Chapter

Infection Control in Dentistry and Drug-Resistant Infectious Agents: A Burning Issue. Part 1

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Abstract

Using molecular biological methods and retrospective investigations, some outbreaks in dental settings have been proven to be caused by mainly blood-borne viruses and water-borne bacteria. Nowadays, drug-resistant bacteria seem further hazards taking into account the worldwide overuse of antibiotics in dentistry, the limited awareness on infection prevention guidelines, and the lapses and errors during infection prevention (reported in more detail in Part 2). We chose MRSA and VRE as markers since they are considered prioritized bacteria according antibiotic resistance threats. Antibiotic-resistant bacterial infections inside of dental setting are relevant, and we argue about some hazards in dentistry, including dedicated surgeries. MRSA has a key role for its colonization in patients and dental workers, presence on gloves, resistance (days-months on dry inanimate surfaces), the contamination of different clinical contact surfaces in dental settings, the ability of some strains to produce biofilm, and finally its estimated low infective dose. For better dental patient and healthcare personnel safety, we need evidence-based guidelines to improve education and training initiatives in surgery.

Keywords: dentistry, surgery, guidelines, infection control, antibiotic resistance, biofilm

1. Introduction

Dentistry seems to provide safe procedures for oral health care taking into account all adverse events (AEs). Nevertheless, death, injury, and malfunctions due to dental devices (DDs) increased from the MAUDE report in 2000–2012, and the endosseous implants were at the top of the DDs involved in AEs [1]. In the same period, the number of malpractice payments in dentistry increased by 12%, while those in other health professions fell [2]. Dental AEs, complaints, and claims seem to be relatively common in different countries [3]. About 4–17% of AEs are due to infection [4, 5]. The iatrogenic infectious risk in dentistry has not been quantify closely yet [6, 7], but recently, some outbreaks caused by infective agents, mainly blood-borne viruses and water-borne bacteria, have been documented in dental settings based on molecular biological assays and/or retrospective investigations [8–11].

Some evidence exists around the hazard due of antibiotic-resistant infectious agents (ARIAs) in dentistry. Fatal adverse events (FAEs) had been reported within

90 days after different instances of dental care [7]. In the last 50 years, FAEs caused by an infection have (a) increased while respiratory complications and bleeding are steady, and those caused by cardiovascular or related to anesthesia have decreased, (b) significant (12%), (c) mainly associated to dental surgery (implant surgery/placement, extractions (>6 erupted teeth or impacted tooth/teeth), surgical extractions, osseous surgery, sinus lift surgery, bone biopsy, orthognathic surgery), and (d) associated with much longer times until death compared with other causes of death [7]. A study on dental malpractice analyzed 4149 legal claims (both in and out of court) from the years of 2000 to 2010 in Spain [12]. About 2.7% of all AEs resulted in death, and 45% of them were caused by infection. In the absence of specific information reported in both papers [7, 12], we do not exclude the possible involvement or nonrecognition of ARIAs or the failure of proper drug treatment in those FAEs. Recently, in an interview, Davies stated that in 20 years time even minor surgeries could be fatal because of infections [13].

We consider that the following two reviews are important and indicative of the limitedness of data published up to 2011–2012 in dentistry [14, 15]. The first review on methicillin-resistant *Staphylococcus aureus* (MRSA) infection concluded that (1) transmission was ascertained during surgical interventions, particularly in surgical units and among head and neck cancer patients; (2) carriage rates among dental healthcare personnel (DHCP) were lower than those among other health-care workers (HCWs); (3) carriage rates among adult patients were low, whereas among pedodontic and special care patients rates were higher than those found in the general population; and (4) MRSA had been detected in the environment of emergency, surgical units, and in dental hospitals [14]. In the second review, multi-resistant bacteria infections had been included among the main healthcare viral and bacterial infections in dentistry [15], but the transmission of Enterobacteriaceae and/or their resistant strains did not exist yet. The interest on Enterobacteriaceae is warranted since they are susceptible to only a few (if any) antibacterial drugs.

Here, we think it is important to update these conclusions in the light of the global, wide, and long-term abuse and misuse of antibiotics in dentistry and selective pressure on opportunistic bacteria by favoring potentially pathogenic strains [16, 17]. In addition, the limited awareness on infection prevention guidelines and lapses and errors during infection prevention according to Centers for Disease Control and Prevention (CDC) dental guidelines [6, 8–11] sustain the evidence of possible reservoirs of ARIAs in humans (patient, dental staff) and in the environment (clinical contact surfaces (CCSs), dental instruments, and dental unit water lines (DUWLs)) and possible hazards in surgical dental setting. Our approach is in line with the CDC recommendation, in which it states that "*Preventing infections negates the need for antibiotic use in the first place, and scientific evidence shows that reducing antibiotic use in a single facility can reduce resistance in that facility*" [18–20].

In addition, the cluster of above problems is important for risk management, since it is rationally "harmful" that opportunistic species and/or ARIAs were involved in implant failures [21, 22], periodontitis [23, 24], endodontic failures [25] and oral mucosal and deep infections [26].

