Consensus statement on antimicrobial treatment of odontogenic bacterial infections

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SUMMARY

The infection of the oral cavity is a common public health problem and constant cause for antibiotic prescription, with 10% of antibiotics used to treat this problem. However, few studies have so far aimed to determine its incidence. Added to this, its relationship with certain sytemic diseases (cardiac, endocrine, etc…) confers this pathology vital importance. In spite of the frequency and importance of odontogenic infection, the current dispersion in criteria regarding key aspects in classification, terminology and therapeutic recommendations is noticeable. The main objective of this document, compiled as a consensus statement by specialists in microbiology and odontology, is to establish useful recommendations for all of those involved in the clinical management of this pathology. Special attention has been placed on the rise in bacterial resistance observed over the last years, specifically the proliferation of betalactamase producing strains. Another important factor causing the resistance to appear is lack of therapeutic compliance, specially what regards dosage and treatment duration. Therefore, this pathology constitutes a complex problem which requires the instauration of broad spectrum antimicrobials, well tolerated and a convenient posology so that patients receive the adequate dose over the necessary period. High doses of amoxicillin/clavulanate (2000 mg / 125 mg) have showed good results and power to overcome resistance. Other agents such as metronidazole and clindamycin, followed by de claritromycin and azithromycin have also proved to be active against most of microorganisms responsible for odontogenic infection.

Key words: Odontogenic infections, classification, diagnose, treatment, odontogenic microorganisms, resistance, antimicrobial agents, antibiotics, amoxicilin, clawlanic acid. microorganismos, odontogénicos, resistencia, antimicrobianos, antibióticos, amoxicilina/ácido clavulánico.

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INTRODUCTION

Although there is very little data regarding the incidence of infections of the oral cavity, no one doubts their relevance. Of these types of infections, odontogenic infections (infections that involve tooth and periodontal tissues) are the most common. It is the most frequent reason for seeking odontological consultation and intervention and it affects the entire population from childhood (especially cavities) throughout a person s entire lifespan (periodontitis, implant complications, etc.), which entails a considerable impact both on public health in general, as well as the economic resources destined to maintain public health. It has been estimated that odontogenic infections in Spain represent approximately 10% of all antibiotic prescriptions(1,2) Scientific evidence has revealed a relationship between some serious oral infections and specific systemic cardiovascular(3), lung and endocrine (diabetes *mellitus*) diseases, as well as with alterations during pregnancy(4,5). Because of this association between infection and other systemic diseases, it is essential that odontogenic infections be avoided as much as possible or failing that, that they be identified and treated promptly and appropriately. On occasion, an odontogenic infection can spread and provoke polymicrobial infections in other locations, such as the paranasal sinuses (odontogenic maxillary sinusitis), cervicofacial subaponeurotic spaces, palate, central nervous system (cerebral abscess), endocardium (endocarditis), etc.(6) However, and despite the frequency and importance of odontogenic infections, when undertaking a review of the literature, the dispersion of criteria in key aspects such as terminology, classification, treatment recommendations, etc. is surprising, as is the paucity of papers in prestigious publications, making it impossible to establish an appropriate level of scientific evidence. Hence, this document is the result of bibliographic review, but, above all, it represents the fruit of the experience accumulated over many years of the participating specialists and of the group discussions held for the purpose of drafting it. The main objective of this document, which has been elaborated by specialists representing 10 public universities in Spain in collaboration with specialists in the microbiology of these kinds of infections, is none other than to establish recommendations that will be of use for all those involved in the daily clinical management of patients suffering from these diseases.

CLASSIFICATION OF ODONTOGENIC INFECTIONS OF THE ORAL CAVITY

Infections of mixed aetiology affecting the oral cavity can be classified into two main groups on the basis of origin: a) Odontogenic: cavities, pulpitis, periapical abscess, gingivitis, periodontitis, pericoronitis, osteitis, and infection of the subaponeurotic spaces; and b) Non-odontogenic: infections of the oral mucosa, infections of the salivary glands, etc (7). In 1999, the *American Academy of Periodontology* organized an international task force to create a classification of periodontal diseases and conditions (8) in response to the criticisms of previous classifications (9) (obscure diagnostic criteria, overlapping of disease-related groups, too much importance given to the patient s age, onset of illness and rate of progression, which are often difficult to determine). The odontogenic infections that present most frequently would be those that result from dental cavities, dentoalveolar infections (infections of the pulpa and periapical abscesses), gingivitis (including necrotising ulcerati-

ve gingivitis), periodontitis (including pericoronitis and the periimplantitis), infections of the sub-aponeurotic spaces, osteitis, and osteomyelitis.

