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REVIEW

Perioperative Antibiotics in Clean-Contaminated Head and Neck Surgery: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: The optimal evidence-based prophylactic antibiotic regimen for surgical site infections following major head and neck surgery remains a matter of debate.
Methods: Medline, Cochrane, and Embase were searched for the current best evidence. Retrieved manuscripts were screened according to the PRISMA guidelines. Included studies dealt with patients over 18 years of age that underwent clean-contaminated head and neck surgery (P) and compared the effect of an intervention, perioperative administration of different antibiotic regimens for a variable duration (I), with control groups receiving placebo, another antibiotic regimen, or the same antibiotic for a different postoperative duration (C), on surgical site infection rate as primary outcome (O) (PICO model). A systematic review was performed, and a selected group of trials investigating a similar research question was subjected to a random-effects model meta-analysis.

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Results: Thirty-nine studies were included in the systematic review. Compared with placebo, cefazolin, ampicillin–sulbactam, and amoxicillin–clavulanate were the most efficient agents. Benzylpenicillin and clindamycin were clearly less effective. Fifteen studies compared short- to long-term prophylaxis; treatment for more than 48 h did not further reduce wound infections. Meta-analysis of five clinical trials including 4336 patients, where clindamycin was compared with ampicillin–sulbactam, implied an increased infection rate for clindamycin-treated patients (OR = 2.73, 95% CI 1.50–4.97, $p = 0.001$).
Conclusion: In clean-contaminated head and neck surgery, cefazolin, amoxicillin–clavulanate, and ampicillin–sulbactam for 24–48 h after surgery were associated with the highest prevention rate of surgical site infection.

Keywords: Evidence based; Guidelines; Head and neck oncology; Head and neck surgery; Meta-analysis; Perioperative antibiotics; Prophylaxis; Systematic review

Key Summary Points

Patients undergoing major head and neck surgery are at risk of developing surgical site infections.

Antibiotic prophylaxis reduces the incidence of surgical site infections significantly; however, there is no agreement on the optimal type and duration of the antibiotic regimen.

A systematic review and meta-analysis of the literature in Medline, Cochrane, and Embase was performed, following the PRISMA guidelines.

The conclusion is that cefazolin, amoxicillin–clavulanate, and ampicillin–sulbactam are the antibiotics of choice, whereas clindamycin monotherapy increases the risk of infection in comparison to standard antibiotics and thus should be avoided. The latter finding is in contrast to current guidelines.

24–48 h of prophylaxis is appropriate, also in patients with an increased risk of infection.

INTRODUCTION

Despite the frequent use of perioperative antibiotic prophylaxis, surgical site infections (SSIs) in general still account for more than 20% of healthcare-associated infections [1]. The Centers for Disease Control and Prevention (CDC) divides surgical wounds into four categories: clean, clean-contaminated, contaminated, and dirty operative wounds. In head and neck surgery, many procedures are clean, i.e., creating wounds without contact with the upper aerodigestive tract (UADT) (e.g., thyroidectomy [2]). In this group, SSIs occur in less than 1% [3].

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Major procedures with exposure to the UADT (e.g., pharyngectomy, laryngectomy) are considered "clean-contaminated". The UADT harbors a large variety of microorganisms, such as gram-positive and facultative anaerobic bacteria, and to a lesser degree gram-negative bacteria, *Candida* species, and bacteria originating from an eventually harvested flap [4]. When patients with a compromised condition, undergoing extensive procedures (with a prolonged operation time and use of foreign bodies such as tracheal cannulas), are exposed to this flora, they experience a higher incidence of SSIs [5, 6]. In the absence of antibiotic prophylaxis, SSI rate ranges between 24% and 87% in this patient group [7]. Head and neck procedures involving free tissue transfer and microvascular reconstruction are particularly prone to SSIs because of the larger post-ablation surgical defects and theoretically decreased vascularity of the donor tissue [8]. Occurring in 20–50% of these patients, SSIs are associated with increased fistula formation, prolonged hospitalization, increased morbidity and mortality, and reconstruction failure, all resulting in increased healthcare costs. Therefore, the effectiveness of antibioprophylaxis (ABP) of SSIs is a topic of major interest [5, 9].

While judicious use of antibiotics reduces the postoperative infection rate, inappropriate use can cause unwanted effects such as rash (0.3–2.1%), acute renal failure, pneumonia, *Clostridium difficile* infections (5%), pseudomembranous colitis (10% for clindamycin), and the development of antibiotic resistance [5, 6, 10].

Regarding the prophylactic perioperative use of antibiotics in major head and neck surgery, administration on the day of surgery is well accepted and implemented in several guidelines [11, 12]. A recent systematic review of existing guidelines shows that there is still wide variation in recommended regimens and indicates that remaining areas to develop consensus on are the postoperative duration of the antibiotic course, the need for gram-negative coverage, and the antibiotic of choice in penicillin-allergic patients [12]. According to Chiesa et al. [12], the most commonly used regimens include cefazolin, cefazolin–metronidazole, ampicillin–sulbactam, and amoxicillin–clavulanate. In penicillin-allergic patients clindamycin is often prescribed, but also vancomycin and gentamicin. The duration of prophylaxis ranges from 1 day to more than 5 days. The CDC states that up to 50% of all administered antibiotics are inappropriate or unnecessary [6].

The aim of this study is to define the optimal antibiotic agent and the optimal duration of prophylaxis to reduce the rate of SSIs in patients undergoing clean-contaminated head and neck surgery.

METHODS

Search Strategy, Study Selection, and Data Extraction

A systematic review with meta-analysis of the evidence on ABP in clean-contaminated head and neck surgery was conducted. Retrieved manuscripts were screened according to the PRISMA guidelines. Studies were eligible if they complied with the predefined PICO model (Population, Intervention, Comparator, Outcome), as detailed in Table 1 [13]. Accordingly, the population of interest (P) consisted of patients over 18 years of age undergoing clean-contaminated head and neck surgery as defined by the CDC [2], with or without tissue transfer (pedicled or free flaps). The intervention (I) was administration of oral or intravenous perioperative ABP, administered preoperatively less than 60 min prior to incision or at induction of anesthesia with intraoperative repetition if needed [14]. Postoperative prophylaxis could range from a short to a prolonged antibiotic course. The comparators (C) are placebo, ABP using a different antibiotic, or ABP using the same antibiotic but for a different postoperative duration. The primary outcome (O) was the rate of SSIs, defined as any infection occurring within 30 days after surgery [2].

