Special Issue Review Article

Antibacterial dental restorative materials: A review

LIANG CHEN, PHD, **BYOUNG IN SUH**, PHD & **JIE YANG**, PHD

ABSTRACT: Purpose: To provide updated summary information about antibacterial dental materials, primarily covering the literature from 2012 through 2017. **Methods:** A key-worded search was conducted of peer-reviewed literature (Titles/Abstracts) indexed by PubMed databases, constrained to "English" and "dental" publications between the years 2012 and 2017. Key words applied to the search included: antimicrobial, antibacterial, primer, bonding agent, adhesive, cement, composite, liner, sealant, etchant, and core-build-up. Titles and abstracts of the articles returned by the search were reviewed and evaluated for appropriateness for inclusion in this review. **Results:** A variety of antibacterial agents have been incorporated into experimental and commercial dental restorative materials to provide antibacterial activity in dental applications. No new antibacterial compounds were introduced in this review period (2012-2017), since the last review of period of 1980-2012. Antibacterial agents include leachable compounds (e.g. benzalkonium chloride, chlorhexidine), polymerizable monomers (e.g. quaternary ammonium methacrylates), and filler particles (e.g. silver nanoparticle). During the 2012-2017 review period, many antibacterial agents were tested in experimental formulations, but only four agents (benzalkonium chloride, chlorhexidine, glutaraldehyde, and MDPB) were used in commercial products. (*Am J Dent* 2018;31(Sp Is B):6B-12B).

CLINICAL SIGNIFICANCE: Leachable antibacterial agents are the most frequently used type of antibacterial dental materials, but their efficacy may be short-lived due to their characteristic burst effect. Solid filler particles appear to be effective antibacterial agents, especially given their ability to reduce biofilm formation, but the color stability of their component metal particles is unfavorable for use in a commercial product. Polymerizable antibacterial agents (MDPB) are theoretically a good choice of material because they are very effective at killing any residual bacteria in a cavity preparation prior to polymerization, however, apart from their proven effect on reduction of biofilm formation, their long-term clinical performance is still questionable.

✉: Dr. Liang Chen, Department of Research and Development, Bisco Inc., 1100 W. Irving Park Road, Schaumburg, IL 60193, USA. E-✉: lchen@bisco.com

Introduction

For both patients and dentists, longevity is one of the most important aspects of dental restorations. In the United States, 50-70% of all dental restorations placed every year are replacements of failed restorations.[1] The most common reason for restoration failure is secondary caries,[2] which are mainly caused by oral bacteria.[3] In recent years, numerous research studies have been conducted with the common goal of developing antibacterial dental restorative materials to be used to eradicate the cause of dental caries.[4] Two comprehensive reviews on antibacterial dental materials were published in the past two decades. The first such review was published in 2003 and focused on antibacterial features and their benefits in dental bonding agents and resin composites.[4] The second review article covered the literature from 1980 to 2012, and focused on the antibacterial effects of dental composites, cement, primers, and adhesives.[5] This review article will provide updated information about antibacterial dental materials, primarily covering the literature from 2012 through 2017. The materials discussed in the review will include those that have both direct contact and no direct contact with tooth structures.

Material and Methods

A search of peer-reviewed literature (Titles/Abstracts) indexed by PubMed databases was conducted and limited to the "English" and "dental" publications between the years 2012 and 2017. Key words used included: antimicrobial, antibacterial, primer, bonding agent, adhesive, cement, composite, liner, sealant, etchant, and core-build-up. Titles and abstracts of articles returned by the search were evaluated for relevance to this review. Papers that were not directly relevant to antibacterial dental restorative materials were excluded.

Table 1. Antibacterial agents used in commercial and experimental dental materials.

Materials	Antibacterial agents used
Cleansers, etchants & bonding agents	Benzalkonium chloride,* chitosan, chlorhexidine,* sodium hypochlorite (NaOCl), urushiol, and titanium tetrafluoride (TiF_4), glutaraldehyde,* epigallocatechin-3-gallate, MDPB*, benzotriazol-hydroxyphenyl-ethylmethacrylate, dimethylamino-hexadecyl methacrylate, silver, copper iodide.
Cements	Cetrimide, cetylpyridinium chloride, chlorhexidine, benzalkonium chloride, epigallocatechin-3-gallate, propolis
Resin composites	Chlorhexidine, carolacton, octenidine dihydrochloride, MDPB, dimethylaminohexadecyl methacrylate, bioactive glass (BAG), silver, zinc oxide

*Antibacterial agent has been used in commercial dental materials.

Results

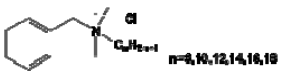
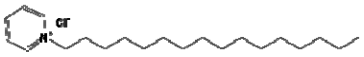
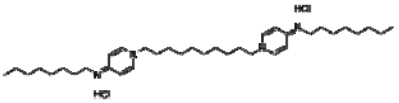
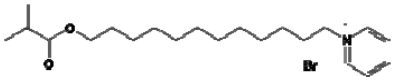
The literature describes a variety of antibacterial agents that have been incorporated into experimental and commercial dental restorative materials to provide antibacterial activity (Table 1).

Discussion

Antibacterial agents

An antibacterial agent is a chemical that interferes with the growth and reproduction of bacteria, thereby eliminating the

Table 2. Chemical structures of representative antibacterial agents.