Here, we discuss briefly main recent evidence and controversy on infections in dedicated dental and mainly in implant surgery, taking into account that many other aspects (i.e. surgery technique, geometry, materials, and surface of dental implants) have already been reviewed extensively [27–30]. Dental implant (DI) complications are a burning issue, since the current demand of DIs is high (20 DIs in Italy and 4 in the USA per year per million of inhabitants), mainly applied in private offices, and the global DI market size was estimated at 3.77 billion USD in 2016 growing at a compound annual growth rate (CAGR) of 7.7% over 2024 [31]. It is important to underline that the incidence of esthetic, technical and infective complications is still high in implantology, and the 5-year infective complication increased from 7.4 to

9.4% [32]. In general, the expected implant-associated infections and the outbreaks from opportunistic pathogens (*Staphylococci*, *Enterococci*, *Pseudomonas*, etc.) will always be more important. In addition, we have to take into account other factors linked to risk management such as the impact on reputation and finances, the loss of protection of insurance coverings and reimbursements, and shocking advertising rapidly spreading through social networks in the case of outbreaks [8–11, 33–35].

Here (Part 1), we focus on the insufficient compliance with infection control (IC) recommendations in oral healthcare and the difficulties and problems of standard precaution implementation also in ambulatory surgical centers [6, 36–42]. In general, dental surgery and implantology are predominantly done in general dental practice under local anesthesia or sedation [43, 44]. This is a very important aspect since the cross-infection is widespread and more difficult to control compared to surgical rooms. We have divided problems and difficulties for infection prevention into different areas concerning the innovative molecular biology techniques; antibiotic misuse and overuse in dentistry; opportunistic pathogens and antibiotic resistance in dental patients and dental healthcare workers; and surgical infection prevention in dentistry. While in the chapter (Part 2), we have reported infection control implementation, not compliance, lapses and errors during infection prevention according to CDC dental guidelines. We focused on hand hygiene, gloves, environment decontamination, and instrument reconditioning in more detail [6, 43–47].

2. Approach

The electronic literature search was conducted via the PubMed and Google Scholar databases (from January 2010 up to and including April 2018) using various combinations of the following key indexing terms: (a) patient safety; (b) infection control; (c) implant; (d) endodontia; (e) sterilization; (f) reconditioning; (g) critical items; (h) semicritical items; (i) hand hygiene; (j) DUWL; (k) sharps safety; (l) personal protective equipment (PPE); (m) disinfection; (n) MRSA; (o) VRE; (p) ARIAs; (q) guidelines; and (r) cross-infection. In addition, manual searches were carried out in INTECH books. Then, bibliographic material from the papers has been used in order to find other or older appropriate sources. A total of 179 papers and links were found suitable for inclusion in this chapter (Part 1). Only few papers do not have a DOI or PubMed classification, but the available link by Internet and accessed date have been added.

3. Focus on molecular biology techniques

Expanded Human Oral Microbiome Database (eHOMD) provides the scientific community with broad and up-to-date information on the bacterial species present in the human aero-digestive tract, including the oral cavity. Genomes for 482 taxa (63% of all taxa, 89% of cultivated taxa) are currently available on eHOMD [48]. Fast and very sensitive molecular biological techniques, classified into nucleic acid-based methods [quantitative real-time polymerase chain reaction (PCR), multiplex PCR, microarray, next-generation sequencing technologies, etc.], are available for the screening, detection, and functional activities of pathogens and antibiotic-resistant bacteria, even those not cultivable by classical microbiological methods and by using both patient biological fluids and samples from inanimate objects (surface, air, DUWL colonization, DDs, and instruments) [49–52]. This is possible because DNA molecules can survive for long time and can be amplified. Current microbiological laboratory approaches based on high-throughput real-time

PCR allow quick, easy, and cheap detection of the oral microbiome and the antibiotic resistome, throughout 300 antibiotic resistance genes [53] as far as the rapid diagnosis of virulent slime-producing strains associated with dental caries [54]. The specificity of MRSA plus MSSA carriage detected with Xpert MRSA is better than standard culturing techniques, being 37.9 vs. 23.6%, respectively [55]. Concerning microbiological features of peri-implantitis cases, culture methods were able to detect 81.4% of the targeted species of the cases, whereas "checkerboard DNA–DNA hybridization" method 99.3%. In relation to the limited association between the bacterial contamination and the severity of the peri-implantitis [56], it is decisive the sampling procedure, around DIs and during swabs on dental items, and the use of the proper primer sequence for specific genes in different strains (i.e. ica genes for *S. epidermidis and S. aureus*) [57]. PCR is more effective in detecting *E. faecalis* than other analytical tools, such as culturing. *E. faecalis* has been found in root-filled teeth associated with periradicular lesions in a range of 0–70% by culture and 0–90% by PCR [58].

It is important to note that microbiological analysis (by culture or DNA-based methods) is rarely used in dentistry mainly because of the difficulties to delay the antibiotic treatment and for the plethora of infective agents involved in inflammatory diseases in dentistry. In addition, specific sampling procedures are needed since the virulence features of microorganisms and problems to sample deep periodontal and peri-implant pocket and abscesses. Sequencing methods that evaluate the entire microbiome are needed to improve identification of microorganisms (pathogen, opportunistic, noncultivable, drug-resistant ones) associated to peri-implant infective diseases and to develop suitable countermeasures with the expertise of clinical oral microbiologists [59]. In addition, emerging approach based on optical nanoprobes, biosensors, and protein biomarkers suitable for peri-implant crevicular fluids has been proposed to identify the severity and progression of the disease and the response to therapy [60, 61].

