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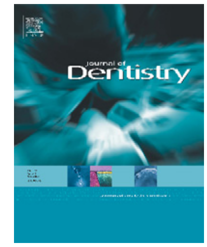

Review

Bacterial resistance and the dental professionals' role to halt the problem

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ABSTRACT

Objectives: In the present review, background information on bacterial antibiotic resistance is presented to dental practitioners. The review provides practical advice for dental professionals to combat and halt bacterial resistance.

Data: Antibiotic use over time has led to the emergence of infectious bacteria that are resistant to several antibiotics. Bacterial resistance is now considered a major threat to public health, and control of resistance is an international priority. Here, we present the current basic knowledge on bacterial antibiotic resistance to dental professionals, and discuss their role in combating and halting resistance.

Sources: The material presented in this review is primarily based on peer-reviewed literature searches in Medline using the phrase "antibiotic resistance" and the following key words: natural, acquired, mechanisms, use, dentists, and role.

Conclusions: Antibiotic resistance is a global problem, and dentists must be involved in halting it. Prudent and judicious use of antibiotic by dentists is an essential method for combating bacterial resistance. Health authorities are encouraged to monitor trends in antibiotic prescriptions by dentists and measure antibiotic consumption in order to assess and limit antibiotic use.

1. Introduction

Since their introduction early in the last century, antimicrobial drugs have revolutionized the treatment of infectious diseases. Sir Alexander Fleming discovered the first antibiotic, penicillin, in 1928, and 10 years later, sulfonamide was discovered. Between the 1950s and the early 1990s, new drug discoveries led to an explosive in antibiotic development. Following the discovery of antibiotics active against both Gram-positive and Gram-negative bacteria, surgeons believed that the ongoing, ancient fight between humans and infectious diseases was nearing its end.

Over the years, antibiotic use led to the emergence of infectious bacteria that are resistant to one or more antibiotics. As a result, there are strains of bacteria today for which only one effective drug treatment is available, and in some cases, there are no treatments available.[1] Antimicrobial resistance is now a major threat to public health, and controlling antimicrobial resistance is an international priority.[2,3]

Antibiotic resistance of oral microbes has become an increasing problem when treating dental infections. In the recent years, dentists have reported a shift from narrow-spectrum to broad-spectrum antibiotic prescriptions due to increasing antibiotic resistance.[4] In the present review, an

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overview of bacterial antibiotic resistance is presented to dental practitioners with an emphasis on their role in halting the global bacterial resistance problem.

2. Antibiotic resistance

Bacterial resistance to antimicrobials can be defined either genotypically, where the bacteria carries certain genetic resistance elements, phenotypically, where the bacteria can survive and grow above a certain level of antibiotics in the laboratory; or clinically, where the bacteria are able to multiply in humans in the presence of drug concentrations during therapy.[5] Bacterial resistance to antimicrobial agents can be either natural (inherent, intrinsic) or acquired.

2.1. Natural (inherent, intrinsic) resistance

In this type of resistance all isolates of a certain bacterial species are not sensitive to the antimicrobial in question. This could be because of a lack of certain structures in bacteria that serve as the target molecules for the antimicrobial or the lack of metabolic processes essential for the activation of the antimicrobial. In agreement with this, bacteria without a cell wall (e.g. the *Mycoplasma* species) are naturally resistant to antimicrobial agents such as β-lactam antibiotics, having activity against the cell wall.[6] Intrinsic resistance attributable to lack of metabolic processes is also noticed among oral bacteria. For example, *Actinomyces* species, *Streptococcus* species, and *Aggregatibacter* lack the enzyme nitroreductase necessary to convert metronidazole to its active metabolites, and are not affected by the drug at normal therapeutic concentrations.[7,8]

2.2. Acquired resistance

In contrast to natural resistance, acquired resistance is detected in only some bacterial species isolates. However, the percentage of resistant isolates can be high. Acquired resistance in bacteria evolves via two genetic mechanisms: chromosomal mutation of the preexisting bacterial genome or, most frequently, by horizontal gene transfer between bacteria, either within or outside the species.[5] Horizontal gene transfer allows the bacterial population to develop antibiotic resistance at a rate significantly greater than would be afforded by mutation of chromosomal DNA. Indeed, horizontal gene transfer is the most frequent pathway for the dissemination of antibiotic resistance genes.

