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THE USE OF ANTIBIOTIC PROPHYLAXIS IN IMPLANT DENTISTRY

A MICROBIOLOGICAL AND CLINICAL PERSPECTIVE

Dalia Khalil

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THE USE OF ANTIBIOTIC PROPHYLAXIS IN IMPLANT DENTISTRY
A MICROBIOLOGICAL AND CLINICAL PERSPECTIVE

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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By

Dalia Khalil

Principal Supervisor:
Associate professor, Margareta Hultin
Karolinska Institutet, Sweden
Department of Dental Medicine

Co-supervisor(s):
Professor, Bodil Lund
University of Bergen, Norway
Department of Clinical Dentistry
and
Karolinska Institutet, Sweden
Department of Dental Medicine

Professor, Björn Klinge
Malmö University, Sweden
Faculty of Odontology
Department of Periodontology
and
Karolinska Institutet, Sweden
Department of Dental Medicine

Opponent:
Associate professor, Morten Enersen
University of Oslo, Norway
Faculty of Dentistry
Department of Oral Biology

Examination Board:
Associate professor, Bengt Götrick
Malmö university, Sweden
Faculty of Odontology
Department of Oral Diagnostics

Associate professor, Andreas Thor
Uppsala University, Sweden
Department of Surgical Sciences, Oral and Maxillofacial Surgery

Associate professor, Margaret Sällberg Chen
Karolinska Institutet, Sweden
Department of Dental Medicine

External Mentor:
Professor, Sofia Tranaeus
Malmö University, Sweden
Faculty of Odontology
Department of Health Technology Assessment

Karolinska Institutet, Sweden
Department of Dental Medicine
and
Swedish Agency for Health Technology Assessment
and Assessment of Social Services, Sweden

“Live as if you were to die tomorrow. Learn as if you were to live forever.”

Mahatma Gandhi

To **Ehab**

Mahmoud, Solaf, Sereen

With love

To my parents **Reda, Seham**

Who will be delighted

ABSTRACT

The current development of antibiotic resistance calls for prudent use of antibiotic prescription. Methods of investigating antibiotic overconsumption, include identifying areas of misuse or overuse, as well as implementing recommendations and guidelines. The efficacy of antibiotic prophylaxis prior to dental implant surgery is debated. However, the rationale for restrictive antibiotic prophylaxis is often based on tradition rather than actual knowledge of negative consequences. Therefore, the general aim of this thesis is to investigate the rationale for restrictive antibiotic prophylaxis in implant dentistry and to determine actual prescription behavior.

Study I: The aim of Study I was to investigate the microbiological consequences on oral microflora in terms of selection for resistance extent, and to determine the ecological disturbance after a single dose of 2 g amoxicillin. Thirty-three healthy participants were given a single dose of 2 g amoxicillin. Saliva was collected prior to administration of antibiotics (day 1), and on days 2, 5, 10, 17 and 24. A large ecological disturbance among oral aerobic microflora was observed. The proportion of viridians streptococci with reduced susceptibility to amoxicillin was significantly increased on days 2 and 5 ($P = 0.00$ and $P = 0.04$, respectively).

Study II: The aim of Study II was to investigate antibiotic prophylaxis prescription behaviors among dentists placing dental implants, and to check the influence of scientific reviews published in 2010. Questionnaires were distributed during two time periods (2008 and 2012). The questionnaires were sent to eligible dentists (120 in 2008, 161 in 2012) in the Stockholm region, Sweden. In 2008, 88% of the dentists routinely prescribed antibiotic prophylaxis during implant surgical procedures, while in 2012 this dropped to 74% ($P = 0.01$). There was a significant change in dentists' prescription patterns with 65% prescribing a single dose prophylaxis in 2012, compared to 49% in 2008 ($P = 0.04$).

Study III: The aim of Study III was to investigate the effect of antibiotics on the outcome of bone augmentation in conjunction with dental implant placement. This was a complex systematic review combining the recommended quality assessment methods for systematic reviews and primary studies. Selected primary studies were reviewed using a protocol for assessment of randomized studies, while scientific evidence was graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Balshem, et al. 2011). The results showed that no relevant systematic reviews pertaining to the topic of this study where found. For primary studies, only two studies were regarded as a moderate risk of bias.

Study IV: The aim of Study IV was to determine antibiotic prescription behavior among dentists performing bone-augmentation procedures prior to, or in conjunction with dental implant surgery, and to check the influence of national recommendations published in 2012. In addition, this study also investigated the occurrence of postoperative infection following these bone-augmentation procedures. A multi-center retrospective study was performed. Four hundred patients' medical charts were investigated during two time periods (2010-2011 and 2014-2015). The results showed that, on comparing the two time periods, there was a

significant reduction in the number of patients treated according to national recommendations (P = 0.02). Moreover, a significant reduction in the duration of antibiotic treatment was also seen (P = 0.03). The number of patients not given antibiotic prophylaxis significantly increased (p = 0.00). In addition, the rate of postoperative infections was low and without significant difference between both time points (3.5% in 2010-2011 and 7% in 2014-2015).

In conclusion, single dose of prophylactic antibiotics induces a significant selection of resistant strains among oral microflora and causes a large ecological disturbance. There is a wide variation in the type, dose and duration of prophylactic antibiotic treatment prior to simple or complicated implant surgery. Knowledge regarding the use of antibiotic prophylaxis for reducing the risk of infection with bone augmentation procedure in conjunction with dental implant placement is lacking. The results of these four studies support a restrictive approach to antibiotic prophylaxis and warrant a thorough revisiting of indications for antibiotic prophylaxis. In addition, safety aspects pertaining to refraining from single antibiotic use need to be fully investigated. There is a need for strict guidelines based on solid scientific evidence to promote the rationale for antibiotic usage.

Keywords: antibiotic prophylaxis, ecological disturbance, oral microflora, antibiotic resistance, dental implant, oral bone augmentation, prescription behavior, scientific evidence, knowledge gap.

LIST OF SCIENTIFIC PAPERS

I. **Khalil D**, Hultin M, Rashid M, Lund B. Oral microflora and selection of resistance after a single dose of amoxicillin. Clinical Microbiology and Infection. 2016; 22 (11): 949-e1.

II. **Khalil D,** Hultin M, Andersson Fred L, Parkbring Olsson N, Lund B. Antibiotic prescription patterns among Swedish dentists working with dental implant surgery: adherence to recommendations. Clinical Oral Implants Research. 2015; 26 (9): 1064-9.

III. Klinge A, **Khalil D**, Klinge B, Lund B, Naimi-Akbar A, Tranæus S, Hultin M. Antibiotics and bone augmentation in dental implant installation: a complex systematic review. (Submitted to Journal of Technology Assessment in Health care).

IV. **Khalil D**, Bazsefidpay N, Holmqvist F, Larsson Wexell C, Nilsson P, Lund B, Hultin M. Antibiotic utilization during bone augmentation procedures in conjunction with dental implant insertion. (Manuscript).

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LIST OF ABBREVIATIONS

AHA	The American Heart Association
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
APUA	The Association for the Prudent Use of Antibiotics
ASA score	American Society of Anesthesiologist score
BKV	Brucella agar with Kanamycin and Vancomycin
BNV	Brucella agar with Neomycin and Vancomycin
CLED	Cystine Lactose Electrolyte Deficient agar
CLSI	Clinical and Laboratory Standards Institute
CONSORT	Consolidated Standard of Reporting Trials
EBM	Eviedence Based Medicine
ESC	The European Society of Cardiology
EUCAST	European Committee on Antimicrobial Susceptibility Testing
g	Gram
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessment
IE	Infective Endocarditis
Log	Logarithm
MALDI-TOF MS	Matrix-assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry
Mg	Milligram
MICs	Minimum Inhibitory Concentrations
MS	Mitis Salivarius agar
NICE	National Institute for Health and Clinical Excellence
PBS	Phosphate Buffered Saline
Penicillin-V	Phenoxymethylpenicillin
PICO	Population, Intervention, Control and Outcome/Observation
P-value	Probability value
RCT	Randomized Control Trials
RR	Risk Ratio

SBU	The Swedish Agency for Health Technology Assessment and Assessment of Social Services
Spp	Species
STRAMA	The Swedish Strategic Programme against Antibiotic Resistance
UK	United Kingdom
USA	United State of America
VMGII	Virulence and Marker Gene
WHO	The World Health Organization

1 INTRODUCTION

Bacteria were amongst the first organisms to live on Earth. They made their appearance over three billion years ago in the oceans before colonizing living species. The majority of bacteria are essential for life, while only a minor proportion are actually pathogenic. Throughout history, harmful bacteria strains have been responsible for infections in the human body, with the immune system serving as a first line of defense against pathogenic attacks. As medical knowledge grew, many factors such as improvements in diet, sanitation and water purification helped strengthen the immune system and prevent infection dissemination. Despite these efforts, without antibiotics the major cause of deaths are infectious diseases. Misuse of antibiotics though, has further lead to the development of antibiotic resistance and we are now facing a massive problem worldwide. Therefore, prescription of antibiotics has become an important aspect for medical and dental practice. Bacterial antibiotic resistance has an impact on the medical and dental fields, and this thesis will focus on the risks of using antibiotic prophylaxis and on antibiotic prescription behaviors in the dental implant field, from a microbiological and clinical aspect.

1.1 ORAL MICROFLORA

Microorganisms within the human host can be of benefit to our body (Relman 2002), or act as commensal organisms meaning they neither benefit nor harm (Dalwai, et al. 2006). The resident microflora can prevent colonization of pathogenic organisms, colonization resistance, by competing with endogenous nutrients, or with co-factors for microbial growth, or with binding sites for microbial attachment on mucosal and dental surfaces (Marsh and Percival 2006; Nord and Kager 1984; Nord 1990; O'Hara and Shanahan 2006). Moreover, production of antibacterial chemicals, and inhibitory factors as a side product of their metabolism, also contribute to colonization resistance (Marsh and Percival 2006; Nord and Kager 1984; Nord 1990; O'Hara and Shanahan 2006). Normal microflora also directly or indirectly effect the organism’s normal development of the physiology, nutrition and defence systems (Grubb, et al. 1989; Marsh 1989; O'Hara and Shanahan 2006; Rosebury 1962). On the other hand, the microflora can act as a reservoir of antibiotic resistant genes (Richard J. Lamont, et al. 2013). There are many factors that affect the qualitative and quantitative balance in indigenous microflora, including host and environmental factors (Brown, et al. 1975; Ezz El-Arab, et al. 2006; Nord, et al. 2009; Rashid, et al. 2012; Richard J. Lamont, et al. 2013). Nevertheless, bacterial tissue interactions, interbacterial adherence, and interbacterial metabolic interactions play an important role in establishing, maintaining and regulating the flora (Schuster 1990; Schuster 1999; Schuster and Burnett 1994; Tanner, et al. 1998).

The oral cavity is a complex community. It constitutes of different habitats, including teeth, gingival sulcus, tongue, cheeks, hard and soft palates, and tonsils. There are more than 750 bacterial taxa that are naturally colonized in the oral cavity (Jenkinson and Lamont 2005), co-existing in a balanced microbial ecosystem. From these, oral streptococci predominate the microbiota of most individuals (Dalwai, et al. 2006). However, the properties of the mouth as a microbial habitat are dynamic and will change over time due to the dietary habits, general health, eruption or extraction of teeth, insertion of dentures, placement of orthodontics bands and any dental treatment (Faran Ali and Tanwir 2012; Marsh PD 2009; Schuster 1999). The most dramatic effect on normal microflora is seen after antibiotic treatment (Nord 1990).

1.2 ANTIBIOTICS

The discovery of antibiotics resulted in one of the greatest revolutions in modern medicine. Responsible for both treating bacterial infections and reducing mortality and morbidity from bacterial diseases. They are today, an essential part of modern medicine and common procedures and treatments could not be performed without the availability of potent antibiotics.

Antibiotics are a compound or substance that kills or slows down the growth of bacteria. Antibiotic use is acknowledged as ones of the most commonly used approaches in treating bacterial infections. However, as knowledge on the cause of various infections and bacterial diseases has grown, new antibiotics consisting of a wider range of antimicrobial compounds have been developed. The compound chosen for treatment needs to have the narrowest spectrum to cover the most likely pathogens involved. Ideally, the chosen treatment should consist of the shortest possible duration for preventing of both clinical and microbiological relapse (Oberoi, et al. 2015). This short cycle duration of antibiotic treatment should ideally display: a rapid onset of action; bactericidal activity; lack of propensity for development of resistant strains; ease of infiltration into the tissues; action against non-dividing bacteria; the ability to be unaffected by adverse infection conditions; administration at an optimal dose, and an optimal and convenient dosing regimen (Rubinstein 2007).

Antibiotics vary in their usage and mechanism. They can be classified using different methods a) by drug origin (such as synthetic or natural); b) by microbiological range (broad-spectrum or narrow-spectrum), c) by type of antibacterial activity (such as killing bacteria or inhibiting bacterial growth); or d) by their cellular mechanism of action such as cell wall inhibitors, inhibitors of nucleic acid synthesis or protein synthesis inhibitors.

From the antimicrobial agents available, only a limited number of systemic antibiotics such as amoxicillin, phenoxymethylpenicillin (penicillin-V), clindamycin and metronidazole, are commonly used in conjunction with dental surgical procedures (Table 1). Moreover, it has been estimated that dental prescriptions are responsible for 5-10 percent of all antibiotic prescriptions among patients in some parts in Europe and the USA (Hicks, et al. 2015; Holyfield G 2009; HPS and ISD 2016; Norm/Norm-Vet 2015; Pipalova, et al. 2014; Swedres-Svarm 2016). In Sweden, it is estimated to be six percent (Swedres-Svarm 2016).

Table 1. Summary of characteristics of the most common antibiotic compounds used in implant dentistry (Lund, et al. 2014). Available from: http://dx.doi.org/10.5772/62681.