Type of antibacterial agent	Name and chemical structure
Leachable agents	 Benzalkonium chloride (BAC)
	 Chlorhexidine (CHX)
	 Cetylpyridinium chloride
	 Octenidine dihydrochloride
Polymerizable monomers	 12-methacryloyloxydodecypyridinium bromide (MDPB)
Filler particles	Nano-silver (Ag); copper iodide (CuI); zinc oxide (ZnO)

bacteria's harmful effects. To improve the long-term outcome of dental restorations, various antibacterial agents have been added to experimental and commercial dental materials (Table 1). The antibacterial properties of these agents and their effects on physical strength and long-term performance of dental restorations have been investigated. Three types of antibacterial agents have been used most commonly in dental materials, including leachable agents, polymerizable agents that can copolymerize with the resin matrix and thus not leach out, and fillers that normally are not soluble in water (Table 2).

Leachable agents typically are water-soluble and therefore can be released into the local area of a restoration under oral conditions. The most frequently used leachable antibacterial agents in dental materials are benzalkonium chloride (BAC) and chlorhexidine.[4] BAC is a positively-charged quaternary ammonium compound (QAC) described by the chemical formula NR_4^+, where R can be different alkyl groups. BAC is a mixture of alkylbenzyl-dimethylammonium chlorides with alkyl carbon chains of various lengths (carbon spacer n = 8, 10, 12, 14, 16, 18). The antibacterial activity of BAC results from its amphiphilicity as it bears both hydrophobic (long alkyl carbon chain) and hydrophilic (cationic ammonium group) regions.[6] BAC's hydrophilic cationic region destabilizes the pathogen's surface by interacting with negatively charged components, which is followed by penetration of the hydrophobic long alky group into the bacterial hydrophobic bilayer leading to cell leakage and lysis. Like BAC, chlorhexidine also is a broad spectrum antibacterial agent, effective against both Gram-negative and Gram-positive microbes. However, some concerns surround the carcinogenic impurity 4-chloroaniline that is present in chlorhexidine. Octenidine dihydrochloride, free of 4-chloroaniline, is used as a substitute for chlorhexidine. Octenidine dihydrochloride is a cationic surfactant derived from pyridine, and normally is more effective than chlorhexidine.

One of the disadvantages of leachable agents is their rapid initial release of antibacterial agents (burst effect), which is accompanied by a dramatic decrease in antimicrobial activity over a short period of time. Polymerizable antibacterial agents, on the other hand, are immobilized in the dental resin matrix by copolymerization with dental resin monomers, which provides antibacterial effects without the release of antibacterial components and offers long-lasting antibacterial protection.[4] A typical polymerizable antibacterial agent consists of a polymerizable group, an antibacterial functional group, and an alkyl chain spacer between them. The polymerizable group is normally a (meth)acrylate which is compatible with and can copolymerize with most of the dental resin monomers in current use. The antibacterial functional groups of polymerizable antibacterial agents normally contain cationic groups such as quaternary ammonium, pyridinium or phosphonium. The counter-anion of these cationic groups and the spacer length of the associated alkyl chain may play an important role in antibacterial activity.[7]

Antibacterial filler particles are normally metal, metal salts or metal oxide. These are usually not water soluble, but a trace amount of metal ions may be released, creating antibacterial effects.[4] Silver has been used as a broad-spectrum antibacterial agent for centuries,[8] and is still one of the most frequently used antibacterial fillers for dental materials. Silver interacts with thiol group compounds found in the bacterial cell wall, resulting in the inhibition of the respiration process.[8]

Bonding agents

Dental bonding agents or adhesives are resin materials used to bond dental restorations (resin composites, dental ceramics, etc.) to tooth structures. Dental bonding agents have direct contact with teeth, but are not exposed to the oral medium or to saliva. As recurrent dental caries at resin-teeth interfaces is the most common reason for restoration failure, investigation of whether application of an antibacterial dental bonding agent would help reduce recurrent caries and thereby improve longevity of dental restorations is highly relevant. Dental bonding agents normally contain volatile solvents, methacrylate and dimethacrylate monomers, and acidic monomers. Some bonding agents also contain fillers to enhance physical strength of the adhesive, reduce sensitivity, and/or increase radiopacity. Incorporated volatile solvents include water, acetone, and/or ethanol, which not only make adhesives thinner, but also help adhesives penetrate into hydrophilic dentin structures to improve mechanical bond strength. Methacrylates and dimethacrylates include BisGMA, UDMA, TEGDMA and HEMA, which are used to improve the physical strength of adhesives. Acidic monomers such as phosphate methacrylate and carboxylate methacrylates are used to promote adhesion between teeth and restorations. Due to the presence of acidic monomers, dental adhesives are normally acidic with pH ranging from 1-5. Although regular dental adhesives without antibacterial agent additives showed almost no antibacterial effect,[4,9] dental adhesives with low pH values produced antibacterial effects against some bacteria, such as *S. mutans*, but not against acid-tolerant bacteria such as *Lactobacilli*.[10,11] Notably, the high acidity (low pH) of adhesives activates matrix metalloproteinases (MMPs), which cause adhesive bond degradation.[6]

Two different methods are used to achieve antibacterial effects via dental bonding. One method involves pre-treatment

Table 3. Methods used to achieve antibacterial dental bonding agents.

