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REVIEW

Antibiotic prophylaxis in otolaryngologic surgery

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Abstract
Since the beginning of the 80s, numerous clinical trials have shown a significant reduction in the incidence of infections in clean-contaminated upper respiratory tract surgery, due to perioperative use of antibiotics; however, there is no consensus about the best antibiotic protocol. Moreover, there are no universally accepted guidelines about flap reconstructive procedures. In otologic and rhinologic surgery, tonsillectomy, cochlear implant and laryngo-pharyngeal laser surgery, the use of antibiotics frequently depends on institutional or personal preferences rather than the evidence available. We reviewed clinical trials on different otorhinolaryngologic procedures, assessing choice of antibiotic, length of treatment and administration route. There are no clinical trials for laryngo-pharyngeal laser surgery. Nor are there clinical trials on implant cochlear surgery or neurosurgical clean-contaminated procedures, but in these circumstances, antibiotic prophylaxis is recommended.

PALABRAS CLAVE
Infección quirúrgica;
Profilaxis antibiótica;
Cirugía otorrinolaringológica

Profilaxis antibiótica en cirugía otorrinolaringológica

Resumen
Desde principios de los años ochenta, numerosos ensayos clínicos han demostrado una reducción significativa en la incidencia de infección en la cirugía limpia-contaminada de la vía aerodigestiva superior debido al uso de antibióticos; sin embargo, no hay consenso sobre las pautas idóneas. Tampoco existe una pauta universalmente aceptada en la reconstrucción con colgajos. En la cirugía otológica, la rinológica, la amigdalectomía, la implantación coclear y la cirugía láser laringofaríngea, el uso de antibióticos perioperatorios depende frecuentemente de preferencias personales e institucionales, y no de la evidencia existente. Revisamos de forma crítica los en-

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sayos clínicos disponibles sobre diversas técnicas quirúrgicas otorrinolaringológicas, evaluando distintos antibióticos, duración del tratamiento o vía de administración. No existen ensayos clínicos sobre la cirugía láser laringofaríngea. Tampoco hay ensayos clínicos sobre implantación coclear y los procedimientos neuroquirúrgicos limpios-contaminados, si bien en estos supuestos se recomienda la profilaxis antibiótica.

Introduction

Surgical antibiotic prophylaxis is defined as the administration of an antimicrobial agent prior to contamination in previously sterile spaces and fluids.[1] Depending on the degree of contamination and the risk of infection, surgical wounds are classified into several categories; we accept the classification of the American National Academy of Science and the National Research, as amended by the American Society of Health-System Pharmacist 1999[2,3]:

- Clean injuries: no opening of respiratory or digestive tract, no prior infection and no violation of asepsis.
- Clean-contaminated injuries: opening of digestive or respiratory tract, minor violation of aseptic technique, closed trauma or clean surgical reintervention within the first 7 days.
- Contaminated injuries: clean-contaminated surgery with non-purulent inflammation, greater violation of aseptic technique and first 4 h of open trauma.
- Dirty injuries: purulent inflammation, perforation of hollow viscera or open trauma for more than 4 h of evolution.

We have decided to apply to our review the levels evidence proposed by the American College of Cardiology and American Heart Association[4] (Table 1). In our view, it is a simple classification that stratifies the quality of the available evidence in a well-defined form.

The incidence of infection in clean surgery of head and neck is estimated at less than 5% and in some series it reaches figures of 0.56%.[5,6] There are no randomised clinical trials (RCTs) showing the benefit of the use of prophylactic antibiotics in clean surgery of the head and neck. Three retrospective cohort studies found no statistically significant relationship between the decrease in the incidence of infections and the use of prophylactic antibiotics.[5-7] Given the low incidence of infection, the design of an RCT would require a large sample size to reduce the error by having enough statistical power.

In both dirty and contaminated surgery, it is assumed that the wound is already infected and, in that case, the antibiotic is administered with therapeutic intent. In clean-contaminated surgery of the head and neck, the incidence of infection is estimated to be between 24% and 87%.[8] There are numerous, well designed double-blind RCTs, as well as meta-analysis, that demonstrate the benefit of perioperative prophylactic antibiotic regimes in reducing the incidence of postoperative infection[9-14] (evidence level A). Table 2 shows the characteristics of some of these trials. In prospective studies using prophylactic antibiotics in this type of surgery, the incidence of infection is between 10 and 25%.[15,16] According to the American Society of Health-System Pharmacist 1999 guideline (ASHP 1999),[3] the ideal antibiotic should be active against the most common contaminants, and must be maintained at appropriate doses for the duration of the contamination, have a good safety profile and be administered in the shortest possible time.

Prophylaxis in clean-contaminated surgery of the head and neck

Resident germs

The most common pharyngeal colonizers are gram-positive cocci, mainly *Peptostreptococcus* and *Peptococcus* species, and anaerobic germs[3,8]: in the oropharynx, the presence of anaerobes is 10 times more frequent than that of aerobes.[17] Gram-negative germs are rare in the secretions of healthy individuals; nevertheless, germs such as *Klebsiella*, *Pseudomonas*, *Proteus* and some *Bacteroides* species (other than *B. fragilis*) are common colonizers of the aerodigestive tract of oncology patients.[8]

The presence of *Streptococcus* and *Staphylycoccus* is common in the nasal cavity, and to a lesser extent than anaerobes. Anaerobes are 10 times more numerous in the oropharynx than in the nasal cavity. Between 18 and 50% of healthy adults are carriers of *Staphylococcus* in their nasal fossa; it is estimated that 0.84% of the population are carriers of *S. aureus* resistant to methicillin (MRSA) in their nasal fossa.[18,19]

The presence of gram-negative germs is common in the isolations performed in postoperative cervical infections.[20] However, it is unclear whether they are infectious agents or colonizers. In a clinical trial, Johnson et al. found no significant differences using a prophylactic regime with

Table 1 Levels of evidence applied in the review[4]

Level of evidence A	Data derived from multiple randomised clinical trials or meta-analyses
Level of evidence B	Data derived from a randomised clinical trial or nonrandomised studies
Level of evidence C	Data derived from consensus of experts or series of cases

Table 2 Double-blind clinical trials evaluating the use of prophylactic antibiotics in clean-contaminated surgery of the head and neck