	Amoxicillin	Clindamycin	Metronidazole	Penicillin-V
Spectrum on oral flora	*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.) T½ Solubility Excretion	 90% ~ 1h Water Urine	 90% ~ 2,5h Fat Gall bladder, feaces, urine	 >95% ~ 8h Fat Urine and gall baldder	 50% ~ 30 min Water Urine
Common side effects	Vomiting, diarrhea, nausea, exanthema (5%)	Vomiting, diarrhea, nausea (8%)	Gastrointestinal upset, metallic taste (5-10%)	Diarrhea, nausea (5%)
Ecological effects Oral Gastrointestinal	 ++ ++	 +++ +++	 ++ +	 ++ +

P.O. Peroral
T½ Half life
+ Mild /no effect, ++ moderate effect, +++ severe effect

1.3 CONSEQUENCES OF ANTIBIOTIC TREATMENT

No antibacterial drug is completely non-toxic and thus without side effects or risks. Therefore, the prescribing healthcare specialist needs to weigh the potential benefits and risks prior to use. The most common side-effect is gastro-intestinal, ranging from a mildly upset stomach to life-threatening pseudomembranous colitis (Golledge, et al. 1992; Lipsky and Baker 1999; Loffeld and Flendrig 1990; Wilton, et al. 1996). Another relatively common adverse effect is hypersensitivity – ranging, most commonly, from a mild skin rash or lesion to rarer life-threatening anaphylactic reactions (Granowitz and Brown 2008). However, a true penicillin

allergy, including amoxicillin, is rare with the estimated frequency of anaphylaxis at 1-5 per 10 000 cases of penicillin therapy, of which 10% of these reactions are fatal (ASCIA 2014; Bhattacharya 2010). However, the risk of adverse reaction is known to be increased with broad-spectrum compounds, and also observed with single dose antibiotic treatment (Thornhill, et al. 2015).

The human normal microflora are often in delicate balance; the optimal distribution of the different microorganisms is considered to be important for health maintenance. Administration of antimicrobial agents commonly causes a disturbance in this microflora. This disturbance, a decrease in the number of microorganisms present and also reduced diversity, is not only due to the spectrum of antimicrobial agents, but is also affected by rate of absorption, route of elimination, possible enzymatic inactivation and/or whether they bind to human tissue and fluids (Sullivan, et al. 2001). Consequently, the disturbance leads to an overgrowth of bacteria with natural resistance, reduces host colonization resistance and establishes new resistant pathologic bacteria (Figure 1) (Nord 1990; Sullivan, et al. 2001; Van der Waaij and Nord 2000). The outcome of antimicrobial treatment is thus dependent on individual variation in normal microflora (Sullivan, et al. 2001).

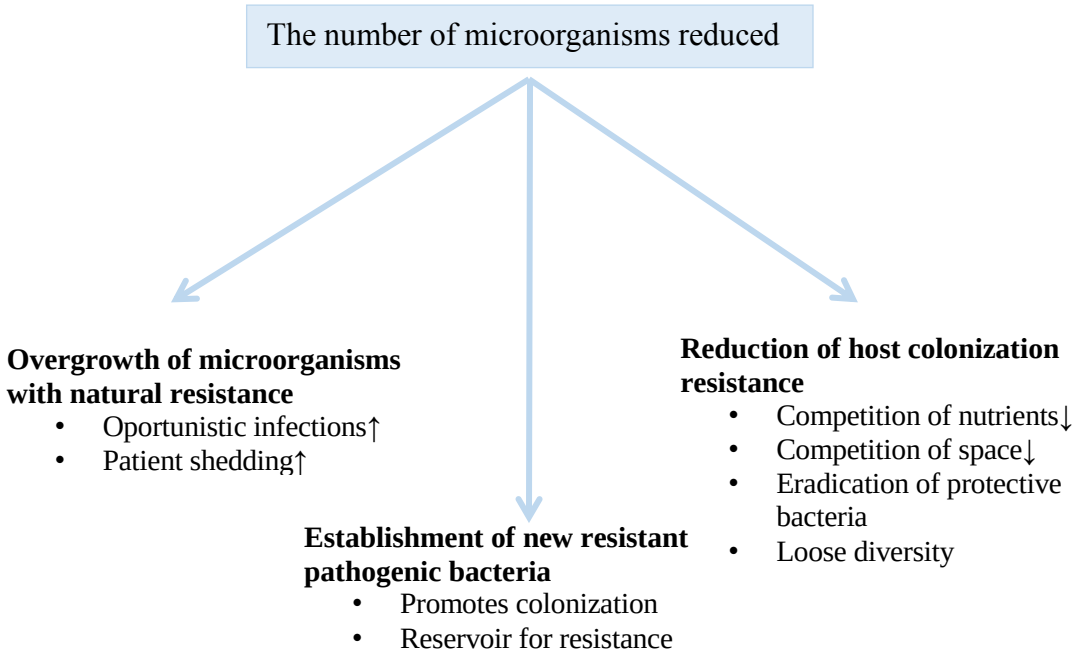

Figure 1. The effect of antibiotic treatment on the ecology of the normal microflora (Nord 1990; Sullivan, et al. 2001; Van der Waaij and Nord 2000). Available from: http://dx.doi.org/10.5772/62681.

Another negative aspect of the frequent use of antibiotics is the financial demand it places on the healthcare system. A previous study suggested that while individual costs for antibiotic treatment may be low, the potential cost to the American healthcare system may reach to over $150 million annually (Lockhart, et al. 2013). Moreover, resistance to antibiotics results in increased cost to patients, healthcare systems and society due to the need for more tests, new and more costly medicines, longer hospital stays, lengthy sick leave or even premature death (Reactgroup 2008).

1.4 ANTIBIOTIC RESISTANCE

Antibiotic resistance has become a global health problem. The World Health Organization (WHO) stated that the golden age of antibiotic therapy is now coming to an end (WHO 2015); some researchers even believe that the end is already here. The World Economic Forum stated that antibiotic resistance has major societal risks (WEF 2017), and that the development of resistant infections result in thousands of deaths and millions of dollars spent on healthcare every year (O'Neill 2014). Therefore, a cautious approach towards prescribing antibiotics needs to be taken in order to try to limit further development of antibiotic resistance. It has previously been suggested, although not shown, that a shorter antibiotic treatment regimen reduces the risk of developing antibiotic resistance (Guillemot, et al. 1998). In a recent study, there was a significant increase in the number of oral streptococci with reduced susceptibility against amoxicillin already after a 3-day treatment course (Chardin, et al. 2009). This suggests that short-term antibiotic treatment may also pose a marked risk for inducing antibiotic resistance. Another serious problem with the development of oral bacterial resistance is that the commensal flora may transfer resistance genes to other more pathogenic bacteria such as *Streptococcus pneumonia* and *Streptococcus pyogenes* (Dowson, et al. 1990; Jonsson and Swedberg 2006).

Pathogens are different in their susceptibility to antibiotics - resistance to one antibiotic may not necessarily mean lack of sensitivity to another (Drlica and Perlin 2011). Antibiotic resistance is categorized into three major types: natural/ intrinsic resistance (the innate ability of a bacterial species to resist the activity of a particular antimicrobial agent), or acquired resistance (acquisition of new DNA through transformation, transduction or conjugation), or genetic resistance (chromosomal mutation) (Dahlén, et al. 2012; Drlica and Perlin 2011). There are five mechanisms by which antibiotics exhibit resistance due to chromosomal mutation: reduced permeability or uptake, enhanced efflux, enzymatic inactivation, alteration or over-expression of the drug target, or loss of enzymes involved in drug activation (Dahlén, et al. 2012; Richard J. Lamont, et al. 2013). Nevertheless, the lowest necessary antibiotic dose needs

to be determined to achieve minimal side effects alongside the highest efficacy to block cell growth (Drlica and Perlin 2011).

Preventive measures such as developing new antimicrobial agents, conducting surveillance, implementing isolation, adapting lab procedures, educating about resistance, improving drug administration and improving drug choice are important and could minimize the prescription of antibiotics (Foucault and Brouqui 2007; McGowan Jr 2001). However, the multifaceted intervention approach seems to be the most efficient in the fight against antimicrobial resistance (Foucault and Brouqui 2007). In fact, coordinated efforts have already initiated by many institutes over the world such as the Association for the Prudent Use of Antibiotics (APUA) and the World Health Organization (WHO) in reaction to the spread of antimicrobial resistance. However, this fight can only be won with the help of government authorities, hospital personnel, community practitioners, the pharmaceutical industry, patient awareness and researchers.

1.5 DENTAL IMPLANTS

Recently, dental implants - titanium devices anchored and integrated into the jawbone - have become an established and successful therapeutic option for partially or completely edentulous jaws. They have been an alternative treatment for missing teeth for over 40 years (Branemark, et al. 1977). Improvements in implant design, surface characteristics, and surgical protocols make implants a secure and highly predictable procedure (Moraschini, et al. 2015). The rate of edentulism has decreased in Europe due to the development of implant dentistry (Müller, et al. 2007). It has been estimated that more than 12 million implants are placed every year, globally (Albrektsson, et al. 2014). In Sweden it was calculated that, in 2014, the number of implant placed yearly were approximately 78,000 in 31,500 patients according to the Swedish Social Insurance Agency.

Implant survival rates were calculated in a recent meta-analysis with a follow up period of up to 20 years. Here, the mean cumulative survival value was 94.6%, ranging from 73.4% to 100%, while implant success rate ranged from 34.9% to 100% (Moraschini, et al. 2015). In this review it was not possible to perform meta-analysis for the success rate due to the variation in the success criteria used and their heterogeneity; 50% of the included studies in the review shared the same criteria, thus the cumulative mean success rate was 89.7%. There are several factors known to determine implant success including survival rates, continuous prosthesis stability, absence of radiographic bone loss, absence of infection in the peri-implant soft tissues, and patient’s subjective evaluation (Albrektsson and Zarb 1998; Albrektsson, et al. 1986;

Annibali, et al. 2012; Buser, et al. 1997; Misch, et al. 2008; Smith and Zarb 1989). A bone loss of up to 1.5 mm within the first year after dental implant insertion, followed by an additional 0.1 mm of annual bone loss is acceptable, according to the Albrektsson guidelines for bone remodeling (Albrektsson, et al. 1986). However, recently Van Velzen stated that the amount of peri-implant bone loss may progress even more rapidly, leading to an increase in incidence rate over time (Van Velzen, et al. 2014).

1.5.1 Bone graft in conjunction with dental implant placement

Bone remodeling is a critical aspect of implant survival when restoring an implant to full functionality. The implant restoration and supporting bone both need to be able to respond to the functional demands placed on them. To achieve the best outcome from dental implant treatment, adequate bone should be available to support and stabilize the implant. Lack of supporting alveolar bone can be due to atrophy, trauma, developmental defect, periodontal disease, tooth loss, and infection/ inflammation (Esposito, et al. 2009; Tonetti and Hämmerle 2008). Therefore, it is common to perform bone augmentation procedures in cases of insufficient bone volume either prior to implant placement, or in conjunction with implant placement. There are different types of bone grafting materials and techniques with varying clinical outcomes to overcome bone deficiencies (Esposito, et al. 2009; Tonetti and Hämmerle 2008). Ideally, graft materials should provide four properties: an osteoconductive matrix, nonviable scaffolding for the ingrowth of bone; osteoinductive factors, chemicals that promote bone regeneration and repair; osteogenic cells, that facilitate bone regeneration; and structural integrity (Gazdag, et al. 1995). Reconstruction of the atrophic alveolar ridge was first performed in 1975 using an autogenous bone graft (Brånemark, et al. 1975). Autograft material is considered the “gold standard” since it combines all properties necessary for grafting material (Gazdag, et al. 1995; Marx 2007; Scarano, et al. 2006). This grafting material has immunologic compatibility, great vascularization potential, will not lead to disease transmission, and has a physical and chemical structure similar to the host site (Gulinelli, et al. 2017). However, the disadvantage of using autograft material is that additional surgical sites, prolonged operative and treatment time, risk of neurovascular injury, unpredictable resorption of the graft, and decrease in the volume of the donor site (Gazdag, et al. 1995; Liu and Kerns 2014). Allograft material is initially referred to a bone graft containing living cells harvested from an individual of the same species. This type of material is not easily recommended because it initiates a cell mediated immune response and it can only survive if the donor is a parent or sibling (Urist 1980). A substitute to the fresh allograft is a bone tissue that derived from an individual of the same species and which contains no viable cells. This material is

prepared by freezing, freeze drying, irradiating or sterilizing the tissue. Allograft has osteoinductive and osteoconductive properties, however some studies have reported that its lack of osteoinductive properties and very modest osteoconductive responses (Pinholt, et al. 1994; Solheim 2001; Urist 1980). Although allograft is inferior to autograft, allografts are commonly used in orthopedic surgery in patients with large bone defects as autographs are either not available in sufficient quantities or their use is accompanied by high morbidity at the donor site (Gocke 2005; Simion, et al. 2001). Moreover, xenograft bone material - material obtained from a genetically different species than the host - has osteoconductive properties and is biocompatible with human recipients (Tadjoedin, et al. 2003; Terheyden, et al. 1999). The disadvantage of using it is its lack of osteoinduction properties (Tadjoedin, et al. 2003; Terheyden, et al. 1999). One of the most commonly used xenografts is Bio-Oss® (Geistlich Pharma AG, Wohlhusen, Switzerland) deproteinized bovine bone mineral that has been treated by removing all of its organic material. Bio-Oss structure greatly increases the surface area and thus results in a material that is good for osteoconduction, increases angiogenesis and enhances new bone growth (Rodriguez, et al. 2003). On the other hand, because of its large porous nature, initial stability may be compromised (Su-Gwan, et al. 2001). However, this material has been proved to be a workhorse in oral surgery (Kao and Scott 2007). Moreover, other xenograft materials are available including coralline hydroxyapatite, chitosan, gusuibu and redalgae (Kao and Scott 2007). Alloplastic graft material is a synthetic bone substitute that serves as a physical framework for bone ingrowth, having two of the four elements of an ideal graft: osteoconduction and osteointegration. There are many synthetic materials available such as bioactive glasses, glass ionomers, calcium sulfate and synthetic hydroxyapatite (Moore, et al. 2001). The use of a mixed type of bone graft - autograft and xenograft – thus has a better effect from a biological perspective than using each one separately (Galindo-Moreno, et al. 2007).