Method	Antibacterial agents used
Pre-treatment of teeth with antibacterial agents	Benzalkonium chloride, chlorhexidine, sodium hypochlorite, urushiol, and titanium tetrafluoride
Incorporation of leachable antibacterial agents into dental adhesives	Benzalkonium chloride, glutaraldehyde, chlorhexidine, epigallocatechin-3-gallate
Incorporation of polymerizable antibacterial agents into dental adhesives	12-methacryloyloxydodecypyridinium bromide (MDPB), benzotriazol-hydroxyphenyl-ethylmethacrylate, dimethylaminohexadecyl methacrylate
Incorporation of antibacterial filler particles into dental adhesives	Nano-silver, copper iodide

of tooth structures using antibacterial etchants or disinfectants and the other method is to incorporate antibacterial agents (leachable agent, polymerizable agent, or filler particle) into dental adhesives (Table 3).

BAC and chlorhexidine are the most frequently used antibacterial agents for pre-treatment of teeth. BAC is stable in acidic media and has been added into commercial phosphoric acid etchants to a final concentration of 1%. Examples of such products include EtCH-37[a] w/BAC or UNI-ETCH[a] w/BAC, which exhibited zone inhibitions of bacteria, without compromising bond strength. In addition, BAC can also inhibit MMPs, thus preserving the dentin-resin bonded interface.[6] Unlike BAC, chlorhexidine is not stable in phosphoric acid and cannot be added to etchants. Chlorhexidine digluconate (2%) has been added to commercial dental disinfectants, such as Cavity Cleanser.[a] Both in vivo and in vitro studies demonstrated that Cavity Cleanser reduced microorganisms in contaminated dentin.[12] Pre-treatment of dentin with chlorhexidine maintained resin-dentin bond strength for up to 14 months, while a control group without chlorhexidine pre-treatment experienced significant bond strength reduction in vivo;[13] the observed enhanced stability was mainly due to inhibition of the degradation of hybrid layers by chlorhexidine.[14] Some other agents added to experimental products, including 6% sodium hypochlorite (NaOCl), 0.01% urushiol, and 2.5% titanium tetrafluoride (TiF_4), also showed antibacterial capability in pre-treatment of dentin, but studies[15,16] suggested that higher bond strength was obtained when the disinfectants were rinsed away.

Leachable agents have been incorporated into both comercial and experimental dental adhesives. For instance, glutaraldehyde was incorporated into Gluma 2 Bond[b] and chlorhexidine was incorporated into Peak Universal Bond.[c] André et al[17] demonstrated that Gluma 2 Bond required at least 24 hours for killing microorganisms, and that Peak Universal Bond killed only strict anaerobic microorganisms after 24 hours. Sabatini et al[18] added BAC into All-Bond Universal,[a] a universal dental adhesive, to create experimental adhesives with final BAC concentrations of 0.5%, 1%, and 2% (wt/ wt).[19] These BAC-containing adhesives delivered higher bond strength than did the control after 1-year storage in artificial saliva, probably because of their ability to inhibit MMPs.[19] Du et al[20] reported that an experimental dental adhesive containing 0.02% epigallocatechin-3-gallate (EGCG) exhibited inhibitory effect on the growth of *S. mutans*, and demonstrated higher bond strength than the control without EGCG after 6 months. Some concerns persist regarding the "burst effect" of leachable agents and more research is needed to investigate the long-term performance of antibacterial adhesives containing leachable agents.

In an attempt to overcome the disadvantage (burst effect) of leachable agents, polymerizable antibacterial agents have been incorporated into dental adhesives. Polymerizable agents are immobilized in the resin matrix system upon polymerization, presumably enabling long-lasting antibacterial effects.[4] One such polymerizable agent is 12-methacryloyloxydodecypyridinium bromide (MDPB), which has been incorporated into a commercial dental adhesive (5% MDPB in Clearfil Protect Bond[d] and used in clinical practice. One study[21] showed that Clearfil Protect Bond inhibited growth of *S. mutans* and *L. gasseri*. In a 14-day in situ study, Pinto et al[22] reported that Clearfil Protect Bond resulted in lower counts of total *Streptococci* as well as *S. mutans* and smaller lesion depths than did a non-MDPB containing adhesive for enamel and dentin restorations, but Clearfil Protect Bond did not prevent demineralization or bacteria growth.[22] In contrast, Vasconcelos et al[23] found no statistically significant difference between Clearfil Protect Bond and a non-antibacterial dental adhesive (All-Bond SE[a]) either in enamel demineralization or in dental biofilm formation, suggesting that Clearfil Protect Bond was unable to inhibit secondary caries in situ. Other studies[24,25] also showed that the performance of Clearfil Protect Bond was similar to that of other non-MDPB containing adhesives in terms of caries formation, and that it did not inhibit secondary caries in a simulated high caries challenge. Polymerizable antibacterial agents such as MDPB are designed to immobilize in the resin matrix, in hopes of producing long-lasting antibacterial effects. However, Clearfil Protect Bond exerted only a short-term antibacterial effect (for 7 days), and lost the antibacterial activity after storage in phosphate-buffered saline for 14 days,[26,27] in direct contrast to the expectation of long-lasting antibacterial effects of polymerizable agents. A possible explanation for this is that immobilization/polymerization of antibacterial agents reduces their antibacterial activity substantially, and that the observed short-term antibacterial effects were mainly a result of unpolymerized MDPB monomers (a resin typically experiences 70-80% polymerization conversion). The antibacterial effects disappeared after all unpolymerized MDPB monomers had leached out.[27]