Year	Author	Patients, No.	Antibiotic	Duration	Infection[a]	*P*
1962	Ketchman[9]	20	Chloramphenicol	10 days	18%versus 0%	<.05[b]
1973	Dor[10]	102	Ampicillin and cloxacillin	5 days	36% versus 17%	<.05
1979	Becker[11]	55	Cefazolin	1 day	87% versus 38%	<.001[b]
1984	Johnson[26]	16	Cefoperazone	1 day	78% versus 0%	<.05
1984	Mandell-Brown[12]	101	Cefazolin/ cefoperazone/ cefotaxime	1 day	33%/ 10%/ 10% versus 78%	<.05
1988	Saginur[13]	20	Cefamandole	1 day	55%versus 33%	<.05[b]

[a]Incidence between treatment group and control group.
[b]Interrupted trials in intermediate analysis by excessive difference of infection between one group and the other.

coverage against gram-positive and gram-negative germs compared with one that covered only gram-positive germs.[21] Nor were there significant differences with regards to coverage or not of gram-negatives in the clinical trials of Rodrigo et al.[15] and Piccart et al.[22]

Isolation of bacteria in infected surgical wounds of clean-contaminated head and neck surgery commonly has polymicrobial characteristics; depending on the series, this ranges between 38 and 95% of isolations.[15,20,23-25] The isolation of gram-positives is more frequent, followed by gram-negatives and anaerobes.[15,23] In most series, the isolation of anaerobic bacteria is less frequent than that of aerobic, except for the series of Johnson et al., in which it reaches up to 42%of isolates in patients who did not receive antibiotic prophylaxis.[26] Moreover, it must be considered that the isolation of anaerobes is more complicated than that of aerobes, so their presence may be underestimated. There are risk factors that favour the presence of anaerobes in the infectious focus, such as concomitant dental extractions[27] and surgery of the oral cavity.[17]

There is little correlation between the results of preoperative cultures of the aerodigestive tract and the postoperative infectious agent. In a review by Suarez et al., only in 44% of cases was it possible to identify the postoperative pathogen in this manner.[8,28] The correlation between microorganisms isolated from postoperative drainage and the agent isolated from the infection ranges between 38%and 54%[8] Only one study found a correlation of 100%[29]

Recommended guidelines

Choice of antibiotic

Historically, and still today, various prophylactic regimes are used depending on the institution and personal experience. The most commonly used antibiotics include cephalosporins, amoxicillin or ampicillin, clindamycin, metronidazole, aminoglycosides, and various combinations thereof.[30] Table 3 details various characteristics of several widely used antibiotics in surgery of the head and neck.[31,32]

The benefit of employing regimes including clindamycin plus an aminoglycoside versus clindamycin alone has not been shown in well-designed RCTs; nevertheless, one of those clinical trials (Piccart et al.) was not completely controlled.[21,22] Furthermore, several double-blind RCTs have not shown with statistical significance the benefit of the use of clindamycin and gentamicin versus cefazolin or amoxicillin-clavulanate. Skitarelic et al., on 189 patients undergoing clean-contaminated surgery of the head and neck, excluding free flaps, found no statistically significant reduction in the incidence of infection between amoxicillin-clavulanate and cefazolin.[20] Rodrigo et al., in RCTs of 159 patients, not including free flaps, who were split into three groups, found no statistically significant differences in terms of infection between amoxicillin-clavulanate, cefazolin and clindamycin + gentamicin.[15] The main differences between cefazolin and amoxicillin-clavulanate are coverage against anaerobes and the resistance against beta-lactamase of amoxicillin-clavulanate. With regard to the need for the use of beta-lactamase-resistant antibiotics, in an RCT on 118 patients that compared cefazolin sensitive to beta-lactamase versus moxalactam resistant to beta-lactamase, there were no significant differences.[33] Table 4 details the characteristics of various RCTs evaluating different prophylactic antibiotic regimes.

There is a single blind RCT with four groups and 120 participants where lower infection is significant in the groups including metronidazole. However, in that test, in which combinations of antibiotics were administered, metronidazole and gentamicin were administered by injection, whereas cephalexin and ampicillin were administered orally in the postoperative period.[34]

For all these reasons and considering that cefazolin is a cheaper antibiotic, with a lesser spectrum and safer than amoxicillin-clavulanate, clindamycin, or aminoglycosides, then cefazolin is recommended as first choice for surgical prophylaxis in clean-contaminated surgery of the head and neck, according to the recommendations of the

Table 3 Antibiotics used for prophylaxis in clean-contaminated surgery of the head and neck[31,32]

	Bacterial coverage	Adverse effects	Dosage[a]	Cost[b]
Clindamycin	Anaero bic Gram-positives	GI intolerance, pseudomembranous colitis, hepatotoxicity, cytopenia	300-900 mg/ 6-8 h	11.5
Gentamicin	Gram-negative aerobes, *S. aureus*	Nephrotoxicity, ototoxicity, neuromuscular blockade	5-7 mg/kg/day in 1-2 doses	1.8
Amoxicillin-clavulanate	Gram-positives, gram-negatives, *Enterococci*, anaerobes	Anaphylaxis, gastrointestinal intolerance, superinfection	1-2 g amoxicillin+ 200 mg clavulanate / 6-8 h	11.5
Ampicillin-sulbactam	Similar to amoxicillin-clavulanate	Similar to amoxicillin-clavulanate	1-2 g ampicillin+ 500 mg sulbactam/ 6-8 h	4
Cefazolin	Gram-positive cocci	Anaphylaxis, GI intolerance	1-2 g/ 6-8 h	9
Vancomycin	Gram-positive aerobes, gram-positive anaerobes, *Clostridium*	Nephrotoxicity, ototoxicity, red man syndrome, phlebitis	20-50 mg/ kg/ day in 2 doses	34.5
Metronidazole	Gram-positive cocci, anaerobes	Gastrointestinal toxicity, metallic taste, polyneuropathy, dizziness	250-750 mg/kg/ 8-12 h	11.5

[a]Dose for an adult.
[b]Euros/ day of treatment, taking as reference generic drugs.

Table 4 Clinical trials evaluating different antibiotics in clean-contaminated surgery of the head and neck

Year	Author	Patients	Antibiotic	Infection, %	*P*
1986	Johnson[33]	118	Moxalactam	3.40	>.05
			Cefazolin	8.50	
1987	Johnson[21]	104	Clindamycin	3.80	>.05
			Clindamycin and gentamicin	3.80	
1997	Rodrigo[15]	159	Amoxicillin-clavulanate	23	.8
			Clindamycin and gentamicin	21	
			Cefazolin	26	
2007	Skitarelic[20]	189	Cefazolin	24	>.05
			Amoxicillin-clavulanate	21	

Antimicrobial Agents Committee of the Surgical Infections Society and ASHP 1999. Clindamycin should be reserved for cases of allergy to beta-lactams. In the absence of RCTs evaluating the efficacy of regimes against anaerobes in patients at risk versus patterns without such coverage, it is postulated that amoxicillin-clavulanate could be the first choice in surgeries at risk of contamination by anaerobes, such as oral or oropharyngeal surgery or concomitant tooth extractions.