4. The broad antibiotic misuse or overuse in dentistry

Globally, antibiotic prescription in dental care has continuously increased over the last 17 years, and a lot of evidence has been published on wide antibiotic misuse or overuse, in industrialized, low- and middle-income countries [62–70]. Dental prescriptions make up 5–11% of all antibiotic prescription among patients in some European countries, Canada, and the USA [19, 20, 65, 71, 72]. The rate of prescription increased the most among dental patients of 60 years or above.

It is important to underline that antibiotic prescription is placed without a microbiological analysis and has mainly prophylactic aim in dentistry. Recently, the prescription of antibiotics in dentistry was reviewed by Holmstrup and Klausen, while the use of antibiotics in odontogenic infections, in addition to the removal of the source of infection, by Martins [73, 74]. A significant percentage (19–37.5%) of microorganisms collected from their patients were penicillin resistant; nevertheless, the relationship between the clinical outcomes and microbial resistance with penicillin is not clear [74].

Recently, to overcome the misuse and abuse of antibiotics in dentistry, different institutions and associations recommended a more restrictive antibiotic policy to improve treatment efficacy and decrease bacterial resistance. Specific guidelines have been published for implantology [17], endodontia [75], oral surgery [17], third molar extraction [76], and medically compromised patients [77] and to prevent infective endocarditis [78, 79] or prosthetic joint infections [80].

5. Focus on opportunistic pathogens and antibiotic resistance in dental patients and dental healthcare workers

Here, based on recent and current knowledge, we focus on two well-known bacterial strains, *S. aureus* and *Enterococcus*, and their resistant strains. It is known that *S. aureus* and *Enterococcus faecalis* have been implicated in implant-associated infections [21, 23, 24, 81], endodontic infections [22, 25, 82], and recently in an outbreak of *Enterococcus* endocarditis [11]. We focus on these Gram-positive bacteria for the high innate resistance or ability to become resistant to most antibiotics along with some other virulence factors (hydrophobicity, adherence to abiotic surfaces (including dental implant materials), biofilm formation, ability to growth also in anaerobic conditions) [83]. These features are important in the exploration of standard precaution failures since bacterial adherence on dental implants, collagen-based biomaterials, or many other inanimate objects is known to be linked with the presence of surface components with nonpolar/hydrophobic vs. polar/hydrophilic characteristics. In addition, we focus on Staphylococci and Enterobacteriaceae as markers since they are considered prioritized bacteria according to antibiotic resistance threats, and better knowledge is available on their virulence factors and for dental settings (i.e. contamination on hands and environments, etc.) [6, 43, 45–47].

5.1 *Staphylococcus aureus* and MRSA

Single dose of prophylactic antibiotics in healthy volunteers induces a significant selection of resistant strains among the dynamic and complex community of resident oral and gastrointestinal bacterial microflora and causes a large disturbance of oral niches [84, 85]. Approximately, one third of participants gained resistant viridans *Streptococci* against amoxicillin, clindamycin, and penicillin-V, while in *Prevotella* spp., there was approximately a 28% gain in resistance to all antibiotics tested. The disturbance could reduce host colonization resistance, select new pathogens, and lead to an overgrowth of resistant bacteria [86].

S. aureus lives as a commensal primarily in the anterior nares and/or throat of 20–70% of adults [87, 88]. Some of the strains develop multidrug resistance and are well known to be involved in hospital-acquired (HA) infections [89]. The following two reviews are important and indicative of the limitedness of data published up to 2011–2012 in dentistry [14, 15]. *S. aureus* was normally absent or its colonization was very low in oral biofilm and ecological oral niches as reported in older evidence or not considered as a topic [14, 43, 90]. More recent data show that the presence of *S. aureus* in the oral cavity is more frequent and, nowadays, is to be considered a member of the oral microbiota (**Table 1**) [15, 84, 91–105]. Recently, metaproteomic analysis of human salivary supernatant from healthy persons was able to identify peptides from 124 microbial species including *Staphylococcus* [85]. The majority of *S. aureus* strains, isolated from the oral cavity of Tunisian patients, were biofilm/slime producers and exhibited some important genes (i.e. *ica, fnb, cna)* associated to adhesion and virulence factors [106, 107]. *S. pneumoniae* and *S. aureus* are common commensals of the upper respiratory tract in children and adolescents [14, 100, 108]. This fact is relevant since orthodontic patients are mainly children and adolescents and the high genotypic expression of peculiar genes (*ica*A/*ica*D) is important for *S. aureus* in the colonization of orthodontic appliances [109]. Recently, RNA-Seq data permit the analysis of active transcripts, assigned to antibiotics and toxic compounds, of the
supragingival dental plaque biofilm in healthy subjects [110]. The transcripts assigned to Acriflavin resistance complex (*AcrA* and *AcrB* genes) were prevalent,

