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ANTIBIOTICS RESISTANCE AND ITS THREAT: A REVIEW

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ABSTRACT

Antibiotic resistance is an imminent threat to worldwide public health. Dental professionals must demonstrate judicious use of antibiotics and educate their patients about the risks associated with their overuse. The aim of this article is to encourage the dental profession to prescribe responsibly in order to optimize the use of antibiotics in dentistry. Antibiotic stewardship programmes are recommended to help reduce the emergence of infections that are multidrug-resistant. Clinical practice audits are encouraged to help dentists ensure conservative prescribing patterns.

KEYWORDS: Antibiotics, Antimicrobial Resistance(AMR), stewardship.

INTRODUCTION

The World Health Organisation has identified antibiotic resistance as a major threat to worldwide public health.[1] Every year there are an estimated 25,000 deaths in Europe due to antibiotic resistance.[2] This is primarily caused by inappropriate prescribing habits, which lead to the over-use of antibiotics. The dental profession is globally responsible for between 7 and 11% of all antibiotic prescriptions.[3] Indiscriminate prescribing practices among dentists need to be targeted. Inappropriate prescribing of antibiotics leads to selection and dominance of resistant microorganisms. The exchange of genetic material can also increase resistance, resulting in resistant genes spreading between populations of bacteria.[4] As a consequence, antibiotics are becoming less effective and contribute to many infections, which are increasingly difficult to treat. The dental profession must demonstrate leadership in helping to reduce the impact of antibiotic resistance.

Development of resistance to drugs by microbes is a natural phenomenon but is enhanced by the irrational use of antimicrobials. A few strains that are naturally resistant and those with acquired resistance emerge as the dominant forms as a result of the selective pressure exerted due to exposure to antimicrobials.[5] Investigations have revealed that many oral microbes such as Streptococcus spp., Prevotella spp., Fusobacteria spp., Haemophilus spp., Veillonella spp., Porphyromonas gingivalis, Aggregatibacter actinomycetem comitans, and Actinomyces have developed resistance to many antibiotics.[6]

The Emergence of Antibiotic Resistance

Since their introduction in the 1940s, antibiotics have saved millions of lives, curing bacterial infections that would have previously proved fatal. However, soon after their earliest trials, it became evident that some bacteria were naturally resistant to these agents. Alexander Fleming warned: 'The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to nonlethal quantities of the drug make them resistant.[7]

Antibiotic resistance is frequently divided into two forms: intrinsic and acquired. In intrinsic or natural resistance, bacteria do not allow the drug to penetrate through their cell wall or do not contain the target chemical the antibiotic acts upon. With acquired resistance, normally susceptible bacteria change their physical or genetic format and acquire new enzymes or proteins that provide a defence against the drug. The genes responsible for these changes are usually located on the plasmid, a small circular form of DNA that can transfer from one bacterium to another, facilitating the spread of resistance between different types of bacteria.[8]

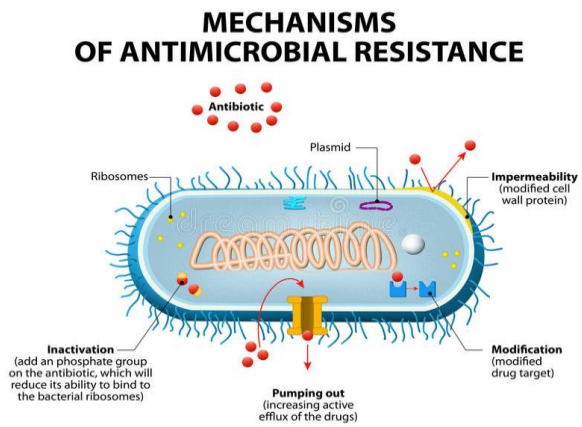
How Bacteria Become Resistant To Antibiotics??[9]

1. New or modified enzymes in the bacteria, e.g. beta-lactamases, degrade the antimicrobial agent

2. A mutation in the antibiotic's target chemical reduces the binding ability of the antibiotic agent
3. Uptake of the antimicrobial agent is reduced through changes to the bacterial cell wall
4. Bacteria increase their capacity to remove the antibiotic by efflux

Medical Factors Increasing The Likelihood Of Antibiotic Resistance[9]