Recommended doses

In one RCT by Robbins et al. on 218 patients, which compared 500 mg of cefazolin versus the same dose of cefazolin with metronidazole, a statistically significant incidence of infection of 23.9% and 11.9%, respectively, was found.[35] In an RCT by Johnson et al. on 50 patients, a higher incidence of infection in the group treated with 500 mg of cefazolin versus clindamycin with gentamicin (33% vs 7%) was significant.[36] In an RCT by Mendell-Brown, which is hampered by low sample size, the administration of 500 mg of cefazolin resulted significantly less effective than cefoperazone or cefotaxime.[12] On the other hand, in a double-blind RCT with over 100 participants, using perioperative cefazolin in doses of 2 g, the significant benefit of other antibiotic regimes was not demonstrated.[15,33]

According to ASHP 1999 and by virtue of the above, doses of 2 g of cefazolin are recommended; the alternative would be 600 mg of clindamycin.[3]

Duration of the prophylaxis

Theoretically, once the mucosa of the contaminated viscera has closed, the source of contamination has ceased and the

administration of antibiotics ceases to have a theoretical basis. If there is any suspicion about the loss of tightness of the compartment, then it is assumed to be dirty surgery and the antibiotic will have a therapeutic intent. Righi et al.[37] consider that postoperative infection produced in a differed manner cannot be considered failure of prophylaxis, but is instead due to persistent contamination by saliva and is attributable to surgical errors, tissue ischemia, abnormal scarring, etc.

In an experimental model of surgical infection in guinea pigs, it was found that concomitant administration of antibiotics prior to incision reduced the incidence of infection. However, the administration of antibiotics with a latency of 3h was associated to an incidence of infection similar to that of the group without antibiotics.[38]

Johnson et al.,[36] in RCTs with 56 patients, found no statistically significant differences between administering clindamycin and gentamicin for 1 day (7% infections) or 5 days (4% infections). Piccart et al.,[22] in RCTs with 140 patients, found no significant differences between batches of carbenicillin for 1 or 5 days. In a more recent clinical trial by Righi et al.[37] on 162 patients, excluding free and pedicled flaps, no significant differences were found between administering antibiotics for 1 or 3 days.

In the absence of favourable evidence for the use of long prophylactic regimes, it is recommended that prophylaxis should not exceed 24h. Long regimes imply higher costs, more risk of adverse side effects and the risk of superinfection. It should be noted that, as the difference between long and short regimes is slight, it would require a large sample size to find significant differences. There is a correlation study[39] with a level of evidence C in which, on 258 patients, an odds ratio (OR) of 1.89 was found for infection occurring in patients treated with long regimes.

According to the above, a dose of 2 g of cefazolin prior to incision, followed by 2 g i.v. every 8 h for 24 h, is recommended as a prophylactic regime for clean-contaminated surgery of the head and neck. An alternative regime recommended is 600 mg i.v. clindamycin before incision, followed by 600 mg every 8h for 24h. This pattern coincides with that recommended by ASHP 1999, but differs from that recommended by the American Academy of Otolaryngology-Head and Neck Surgery (AAOHNS) in the eighth edition of its antimicrobial guide,[40] which recommends clindamycin and gentamicin or ceftazidime as a first choice. When there is a risk of infection by anaerobes, the AAOHNS recommends alternative regimes, such as ampicillin-sulbactam or cefazolin with metronidazole. Although there is no scientific evidence, we recommend amoxicillin-clavulanate if there is a risk of contamination by anaerobes; that is, in oral and oropharyngeal surgery or when performing concomitant dental extractions.[3,40]

Role of topical antibiotics

Topical preoperative washing with antibiotics or antiseptics and irrigation of the surgical field prior to closure are both considered as topical prophylaxis. They do not fit the given definition of antibiotic prophylaxis. The preoperative washing seeks to reduce the concentration of the inoculum, while the irrigation of the field assumes that the wound has already been contaminated. Its effectiveness has been demonstrated in colorectal surgery, but there are few studies on head and neck surgery.[41]

The major source of bacteria is located on the tongue and to a lesser extent in the teeth and gums; therefore, toothbrushing does not afford sufficient prevention.[42] The bacterial concentration in saliva is higher in the morning and decreases with food intake, oral washings and toothbrushing.

Experimental studies in guinea pigs inoculated with *S. aureus* have shown that adjuvant systemic antibiotic treatment with topical antibiotic increases efficacy.[43] Other studies suggest that highly contaminated wounds are those that benefit most from the administration of topical antibiotics, which provide no benefit in scarcely contaminated wounds.[44] Moreover, regression analysis has identified the presence of colony forming units (cfu) in the neck at the time of closure as the foremost risk factor for infection.[45]

In the time before the routine use of prophylactic systemic antibiotics, in 22 randomised patients undergoing total laryngectomy, it was proven that washing the wound with topical ampicillin and carbenicillin significantly reduced infection, from 67% in the control group to 18% in the group with washings[46] (level of evidence B). In a pilot study on 20 patients undergoing total laryngectomy, a lower cfu concentration was found in the neck of patients who underwent topical wound washing and preoperative rinsing with beta-lactams, versus intravenous clindamycin.[47] There are no RCTs which demonstrate the benefit of combining washings of the wound with antibiotics and systemic prophylaxis versus systemic prophylaxis alone.

Oral culture studies in healthy adults have shown that oral washes with clindamycin produced a 4-hour reduction in the concentration of aerobic cfu that was significant and of anaerobic cfu that was not significant.[42] In the study by Kirchner et al.,[48] the drag effect of fluids explains that washings with placebo diminished cfu in saliva; however, the cfu reduction in the group treated with oral clindamycin washes was 14% for aerobes and 11% for anaerobes after 4h, whereas in the placebo group the reduction was 67% and 95%, respectively. Parenteral clindamycin reduces cfu in the wound, but not in saliva.[47] On healthy volunteers, the reduction of bacterial concentration in saliva with preoperative washings using amoxicillin-clavulanate, clindamycin and povidone was significant when compared with placebo.[49] Washing with amoxicillin-clavulanate is more effective, but did not reach statistical significance.