Study	References	Study population	Number of subjects	Study carried out (years):	Country	Sampling, specimen, assay	*S. aureus* carriage (%)	MSSA carriage (%)	MRSA carriage (%)
Roberts et al. (2011)	[91]	Dental students	61	#	USA	Swab, anterior nose; §	#	21	21.3
Martınez-Ruız et al. (2014)	[92]	Dental students	100	#	Mexico	Paired nasal and throat swabs; §	#	#	20
Petti et al. (2015)	[93]	Dental students	157	#	Italy	Dry cotton swabs from the mouth, nose, and skin between fingers of the nondominant hand; §	15.3 (9.7–20.9), any site	#	0, any site
Baek et al. (2016)	[94]	Dental students	159	#	Korea	Nasal samples; §	#	#	3.1
Hema et al. (2017)	[95]	Dental students	200	#	India	Swab, anterior nares; §	#	#	24.5
Zimmerli et al. (2009)	[96]	500 dental patients >18 years	500	2006	Switzerland	Swab, anterior nares; §	42	41.6	0.4
McCormack et al. (2015)	[97]	10-year retrospective analysis of laboratory data	1429	1998–2007	UK	Perioral clinical specimens (no. 1986); §		90	10
Kabanova et al. (2017)	[98]	Patients from 5 maxillofacial departments	2920	2014	Belarus	Swabbing the area after the incision (no. 162); §	15–70	#	5.6–27.8
Dulon et al. (2014), review	[99]	HCW in non-outbreak settings	21,289 subjects from 31 studies	#	#		#	#	1.1–5.4 from high quality studies

Study	References	Study population	Number of subjects	Study carried out (years):	Country	Sampling, specimen, assay	*S. aureus* carriage (%)	MSSA carriage (%)	MRSA carriage (%)
Esposito et al. (2015)	[100]	Healthy subjects aged 6–17 years	497	2013	Italy	Oropharyngeal and nasal swabs; multiplex real-time PCR	#	49.7 from 6–9 years.; 54.9 from 10–14 years.; 52.9 from 15–17 years	3.5 (15–17 years)
Koukos et al. (2015)	[101]	Healthy patients	154	2010–2014	Greece	Subgingival samples and PCR assay	10	#	0
Kharialla et al. (2017)	[102]	Patient and DHCP	#	2013	Egypt	Swab, anterior nares, (no. 1300); culture plus molecular typing	8.6	#	11.1 patients; 6.7 nurses; 9.3 dentists
Yoo et al. (2018)	[103]	DHCP	139		Korea	Swab, anterior nares; §	#	#	2.9

§: using microbiological culture methods; PCR: polymerase chain reaction; #: not indicated.

Table 1.
Staphylococcus aureus, methicillin-sensitive Staphylococcus aureus (MSSA), and methicillin-resistant Staphylococcus aureus (MRSA) carriage rates among dental students, dental patients, dental healthcare personnel (DHCP), and healthcare workers (HCWs).

while those encoding for putative macrolide-specific efflux system or proteins involved in acid stress and bacteriocins are less represented. High percentages of *Staphylococcus* species, MRSA, *P. aeruginosa*, and *C. albicans* were detected in the mouths of elderly patients [111, 112]. By PCR, a notable occurrence of MRSA, vancomycin-resistant *S. aureus* (VRSA), and VSSA have been observed in the oral cavity of patients with dental caries [113]. Chronic periodontitis showed extensive antibiotic-resistant subgingival periodontal pathogens in cultivable microbiota, associated with red and orange complex species, and also to Gram-negative enteric rods/Pseudomonads, *E. faecalis*, and *S. aureus* [21, 23, 24, 114].

Here, we report updated data on *S. aureus* and MRSA carriage rates among dental students, dental patients, HCWs, and dental healthcare personnel (DHCP) in **Table 1** [91–103]. Despite the many differences between studies, nowadays there is a probable occupational exposure, from carriage rates, among DHCP and HCWs. This is higher in dental students (**Table 1**), but would seem evident in the last years [14, 91–95]. Nasal MRSA colonization, confirmed by the presence of the *mecA* gene that encodes a low-affinity penicillin-binding protein, occurs in dental students (3.1%), especially those who have clinical experience [94]. MRSA hand and nasal carriage rates in patients, nurses, and dentist are significant in dental settings (**Table 1**) [102]. The majority of MRSA isolates were multidrug resistant, and full resistance was generally higher for personnel than for the environmental isolates.

5.1.1 Community- and hospital-acquired MRSA infections and dentistry

Taking into account MRSA carriage in dental patients and DHCP, the effectiveness of MRSA decolonization, and the violation of IC precautions (see below and in Part 2), MRSA in the oral cavity could potentially be disseminated by carriers (patient and DHCP) to the environment [115]. It is well known that community-acquired MRSA (CA-MRSA) infections often occur in young and healthy individuals, whereas HA-MRSA infections occur predominantly in elder or immunocompromised patients in healthcare settings and vary considerably between different countries [116, 117].

