Chapter 2

Antibiotics in Implant Dentistry

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Abstract

Antibiotics have been recommended either as an extended treatment for several days or as a single antibiotic prophylaxis dose since the development of dental implant osseointegration technique in the 1970s. It is also performed as part of surgical protocol during the peri-operative phase in the treatment of peri-implantitis. To date, there is a lack of scientific evidence regarding the additive effect of antibiotics in the treatment of dental implant. This has thus left the clinician with inconclusive recommendations, leading to increase antibiotic prescription. With this increase, the development of antibiotic resistance is becoming a threat to modern healthcare that requires revisiting of current indications and implementation of rational treatment strategies. Therefore, more studies are needed to assess the benefit of antibiotic prescription and whether it is safe to refrain from its use.

Keywords: Dental implant failure, dental implant surgery, antibiotic prophylaxis, treatment of peri-implantitis, selection of antibiotic resistance

1. Introduction

Since the introduction of dental implants as treatment for missing teeth, systemically administered antibiotics have been used to prevent and treat implant failure. In conjunction with implant placement, antibiotics have been recommended either as extended treatment or short-term prophylaxis during the peri-operative period. In the treatment of peri-implantitis, the majority of surgical flap protocols described in the literature also include administration of systemic antibiotics in the peri-operative phase.

Today, antibiotic resistance is the largest threat to modern healthcare where many treatment options, including advanced surgical interventions, require access to effective antibiotics [1].

Therefore, original or consensus-based recommendations, such as the use of antibiotics in implant dentistry, are being reevaluated. Previous policies of prescribing antibiotics, until it is proven safe to refrain from their use, are today considered an outdated option in otherwise healthy patients. Currently, the potential risk of using antibiotics must be weighed against possible benefits for individual patients when undergoing dental implant treatment.

A dental implant is a titanium device anchored and integrated into the jawbone. Osseointegrated dental implants have been an established treatment modality for replacing missing teeth since the beginning of the 1970s [2]. A substantial number of studies using long-term follow-ups have shown successful results for patients with partially and completely edentulous jaws [3–8]. Survival rates of 90–100% of inserted implants have been reported in several longitudinal studies during follow-ups of up to 20 years later [4, 9–14]. Despite the high success rate of dental implants, failures do occur.

Biological implant failures may be categorized into early failures, that is, failure to achieve osseointegration due to surgical trauma, infection, lack of primary stability [15], or late failures, that is, failure to maintain the achieved osseointegration, due to occlusal overload, peri-implantitis, or both [15]. Implant failure is an outcome that may require implant removal [15].

2. Prophylactic use of antibiotics during surgery

2.1. Peri-operative antibiotic treatment and extended prophylaxis

The empirically based tradition of using a peri-operative systemically administered prescription of antibiotics originates from the introduction of the treatment method by PI Brånemark and collaborators [2] during the 1970s. The original implant placement protocol recommended the use of antibiotic treatment during the initial phase of healing, for up to 10 days, to prevent postoperative infection and early implant failure [16, 17]. A two-staged surgical protocol for implant placement was initially introduced to further prevent infection [18]. The rationale for prescribing the extended antibiotic prophylaxis was, at the time of introduction, based on empiric medical/orthopedic considerations. Today, one has to remember that one of the key factors in making the method successful was the addition of a tissue preserving surgical technique. This technique minimized the risk of bacterial contamination during surgery, which at the time included the extended use of systemic antibiotic treatment.

It has been shown that bacterial contamination during implant insertion may be one of the major reasons for early implant failure [19]. Oral implant surgical procedures are often graded as class II surgical procedures (clean-contaminated surgery) [20, 21]. Clean-contaminated surgery has a local infection rate of 10–15% (**Figure 1**). However, the incidence of infection can be reduced to 1% or less with proper surgical technique and the use of prophylactic antibiotics [20, 21]. Conversely, prophylactic antibiotics can never make up for poor surgical technique and hygienic measures. However, during the past decade, due to the emergence of bacterial antibiotic resistance, the recommendation of extended prophylactic antibiotic treatment has been challenged. Scientific evidence from various surgical fields including placement of dental

implants shows no benefit of antibiotic prophylaxis beyond the day of surgery in uncomplicated routine cases [22–25]. Therefore, this extended antibiotic treatment is now increasingly being replaced by a single-dose antibiotic prophylaxis.

