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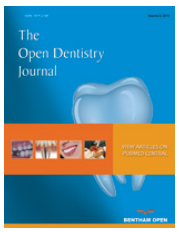

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REVIEW ARTICLE

Antibiotics in Dentistry: A Narrative Review of Literature and Guidelines Considering Antibiotic Resistance

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Abstract:

Background:

Antibiotic resistance is an important issue for public health.

Objective:

The aim of this work is to investigate the clinical situations which require the administration of antibiotics in dentistry.

Methods:

The authors want to do a review of the literature and a comparison of guidelines in dentistry among different countries. The research method was based on the use of Pubmed and the research of indexed articles and documents published by authorities and boards about the antibiotic prescription in dentistry. The paper is an analysis deep inside the physiological and pathological situations that, according to different guidelines, require the use of antimicrobics. The spirit is a clinical one because this paper wants to be a guide for dentists, especially before the administration, in order to moderate the use of antimicrobials. We must remember that the World Health Organisation organizes each year the World Antibiotic Awareness Week, in order to fight against the improper administration of antibiotics in medicine, dentistry, veterinary medicine, and industrial livestock.

Results:

Different guidelines converge on a very calibrate and proper administration of antibiotics. Antibiotics should be used only in recommended situations for risk patients. The authorities and boards should investigate the habits of antibiotic administration, which according to some papers seem to be large and diffused use, not only limited to situations described in guidelines.

Conclusion:

Dentists, together with the General Practitioners and Paediatricians, should be cautious and accurate and should administrate antibiotics only if recommended by guidelines and effective and safe.

Keywords: Antimicrobics, Antibiotic resistance, Dentistry, Endodontology, Periodontology, Otorhinolaryngology.

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1. INTRODUCTION

The aim of this paper is to compare different guidelines for the administration of antibiotics in dentistry. All medical professionals should consider that the use of chemotherapy has to be modulated according to the recent studies on anti-microbial resistance, considering the advantage for therapies and contraindications. In particular, the weekly antimicrobial therapy, if administrated outside the indicated cases, can be dangerous for public health and for the treatment of the same infections in the future.

The authors want to do a comparison of different guidelines and support a conscious administration of antibiotics by clinicians, considering that the World Health Organisation (WHO) has developed a strategy in order to fight against Antimicrobial Resistance (AMR) and to promote awareness about antibiotics. Recently, during the antibiotic awareness week, the WHO organised events to encourage the best practice among the general public, health workers, and

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policymakers to avoid the further emergence and spread of antibiotic resistance [1]. The authorities and boards should investigate the habits of antibiotic administration, which according to some papers [2 - 6], seem to be large and diffused use, not only limited to situations described in guidelines.

2. BACKGROUND

The use of antibiotics began in 1928, after the discovery of penicillin by Fleming. After that, they acquired a progressive, increasing importance to control infections and to reduce the significance of infectious diseases. Before the wide use of this therapeutic medium, infectious diseases were the first cause of death and the only effective way to reduce them was represented by the diffusion of the antibiotics.

During the 1950s and 1960s, the spread of antibiotics in western countries and then in all the continents caused a progressive change of resistance of microorganisms [7]. During the same period, the progressive reduction of pathologies of infectious origins allowed a progressive improvement for daily life in the whole American continent, in the whole of Europe, and in the Soviet Union. The spread of these therapies was associated with a better and longer life, leaving a wonderful image of the two kinds of therapeutic media used to obtain this result: antibiotics and vaccines.

The vaccines were and are used with a high level of safety in order to reduce morbidity and mortality. The combined use of antibiotics and vaccines caused a dramatic reduction of the significance of diseases caused both directly and indirectly by bacteria.

In this period, dentistry was an independent science and field of study and research only in the American continent and in Northern Europe. This caused the absence of separate statistics considering the habits of dentistry and oral medicine. Dentistry was considered a subsidiary and an ultra-specialization of otorhinolaryngology, so the administration of antimicrobial agents was performed after apical abscesses for preventing systemic diffusion of bacteria. According to this, some differences have to be considered prior to the discussion.

First of all, the historic period after the Second World War saw an improvement regarding access to food for the so-called "Western Countries" population, and this improvement was linked to better health conditions and to a rapid increase of the mean life age of men and women.

On the other side, the reader has to consider that in the same period there was the third industrial revolution, linked to a change in life habits and in food ones. In particular, in the western countries, there was the spread of sweets and refined carbohydrates. The maximum incidence of dental caries manifested during 1964, according to some papers [8].