HA-MRSA and CA-MRSA have opposite features concerning competitive fitness, virulence, and antimicrobial resistance [118]. Only rarely HA-MRSAs cause infections in healthy subjects, but at least two CA-MRSAs (USA300 and ST30) cause HA infections. It is not known if these strains acquire multiple resistant genes from HA-MRSA or if they increase bacterial fitness and survival despite the antibiotic resistance. Taking into account that their extracellular proteome seems to be differently involved, we think that this epidemiological change is not soothing for future dental epidemiology. In fact, from a 10-year retrospective analysis of laboratory data, obtained from oral and perioral clinical specimens, most of the MRSA isolates were epidemic MRSA-15 (EMRSA-15) or EMRSA-16 lineage, known to cause both very dangerous HA-MRSA infections [97]. No MRSA isolates belonging to community-acquired recognized lineages were identified. An alarming genetic similarity has been shown between seven MRSAs isolated in dental clinic and the EMRSA-15 clone [102]. In addition, *S. aureus*, MSSA, and EMRSA-15 harbored differently on dentures of in- and outpatients [119].

5.2 *Enterococcus faecalis*

It is well known that antibiotic administration causes intestinal overgrowth of *Enterococci* and their translocation across a histologically normal intestinal epithelium; then, they can reach and avidly bind other soft tissues and endocardial tissue matrix components, causing infections, abscess, and endocarditis. There are some

reasons to consider *Enterococci* important for our topic. *E. faecalis* occurs in transient opportunistic infections involving the oral cavity and has been found in common dental diseases (i.e. caries, endodontic infections, periodontitis) and peri-implant infective disease, and its strains are peculiar in comparison to food ones [120]. Recently, public health officials reported an incidence rate of enterococcal endocarditis among the total patient population at the oral surgery practice, more than 200 times the expected rate among general population [11].

In addition, *E. faecalis* is so invasive that it is used to test dental materials (composite fillings, endodontic sealers, etc.) and the connection between DI and the abutment [121]. Since it is highly adhesive, has many virulence factors (resistance to extreme conditions (oxygen tension, pH, salts), collagen-binding proteins, gelatinase E, surface proteins), and the ability to form biofilm, *E. faecalis* can reside widely in and around tooth root canals, in the surrounding bone trabeculae, and in heavily infected subgingival sites [122, 123]. It is known that *E. faecalis* resistance to antibiotics has been increasing over time. Then, the oral cavity can constitute a reservoir for virulent E. faecalis strains possessing antibiotic resistance traits, able to transfer vanA resistance genes to MRSA [102] and with biofilm formation capabilities. The latter facilitates the exchange of genetic material (via horizontal gene transfer) important for resistance acquisition [120]. Tetracycline, erythromycin, clindamycin, and metronidazole revealed poor levels of *in vitro* activity against human subgingival *E. faecalis* clinical isolates [122].

Nowadays, Enterobacteriaceae and some resistant strains are present in oral cavity of dental patients, and recently, the transmission in dental practice has been proven [11, 120–124]. For dentistry of the future, whole-genome sequencing seems promising to study *Enterobacteriaceae* antimicrobial resistance based on genotype alone [125] and the role in dental implant-associated infections.

6. Surgical infection prevention in dentistry: from gold standard to reality

It is well known that the best choices for dental and implant surgery are a specialized and well-trained dental staff (surgeon, clean nurse, second nurse, anesthetist, etc.) and a specific designed surgical room with proper isolation, clean air system ventilation, instruments for automatic surface decontamination and ISO standards (UNI EN ISO 14644-ISO 5) that allow a very low environmental contamination, and proper antiseptic procedures (including hand washing, wearing, safe instruments passages). Unfortunately, this setting up is used in the case of maxillofacial surgery, and it is commonly present and economically sustainable in hospital surgical dental department. In ambulatory dental offices, there is no isolation and a full separation of the environments used for general dentistry and those used for implant surgery or dental extractions. Only rarely is present a clean air ventilation system according to ISO standards. This difference is very important since in general dental practices the cross-infection is widespread, and the infection prevention is more difficult or less controllable (i.e. absence of the second nurse, environmental contamination) compared to hospital surgical rooms. There are few controls legislated over the operating environment in ambulatory and private dental offices.

Bearing in mind the higher risk of contamination of ambulatory surgical areas, above all during long surgeries (sinus lift, several implant placing, guided bone regeneration (GBR)) and in medically compromised patients, we cannot exclude that a part of implant failures is the result of a chain of personnel latent errors, including some improper antiseptic measures (not surgical hand hygiene, unsterile

gloves, improper use of mask, contamination of operating surface or room air, unsterile barrier covering, lack of surgical guide disinfection and mouth rinses, suture contamination by perioral skin bacteria, among others), as far as untrained professional practice [17, 41, 42, 44, 126].

Maintaining sterile conditions during the surgical procedure is of utmost importance. Saliva, perioral skin, unsterile instruments, contaminated gloves, operating room air, or air expired by the patient, all interfere in the surgical procedure leading to contamination of the implant site [43, 45–47]. It has been reported that the prevalence rate of MRSA was the highest in samples from dental surgery compared to other dental environments [102]. MRSA's involvement in surgical infections is in line with the estimated infective dose, which is very low (4 CFU), and surface contamination (<10 CFU/cm^2) [127, 128]. In ambulatory surgical centers, the main infection control lapses identified were hand hygiene and use of PPE, injection safety and medication handling, equipment reprocessing, and environmental cleaning [41, 42, 129].