In a prospective study with one group of 10 patients who underwent total laryngectomy without systemic antibiotic prophylaxis, the administration of topical clindamycin in the form of preoperative washing reduced by 99% the cfu in the wound at the time of closure with respect to previous oral cultures; topical washing reduced cfu concentration in the neck by an additional 90%.[50] The most comprehensive study in this regard is the prospective randomised clinical trial of Redleaf et al.[51] on 106 patients undergoing clean-contaminated oral or oropharyngeal surgery. The group with topical antiseptic wash prior to surgery showed an incidence of infection of 4.6%, while the incidence in the group without washing stood at 31.7% ($P<.01$). However, that study was

not completely controlled; almost all received systemic antibiotic, but it was not specified whether the distribution was homogeneous in both groups. With the exception of that study, there are no RCTs that demonstrate the benefit of prior washing with topical antibiotics.

Antibiotic prophylaxis in flaps

There is controversy over whether reconstruction with flaps is associated with an increased rate of infection; there is also discussion about what kind of flap is associated with an increased risk of infection. In one RCT on oral or oropharyngeal surgery, no statistically significant difference was found between direct closure and reconstruction with free flap. In that same study, it is significant that direct closures become infected less often than pedicled flaps.[51] Other studies have found no significant difference between direct closure and pedicled flaps,[15] and in the retrospective study of Girod et al.,[52] reconstruction with flaps was associated with a higher rate of complications, but not of infections ($P<.05$). However, most studies estimate an increased incidence of infection with the use of flaps (20%-25%) versus direct closure (5-10%).[53] Lotfi et al.[39] found an increase of 2.2% in the risk of infection in the reconstruction with flaps and several studies indicate that primary closure has a better evolution.[54,55]

Different antibiotics are not recommended in the case of closure with flaps. It has been speculated that clindamycin protects from tissue necrosis associated with infection. However, in a RCT of 100 cancer patients undergoing oncologic reconstruction with flaps, no significant differences were found between clindamycin and cefazolin (19.6% compared to 21.6%; $P>.05$).[56]

The main issue discussed was the need for longer prophylaxis regimes. In double-blind RCT on 109 patients undergoing reconstruction with pedicled flaps, no significant difference was found between the administrations of cefoperazone for 1 or 5 days.[57] In fact, in that study, infection in the 5-day group was more common (25% versus 18.9%). In another single-blind RCT on 74 patients with reconstructions using free flaps, there were no significant differences between the 1-day and 5-day clindamycin regimes.[58] In the study by Simons et al.[53] on 62 patients undergoing reconstruction with free and pedicled flaps, no benefit was found in adding topical piperacillin to the systemic prophylactic treatment for 2 days with piperacillin/tazobactam.

In short, the few published RCTs have not proven the benefit of clindamycin over cefazolin or a lower rate of infection with long antibiotic regimes or with topical antibiotic. The use of long regimes is supported by the suspicion of a loss of sealing, in which case the intention is therapeutic.

Antibiotic prophylaxis in special situations

Antibiotic prophylaxis in laser surgery

Laser surgery of the upper aerodigestive tract may be followed by perichondritis and chondronecrosis, as well as by visceral perforation. The treatment of choice for perichondritis is the administration of systemic antibiotics such as clindamycin, which the cartilage absorbs with great avidity, together with debridement of affected areas.[59]

In a prospective study of 275 patients undergoing laser resection of tumours of the larynx and hypopharynx, the appearance of perichondritis was found in 0.72% of patients; the affected patients had undergone resections with wide exposure of the thyroid cartilage.[60] Studies on retrospective series reach an incidence of perichondritis of 0.8%.[61]

In a retrospective series of patients treated through CO_2 laser resection of malignant lesions at the level of the upper aerodigestive tract, no case of perichondritis was found in 337 patients with glottic T1. In patients with glottic T2b, perichondritis was found in 1.7% of 115 patients and in 1.1% of those with glottic T3. In 216 patients with supraglottic carcinoma, there were no cases of perichondritis, nor were there any in 174 patients with carcinomas of the pyriform sinus.[59] There are no RCTs that examine the relationship between the use of antibiotics and a reduction in the incidence of perichondritis. However, because this is a rare phenomenon, a large sample size would be required to show statistical significance. There are also no randomised studies that demonstrate the usefulness of antibiotics in the endoscopic treatment of Zenker's diverticulum. Van Overbeek,[62] in a retrospective analysis of 216 patients treated with CO_2 laser who were receiving antibiotic once a week, showed an incidence of mediastinitis of 2.4%, and of subcutaneous emphysema of 3.2%. A retrospective series[63] of 61 patients, of whom 92% received prophylactic cefuroxime, revealed a perforation rate of 8%.

Due to the lack of conclusive studies, the use of antibiotics is not recommended in laser surgery of the larynx or hypopharynx or in the endoscopic treatment of Zenker's diverticulum.

Antibiotic prophylaxis in rhinologic surgery

Healthy individuals have potentially pathogenic species in their nostrils such as *S. aureus*, *Klebsiella* sp. or *Escherichia coli* in 77% of cases.[64] Between 18% and 50% of patients are colonized by *S. aureus*. In patients diagnosed with chronic rhinosinusitis, multiple batches of antibiotic treatments select for resistant pathogenic species. Up to 90% of patients undergoing endoscopic sinonasal surgery present positive cultures, and most species are resistant to penicillin and 65% are resistant to cephalosporines.[65]

The risk of bacteraemia with nasal packing is estimated at around 12% in patients who have not undergone surgery.[66] Up to 15% of patients undergoing septoplasty and septorhinoplasty with nasal packing develop bacteraemia.[67] Bacteraemia may lead to endocarditis in patients at risk by cardiopathies, carriers of prosthetic valves, patients with cardiac transplantation or a history of endocarditis; in these cases, antibiotics are recommended for the duration of the bacteraemia. Nevertheless, endocarditis has also been described in native valves in patients with nasal packing.[68]

The 2007 clinical guidelines of the American Heart Association recommend the use of amoxicillin or ampicillin as a single dose 30 min before the mucosal incision; this document does not make reference to bacteraemia

associated to nasal packing.[4] There are no RCTs to demonstrate a reduction in the incidence of bacteraemia in patients with nasal packing when using antibiotics. Another of the infectious complications ascribed to the use of nasal packing is staphylococcal toxic shock syndrome, which is estimated at 16.5/100,000 rhinologic interventions.[69] It has not been shown that perioperative use of antibiotics is beneficial in preventing this complication.[70]