The clinician has to consider that the clinical necessity of antibiotics in dentistry was principally linked to apical abscesses and endodontic complications. The antibiotic was prescribed in order to mitigate the local infection and to prevent its systemic diffusion. There was not a pervasive use of systemic chemotherapy for periodontal treatment, and the endodontic treatment was uncommon, too. In case of deep and uncurable cavity processes, the therapy was represented by tooth extraction [9].

Thus, antibiotics remained and remain now the elective choice for treatment of infectious diseases and infections, and for prevention in a lot of medicine and dentistry sectors [10].

This study wants to check different guidelines in different countries, and summarise in a narrative way, the appropriate way of administrating antibiotics.

The reader should consider that this narrative review cannot explain the real gap between therapeutic theoretical indications of antibiotic prescription and the real habits of dental practitioners in different countries. This question needs to be investigated in other future papers.

3. MATERIALS AND METHODS

We use PUBMED, MEDLINE Ovid, and Cochrane database to perform this work. We use the following keywords in order to search recent literature data:

1- Antibiotic*.

2- Antibiotic* Dentistry.

3- Antibiotic* endo tooth.

4- Antibiotic* perio tooth.

5- Antibiotic* abscess endo.

6- Antibiotic* administration dentistry.

7- Antibiotic* resistance dentistry.

We scheduled a comparison between different guidelines for clinicians from Italy [11], Europe [3, 12, 13], and America [14] in order to describe and understand these guidelines.

We did a comparison of suggestions and recommendations for the administration of antibiotics in oral surgery, periodontal surgical and non-surgical treatments, endodontics, and oral medicine.

The antibiotics are normally used to treat infectious diseases of the mouth, according to different guidelines. The use of antibiotics is, however, focused on the treatment of systemic infectious disease, which can affect, with a side effect, the oral cavity. Non-surgical periodontal treatment is now focused on oral hygiene and different antibiotics [15]. For these uses, antibiotics are not a consequence or an ancillary aspect of the therapy, but they are the central device.

4. ACTUAL USE OF ANTIMICROBIAL AGENTS IN DENTISTRY AND ORAL MEDICINE

Actually, there is a common use of antibiotics in dentistry. Oral infections are polymicrobial [16]. The oral microbiota evolves during life and its evolution starts during the eighth week after birth [17]. The complete and healthy composition of the oral microbiota is a crucial element for the health of the oral cavity and the whole human body [18]. Antimicrobial agents can be used in dentistry to prevent infections or to manage infections, both from a dental origin and from an extra-oral one. Normally, the typical situations which could require the use of antibiotics during the dental procedures, are:

1- Management of complications in endodontics [4, 19];

2- Apical abscess [20];

3- Oral infections;

4- Tooth replantation;

5- Antimicrobial therapy in periodontology;

6- Pre- and post-extraction prophylaxis [21, 22];

7- Other oral surgery procedures.

5. ENDODONTICS AND APICAL ABSCESSES

In Europe, there were several studies about the use of chemotherapy in endodontics, both in preventive and therapeutic questions. According to several studies, antibiotic prescription habit is linked to different clinical patterns. In Belgium, for example, the administration of antibiotics interested 4.4% cases of pulpitis and 51.9% cases of periodontal abscess [6]. In Spain, for the case of irreversible pulpitis, 40% of Endodontic Specialists have the habit to prescribe antibiotics. Amoxicillin was always the first choice for administration during endodontic treatment [5, 23, 24]. In case of allergy, clindamycin and erythromycin were the preferred antibiotics [12].

We have to consider that the use of chemotherapy was demonstrated to be unnecessary in irreversible pulpitis, necrotic pulps, and acute apical abscesses which have not already become oversized [25]. So, the administration should be limited to cases at risk of systemic complications, as described in guidelines [25].

6. ORAL INFECTIONS

The human oral cavity contains more than 500 [26] or 350 [27] bacterial species, depending on the age of the study. The oral environment hosts all these bacteria physiologically. In case of a change both in proportion or place, the result is an oral disease caused by bacteria, viruses, or fungi. These changes can occur after a diet modification or a dental or orthodontic treatment [28, 29].

Frequent oral infections are:

- Aphthous stomatitis

- Infections following Bechet's disease

- Fungal infections

- HIV-linked infections

In this case, the management of bacterial infection is properly done by the use of correct chemotherapy [26].

