention of surgical-site infection recommends that, for clean and clean-contaminated procedures, additional prophylactic antimicrobial doses not be administered after the incision is closed in the operating room, even when a drain is present[14]. This is a general SSI recommendation and should be reconciled with the procedure-specific evidence and applicable local policy; it should not be quoted as if it were derived solely from head and neck free-flap trials.

Prophylaxis is intended to establish effective antimicrobial concentrations at the time of incision and maintain them for the period of exposure. Dose selection, administration timing, redosing for prolonged

procedures or major blood loss, and source control are therefore central. Extending a course exposes patients to drug reactions, diarrhoea and Clostridioides difficile infection, selection of resistant organisms, drug interactions and additional cost. The potential harms become more consequential when prolonged broad-spectrum agents are used without a defined indication.

A drain, tracheostomy, reconstruction plate or free flap should not automatically be treated as proof that prolonged prophylaxis is beneficial. Conversely, fever, purulent drainage, evolving cellulitis, collection or a diagnosed infection should prompt clinical assessment and a treatment strategy rather than simply extending the prophylactic prescription.

VIII. Clinical synthesis

Three practical messages emerge from the evidence. First, the choice and delivery of prophylaxis matter: the agent should cover the expected flora, be given at the right time and be redosed when indicated. Second, randomised trials and major reviews have not consistently shown fewer SSIs when prophylaxis is extended to three or five days after routine clean-contaminated surgery. Third, evidence for complex free-flap reconstruction remains uncertain; differences in study populations, antibiotic regimens and study design should prompt careful protocol review rather than a universal duration rule.

An institutional protocol should distinguish between procedures such as mucosal resection without a flap, pedicled-flap reconstruction, microvascular soft-tissue flaps, osteocutaneous flaps with hardware and reconstruction in previously irradiated patients. It should identify first-line and allergy alternatives, define timing and redosing, and state when prophylaxis stops. If antibiotics are continued beyond that point, the reason should be documented and reviewed. Local SSI surveillance, stratified by procedure and regimen, may be more informative than unstructured postoperative extension. The corresponding decision summary is provided in Table 2, with an overview in Figure 3.

Table 2. Translating the evidence into clinical decisions

Clinical scenario	Evidence-based reading	Practical implication
Clean-contaminated cancer surgery without complex flap	Two Righi RCTs and older duration trials did not show benefit from extending 1 day to 3–5 days.	Choose appropriate prophylaxis and delivery; avoid routine prolonged courses without a specific indication.
Pedicled-flap reconstruction	Johnson et al. found no significant benefit from 5 days vs 1 day in a randomised trial.	Do not assume that a flap alone establishes benefit from prolonged prophylaxis.
Microvascular soft-tissue free flap	Evidence mixed; 2018 adjusted estimate attenuated after accounting for antibiotic type.	Follow a defined local protocol; review patient and operative risks, agent choice, redosing and stop point.
Osteocutaneous free flap with hardware	2025 cohort found no significant SSI or hardware-exposure difference with >72 h vs 24–72 h.	Hardware presence alone is not evidence that >72 h is superior.
Previously irradiated reconstruction / ORN	Evidence is limited; assess patient risk, local microbiology and institutional guidance.	Potential subgroup signal only; assess local microbiology and stewardship; do not generalise without validation.
Established infection or postoperative complication	This is treatment, not prophylaxis.	Investigate source, obtain cultures when appropriate, achieve source control and prescribe therapeutic antibiotics according to clinical findings.

Figure 3. A decision framework for prophylaxis in cancer surgery

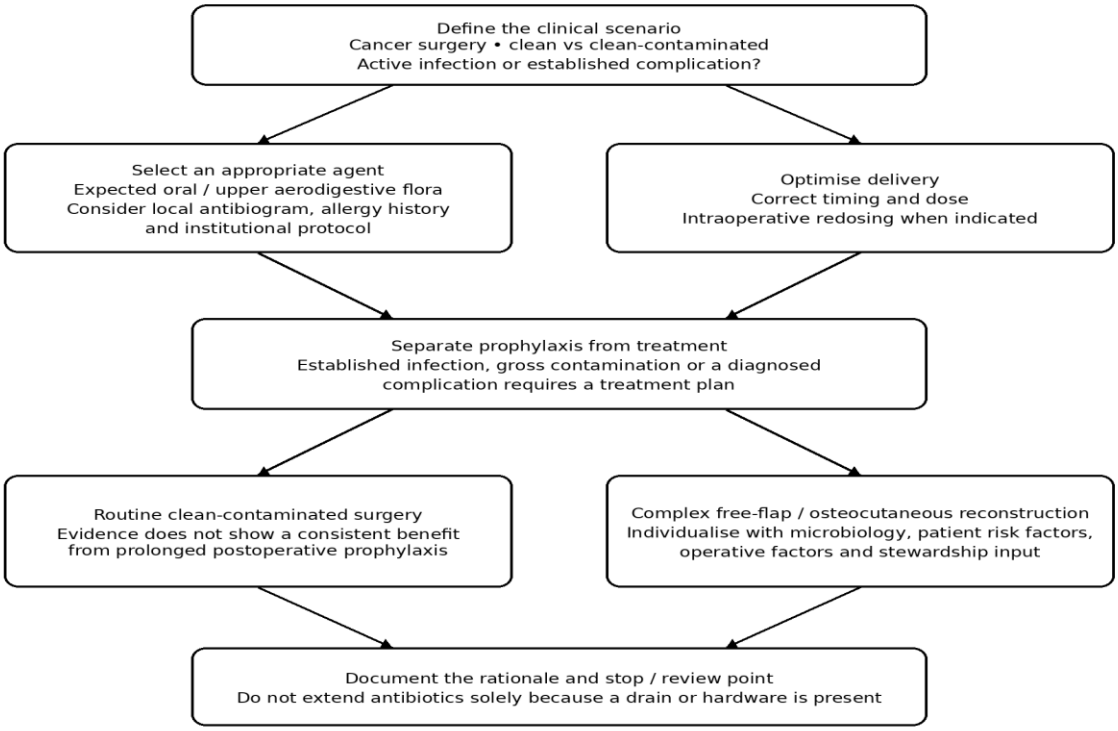


Figure note: This schematic summarises decision domains and evidence uncertainty; it is not a substitute for local antimicrobial guidelines or patient-specific prescribing.

IX. Conclusion

For oral and head and neck cancer surgery, the evidence supports choosing an appropriate regimen and delivering it reliably rather than routinely continuing prophylaxis for several postoperative days. In standard clean-contaminated surgery, randomised trials and systematic reviews have not shown a consistent benefit from longer courses. Uncertainty remains in free-flap and osteocutaneous reconstruction: available observational evidence cannot isolate a causal effect of prophylaxis duration. Procedure-specific risk, prior radiotherapy, local resistance patterns and antimicrobial stewardship should guide institutional protocols. A definitive systematic review would require a separately planned and reproducible multi-database search, duplicate screening and formal risk-of-bias assessment.

Declarations

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Author contributions: Dr. Abhishek Khatua conceived the review topic. Both authors contributed to the literature search, interpretation of the evidence, drafting and critical revision of the manuscript. Both authors read and approved the final manuscript.

Ethics approval: Not applicable; this article reviews published literature and reports no new human-participant data.

Data availability: No new dataset was generated for this narrative review.

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