The majority of DIs are predominantly placed in general dental practice under local anesthesia. Concerning local anesthesia, hand contact is the main source of the wide contamination reported on anesthetic syringes and anesthetic tubes used in dentistry [130]. Then, DHCP has to follow scrupulously key recommendations for safe injection reported in CDC guidelines [6]. Taking into account the recent outbreaks, the violations seem very hazardous in dentistry [8, 11]. In addition, it is absolutely forbidden and highly risky in the reuse of whatsoever single use sterile medical devices (i.e. irrigation sets) and the use of the water from DUWLs during implant and piezoelectric surgery, etc. [6]. The use of sterile devices and instruments is a need during surgical cares, but even after reconditioning, the contamination of surgical dental instruments and drills is significant even in hospital settings [131–134]. Many other specific failures concerning dental instrument reconditioning will be discussed in Part 2. The importance of hand hygiene, sterile gloves, mask, and eye protection during surgery is well known. Violations are frequent and often surgical videos in dentistry show the surgical mask *under the nose,* that is risky taking into account MRSA nose colonization in dentists and dental nurses. We underline that it is a hazard to touch the barrier membranes during GBR with gloved hands: this is a frequent slip observed in untrained surgeons.

6.1 Infections associated to craniofacial skeleton

The most relevant infections are lateral and apical periodontitis, osteomyelitis, peri-implantitis, and their complications, such as facial cellulitis and other infections involving deep spaces of face and neck [135]. Microbiota associated with infections of the craniofacial skeleton, particularly maxilla and mandible, are polymicrobial in nature and a mix of aerobic-anaerobic genera. In head and neck space odontogenic infections, the most common bacteria isolated were Gram-positive cocci (*Viridans streptococci, Prevotella, Staphylococci, and Peptostreptococcus*), and discordant data have been reported on antibiotic resistance of *Viridans streptococci,* while very few isolates of *Staphylococcus* are now susceptible to penicillin [136, 137].

Taking into account the increasing life expectancy, it is important to underline that older patients, even without systemic diseases, are more prone to development of oral pathology infections because of often lower immunological response [138]. Concerning systemic and local odontogenic infection complications requiring hospital care, an analysis showed that medically compromised patients appear more susceptible to systemic rather than local infection complications with a need for significantly longer hospital stay and with an increased risk for fatal complications [139].

The main causative agents of maxillofacial inflammatory diseases are *S. aureus*, *S. epidermidis*, *Streptococcus* spp., *Escherichia coli*, and *Proteus* spp. [85]. Concerning the risk of maxillofacial surgeries, 4% of their patients showed odontogenic infections, and about 2–20% required intensive medical therapy after surgery [140, 141]. These compliances are expected to worse taking into account the current oral carriage of *S. aureus* and MRSA (**Table 1**) and the presence of epidemic MRSA-15 (EMRSA-15) or EMRSA-16 lineage in dental settings.

Results have been conflicting concerning the occurrence of bacteremia after dental procedures; antimicrobial prophylaxis before an invasive dental procedure does not prevent bacteremia, although it can decrease both its magnitude and its persistence [142]. Delayed-onset infections (DOI) after mandibular third molar extractions are rare complications and usually occur about 30 days after the extraction, but they may also develop much later on [143]. The bacteria identified in DOI are *Fusobacterium, Prevotella, Bacteroides,* and *Peptostreptococcus.* A recent review reported in detail several oral and maxillofacial fungal infections, including mucormycosis, candidiasis, aspergillosis, blastomycosis, histoplasmosis, cryptococcosis, and coccidioidomycosis [144].

6.2 Infective agents in dental implantology

In general, dental implant procedures are considered clean-contaminated surgeries (graded as class II surgical procedures), since micro-organisms living in the oral mucosa and in saliva contaminate the surgical wound facilitating the infection, with local infection rates of 10–15% and an incidence of infection to 1% or less by the use of both prophylactic antibiotics and proper surgical technique [71]. Despite the statements reported between 1980 and 1990, even in the case of the use of prophylactic antibiotics, the reported prevalence of postoperative infection after implant installation ranges from 0 up to 11.5% and the prevalence of peri-implantitis varied from 4.2 to 47% of all implants [21, 56, 69, 71, 84, 114, 145–149]. These data are higher than the annual infection rate for cardiovascular implants and orthopedic implants, that is, 7.4 and 4.3% respectively, in USA hospital settings. Unfortunately, data are not available on the concurrent nasal/throat colonization of MRSA as possible patient-implant related factors and DI failure.

Clinical recommendations for avoiding and managing surgical complications associated with implant dentistry have been recently published [150, 151]. However, despite careful planning, infection is one of the early and late implant complications and iatrogenic actions are regarded as accidents during surgical procedures, complications, or failures caused by a deficient praxis of the professional. Infection is the most common explanation for complications such as swelling, suppuration, fistulas, and early/late mucosal dehiscence that may point to implant failure.

Many papers have reported improvements (mainly on the topography and surface features; antimicrobial dental implant functionalization strategies) of DIs and surgery techniques to get better osteointegration and to reduce the infective complications and then to improve long-term success (longevity and function of implants and uploaded prosthesis) [27–30, 32].