Some other polymerizable antibacterial monomers have been evaluated in experimental dental adhesives. For instance, 5% 2-[3-(2H-benzotriazol-2-YL)-4-hydroxyphenyl] ethyl methacrylate in a dental adhesive showed higher antibacterial activity than did the negative control.[28] A new antibacterial monomer, dimethylaminohexadecyl methacrylate (carbon chain length 16) was synthesized and added (5%) into a dental adhesive. The experimental adhesive showed a great ability to reduce biofilm accumulation and to decrease lactic acid production without impairing bond strength.[29,30]

Some filler particles have been added to experimental dental adhesives to improve their antibacterial activity. One of the most frequently used antibacterial particles is nano-silver. Studies[31,32] have shown that the addition of 0.05% silver nanoparticle (particle size 2.7 nm) into dental adhesives significantly reduces biofilm viability, colony-forming unit

(CFU) counts, and lactic acid production, without compromising dentin bond strength. One of the biggest issues for silver particles is color stability.[4] Antibacterial fillers that demonstrate better color stability than silver also have been incorporated into experimental dental adhesives. For example, the addition of polyacrylic acid-modified copper iodide particles (1 mg/ml) into adhesives reduced Streptococcus mutans viable cell counts by 79-99% even after aging for 1 year in vitro and no significant differences in bond strength or cytotoxicity were detected between these experimental adhesives and their corresponding controls.[18] Chitosan has long been known for its antimicrobial activity and is also a promising additive in dental materials. A recent study reported that total-etch adhesive systems supplemented with chitosan (at concentrations of 0.2% and 0.5%) displayed similar inhibitory effects on *S. mutans* and *L. casei* as a commercial conventional 2-step adhesive system (Adper Single Bond 2®). The antimicrobial activity of chitosan may be derived from a combination of factors including pH, metal chelating capacity, and the positive charge of its gluco-samine groups interacting with the negative charge of the bacteria cell surface.[33,34]

Cements

Dental cements function in luting or adhesion of indirect restorations with tooth structures, and can be classified as four different types: (1) water-based acid-base cements, including glass ionomer cement (GIC), resin-modified glass ionomer cement (RM-GIC), and zinc phosphate cement; (2) oil-based acid-based cements, such as zinc oxide eugenol and non-eugenol zinc oxide; (3) self-adhesive resin cements; and (4) non-self-adhesive resin cements. The first three types of cements have direct contact with tooth structures whereas the 4th type has no direct contact with tooth structures and requires the application of separate primers and/or adhesives.

Among the above four types of cements, zinc oxide-based cements possess antibacterial properties without the addition of a separate antibacterial agent[35] whereas the third and fourth types of cements normally do not display antibacterial activities. GIC and RM-GIC release fluoride for a long period, but their antibacterial activity is usually low.[36,37] Additives have been included to enhance the antimicrobial activity of these cements, and the physical properties of the resulting cements have been studied. Propolis, a natural resinous substance produced by honeybees, improved antimicrobial effects of GIC but significantly decreased the compressive strength and increased solubility of the cement.[38] Conventional luting cements, such as zinc phosphate (ZP), zinc polycarboxylate (PC), and GIC, containing 5% chlorhexidine diacetate/ cetrimide demonstrated long-lasting antibacterial effects for up to 180 days despite reduced physical strength and increased solubility of the cements.[39] Similarly, the addition of a paste of chlorhexidine-hexametaphosphate into GIC exhibited a sustained release of chlorhexidine for at least 14 months, accompanied by compromised cement strength.[40] Addition of different antibacterial agents (1-2%), such as cetrimide, cetylpyridinium chloride, chlorhexidine and BAC, to conventional GIC also impaired the cement's microhardness during 90-day water storage.[41] Nonetheless, incorporation of a lower concentration (0.5%) of chlorhexidine seemed to produce an optimum favorable outcome as it increased antibacterial activity without adversely affecting physical-mechanical properties.[42] Therefore, using low concentrations of additives might be a promising approach for enhancing conventional cements with antibacterial activity. For example, 0.1% epigallocatechin-3-gallate in GIC increased not only its antibacterial activities, but also its flexural strength and surface hardness[43] and GIC supplemented with a quaternary ammonium monomer, DMADDM (dimethylaminododecyl methacrylate), even at the high concentrations of 1.1% and 2.2%, showed improved material performance and antibacterial properties.[44]

Unlike GIC, the physical strength of other types of cements seemed to be less sensitive to additives. For example, the incorporation of up to 4.5% doxycycline hyclate into RM-GIC or the addition of 7.5% chlorhexidine diacetate to provisional cements did not compromise their physical strength.[45,46]

Table 4. Methods used to produce antibacterial resin composite

Method	Antibacterial agents used
Incorporation of leachable antibacterial agents into composites	Chlorhexidine, carolacton, octenidine dihydrochloride
Incorporation of polymerizable antibacterial agents into composites	MDPB, dimethylaminohexadecyl methacrylate
Blending of antibacterial filler particles with existing composite fillers	Bioactive glass (BAG), silver, zinc oxide

Resin composites

Dental resin composites are used as restorative materials. Resin composites are normally placed on top of dental adhesives and usually are not in direct contact with caries or tooth structures. Some dental composites are used for enamel restorations and as such are exposed to the oral medium and to saliva. Resin composites are composed mainly of inert inorganic fillers and organic monomers. Unlike amalgam which has antibacterial activities by virtue of releasing a trace amount of metal ions, cured resin composites typically lack antibacterial activity, resulting in bacterial adherence and plaque accumulation on their surfaces.[4,47,48] The reason for the lack of antibacterial activity exhibited by dental resin composites is that the quantity of monomers and other components leached out from composites is much lower than the minimum concentration required for bacterial inhibition. The fillers used in composites are normally inert silica fillers with no antibacterial activity, as opposed to the metal-containing fillers described above. To produce an antibacterial resin composite, an antibacterial agent could be dissolved in the composite's resin monomers, or, if the antibacterial agent is not soluble in resin monomers, could be blended with filler particles (Table 4).