7. ORAL SURGERY PROCEDURES

Several studies demonstrate that the use of antibiotics before tooth replantation is suggested in order to preventive successive complications [30].

In 2009, a systematic review demonstrated instead that there are insufficient clinical benefits for the administration of antibiotics after tooth reimplantation [31].

When the tooth reimplantation is done after endodontic treatment, some state guidelines prescribe the administration of systemic antibiotics in order to prevent possible further complications [9, 32].

The risk of infection after extracting wisdom teeth in young and healthy people is about 10%. This percentage can increase in case of low immunity or systemic disease [33].

There is low-quality evidence that the prophylactic use of an antibiotic can reduce the risk of systemic infection following tooth extraction [34]. Compared to a placebo, antibiotics probably reduce the risk of infection in patients undergoing third molar extraction or impacted tooth extraction.

There is also low evidence that patients undergoing extraction can experience a reduction of pain in the following seven days after surgery, by the administration of systemic antibiotics. They can also reduce dry socket.

According to other studies, there are no randomised control trials specifically designed which clearly demonstrate that the antibiotic prophylaxis is clearly indicated, and which demonstrate that the benefits, in general, are more than contraindications [35].

For the other types of procedures, such as frenulectomy or minor oral surgery, indications and guidelines are the same as systemic surgery prophylaxis.

For implant surgery, many reviews suggest very limited and prudent use of systemic antibiotics in order to prevent pre-operative and post-operative infection. In particular, the single-dose oral amoxicillin (SDOAP) is quite beneficial, while post-operative use is not [21, 22, 2].

8. ANTIMICROBIAL THERAPY IN PERIODONTOLOGY

Mechanical and surgical treatment, together with personalized oral hygiene procedures can reduce supra and subgingival bacteria [36]. The periodontal treatment is very important, for overall systemic health, even in the case of hypertension [37].

About periodontology, antibiotics are defined as substances which, in low concentrations, inhibit or eliminate specific kinds of microorganisms [38]. The better patients for systemic antimicrobial therapy are those ones exhibiting attachment loss after optimal conventional therapy, or patients with aggressive kinds of periodontitis or associated with severe medical conditions [39].

In patients affected by periodontitis, some pathogens such as Porphyromonas Gingivalis, Aggregatibacter Actinomycetemcomitans, Fusobacterium Nucleatum, and Treponema Denticola, can persist in furcations or in other structures, not easily reached by periodontal instruments. The red complex bacteria tend to remain on the biofilm attached to the epithelial surface, difficulty reached by normal oral hygiene movements [15, 40]. In these cases, the use of systemic antibiotics is accepted and suggested, according to different guidelines, in severe periodontitis in order to reduce the power of pathogen bacteria.

PERIO-PATHOGENS	ANTIMICROBIALS USED
A. Actinomycetemcomitans b *S. noxia* *A. Actinomycetemcomitans a* *E. corrodens* *C. sputigena* *C. gengivalis* *C. concisus* *C. ochracea* *C. gracilis* *P. micros* *F. nucleatum ss nucleatum* *F. periodonticum* *F. nucleatum ss vincentii* *F. nucleatum ss polymorphum* *P. intermedia* *P. nigrescens* *C. showa* *C. rectus* *E. nodatum* *S. constellatus* *S. mitis* *S. oralis* *S. sanguis* *S. intermedius* *Streptococcus sp.* *S. gordonii* *V. parvula* *A. odontolyticus* *A. naeslundii 2 (A. viscosus)* *P. gingivalis* *B. forsythus* *T. denticola* [41]	- Penicillin - Erythromycin - Monocycline microspheres - Doxycicline - Clindamycin - Tetracyclines - Minocycline - Spiramycin [42] - Azithromycin - Aminoglycosides - Metronidazole - Metronidazole + Ciprofloxacin [43] - Amoxicillin - Amoxicillin + clavulanate potassium - Cephalosporins - Ciprofloxacin - Macrolides - Antibiotics in combination [44]

In periodontology, various types of pathologies can be fought using antibiotics. The following situations are the most indicated:

- Chronic periodontitis;

- Aggressive periodontitis;

- Necrotizing periodontal disease;

- Periodontal abscess.

These types of antimicrobics can even be used in association in order to fight the infection. Metronidazole and amoxicillin are used in association to fight infections by *Aggregatibacter Actinomycetemcomitans* and *Porphyromonas Gingivalis* [45].