Medline (Pubmed), Embase (Scopus), and Cochrane databases were searched using the keywords "perioperative", "preoperative", "postoperative", "antibiotic", "prophylaxis", "head and neck surgery", "clean-contaminated",

Table 1 Inclusion criteria for study selection, based on the PICO model

Population	Patients > 18 years old
	Clean-contaminated head and neck surgery
	With or without free flap reconstruction: pedicled or free flap
Intervention	Perioperative antibiotic prophylaxis or comparator
	Oral or intravenous
Comparator	Type of antibiotic
	Postoperative prolongation of antibiotic course
Outcome	Surgical site infection
	Fistula formation
Study type	Systematic reviews, randomized controlled trials, meta-analyses, and prospective or retrospective cohort studies
Other	English language
	Full-text available

and "surgical site infection". Publications written in English and with a full text available were included. The study types of interest were systematic reviews, randomized controlled trials (RCT), meta-analyses, and prospective or retrospective cohort studies. Abstracts that did not meet the inclusion criteria were excluded. Relevant abstracts were uploaded in a reference manager and duplicates were removed. Full texts were reviewed. Publications that did not meet the criteria of the PICO model and did not include statistical data analysis were excluded. Finally, data on study population, antibiotic regimen, duration of the antibiotic course, and the rate of postoperative SSIs were extracted. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. Ethical exemption was provided by the Education-Support Committee (OBC) or the Research Ethics Committee of KU Leuven.

Statistical Analysis

Articles were selected for inclusion in the systematic review on the basis of the type and duration of ABP. Articles were included in the meta-analysis if they studied the same intervention and control group, if the duration of the antibiotic course was less than 24 h, and if the article provided the essential effect measures to be submitted to meta-analysis, i.e., the number of SSIs and total number of patients in group A (antibiotic type A) and number of SSIs and total number of patients in group B (antibiotic type B). Systematic reviews were excluded.

The included studies thus were both RCTs and retrospective cohort studies comparing the rate of postoperative SSIs in patients undergoing clean-contaminated head and neck surgery, treated prophylactically with ampicillin–sulbactam versus with clindamycin. Quality of the included studies was assessed by screening for study design, study characteristics (language, PICO, publication status), methodology, and summary measures (odds ratio, p value, confidence interval). Risk of bias was assessed using the Cochrane checklist.

Data from the included studies were extracted by one independent reviewer. The overall pooled risk was then calculated using a random-effects model with the RevMan 5 program (Cochrane), using the Mantel–Haenszel method. A random-effects model was used because of the differences in study population, the fact that studies span 30 years, and the potential differences in antibiotic susceptibility and the standard of medical care. Additionally, presence or absence of heterogeneity was assessed using the I^2 and chi-square statistic. Finally, a forest plot was constructed. For the pooled effect measure, a p value less than 0.05 was considered statistically significant.

RESULTS

Database searching retrieved a total of 88 studies. Searching of the references by hand resulted in 12 additional studies on the impact of different antibiotic regimens on the rate of SSIs in

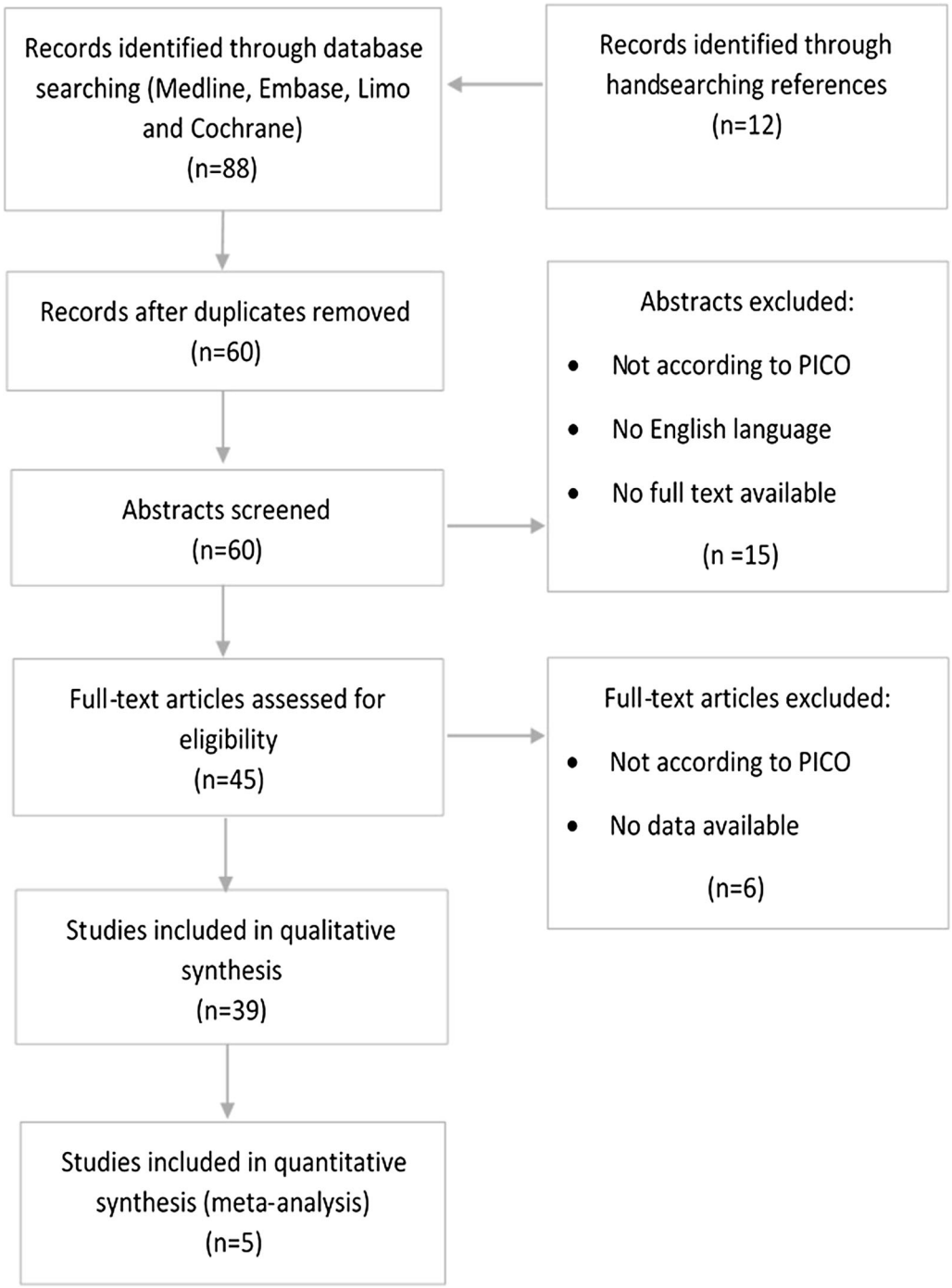

Fig. 1 Search strategy and study selection summarized in a flow diagram, based on the PRISMA guidelines