Many leachable antibacterial agents have been incorporated into experimental dental resin composites (Table 4). Chlorhexidine, one of the most frequently used antibacterial agents, was released faster in media of lower pH values due to its higher solubility at lower pH.[49] Release rate also may be influenced by hydrophilicity of resin. Composites with hydrophilic resin tended to release chlorhexidine faster as chlorhexidine-containing resin lost antibacterial activities after storage in water for 2 weeks.[50] To improve its long-term release, chlorhexidine has been encapsulated using mesoporous

silica nanoparticles, and composites containing encapsulated chlorhexidine showed controlled release of chlorhexidine over a long period of time.[51] Due to concerns surrounding the carcinogenic impurity 4-chloroaniline present in chlorhexidine, octenidine dihydrochloride has been considered as an alternative to chlorhexidine. Addition of 3 wt% of octenidine dihydrochloride into dental composites significantly reduced biofilm formation.[1] Furthermore, carolacton was found to be a more effective antibacterial agent than chlorhexidine and triclosan when incorporated into resin composites. A small amount of carolacton (0.002%,w/w) in experimental resin composite reduced biofilm viability by up to 64% and reduced CFUs by 98%, with no adverse effects on physical properties. The anti-biofilm activity of carolacton-containing composite was stable over a period of 42 days.[52]

Incorporation of a polymerizable antibacterial monomer into a dental composite is another way to produce antibacterial composites. After antibacterial monomers copolymerize with resin composites, the antibacterial agents are not expected to leach out from the composite matrix, presumably resulting in long-lasting antibacterial effects via inhibition of bacterial growth on the composite surface upon contact. Imazato et al[53] reported that MDPB-containing composites demonstrated significant antibacterial effects even after 90 days of immersion in water. Another antibacterial monomer, dimethylamino-hexadecyl methacrylate, also was incorporated into experimental dental composites and demonstrated good biofilm inhibition.[54] One of the disadvantages of immobilization of polymerizable agents is that these then can kill bacteria only upon contact. In addition, the immobilization of antibacterial agent limits their capacity for penetration into bacterial cell membranes, which may reduce antibacterial functionality.

Blending of antibacterial particles into composites is one more way to produce an antibacterial dental composite. Antibacterial particles include polymer nanoparticles, bioactive glass (BAG), and metal/metal oxide. Compared to leachable antibacterial agents, polymeric antibacterial particles have many advantages, including nonvolatility, chemically stability, long-term activity, and non-permeability through skin.[55,56] Incorporation of cross-linked quaternary ammonium polyethylenimine nanoparticles into dental resin composites induced antibacterial activity without affecting mechanical properties.[55,56] Bioactive glass (BAG) is known to possess antibacterial properties due to its alkalinity and incorporation of alkali-ion substituted calcium phosphate fillers into experimental dental composites which resulted in a reduction of the bacterial population by 25-70%.[57] Khvostenko et al[58] reported that incorporation of 15% BAG into composites reduced biofilm penetration into marginal gaps of simulated tooth restorations and had no adverse effects on the physical properties of the composite.[59] Addition of nano-silver particles (0.5-1%) to composite resin significantly reduced bacterial growth.[60] However, nano-silver increased monomer elution from composites[61] and silver has poor color stability due to oxidation. Addition of zinc oxide (0-5%) into composite significantly reduced bacterial growth without adversely affecting physical strength, but also significantly lowered depth of cure due to the opacity of zinc oxide.[62]

Antibacterial agents have been added to other experimental products, such as pit and fissure sealants, orthodontic materials, and core build-up materials. Some commercial varnish products that have short body contact duration also contain antibacterial agents. For instance, EC 40[f] contains 35% chlorhexidine, and Cervitec[g] and Cervitec Plus[g] contain 1% chlorhexidine plus 1% thymol. An in vitro study showed that EC40 killed 100% of all bacteria strains except for *E. faecalis* ATCC 29212 (98.78% kill). Cervitec and Cervitec Plus showed antimicrobial activity against all oral bacteria strains, but with lower efficacy (30-40% kill). EC40 completely inhibited the formation of biofilm, while Cervitec and Cervitec Plus achieved 76-92% of biofilm reduction.[63] Recent research[64] suggests that the development of secondary caries might be influenced by restorative materials. However, other factors such as patient and clinic-related factors also are very important determinants of secondary caries.