It is estimated that the infection rate in septoplasty is approximately 2.5% An incidence of infection of 0.48%was detected in a study of 1040 septoplasties with blockage and without perioperative antibiotics.[71] Caniellas et al.,[72] in their RCT of 35 patients undergoing septoplasty with packing, found no significant differences in pain, morbidity or complications in patients treated with cefazolin during anaesthetic induction, with the antibiotic for 1 week or without antibiotic. In the RCT of Manzini et al.[73] on 100 patients undergoing septoplasty, divided into four groups with and without antibiotic and with and without packing, there were no significant differences with regard to infection. There are no RCTs that have shown the benefit of perioperative systemic antibiotics in septoplasty; nor has it been demonstrated that they reduce colonization of the packing. However, despite these data, up to 66% of U.S. otolaryngologists routinely use antibiotics in septoplasties.[74] In the UK, it is estimated that only 22%of hospitals do not use perioperative antibiotics and 37% use them for more than 24 h.[71]

Bandhauer et al.,[75] in their RCT on 95 patients undergoing septoplasty with parking, found a significantly lower growth of *S. aureus* and other pathogenic species in the group treated with single doses of Terra-Cortril® on the packing. Several RCTs confirm the usefulness of topical antibiotics in reducing the colonization of packings.[66,76] The benefits of the use of Synalar® on the packing have been shown in patients undergoing endoscopic surgery for chronic rhinosinusitis, significantly reducing (by up to 36%) the colonization of Merocel®, but no differences were found with regard to postoperative rhinorrhea.[66]

In complex nasal surgery, understanding as such review septorhinoplasties, nasal graft surgery or the repair of septal defects, the infection rate reaches 27%.[18] It has been suggested that these patients might benefit from using antibiotics, but there are no RCTs comparing the perioperative use of antibiotics versus placebo. In the RCT by Andrews et al.[18] on 164 patients undergoing complex septorhinoplasty, no significant differences in infection were found between the administration of systemic antibiotics during 1 day vs 3 days. Schafer et al.,[77] in their RCT on 100 patients undergoing complex septorhinoplasty with packing and topical antibiotics on the packing, found 8% of infection in the group treated for 12 days with propicillin compared to 27% in the group without systemic antibiotics.

Based on the foregoing, we recommend the use of topical antibiotic on the parking in patients undergoing septoplasty and septorhinoplasty, for there is no evidence that systemic antibiotic is beneficial. There is still uncertainty about the usefulness of perioperative antibiotics in complex septorhinoplasties. Patients with packing and at risk for endocarditis should be treated with systemic antibiotics to prevent bacteraemia.

Antibiotic prophylaxis in amygdalectomy

It has been suggested that colonization by the oropharyngeal flora of the open tonsillar fossa produces a local inflammatory response that exacerbates postoperative pain.[78] It is widely accepted that infection causes secondary bleeding, while only 16% of patients with bleeding after tonsillectomy presented positive cultures in the oropharynx.[79] Furthermore, in patients undergoing tonsillectomy, bacteraemia occurs in 40% of cases, without this being related to an increased incidence of fever or discomfort.[80] However, it is important to prevent bacteraemia in patients at risk for endocarditis. In a 1955 study,[81] treatment with penicillin-procaine for 4 days in the postoperative period in 20 patients undergoing tonsillectomy was followed by bacteraemia in 5.5% of cases; however, in the 68 control patients, the incidence of bacteraemia was 28% For patients at risk for endocarditis, 2 g of amoxicillin 30 min before incision is the recommended dose (the paediatric dose is 50 mg/kg); alternatively, clindamycin is preferred in allergic patients, with a dose of 600 mg.[4]

Grandis et al.,[82] in an RCT of 101 adult patients, showed that administration of beta-lactam antibiotics for 7 days significantly reduced the duration of halitosis and the time of return to a normal diet and daily activities. The meta-analysis of Dhiwakar et al.,[83] which included five RCTs with adult and paediatric patients, and both systemic and topical treatments, showed a significant reduction in the incidence of postoperative fever (r=0.62), duration of halitosis (2 days less) and time to return to normal activities (0.64 days less) in the group treated with antibiotics; the differences in pain reduction, return to normal diet, the need for analgesia and secondary bleeding were not significant. Similar results were confirmed in a more extensive meta-analysis by the same authors[84]; in nine RCTs, there was a significant reduction in the incidence of fever (RR=0.63) in the group treated with antibiotics, but not of pain or secondary bleeding. Neither was the incidence of adverse events significant in patients treated with antibiotics. In a third meta-analysis, by Burkat et al.[85] on seven RCTs, the only parameters that showed significantly reduced incidence in the group with antibiotic treatment were the reduction of one day in the return to normal diet and return to normal activity. Considering these data (which correspond to a level of evidence A), we conclude that perioperative treatment with systemic antibiotics reduces the incidence of fever and halitosis; to a lesser degree and in a very subtle manner, it enables an early return to habitual diet and activity. There is no evidence that antibiotics reduce pain and bleeding. It must be kept in mind that these studies mixed paediatric and adult populations, various antibiotic regimes and various surgical techniques.

Telian et al.,[86] in their RCT on 100 paediatric patients undergoing tonsillectomy, evaluated preoperative administration of intravenous ampicillin followed by amoxicillin for 7 days versus placebo. There were significant differences in the incidence of fever, halitosis (4 days less) and return time to diet (1 day less) and daily activity (1 day less) in the group treated with antibiotics; it must be taken into account that that study excluded 7 patients from the final analysis due to postoperative

infection (6 in the group without antibiotics) and that 3 of the patients experienced bleeding (all in the group without antibiotics). Pain was not assessed with a linear scale; however, there was a significant reduction in the duration of the painful period (3.3 versus 4.4 days) in the group treated with antibiotics. Ramos et al.,[87] in an RCT on 58 children, found no significant differences in terms of fever or pain in patients treated with amoxicillin-clavulanate in the postoperative period. In the meta-analysis of Lyer et al.,[88] in paediatric patients undergoing tonsillectomy, only the association between shorter time until return to normal diet (1 day) and the perioperative use of antibiotics was significant. In a study[89] with no randomisation or blinding on paediatric patients, significantly reduced pain and better oral tolerance were found in the group treated with antibiotics. Paradoxically, Lee et al.[90] found a significantly increased incidence of ear pain and need for analgesia on the fifth postoperative day in patients treated with amoxicillin for 5 days. However, this was not a blind study and follow-up was carried out by telephone. In the light of these studies, there is no evidence that perioperative systemic antibiotics in the paediatric age decrease the incidence of bleeding and infection. The level of evidence is B with respect to the reduction of the duration of halitosis, fever and earlier return to daily activities in paediatric patients treated with antibiotics. The administration of antibiotics in paediatric patients significantly reduces the early return to normal diet (level of evidence A). The regimes most frequently used in the literature include 5 to 7 days of treatment with beta-lactams.