patients undergoing clean-contaminated head and neck surgery, mostly in an oncological setting. Excluding duplicates and applying inclusion and exclusion criteria reduced these 100 studies to a total of 39 studies. Some studies focused mainly on patients with free flap reconstruction. The antibiotic regimens varied a lot. Most commonly used antibiotics were penicillins, cephalosporins, quinolones, aminoglycosides, clindamycin, and

metronidazole. The duration of the antibiotic course ranged from 1 day to more than 7 days. The PRISMA-based selection process is summarized in Fig. 1. The following section details the results of the systematic review and comments on, respectively, the initial studies indicating the need for ABP, the factors increasing the SSI risk, the microbiology involved, the ideal antibiotic agent, and the duration this agent needs to be given, according to today's best evidence.

Need for Perioperative Antibiotic Prophylaxis

In 1978, Seagle et al. [15] published an RCT to evaluate the benefit of perioperative ABP in patients undergoing head and neck surgery. Fifty patients were randomized into two groups: 25 patients received cefazolin and 25 patients received placebo. In the cefazolin group 16% of the patients developed an SSI, and 48% in the placebo group. Two years later, Becker et al. [16] carried out a similar RCT and concluded that the administration of cefazolin significantly reduces the risk of wound infection in comparison to placebo ($p < 0.001$).

Additionally, an RCT by Raine et al. was carried out to compare the risk of wound infection after administration of amoxicillin–clavulanate and placebo. The incidence of infection was three times higher in the placebo group ($p < 0.025$) [17]. Table 2 summarizes these landmark studies.

Factors Increasing Risk of Surgical Site Infections

Different patient-related factors can increase the risk of SSIs. Diabetes [10, 18, 19], increased body mass index (BMI) [10, 19–21], malnutrition [21, 22], anemia [10, 21], and elevated American Society of Anesthesiologists (ASA) score [23, 24] are associated with an increased risk of infection. Two studies [10, 25] also identify undertreated hypothyroidism as a risk factor, whereas another study does not [19]. Tumor-related factors also play a role: according to Busch et al. [7] the risk of infection is higher in patients with advanced disease ($p = 0.012$) and positive lymph nodes ($p = 0.002$). In contrast, other studies show that T or N category are not associated with an increased infection risk ($p > 0.05$) [4, 26, 27]. Regarding treatment-related factors, the type of surgery also relates to the infection rate: the incidence is 2.2–2.8 times higher in patients undergoing free flap reconstruction [8]. Patients with a tracheotomy, both prior to or concurrent with their surgery, have a threefold increased wound infection risk [7, 20] and a higher chance to develop postoperative pneumonia [7, 22]. A total laryngectomy is associated with the highest risk of infection and fistula formation [17, 18]. Preoperative

Table 2 Comparative studies evaluating the effect of antibiotic prophylaxis on the rate of wound infections

Article	Study type	Antibiotic regimen	Duration	Incidence SSI (%)	*p* value
Seagle et al. (1978) [15]	RCT ($n = 50$)	Cefazolin ($n = 25$)	1 day ($n = 50$)	16	< 0.05*
		Placebo ($n = 25$)		48	
Becker et al. (1979) [16]	RCT ($n = 55$)	Cefazolin ($n = 32$)	1 day ($n = 55$)	38	< 0.001*
		Placebo ($n = 23$)		87	
Raine et al. (1984) [17]	RCT ($n = 32$)	Amoxicillin–clavulanate ($n = 16$)	2 days ($n = 32$)	25	< 0.025*
		Placebo ($n = 16$)		75	

RCT randomized controlled trial, *n* number of participants
*$p < 0.05$ is considered statistically significant

radiotherapy does not seem to increase the SSI risk in many studies [4, 7, 15–19, 25, 28]. Many other studies, however, did find an association with preoperative radiotherapy, with the highest risk in patients exposed to more than 60 Gy [29–33]. One study found a borderline association of SSIs with prior radiation ($p = 0.08$, OR = 2.82, 95% CI 0.84–9.14) [34].The same authors also mentioned previous chemotherapy as a significant risk factor ($p = 0.01$).

Microbiology of Surgical Site Infections

The mouth and oropharynx harbor a large variety of microorganisms. In oropharyngeal secretions of healthy subjects, mainly anaerobic and gram-positive aerobic organisms are isolated [4, 35]. Saliva bacterial flora mainly consists of anaerobic colonizers, e.g., *Peptostreptococcus* and *Fusobacterium* species. Gram-positive aerobic bacteria include *Streptococcus* spp. Gram-negative aerobes are not part of the head and neck microbiome in healthy subjects [4, 36], but they colonize the oropharynx in patients with UADT cancer [4, 27]. In patients with poor general health, opportunistic microorganisms such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* [37] can colonize the oropharynx. In addition, *Candida* spp. are isolated mostly in tracheotomised patients [23, 38].

Pathogens isolated from head and neck SSIs are polymicrobial [6, 16–18, 27, 28, 35, 37–40]. Mainly aerobic gram-positive and gram-negative bacteria are cultured [17, 18, 27]. The most common gram-positive pathogens are *S. aureus, Staphylococcus epidermidis*, and *Streptococcus* spp. Frequently isolated gram-negative bacteria include *Escherichia* spp., *Enterobacteriaceae* spp., *P. aeruginosa, Klebsiella pneumoniae, Haemophilus influenzae*, and *Proteus mirabilis*. Occasionally, anaerobic bacteria, e.g., *Bacteroides* spp. [4, 37, 40] and *Candida* spp. can be isolated [4]. According to Johnson et al. [28], a plausible mechanism of postoperative SSIs is the continuous drainage of saliva in the wound. Since most bacteria are also part of the commensal oropharyngeal flora, differentiation between colonizing and pathogenic organisms can be difficult.

Choice of Antibiotic Agent

Table 3 summarizes the most informative studies with the highest level of evidence.

First-generation cephalosporins are the drug of choice in the prevention of SSIs in general surgery. They have a broad coverage of aerobic gram-positive and some gram-negative bacteria. Skitarelic et al. [27] examined the difference between the administration of cefazolin and amoxicillin–clavulanate in an RCT. The difference between both groups was statistically insignificant ($p > 0.05$). An RCT by Rodrigo et al. [18] concluded the same: cefazolin was equally effective as amoxicillin–clavulanate ($p = 0.8$).