Thus, we have to consider that doxycycline with metronidazole can be used locally, into the gingival socks, in order to reduce bacteria in the socks. This therapy is used in order to treat severe gingivitis. There are new studies *in vitro* about their clinical efficacy [46].

9. GUIDELINES

Considering the wide use of antibiotics and the administration easiness, one of the most important problems for world public health is the growth of multi-resistance organisms, because of the over-use of antibiotics.

There are different guidelines about the use of antibiotics in dentistry. As indicated below, we try to provide a description of the situations described. We described Italian, European, and American guidelines.

10. ITALIAN GUIDELINES

In Italy, according to the last version of Clinical Guidelines in Dentistry, published by the Ministry of Health in September 2017 [11], the use of antibiotics is suggested for the following situations:

1- Systemic side effects after paediatric oral surgery;

2- Orthograde endodontic therapy, in order to control pain [47];

3- Tooth replantation [48];

4- Side effects of acute apical abscess [49];

5- Antimicrobic therapy for severe periodontitis.

11. EUROPEAN GUIDELINES

According to the European Society of Endodontology [3], antibiotics can be administered in the following situations:

- Acute apical abscess in medically compromised patients.

- Acute apical abscess with systemic involvement.

- Progressive infections.

- Replantation of avulsed permanent teeth.

- Soft tissue trauma requiring treatment.

The most used types in order to treat the pathologies listed before are beta-lactam antibiotics. Penicillin V must be the first choice, the combination of penicillin V and metronidazole or amoxicillin with clavulanic acid is recommended. In case of allergy, alternatives are represented by clindamycin, clarithro-

mycin, or azithromycin.

On the other side, according to the same guidelines, administration of antibiotics should be avoided in the following situation:

- Symptomatic irreversible pulpitis.

- Pulp necrosis.

- Symptomatic apical periodontitis.

- Chronic apical abscess.

- Acute apical abscess without systemic involvement.

So, we can conclude that the European Guidelines are quite similar to Italian ones, and suggest to avoid antibiotic prescription in case of pulp necrosis and acute abscess without systemic involvement.

12. AMERICAN GUIDELINES

According to American guidelines, there is no association between dental procedures and the occurrence of periprosthetic joint infections [14]. For patients at risk of endocarditis, current guidelines support premedication for a quiet small set of patients. In normal conditions, the risk of adverse reactions to antibiotics generally outweighs the benefits of prophylaxis for dental procedures. According to this statement, prophylaxis is recommended only in case of the highest risk of adverse outcome for infective endocarditis [50, 51]. For this cohort of patients, the administration is recommended for all dental procedures that involve manipulation of gingival tissue or the periapical region of the tooth. However, there are a lot of clinic conditions in which the administration of chemotherapy can be planned by the clinician.

Indeed, according to ADA guidelines, for adult patients, the use of antibiotics for preventive reasons should be limited to those with health conditions that may predispose them to infective endocarditis, and those who have a prosthetic joint and may be at risk of developing haematogenous infections at the site of the prosthetic.

So, comparing American Guidelines with European and Italian ones, we can obtain the same prudent approach to the antibiotic administration, even if they are more specific on risk categories, referring especially to cardiac pathologies which are linked to risk of endocarditis. In the US and in Canada, the awareness of an unnecessary and high antibiotic prescription was analysed by ADA [52], so the guidelines now are specific and finite.

13. ANTIMICROBIALS IN PAEDIATRIC DENTISTRY

In paediatric dentistry, the current guidelines of different countries converge on the fact that for odontogenic infections in temporary or permanent dentition, local treatment should be firstly recommended, instead of systemic one.

According to the European Academy of Paediatric Dentistry, antibiotics in dentistry can be used mainly in the following purposes:

- As adjuncts to therapy of orofacial infection;

- To prevent local infection associated with dental procedures.

- To prevent the spread of oral micro-organisms to susceptible sites elsewhere in the body.

14. WORLD HEALTH ORGANISATION STRATEGY ON ANTIMICROBIAL RESISTANCE

The World Health Organisation elaborated an integrated strategy in order to control and rationalise the use of antibiotics and prescriptions of physicians and dentists.

The resistance has to be considered an intrinsic characteristic of bacteria, because of their long evolutive history. A comparable characteristic has been described in anti-cancer fields, even if it is a different phenomenon [53]. The resistance is a proper evolution of bacteria, subsequently to the "non-natural" selection induced by the antibiotics.