Conclusions

No new antibacterial compounds were introduced in the period 2012-2017, since the previous review period of 1980-2012. Antibacterial agents include leachable compounds (e.g. BAC and chlorhexidine), polymerizable monomers (e.g. quarternary ammonium methacrylates), and filler particles (e.g. silver nanoparticle). Many antibacterial agents have been tested in experimental formulations, but only four agents (BAC, chlorhexidine, glutaraldehyde, and MDPB) are used in commercial products currently. Leachable antibacterial agents are most frequently used despite their potential short-lived efficacy (a result of their characteristic burst effect). Solid filler particles appear to be effective antibacterial agents, especially in reducing biofilm formation, but the color stability of their component metal particles is unfavorable for use in a commercial product. Polymerizable antibacterial agents (MDPB) are theoretically a good choice of material because they are very effective at eliminating residual bacteria in a cavity preparation prior to polymerization, however, apart from their proven effect on reduction of biofilm formation, their long-term clinical performance is still unknown.

a. Bisco, Schaumburg, IL USA.
b. Heraeus Kulzer GmbH, Hanau, Germany.
c. Ultradent Products, South Jordan, UT, USA.
d. Kuraray, Kurashiki, Japan.
e. 3M ESPE, St. Paul, MN, USA.
f. Bio-Dent, Amsterdam, The Netherlands.
g. Ivoclar Vivadent, Schaan, Liechtenstein.

Disclosure statement: The authors are employees of Bisco Inc.

Dr. Chen is Chief Scientist and Director of R&D, Department of Research and Development, Dr. Suh is President and Dr. Yang is a Postdoctoral Researcher, Bisco Inc., Schaumburg, Illinois, USA.

References

1. Rupf S, Balkenhol M, Sahrhage TO, Baum A, Chromik JN, Ruppert K, Wissenbach DK, Maurer HH, Hannig M. Biofilm inhibition by an experimental dental resin composite containing octenidine dihydrochloride. *Dent Mater* 2012;28:974-984.
2. Featherstone JD. The continuum of dental caries – Evidence for a dynamic disease process. *J Dent Res* 2004;83(Sp Is C):C39-C42.
3. Sakaguchi RL. Review of the current status and challenges for dental posterior restorative composites: clinical, chemistry, and physical behavior considerations. *Dent Mater* 2005;21:3-6.
4. Imazato S. Antibacterial properties of resin composites and dentin bonding systems. *Dent Mater* 2003;19:449-457.
5. Chen L, Shen H, Suh BI. Antibacterial dental restorative materials: A state-of-the-art review. *Am J Dent* 2012;25:337-346.