Murphy et al. [44] carried out a retrospective cohort study evaluating the rate of SSIs in patients undergoing osteomyocutaneous free flap reconstruction. Patients developed an SSI in 44% after administration of cefazolin (OR = 1.2, 95% CI 0.3–4.8), a little higher than the group treated with ampicillin–sulbactam (OR = 1) but not statistically significant ($p = 0.73$). Mücke et al. [24] compared patients undergoing flap reconstruction that received amoxicillin–sulbactam, cefuroxime, or benzylpenicillin to a reference group of patients receiving no antibiotics. Patients receiving cefuroxime, a second-generation cephalosporin (OR = 0.35, 95% CI 0.13–0.91, $p = 0.034$), and amoxicillin–sulbactam (OR = 0.29, 95% CI 0.1–0.81, $p = 0.018$) showed a significant reduction in SSIs when compared to the reference group. There was no difference between the administration of benzylpenicillin and no antibiotics (OR = 0.45, 95% CI 0.17–1.19, $p = 0.11$) [24].

Need for Coverage of Anaerobic Bacteria

Phan et al. [37] conducted a trial comparing ampicillin–sulbactam to clindamycin–amikacin. No difference in efficacy was found, but a significantly ($p < 0.05$) higher proportion of anaerobes was isolated in the ampicillin–sulbactam group, indicating the need for anaerobic coverage. In an RCT carried out to

Table 3 Comparative studies evaluating the preferable type of antibiotic in the prevention of surgical site infections

Article	Study type	Antibiotic regimen	Duration	Rate SSI	*p* value	Odds ratio, confidence interval
Robbins et al. (1988) [35]	RCT (n = 330)	Cefazolin–metronidazole (n = 158)	< 5 days (n = 306)	11.9%	< 0.05*	N/A
		Cefazolin (n = 172)	> 5 days (n = 24)	23.9%		
Swanson et al. (1991) [40]	RCT (n = 99)	Cefonicid (n = 50)	1 day (n = 99)	24%	< 0.05*	N/A
		Clindamycin (n = 49)		8.2%		
Phan et al. (1992) [37]	RCT (n = 99)	Ampicillin–sulbactam (n = 42)	1 day (n = 99)	33%	0.19	N/A
		Clindamycin-amikacin (n = 43)		21%		
Weber et al. (1992) [41]	RCT (n = 212)	Ampicillin–sulbactam (n = 105)	1 day (n = 212)	13.3%	< 0.05*	OR = 0.41, 95% CI 0.2–0.84
		Clindamycin (n = 107)		27.1%		OR = 1.00
Rodrigo et al. (1997) [18]	RCT (n = 159)	Amoxicillin–clavulanate (n = 57)	1 day (n = 159)	22.8%	0.8	N/A
		Clindamycin–gentamicin (n = 52)		21.2%		
		Cefazolin (n = 50)		26%		
Johnson et al. (1997) [42]	RCT (n = 169)	Ampicillin–sulbactam (n = 81)	1 day (n = 169)	14%	0.92	OR = 1.00
		Clindamycin (n = 88)		14%		OR = 0.96, 95% CI 0.45–2.407
Callender (1999) [43]	RCT (n = 212)	Clindamycin (n = 107)	2 days (n = 212)	27.1%	0.02*	N/A
		Ampicillin–sulbactam (n = 105)		13.3%		
Skitarelic et al. (2007) [27]	RCT (n = 189)	Cefazolin (n = 92)	24 h (n = 155)	24%	> 0.05	N/A
		Amoxicillin–clavulanate (n = 97)		21%		

Table 3 continued

Article	Study type	Antibiotic regimen	Duration	Rate SSI	*p* value	Odds ratio, confidence interval
Mücke et al. (2015) [24]	OBS (n = 350)	Amoxicillin–sulbactam (n = 88)	10 days (n = 350)	19.3%	0.018*	OR = 0.29, 95% CI 0.1–0.81
		Benzylpenicillin (n = 122)		27%	0.11	OR = 0.45, 95% CI 0.17–1.19
		Cefuroxime (n = 120)		20.8%	0.034*	OR = 0.35, 95% CI 0.13–0.92
		Placebo (n = 20)		50%		OR = 1.00
Mitchell et al. (2015) [25]	OBS (n = 427)	Ampicillin–sulbactam (n = 227)	< 24 h (n = 96)	Overal SSI rate 21.8%	0.01*	OR = 1.00
		Clindamycin (n = 156)				OR = 2.54, 95% CI 1.25–5.14
		Other (n = 44)	> 24 h (n = 331)			OR = 0.84
Langerman et al. (2015) [10]	OBS (n = 1865)	Standard antibiotics (n = 836)[b]	< 4 days (n = 585)	5.1%	N/A	OR = 1.00
		Clindamycin (n = 287)		17.4%		OR = 3.87, 95% CI 2.31–6.49
		Clindamycin + other (n = 166)	> 4 days (n = 1280)	11.4%		OR = 2.69, 95% CI 1.43–5.05
		Non-standard antibiotics[b] (n = 444)		5.0%		OR = 0.95, 95% CI 0.53–1.69
		Placebo (n = 132)		12.9%		OR = 2.17, 95% CI 1.06–4.14
Khariwala et al. (2016) [34]	OBS (n = 149)	Cephalosporins (n = 10)	< 2 days (n = 64)	Overall SSI rate 22.2%	1.00	N/A
		Penicillins (n = 107)	> 2 days		0.04*	
		Quinolones (n = 4)	(n = 85)		0.21	
		Clindamycin (n = 25)			0.02*	
Pool et al. (2016) [19]	OBS (n = 266)	Standard antibiotics (n = 255)[a]	N/A	8%	0.01*	OR = 1.00
		Non-standard antibiotics[a] (n = 41)		27%		OR = 3.78, 95% CI 1.4–10.5