Peri-implantitis is a nonspecific, polymicrobial, and heterogeneous diseases of endogenous (caused by commensal oral strains) and iatrogenic nature, with an increased level of pathogenic bacteria from the orange and red complexes and towards a flora with a greater proportion of Gram-negative, motile, anaerobic bacteria [29, 152]. Compared to periodontal disease, the microbial biofilm harbored in peri-implant infective diseases is generally changeable and composed of opportunistic and Gram-negative species. Implant failure can occur at any time during the implant treatment by bacterial infection, but early healing period is quite important due to impaired wound healing.

These microorganisms have been found differently associated to implant infections: *Porphyromonas gingivalis; endodontalis* and spp.*; Tannerella forsythia and socransky; Prevotella nigrescens, oris,* and *intermedia; Fusobacterium* spp. *and nucleatum; Synergistetes* spp. *HO T—360; Pseudoramibacter alactolyticus; Eubacterium* spp.; *Veillonella* spp.*; Enterobacteriaceae; Candida* spp.*; Filifactor alocis; Dialister invisus; Mitsuokella* spp. *HOT 131; Peptococcus* spp. *HO T-168; Clostridiales [F-1] [G-1]* spp. *HO T-093; Catonella morbid; Chloroflexi* spp.*; Tenericutes* spp.*; Aggregatibacter actinomycetemcomitans; Staphylococcus aureus, anaerobius,* and *intermedius; Streptococcus mitis; spirochete including Treponema denticola,* with some differences associated to the type of DI and bacterial infiltration in the internal screw threads of implants [29, 153–155]. Moreover, implants with a peri-implant lesion had a higher frequency of superinfecting bacteria, mainly *Klebsiella pneumoniae* and *Burkholderia cepacia*, which are considered environmental and multidrug-resistant bacteria. Significantly higher bacterial counts (*Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Prevotella intermedia, and Fusobacterium nucleatum*) were found for periodontal pathogenic bacteria within the implant-abutment interface of implants in patients with peri-implantitis compared to those implants surrounded by healthy peri-implant tissues [156]. Using next-generation sequencing methods, recent results indicate that peri-implantitis and periodontitis are both polymicrobial infections with different causative pathogens, and the severity of the peri-implantitis was species-associated, including with *Eubacterium minutum* and an uncultured *Treponema* sp. [157, 158]. Opportunistic microorganisms (enteric rods and *S. aureus*) were found differently in peri-implantitis sites [21, 145].

We underline that some of them (*Enterobacteriaceae, Candida, Staphylococcus, and Streptococcus*) have been indicated as prioritized bacteria in CDC recommendation [18]. Some authors reported that antibiotics do not seem to reduce the incidence of postoperative infections and 2/3 of the infected implants failed before prosthetic loading [21, 146–149]. The majority of bacterial pathogens isolated from peri-implantitis were resistant in vitro to one or more of the tested antibiotics (clindamycin, amoxicillin, doxycycline, or metronidazol) [21].

Nevertheless, microbial investigations seem not contributory to clinician decisions or to be easily applicable nowadays in private practice; the standard procedures (probing, bleeding on probing, probing depth, radiographic assessment, implant mobility) and the visual evaluation of the hyperplastic soft tissues, color changes of the marginal peri-implant tissues, and suppuration are widely used to evaluate the consequences of implant-associated complications [158].

6.2.1 Why does the debridement in dentistry?

Here, we think important to underline some cellular events in relation to implant failures and surgical infections in dentistry. Osseointegration is completed within 3–6 months after implant placement into the dental alveolus, and infection may develop in the early operative period (early infection) or after the process of implant integration (late infection).

At the cellular level, implant-associated infections are the result of two critical phases in the first 6 h post implantation; firstly, the bacterial adhesion to a biomaterial surface by weak and unspecific forces within 1–2 h after implantation, and approximately 2–3 h later, a stronger adhesion with the formation of microcolonies and biofilm, which precedes clinical infection [63]. It is important that *Staphylococcus* species, isolated in dental settings, show high affinity to titanium and good biofilm production [102, 159], which are concurrent detrimental factors for osteogenesis [160, 161]. In addition, during the stationary phase, at least 1% of bacterial cells in biofilms become tolerant to antibiotics [162]. Moreover, the extracellular matrix should provide a

stable physical environment for cell to-cell contact, which allows the dissemination of antibiotic resistance by horizontal gene transfer among *S. aureus* [163].

In is well known that smoking is associated with DI failures [159] and that some infective agents (i.e. *Porphyromonas gingivalis*, SA, etc.) showed increased colonization in smokers. Cigarette smoking induces Staphylococcal biofilm formation in an oxidant-dependent manner and enhancement of fibronectin, an important extracellular matrix protein, binding in *S. aureus* [164]. This is relevant for adherence, invasion, and colonization since Staphylococci, in particular *S. aureus*, are the main causes of bone infections [165]. In addition, by molecular mechanisms, *Staphylococci* are able to invade *in vivo* host bone cells (osteoblasts and osteocytes), endothelial cells, and the canaliculi of live cortical bone leading to biofilm formation in osteocyte lacunae [166]. *Staphylococci,* as facultative intracellular pathogens, are shielded from immune response and antibiotics and are expected to induce a highly programmed and regulated cell death of osteogenic cells and then to impair bone formation. *E. faecalis* too is capable of surviving in a vegetative state in healed bone and of reactivation upon DI placement [22].