There are multiple surgical techniques to augment bone volume horizontally or vertically: only graft, inlay graft, ridge expansion, distraction osteogenesis. To date, there is insufficient evidence regarding which is the most effective. Onlay bone graft is where graft material is lain over the treatment area in order to increase the alveolar jawbone width or height (Kahnberg, et al. 1989). Inlay graft is where part of the jawbone is surgically separated and graft material sandwiched between the two sections (Keller 1992). Ridge expansion is where the alveolar ridge is surgically split then parted, allowing the implant or grafted material, or both, to be inserted. Finally, distraction osteogenesis is a where a surgical fracture is made, then gradually displaced to increase bone volume (Chin 1999). The gap created during the displacement is loaded with immature non-calcified bone. This bone is then allowed to mature. Moreover, there

are some procedures associated with bone graft techniques such as placement of a barrier membrane that acts as a barrier to prevent soft tissue growth and forms a chamber to guide the bone regeneration process in a defect area (Gottlow 1993; Meinig 2010; Retzepi and Donos 2010). Maxillary sinus procedures are sometimes needed if the available bone for implant placement is of reduced alveolar height. Osteotomies where the bone is cut, modified and realigned to correct bone deformity can be also incorporated in the graft procedure. These different surgical techniques can be used in combination with different graft materials (Esposito, et al. 2009). Augmentation procedures can fail to produce adequate bone volume in which to place dental implants and do not necessary result in long term survival rates (Tonetti and Hämmerle 2008). However, it has been reported in a systematic review that dental implant survival rates are high irrespective of whether implants were placed in native or in augmented bone (Al-Nawas and Schiegnitz 2014; Hämmerle, et al. 2002).

1.5.2 Complications associated with dental implant placement

Complications with dental implants do occur, and are associated with infection, failure and/or implant loss (Albrektsson and Donos 2012; Donos, et al. 2012). Oral postoperative infections in healthy patients are commonly wound infections caused by endogenous aerobic and anaerobic microorganisms in the oral cavity (Heimdahl and Nord 1990). The reported prevalence of postoperative infection after implant installation varies across published studies reaching up to 11.5% even with the use of prophylactic antibiotics, (Table 2) (Abu-Ta'a, et al. 2008; Anitua, et al. 2009; Caiazzo, et al. 2011; Camps-Font, et al. 2015; Esposito, et al. 2010; Esposito, et al. 2008; Gynther, et al. 1998; Nolan, et al. 2014). To date, there is no standard routine therapeutic approach for postoperative infections that safely predict an improvement in the survival and success rates of these implants.

Dental implant failures are classified, according to Esposito el at. (Esposito, et al. 1998), into four different categories: a) biological implant failures which are categorized as early failures i.e. failure to achieve osseointegration due to surgical trauma, infection, or lack of primary stability (Sakka, et al. 2012), or late failures i.e. failure to maintain the achieved osseointegration due to occlusal overload, peri-implantitis, or both (Sakka, et al. 2012), b) mechanical implant failures, which include fracture of the implants or suprastructure, c) iatrogenic implant failures, where osseointegration is achieved but due to improper implant alignment or angulation, or nerve damage, implants have failed, and d) inadequate patient adaptation with phonics, esthetic and psychological problems due to dental implants. Implant failure may result in the need for implant removal (Sakka, et al. 2012). There are several risk factors for implant failures including systematic, local, prosthodontics and genetic factors

(Antoun, et al. 2017; Chrcanovic, et al. 2016; Jemt, et al. 2017; Renvert and Quirynen 2015). However, some factors shown to be strongly associated with increased risk of dental implant failure such as history of periodontitis and smoking habits (Antoun, et al. 2017; Chrcanovic, et al. 2016; Jemt, et al. 2017; Renvert and Quirynen 2015).

Peri-implantitis is the most commonly reported cause of implant failure, defined as inflammation in the peri-implant tissue associated with a loss of supporting bone around a functioning implant (Lindhe, et al. 2008). Pontoriero et al. discovered in 1994 that bacterial plaque accumulation in the soft tissue around dental implants caused inflammatory changes (Pontoriero, et al. 1994). Recent reviews have reported wide variations in the prevalence of peri-implantitis. Thus the incidence of peri-implantitis may be dependent on diagnostic criteria, patient selection and the variation in length of follow up. The complexity of case selection in prospective studies might explain the wide variation in the reported prevalence. In 2012, the EAO Consensus Conference stated that peri-implantitis occurred in one of five patients within five years following implant surgery (Klinge, et al. 2012). A recent review showed the prevalence of peri-implantitis varied from 4.2% to 47% of all implants (Tomasi and Derks 2012; Van Velzen, et al. 2014).

Table 2. Published studies on the prevalence of postoperative infections after dental implant placement treated with systematic antibiotic

Published studies	Study design	Number of treated patients	Number of reported postoperative infection	Prevelance of postoperative infection
(Gynther, et al. 1998)	Retrospective	147	9	6.1%
(Abu-Ta'a, et al. 2008)	Prospective RCT	40	1	2.5%
(Esposito, et al. 2008)	Prospective RCT	158	3	1.9%
(Anitua, et al. 2009)	Prospective RCT	52	6	11.5%
(Esposito, et al. 2010)	Prospective RCT	252	4	1.6%
(Caiazzo, et al. 2011)	Prospective RCT	75	0	0
(Nolan, et al. 2014)	Prospective RCT	27	0	0
(Camps-Font, et al. 2015)	Retrospective	337	22	6.5%

1.6 ANTIBIOTIC PROPHYLAXIS IN DENTISTRY

Historically, antibiotic prophylaxis has been offered to patients either with inherent increased risk of developing an infection, or because the treatment procedure in itself is coupled with increased risk of infection. Examples of putative risk patients, with either increased

susceptibility to infection or at risk of developing a serious infection due to a locus minoris, are those at risk for infective endocarditis (IE) or those with severe neutropenia. Patients with multiple risk factors of which each one by itself might not indicate antibiotic prophylaxis may be candidate for prophylaxis because of the additive effect of multiple factors. Suggested risk procedures in dentistry, from an infection perspective, are placement of dental implants, orthognathic surgery and surgical treatment of jaw fractures. However, the efficacy of antibiotic prophylaxis lacks solid scientific evidence and is still under discussion.

1.6.1 Oral bacteremia

Bacteremia originating from bacteria within the oral cavity usually occur passive and don't affect the host but may sometimes lead to several severe health consequences. The host's immune response to the bacteria can cause sepsis and septic shock that results in a high mortality rate (Singer, et al. 2016). Bacteria can also spread via the blood to different parts of the body causing infections distant from the original infection site, such as endocarditis, meningitis or osteomyelitis. The incidence of induced bacteremia varies depending on the procedure. Recorded incidences range from 2% for a cardiac catheterization, to 88% for periodontal surgeries (Durack 1995). However, daily activities such as chewing food and tooth brushing also resulted in frequent episodes of bacteremia (Legout, et al. 2012; Lockhart, et al. 2009; Termine, et al. 2009). These frequent episodes may carry a greater risk for the development of infective endocarditis than the transient bacteremia that follows an invasive dental procedure (Lockhart, et al. 2008; Lockhart, et al. 2009).

Antibiotic prophylaxis to prevent infective endocarditis (IE) began to be recommended in 1955 (Jones, et al. 1955). Since then, several modifications in the recommendations have been published. In 2008, the National Institute for Health and Clinical Excellence (NICE) in the UK recommended cessation of antibiotic prophylaxis for patients undergoing a dental procedure (NICE 2008.). However, antibiotic prophylaxis prior to dental procedures in high-risk patients was recommended by the European Society of Cardiology (ESC) guidelines in 2009, and the American Heart Association (AHA) guidelines in 2007 (Habib, et al. 2009; Wilson, et al. 2007). A study performed on data collected in Great Britain two years after the NICE recommendations showed that there was no significant increase in the incidence of IE with the dramatic decline in antibiotic prescriptions (Thornhill, et al. 2011). Moreover, Dayer reported an increase in the incidence of infective endocarditis in England after five years of cessation of antibiotic prophylaxis (Dayer, et al. 2015). During the same period, a study performed in the UK demonstrated that the incidence of adverse drug reactions associated with antibiotics used for IE prophylaxis was much lower than previously estimated (Thornhill, et al. 2015). Although

these data do not establish a definite causal link, epidemiologic variation in occurrence cannot be ruled out, and the figures call for attention. In 2015, the NICE and the ESC published their updated guidelines. The NICE reported that there was insufficient evidence to modify their existing guidelines and continued to advise against antibiotic prescription (NICE 2015). The European Society of Cardiology continued their guidance to prescribe antibiotic prophylaxis for high-risk individuals undergoing high-risk invasive dental procedures using an antibiotic regimen that remained unchanged from 2009 (Habib, et al. 2015). In July 2016, NICE added the word "routinely" to their recommendations: antibiotic prophylaxis to prevent IE is not recommended routinely for patients undergoing dental procedure. Up to date, there are no randomized controlled clinical trials in humans supporting antibiotic prophylaxis to prevent IE (Thornhill, et al. 2017). In Sweden in 2012, guidelines recommended the cessation of antibiotic prophylaxis prescriptions to prevent IE prior to dental procedures. In a recent endocarditis report in Sweden, the total number of registered cases gradually increased to reach more than 500 in the period from 1995 to 2011. After 2011, the number dropped to less than 450 cases and then increased again to reach almost 500 cases yearly (Olaison 2017). Regarding the microbiological etiology for diagnosed endocarditis, it was reported that 35% of the diagnosed cases in 1995 were due to viridians streptococci. This reduced to 25% in 2011-2014 and then increased slightly to 27% in 2016 (Olaison 2017).

However, a recent health economic study reported that the use of antibiotics to prevent IE in high-risk patients is likely to be very cost-effective, and even cost saving (Franklin, et al. 2016). This is due to the reported serious consequences and high costs associated with development of IE and the comparatively low costs associated with the usage of antibiotics (Franklin, et al. 2016). Until recently, studies on the rationale for a restrictive approach towards antibiotic prophylaxis have been lacking.

1.6.2 Dental implant placement

Dental implant procedures are graded as class II surgical procedures (clean-contaminated surgery) with local infection rates of 10 to 15% (Figure 2) (Olson, et al. 1984; Peterson 1990). The use of prophylactic antibiotics alongside proper surgical technique in clean-contaminated surgery has been shown to reduce the incidence of infection to 1% or less (Olson, et al. 1984; Peterson 1990).

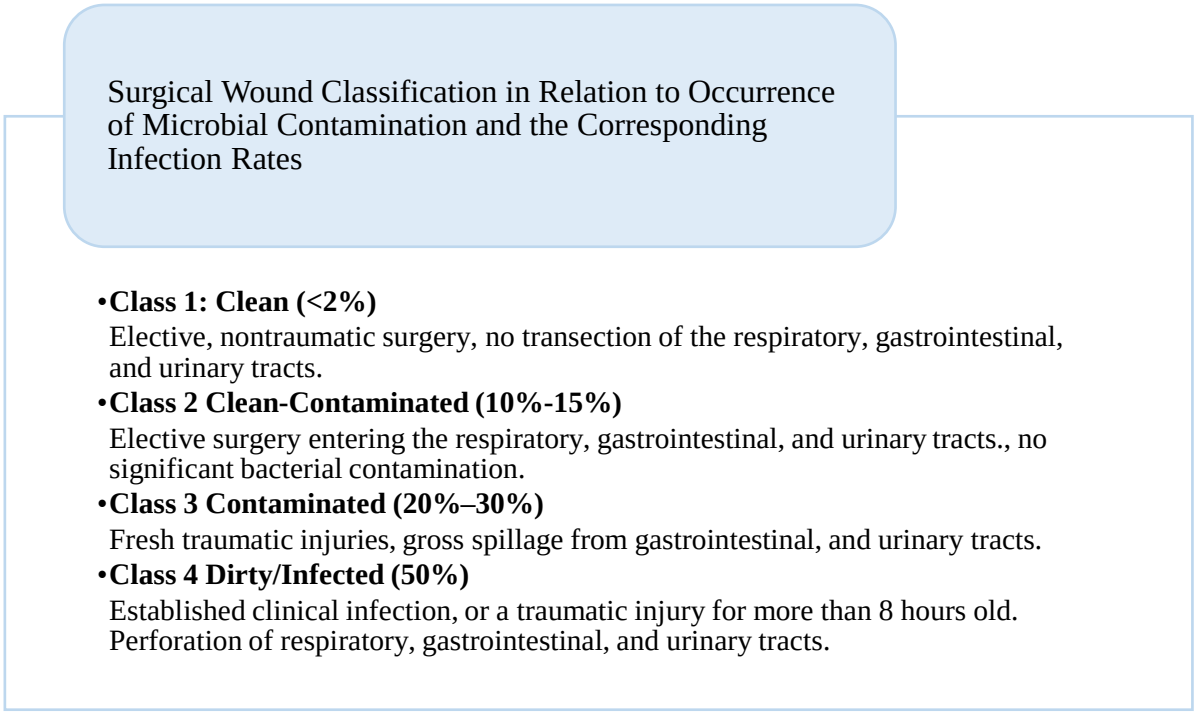

Figure 2. Surgical wound infection classification and the estimated percentage risk for postoperative infections (Olson, et al. 1984; Peterson 1990). © 2016 Khalil D, Lund B, Hultin M. Published in InTech under CC BY 3.0 license. Available from: http://dx.doi.org/10.5772/62681.

The rationale for prescribing extended antibiotic prophylaxis beyond the day of surgery was initially based on empirical tradition. The prophylaxis treatment regimen was introduced by PI Brånemark and collaborators during the 1970s. Under their original protocol, dental implants were inserted in a two-staged surgical protocol to prevent infection (Branemark, et al. 1977; Lekholm 1983). In addition, antibiotic treatment for up to 10 days during the initial healing phase following the implant surgery was recommended to prevent postoperative infection and early implant failure (Branemark, et al. 1977; Lekholm 1983). During the past several years, the recommendation for extended prophylactic antibiotic treatment has been questioned. The Swedish Strategic Programme against Antibiotic Resistance (STRAMA) published revised recommendations for the use of antibiotics in conjunction with implant surgery (Blomgren, et al. 2009). The Swedish agency for Health Technology Assessment (SBU), which is responsible for the assessment of several scientific topics in medical and dental healthcare, published a review with over 600 references regarding the use of antibiotic prophylaxis in surgery, including dental implant procedures (SBU 2010). They could not find any evidence to support antibiotic prescription beyond the day of surgery to prevent the risk of postoperative infection and implant failure. In Sweden, the use of single dose antibiotic prophylaxis prior to bone augmentation procedures in conjunction with dental implant surgery was recommended by the national authority in 2012. Therefore, the use of extended antibiotic prophylaxis beyond the day of surgery is considered an outdated approach.