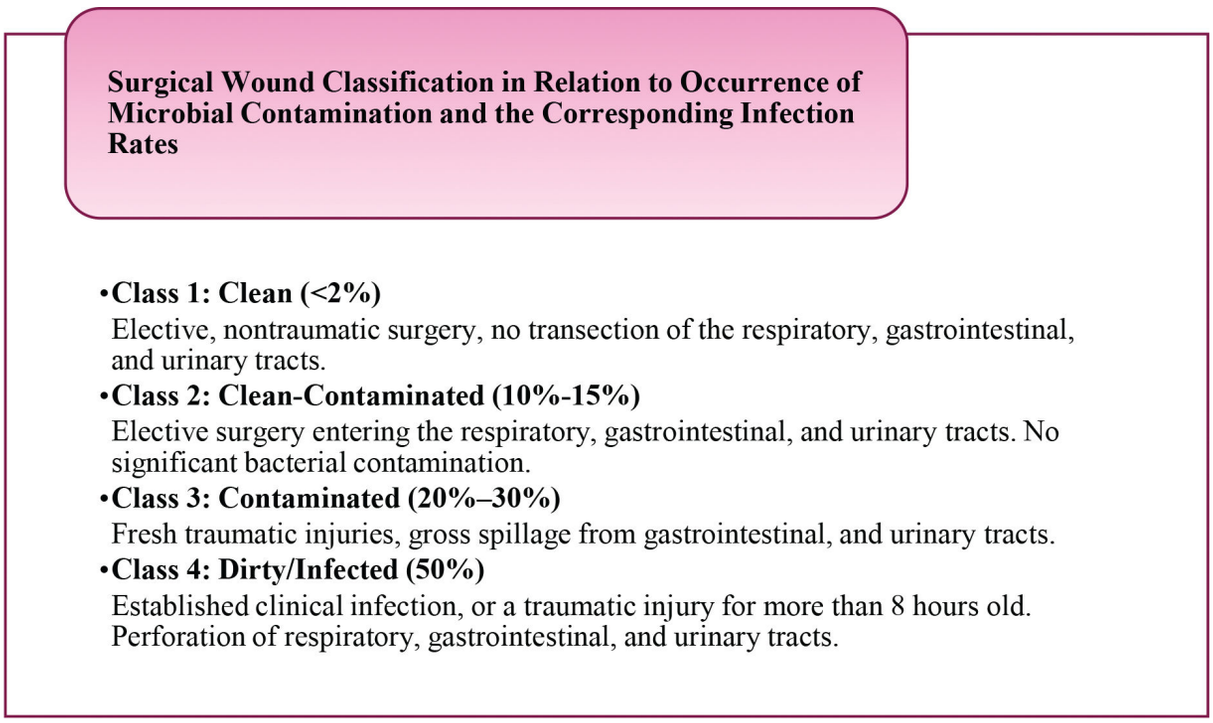

Figure 1. Surgical wound infection classification and the estimated percentage risk for postoperative infections [20, 21].

2.2. Short-term, single-dose antibiotic prophylaxis

There are several clinical studies [26–36] summarized in systematic reviews showing that the use of prophylactic antibiotics during dental implant insertion reduces the risk of implant failure [22, 37]. However, this finding has recently been questioned [38, 39]. For example, none of the randomized controlled studies included in a recent meta-analysis [38] showed a statistically significant beneficial effect of antibiotic prophylaxis on their own [27, 30, 31, 40, 41], although the beneficial effect could not be excluded in complex or compromised patients [38, 42]. Therefore, this issue remains a controversial subject under constant revision, and recommendations based on sound scientific evidence are still lacking. Despite this, the routine use of antibiotics during implant placement continues to be common among the majority of dentists in most countries [43–45]. These results today have thus left the clinician with inconclusive recommendations. However, it should also be kept in mind that there are several factors in addition to the use of prophylactic antibiotics during implant placement that can affect implant success rates, such as implant systems, duration of surgery, the number of implants placed, as well as surgical skills [29].

