Journal of Oral Health & Community Dentistry

REVIEW ARTICLE

Addressing Antimicrobial Resistance in Dentistry

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ABSTRACT

Background: Antimicrobial agents are life saving drugs which are used in management of various life threatening infections but irrational use of antibiotics have led to resurgence of multidrug resistant bacteria which are associated with global increase in mortality due to various infections. Dentists are one among important health care personnel who prescribe antibiotics routinely to treat various oral infections.

Objectives: To summarise the evidence of antimicrobial resistance (AMR) encountered in dental practice, discuss factors associated with it and suggest measures to prevent antimicrobial resistance in dentistry.

Methodology: Articles were identified by searching in electronic data bases such as PubMed, Medline, Embase, Google Scholar and Cochrane data bases using key words like antibiotics, antimicrobial resistance, and antibiotic resistance in dentistry. The articles fulfilling the objectives were included.

Results and Conclusions: Dentists also contribute significantly to the global burden of antimicrobial resistance due to irrational use of antibiotics. Antibiotic stewardship is essential to prevent antimicrobial resistance in dental practice and hence there is an urgent need to educate not only dentists but general public as well. The article describes the gravity of the AMR and the importance of prudent use of antibiotics is discussed.

Keywords: Antibiotics, Antimicrobial, Resistance, AMR, Antibiotic stewardship, NDM-1, Superbug, MRSA

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J Oral Health Comm Dent 2013;**7**(2)101-107

INTRODUCTION

The accidental discovery of a mould called "Penicillium Notatum" which had the potential of inhibiting Staphylococcus colonies by Alexander Flemming in 1928 paved the way for the miracle drug "Penicillin" which saved millions of lives and opened a new era of curative medicine (1). Penicillin is referred as the mother of all antibiotics and the discovery proved to be a boon to mankind. There are various generations of antibiotics at present which are effective against wide spectrum of microbes but at the same time many microbes have developed resistance even to last known generation of antibiotics and threatening to push us to the pre-antibiotic era.

The resistant microbes become super bugs and the discovery of New Delhi Metallo

β-lactamase-1 (NDM-1) in India by Kumarswamy KK *et al.* in 2010 (2) has brought back the issue of antibiotic resistance in to spotlight. Recent report suggests that this super bug (NDM-1) is not only confined to some of the hospitals in India but in drinking water of New Delhi as well (3). The newly discovered super bug NDM-1 is actually an enzyme which gets transmitted to gram negative organisms like Escherichia coli and Klebsiella pnuemoniae which are resistant even to carbapenem group of drugs (2,3). A wide variety of gram negative microorganisms are present in oral cavity which are associated with periodontal diseases and if NDM-1 enzyme gets transmitted to them, then there may be catastrophic consequences in the oral cavity and hence as dentists, we should be updated regarding current scenario and prevent superbugs in the oral cavity.

It is not only the problem of the superbugs but many microbes which cause life threatening infections like tuberculosis, malaria, influenza, pneumonia, and viruses like HIV have become resistant to standard and even to combination of antimicrobial drugs. The problem is further compounded by Methicillin-resistant Staphylococcus aureus (MRSA), pathogenic coagulase negative staphylococcus aureus and Vancomycin resistant enterococci (VRE) (4).

Even though, World Health Organisation (WHO) had warned about the threat of antimicrobial resistance as early as 2000 (5), it was neglected in aftermath of 9/11 but at present we are staring at an impending deep public health crisis and realising its impact on mankind, World Health Organisation (WHO) has dedicated the theme of World Health Day 2011 to combat drug resistance with a slogan of "No action today; No cure tomorrow (6)."

Dentists prescribe antibiotics for treating various oral infections and reports highlight that many oral microbes have developed resistance to wide variety of antibiotics largely due to irrational use (7). At the present rate of antimicrobial resistance (AMR), we are at the risk of utilising all the available higher generation of antibiotics where in, it will be difficult to control various life threatening infections and hence all health care practitioners, policy makers, patients should be aware about this stark reality and work together in a coordinated manner to save the life saving antibiotics for our future generations also.

This article provides evidence regarding resistance of various oral micro organisms to wide spectrum of antimicrobial drugs, explains factors affecting prescription of antibiotics among dentists and suggests guidelines to prevent antibiotic resistance in dentistry.

ANTIMICROBIAL RESISTANCE (AMR)

Antimicrobial resistance (AMR) is a fast emerging global public health problem and can be defined as resistance of a microbial agent against an antimicrobial drug to which it was susceptible before. AMR is the result of misuse of antimicrobial medicines and develops when a microorganism mutates or acquires a resistance gene (8).

MECHANISM

Development of resistance to drugs by microorganisms is a natural phenomenon but is enhanced by irrational use of antimicrobials. Naturally resistant strains and those which have acquired resistance, emerge due to selective pressure exerted by exposure to antimicrobial drugs. The genetic information is passed on through horizontal gene transfer between microbes which allow resistance determinants to spread within harmless environmental or commensal microorganisms and pathogens, thus creating a reservoir of resistance. Resistance is also spread by the replication of microbes that carry resistance genes, a process that produces genetically identical (clonal) progeny (9).