Then, it is not surprising that a nightmare and a difficult problem are to eradicate implant infections in present dental practice [149]. For the success of the DI surgery, it seems important a careful debridement of the alveolus from infective agents, frequently drug resistants, above all in the case of immediate DI loading after dental extraction and to defer DI placement after a dental extraction [27, 167].

6.3 Focus on orthodontia-associated surgery

Infections complications in orthognathic surgery are lower only to those caused by nerve injury [168]. The incidence of surgical site infections was limited to 1% of patients after bimaxillary orthognathic, osseous genioplasty, and intranasal surgery and under antibiotic treatment [162]. No attention is given to ARIAs in orthodontia and orthognathic surgery. To date, there is no gold standard for the treatment of postoperative infections in orthodontic surgery and the use of prophylactic antibiotics before some orthodontic procedures (orthodontic band placement, separator placement, or screw insertion) in patients with a medical history that reveals the presence of diseases affecting the host defense system (aging, patient on corticosteroids or bisphosphonates or anticoagulants, diabetes mellitus, HIV/AIDS) since they are at high risk of developing oral infection [37, 169]. Endocarditic prophylaxis is indicated only during the initial placement of orthodontic bands (not brackets).

We previously reviewed the problems related to task-specific evidence-based guidelines for cross-infection control when placing different temporary orthodontic anchorage devices [37]. Infection occurred in 17.3% of the installed miniplates and was caused by predominantly anaerobic, mainly Gram-negative bacteria and associated to immune aging [37, 170, 171]. The failure rate of mini-implants is about threefold to fivefold higher than that of dental implants and mini-plates; nevertheless, the mechanism that leads to mobility and then to their clinical failure is still unknown and more tricky to understand [172]. Recently, interest is arising on the use of antibiotics/antiseptics for some potential beneficial effects on tooth stability after orthodontic treatment, but the advantages should be very carefully balanced in accordance with the risk of antibiotic resistance [173].

7. Conclusion

Human infectious diseases will be never-ending [174]. After limitation of dental benefits, there was an increase in the volume and severity of odontogenic infections,

surgical cares increased 100%, and the related healthcare cost skyrockets [175]. The reported data show that opportunistic species and/or ARIA infections are nearby and expected to increase in dental setting [21–26, 29, 81, 82, 85, 91–99, 101–105, 109–114, 120–124, 136–141, 145–149, 153–155, 159, 160, 165] due to the overuse of antibiotics in dentistry and the limited awareness on infection prevention guidelines and the lapses and errors during infection prevention [176]. Moreover, it is considered alarming the genetic connection or similarity between MRSAs isolated in dental clinics and on dentures and the EMRSA-15 or EMRSA-16 clone [97, 102, 119]. In addition, Enterobacteriaceae and some resistant strains are present in oral cavity of dental patients, and recently, the transmission in dental practice has been proven [11, 120–124]. The incidence rate of enterococcal endocarditis among the total patient population at the oral surgery practice has been reported to be more than 200 times the expected rate among general population [11].

Then, dental teams have to face occupational and clinical hazards due to ARIA infections in dental facilities. In the absence of or limited new effective antibiotic discovery, the sustainable use of antibiotics is essential but have delayed significant effects [177] based on many collective actions (people information, professional dental-care providers, policy-maker and regulators, industry stakeholders). On the contrary, the prevention of cross infection by adopting guidelines is easily applicable and has had early significant effects on infection prevention and cost-saving [178, 179]. Moreover, it is basic to safeguard dental team reputation, insurance coverings, and reimbursements [8–11, 33–42, 176] and to limit the nightmares to get rid of current dental implant infections [149].

Conflict of interest

L.B. had a service agreement with KerrHawe and is a consultant for Dental Trey Il Blog (http://blog.dentaltrey.it/), neither of which gave any input or financial support to the writing of this article. There are no other conflicts of interest to report.

Abbreviations

AE	adverse event
ARIA	antibiotic-resistant infectious agents
CAGR	compound annual growth rate
CA-MRSA	community-acquired MRSA
CDC	Centers for Disease Control and Prevention
CCSs	clinical contact surfaces
cna	collagen
DD	dental device
DHCP	dental healthcare personnel
DI	dental implant
DOI	delayed-onset infections
DUWL	dental unit water line
eHOMD	expanded human oral microbiome database
EMRSA	epidemic MRSA
EPS	extracellular polysaccharides
FAE	fatal adverse event
fnb	fibronectin
GBR	guided bone regeneration
HA	hospital-acquired

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HA-MRSA	hospital-acquired MRSA
HCW	healthcare workers
HPC	heterotrophic plate count
ica	*i*nter*c*ellular *a*dhesion
HSV	herpes simplex virus
IFU	instruction for use
MAUDE	manufacturer and user facility device experience database
MRSA	methicillin-resistant *Staphylococcus aureus*
PCR	polymerase chain reaction
VRE	vancomycin-resistant *Enterococcus*

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