An action plan about antimicrobial resistance, including antibiotic resistance, was approved during the World Health Assembly in May 2015 [54]. This plan has the objective to ensure the prevention and treatment of infectious diseases with safe and effective medicines. The plan 5 objective strategies are:

1- To improve awareness of antimicrobial resistance;

2- To strengthen surveillance;

3- To reduce the incidence of infections;

4- To optimise the use of antibiotics;

5- To guarantee investment in countering antimicrobial resistance.

So, considering the daily job of dentists, the prescription of antibiotics must be safe and clinically recommended by contemporary guidelines, as described in the previous paragraph.

The dental surgery prophylaxis is based upon the principal use of amoxicillin and clavulanate, in order to prevent endocarditis and problems for prosthetic joints patients.

The most common procedures and pathologies of dental practice are not the use of antibiotics as elective or recommended treatment [10]. In fact, the American Dental Association guidelines are very cautious about antimicrobial prophylaxis in dentistry, as well as the European and Italian ones [50, 55].

15. TREATMENT INDICATIONS

One of the types of antibiotics most used in dentistry is represented by penicillin. This antibiotic is used in the form of amoxicillin and clavulanate in most cases of prescription [4, 5, 20, 22, 23, 56].

Other antibiotics mostly used, according to current guidelines, are metronidazole (in periodontology only), azithromycin [57], clindamycin, clarithromycin, doxycycline, and erythromycin.

Amoxicillin/clavulanate can be administrated for 7-10 days for prophylactic use before and after surgery, only in cases indicated in the previous sections. In fact, the efficacy for routine surgery for third molar extraction has not been proven [33, 58]. We have to remind that the efficacy of systemic

chemotherapy after an acute abscess has not been proven with certainty [59, 60].

Azithromycin has to be administered for 4 days or 3 days by tablets of 500 mg. In this case, it is used systemically in order to reduce the concentration of periodontal bacteria. It has shown effective inhibitory effects on Porphyromonas gingivalis ATCC33277, so it can be used as a biofilm treatment used for porphyromonas gingivalis [61]. The same drug can have a positive effect on the treatment of chronic periodontitis in type II diabetes patients. The administration of a 0.5% azithromycin gel into the periodontal pockets can improve the clinical status of patients [62].

Doxycycline and erythromycin can be used in the same way of amoxicillin and clavulanate/amoxicillin, in cases of allergy or other contraindications for amoxicillin/clavulanate.

Metronidazole, in combination with amoxicillin, showed efficacy in periodontal therapy, to improve the clinical outcome of scaling and root planning. Optimal dosage, however, could not be determined exactly, because further studies are needed [63]. Metronidazole in association with doxycycline can be used in the form of gel for therapy of periodontal socks [64, 65]. In this case, the substance is administrated locally.

Clarithromycin can be used as advice in non-surgical periodontal therapy, against Porphyromonas Gingivalis and other kinds of bacteria associated with the increase of pockets depth.

According to some papers [66], clindamycin has proven to be safe and effective for prevention in all surgical strategies in dentistry. The reader has to consider that pseudomembranous colitis, once associated with the administration of clindamycin, rarely occurs after the administration of this substance. In particular, this antibiotic is safe and can reach a high concentration in tissues.

The administration of antimicrobics should be safe and be modulated when there is a risk of allergies. In these cases, the choice of administration should be considered by the clinician case by case.

CONCLUSION

According to this paper, the clinician could administrate antibiotics only in cases indicated by guidelines, in the prescribed dosage. For this, the ordinary use of antibiotics for the prevention of systemic infections should be avoided in routine surgery for healthy patients.

Actually, there is evidence that the damage given by the increase of antimicrobial resistance can overcome the possible advantage given by the administration of antibiotics.

The clinician has to evaluate case by case the necessity of administrating antibiotics, for patients considered “at risk” according to examined and discussed guidelines. In case of general administration, without restriction among risk categories, dentists can contribute to increasing antibiotic resistance. For this reason, in the same way as medical doctors, pharmacists, veterinarians, farmers, and industrial producers of meat and derivates, dentists must relate to the problem of antibiotic resistance and should operate in a safe and prudent way. According to the authors, dentists should administrate antibiotics according to guidelines, only if treatments or therapies require it.

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CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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