Table 3 continued

Article	Study type	Antibiotic regimen	Duration	Rate SSI	*p* value	Odds ratio, confidence interval
Murphy et al. (2017) [44]	OBS (n = 102)	Ampicillin–sulbactam (n = 58)	12 days	28%		OR = 1.00
		Clindamycin (n = 24)	16 days	64%	0.002*	OR = 7, 95% CI 2.1–26.5
		Cefazolin (n = 16)	N/A	44%	0.73	OR = 1.2, 95% CI 0.3–4.8
		Other (n = 6)[e]	N/A	50%	0.13	OR = 4.6, 95% CI 0.6–36.1
Saunders et al. (2017) [5]	OBS (n = 72)	Cefazolin–metronidazole (n = 50)	7 days (n = 72)	32%	0.02*	OR = 1.00
		Clindamycin (n = 9)		100%		
		Other (n = 13)[c]		23.1%		OR = 14.4, 95% CI 1.52–135.9
Haidar et al. (2018) [8]	SR (n = 697)	Ampicillin–sulbactam (n = 482)	< 1 day	Overall SSI rate 6.6–22.1%	< 0.001*	RR = 2.85, 95% CI 1.95–4.17
		Clindamycin (n = 169)	> 1 day			
		Other (n = 46)[d]				
Veve et al. (2018) [23]	OBS (n = 1307)	No gram-negative coverage[f] (n = 171)	< 6 days vs > 6 days	Overall SSI rate 15%	< 0.001*	OR = 2.2, 95% CI 1.5–3.3
		Enteric gram-negative coverage[f] (n = 522)			0.42	OR = 0.58, 95% CI 0.42–0.80
		Antipseudomonal gram-negative[f] (n = 311)				

RCT randomized controlled trial, *OBS* observational study, *SR* systematic review, *n* number of participants, *CI* confidence interval, *OR* odds ratio, *N/A* not applicable

*$p < 0.05$ is considered statistically significant

[a] Standard antibiotics include cefazolin–metronidazole, cefuroxime–metronidazole, and amoxicillin–clavulanate. The alternative group includes clindamycin, clindamycin–gentamicine, and clindamycin–metronidazole

[b] Standard antibiotics include ampicillin–sulbactam, cefazolin–metronidazole, and cefuroxime–metronidazole

[c] Other antibiotics include cefazolin, levofloxacin, vancomycin, or a combination

[d] Other antibiotics include levofloxacin, vancomycin, cefazolin, ampicillin–sulbactam, cefepime, piperacillin–tazobactam, ciprofloxacin, or combinations

[e] Other antibiotics include vancomycin, piperacillin–tazobactam, daptomycin, or combinations

[f] Antibiotics without gram-negative coverage include clindamycin, metronidazole, linezolid, and vancomycin. Antibiotics with enteric gram-negative coverage include cefazolin, cephalexin, ceftriaxone, amoxicillin–clavulanate, ampicillin–sulbactam, cefoxitin, cefotetan, ertapenem, moxifloxacin, doxycycline, trimethoprim–sulfamethoxazole. Antibiotics with enteric gram-negative and antipseudomonal coverage include aztreonam, gentamicin, cefepime, ciprofloxacin, levofloxacin, imipenem–cilastatin, meropenem, and piperacillin–tazobactam

Table 4 Comparative studies evaluating the preferable postoperative prolongation of the antibiotic course

Article	Study design	Duration	Antibiotic regimen	Rate SSI	*p* value	Odds ratio confidence interval
Johnson et al. (1986) [28]	RCT (n = 109)	1 day (n = 53)	Cefoperazone sodium (n = 109)	18.9%	> 0.05	N/A
		5 days (n = 56)		25%		
Sawyer et al. (1990) [45]	RCT (n = 50)	2 days (n = 25)	Cefazolin–metronidazole (n = 50)	32%	0.04*	OR = 12.9, 95% CI 1.12–148.0
		>7 days (n = 25)		20%		OR = 1.00
Mustafa and Tahsin (1993) [46]	RCT (n = 60)	1 day (n = 30)	Cefotaxime sodium (n = 60)	13%	> 0.05	N/A
		7 days (n = 30)		10%		
Righi et al. (1996) [4]	RCT (n = 162)	1 day (n = 81)	Clindamycin–cefonicid (n = 162)	2.5%	> 0.05	N/A
		3 days (n = 81)		3.7%		
Carroll et al. (2003) [47]	RCT (n = 74)	1 day (n = 35)	Clindamycin (n = 74)	11%	0.99	N/A
		5 days (n = 39)		10%		
Sepehr et al. (2009) [22]	OBS (n = 407)	< 4 days (n = 202)	Cefazolin–metronidazole (n = 407)	7%	0.06	N/A
		> 5 days (n = 205)		13%		
Taghy et al. (2010) [26]	RCT (n = 90)	2 days (n = 45)	Cefazolin (n = 90)	4.4%	> 0.05	N/A
		5 days (n = 45)		5.6%		
Busch et al. (2016) [7]	OBS (n = 418)	< 7 days	Various antibiotics[a]	14.6%	0.689	N/A
		> 7 days		13.2%		

Table 4 continued

Article	Study design	Duration	Antibiotic regimen	Rate SSI	*p* value	Odds ratio confidence interval
Langerman et al. (2016) [48]	OBS (n = 8836)	1 day (n = 695)	Ampicillin–sulbactam (n = 2230)	N/A	0.001*	OR = 1.00
		> 1 day (n = 7382)	Other[b] (n = 6606)			OR = 0.28, 95% CI 0.13–0.61
Khariwala et al. (2016) [34]	OBS (n = 149)	< 2 days (n = 64)	Cephalosporins (n = 10)	15.6%	0.74	N/A
		> 2 days (n = 85)	Penicillins (n = 107)	17.7%		
			Quinolones (n = 4)			
			Clindamycin (n = 25)			
Vila et al. (2017) [49]	SR (n = 340)	1 day 5 days	Various antibiotics[c]	N/A	0.718	RR = 0.98, 95% CI 0.58–1.61
Haidar et al. (2018) [8]	SR (n = 861)	< 1 day	Ampicillin–sulbactam (n = 112)	Overall SSI rate 6.6–22.1%	0.006*	RR = 1.56, 95% CI 1.13–2.14
		> 1 day	Clindamycin (n = 39)			
			Other (11%)[d]			
Bartella et al. (2017) [6]	RCT (n = 75)	1 day (n = 50)	Ampicillin–sulbactam (n = 50)	44%	0.013*	N/A
		5 days (n = 25)	Ampicillin–sulbactam and enhanced local aseptic care (n = 25)	12%		
Bartella et al. (2018) [20]	RCT (n = 901)	1 day (n = 536)	Ampicillin–sulbactam	1.77%	0.831	N/A
		5 days (n = 365)	Clindamycin in penicillin allergic patients	0.77%		

Table 4 continued

Article	Study design	Duration	Antibiotic regimen	Rate SSI	*p* value	Odds ratio confidence interval
Veve et al. (2018) [23]	OBS (n = 1307)	< 6 days	No gram-negative coverage[e] (n = 171)	Overall SSI rate 15%	0.08	OR = 1.00
		> 6 days	Enteric gram-negative[e] (n = 522)			OR = 0.71, 95% CI 0.51–1.1
			Antipseudomonal gram-negative[e] (n = 311)			

RCT randomized controlled trial, *OBS* observational study, *SR* systematic review, *n* number of participants, *OR* odds ratio, *CI* confidence interval, *N/A* not applicable