While studies using systemic antibiotics are numerous, those that assess the efficacy of topical antibiotics are scarce. In the RCT of Mann et al.[78] on adult patients, topical treatment was assessed before and after surgery with both clindamycin and amoxicillin versus systemic treatment with amoxicillin for 1 week and treatment with placebo. Patients treated with topical antibiotics had a significantly lower growth of cfu in oral secretions. Odour and pain were significantly lower in patients with topical antibiotics, but otalgia, fever, and return to everyday activity were not. In an RCT[90] on 60 paediatric patients, no significant difference was found between fusafungine, fusafungine with analgesics and amoxicillin-clavulanate with analgesics in terms of pain in the first 10 days; however, from day 10 the pain was significantly less and scarring was better in the groups with topical fusafungine.[91] There are no more clinical trials comparing topical versus systemic antibiotic treatment. One RCT on 101 patients over 12 years found significant benefit with respect to time to normal diet in patients receiving oral and topical treatment versus the group without treatment; pain and fever were not significantly reduced.[82] In one RCT on 68 patients, the topical use of fusafungine, an antibacterial and anti-inflammatory peptide, reduced pain during the first days and also reduced the consumption of analgesics significantly.[92] Through all these data, there is a B level of evidence to recommend the use of topical antibiotics in adult patients undergoing tonsillectomy in terms of reduced postoperative morbidity, and a level of evidence A to conclude that systemic antibiotics do not offer benefits over topical antibiotics.

Antibiotic prophylaxis in otologic surgery

Most otologic surgery falls into the category of clean surgery. However, surgery for chronic otitis media, with or without cholesteatoma, should be considered clean-contaminated; if there otorrhea during surgery, it is considered contaminated or dirty, so the use of antibiotics would have a therapeutic intention.[93]

Postoperative infection in otology manifests itself as a loss of the neotympanic graft, labyrinthitis, surgical wound infection or the occurrence of medial or external otitis. In order to systematise otologic interventions based upon the risk of infection, we will take the classification proposed by Verschuur et al.[94]:

- Clean surgery: myringoplasty, stapedectomy, ossicular reconstruction and dry ears.
- Clean-contaminated or dirty surgery: ears with preoperative suppuration (chronic otitis media with or without cholesteatoma).
- Insertion of transtympanic drainage tubes: ears without effusion are considered clean; with seromucous effusion, clean-contaminated; and with purulent effusion, dirty.

The incidence of postoperative infection in clean surgery has been estimated as less than 5%, whereas, it has been estimated as between 7 and 14% for clean-contaminated surgery.[95-97] The most common infectious agents in clean otologic surgery are species of *S. aureus* and other gram-positives.[93] In chronic otitis media without cholesteatoma, the most frequently isolated germs are *Pseudomonas aeruginosa* and *Staphylococci* species, mainly *S. aureus*. Different species of gram-negative organisms follow in order of frequency, such as *Klebsiella*, *Proteus* or *Haemophilus* and gram-positive bacteria, with predominance of *Streptococci*; the isolation of anaerobes is uncommon. The *Pseudomonas* species isolated are highly sensitive to polymyxin B, ciprofloxacin and gentamicin, while *Staphylococci* species are sensitive to cloxacillin, gentamicin and ciprofloxacin.[40,98] The isolates in the periods of otorrhea are mostly polymicrobial. The microbiological profile of otitis media with cholesteatoma is similar to that of simple chronic otitis media, with the exception that anaerobes are more frequent, mainly *Bacteroides* and *Peptococcus*; anaerobes have been isolated in up to two thirds of otorrhea with cholesteatoma.[40,97] Although it is assumed that otitis media with effusion does not present active infection, microorganisms are isolated in up to 50% of cases, most frequently *Haemophilus influenza*, *M. catarrhalis* and *Streptococcus pneumoniae*.[40]

Clean otologic surgery

Because the incidence of infection is so low in clean otologic surgery, the risk of beta error is very high; a very large sample size would therefore be required to show statistically significant differences. Most studies do not differentiate between clean, clean-contaminated and dirty surgery.

Donaldson et al.,[99] in a double-blind RCT on 96 patients undergoing myringoplasty, showed no statistically significant

differences between using oral sulfamethoxazole or placebo. However, this study did not specify the length of treatment and the packing was impregnated with polymyxin B and neomycin. John et al.[100] conducted a single blind RCT on 130 patients undergoing myringoplasty, with one group of patients receiving systemic antibiotics (ampicillin and flucloxacillin). No significant differences were found in terms of graft success; in fact, graft failure was more frequent in the group treated with antibiotics. In that study, patients did not receive antibiotics on the packing they carried for 1 week.

The incidence of perichondritis in patients undergoing ear pavilion surgery is estimated at between 0% and 5.56%. In an RCT[101] on 84 patients undergoing ear pavilion surgery with closure for second intention, no significant benefit in the use of systemic levofloxacin was shown.

In view of these clinical trials with evidence level A, there is no evidence to recommend the perioperative use of systemic antibiotics in patients undergoing clean otologic surgery with packing. It must be kept in mind that there are no clinical trials that evaluate the efficacy of topical antibiotic versus placebo; the study population in these clinical trials is composed of patients undergoing myringoplasty. Some authors have recommended the use of systemic antibiotics to reduce the risk of labyrinthitis; however, this has not been corroborated by clinical trials.

Clean-contaminated and dirty otologic surgery

There are few RCTs in which the study population is composed exclusively of patients undergoing "unclean" surgery. In the RCT of Tong et al.[102] on 101 patients with chronic otitis media undergoing type I tympanoplasty, preoperative topical ofloxacin was administered for 2 weeks. Although a significant negativisation was shown in the cultures, there were no statistically significant differences in postoperative infection. It can be concluded that a colonized ear does not necessarily imply infection. There are no other clinical trials comparing treatment with topical antibiotics versus placebo in surgery for chronic otitis. Thus, the benefit of preoperative topical treatment has not been demonstrated (level of evidence B). However, this study should be assessed with caution, since there are no clinical trials that evaluate the usefulness of postoperative topical antibiotics in clean-contaminated and dirty surgery.