The shift from using extended antibiotic prophylaxis dose to a single dose prior to dental implant placement has been investigated. However, it is still debated as to whether a single dose antibiotic prophylaxis is necessary or not. Several systematic reviews reported that while the risk of implant failure, i.e implant loss, was reduced when prophylactic antibiotics were used (Ata-Ali, et al. 2014; Chrcanovic, et al. 2014; Esposito, et al. 2013; Rizzo, et al. 2010; Sharaf, et al. 2011; Surapaneni, et al. 2016), but the incidence of postoperative infection did not significantly minimize (Ata-Ali, et al. 2014; Chrcanovic, et al. 2014; Esposito, et al. 2013). On the other hand, recent reviews showed that healthy patients undergoing implant surgery or straight forward cases did not benefit from antibiotic prophylaxis (Ahmad and Saad 2012; Lund, et al. 2015; Park, et al. 2017; Schwartz and Larson 2007). However, for complex or compromised patients, the results were inconclusive (Lund, et al. 2015). These findings were accepted by the European Association of Osseointegration (Klinge, et al. 2015). Due to such contradictions in the results of clinical studies, differences in quality, and the sheer number of uncontrolled variables making it difficult to ascertain cause and effect, the issue of whether there is a benefit to using a single dose antibiotic prophylaxis with implant surgery remains questionable, and thus general recommendations based on scientific data still cannot be made. Despite this, antibiotics continue to be routinely used by dentists during implant surgery (Datta, et al. 2014; Deeb, et al. 2015; Froum and Weinberg 2015; Ireland, et al. 2012; Khalil, et al. 2015; Pyysalo, et al. 2014).

1.7 IMPORTANCE OF SYSTEMATIC QUALITY ASSESSMENT OF SCIENTIFIC PUBLICATIONS AND GUIDELINES

Research in healthcare has developed rapidly, and stricter demands now mean that guidelines are required to be based on scientific observation. Demands are placed on the inclusion of evidence-based medicine, or evidence-based care (EBM) when choosing treatment interventions. The concept of EBM is an approach that involves critical appraisal of interventions based on the best available scientific evidence (Sackett, et al. 1996). However, this also means that the caregiver needs to be updated with the latest research in order to choose the best available treatment methods. The number of scientific articles published each year continues to grow and thus caregivers are required to spend more and more time keeping up to date with the latest research in their field. Estimates show that more than 1.4 million medical articles are published annually, of which, approximately 10–15 percent are considered to be of practical value to patients (SBU 2017). This means that an average of 17–20 primary studies would be needed to be read every day in order for caregivers to be updated (Haynes and Sackett 1995). Thus reviews are commonly used by clinicians as a method of surveying the current

medical literature in a time-effective manner. However, in order to determine whether the systematic review has omitted important literature, and to adequately appraise the trustworthiness of the conclusions, there needs to be strict methodological guidelines (Liberati, et al. 2009; Moher, et al. 2009; Whitlock, et al. 2008). The alternative is that every primary study in the review would need to be obtained, read and critically assessed independently by the reader. One validated and reliable tool that is increasingly being used for the evaluation of systematic reviews is AMSTAR (Shea, et al. 2007a; Shea, et al. 2007b; Shea, et al. 2009). It has been suggested that pre-existing reviews should, in combination with primary studies, be incorporated into new complex systematic reviews (Whitlock, et al. 2008). A strict predefined PICO (population, intervention, control and outcome/observation) is mandatory in this process, as well as thorough reproducible literature search, transparent exclusion process, and quality assessment by independent reviewers, thus resulting in strict inclusion of high-quality systematic reviews.

Clinical guidelines, systematically developed statements to assist practitioners about appropriate health care for specific circumstances, act as tools both for reducing variations in health care and for improving patient quality of care, which includes prescribing behavior (Borowitz and Sheldon 1993; Feder, et al. 1999; O'Brien, et al. 2000). However, the majority of guidelines have not undergone a rigorous methodological selection criteria, making it difficult for the clinician to follow (Grilli, et al. 2000). Besides efforts to improve quality, common standards for reporting guidelines should be followed (Grilli, et al. 2000). Effecting change is difficult to achieve when the goal is to change well-established practice patterns (Sbarbaro 2001). When firm and clear practice guidelines are available alongside scientific supporting evidence, still physician's acceptance is minimal (Sbarbaro 2001). However, acceptance is increased when leading physicians within a community and the local and national professional organizations accredit and approve the change and incorporate it into their practice (Lomas and Haynes 1988). Therefore, physicians' prescription behavior can be influenced but it will be a slow and challenging process as habit and time are the brutal enemies of change (Sbarbaro 2001).

2 AIM

2.1 GENERAL AIM

- To investigate the rationale for restrictive antibiotic prophylaxis in implant dentistry, and the microbiological consequences of antibiotics
- To investigate the utilization of antibiotic prophylaxis in implant dentistry in order to identify areas for overconsumption, and determine the available scientific evidence for supporting or opposing its use

2.2 HYPOTHESES

- Single doses of antibiotics induce the selection and development of antibiotic bacterial resistance strains
- Prolonged antibiotic prophylaxis beyond the day of surgery is commonly used as a prophylactic dose in implant dentistry and thus an area of improvement potential
- Antibiotic utilization with bone augmentation procedures in implant dentistry is a knowledge gap

2.3 SPECIFIC AIMS

Study I: Oral microflora and selection of resistance after a single dose of amoxicillin

- To determine the ecological impact of a single-dose antibiotic prophylaxis, 2 g amoxicillin, on host oral microflora
- To investigate the selection for resistance following a single-dose antibiotic prophylaxis, over a period of several weeks

Study II: Antibiotic prescription patterns among Swedish dentists working with dental implant surgery: adherence to recommendations

- To investigate antibiotic prescription patterns among dentists in Sweden performing dental implant placements
- To assess adherence to and influnce of recent recommendation and scientific reviews on antibiotic routines during dental implant surgery

Study III: Antibiotics and bone augmentation in dental implant installation: a complex systematic review

- To assess the available scientific literature regarding the efficacy of antibiotic use during bone augmentation procedures in conjunction with dental implant placement

Study IV: Antibiotic utilization during bone augmentation procedures in conjunction with dental implant insertion

- To investigate antibiotic prescription patterns among Swedish dentists carrying out bone-augmentation procedures with dental implant placement
- To investigate the effect of national recommendations on antibiotic prescription patterns
- To investigate the effect of antibiotic prophylaxis prescription on the occurrence of postoperative infections following bone-augmentation procedures

3 MATERIALS AND METHODS

3.1 Formal permissions

3.1.1 Ethical application

Studies I & IV were approved by the Karolinska Institutet Regional Ethics Committee, Dnr No: 2013/706-31/1, and 2016/609-31, respectively. Studies II & III did not require ethical approval since there were no patients involved. In Study I, informed consent was obtained from all participants prior to the study onset.

3.1.2 Approval to perform a clinical pharmaceutical study

For Study I, approval from the Drug Medical Agency, Uppsala, Sweden was obtained. This study is registered in ClinicalTrial.gov: NCT01829529, with EudraCT, number 2013-000405-23.

3.2 INVESTIGATION OF MICROBIOLOGICAL CONSEQUENCES OF ANTIBIOTIC PROPHYLAXIS (STUDY I)

3.2.1 Study population

Study I included thirty-three healthy volunteers. An announcement at the Department of Dental Medicine, Karolinska Inistitutet, Stockholm, Sweden was made in order to recruit volunteers. Participants were excluded if they had taken antibiotics within the past three months, were pregnant, breastfeeding, taking probiotics, had a penicillin or aspartame (E951) allergy, or had phenylketonuria.

3.2.2 Intervention and sample collection

All participants underwent a thorough medical history. A 5 ml unstimulated salivary sample was obtained from fasting participants in the morning before drinking, brushing teeth, and/or smoking (day 1, control sample). Thereafter, all candidates received 2 g amoxicillin orally under strict observation. Samples taken on days 2 (24 hours), 5, 10, 17 and 24 were, after careful oral and written instructions, collected by the participants at home and promptly delivered to the Division of Clinical Microbiology, Institution of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden, and immediately stored at -70°C until analysis (Figure 3).

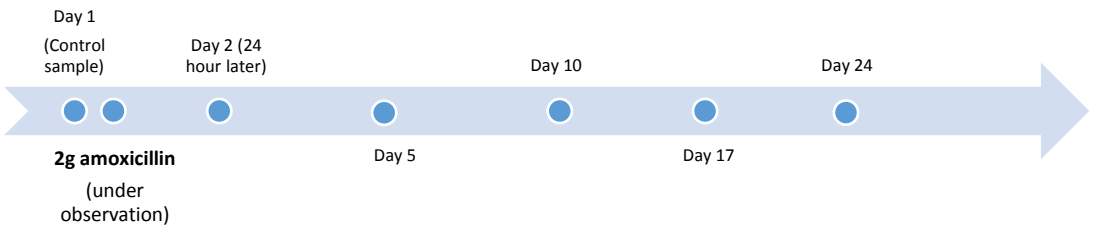

Figure 3. Collecting of saliva during study period

3.2.3 Microbiological culture

One ml saliva was added to a vial with 4 ml of VMGII buffer and diluted ten-fold in PBS (10^{-1} – 10^{-5}). A total of 0.1 ml from each dilution was inoculated onto selective agar plates (Mitis Salivarius agar (MS), Cystine lactose electrolyte deficient agar (CLED), Aesculin agar, Haematin agar, Sabouraud agar, Brucella agar with kanamycin and vancomycin (BKV), Brucella agar with neomycin and vancomycin (BNV), Rogosa agar, blood-agar plates containing 2 mg/ L amoxicillin, and non-selective agar plates (blood-agar) (Heimdahl and Nord 1979). The aerobic plates were incubated at 37°C for 24 hours, and the anaerobic plates were incubated at 37°C in an anaerobic jar for 48 hours. After incubation, the plates were examined and the different microorganisms counted for quantitative evaluation. Each bacteria type was re-isolated to obtain a pure culture. All isolates were examined by Gram-stain and colony morphology, and identified by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonik, Gmbh, Germany) (Angeletti, et al. 2015; Panda, et al. 2014). $\geq$ 2 log number of bacteria per ml saliva was considered as the level of detection for culturing. A 0-value was assigned for all date below this level.

3.2.4 Antibiotic susceptibility tests

The minimum inhibitory concentrations (MICs) were determined for strains isolated from antibiotic-containing agar using the agar-dilution method according to the Clinical and Laboratory Standards Institute (CLSI) (CLSI 2012a; CLSI 2012b). The following antimicrobial agents were tested: amoxicillin, penicillin-V, clindamycin, and metronidazole. Reference strains for MICs were: *Escherichia coli* ATCC25922, *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Bacteroides fragilis* ATCC 25285, and *Clostridium difficile* ATCC 700057. The break-point was established according to the recommendations from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (www.eucast.org). In cases where EUCAST break-points were lacking, CLSI break-points were used.

3.3 ANTIBIOTIC PRESCRIPTION PATTERNS AMONG SWEDISH DENTISTS WORKING WITH DENTAL IMPLANT SURGERY (STUDY II)

3.3.1 Study design

Study II is an observational questionnaire survey conducted in 2008 and 2012 and included dentists who placed more than 20 implants per year. The two time periods studied were before and after the publication of revised recommendations on the use of antibiotics by The Swedish Strategic Programme against Antibiotic Resistance (STRAMA) (Blomgren, et al. 2009), and a literature review of antibiotic prescription in conjunction with implant surgery by the Swedish Agency for Health Technology Assessment (SBU) (SBU 2010). An online search service of two Swedish telephone directories (www.hitta.se and www.eniro.se) using the key words "implant", "dental clinic", and "Stockholm region" was used to identify dental clinics in Stockholm region. Clinics were contacted by telephone to explain the study to the dentists. Questionnaires were sent with a prepaid envelope and a cover letter to explain the purpose of the study and to ensure confidentiality would be maintained. Reminder letters were sent to all included clinics

Anonymous questionnaires were sent to 76 clinics in 2008. In 2012, the questionnaires were sent again to the same clinics that participated in 2008, and to additional new clinics established during the intervening period (in 2008, 120 dentists in 76 clinics participated, while in 2012, 161 dentists in 105 clinics participated).

3.3.2 Questionnaire

The questionnaire composed of two open and 10 closed questions. The first section included demographic data on gender, age, undergraduate training, number of years of clinical experience, implant surgical experience, and implant education. The second section asked about dentists' routines used at the clinic and policies regarding antibiotic prescription prior to implant insertion, as well as local or systematic factors influencing prescription patterns. Two questions focused on the potential benefits from the establishment of national guidelines and interest in gaining information about antibiotic resistance.

The 2012 questionnaire had five additional questions concerning respondents' knowledge of the recent recommendations and scientific review from STRAMA (Blomgren, et al. 2009) and SBU (SBU 2010), and asked whether these had influenced their prescribing behavior. Data regarding antibiotic prescription regimens were extracted from the questionnaire. The data for those who prescribed antibiotics merely under special circumstances, such as medical or local surgical factors, was interpreted as not prescribing routinely.

3.4 METHODOLOGY FOR SCRUTINIZING THE LEVEL OF SCIENTIFIC PUBLICATION FOR USING ANTIBIOTICS AS A PROPHYLAXIS IN IMPLANT DENTISTRY WITH BONE AUGMENTATION PROCEDURES (STUDY III)

3.4.1 Defining the review questions

Study III is a complex systematic review conducted on studies including patients who underwent bone augmentation prior to, or in conjunction with dental implant surgery. Criteria for inclusion of reviews were that they needed to be a systematic review or systematic meta-analysis. Included primary studies needed to be randomized control trials (RCT) and contain an abstract in English. Exclusion criteria were any papers in a language other than English, German, French or Swedish. In addition, reviews were excluded if they were non-systematic, published as guidelines, a letter, position paper or consensus statement. Primary studies were also excluded if they were animal studies, in-vitro studies, were of any study design other than RCT, or lacking in follow up. The predefined study population, intervention, comparing therapies, and outcome parameters (PICO) for the eligible studies are summarized in Table 3.