1. Suboptimal use of antimicrobials for prophylaxis and treatment of infection
2. Noncompliance with infection-control Practices
3. Prolonged hospitalization
4. Increased number and duration of stays in intensive care units
5. Multiple comorbissdities in hospitalized patients
6. Ineffective infection-control practices
7. Transfer of colonised patients between hospitals
8. Grouping of colonised patients in long-term care facilities, e.g. residential homes
9. Antibiotics in agriculture and household cleaning products



Mechanism of Antimicrobial Resistance

Genetic Basis of Antimicrobial Resistance[10]

Bacteria have a remarkable genetic plasticity that allows them to respond to a wide array of environmental threats, including the presence of antibiotic molecules that may jeopardize their existence. As mentioned, bacteria sharing the same ecological niche with antimicrobial-producing organisms have evolved ancient mechanisms to withstand the effect of the harmful antibiotic molecule and, consequently, their intrinsic resistance permits them to thrive in its presence. From an evolutionary perspective, bacteria use two major genetic strategies to adapt to the antibiotic "attack", **i)** mutations in gene(s) often associated with the mechanism of action of the compound, and **ii)** acquisition of foreign DNA coding for resistance determinants through horizontal gene transfer (HGT).

Mutational Resistance[11]

In this scenario, a subset of bacterial cells derived from a susceptible population develop mutations in genes that affect the activity of the drug, resulting in preserved cell survival in the presence of the antimicrobial molecule. Once a resistant mutant emerges, the antibiotic eliminates the susceptible population and the resistant bacteria predominate. In many instances, mutational changes leading to resistance are costly to cell homeostasis (i.e., decreased fitness) and are only maintained if needed in the presence of the antibiotic.

Horizontal Gene Transfer[12]

Acquisition of foreign DNA material through HGT is one of the most important drivers of bacterial evolution and it is frequently responsible for the development of antimicrobial resistance. Most antimicrobial agents used in clinical practice are (or derive from) products naturally found in the environment (mostly soil). As mentioned before, bacteria sharing the environment with these molecules harbor intrinsic genetic determinants of resistance and there is robust evidence suggesting that such "environmental resistome" is a prolific source for the acquisition of antibiotic resistance genes in clinically relevant bacteria. Furthermore, this genetic exchange has been implicated in the dissemination of resistance to many frequently used antibiotics. Classically, bacteria acquire external genetic material through three main strategies, i) transformation (incorporation of naked DNA), ii) transduction (phage mediated) and, iii) conjugation (bacterial "sex").

Mechanistic Basis of Antimicrobial Resistance[13]

Bacterial species seem to have evolved a preference for some mechanisms of resistance over others. For example, the predominant mechanism of resistance to β-lactams in gram-negative bacteria is the production of β-lactamases, whereas resistance to these compounds in gram-positive organisms is mostly achieved by modifications of their target site, the penicillin-binding proteins (PBPs). It has been argued that this phenomenon is likely due to major differences in the cell envelope between gram-negatives and gram-positives. In the former, the presence of an outer membrane permits to "control" the entry of molecules to the periplasmic space. Indeed, most β-lactams require specific porins to reach the PBPs, which are located in the inner membrane.

In order to provide a comprehensive classification of the antibiotic resistance mechanisms, we will categorize them according to the biochemical route involved in resistance, as follows: i) modifications of the antimicrobial molecule, ii) prevention to reach the antibiotic target (by decreasing penetration or actively extruding the antimicrobial compound), iii) changes and/or bypass of target sites, and iv) resistance due to global cell adaptive processes.

Modifications of The Antibiotic Molecule[14]

One of the most successful bacterial strategies to cope with the presence of antibiotics is to produce enzymes that inactivate the drug by adding specific chemical moieties to the compound or that destroy the molecule

itself, rendering the antibiotic unable to interact with its target.