WHAT ARE THE MOST IMPORTANT MICROORGANISMS IN ODONTOGENIC INFECTION?

The oral cavity is a complex ecosystem made up of more than 500 bacterial species (10). Overall, the *Streptococcus*, *Peptostreptococcus, Veillonella, Lactobacillus, Corynebacterium and Actinomyces* genera represent more than 80% of all cultivable flora

TABLE 1.- MICROORGANISMS INVOLVED IN MIXED BACTERIAL INFECTIONS OF THE ORAL CAVITY (62)

Infection process	Predominant bacteria
Cavities	*Streptococcus mutans* *Actinomyces spp* *Lactobacillus spp*
Gingivitis	*Campylobacter rectus* *Actinomyces spp* *Prevotella intermedia* *Streptococcus anginosus*
Periodontitis	*Porphyromonas gingivalis* *Bacteroides forsythus* *Actinobacillus actinomycentemcomitans* *Prevotella intermedia* *Fusobacterium nucleatum*
Periapical abscess	*Peptostreptococcus micros* *Prevotella oralis* *Prevotella melaninogenica* *Streptococcus anginosus* *Porphyromonas gingivalis*
Pericoronitis	*Peptostreptococcus micros* *Porphyromonas gingivalis* *Fusobacterium spp*
Periimplantitis	*Peptostreptococcus micros* *Fusobacterium nucleatum* *Prevotella intermedia* *Pseudomonas aeruginosa* *Staphylococcus spp*
Endodontitis (pulpitis)	*Peptostreptococcus micros* *Porphyromonas endodontalis* *Prevotella intermedia* *Prevotella melaninogenica* *Fusobacterium nucleatum*

(11). In the aetiology of periodontal disease, a whole series of species such as *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia* and *Tannerella forsythensis* can be especially highlighted due to their frequency and the importance of the complications that may arise from them. Facultative gram-negative bacilli are uncommon in healthy adults and are seen almost exclusively in elderly, hospitalised patients with serious medical diseases (12).

The ploymicrobial nature of odontogenic infection has been demonstrated in many papers. For example, in a study conducted by Brook et al.(13) in 32 patients with periapical abscess, 78 bacterial isolates were obtained (55 anaerobic and 23 aerobic), with a mean of 2.4 isolates per sample. Only anaerobic bacteria were found to be present in 16 patients (50%), only aerobic in 2 (6%) and mixed aerobic and anaerobic flora, in 14 (44%). The main isolates consisted of bacteria belonging to the *Peptostreptococcus*, *Prevotella* and *Porphyromonas* genera. Of the facultative anaerobic bacteria, oral *streptococci* are the most frequent. Table 1 shows the most commonly found bacteria in each oral condition.

WHEN IS COMPLEMENTARY DIAGNOSTIC TESTING INDICATED?

The diagnosis of odontogenic infection is based on anamnesis, observation and examination that allows symptoms and signs to be recorded. Information regarding the patient s history of the following conditions is essential, as it will necessarily influence treatment and prophylaxis: endocarditis, implants, diabetes, immunodepression, etc. Radiological diagnosis is fundamental in determining the location, extension and possible complications of these lesions. The role of the laboratory in diagnosing odontogenic infections in routine practice in dentists offices is controversial. Non-specific analytical data (leucocytes, complement, lymphocytes, immunoglobulins, glycaemia, etc.) must be requested when dealing with repeated or unusual infections or infections that are suspicious of any underlying disease that can have repercussions in the oral cavity. Better still, the internist s report should be requested before undertaking any kind of

action. The patient can be spared serious medical complications and the professional can avoid legal complications. Bear in mind conditions such as endocarditis, diabetes, AIDS, hepatitis, etc. Insofar as microbiological studies are concerned, pathology samples will be taken prior to commencing with antibiotic treatment and will be sent to the laboratory following proper standards. The rapid techniques currently on the market can be a great diagnostic aid. The microbiological diagnosis seeks to rule out a specific aetiology, identify the aetiology of the condition and obtain overall information that is currently lacking, as well as to determine sensitivity to antimicrobial agents. These data will be useful in deciding on the treatment to be administered, whether to effect a change in the event that the empirical treatment fails and to establish general empirical therapies.