Table 3. A predefined study population, intervention, comparing therapies and outcome parameters (PICO), (Study IV)

P	Patients subjected to bone augmentation procedures with simultaneous or delayed implant placement
I	Antibiotics on day of surgery (short-term prophylaxis) Antibiotics more than day of surgery (extended prophylaxis) Head-to-head comparison of different antibiotic compounds or regiments
C	No antibiotic treatment Placebo Other non-antibiotic treatment e.g. such as antibacterial rinsing Other/comparing antibiotic treatment (alternative compound) Same compound, different dose/duration
O	Infection (primary) Quality of life (primary) Pain (primary) Implant loss Loss of transplant Sequestrum/sequestra Bone gain assessed by increased volume Health economy Ethical aspects

3.4.2 Literature search

Literature searches on the following databases were searched until October 20, 2015: Medline (OVID), The Cochrane Library (Wiley), EMBASE (embase.com), and PubMed (non-indexed articles). No filters were used during the initial search phase for primary studies. Thereafter, a search was performed with filters for systematic reviews. A complementary search was performed in PubMed on November 24, 2016 for additional recent publications. This additional

search did not use any filters. Health technology assessment (HTA) organisations were searched until October 30 2015: NICE, http://www.nice.org.uk/; CADTH, http://www.cadth.ca/; CRD database,http://www.crd.york.ac.uk/CRDWeb/; Kunnskapssenteret, http://www.kunnskapssenteret.no/home?language=english;ASERNIP-S, http://www.surgeons.org/for-health-professionals/audits-and-surgical-research/asernip-s/publications/. The reference lists of all eligible studies were hand-searched for complementary studies.

3.4.3 Assessing a study's relevance

The retrieved list of publications was reviewed to a crude exclusion of irrelevant publications based on title. Uncertain publications remained included until the next selection step. The next selection step was examination of the abstracts through independent reading by three reviewers in duplicate. All selected systematic reviews and primary studies were each read in full-text by three reviewers. In the case of disagreement during the screening process, a group discussion was undertaken.

3.4.4 Assessing the quality and the scientific evidence of intervention studies

No systematic reviews were included for quality assessment. The quality of the recruited primary studies were assessed using randomized studies assessment protocol (Guyatt, et al. 2011). The quality of scientific evidence in the primary studies was graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and set as high, moderate, low or very low (Balshem, et al. 2011).

3.4.5 Data extraction

No systematic reviews were included for data extraction. For primary studies, data regarding number of included patients, age, gender distribution, length of follow-up, type of intervention, type of control treatment and relevant treatment outcomes were extracted.

3.5 INVESTIGATION OF ANTIBIOTIC UTILIZATION DURING BONE AUGMENTATION PROCEDURES IN IMPLANT DENTISTRY (STUDY IV)

3.5.1 Study design

Study IV is a multicenter retrospective cross-sectional study, conducted during two time periods (2010-2011 and 2014-2015), reviewing the utilization of antibiotic prophylaxis in bone augmentation procedures in conjunction with dental implant placement. It includes four

specialized Swedish dental clinics performing implants with bone augmentation procedures. The two time periods were before and after the publication of the Swedish national recommendations on antibiotic prophylaxis in 2012 in order to determine the influence of the recommendations on antibiotic prescribing behavior (Läkemedelsverket 2012). The four clinics included were the Department of Periodontology at the Odontology Institution in Jönköping, the Department of Oral and Maxillofacial Surgery at the Odontology Institution in Jönköping, the Department of Oral and Maxillofacial Surgery at the Eastman Institute, Stockholm, and the Department of Oral and Maxillofacial Surgery at Södra Älvsborgs Sjukhus, Borås. Each clinic contributed with 100 cases based on power calculation, 50 from each time period. Inclusion criteria were intraoral bone augmentation procedures performed on the indication of insufficient bone volume for immediate or later placement of dental implants. Patients below the age of 18 years, or those with incomplete or missing patient records were excluded from the study. Patients list were searched and retrieved by using treatment codes.

3.5.2 Data collection

Data regarding patient characteristics and general health, medications, allergies, smoking habits, risk factors for infection, and the surgeon's type of training and education were obtained. In addition, type of surgical procedure, anatomical location, prescription of antibiotics, type of compound, dose and duration, choice of material used for bone augmentation, membrane used or not, sinus lift performed or not, and whether the implant was inserted immediately or not with bone augmentation procedure, were collected. All postoperative infections occurring during the first three months after surgery were registered, as well as how they were handled. Data were collected using a standardized case record form.

3.6 DATA ANALYSIS

Statistical analysis was performed using SPSS for Windows release 21.0 (SPSS Inc., Chicago, IL, USA). Absolute frequencies were used to describe the data. In Study III, statistical analysis was not applicable due to the few number of studies included.

3.6.1 Sample size

In Study I, a power calculation based on estimated data using the results from Chardin et al 2009 (Chardin, et al. 2009), gives 80% power at P = 0.05 determined by a sample size of 30, plus an additional 10% to compensate for eventual drop out (n = 3). In the above-mentioned study, the base-line value for amoxicillin resistant streptococci was 1.3 %, while on day 9 after 3 days of

amoxicillin administration, the level was 23 %. This thus corresponds to a difference of 21.7% between test and control.

In Study IV, a power calculation based on the hypothesis that 80% of the patients received prolonged antibiotic prophylaxis prior to the national recommendations, and 60% after, gave a total required sample size of 200 patients at 80% power and P = 0.05. Since this sample size calculation was based on a crude estimation it was decided to double the number to 400 patients.

3.6.2 Wilcoxon signed rank test

Changes in median log number of bacteria per ml saliva in Study I were compared to baseline values (day 1, control sample) using a Wilcoxon signed rank test. A P-value of ≤ 0.05 was considered statistically significant, while P-values ranging from 0.05-0.10 were interpreted as having a tendency towards a difference.

3.6.3 T-test

In Study I, changes in the proportion of bacteria with reduced susceptibility to amoxicillin were compared using a paired two-tailed *t*-test. A P-value of ≤ 0.05 was interpreted as statistically significant.

In Study IV, an independent *t*-test was used to determine the differences between the two time periods (2010-2011, and 2014-2015). A P-value of ≤ 0.05 was considered statistically significant.

3.6.4 Chi-square tests

In Study II, a chi-square test was used to assess statistically significant differences. The level of significance was set to $P \leq 0.05$.

3.6.5 Pearson´s correlation

In Study IV, the relationship between variables was tested using Pearson´s correlation coefficient. A P-value of ≤ 0.05 was considered statistically significant.

4 RESULTS

4.1 MICROBIOLOGICAL CONSEQUENCES OF ANTIBIOTIC PROPHYLAXIS (STUDY I)

There was no drop out from the study. However, due to incomplete collection of salivary samples, four volunteers were excluded. Therefore, 29 volunteers were included in the analysis, 14 males and 15 females, aged between 19-45 years with a mean age of 30 years. Eight of the volunteers reported a total of ten self-limiting adverse events during the study, including flu, chills, headache, diarrhea, xerostomia, muscular neck discomfort, and sore throat.

A change in the distribution of oral microflora was shown throughout the study period (Table 4). A significant reduction in the number of viridans streptococci was reported, such as *Streptococcus sanguis* and *Streptococcus anginosus* on day 2 ($P = 0.04$), and *Streptococcus salivarius* on days 2 and 5 ($P < 0.001$). *Neisseria* spp. significantly increased on day 2 ($P = 0.02$). There was a tendency towards a reduction in *Micrococcus* spp on days 2 and 17 ($P = 0.06$ and $P = 0.09$, respectively). There were no significant changes in any other aerobic species. Regarding the anaerobic microflora, *Prevotella* spp showed a tendency towards a reduction on days 5, 17, and 24 ($P = 0.09$, $P = 0.07$, and $P = 0.06$, respectively). There were no significant changes in any other anaerobic species.

There was a significant increase in the proportion of viridans streptococci with reduced susceptibility to amoxicillin on days 2 and 5 ($P = 0.00$ and $P = 0.04$, respectively). The MIC50 for viridans streptococci isolated from amoxicillin-containing agar tested against amoxicillin were 4 mg/L on all days, while for MIC90 it was in the range of 4 to 256 mg/L (breaking point is 2 mg/L) throughout the study period. The MIC50 for Prevotella spp isolated from amoxicillin-containing agar tested against amoxicillin were 16 mg/L on all days except for day 24 where it was 8 mg/L. MIC90 was 64 mg/L on all days except for days 5 and 10 where it was 128 mg/L (breaking point is 2 mg/L). Therefore, the majority of viridans streptococci and Prevotella spp. selected from the amoxicillin-containing agar were resistant to amoxicillin and penicillin-V (Table 5).

Table 4. Distribution of oral microflora throughout the study period

	N^a	Day 1 M (min – max)	N^b	Day 2 M (min – max)	N^b	Day 5 M (min – max)	N^b	Day 10 M (min – max)	N^b	Day 17 M (min – max)	N^b	Day 24 M (min – max)	N^b
Aerobic bacteria													
Streptococcus salivarius spp	29	16,8 (10,1 - 19,1)	29	12,6 (0 – 18,1)	23	13,1 (6,9 – 18,8)	29	16,11 (7,82 – 19,11)	29	15,76 (9,62 – 18,83)	29	16,1 (5 – 20)	29
Other viridans streptococci	29	17,7 (13,1 - 19,7)	28	16,5 (12,4 - 19,1)	29	16,8 (10,8 – 19,1)	28	17,73 (13,12 – 19,52)	29	17,73 (12,43 – 20,03)	29	17,9 (14,5 – 22,5)	28
Neisseria spp	25	15,8 (9,2 – 17,4)	18	15 (10,8 – 20)	25	15,4 (7,3 – 17,7)	19	16,12 (11,51 – 18,83)	21	14,22 (7,31 – 17,73)	22	15,4 (9,2 – 18,4)	21
Micrococcus spp	9	16,8 (14,4 – 20,0)	9	15,5 (13,1 – 16,5)	7	13,8 (11,5 – 17,7)	8	17,03 (11,92 – 18,42)	9	14.73 (11,92 – 17,37)	7	16,1 (14,2 - 17,7)	9
Staphylococcus aureus	8	10,8 (7,3 – 18,1)	7	11,5 (8,5 – 15,4)	6	13,7 (6,9 – 18,4)	6	10,46 (9,21 – 14,29)	7	12,32 (8,52 - 15,42)	8	10,8 (7,3 – 15,4)	5
Candidia spp	3	7,8 (6,9 – 8,8)	2	7,6 (7,3 – 8,4)	3	7,3 (6,2 – 8)	3	6,76 (6,21 – 7,31)	2	7,46 (7,31 – 7,60)	2	8,2 (8 – 8,3)	2
Enterobacteriacae spp	3	9,4 (8,3 – 10,8)	3	7,3 (7,3 – 7,3)	2	8,1 (7,6 - 8.5)	2	10,82	1	17,73	1	9 (7,6 – 11,5)	3
Staphylococcus epidermidis	2	10,1	1		0	15,1	1	16,81	1	12,8 (8,52 – 17,03)	2	17 (16,5 – 17,4)	2
Haemophilus spp	1	11,9	1		0		0	15,42	1		0		0
Cornybacterium spp	1		0	14,2	1	14,7	1		0		0		0
Enterococcus spp	1		0		0		0		0	9,2	1	10,8	1
Anaerobic bacteria													
Prevotella spp	27	15,4 (9,6 -19,7)	26	13,8 (8,3 - 19,1)	27	14,5 (6,9 – 19,3)	20	13,5 (8,5 – 19,1)	25	13,8 (6,9 – 18,4)	24	13,5 (6,2 – 19,3)	27
Leptotrichia spp	19	8,5 (6,2 – 17,7)	15	9,21 (6,2 – 13,1)	16	9,2 (7,3 – 13,1)	17	9,2 (6,2 – 12,4)	16	8,4 (6,2 – 17)	17	8,7 (6,2 – 15,4)	19
Lactobacillus spp	13	8,3 (5,30 – 10,82)	13	9 (7,3 – 17,7)	13	8,5 (4,6 – 10,6)	12	8,9 (6,2 – 9,2)	12	7,6 (6,2 – 10,1)	13	8,5 (6,2 – 10,8)	12
Fusobacteria spp	13	9,2 (6,2 – 12,6)	8	8,3 (6,2 – 12,4)	13	9,3 (6,2 – 15,4)	9	7,6 (6,2 – 9,6)	7	8,9 (6,2 – 14,4)	7	8,5 (6,2 – 13,1)	10
Veillonella spp	8	17 (9,2 – 19,1)	8	14,7 (13,1 – 17,7)	4	14 (6,9 – 17,5)	7	17,5 (15,4 – 18,4)	5	15,4 (8,5 – 20)	6	12,3 (8,5 – 15,4)	5
Anaerobic cocci spp	5	17,2 (7,3 – 17,4)	5	13 (12,6 – 13,4)	2	13 (10,1 – 13,8)	3	13,5 (10,8 – 16,1)	4	11,3 (6,2 – 17,7)	3	10,2 (4,6 – 16,5)	4
Actinomyces spp	3		0	14,5	1	16,5	1	10,8	1	15,9	1		0

M, Median of log values of the number of microorganisms above the detection level per mL saliva.
(minimum - maximum)
Na, Number of patients with detectable levels of microorganisms within the sampling period.
Nb, Number of patients with detectable levels of microorganisms at the actual sampling day.

Table 5. MIC_{50}, MIC_{90}, and the range of viridans streptococci and *Prevotella* spp, isolated from blood agar containing 2 mg/L amoxicillin

Antibiotic	Amoxicillin				Clindamycin				Penicillin-V				Metronidazole			
	MIC mg/L			BP	MIC mg/L			BP	MIC mg/L			BP	MIC mg/L			BP
	MIC 50	MIC 90	Range		MIC 50	MIC 90	Range		MIC 50	MIC 90	Range		MIC 50	MIC 90	Range	
Viridans streptococci																
Day 1	4	4	(4 - 4)		0,016	0,125	(< 0,016 –0,125)		2	2	(0,5 – 2)		256	256	(128 – 256)	
Day 2	4	8	(0,25 – 8)		0,032	32	(< 0,016 – 32)		2	4	(0,5 – 4)		256	256	(128 – 256)	
Day 5	4	16	(0,064 - 16)		0,016	16	(< 0,016 – 16)		2	16	(0,5 – 16)		256	256	(128 – 256)	
Day 10	4	8	(0,064 - 8)	2 mg/L	0,032	32	(< 0,016 – 32)	0.5 mg/L	2	8	(0,5 – 8)	2 mg/L	256	256	(64 – 256)	NA
Day 17	4	16	(0,25 – 16)		0,125	256	(< 0,016 - 256)		2	8	(0,125 – 8)		256	256	(256 – 256)	
Day 24	4	256	(0,25 - > 256)		0,125	256	(< 0,016 - > 256)		2	256	(0,5 - >256)		256	256	(256 – 256)	
***Prevotella* spp**																
Day 1	16	64	(0,032 - 256)		0,032	0,064	(< 0,016 - > 256)		2	8	(<0,016 -16)		1	4	(0,016 - 8)	
Day 2	16	64	(0,032 - 64)		0,032	256	(< 0,016 - > 256)		4	16	(<0,016 - 16)		1	256	(0,250 - > 256)	
Day 5	16	128	(0,064 - 128)		0,016	0,064	(< 0,016 - 256)		2	16	(<0,016 - 16)		1	8	(0,5 - 8)	
Day 10	16	128	(0,032 - 128)	2 mg/L	0,032	256	(< 0,016 - > 256)	4 mg/L	2	8	(<0,016 - 16)	2 mg/L	1	4	(0,064 - > 256)	4 mg/ L
Day 17	16	64	(0,032 - 64)		0,016	0,5	(< 0,016 - > 256)		2	4	(<0,016 - 4)		0,5	4	(0,125 - 8)	
Day 24	8	64	(0,032 - 128)		0,032	32	(< 0,016 - > 256)		2	16	(<0,016 - 32)		0,5	8	(< 0,016 - 16)	

BP, Breaking points.
NA, Not available.