3. The use of antibiotics for the treatment of peri-implant infection

When a dental implant is inserted into the oral cavity, it provides a new and physically different surface for the colonization of microorganisms. The development of this new biofilm is a process strongly resembling biofilm formation on natural teeth [46–51]. The colonization of microorganisms on this new surface has been shown to start within hours after insertion, with a microflora already resident in the oral cavity [52, 53].

Peri-implantitis was initially defined as "a site-specific infection with many features in common with chronic adult periodontitis" [54] and/or as "an inflammatory, bacterial-driven destruction of the implant supporting tissues" [55]. Both definitions imply that bacteria may play a crucial role in the initiation and progression of peri-implantitis. With time varying from months to years, the implant microflora has shown to become more complex if soft tissue inflammation and pocket formation develop around a dental implant (i.e., clinical signs of peri-implantitis) [56].

Studies have shown that when comparing clinically healthy peri-implant sites to sites with peri-implantitis, a transition in microflora composition can be seen [57, 58]. A shift from predominantly nonmotile, aerobic, and facultative anaerobic bacteria to a biofilm with a high proportion of gram-negative, motile, anaerobic bacteria has occurred [59, 60]. Moreover, residual teeth (not edentulous or partially edentulous) and clinical condition (periodontally healthy teeth or persisting ongoing periodontitis with residual probing) have been shown to influence the development of the subgingival microflora around dental implants [61, 62]. In partially edentulous patients, the adjacent teeth play a role in the periodontal pathogen colonization [63–65]. Accumulation of a microbial biofilm on the implant surface promotes an inflammatory response in the peri-implant mucosa, resulting in peri-implant mucositis. This is characterized as a reversible inflammation of the soft tissues, with reddening, swelling, and bleeding on probing [66–68]. Persistence of inflammation may result in the loss of peri-implant supporting tissues which is defined as peri-implantitis [42, 54, 55, 68]. Peri-implantitis appears to be associated with a similar microflora as that found in chronic periodontitis such as *Porphyromonas gingivalis, Tannerella forsythia,* and *Aggregatibacter actinomycetemcomitans* [69–73]. However, compared with periodontitis, some bacteria, which are not part of the typical periodontopathic microbiota, have been found in peri-implantitis lesions such as staphylococci, enteric rods, and Candida [74, 75].

Peri-implantitis has become a prevalent, notable disease, affecting a substantial number of patients [76]. However, a recent review indicates a wide variation in the incidence and prevalence of peri-implantitis [76]. This variation is most likely due to patient/case selection, diagnostic criteria used, and varying time of follow-up. Tomasi and Derks [76] in a recent review stated that the prevalence of peri-implantitis varies between 8.9 and 47% of implants. In 2012, the EAO Consensus Conference stated that peri-implantitis occurred in one of five patients within 5 years following implant placement [77].

Treatment of peri-implantitis is directed towards removing the biofilm, resolving the inflammation, and arresting the progression of bone loss. Various protocols have been suggested as

a method for achieving this [78]. The primary objective was to alter the microbiota and induce the host immune system to eliminate putative pathogens [79]. Mechanical debridement and disinfection of implant surfaces are directed to remove the oral biofilm and perio-pathogenic microbes to a certain extent [80]. Indeed, the surface characteristics and the screw-shaped configuration of most current implants may influence the resolution of the inflammation in the surrounding tissues [79]. Conventional mechanical therapies currently used in the treatment of periodontitis may therefore be difficult to apply around dental implants [79].

It is therefore difficult to treat peri-implantitis, and the outcome may not be predictable [68]. To date, there is no standard protocol for the treatment of peri-implantitis. A nonsurgical treatment alone appears to be insufficient in resolving peri-implantitis lesions and is less successful in arresting disease recurrence in long-term follow-up [68, 81].