*$p < 0.05$ is considered statistically significant

[a] Various antibiotics include cefazolin, clindamycin, cefuroxime, ampicillin–sulbactam, metronidazole, or combinations

[b] Other antibiotics include ampicillin–sulbactam, clindamycin, cefazolin–metronidazole, and cefazolin

[c] Various antibiotics include cefazolin, cefonicid, cefotaxime, cefamandole, moxalactam, clindamycin, carbenicillin, ampicillin–sulbactam, amoxicillin–clavulanate, or combinations

[d] Other antibiotics include levofloxacin, vancomycin, cefazolin, ampicillin–sulbactam, cefepime, piperacillin–tazobactam, ciprofloxacin, or combinations

[e] Antibiotics without gram-negative coverage include clindamycin, metronidazole, linezolid, and vancomycin. Antibiotics with enteric gram-negative coverage include cefazolin, cephalexin, ceftriaxone, amoxicillin–clavulante, ampicillin–sulbactam, cefoxitin, cefotetan, ertapenem, moxifloxacin, doxycycline, trimethoprim–sulfamethoxazole. Antibiotics with enteric gram-negative and antipseudomonal coverage include aztreonam, gentamicin, cefepime, ciprofloxacin, levofloxacin, imipenem–cilastatin, meropenem, and piperacillin–tazobactam

determine the need for anaerobic coverage, Robbins et al. [35] compared cefazolin alone to cefazolin–metronidazole and found a significant SSI risk reduction for the combination ($p < 0.05$). Rodrigo et al. [18] compared cefazolin to amoxicillin–clavulanate and clindamycin–gentamicin; again, no difference in efficacy was found ($p = 0.8$) and they did not find a higher proportion of anaerobes in the cefazolin group, suggesting that anaerobic coverage is not necessary.

Need for Coverage of Gram-Negative Bacteria: Clindamycin

Clindamycin, a lincosamide with broad anaerobic coverage, is often given to patients with a known penicillin allergy. Johnson et al. [42] conducted a trial in 1997 comparing the efficacy of clindamycin and ampicillin–sulbactam and stated that both agents are equally effective ($p = 1.00$). This conclusion is in contrast to other RCT findings [41, 43]. Callender [43] found ampicillin–sulbactam more effective than clindamycin ($p = 0.02$). Another RCT also showed a lower SSI rate in the ampicillin–sulbactam group [41]. A recent meta-analysis confirmed again that, compared with ampicillin–sulbactam, clindamycin had an increased risk of SSIs ($p = 0.02$, RR = 2.85, 95% CI 1.95–4.17) [8]. These studies thus suggest that gram-negative coverage is essential, a finding underlined by Veve et al. [23], who confirmed that lack of gram-negative coverage implies a higher risk of SSIs (OR = 2.2, 95% CI 1.5–3.3). Antipseudomonal treatment did not result in a significant SSI reduction compared with regimens that did not address *Pseudomonas* ($p = 0.42$).

These findings are in contrast to an earlier prospective RCT of 1990, where clindamycin was found superior to cefonicid in the prevention of SSIs ($p > 0.05$) [40].

Langerman et al. compared the SSI rate in patients undergoing a laryngectomy given clindamycin alone or clindamycin together with another antibiotic. Placebo (OR = 2.17, 95% CI 1.06–4.14), clindamycin administered alone (OR = 3.87, 95% CI 2.31–6.49), or in combination with another antibiotic (OR = 2.69, 95% CI 1.43–5.05) showed a higher SSI risk compared with standard antibiotics, such as ampicillin–sulbactam, cefazolin–metronidazole, or cefuroxime–metronidazole. The use of clindamycin alone was also associated with a threefold risk of wound dehiscence and antibiotic-induced complications, when compared with standard antibiotics (OR = 3.01, 95% CI 1.59–567). These complications include the development of *Pseudomonas, C. difficile*, and methicillin-resistant *S. aureus* (MRSA) infections [10].

Phan et al. [37] added amikacin, characterized by a broad gram-negative coverage, to clindamycin and compared it to ampicillin–sulbactam in an RCT; both regimens were equally effective ($p = 0.19$). As mentioned, an RCT by Rodrigo et al. [18] compared amoxicillin–clavulanate to clindamycin–gentamicin and cefazolin and found no difference between the three regimens ($p = 0.8$).

Patients undergoing free flap reconstruction form a special entity in many aspects, but clindamycin is also less effective in this group. Pool et al. [19] reviewed 266 patients undergoing head and neck free flap reconstruction and found that use of clindamycin implies a fourfold increased risk of wound infection (OR = 3.78, 95% CI 1.4–10.5). The same relation was found in an RCT [25] (OR = 2.54, 95% CI 1.25–5.14), and also in another review [34]. In 72 patients undergoing microvascular free flap reconstruction, Saunders et al. [5] found that cefazolin–metronidazole, the most used regimen, implied an infection rate of 32%; clindamycin, given in penicillin-allergic patients, was associated with a 100% infection rate. The average hospitalization was also longer in patients receiving clindamycin, compared with other agents ($p < 0.05$, OR 7.1, 95% CI 3.86–10.75).

Comparison Between Ampicillin–Sulbactam and Clindamycin: A Meta-Analysis

The 39 included studies are listed by type of antibiotic (Table 3) and duration of the antibiotic course (Table 4). Manuscripts having the same intervention and comparator were screened [8, 10, 19, 20 25, 42–44]. We found eight manuscripts comparing clindamycin to ampicillin–sulbactam. Three manuscripts were excluded: one systematic review [8] and two manuscripts with insufficient data available (number of events) [19, 20].