In 21% (n = 6/29) of individuals, penicillin-V and amoxicillin resistant viridans streptococci were isolated before antibiotic taken. The carrier rate for amoxicillin resistant *Prevotella* spp. prior to antibiotic administration was reported in 59% (n = 17/29) of the volunteers, and the corresponding figure for penicillin-V resistance was found in 62% (n = 18/29). Throughout the study period, approximately one third of participants gained resistant viridans streptococci against amoxicillin, clindamycin, and penicillin-V. While in *Prevotella* spp., there was approximately 28% gain in resistance to all antibiotics tested (Figure 4).

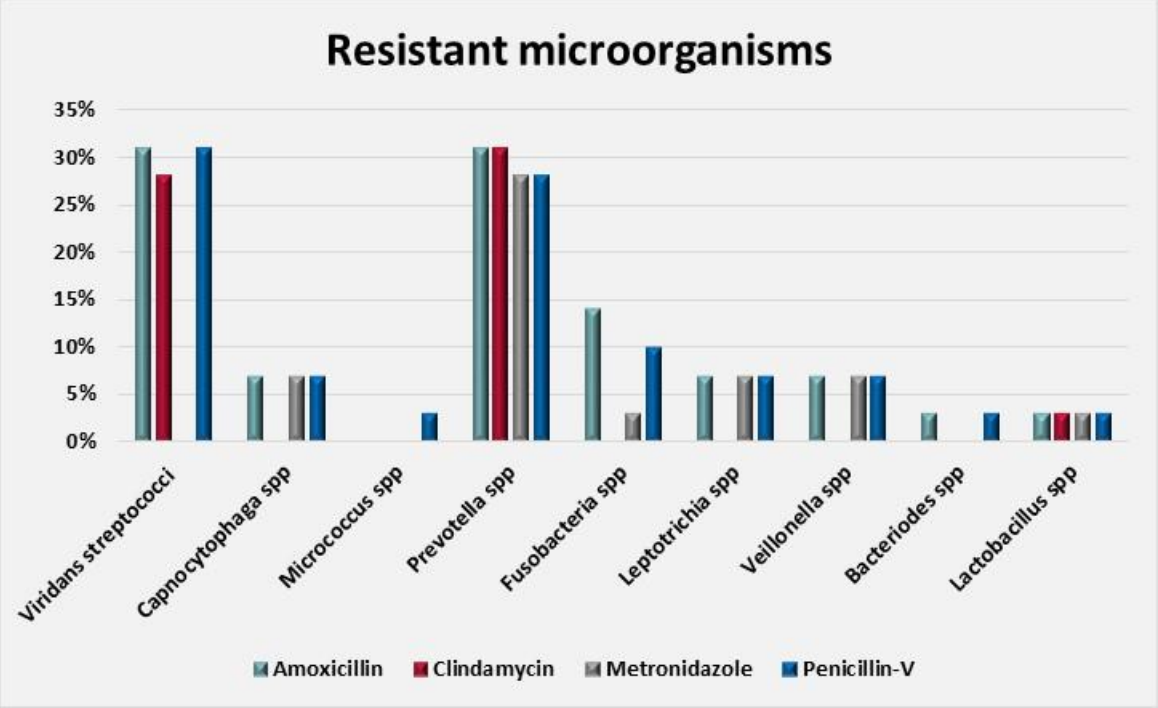

Figure 4. Percentages of individuals who gained resistant microorganisms after administration of 2 g amoxicillin (Khalil, et al. 2016).

4.2 ANTIBIOTIC PRESCRIPTION PATTERNS AMONG SWEDISH DENTISTS WORKING WITH DENTAL IMPLANT SURGERY (STUDY II)

The response rate for the distributed questionnaire in 2008 was 75% (n = 90), and 88% (n = 142) in 2012. Consequently, 85 questionnaires in 2008 and 133 in 2012 were included, after excluding five questionnaires in 2008 and nine in 2012 due to missing data concerning the use of antibiotics with dental implant placement. Males dominated amongst the participating dentists (79% in 2008; 75% in 2012), and the majority of questioned dentists were in the age group of 55 years or older. The majority of dentists had completed their undergraduate education at a Swedish university (98% in 2008; 97% in 2012). Regarding their implant education, in 2008, 46% had received clinical postgraduate specialty training, while in 2012, 40% had. On the other hand, 54% reported they had participated in a single course in implant dentistry in 2008, while 60% had in 2012. Ninety-three percent of dentists in 2008, and 92% of dentists in 2012 replied that they had

received information regarding antibiotic usage during their implant education. More than half of the dentists questioned had worked in clinical practice for more than 20 years (65% in 2008; 60%, in 2012). Moreover, 53% had over 10 years of experience in implant surgery in 2008, with 64% in 2012. There were no significant differences in regard to the demographic data between the two years measured. However, dentists without specialty clinical training were significantly more prone to extend antibiotic prophylactic administration beyond the day of surgery ($P < 0.01$).

There was a significant reduction in the number of routinely prescribed antibiotics between 2008 and 2012 ($P = 0.01$) (Table 6). There was also a significant change in the type of antibiotics prescribed ($P = 0.01$). The majority of dentists in 2008 (67%) prescribed penicillin-V, and 21% prescribed amoxicillin. In 2012, 43% of dentists prescribed penicillin-V and 47% prescribed amoxicillin. Other antibiotics such as clindamycin and metronidazole were less frequently prescribed. There was a significant reduction between the two time periods in the number of dentists prescribing antibiotics beyond the day of surgery ($P = 0.04$). In 2012, 65% of the respondents prescribed a single dose of antibiotics, while 35% prescribed an antibiotic course for ≥2 days. In 2008, 49% of the dentists prescribed single dose compared to 51% for ≥2 days (Figure 5).

Table 6. Antibiotic prescription pattern with dental implant placement in Study II, III

Antibiotic prescription pattern	Before recommendation N (%)	After recommendation N (%)	p-value
Study II: (Dentists self-reporting)			
Yes	75 (88)	98 (74)	0.01
No	10 (12)	35 (26)	
Study III: (Patients receiving AB)			
Yes	174 (87)	145 (72.5)	0.00
No	26 (13)	55 (27.5)	

N, number of participants; AB, antibiotic;
Study II, Antibiotic prescription pattern with dental implant placement;
Study III, Antibiotic prescription pattern with dental implant placement associated with bone augmentation procedure.

The majority of the dentists in 2008 reported the need for national recommendations regarding the use of antibiotics in implant surgery and more than half were interested in information about antibiotic resistance. For the additional questions in the 2012 survey, 58% of the respondents stated that they had read the recent publications on antibiotic prescription in implant dentistry, 82% of those said they had benefited from the information, and 33% stated to have changed their antibiotic prescription pattern. Therefore, this data suggests that the dentists who read the publication were more likely to prescribe single dose antibiotics ($P = 0.00$).

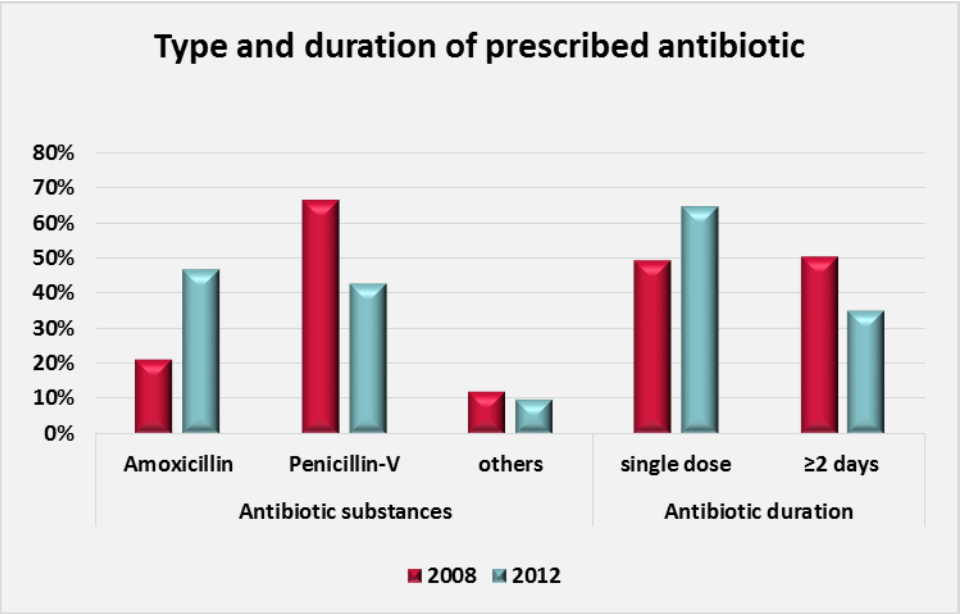

Figure 5. Type and duration of dentists self-reporting antibiotic type and duration
Others: clindamycin and metronidazole

4.3 ANTIBIOTICS AS A PROPHYLAXIS IN IMPLANT DENTISTRY WITH BONE AUGMENTATION PROCEDURES: A COMPLEX SYSTEMATIC REVIEW (STUDY III)

The search resulted in a total of 1305 primary studies and systematic reviews for screening after deduplication. Flow-charts of the screening process for primary studies and systematic reviews are described in Figure 6. Abstract screening resulted in a total of six reviews, which were allocated for full-text inspection. All these reviews were then excluded because the studies were out of topic (n = 4), or not considered a systematic review (n = 2). Therefore, none were left for quality assessment. For the primary studies, ten papers were read in full-text. Consequently, six studies were then excluded, yielding four primary studies included for further analyses. The excluded studies were either a letter to the editor (n = 2), case series (n = 1), not in English (n = 1) or out of topic (n = 2).

On performing quality assessment and data extraction for the primary studies, two studies were found to have high risk of bias (Lee, et al. 2012; Lindeboom and van den Akker 2003) and were thus excluded from this review. The reasons for high risk of bias were short-comings in study design and uncertainties in the randomisation process. The two remaining primary studies were classified as moderate risk of bias (Lindeboom, et al. 2006; Lindeboom, et al. 2005) and were included in the current complex systematic review. They were assessed as having moderate risk of bias due to having no published study protocol, unclear blinding, unclear randomization and no reports of loss during the follow up.

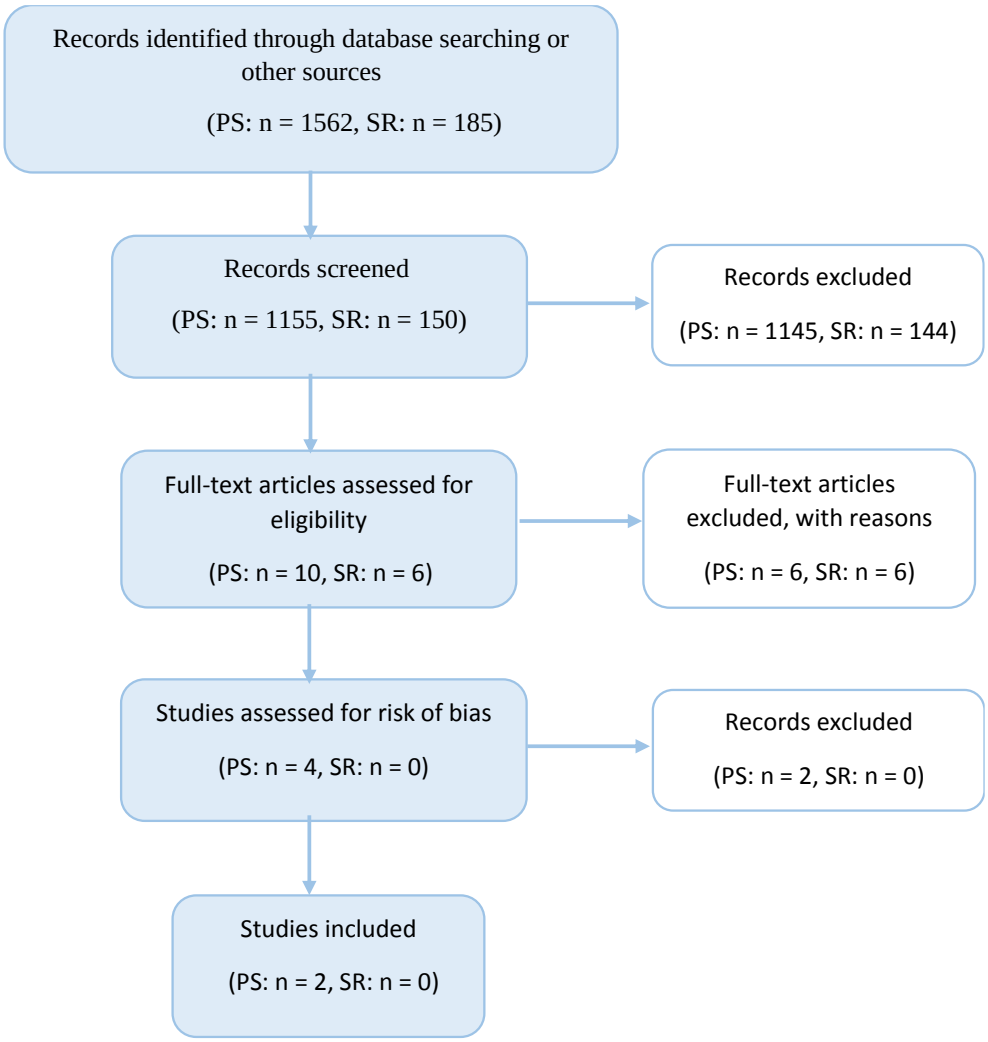

Figure 6. Flow chart for primary studies and systematic review.
PS: primary studies, SR: systematic review, n: number of articles

One of the two included primary studies, Lindeboom et al. 2005, compared a single dose of clindamycin 600 mg preoperatively followed by four doses of placebo tablets every six hours for 24 hours, with the same preoperative dose followed by four doses of 300 mg every six hours for 24 hours (Lindeboom, et al. 2005). This study resulted in two patients developing a postoperative infection at the receptor site in the single dose group, while three patients developed infections in the group treated with clindamycin for 24 hours (RR, 0.67). The second primary study, compared a single dose prophylaxis of two different types of antibiotic compounds (penicillin and clindamycin) (Lindeboom, et al. 2006). In this study, four patients developed a postoperative infection at the receptor site in the group treated with 2 g penicillin 1 hour preoperatively, while two patients developed infection in the group treated with 600 mg clindamycin 1 hour preoperatively (RR, 2.00), (Table 7).