Surgical treatment of peri-implantitis allows better access for the removal of granulation tissue and decontamination of exposed implant surfaces [68]. Since the etiology of peri-implantitis is similar to periodontitis, the anti-infective protocol used with periodontitis has been adopted in the treatment of peri-implantitis. In the treatment of aggressive periodontitis, the use of adjunctive systematic antibiotics (amoxicillin and metronidazole) has shown an additional effect. The combination of amoxicillin and metronidazole has the potential to decrease a wide range of oral bacteria usually associated with peri-implantitis [82]. Studies including surgical treatment of peri-implantitis in combination with the use of amoxicillin (500 mg) and metronidazole (400 mg) for 7 days have shown a 58% success rate for implants with machined surfaces [83, 84]. However, in a majority of prospective clinical studies, the parallel effect of several procedures has been evaluated simultaneously [83–86]. These procedures include access flap procedures as well as reconstructive/regenerative procedures. Regardless of surgical technique, adjunctive treatment of systemically administered antibiotics has been used. Therefore, the knowledge of a single specific intervention, such as the adjunctive use of systematic antibiotic, is still limited [87, 88].

In a recent RCT including 100 patients, surgical treatment of peri-implantitis was performed with or without adjunctive systemic antibiotics [89]. The results of this study showed that the use of adjunctive systematic antibiotics combined with surgical treatment of peri-implantitis had a limited significant effect on implant success. However, there is an increase in the probability of treatment success of implants with a modified surface, but not at implants with a nonmodified/smooth surface [89]. The overall implant treatment success after a 1-year follow-up was 45% [89]. As presented in the scientific literature to date and concluded in a consensus from 2012 at the 8th European Workshop in Periodontology [88], the adjunctive use of systemic antibiotics on treatment outcome is still limited in the treatment of peri-implantitis.

4. Antibiotic delivery route with dental implants

The use of oral antibiotics is one of the most common approaches in treating bacterial infections. Antibiotics can be delivered either systemically or by direct placement into the pocket around the dental implant. Each method of delivery has specific advantages and disadvantages. However, based on clinical and microbiological evidence, the type of microorganisms

responsible for the infection is treated on a presumptive basis, founded on probabilistic reasoning [90]. A wide range of antibiotic compounds and dose regiments is presented in the literature. Ideally, antibiotic treatment duration should include the shortest efficient cycle for preventing both clinical and microbiological relapse [91]. However, this short cycle should ideally have certain characteristics such as rapid onset of action; bactericidal activity; lack of propensity to promote resistant mutants; ease of invasion into tissues; activity against nondividing bacteria; unaffected by adverse infection conditions (low pH, presence of pus, etc.); administration at an optimal dose; and an optimal and convenient dosing regimen [92].

4.1. Local use of antibiotics

Local delivery facilitates the application of antimicrobial agents at levels that cannot be reached by the systemic route. However, these levels need to be maintained at a high local concentration for a long period of time, and the agents should reach the entire affected area, that is, the base of the pocket, in order to be efficient. This type of delivery varies from simple pocket irrigation and specifically placed drug-containing ointments and gels, to sophisticated tools for sustained release of antibacterial agents. However, it is unlikely that mouth rinse or supragingival irrigation could predictably deliver an agent to the deeper parts of the defect because the crevicular fluid rapidly washes out agents from the pockets [93, 94]. Nevertheless, there is a low incidence of side effects with locally applied antibiotics. The use of local antibiotics as an adjunctive in the treatment of peri-implantitis has shown no or limited effect on the reduction of periodontal pocket depth and gain in clinical attachment level [95, 96]. This lack of significant clinical additive effects of local antibiotic supplement is may be due to inadequate exposure of the subgingival bacteria to the compound.

4.2. Systematic use of antibiotics

Systemic use of antibiotics is commonly recommended when the targeted bacteria are more widely spread, which is beyond the site of initial infection. The periodontal bacteria may be found throughout the whole oral cavity including on non-dental sites such as the dorsum of the tongue or tonsillary crypts [97–103]. However, this colonization of perio-pathogens at various oral ecological niches is not to be regarded as a systemic infection and does not call for systemic antimicrobial treatment. The drawback of systematic administration is the high rate of drug dissemination throughout the body, where only a small portion reaching the subgingival microflora in the periodontal pocket [104]. Moreover, adverse drug reactions are of greater concern. Systemic antibiotics should never be applied as compensation for inadequate oral hygiene.