Several studies have evaluated the use of systemic antibiotics versus not using antibiotics. In an RCT[103] on 26 patients with chronic otitis media and positive cultures for *P. aeruginosa*, the perioperative use of systemic ceftazidime has been shown to be statistically significant in reducing postoperative otorrhea. Another RCT[97] on 72 patients diagnosed with chronic suppurative otitis undergoing closed tympanomastoidectomy, of which 40 had cholesteatoma, evaluated the efficacy of perioperative clindamycin and gentamicin. There were no statistically significant differences with regard to infection between the group treated with antibiotics and the untreated one (11 vs 14%). Bagger-Sjoback et al.,[104] in another double-blind RCT on 100 patients undergoing middle ear surgery, including chronic otitis media, showed no statistically significant benefit in terms of infection in patients treated with placebo or phenoxypenicillin; nevertheless, a significant reduction in the growth of pathogens was proven ($P<.04$). Based on these studies, the benefit of using systemic antibiotics versus placebo or not treating has not been clearly shown in clean-contaminated otologic surgery. Nevertheless, there are subgroups, such as patients in the otorrhea phase, for whom it is useful. Further prospective studies would be necessary, as well as randomised studies with a population that includes only clean-contaminated surgery and dirty surgery.

Several clinical trials have evaluated the use of systemic and topical antibiotics versus topical antibiotics. These studies lack rigor when it comes to segregating patients with chronic suppuration from those with clean ears. In the RCT of Govaerts et al.[105] on 750 patients undergoing middle ear surgery and using a packing impregnated with polymyxin B and neomycin, including patients with chronic otitis, no significant difference was found in terms of infection by adding perioperative cefuroxime for less than 24h; the higher incidence of early infection in patients with cholesteatoma who were not treated with cefuroxime was significant in that study, although later on the incidences were matched. Jackson et al.,[93] in a double-blind RCT on 3,481 patients undergoing clean, clean-contaminated and dirty middle ear surgery, in addition to neuro-otologic procedures, showed no significant benefit in using oral antibiotics for 24 h prior to a packing impregnated in polysporin used by both groups. Separately analysing clean and dirty ears resulted in no significant relationships either between adding topical antibiotic to the oral antibiotic and a lower incidence of infection. A significant relationship was found between infection and dirty ears (17.2% in dirty ears and 4.4% in clean ears; $P<.05$). Hester et al.,[106] in an RCT on 146 patients undergoing middle ear surgery for chronic suppurative otitis, assessed the usefulness of systematically administering ampicillin-sulbactam during the intervention and amoxicillin-clavulanate for 5 days; all patients carried *gelfoam* and colistin in the middle ear and a packing with bacitracin, in addition to taking neomycin and polymyxin B after removal of the packing. No significant differences were found in infection or graft failure between the groups. Considering the above, studies with evidence level A have failed to demonstrate the benefit of adding systemic antibiotics to topical antibiotics in clean-contaminated and dirty surgery.

A recent meta-analysis[94] published in 2007 evaluated several randomised and prospective trials on antibiotic prophylaxis in clean and clean-contaminated otologic surgery. The subgroups could not be analysed. No significant difference was found between using antibiotic or not, using systemic antibiotic or not, using topical antibiotic or not, or using systemic and topical antibiotic compared with topical antibiotic alone.

Prophylaxis in transtympanic drains

Postoperative otorrhea in patients with transtympanic drains (TTD) ranges between 3.4 and 74%, although the real figure is closer to 15-19%.[107] In a meta-analysis[108] from 2006, the relative risk in terms of occurrence of postoperative otorrhea in the patient group with TTD

treated for more than 48 hours with a topical antibiotic compared with untreated patients was 0.52% (0.39%-0.69%); topical antibiotic treatment reduces the incidence of postoperative otorrhea by up to 48%. The benefit of topical antibiotics in reducing postoperative otorrhea is demonstrated with a level of evidence A. No significant differences were found between ofloxacin and neomycin with polymyxin B.

Several well-designed RCTs have shown no significant differences in the incidence of otorrhea in patients treated with normal intraoperative serum washings, postoperative oral antibiotic, postoperative topical antibiotic or perioperative washings with oxymetazoline.[109,110] As the greater efficacy of intraoperative irrigation with saline solution is confirmed in another randomised clinical trial,[111,112] there is a level of evidence A to recommend washing with saline solution; it is a cheaper treatment and also has a better safety profile. We thus conclude that it should be the routine treatment in patients undergoing TTD placement.

Antibiotic prophylaxis in cochlear implants

Surgical wound infection in surgery for cochlear implantation is a rare phenomenon, estimated at around 4% (depending on the series, between 0.9% and 11.8%).[113,114] Cochlear implant surgery is framed within clean surgery, and the low incidence of local infection implies that perioperative antibiotics will not be recommended in the first years of the technique. However, there are no randomised studies comparing the incidence of local infection in patients with and without antibiotic treatment. In a survey conducted in 1989, 56.4% of 1,030 implanted patients had received perioperative antibiotics; in 4.5% of patients without antibiotic treatment it was necessary to remove the implant, while this decision was taken in only 0.9% of patients with prophylaxis.[115]

However, the FDA reported in 2002[116] an increase of bacterial meningitis in implanted patients; until 2003, there were 118 cases of bacterial meningitis, predominantly streptococcal, in patients aged between 13 months and 81 years. The latency period between the intervention and the onset of symptoms ranged from less than 24h to over 6 years. Of these cases, a cerebrospinal fluid (CSF) culture was carried out in 69, which was positive for *S. pneumoniae* in 46. In this 2003 alert as in a new one in 2006, evaluating the use of perioperative antibiotics to prevent this complication was recommended; however, the recommendation is ambiguous and does not specify the type of antibiotic, its dose or the duration of the treatment.[116,117]

It has been suggested that cochlear implant placement lowers the threshold to cause meningitis, a circumstance that seems to be influenced by the use of placeholders (now obsolete), the traumatic placement of the implant and the reduction in the intracochlear defensive capacity produced by a foreign body, all based on studies in animal models.[118] In animal implantation models, it has been shown that the concentration of *S. pneumoniae* inoculum that causes meningitis is less if the inner ear is inoculated than if it is administered systemically; the concentration required is greater when the middle ear is inoculated.[119]

Hirsch et al.,[114] in a retrospective study on 95 implanted patients, declared no major infection and 1% of minor infections; 83% of patients received at least 4 doses of perioperative cefazolin. Basavaraj et al.[113] retrospectively analysed 292 implanted patients and registered 4 major infections (3 of which occurred in patients treated with long antibiotic regimes), 8 minor infections and no meningitis; the use of long antibiotic regimes was significantly associated with postoperative infection (5.6% in treatment for 5 days and 13% in treatment for 7 days) versus administration of single doses. However, this was a retrospective study and the assignment was not randomised, so patients with long regimes may have been those who showed signs of infection early.