Table 7. Characteristics, quality assessment and outcome of included primary studies with low or moderate risk of bias

Included studies	Population	Study period	Intervention	Control	Postoperative infection at receptor site		Results
					Intervention	Control	
Lindeboom et al. 2005 Netherlands	N: 124 Age: 18-59 years Gender (M/F): 50/74 Augmentation: Onlay buccal bone graft Smokers: none (exclusion criteria)	8 weeks	600 mg clindamycin 1 hour prior surgery – placebo capsules every 6 hour for 24 hours postoperatively	600 mg clindamycin 1 hour prior surgery – 300 mg clindamycin every 6 hour for 24 hours postoperatively	2/62 (3%)	3/62 (5%)	RR 0.67
Lindeboom et al. 2006 Netherlands	N: 150 Age: 18-67 years Gender (M/F): 52/98 Augmentation: Onlay buccal bone graft Smokers: none (exclusion criteria)	8 weeks	2 g penicillin 1 hour prior surgery	600 mg clindamycin 1 hour prior surgery	4/75 (5%)	2/75 (3%)	RR 2.00

N, number of patients; M/F, male/female; mg, milligram; g, gram; RR, risk ratio.

4.4 ANTIBIOTIC UTILIZATION DURING BONE AUGMENTATION PROCEDURES IN IMPLANT DENTISTRY (STUDY IV)

In this study, 200 patient files were included in each time period. In 2010-2011, participants consisted of 44.5% males and 55.5% females, with a mean age of 55 years, while in 2014-2015 participants consisted of 48.5% males and 51.5% females, with a mean age of 54 years. More than half of the recruited patients were healthy and not taking any medication (53.5% in 2010-2011 and 58.5% 2014-2015). Smoking was recorded in 21% of the patients in 2010-2011, and in 16.5% in 2014-2015. In 2010-2011, three patients were under bisphosphonate treatment. Dentists' specialties included oral maxillofacial surgeons, periodontist, general dentist or resident in those specialties during the study. The majority were oral maxillofacial surgeons (51.5% in 2010-2011 and 55% 2014-2015). There were no significant differences in regard to the demographic data between the two time periods studied. In 2014-2015, there was a weak significant relationship between the dentist under residency training programme and the practice of not prescribing antibiotics (P = 0.00, R = 0.19).

The extent of the bone augmentation surgery varied from an area of one missing tooth (62% in 2010-2011, 48% in 2014-2015) to a full arch (least common, 1% in both time periods). The majority of patients underwent autograft bone procedures during the study period (57.5% in 2010-2011, 41% in 2014-2015). The frequency of other types of bone graft is presented in Table 8. In 2010-2011, 25% of bone graft surgery cases were performed with sinus lift procedures and the same percentage were associated with placing resorbable membranes. In 2014-2015, 23% of cases were performed with sinus lift procedures, while the membranes were placed in approximately half of the patients (47%).

Table 8. The distribution of the number and percentage the different bone grafts used during the two time periods.

Type of bone graft:	2010-2011 Before recommendation N (%)	2014-2015 After recommendation N (%)	P-value
Autograft	115 (57.5)	82 (41)	0.00
Xenograft	66 (33)	83 (41.5)	NS
Mixed (xenograft and autograft)	19 (9.5)	35 (17.5)	0.02

N, number; %, percentage, NS, non-significant

This study showed that the number of patients not treated as recommended by the 2012 national guidelines of a single dose 2 g amoxicillin, was high and unchanged between the two time periods

(58%, and 57%, respectively). On the other hand, the total number of patients treated as recommended in the national guidelines significantly decreased (P = 0.02), (29% and 15.5%, in the two time periods, respectively). However, there was a significant reduction in the total number of antibiotics prescribed between the time periods (P = 0.00) (Table 6).

Regarding the type of antibiotic prescribed, or deviation from the recommended dose, there was no significant difference comparing the two time periods. However, the most common antibiotic prophylaxis prescribed was penicillin-V (35%, and 49%, in the two time periods, respectively) (Figure 7). Antibiotic treatment duration for five to seven days remain constant and unchanged between the two time periods. Significant changes in antibiotic duration were reported when comparing the two time periods: the single prophylactic preoperative dose differed from that recommended, the extended prophylactic antibiotic dose on operation day increased (P = 0.03), while the ten-day antibiotic treatment duration decreased (P = 0.04), (Figure 8).

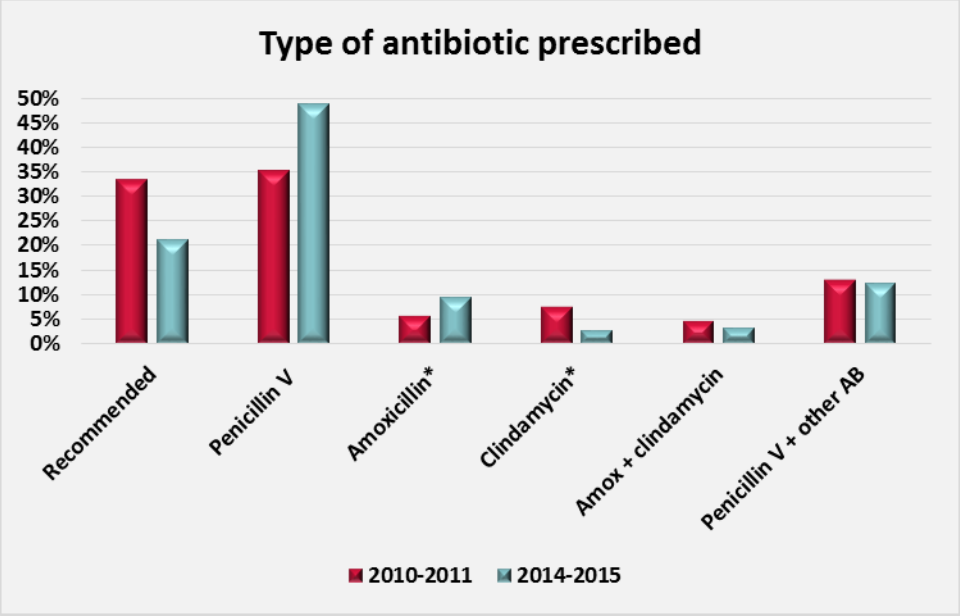

Figure 7. The type of prescribed antibiotics in the two time periods
Recommended: 2g amoxicillin preoperatively or 600 mg clindamycin according to Swedish guidelines published in October 2012 (Läkemedelsverket 2012).
*Antibiotic type in dosage differ from the recommended
Amox: Amoxicillin, Penicillin V: phenoxymethylpenicillin, other AB: amoxicillin or metronidazole or benzyl penicillin IV

Before the publication of the Swedish guidelines, there was a positive correlation between membrane placement during bone augmentation procedures and antibiotic prescription (P = 0.03, R = 0.14). After the publication, there was a positive correlation between sinus lift procedure during bone augmentation surgeries and the prescription of antibiotics (P = 0.00, R = 0.31). Moreover, a significant inverse relationship between both the use of xenograft bone type and

number of missing teeth in the graft area, with antibiotic prescription was reported (P = 0.00, R = - 0.23, and P = 0.00, R = - 0.19, respectively).

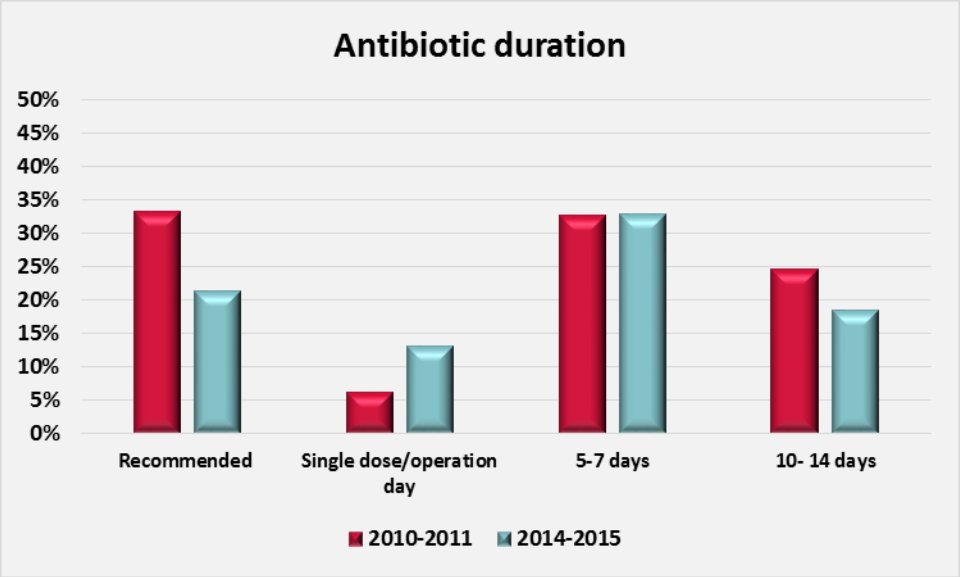

Figure 8. The duration of prescribed antibiotics in the two time periods
Recommended: 2 g amoxicillin preoperatively or 600 mg clindamycin according to Swedish guidelines published in October 2012 (Läkemedelsverket 2012).

Regarding the risk of developing postoperative infection following bone augmentation procedures, there was no significant difference found between the two time periods (P = 0.12). Postoperative infection was reported in seven patients in 2010-2011, and 14 patients in 2014-2015 (Table 9), diagnosed within the first month after surgery. Of those 21 patients diagnosed with infection, 13 received no antibiotics, three received the recommended dosage and five were prescribed either different antibiotic type or duration. The relationship between not prescribing antibiotics and increasing the risk of postoperative infection was weak but significant (P = 0.00, R = 0.24). The patients who developed postoperative infections were treated either locally by irrigation (n = 2), with removal of the membrane (n = 3) or with removal of grafted bone or placed implant (n = 3). Systematic antibiotics were prescribed for the majority of the patients who developed the infection (n = 19). The antibiotics were either clindamycin (n = 3), penicillin-V (n = 11), amoxicillin (n = 3) or combination between penicillin-V and metronidazole (n = 2). Antibiotic duration for these patients were varied from 7 days up to 2 weeks.

Table 9. The number of patients who developed postoperative infection.

Postoperative infection	2010-2011 N (%)	2014-2015 N (%)	P-value
Yes	7 (3.5)	14 (7)	0.12
No	193 (96.5)	186 (93)	

5 DISCUSSSION

5.1 MICROBIOLOGICAL CONSEQUENCES OF ANTIBIOTIC PROPHYLAXIS (STUDY I)

The results show that a single-dose antibiotic prophylaxis (2 g amoxicillin) disturbs oral microflora and can result in resistant viridans streptococci in healthy individuals, peaking on day 2 (24 hours), and day 5 after administration. The relationship between antibiotic consumption and development of antibiotic resistance is well established (Foucault and Brouqui 2007; Livermore 2005). It has previously been suggested that short-term antibiotic treatments reduce the risk of developing antibiotic resistance (Guillemot, et al. 1998). However, research supporting this assumption is lacking and no previous studies have investigated the effect of a single-dose antibiotic prophylaxis on oral microflora for longer than 24 hours. Thus, due to the present results demonstrating a link between single-dose antibiotics and the development of antibiotic resistance, further research regarding whether it is safer to refrain even from short-term antibiotic prophylaxis use in many surgical fields is warranted. The weighing of the risk against benefits can then form a basis for solid recommendations regarding the use of antibiotic prophylaxis. Also, the necessary number needed to treat must be evaluated against any putative adverse effects. The results also show that approximately one third of participants gained resistant viridans streptococci against amoxicillin, clindamycin, and penicillin-V during the study period. Thus, it may be prudent to recommend caution when prescribing to healthy patients in order to avoid development of antibiotic resistance.

The present study demonstrated that the greatest disturbance in viridans streptococci ecology occurred on day 2, 24 hours after administration of a single-dose antibiotic. The decrease in number of viridans streptococci has been reported in previous studies where amoxicillin was used for 3 to 7 days (Brismar, et al. 1993; Chardin, et al. 2009). A recent study showed a lack of significant changes on facultative anaerobic and streptococci in saliva prior to 24 hours after single-dose antibiotic administration (Larsson Wexell, et al. 2015). However, this study did not provide data after 24 hours so it is unknown whether similar changes would have been observed during a longer period. Although the present study indicated that ecological disturbance is short-term, peaking around day 2, this disturbance does occur during the highest risk period of acquiring a postoperative infection, which is during the first few days after surgery. Since the source of such infection is mainly endogenous (Heimdahl and Nord 1990), the risk of causative bacteria rendering treatment difficulty due to resistance therefore increases. Furthermore, the ecological disturbance increases the risk of acquiring and becoming colonized with antibiotic resistant bacterial strains (Nord 1990; Van der Waaij and Nord 2000).