6. Tezvergil-Mutluay A, Mutluay MM, Gu LS, Zhang K, Agee KA, Carvalho RM, Manso A, Carrilho M, Tay FR, Breschi L, Suh BI, Pashley DH. The anti-MMP activity of benzalkonium chloride. *J Dent* 2011;39:57-64.
7. Kenawy ER, Worley SD, Broughton R. The chemistry and applications of antimicrobial polymers: A state-of-the-art review. *Biomacromolecules* 2007;8:1359-1384.
8. Rai M, Yadav A, Gade A. Silver nanoparticles as a new generation of antimicrobials. *Biotech Adv* 2009;27:76-83.
9. Imazato S, Kuramoto A, Kaneko T, Ebisu S, Russell RR. Comparison of antibacterial activity of simplified adhesive systems. *Am J Dent* 2002;15:356-360.
10. Herrera M, Carrión P, Bravo M, Castillo A. Antibacterial activity of four dentin bonding systems. *Int J Antimicrob Agents* 2000;15:305-309.
11. Imazato S, Imai T, Ebisu S. Antibacterial activity of proprietary self-etching primers. *Am J Dent* 1998;11:106-108.
12. Borges FM, de Melo MA, Lima JP, Zanin IC, Rodrigues LK. Antimicrobial effect of chlorhexidine digluconate in dentin: In vitro and in situ study. *J Conserv Dent* 2012;15:22-26.
13. Carrilho MR, Geraldeli S, Tay F, de Goes MF, Carvalho RM, Tjäderhane L, Reis AF, Hebling J, Mazzoni A, Breschi L, Pashley DH. In vivo preservation of the hybrid layer by chlorhexidine. *J Dent Res* 2007;86:529-533.
14. Hebling J, Pashley DH, Tjäderhane L, Tay FR. Chlorhexidine arrests subclinical degradation of dentin hybrid layers in vivo. *J Dent Res* 2005;84:741-746.
15. Cha HS, Shin DH. Antibacterial capacity of cavity disinfectants against Streptococcus mutans and their effects on shear bond strength of a self-etch adhesive. *Dent Mater J* 2016;35:147-152.
16. Bridi EC, Amaral Flávia Lucisano Botelho, França Fabiana Mantovani Gomes, Turssi Cecilia Pedroso, Florio FM, Basting RT. In vitro effects of 2.5% titanium tetrafluoride on Streptococcus mutans and Lactobacillus casei in dentin followed by self-etching adhesive systems. *Eur J Prosthodont Restor Dent* 2015;23:179-186.
17. André CB, Gomes BP, Duque TM, Stipp RN, Chan DC, Ambrosano GM, Giannini M. Dentine bond strength and antimicrobial activity evaluation of adhesive systems. *J Dent* 2015;43:466-745.
18. Sabatini C, Mennito AS, Wolf BJ, Pashley DH, Renné WG. Incorporation of bactericidal poly-acrylic acid modified copper iodide particles into adhesive resins. *J Dent* 2015;43:546-555.
19. Sabatini C, Pashley DH. Aging of adhesive interfaces treated with benzalkonium chloride and benzalkonium methacrylate. *Eur J Oral Sci* 2015;123:102-107.
20. Du X, Huang X, Huang C, Wang Y, Zhang Y. Epigallocatechin-3-gallate (EGCG) enhances the therapeutic activity of a dental adhesive. *J Dent* 2012;40:485-492.
21. Jacobo C, Torrella F, Bravo-González LA, Ortiz AJ, Vicente A. In vitro study of the antibacterial properties and microbial colonization susceptibility of four self-etching adhesives used in orthodontics. *Eur J Orthod* 2014;36:200-206.
22. Pinto CF, Berger SB, Cavalli V, Da Cruz SE, Gonçalves RB, Ambrosano GM, Giannini M. In situ antimicrobial activity and inhibition of secondary caries of self-etching adhesives containing an antibacterial agent and/or fluoride. *Am J Dent* 2015;28:167-173.
23. Vasconcelos SM, Melo MA, Wenceslau JP, Zanin IC, Beltrao HC, Fernandes CA, Almeida PC, Rodrigues LK. In situ assessment of effects of the bromide- and fluoride-incorporating adhesive systems on biofilm and secondary caries. *J Contemp Dent Pract* 2014;15:142-148.
24. Lobo MM, Gonçalves RB, Pimenta LA, Bedran-Russo AK, Pereira PN. In vitro evaluation of caries inhibition promoted by self-etching adhesive systems containing antibacterial agents. *J Biomed Mater Res B Appl Biomater* 2005;75:122-127.
25. de Carvalho FG, Puppin-Rontani RM, Soares LE, Santo AM, Martin AA, Nociti-Junior FH. Mineral distribution and CLSM analysis of secondary caries inhibition by fluoride/MDPB-containing adhesive system after cariogenic challenges. *J Dent* 2009;37:307-314.
26. Hegde MN, Hegde P, Shetty V, Sampath PB. Assessment of antibacterial activity of self-etching dental adhesive systems: An in vitro study. *J Conserv Dent* 2008;11:150-153.
27. Feuerstein O, Matalon S, Slutzky H, Weiss EI. Antibacterial properties of self-etching dental adhesive systems. *J Am Dent Assoc* 2007; 138:349-354.
28. Centenaro CC, Rostirolla FV, Leitune VC, Parolo CF, Ogliari FA, Samuel SM, Collares FM. Influence of addition of 2-[3-(2H-benzotriazol-2-YL)- 4-hydroxyphenyl] ethyl methacrylate to an experimental adhesive system. *Acta Odontol Latinoam* 2015;28:72-78.
29. Zhang K, Wang S, Zhou X, Xu HH, Weir MD, Ge Y, Li M, Wang S, Li Y, Xu X, Zheng L, Cheng L. Effect of antibacterial dental adhesive on multispecies biofilms formation. *J Dent Res* 2015;94:622-629.
30. Li F, Weir MD, Xu HH. Effects of quaternary ammonium chain length on antibacterial bonding agents. *J Dent Res* 2013;92:932-938.
31. Cheng L, Zhang K, Melo MA, Weir MD, Zhou X, Xu HH. Anti-biofilm dentin primer with quaternary ammonium and silver nanoparticles. *J Dent Res* 2012;91:598-604.
32. Zhang K, Melo MA, Cheng L, Weir MD, Bai Y, Xu HH. Effect of quaternary ammonium and silver nanoparticle-containing adhesives on dentin bond strength and dental plaque microcosm biofilms. *Dent Mater* 2012;28:845-852.
33. Labato MF, Turssi CP, Amaral FL, França FM, Basting RT. Chitosan incorporated in a total-etch adhesive system: antimicrobial activity against Streptococcus mutans and Lactobacillus casei. *Gen Dent* 2017;65:62-66.
34. Elsaka S, Elnaghy A. Effect of addition of chitosan to self-etching primer: Antibacterial activity and push-out bond strength to radicular dentin. *J Biomed Res* 2012;26:288-294.
35. Tchaou WS, Turng BF, Minah GF, Coil JA. In vitro inhibition of bacteria from root canals of primary teeth by various dental materials. *Pediatr Dent* 1995;17:351-355.
36. Unosson E, Cai Y, Jiang X, Lööf J, Welch K, Engqvist H. Antibacterial properties of dental luting agents: Potential to hinder the development of secondary caries. *Int J Dent* 2012:529495.
37. van Dijken JW, Kalfas S, Litra V, Oliveby A. Fluoride and mutans streptococci levels in plaque on aged restorations of resin-modified glass ionomer cement, compomer and resin composite. *Caries Res* 1997;31:379-383.
38. Subramaniam P, Girish Babu KL, Neeraja G, Pillai S. Does addition of propolis to glass ionomer cement alter its physicomechanical properties? An in vitro study. *J Clin Pediatr Dent* 2017;41: 62-65.
39. Korkmaz FM, Tüzüner T, Baygin O, Buruk CK, Durkan R, Bagis B. Antibacterial activity, surface roughness, flexural strength, and solubility of conventional luting cements containing chlorhexidine diacetate/cetrimide mixtures. *J Prosthet Dent* 2013;110:107-115.
40. Bellis CA, Nobbs AH, O'Sullivan DJ, Holder JA, Barbour ME. Glass ionomer cements functionalised with a concentrated paste of chlorhexidine hexametaphosphate provides dose-dependent chlorhexidine release over at least 14 months. *J Dent* 2016;45:53-58.
41. Tüzüner T, Ulusu T. Effect of antibacterial agents on the surface hardness of a conventional glass-ionomer cement. *J Appl Oral Sci* 2012;20:45-49.
42. Marti LM, Mata Md, Ferraz-Santos B, Azevedo ER, Giro EM, Zuanon AC. Addition of chlorhexidine gluconate to a glass ionomer cement: A study on mechanical, physical and antibacterial properties. *Braz Dent J* 2014;25:33-37.
43. Hu J, Du X, Huang C, Fu D, Ouyang X, Wang Y. Antibacterial and physical properties of EGCG-containing glass ionomer cements. *J Dent* 2013;41:927-934.
44. Wang SP, Ge Y, Zhou XD, Xu HH, Weir MD, Zhang KK, Wang HH, Hannig M, Rupf S, Li Q, Cheng L. Effect of anti-biofilm glass-ionomer cement on Streptococcus mutans biofilms. *Int J Oral Sci* 2016;8:76-83.
45. Lewinstein I, Zenziper E, Block J, Kfir A. Incorporation of chlorhexidine diacetate in provisional cements: Antimicrobial activity against Streptococcus mutans and the effect on tensile strength in vitro. *Int Endod J* 2012; 45:1010-1017.
46. de Castilho AR, Duque C, Negrini Tde C, Sacono NT, de Paula AB, Sacramento PA, de Souza Costa CA, Spolidorio DM, Puppin-Rontani RM. Mechanical and biological characterization of resin-modified glass-ionomer cement containing doxycycline hyclate. *Arch Oral Biol* 2012;57:131-138.
47. Svanberg M, Mjor IA, Orstavik D. Mutans streptococci in plaque from margins of amalgam, composites, and glass-ionomer restorations. *J Dent Res* 1990;69:861-864.
48. Al Ghadban A, Al Shaarani F. Antibacterial properties of amalgam and composite resin materials used as cores under crowns. *Eur J Prosthodont Restor Dent* 2012;20:71-76.
49. Anusavice KJ, Zhang NZ, Shen C. Controlled release of chlorhexidine from UDMA-TEGDMA resin. *J Dent Res* 2006;85:950-954.
50. Hiraishi N, Yiu CK, King NM, Tay FR, Pashley DH. Chlorhexidine release and water sorption characteristics of chlorhexidine-incorporated hydrophobic/hydrophilic resins. *Dent Mater* 2008;24:1391-1399.
51. Zhang JF, Wu R, Fan Y, Liao S, Wang Y, Wen ZT, Xu X. Antibacterial dental composites with chlorhexidine and mesoporous silica. *J Dent Res* 2014;93:1283-1289.
52. Apel C, Barg A, Rheinberg A, Conrads G, Wagner-Döbler I. Dental composite materials containing carolacton inhibit biofilm growth of Streptococcus mutans. *Dent Mater* 2013;29:1188-1199.