Antibiotic Use in Dentistry

Dental practitioners are responsible for approximately 9-11% of all community antibiotic prescriptions.[3] Within dentistry, large numbers of antibiotics are prescribed for acute dental conditions such as symptomatic apical periodontitis and abscesses. However, clinical guidelines recommend that the first-line treatment of these conditions should be primarily based on local measures, such as dental extraction, pulpal extirpation or incision and drainage of a swelling, and that antibiotics are not indicated in the management of odontogenic infections in the absence of spreading infection and systemic upset in healthy patients.[15] Antibiotics are being used as a substitute for local measures in emergency appointments.[16] This inappropriate use of antibiotics, in addition to intensifying resistance, wastes resources, exposes patients to potentially serious side effects and encourages patient expectations of antibiotics for dental problems in the future.[17]

According to the World Health Organization, up to 50% of antimicrobial use is inappropriate.[18,19] Antibiotics are routinely:

1. Given when they are not needed
2. Continued when they are no longer necessary
3. Given at the wrong dose
4. Broad spectrum agents are used to treat very susceptible, non-resistant bacteria
5. The wrong antibiotic is given to treat an infection

Additionally, the increase in the number of bootleg drugs has compounded the problem. Patients may be given drugs with little or no active drug, or even a different drug. In the U.S., the FDA estimates that 1% of prescription drugs are actually counterfeit. The Internet is a perfect avenue for the sale of bootleg or counterfeit pharmaceuticals.[19]

Inappropriate Prescribing

Relatively little is known about why dentists prescribe antibiotics where they are not recommended by clinical guidelines. However, time or workload pressures (e.g. when emergency appointments are double booked in addition to existing patient appointments) and uncertainty around diagnosis may have significant effects on the prescribing behaviours of dentists.[20]

Furthermore, it is likely that some inappropriate prescribing may occur in response to patient expectations or requests for antibiotics. Despite intensive media coverage of pathogens such as.

MRSA and Clostridium difficile, many patients still feel let down if they do not get a prescription for antibiotics for an infection, irrespective of the seriousness or potential duration.[21] Patients not only pressurise theirdentist for an antibiotic prescription but also self-medicate with antibiotics.

Improved Education

Education is key to improving patients' satisfaction and willingness to accept local measures as their only treatment, rather than get a prescription for antibiotics for an acute dental condition. Encouragingly, evidence suggests that only 3% of patients who expect but do not receive an antibiotic for a dental problem are dissatisfied with their dentist's decision.[22]

Good communication on the relative benefits and risks of both operative and pharmacological treatment options will often reduce a patient's expectations of antibiotics. Interventions are also required to optimise antibiotic prescribing among dental professionals. In the past, clinical audit and pharmacist-led educational courses have improved prescribing behaviour.[21,22] However, it is often unclear whether practitioners maintain this improvement in the long term.

Length of Course

A prescription for antibiotics is necessary for certain odontogenic infections, especially if there are signs of spreading infection or systemic involvement. In these cases, patients are generally prescribed a course of antibiotics of five to seven days in duration.[21]

However, this advice may be frequently inappropriate as the duration of antibiotic therapy in most patients with acute dentoalveolar infections can safely be two to three days, provided that drainage has been carried out.[23] In an audit conducted at Bristol Dental Hospital, following drainage and removal of the source of infection, a three-day standard dose antibiotic regimen was effective in the management of acute apical abscesses in all reviewed patients showing associated signs of systemic symptoms.[24]

Approach to The Patient

The dentist should take a well-reasoned, step-wise approach to a patient with an infection before prescribing an antibiotic (Table I,II). The first step is to make a tentative diagnosis based on data from the history and physical examination. Often, it is difficult to distinguish a bacterial from a viral illness by clinical features alone. Clinical and laboratory factors can be helpful in selecting subsets of patients more likely to have bacterial disease. More important than the actual microbiologic cause of the infection is knowledge of whether antibiotics will affect the course of the illness.

Table I

STEPS IN APPROACHING PATIENTS WHEN CONSIDERING ANTIBIOTIC THERAPY
Make a tentative diagnosis based on the history and physical examination.
Determine if antibiotic therapy is necessary for the given infection
Choose the individual agent for the infection based on the following: In vitro activity of the antibiotic against the most likely pathogens in the disease Clinical trial results demonstrating efficacy and safety of the antibiotic in that disease and in patient populations similar to that of the presenting patient
Side effect profile of the drug: Allergic reactions Direct adverse effects of drug Drug-drug interactions Drug-food interactions
Use least expensive and narrowest-spectrum drug possible