5. Antibiotic compounds commonly used in implant dentistry

Antibiotic compounds can be classified in a number of different ways: (a) by their origin (natural, semisynthetic or synthetic drugs); (b) by their mode of antibacterial activity as bacteriostatic (growth inhibiting), or bacteriocidal (drugs kill the bacteria); (c) by antibacterial

spectrum (broad-spectrum or narrow-spectrum), or (d) by their cellular mechanism of action, for example:

i. Cell wall inhibitors, such as the beta-lactam antibiotics penicillin and carbapenem

ii. Inhibitors of nucleic acid synthesis, such as quinolones and metronidazole, which inhibit DNA synthesis, and rifampincin which inhibits RNA synthesis

iii. Protein synthesis inhibitors, such as tetracycline and clindamycin

iv. Anti-metabolites, such as the sulfa drugs

v. Antibiotics that can damage the cell membrane, such as polymyxin B and daptomycin

	Amoxicillin	**Clindamycin**	**Metronidazole**	**Penicillin-V**
Spectrum	*Streptococcus* *Peptostreptococcus* *Actinomyces* *Fusobacterium* *Capnocytophaga*	*Streptococcus* *Staphylococcus* *Bacteroids* *Fusobacterium* *Prevotella* *Anaerobic cocci*	*Peptostreptococcus* *Clostridium* *Bacteroids* *Prophyromonas* *Prevotella* *Fusobacterium* *Capnocytophaga*	*Streptococcus* *Peptostreptococcus* *Actinomyces* *Fusobacterium* *Capnocytophaga*
Effect	Time dependent	Concentration dependent	Concentration dependent	Time dependent
Pharmacokinetic				
Absorption (p.o.)	90%	90%	>95%	50%
T½	~1 h	~2, 5 h	~8 h	~30 min
Solubility	Water	Fat	Fat	Water
Excretion	Urine	Gall bladder, feces, urine	Urine and gall bladder	Urine
Common side effect	Vomiting, diarrhea, nausea, exanthema (5%)	Vomiting, diarrhea, nausea (8%)	Gastrointestinal upset, metallic taste (5–10%)	Diarrhea, nausea (5%)
Ecological effect				
Oral	++	+++	++	++
Gastrointestinal	++	+++	+	+

P.O. peroral; T½ half time; + mild/no effect; ++ moderate effect; +++ severe effect.

Table 1. Summary of characteristics of the most common antibiotic compounds used in implant dentistry.

Although there are numerous antimicrobial agents available, only a limited number of systemic antibiotics such as amoxicillin; phenoxymethylpenicillin (PcV); clindamycin;

metronidazole; and the combination of amoxicillin and metronidazole have been widely used in the implant dentistry field (**Table 1**).

5.1. Amoxicillin

Amoxicillin is derived from one of the oldest antibiotics, penicillin, which was discovered in 1928 by Alexander Fleming. It is a broad-spectrum antibiotic compound commonly used during invasive dental procedures as it shows a good and predictable absorption and bioavailability [106]. It has a bactericidal activity against gram-positive and gram-negative microorganisms. In addition, it is active against several members of the oral commensal microflora, such as viridans streptococci, and is thus expected to reduce the risk of local and systemic infection after dental procedures. The molecular structure of amoxicillin includes a β-lactam ring that may be cleaved by bacterial enzymes.

The combination of amoxicillin and clavulanic acid, the beta-lactamase inhibitors, is used to treat infections with β-lactamase producing bacteria. This combination results in an antibiotic with a broader spectrum of action and restored efficacy against amoxicillin-resistant bacteria, which produce β-lactamase.