The haemato-labyrinthine barrier may be a hindrance for the penetration of antibiotics. There are no studies on the use of topical antibiotics in humans, but there are some in experimental models. Wei et al.[120] showed that coating the implant with ciprofloxacin had a significant protective effect in terms of onset of meningitis when *S. pneumoniae* was inoculated in blood; however, this was not significant for inoculation in the inner or middle ear.

For all these reasons, there is a level of evidence C to recommend the use of perioperative systemic antibiotics in cochlear implantation; there are no clinical trials and hardly any retrospective studies that evaluate the use of antibiotic versus placebo or different antibiotic regimes. The most widely used antibiotic is cefazolin, which provides good coverage against gram-positive cocci, with highly variable regimes depending on the institution.

Antibiotic prophylaxis in dural exposure

In clean neurosurgical procedures, there is no penetration into the respiratory and gastrointestinal tracts and aseptic technique is not violated. This group includes craniectomies, including neuro-otologic approaches. The incidence of local infection is around 2%-3%[121] and the most important risk factor is CSF fistula.[122]

There are several double-blind RCTs[122,123] that evaluate the administration of antibiotic prophylaxis versus placebo in clean craniectomies, and the reduction of surgical infection in patients receiving antibiotics is significant. A meta-analysis by Barker et al.[125] assessed the presence of surgical wound infection in patients undergoing clean craniectomies, such as transtemporal approaches, and a local infection incidence of 8.7% was calculated for the group not receiving antibiotic versus 1.8% for the treated group (significant differences). Therefore, there is evidence of level A to recommend the prophylactic use of systemic antibiotics in clean craniectomies.

In 2007, Barker[126] published a new meta-analysis that evaluated the incidence of meningitis in clean craniectomies regardless of the application or not of antibiotic prophylaxis. Of the six RCTs included, none detected statistical significance; combining the individual data, the incidence of meningitis in the groups with and without antibiotics was 1.1% and 2.7%, respectively (not a significant difference); on the other hand, the number of patients who required treatment to prevent a case of meningitis was 65.

Table 5 Main conclusions on antibiotic prophylaxis in head and neck surgery, based on currently- available evidence

Laryngopharyngeal clean-contaminated surgery	
Amoxicillin-clavulanate does not decrease the incidence of infection versus cefazolin	Level A
The combination of clindamycin and gentamicin does not reduce the incidence of infection compared with clindamycin	Level B
The combination of clindamycin and gentamicin does not reduce the incidence of infection versus cefazolin or amoxicillin-clavulanate	Level B
There is no evidence that regimes prolonged further than 24h decrease the incidence of infection compared to perioperative regimes	Level A
Topical washings with antibiotics significantly reduce colony forming units in saliva compared to systemic antibiotics	Level A
Washings with topical antibiotics reduce the incidence of infection compared to placebo	Level B
The combination of topical and systemic antibiotics reduces the incidence of infection compared to systemic antibiotics alone	Level B
Flap reconstruction in clean-contaminated surgery	
Clindamycin does not decrease the incidence of infection with respect to cefazolin	Level B
Prolonged 5-day prophylactic regimes do not reduce the incidence of infection with respect to 1-day regimes	Level A
Laryngopharyngeal laser surgery	
There are no clinical trials or expert consensus in this respect	
Rhinologic surgery	
Perioperative systemic antibiotics do not decrease morbidity or infection in septoplasty	Level A
Topical antibiotics reduce the colonization of the packings in septoplasty	Level A
Tonsillectomy	
Perioperative systemic antibiotics reduce fever and halitosis and enable an early return to the usual diet and activity	Level A
Perioperative systemic antibiotics do not reduce pain or the risk of bleeding	Level A
Systemic antibiotics do not provide benefits with respect to topical antibiotics	Level A
Topical antibiotics reduce pain with respect to systemic antibiotics	Level B
Otologic surgery	
Systemic antibiotics do not reduce the incidence of infection in clean surgery	Level A
Systemic antibiotics do not reduce the incidence of infection in clean-contaminated surgery	Level B
Systemic antibiotics provide no benefit with respect to topical antibiotic treatment in clean-contaminated surgery	Level B
Perioperative systemic antibiotics reduce infection in clean-contaminated surgery and with positive preoperative cultures	Level B
Without stratifying the different categories of otologic surgery, perioperative antibiotics do not reduce incidence of infection	Level A
Postoperative topical antibiotics reduce the incidence of otorrhea after the placement of transtympanic drains, although they do not provide benefits with respect to intraoperative washing with serum	Level A
Cochlear implant	
Perioperative systemic antibiotics reduce the incidence of meningitis	Level C
Neurological approaches	
Prophylactic systemic antibiotics reduce the incidence of infection and meningitis in clean craniectomies	Level A
Perioperative systemic antibiotics reduce the incidence of infection in clean-contaminated approaches: skull base surgery and endoscopic approaches	Level C

There are no RCTs that assess the duration of antibiotic prophylaxis. Most studies used regimes of 24h or less[123,124,127,128] and Barker's meta-analysis[125] demonstrated no difference between the use of a single dose or of multiple doses. There are no RCTs demonstrating the benefit of one antibiotic regime over another; it is necessary to cover gram-positives and the benefit in extending coverage to gram-negatives has not been shown.[121,125] Given the safety profile, lower cost, reduced spectrum, low presence of gram-negative in infection and the absence of RCTs that refute their suitability,

we recommend cefazolin as prophylaxis, according to the ASHP.[3] Following administration of 1 g of cefazolin, the serum peak is reached after one hour. Concentrations above the MIC of most common germs in postoperative infections are maintained for 12h in the wound and serum, with the exception of *E. coli* and *A. faecalis*; however, this is only maintained for 5h in cerebrospinal fluid.[129] Therefore, doses should be repeated at 4-hour intervals.

In clean-contaminated neurosurgical procedures, there is a communication between the intracranial cavity and the respiratory or gastrointestinal tract. The anterior or lateral approaches of skull base surgery, transsphenoidal surgery and endoscopic surgery of the skull base belong to this category.[130] The incidence of infectious complications in craniofacial resections ranges between 18% and 38%.[131] Antibiotic prophylaxis is recommended for the duration of exposure in these cases. There are no RCTs that assess the need for antibiotic prophylaxis in clean-contaminated surgery, different regimes or topical antibiotic treatment. There is no evidence to suggest one regime over another.

Antibiotic treatment with therapeutic intent is recommended in contaminated or dirty procedures.

Conclusions

Table 5 summarises some of the conclusions that can be drawn from this review in the form of statements and their corresponding level of evidence.

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