Table II

APPROACH TO PATIENTS WHEN ANTIBIOTICS ARE WITHHELD
Explain to patients the probable viral nature of common respiratory infections and that antibiotics have no effect on duration of symptoms of viral infections.
Explain to patients that antibiotics are potentially harmful in the following ways: Increased colonization and infection with resistant pathogens in patients with prior antibiotic therapy Increased antimicrobial resistance in the community Unwanted allergic reactions and adverse effects of antibiotics Cost of unnecessary therapy
Empathize with patients about the effect of symptoms on their daily activities
Provide educational materials
Prescribe therapies for symptoms

Antibiotic Stewardship

Antimicrobial stewardship is an organisational approach to promoting and monitoring conservative use of antimicrobials to maintain their ongoing effectiveness.[25,26]

The objective of antimicrobial stewardship is to improve antibiotic prescribing patterns. Antibiotic resistance poses a threat to the elderly, to children, and to patients with weakened immune systems. However, an increase in infections that are more difficult to treat not only affects vulnerable patients but also the wider community. Bacterial resistance can complicate the treatment of even mild infections.

Educating the dental profession and the public in the judicious use of antibiotics as part of an antimicrobial stewardship programme is imperative insafeguarding this vital medicine. Unfortunately, patients have come to expect antibiotics for 'toothache', which is an inflammatory condition and best managed with local measures in combination with analgesics. Good communication and reassurance by the dental profession must enforce antibiotic stewardship. However, an unscheduled emergency often presents a profoundly difficult situation for the dentist. As a profession, we are increasingly vulnerable to regulatory criticism if we cannot justify our care to our patients in circumstances of acute pain.

Doron and Davidson stressed three important aims with antimicrobial stewardship[26]:

- Optimise treatment for patients;
- Prevent inappropriate prescribing; and,
- Reduce the development of resistance in the individual patient and therefore the wider community.

The dental profession must show leadership in slowing the development of antimicrobial resistance by demonstrating more judicious prescribing in both private and hospital settings.

Auditing Current Practice

It is clear that more short period antibiotic audits, which are held at regular intervals with stakeholder feedback, are needed. These help to ascertain the number of prescriptions written, their appropriateness, and also to highlight areas of prescribing knowledge lacking in the dental practice. Within clinical practice, audits have been shown to positively encourage appropriate prescribing patterns.[27] However, it must also be understood that prescriptions are an indirect measure of antibiotic consumption and do not precisely reflect the rate of emerging resistance, which is multifactorial.[28]

Dental Prescribing By Practitioners Outside The Dental Profession

In the case of out-of-hours emergencies, patients often consult their GP before their dentist. GPs are more likely to prescribe antibiotics than dentists for acute dental

problems.[29] Therefore, where oral infections are concerned, antibiotic prescribing is not exclusive to dentists. Other healthcare professionals also contribute to the threat of antibiotic resistance. The Infectious Diseases Society of America recommends the use of specific antibiotic order forms to prevent inappropriate prolongation of antibiotic prophylaxis. These have been shown to reduce inappropriate prescribing from 64% to 21 %.[30]

Use of Microbiology Laboratories by The Dental Profession

Diagnostic microbiology laboratories are an excellent resource for helping dentists with therapeutic decisions. Yet within the profession bacteriological sampling mostly occurs when empirical therapy has proven unsuccessful.[31]

Evidence of inappropriate prescribing within the dental profession indicates that the facility is grossly underused. Diagnostic microbiology laboratories could also assist more in resistance surveillance and in the development of local policies and guidelines.[32]

We can counter the rise of antimicrobial resistance by:

1. Surveillance – of, for example, prescribing patterns, emerging resistance
2. Prevention of infection
3. Preserving effectiveness of existing drugs
4. Promotion of new antimicrobial agents and diagnostic technologies

CONCLUSION

Strategies aimed at educating patients and reducing their demand for unnecessary antibiotics should be implemented in dentistry. Dental infections are biofilm‐associated infections, wherein there are usually interventionsthat can be used as first‐line treatments rather than the prescription of antibiotics. By choosing to adopt these various strategies, a sustainable reduction in antibiotic prescription in general dentistry can be achieved. This will definitely tone down our role toward this impending “antibiotic apocalypse” which may be expected in the near future.

Antibiotic resistance is a real and imminent threat to the health and well-being of our nation and indeed the global community. Action is urgently needed to slow resistance by pledging to cut antibiotic overuse. As a profession we have a duty of care to follow the 'path of least resistance' in protecting this lifesaving medicine.

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