5.2. Penicillin-V

Penicillin-V is a widely used antibiotic in dentistry and possesses several beneficial characteristics. It achieves peak serum levels within 30 min, and persistent, detectable levels for up to 4 h after administration [106]. It has a bactericidal action with a narrow microbial spectrum, and it is highly effective against most *Streptococcus* species and oral anaerobes [106]. Penicillin-V is recommended as the drug of choice for the treatment of dental infections in Scandinavian countries. However, it is seldom used outside Scandinavia mainly because it is not available for purchase in many countries. The wide use of penicillin-V instead of broad-spectrum compounds is considered to be an important factor contributing to the low rates of antibiotic resistance seen in Scandinavian countries.

5.3. Metronidazole

Metronidazole has a unique bactericidal effect against anaerobic bacteria. It is a narrow-spectrum antibiotic, which minimizes the risk of opportunistic pathogens among commensal microbiota and reduces the risk of developing a resistant species. There is no known allergic or hypersensitivity reactions to metronidazole, and it has limited side effects which are generally tolerable, transient, or reversible [107].

5.4. Clindamycin

Clindamycin is a broad-spectrum compound active against oral anaerobic and aerobic bacteria, such as streptococci and staphylococci, although its use in dentistry is recommended mainly in patients with a penicillin allergy [106]. It is bacteriostatic in normal concentrations and has good bone penetration [91]. Because of its broad-spectrum effect, it gives significant

and long-term effects on the protective resident microflora and is associated with the development of *Clostridium difficile* gastroenteritis [108, 109].

5.5. Antibiotic combination therapy

Peri-implant subgingival microbiota contains several putative periodontopathic species with different antimicrobial susceptibility. Therefore, antibiotic combination may be useful because of its wider spectrum of activity compared with a single agent. Combination drug therapy may reduce the possibility of developing bacterial resistance due to antimicrobial spectrum overlap, or it may be combined in a synergetic way when targeting organisms, allowing the dose of a single agent to be lowered [110]. However, such combinations may lead to increased adverse reactions. Recently, the combination of metronidazole and amoxicillin has become a popular treatment modality for many dentists and researchers.

6. Consequences of antibiotic treatment

No antibacterial drug is completely nontoxic, and its use carries accompanying risks, which has to balance the benefits and risks of its use before prescribing. The most common side-effects are gastrointestinal, ranging in severity from frequent self-limiting gastrointestinal upset to rare life-threatening pseudomembranous colitis. Other relatively common adverse effects are hypersensitivity reactions ranging from mild to life-threatening anaphylactic reactions [110]. However, the majority of these reactions are mild and limited to a rash or skin lesions in the head or neck region. Another negative impact of the over prescription of antibiotics is the cost to the healthcare system. A survey performed in USA suggested that while the cost of antibiotic prophylaxis is low to the individual, the potential cost to the healthcare system may be well over $150 million annually [111].

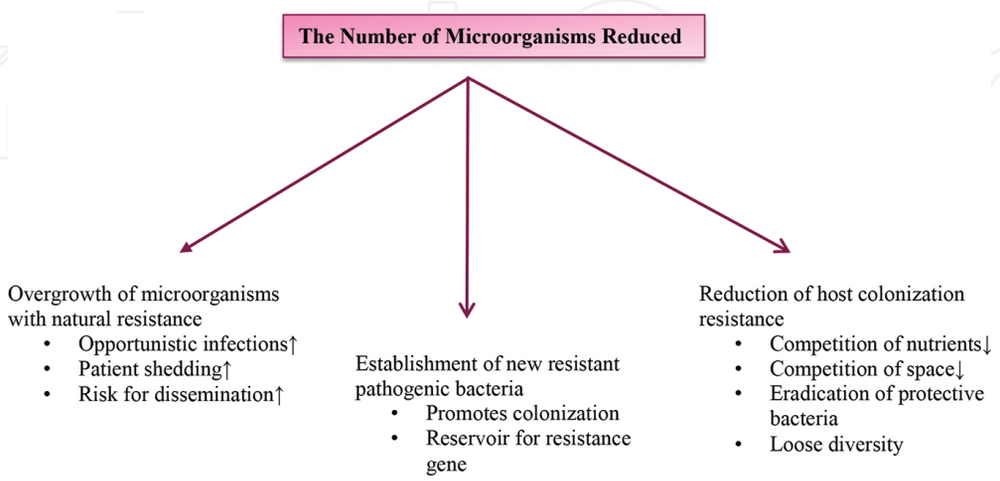

Figure 2. The effect of antibiotic treatment on the ecology of the normal microflora [112–114].