THERAPEUTIC MANAGEMENT OF ODONTOGENIC INFECTION

The issue of odontogenic infection must be approached from three, mutually complementary treatment areas. Aetiological odontological treatment, which often includes surgical interventions of varying magnitude and requiring different levels of professional expertise; systemic support treatment, which covers a broad spectrum ranging from symptomatic pain management and controlling the inflammation, all the way to physical measures, hydration, fever control, glycaemic control, etc. Finally, antimicrobial treatment should only be applied on rare occasions and on the basis of rational, efficiency criteria. In general, antimicrobial treatment must be initiated whenever the condition presents clear clinical manifestations of infection. Antimicrobial treatment of odontogenic infections aims to prevent local spread and spread to neighbouring areas, to decrease the bacterial inoculum in the infectious focus and to prevent complications derived from disemination via the circulatory system (14,15). Antimicrobial treatment is not the only treatment option for odontogenic infection, since antibiotic administration alone is often not sufficient to eradicate the infection. Depending on the infection and the patient s characteristics, the optimum treatment for a give infection may require systemic or local antimicrobial agents, odontological treatment or surgery, or a combination of the above (6,16,17) .

IN WHAT SITUATIONS IS ANTIMICROBIAL TREATMENT WARRANTED?

Not all odontogenic infections require antimicrobial treatment. In some cases, surgical treatment is also necessary and in others, the best course of treatment is debridement, irrigation and drainage.

-Endodontic Infections Arising from the Pulpa
In some situations, acute endodontic treatment can be complemented with systemic antibiotics, as well as with analgesics and/ or anti-inflammatory drugs (18). Antibiotics are also indicated in cases in which the patient is immunodepressed and requires prophylaxis.

-Chronic Gingivitis and Necrotising Ulcerative Gingivitis (NUG)
Generally speaking, the treatment of mild gingivitis does not include systemic antibiotic administration. It requires local treatment to eliminate dental plaque and to disinfect the gingival grooves. Useful measures include rinsing with chlorhexidine, brushing with a mixture of sodium bicarbonate and hydrogen peroxide, and/ or frequent rinsing with saltwater. One exception is NUG, in which systemic antibiotic use is recommended. The same is true of streptococcal gingivitis, caused by group A beta haemolytic streptococcus (*Streptococcus pyogenes*) that presents as a complication of acute streptococcal pharyngitis/ tonsillitis, in which active antibiotics should be used against this microorganism (19). In the case of NUG, in addition to antibiotic treatment, debridement with ample irrigation is recommended (16). Topical application of mouthwash containing chlorhexidine or saline solution is effective in controlling the pain and ulceration that accompanies this condition.

-Periapical Abscess This comprises a clear indication for debridement and surgical drainage complemented with systemic antibiotics.

-Periodontal Abscess
Treatment consists of debriding and draining the

purulent pocket. Antibiotic treatment is reserved for those situations with there is local or systemic dissemination.

-Periodontitis
Debridement, elimination of the calculus and root planning to remove subgingival plaque deposits constitute the first line of treatment. Subgingival irrigation should also be performed using ultrasound tartar removal equipment to disinfect the gingival sulcus. Other useful measures consist of rinsing the mouth with chlorhexidine or brushing with a mixture of sodium bicarbonate and hydrogen peroxide. Systemic antibiotics are indicated especially for the treatment of aggressive periodontitis (16).

-Pericoronitis
Systemic antibiotics are almost always necessary to keep the infection from spreading. Local treatment consisting of debridement, irrigation and drainage of the affected areas, or even tooth extraction can also be performed.

-Periimplantitis
Systemic antibiotic therapy in certain cases may be accompanied by mechanical debridement. Rinsing the mouth with chlorhexidine for 30 seconds after brushing teeth may also be useful as coadjuvant treatment (20).