53. Imazato S, Torii M, Tsuchitani Y, McCabe JF, Russell RR. Incorporation of bacterial inhibitor into resin composite. *J Dent Res* 1994;73:1437-1443.
54. Wu J, Zhou H, Weir MD, Melo MA, Levine ED, Xu HH. Effect of dimethylaminohexadecyl methacrylate mass fraction on fracture toughness and antibacterial properties of CaP nanocomposite. *J Dent* 2015;43:1539-1546.
55. Shvero DK, Zatlsman N, Hazan R, Weiss EI, Beyth N. Characterisation of the antibacterial effect of polyethyleneimine nanoparticles in relation to particle distribution in resin composite. *J Dent* 2015;43:287-294.
56. Beyth N, Yudovin-Farber I, Perez-Davidi M, Domb AJ, Weiss EI. Polyethyleneimine nanoparticles incorporated into resin composite cause cell death and trigger biofilm stress in vivo. *Proc Natl Acad Sci USA* 2010;107:22038-22043.
57. Herzlieb W, Köhler KM, Ewald A, Hofmann N, Gbureck U. Antimicrobial and physicochemical properties of experimental light curing composites with alkali-substituted calcium phosphate fillers. *Dent Mater* 2012;28:597-603.
58. Khvostenko D, Hilton TJ, Ferracane JL, Mitchell JC, Kruzic JJ. Bioactive glass fillers reduce bacterial penetration into marginal gaps for composite restorations. *Dent Mater* 2016;32:73-81.
59. Khvostenko D, Mitchell JC, Hilton TJ, Ferracane JL, Kruzic JJ. Mechanical performance of novel bioactive glass containing dental restorative composites. *Dent Mater* 2013;29:1139-1148.
60. Azarsina M, Kasraei S, Yousef-Mashouf R, Dehghani N, Shirinzad M. The antibacterial properties of composite resin containing nanosilver against Streptococcus mutans and Lactobacillus. *J Contep Dent Pract* 2013;14:1014-1018.
61. Durner J, Stojanovic M, Urcan E, Hickel R, Reichl FX. Influence of silver nano-particles on monomer elution from light-cured composites. *Dent Mater* 2011;27:631-636.
62. Tavassoli Hojati S, Alaghemand H, Hamze F, Ahmadian Babaki F, Rajab-Nia R, Rezvani MB, Kaviani M, Atai M. Antibacterial, physical and mechanical properties of flowable resin composites containing zinc oxide nanoparticles. *Dent Mater* 2013;29:495-505.
63. Arias-Moliz MT, Ferrer-Luque CM, González-Rodríguez MP, Navarro-Escobar E, de Freitas MF, Baca P. Antimicrobial activity and enterococcus faecalis biofilm formation on chlorhexidine varnishes. *Med Oral Patol Oral Cir Bucal* 2012;17:e705-e709.
64. Nedeljkovic I, Teughels W, De Munck J, Van Meerbeek B, Van Landuyt KL. Is secondary caries with composites a material-based problem? *Dent Mater* 2015;31:e247-e277.