It is well known that the administration of antimicrobial agents causes a disturbance in the oropharyngeal and intestinal microflora, which is considered to be important for health maintenance. This disturbance is not only due to the spectrum of agents, but also to their degree of absorption, route of elimination, possible enzymatic inactivation and/or binding to human fluids and intestinal material [112]. Individual variations in normal microflora further determines the ecological outcome of antimicrobial therapy [112]. Selective pressure by the administration of antibiotics will decrease the number of microorganisms in the oral cavity. Consequently, this leads to a disturbance in human microbial ecology as shown in **Figure 2** [112–114].

Antibiotic resistance has become a global growing health problem. The golden age of antibiotic therapy is now coming to an end as stated in 2014 by WHO [115]. However, some researcher believes that we are already in the pre-antibiotic era. The Global Economic Forum reported that the development of antibiotic resistance has major societal risks and increases both morbidity and mortality of affected individuals [115, 116]. Each year there are thousands of deaths, and millions of dollars spent on healthcare costs due to resistant infections [117]. Therefore, a restrictive approach towards using antibiotics is mandatory in order to limit the development of microbial antibiotic resistance and avoid the risk of unwanted systemic effects of antibiotics for the treated individual.

7. Future prospective and knowledge gap

The prescription of antibiotics in medical practice needs to be addressed globally, particularly in the dental field, including dental implant procedures [29]. In fact, there is a decrease in surgical infection rate incidence even without the use of antibiotics, yet there is still an increase in antibiotic prescriptions [118]. There are a lot of factors influencing the prescription of antibiotics by healthcare practitioners including patients request, gap in knowledge and practitioner's education. Indeed, considering the serious situation regarding emerging and quickly disseminating antibiotic resistance there is no justification for prescription antibiotics without medical indication [29].

Within the literature, there is a lack of scientific evidence showing the additive effect of antibiotics, either prophylactic or therapeutic, in the treatment of dental implant. However, with the demands on restrictive antibiotic policy more studies are needed to assess the benefit of antibiotic prescription and the safety to refrain from its use. In order to restrict antibiotic use to fields where it has unquestioned medical value, it is important to investigate the need for antibiotics. Therefore, additional RCTs with larger sample sizes and longer follow-up period are needed to determine the role of antibiotic prophylaxis during implant insertion to prevent early implant failure in both uncomplicated/straight forward and complicated cases. Furthermore, different type of complicated cases such as immediate insertion into extraction site, bone augmentation procedures, full jaw surgery and implant surgery in the medically compromised patient, may pose a variable risk of postoperative infection and should therefore be studied separately. In the treatment of peri-implantitis, there is a critical need for double-

blinded placebo-controlled randomized clinical trials to demonstrate the efficacy of adjunctive use of systemically delivered antibiotics [80]. Furthermore, more studies are needed to evaluate antibiotic prescriptions from the societal and cost-effective perspectives, not just from the healthcare perspective.

MESSAGE TO THE CLINICIAN

1) Antibiotics can never compensate for not performing high standard hygiene measures.

2) Antibiotic prophylaxis is not indicated in straight forward implant surgery.

3) In complicated implant surgery a single dose of antibiotic prophylaxis may prevent implant losses.

4) There is no clinical value of extending the antibiotic prophylaxis beyond the day of surgery.

5) Peri-implantitis should be treated surgically. Antibiotics alone cannot replace proper surgical intervention.

Figure 3. Tips for the clinician regarding antibiotic prescription in implant dentistry.

Finally, there is a need for recommendations to limit and optimize the utilization of antibiotics in the dental implant field. This recommendation may result in a more sustainable antibiotic usage, preventing the risk of infection, which in turn can improve the results of a surgical intervention, reduce the risk of resistant bacterial strains developing, reduce the total use of antibiotics, and possibly reduce the cost of care [119]. Based on available evidence some summarized suggested advices to the clinician are presented in **Figure 3**.

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