-Severe Infections of the Fascia and Deep Head and Neck Tissues
The treatment of infections located in the cervicofacial aponeurotic spaces include the following measures: 1) aetiological treatment, 2) incision, debridement and drainage of purulent accumulations and 3) antibiotic therapy. Odontogenic infections are caused by a highly predictable group of bacteria, so the first choice of antibiotic is made empirically. However, if evolution is unfavourable, the antibiotic chosen can be substituted by another one or more than one after identifying the causal microorganisms by means of culture and antibiogram typing. 4) Finally, complementary systemic care is also required (hydration, nutritional support, analgesics, antipyretics and anti-inflammatory drugs). Attention must be paid at all times to *alert criteria* that indicate the need to transfer the patient to a hospital, possibly on an emergency basis (Table 2).

TABLE 2.- CRITERIA FOR REFERRING PATENTS TO HOSPITAL

Rapidly progressive cellulitis
Dyspnea
Dysphagia
Spread to deep facial spaces
Fever of more than 38º C
Intense trismos (distance between incisors of less than 10 mm)
Non-collaborative patient or one who is incasable of following prescribed outpatient treatment on his/her own
Failure of initial treatment
Severe involvement of general health status
Immunocompromised patients (diabetes, alcoholism, malnutrition, treatment with corticoids, HIV infection...)

WHAT CHARACTERISTICS MUST THE IDEAL ANTIBIOTIC HAVE FOR THE TREATMENT OF ODONTOGENIC INFECTION?

The ideal antibiotic for treating an infection must have a series of characteristics such as: a) it must be active against the microorganisms involved in the infection; b) it must meet appropriate pharmacokinetic parameters (good penetration and diffusion at the site of infection); c) it must be well tolerated and have few adverse effects (21), and d) it must allow for a dosing schedule that facilitates treatment compliance. The ploymicrobial component of odontogenic infection advises the use of antibiotics that are active against both aerobic and anaerobic bacteria are recommended, requires that the proper antibiotic be used for treatment. It is often necessary to administer combinations of antibiotics that can achieve a spectrum of activity and are more appropriate to the type of infection.

HOW SENSITIVE ARE THE PATHOGENS INVOLVED IN ODONTOGENIC INFECTION TO THE MOST COMMONLY USED ANTIMICROBIAL AGENTS?

The increased prevalence of bacterial resistance means that antibiotics that have been useful in the

TABLE 3.- ACTIVITY OF DIFFERENT ANTIMICROBIAL AGENTS AGAINST PERIODONTOPATHOGENS (21).

	Aa Actinobacillus actinomycetemcomitams	*Peptostreptocococcus spp*	*Prevotella spp*	*Porphyromonas spp*	*Fusobacterium spp*	*Oral streptococci*
Penicilina G	±	+	±	±	+	+
Amoxicilin	+	+	±	±	+	+
Amoxicilin/ Ac. Clavulanate	+	+	+	+	+	+
Doxicyclin	+	±	±	±	+	±
Clindamycin	O	+	+	+	+	+
Metronidazol	O	+	+	+	+	O
Macrolides	±	±	±	±	±	±

+ More than 80% of sensitive strains / O Less than 30% of sensitive strains / ± Between 30-80% of sensitive strains

TABLE 4.- ANTIBIOTICS AND INTISEPTICS OF USE IN ODONTOGENIC INFECTIONS

Odontogenic infection	*Drug of choice (oral and/or topical)*	*Alternative (oral and/or topical)*
Marginal gingivitis	Chlorhexidine	
Necrotising ulcerative gingivitis	Amoxicillin/clavulanate or amoxicillin + metronidazole+ chlorhexidine	Clindamycin + chlorhexidine
Chronic periodontitis	Amoxicillin/clavulanate or metronidazole+ chlorhexidine	Clindamycin or doxicycline + chlorhexidine
Aggressive periodontitis	Amoxicillin/clavulanate or metronidazole or oral doxicycline + chlorhexidine	Clindamycin or azithromycin or clarithomycin
Acute pulpitis	Amoxicillin/clavulanate	Clindamycin or azithromycin or clarithomycin
Periapical abscess	Amoxicillin/clavulanate	Clindamycin or azithromycin or clarithomycin
Periodontal abscess	Amoxicillin/clavulanate	Clindamycin or azithromycin or clarithomycin
Pericoronitis	Amoxicillin/clavulanate	Clindamycin or azithromycin or clarithomycin
Periimplantitis	Amoxicillin/clavulanate	Clindamycin or azithromycin or clarithomycin
Cellulitis	Amoxicillin/clavulanate	Clindamycin or azithromycin or clarithomycin

(This table is indicative of the antibiotics used, which is not to say that they are hended in all cases).