Three RCTs [41–43] and two retrospective cohort studies [10, 44] comparing clindamycin and ampicillin–sulbactam in the prevention of SSIs in patients undergoing clean-contaminated head and neck surgery were included in a meta-analysis. The mean duration of follow-up in the included studies is 30 days; Weber et al. [41] and Callender [43] mentioned no duration of follow-up. In 4336 patients, the overall pooled OR was 2.73 (95% CI, 1.50–4.97, $p = 0.001$) for patients receiving clindamycin, compared with those receiving ampicillin–sulbactam. The test for heterogeneity showed an I^2 value of 73%, so

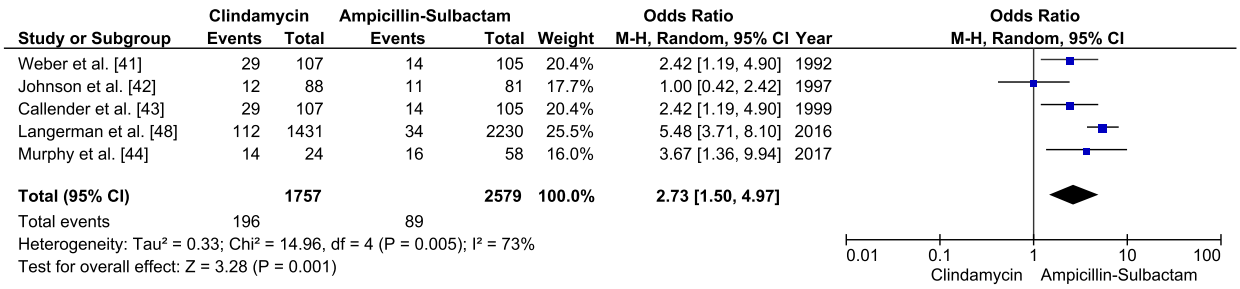

Fig. 2 Comparison between the efficacy of ampicillin–sulbactam and clindamycin in the prevention of surgical site infections: a meta-analysis

a random-effects model was warranted. The findings are summarized in Fig. 2 [42–44, 48].

Duration of Postoperative Antibiotic Course

The efficacy of short- versus long-term ABP has been investigated extensively (Table 4). Mustafa and Tahsin compared the administration of a third-generation cephalosporin, cefotaxime, for either 1 day or 7 days [46]. SSI incidence was 13% and 10%, respectively, but still statistically insignificant ($p > 0.05$). Recently, Busch et al. also found no difference between ABP for less or more than 7 days ($p = 0.689$) [7]. Similarly, a large cross-sectional study showed that a postoperative antibiotic course for longer than 6 days did not further reduce the rate of SSIs ($p = 0.08$) [23]. Finally, a systematic review found no significant difference between 1 day and or 5 days of prophylaxis using various types of antibiotics including penicillins, cephalosporins, and clindamycin ($p = 0.718$, RR = 0.98, 95% CI 0.59–1.61) [49]. Sepehr et al. [22], comparing cefazolin–metronidazole for less or more than 5 days, showed the same SSI rate in both groups ($p = 0.06$). In contrast, Bartella et al. [6] randomized 75 patients to receive ampicillin–sulbactam and clindamycin in case of penicillin allergy for more or less than 5 days. Initially they found significantly less SSIs when ABP was prolonged until the 5th postoperative day ($p = 0.013$). However, they then conducted a larger RCT ($n = 901$) comparing ABP on the day of surgery versus until the 5th postoperative day and found no difference in SSI rate ($p = 0.831$) [20].

Also, regarding clindamycin, different regimen durations have been examined. Righi et al. [4] performed an RCT comparing the administration of clindamycin–cefonicid for 1 day versus for 3 days. In the 1-day group wound SSIs occurred in 2.5% versus in 3.7% in the 3-day group ($p > 0.05$). Langerman et al. [48] evaluated the difference between the administration of antibiotics for 1 day or for 2 days. Prolonged administration of ampicillin–sulbactam reduced the risk of SSI by over two-thirds ($p = 0.001$, OR = 0.28, 95% CI 0.13–0.65). The administration of clindamycin for 2 days was associated with an increased risk of infection compared with patients who received standard antibiotics ($p = 0.078$, OR = 1.82, 95% CI 0.93–3.56) and prolonged clindamycin even appeared less efficient than ampicillin–sulbactam for 1 day ($p = 0.006$, OR = 2.66, 95% CI 1.33–5.30). However, the authors did not see an increased SSI rate compared with ampicillin–sulbactam when clindamycin was only given on the day of surgery ($p = 0.419$, OR = 1.46, 95% CI 0.58–3.61).

Prolonged Antibiotic Course in Patients Undergoing Flap Reconstruction

In 1986, Johnson et al. [28] randomized 109 patients undergoing major head and neck surgery with pedicled flap reconstruction into two different ABP regimens based on cefoperazone sodium, a third-generation cephalosporin. The first group received 1 day of prophylaxis (SSIs in 18.9%), the second group 5 days (SSIs in 25%; $p > 0.05$). Carroll et al. [47] confirmed this for clindamycin in patients undergoing free flap reconstruction, finding no difference in the SSI rate between 1 or 5 days of ABP ($p = 0.99$). These data suggest no beneficial effect from an antibiotic course for longer than 24 h. Contrary to this finding, Sawyer et al. [45] compared 2 days of administration of cefazolin–metronidazole to more than 7 days in patients undergoing free flap reconstruction and found less cases of wound infection in the long-term group ($p = 0.04$). This conclusion is again in contrast to a more recent review in which the authors found no difference in efficacy between administration of antibiotics for less or more than 2 days ($p = 0.74$), but a higher risk of pneumonia in patients undergoing long course antibiotic regimens ($p = 0.03$) [34].

Prolonged Antibiotic Course in Patients with Otherwise Increased Risk of Postoperative Wound Infection

In patients with other factors associated with an increased risk of postoperative SSIs, Busch et al. [7] compared the rate of infection between short- and long-term prophylaxis in patients with a tracheotomy (no difference; $p = 0.689$),

in patients with diabetes (no advantage; $p = 0.443$), or an increased BMI (no difference; $p > 0.05$). These findings are confirmed by Sepehr et al. [22], who also found no SSI rate reduction after prolonged prophylaxis in patients with malnutrition ($p = 1.00$). Also in the specific high-risk group of laryngectomy patients, 5 days of cefazolin had no advantage over 2 days of prophylaxis: no difference in fistula development rate was observed ($p > 0.05$) [26]. Likewise, Busch et al. [7] also found that the duration of prophylaxis did not influence the rate of fistula formation after major procedures.

DISCUSSION

Patients undergoing clean-contaminated head and neck surgery are at risk of developing postoperative complications: surgical wound infections, fistula formation, flap dehiscence, and donor site infection, all increasing hospital stay, morbidity, and mortality [5, 9]. In preparing this review, we found a wound infection rate after clean-contaminated head and neck surgery ranging between 2.5% and 64%, and polymicrobial in origin [6, 16–18, 27, 28, 35, 37–40]. Higher BMI, malnutrition, diabetes, liver disease, anemia, peripheral vascular disease, chronic obstructive pulmonary disease, immunosuppressive medication, and higher ASA score increase the risk of wound infection [10, 18–24]. Other factors include extensive surgery with flap reconstruction and neck dissection, previous chemotherapy, and a perioperative tracheotomy [7]. A total laryngectomy is associated with fistula formation implying the highest risk of wound infection [17, 18, 39]. Different studies found, counter-intuitively, that preoperative radiotherapy does not increase the risk of SSI [4, 7, 15–18, 25, 28, 33]. Other studies do suggest a positive association between preoperative radiotherapy and SSI development [29–33].