During horizontal gene transfer, a resistance gene can be inserted into a transferable genetic element (plasmid, transposon, or integron) and be linked to other resistance genes contained in the element. The movement and introduction of transferable genetic elements carrying antibiotic resistance gene(s) into a bacterium can occur via three mechanisms, namely, transformation, transduction, and conjugation.[9] In *transformation*, exogenous segments of DNA that carry resistance genes are acquired by the bacteria from the environment. The bacteria enter an altered physiological state, termed competence, during which the bacteria can take up and integrate exogenous DNA from their environment. Natural transformation was first demonstrated by Griffith in *Streptococcus pneumonia* in 1928.[10] Transformation occurs in bacterial species that are naturally competent, such as pneumococci, haemophilus, and some oral streptococci.[11] Transformation is believed to be responsible for the development of mosaic genes and the mosaic structure of Penicillin Binding Proteins (PBP), which are responsible for penicillin resistance in streptococci.[12] *Transduction*, which was first described in 1952,[13–15] is similar to transformation except that the exogenous bacterial DNA is transferred from one bacterium to another via a phage particle. The last mechanism in horizontal gene transfer is *conjugation*, which was discovered by Edward Tatum and Joshua Lederberg in 1947.[16] After mixing two different strains of *Escherichia coli*, they discovered recombinant types of bacteria that were different from the two parental strains. This phenomenon resulted from direct physical contact between the two strains, which facilitated transfer of plasmid DNA from a donor to a recipient bacterium. Many conjugative plasmids are resistant to a variety of antibiotics, and they have the ability to transfer resistance to a wide range of bacteria. Mobilizable plasmids are not conjugative,[17] but can be transferred to a recipient when conjugative functions are provided by a separate, self-transmissible plasmid in the donor. Mobilizable plasmids have not been as thoroughly studied as conjugative plasmids, but they may also play a role in the spread of antibiotic resistance genes and the development of multidrug-resistant bacteria.[17]

Transposons and integrons are mobile DNA elements that can be integrated into bacterial chromosomes or plasmids. Transposons that are associated with antibiotic resistance fall into three major classes based on their general structure and method of insertion. The first two classes are composite and noncomposite transposons, which integrate into the target DNA by generating direct repeats in the target sequence.[17] Composite and noncomposite transposons typically contain genes that are not essential for transposition, such as antibiotic resistance determinants, between flanking terminal insertion sequences (composite) or inverted repeats (noncomposite). Because transposition can involve excision and transfer of the entire element, transposons are capable of spreading antibiotic resistance genes.[17] The third class of transposons are conjugative transposons, which are capable of excising from a chromosome or plasmid in a donor cell and transferring the DNA via conjugation into a recipient bacterium. Conjugative transposons have a broad host range, which is not constrained to closely related bacteria. For instance, the Tn916 and Tn1545 family can transpose into 50 different species and 24 genera of both Gram-negative and Gram-positive bacteria.[17] Conjugative transposition begins with the excision of the transposon from either the bacterial chromosome or plasmid DNA. The transposon circularizes, and the single-stranded DNA copy is transferred into the recipient cell by conjugation. A wide variety of antibiotic resistance genes have been identified on large conjugative transposons, and they are believed to significantly contribute to the spread of antibiotic resistance in Gram-positive bacteria.

The last type of mobile genetic element is the integron. Integrons consist of an integrase gene, two promoters transcribing in opposite directions, and an array of other genes, which often include antibiotic resistance genes.[17]