TABLE 5.- DOPING SCHEDULES OF DIFFERENT ANTIBIOTICS

Antibiotic	*Adult Dosis*	*Paediatric Dosis*	*Observations*
Amoxicillin	1000 mg/8-12 hours	50 mg/Kg/day in 3 doses	
Amoxicillin + Clavulanate	2000 mg+125 mg/12 h 875 mg+125 mg/8 h	40-80 mg/Kg/day in 3 doses 500 mg+125 mg/8 h	
Clindamycin	150-450 mg/6 hours	25 mg/Kg/day in 3-4 doses	
Claritromicina	500 mg/12 hours	7,5-15 mg/kg/day 12 hours	
Doxiciclina	100 mg/12 hours	2 mg/Kg/day 12 hours	In children, try another antimicrobial
Eritromicina	500-1000 mg/6 hours	50 mg/Kg/day in 3 doses	
Metronidazol	500-750 mg/6-12 hours	45 mg/Kg/day in 3 doses	
Azitromicina	500 mg/day for 3 consecutive days	10 mg/Kg/day for 3 consecutive days	

past are currently no longer as effective as they once were, as is the case with certain dose levels. In this regard, in the last 10-15 years the number of resistant microorganisms in the oral cavity has doubled (22). We can cite the following example: studies have revealed the presence of beta-lactamase producing species in 74-88% of patients with periodontitis (23,24). Likewise, over the course of recent years as seen with other pathogens such as *Streptococcus pneumoniae,* the levels of resistance to macrolides, beta-lacta-mase and clindamycin of several *viridans* group streptococci species have increased notably (25-28) . Whereas an increase in the macrolide doses does not lead to increased coverage against the resistant strains, in the case of beta-lactam, higher doses can lead to better coverage (29). Table 3 shows the activity of several antimicrobial agents against the most important microorganisms that cause periodontal disease.

WHICH ANTIBIOTICS AND WHAT DOSES ARE ADEQUATE FOR TREATING ODONTOGENIC INFECTION?

Treatment duration with antibiotics depends on the type of infection, the extension of the condition and on the antibiotic chosen. Overall, treatment duration will vary between 5 and 10 days; in other words, treatment should continue for 3 or 4 days after clinical manifestations have disappeared (30). Amoxicillin, amoxicillin/ clavulanate, cephalosporins, doxicycline, metronidazole, clindamycin and macrolides, such as erythromycin, clarithromycin and azithromycin, all stand out amongst the large variety of systemic antimicrobials used to treat odontogenic infection. Tables 4 and 5 present antimicrobial agents and the dosing schedules recommended for each indication.

Penicillins

Penicillin, ampicillin and amoxicillin are bactericides that are useful in treating the acute phase of odontogenic infection, in addition to preventing associated complications (7). Due to their effectiveness against facultative aerobic and anaerobic pathogens, they are considered to be the antibiotics of choice in the treatment of infections of mixed aetiology in the oral cavity (31). However, there are more and more beta-lactamase producing bacteria, enzymes that are capable of hydrolysing penicillins and, therefore, leading to treatment failure (32-34) particularly when strains of the *Prevotella, Porphyromonas and Fusobacterium* genera are present (35-37). In fact, penicillin administration has been linked to the appearance of beta-lactamase producing bacilli in the oropha-rynx (38,39). Amoxicillin and ampicillin increase penicillin s spectrum to cover enteric gram-negative bacilli. Amoxicillin is better than ampicillin because of its superior enteric absorption (60-80% versus 30-55%) (40, 41). Given the increased prevalence of beta-lactamase producing microorganisms, the association of a penicillin with a betalactamase inhibitor such as amoxicillin/ clavulanic acid has become the treatment of choice in many of these conditions (42,43). The increased resistance of some species of oral streptococci indicates that high doses of amoxicillin be used to treat infections in which these pathogens might be involved. In this regard, a new pharmacokinetically enhanced formulation of amoxicillin/ clavulanate has been developed (amoxicillin/ clavulanate, 1000/62.5 mg) that, in addition to lowering the number of daily doses to two, also eradicates strains considered to be resistant to conventional formulations (44-46). Furthermore, this new formulation, when administered along with high doses of Amoxicillin, can delay or decrease the risk of increasing the prevalence rate of oral streptococci resistance, as seen in children with *Streptococcus pneumoniae* and a high dosis, short course of treatment with amoxicillin (5-7 days) (47,48).