Compared with placebo, perioperative antibiotics significantly reduce the risk of SSIs and are therefore routinely used [15–17]. The antibiotic should be administered preoperatively, less than 60 min prior to incision or at induction of anaesthesia, and should be intraoperatively repeated if the surgery lasts more than 4 h [14]. 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 [18, 24, 27]. Other antibiotics, such as benzylpenicillin [24] and clindamycin [5, 8, 10, 19, 23, 27, 38, 43], are inferior. Of note, in the USA, ampicillin–sulbactam is available as a single pharmacologic preparation.

Coverage of anaerobic bacteria with metronidazole has been found effective in one RCT [43], but not in others [18]. In a recent systematic review, Veve et al. [38] recommended anaerobic coverage, despite conflicting clinical evidence. A large-scale multicenter study by the same authors [23] suggests anaerobic coverage in all head and neck surgery with flap reconstruction, e.g., using ceftriaxone–metronidazole or ampicillin–sulbactam. We failed to find other studies investigating the efficacy of metronidazole. Further studies on the indications for anaerobic coverage are needed. It should be noted that anaerobic bacteria are part of the flora of the head and neck region and are often not isolated or properly collected to allow anaerobic cultures. According to our meta-analysis of five trials, clindamycin is less efficient than ampicillin–sulbactam in the prevention of postoperative wound infections (OR = 2.73, 95% CI 1.50–4.97). Therefore, the use of clindamycin alone as prophylactic agent should be avoided. In SSIs despite clindamycin prophylaxis, gram-negative bacteria are often isolated, i.e., their coverage is insufficient. This finding is consistent with multiple RCTs concluding that clindamycin ABP carries an increased SSI rate [5, 8, 10, 19, 23, 27, 38, 43] and a higher risk of antibiotic-related complications, such as *Pseudomonas*, MRSA, and *C. difficile* infections including pseudomembranous colitis [6, 10]. Contrary to this finding, and like many other guidelines [12], the Leuven University Hospitals' guidelines still recommend clindamycin as an alternative for penicillin-allergic patients [11], because there are only few studies studying alternative agents in patients with a true penicillin allergy. Langerman et al. [10] suggest adding aminoglycosides,

ciprofloxacin, or aztreonam to clindamycin to expand the gram-negative coverage. Adding an aminoglycoside to clindamycin reduces the risk of infection and is equally effective as cefazolin, amoxicillin–clavulanate, or ampicillin–sulbactam according to different studies [18, 37], but is also associated with an increased risk of drug toxicity (ototoxicity, nephrotoxicity) [50]. In contrast, Langerman et al. concluded that the use of clindamycin in any combination of antibiotics had higher rates of wound infection, wound dehiscence, and antibiotic-related complications [10], and thus suggest alternative regimens (ciprofloxacin, aztreonam–metronidazole, or vancomycin). Another recent study suggested the combination of levofloxacin and metronidazole [5]. Patients with a true penicillin allergy are known to have cross-reactivity to first-generation cephalosporins in only 2% of cases [51]. Second- and third-generation cephalosporins can be considered in patients with a penicillin allergy, because there is even less cross-reactivity in this group. Cefuroxime, a second-generation cephalosporin, was found to be effective as prophylactic agent in one RCT [24], and thus can be considered an alternative in penicillin-allergic patients. To confirm this, further studies are needed to compare cefuroxime to standard antibiotics. Of note, 90% of patients that mention an alleged penicillin allergy have a negative skin-prick test [51]. Thus, confirmation of a true penicillin allergy with skin testing or serum IgE testing is of paramount importance.

Multiple studies evaluated the difference in SSI rate between short- and long-term prophylaxis. 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 [6, 7, 22, 24, 38, 49]. Similarly, one RCT [4] could not demonstrate a beneficial effect in patients receiving prophylaxis for 3 days, compared with 1 day. Langerman et al. [48] examined the difference between ABP for 24 h versus 48 h and concluded that prolongation of ampicillin–sulbactam was beneficial in the prevention of wound infections, whereas clindamycin was associated with a higher risk of SSI. In contrast, a recent review by Haidar et al. [8] concluded that less than 24 h of appropriate prophylaxis is likely sufficient. Further investigations should be carried out to compare the efficacy between 1 day and 2 days of ABP.

Surgeons tend to prolong postoperative ABP in patients with an increased risk of complications, e.g., after a total laryngectomy with flap reconstruction or after previous radiotherapy. Various studies fail to show a beneficial effect of long-term prophylaxis in patients undergoing laryngectomy, free flap reconstruction, or in patients with other risk factors including diabetes, increased BMI, malnutrition, or a tracheotomy [7, 22, 26]. Our findings are consistent with recent systematic reviews by Patel et al. [52] and Jethwa and Khariwala [53], and also concur largely with the conclusions of a recent meta-analysis of existing guidelines [12]. Therefore we suggest a short course of postoperative ABP for 24–48 h in all patients undergoing clean-contaminated head and neck surgery.

Limitations

The limitations of this study are that the meta-analysis is conducted on the basis of only five studies. The predefined inclusion criteria did not allow inclusion of more studies. We were able to compare ampicillin–sulbactam to clindamycin, but there were insufficient data to compare other types of antibiotics. The included studies also appeared to be heterogeneous based on the I^2 statistic.

CONCLUSION

On the basis of this systematic review of the evidence, perioperative antibiotics clearly reduce the incidence of SSIs after clean-contaminated head and neck surgery. To date, the antibiotics of choice are cefazolin, ampicillin–sulbactam, and amoxicillin–clavulanate. In patients with alleged penicillin allergy, detailed allergy testing should be carried out. If penicillin allergy is confirmed substitution with clindamycin increases the risk of wound infection when compared to ampicillin–sulbactam, according to our meta-analysis, and should be

avoided. Future studies are needed to identify the ideal substitute in penicillin-allergic patients. Also, more studies are desirable to confirm the need for coverage of anaerobic bacteria by adding metronidazole.

The current antibiotic regimens ideally are administered less than 60 min prior to incision and should be repeated intraoperatively if the surgery lasts more than 4 h. A 24-h regimen is likely sufficient. Some evidence suggests to prolong administration to 48 h, but ABP for more than 48 h does not further reduce the rate of infection and is associated with an increased risk of adverse effects, such as antibiotic-related complications or hospital-acquired pneumonia.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. Ethical exemption was provided by the Education-Support Committee (OBC) or the Research Ethics Committee of KU Leuven.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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