In the current study, a significant increase in the proportion of viridans streptococci with reduced susceptibility to amoxicillin was detected after a single dose of amoxicillin. This may be due to pre-existing resistant strains, but below the detection level, being given the opportunity to multiply under antibiotic pressure, or actual newly colonizing strains developing due to ecological disturbance, or a combination of both. The increase in the number of resistant bacteria gives enhanced shedding and may thereby accelerate the dissemination of resistant strains. This could also mean that the protective efficacy of amoxicillin prophylaxis may be compromised. Understanding the process of resistance selection is becoming vital, considering the problem of growing antibiotic resistance. However, updated epidemiological data regarding carrier rates of resistant strains in the oral microflora are, to our knowledge, lacking. An interesting result in the current study is that the study participants were from a part of the world known to have one of the lowest rates of resistance (ECDC 2017), yet they exhibited relatively high commensal flora resistance carrier rates. This may imply that actual carrier rates of resistant viridans streptococci in the oral microflora are possibly greater than previously anticipated and may be gravely underestimated in countries where resistance is known to be higher.

5.2 ANTIBIOTIC PROPHYLAXIS PRESCRIPTION PATTERNS IN IMPLANT DENTISTRY (STUDY II, STUDY IV)

There was a wide variation in the type, dosage and duration of prophylactic antibiotic usage in conjunction with dental implant placement both in simple and complicated cases where bone augmentation was required. The results showed that the majority of dentists routinely prescribed prophylactic antibiotics prior to dental implant surgery. This finding is in agreement with other studies where 72% - 85.5% of the surveyed data, from Finland, India, the USA and the UK, routinely prescribed prophylactic antibiotics in conjunction with implant insertion (Datta, et al. 2014; Deeb, et al. 2015; Froum and Weinberg 2015; Ireland, et al. 2012; Pyysalo, et al. 2014). While the dentists' survey concluded that they were influenced by scientific reviews, the results extracted from patients' medical charts reported that the majority were treated with antibiotic doses, durations and types differing from that recommended by the national guidelines. One explanation is that the dental practitioners were more cautious and precise when answering the questionnaire but in practice they do not always follow clinical guidelines. In addition, investigators have recently discovered that dentists do not always keep themselves updated, despite the availability of information (Oberoi, et al. 2015; Palmer and Batchelor 2004). Even so, with scientific evidence regarding the use of prophylactic antibiotics in conjunction with implant surgery still inconclusive, the available information does not

provide the clinician with clear guidance. It may also be that the clinician, under certain circumstances, may prescribe antibiotics to protect the patient, and themselves, from treatment complications and any resulting financial consequences (Wardh, et al. 2009).

In the results for both Studies II and IV, there was a significant increase in the number of patients treated without antibiotic prescription prior to dental implant treatement between the two time periods. This may either be due to the lack of solid evidence regarding the benefit of prescribing antibiotics to decrease the risk of postoperative infection/ implant failure, or that the dentists' knowledge increased regarding the undesirable effects of the antibiotics they had been prescribing and they became more cautious.

The more conservative approach to antibiotic prescription prior to dental implant placement was observed in the questionnaire filled in by dentists with postgraduate clinical training. Moreover, in the other study (Study IV) there was a significant but weak relationship between the dentists under residency training and restrictive antibiotic prescription. This may be due to dentists', either under residency training or who had completed their training programmes, clinical training which focused on both the benefits and the undesirable effects of antibiotics. In a study testing the effect of a short-term antibiotic educational programme on dentists' behaviors, promising results regarding antibiotic usage were shown (Öcek, et al. 2008).

On comparing the two time periods, there was a noticeable change in the type of antibiotic prescribed as reported by the dentists' questionnaire (Study II). Amoxicillin became the preferred drug of choice. Thus can be clarified by the implementation of the scientific reviews and recommendations that favour the prescription of amoxicillin preoperatively. Amoxicillin is widely used in conjunction with dental implant surgery, and its effect on reducing the risk of implant failures has been studied (Dent, et al. 1997; Laskin, et al. 2000). It has a good coverage of the oral microflora, moderate oral and gastrointestinal ecological effect, rapid and extensive oral absorption and therefore is a suitable choice for antibiotic prophylaxis in oral surgery. In the other study (Study IV), the patients' medical charts show that the majority of the bone augmentation procedure patients took penicillin-V. In dentistry, penicillin-V is a widely prescribed and has several beneficial characteristics. It has a bactericidal action with a narrow spectrum, it is effective against most *Streptococcus* species and oral anaerobes, and it has a mild to moderate ecological effect when used to treat dental infections (Lund, et al. 2014; Resnik and Misch 2008).

A change in antibiotic prescription duration was observed between the two time periods in the studies, reflecting the effect of the scientific reviews and national recommendation. More than

half the surveyed dentists reported that they prescribed a single preoperative dose post guidelines, rather than an extended regimen. Moreover, in the present study on bone augmentation surgery prior to dental implant placement, there was a dramatic reduction of the length of prophylactic antibiotic treatment. This could reflect the efforts to reduce antibiotic prescription as the clinician might not feel confident to refrain totally from extended prophylaxis. Therefore, this issue is still contradictory, with the need for providing recommendations based on sound scientific evidence. While great effort has gone into improving the guidelines in Sweden, solid information is still lacking. However, changing dentists' antibiotic prescription behavior requires time. Therefore, a follow-up study is mandatory to check the influence of these recommendations and to remind practitioners to secure a professional attitude when prescribing antibiotics.

The positive relationships between using resorbable membranes, sinus lift procedures and antibiotic prescription reported in the current bone augmentation study, to our knowledge, have not been observed in previous studies. The infection rate associated with these procedures is considered infrequent (Testori, et al. 2012). However, in a study that published a clinical consensus and recommendations for sinus lift procedures, the use of antibiotic prophylaxis for 7 days to reduce the risk of infection was favoured (Testori, et al. 2012). Moreover, the present study reported that increasing the number of treated edentulous areas will increase the number of restrictive, no antibiotic prescriptions by dentists. Inserting several implants requires a larger mucoperiosteal flap, prolonged operating time, and poses a higher risk for wound contamination (Figueiredo, et al. 2015). Explanations for our results could be that a dentist placing more than three implants is more confident with their surgical and aseptic techniques than other dentists performing single implant surgery, or this may just be a coincidence, or due to the small number of cases. Therefore, there is a need for further RCT to determine the reasons behind the influencing choice for antibiotic prescription. This would also form an important base for motivating dentists to be restrictive.

Five percent of the patients who performed bone augmentation procedures prior to dental implant placement developed postoperative infections. In the current study, patients who were not treated with antibiotics had a weak significant relationship with the development of postoperative infection. This is probably due to the fact that this kind of surgery (clean-contaminated surgery) carried a risk of infection, but this risk can be reduced with the use of prophylactic antibiotics (Olson, et al. 1984; Peterson 1990). However, since the rate of infection is low in relation to the sample size of the study, larger clinical studies are required to

confirm this result. To date, there is no gold standard for the treatment of postoperative infections, and thus probably explains the difference in dealing with this situation among implant surgeons.

The majority of the dentists surveyed reported a need for the national guidelines to determine the need of antibiotics in implant surgery. The implementation of practice guidelines is expected to improve antimicrobial treatment behaviors, and reduce infection rates (Foucault and Brouqui 2007). Thus, strong scientific evidence are mandatory in the area of implant dentistry. It should be kept in mind that guidelines for antibiotic selection should be modified according to local factors, such as local resistant bacteria status, and professional realities (Mainjot, et al. 2009).

5.3 ANTIBIOTICS AS A PROPHYLAXIS IN IMPLANT DENTISTRY WITH BONE AUGMENTATION PROCEDURES: A COMPLEX SYSTEMATIC REVIEW (STUDY III)

The systematic review identified only a few studies that met the inclusion criteria and illustrates the lack of scientific evidence regarding the effect of prophylactic antibiotics on oral bone augmentation procedures in conjunction with dental implant placement. Lindeboom et al. 2005 showed that the number of postsurgical infections were few in both the single dose prophylaxis and 24-hour antibiotic dose groups. However, there was a 33% reduction, not statistically significant, in the risk of developing a postsurgical infection at the bone graft receptor site among patients who took a single dose of antibiotic prophylaxis compared to patients receiving a more extended 24-hour dose of clindamycin. In the Lindeboom et al. 2006 study, there was no significant difference in the risk of postsurgical recipient site infection on comparing two different single dose antibiotic prophylaxis compounds - penicillin and clindamycin. Therefore the results of a statistical comparison in both studies between the two groups may be hampered by insufficient power. Both studies indicated that wound infection rate using a single dose of prophylactic antibiotics was low.

While there are many published systematic reviews regarding the beneficial effect of using antibiotics in dental implant surgery, none were found to fulfil the current study's inclusion criteria. The two primary studies fulfilling the inclusion criteria were considered to be of moderate risk of bias (Lindeboom, et al. 2006; Lindeboom, et al. 2005). Therefore, definite conclusions regarding whether prolonged or single dose antibiotic prophylaxis is needed to reduce the risk of postoperative infection during bone grafting procedures cannot be drawn. Consequently, efficacy of antibiotic prophylaxis, regardless of its duration, compared to no use for prevention of postoperative infections after bone grafting procedures is needed.

Large numbers of systematic reviews are often seen in fields where primary studies are sparse and the results contradictory. Due to the lack of solid evidence, possibly from primary studies with few participants or low power, systematic reviews are often undertaken in an attempt to summarize and synthesize what data are available. Randomized clinical trials on the topic of antibiotics and bone augmentation procedures are lacking, thus there is a great need for high quality primary research in this field. The results of the present study serve to emphasize the fact that one needs to be vigilant about drawing conclusions from the current published systematic reviews in the field.

It has been proven that clinicians are responsible for the link between treatment decisions and the problem of antibiotic resistance, via their prescribing behavior (Costelloe, et al. 2010). Antibiotic resistance is one of the biggest problems now facing healthcare providers. In addition to the diminishing number of new agents entering clinical practice (Bencharit 2012), such resistance is becoming a major threat to public health (WHO 2015). Recently, the World Health Organization reported that some common infections are becoming more difficult to manage and may need longer recovery period due to antibiotic resistant bacteria (WHO 2015).

5.4 LIMITATIONS

Study I: The purpose of this study was to investigate the effects of a single-dose antibiotic prophylaxis on normal oral microflora in terms of ecological composition and selection for resistance. The rate and selection of antibiotic resistance by MIC and culturing methods, with drawbacks of, for example, loss of uncultivable bacteria, were chosen. New sensitive molecular methods do not permit antibiotic sensitivity tests. Furthermore, DNA-based methods cannot discriminate between viable/non-viable bacteria and therefore hamper quantitative analysis.

Study II: The questionnaire distributed in this study has not been formally validated. However, the results showed that recommendation and postgraduate clinical training are important in restricting antibiotic usage in dental implant surgery. Since the responses to the questionnaires were anonymous, it was not possible to analyze changes in individual dentist behaviors between the two time periods.

Study III: In this complex systematic review, it was not possible to perform a meta-analysis to draw a definite conclusion since there were only a limited number of studies that fulfilled the inclusion criteria. However the results of this study highlight the need for scientific based evidence.

Study IV: This is a retrospective study design. Therefore, there are limitations in obtaining the exact description for each augmentation procedure. Thus can slightly compromise the accuracy of the data but this design allowed the inclusion of a large number of patients.

6 CONCLUSIVE REMARKS

Study I: A single dose of 2 g amoxicillin induced the selection of bacterial resistance and caused ecological disturbances in normal oral microflora and therefore supports a restrictive approach regarding antibiotic prophylaxis.

Study II: There was a wide variation in the type, dose and duration of antibiotics prescribed by dentists prior to routine dental implant procedures. A reduction in antibiotic prescription of a single dose prophylaxis was observed on comparing the two time periods. This leads support to the fact that scientific reviews and recommendations have influenced dentist antibiotic prescription behavior.

Study III: There are a limited number of scientific studies containing evidence regarding the use of antibiotic prophylaxis to reduce the risk of infection in conjunction with bone augmentation procedures prior to dental implant placement. This review showed that the infection rate using a single dose antibiotic prophylaxis was low. However, the infection rate is still unknown in comparison to non-usage of prophylactic antibiotics. Therefore, this study supports the need for further primary randomized controlled studies to evaluate the benefit of antibiotic prophylaxis in conjunction with bone augmentation procedures prior dental implant placement.

Study IV: Misuse and overuse of antibiotics during bone augmentation procedures prior to dental implant placement was observed. Large variations between observed and recommended practices were seen. A weak relationship was observed between the risk of developing postoperative infection after bone augmentation surgery prior to dental implant placement, and no antibiotic prophylaxis prescribed. Therefore, strict, solid guidelines based on scientific evidence are mandatory to improve dentists' prescription behaviour.

7 FUTURE PRESPECTIVES AND RECOMMENDATIONS

Today, the use of antibiotics in medical practice is an important subject that needs to be understood. While there is a beneficial effect from antibiotic use, side effects are reported. Recently, there has been an increase in prophylactic antibiotic prescriptions, even without any evidence to indicate that such use of prophylactic antibiotics would decline the risk of postoperative infection. With the increasing emergence of antibiotic resistance, it is necessary to limit antibiotic use. There is a lack of scientific evidence on the beneficial effect of prophylactic antibiotics in the literature, and consequently no solid recommendations on the use of antibiotics in simple or complicated dental implant surgical cases. In addition, the effect of antibiotic prophylaxis in human microflora needs to be further investigated. Therefore, well-designed RCTs with larger sample sizes and longer follow-up periods are essential to be able to assess the benefit risk ratio in using antibiotic prophylaxis during implant insertion. Such studies should be reported according to the Consolidated Standard of Reporting Trials (CONSORT) guidelines (Moher, et al. 2001) and should evaluate treatment safety, efficacy and cost-effectiveness. The growing number of RCTs published over the last few years, and fulfilling these criteria positively indicate that we might finally reach ‘evidence based medicine’ rather than a traditional ‘opinion based’ approach to clinical decision making (Esposito, et al. 2009). Moreover, the need to spread the knowledge regarding the use of antibiotics and their desirable effects to all healthcare providers is mandatory. It has been reported that cooperation between countries has led to success in the fight against communicable diseases such as smallpox, polio, tuberculosis and measles. Initiative strategies have been taken by international associations and by governments and experts in individual countries in order to contain antibiotic resistance. The only way we can secure a future with effective antibiotics is through working together, and this should begin now. The WHO clearly states: No action today, no cure tomorrow. Therefore, there is a need to establish strict guidelines to improve the utilization of antibiotics in the dental implant field. These guidelines should prevent the risk of infection through better surgical intervention, decrease the risk of resistant bacterial strains developing, reduce total antibiotics usage, and possibly reduce the cost of care. It also should be as simple and specific as possible rather than attempting to cover all clinical situations (Durack 1995).

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