Cephalosporins

Cephalosporins are classified in generations, based on their antibacterial spectra, regardless of when they were synthesised. In general, as we move further along the generations, activity against gram-negative germs improves, while effectiveness against gram-positive germs decreases (49). They present the disadvantage of having very poor activity against anaerobic bacteria, with the exception of cephamycins (cefoxitine, cefminox and cefotetan) for which there are no oral formulations (21).

Tetracyclines

Tetracyclines have classically been the standard antibiotic of use in treating odontogenic infection, although at present, they exert limited activity as a

result of increased resistance, particularly in countries such as Spain where there is a high level of antimicrobial use (50). Because of their high affinity for bone and dental tissue, its use is not recommended during pregnancy, while nursing or in children less than eight years of age, since when deposited on teeth and bones during development they can produce alterations such as dental hypoplasia, bone deformities and abnormal tooth colour (51).

Nitroimidazoles

Metronidazole, ornidazole and tinidazole are antibiotics with excellent activity against anaerobic gram-negative bacilli and spirochete, but hardly act, if they act at all, against anaerobic cocci and facultative, aerobic bacteria of the oral cavity (7,52). They should be administered in combination with other antibiotics in mixed infections of the oral cavity that involve oral aerobic or facultative streptococci.

Lincosamides

Clindamycin continues to be the treatment of choice in patients who are allergic to beta-lactams in most odontogenic infections. It presents a good level of activity against anaerobic bacteria, although more and more resistant strains are emerging (53,54). More than 25% of the *viridans* group streptococci present a high degree of resistance (55) that cannot be overcome with high doses of this antibiotic, nor is it active against some gram-negative bacilli, such as *A. actinomycetemcomitans, Eikenella corrodens* and *Capnocytophaga spp* (56-58).

Macrolides

Macrolides are bacteriostatic antibiotics with a spectrum of activity that covers gram-positive bacteria, some gram-negative bacilli, bacteria growing intercellularly and several anaerobic bacteria, including *Porphyromonas* and *Prevotella*genera. *Bacteroides* spp and *Fusobacterium* spp tend to be resistant to these antibiotics (59). Like other streptococci species (*S. pneumoniae, Streptococcus pyogenes*) (60), the prevalence of resistance to oral streptococci has increased significantly, with rates of more than 50% in many areas of our country (55,61). Amongst representatives of this drug family, clarithromycin show the greatest *in vitro* activity against anaerobic gram-posi-tive bacilli and azithromycin, against anaerobic gram-negative bacilli.

CONCLUSIONS

1. There are a host of microorganisms in the oral cavity whose taxonomy is difficult to ascertain and it is not always easy to determine how they relate to clinical presentations.
2. Microbial- and host-related factors play a role in oral and facial infections, which means that the response obtained *in vivo* may differ from what occurs *in vitro*.
3. Many oral bacteria produce beta-lactamases, which can so-metimes complicate antibiotic therapy.
4. There are some individuals who are especially susceptible and in whom microorganisms produce more severe clinical symptoms and are more resistant to certain treatments.
5. Certain factors alter patients susceptibility to different microorganisms (age, blood dyscrasias, drug treatment, hospitalisation, avitaminosis and others).
6. Antibiotic efficacy is multifactorial and success depends on different parameters being met, such as dosing schedule, time, etc.
7. Amoxicillin/ clavulanate, metronidazole and clindamycin are active against most of the microorganisms that are responsible for odontogenic infections. Other alternatives, such as clarithromycin and azithromycin, complete the therapeutic arsenal.

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