FACTORS AFFECTING ANTIBIOTIC RESISTANCE

According to World Health Organisation, the antimicrobial resistance is a multifactorial problem and can be summarized due to deficient antimicrobial policies and guidelines at the national level, inadequate community participation, weak or absent monitoring systems, availability of poor quality medicines, misuse of antibiotics, poor infection control protocols in the hospitals, low level of accessibility to diagnostics, medicines and vaccines along with insufficient research efforts for the development of new generation of drugs (8,9).

ANTIBIOTIC RESISTANCE IN INDIA

Indian subcontinent is perceived as a hot bed for resistant microbes and a plethora of factors are responsible such as irrational prescription of antibiotics by health care practitioners like prescription of antibiotics for viral infections, advising antimicrobials without a culture and sensitivity report, use of higher generation of antibiotics, increased pressure to prescribe newer antibiotics, self medication and often non-compliance of full course of antibiotics by patients, availability of antibiotics over the counter (OTC), poor quality of the drugs, coupled with primitive infection control in hospitals and weak or deficient sanitation (10,11). It is also compounded through weak surveillance systems and non-availability of antibiotic policy at the national level but now India is all set to see its first antibiotic policy being passed by the central government very soon which is a positive step in tackling antimicrobial resistance (12).

ANTIBIOTIC USE IN DENTISTRY

Dentists account for approximately 7-11% of all antibiotic prescriptions in the world (13-17). Although, the percentage is less when compared to medical practitioners, antibiotics are one among frequently prescribed drugs which significantly contributes to national and or global patient consumption of antibiotics and hence a matter of deep concern (13, 14). The rate of resistance development may be delayed if dentists, along with other health care practitioners use antibiotics more judiciously. In dental practice, antibiotics are invaluable adjuncts in treatment of oro-facial infections which are usually prescribed for management of acute odontoge-nic infections, non-odontogenic infections, as prophylaxis against focal infection in patients at risk (en-docarditis and joint prosthesis), as

prophylaxis against local infection and systemic spread (14,15).

Epstein JB *et al* (16) reported that the sampled dentists in British Columbia, Canada prescribed an average of 4.45 antibiotics prescriptions per week after treatment which were primarily penicillin and its derivatives. Similarly Mainjot A *et al* (17) have reported a median number of prescriptions per dentist to be 3 per week among Belgian dentists. 82% of all prescriptions were for amoxycillin, amoxycillin-clavulanic acid and clindamycin.

DEVELOPMENT OF RESISTANCE AMONG ORAL MICROBES

The oral cavity is colonised by a diverse range of microbial flora which comprise of more than 700 species of bacteria, fungi and protozoa, of which only 10% are regularly isolated using conventional culture techniques (18,19).

DEVELOPMENT OF RESISTANCE BY ORAL MICROBES TO VARIOUS ANTIMICROBIAL AGENTS

ß-LACTAMS

β- lactum antibiotics are commonly used in dental practice which include penicillins, cephalosporin and related compounds are active against many gram-positive, gram-negative and anaerobic organisms but becomes ineffective due to production of β-lactamases by certain strains of bacteria (20). Streptococcus viridans which is associated with bacterial endocarditis is resistant to Penicillin G and also β- lactamase producing Prevotella species and hence choice of other effective antibiotic is necessary (21).

Amino-penicillin group are one among main antibiotics used routinely in dental practice which include amoxicillin and ampicillin (16,17). Report suggests that many oral microbes have developed resistance to these drugs which may be associated with past history of administration of β-lactams hence β-lactamase stable antibiotics should be prescribed to patients with unresolved infections who have received â-lactams earlier (22,23).

It has been reported that micro organisms like S. sanguis, black-pigmented Prevotella and nonpigmented Prevotella were resistant to amoxicillin, ampicillin, cefazolin and cefotaxime (23,24). β-lactamase production have also been detected in some species of Clostridia, Fusobacteria, Prevotella, Porphyromonas and in some other anaerobic bacteria (25).

Since amoxicillin is prescribed by dentists than any others, it may lead to emergence of resistant strains (16,17). It has been confirmed by many studies in which a total of 224 amoxicillin-resistant bacteria were isolated which belonged to Haemophilus species, Streptococcus species, and Veillonella species. This study has demonstrated that a diverse collection of amoxicillin-resistant bacteria is present in oral cavity (26). Presence of amoxicillin resistant organisms (ARO) isolated from dental plaques adds furthermore evidence to AMR (27,28).

Various generations of cephalosporins are used as an alternative to amoxicillin in dentistry as they are less allergenic, have decreased toxicity risks, added with broad spectrum of activity. It is the latter feature however, that encourages the selection of microorganisms that are resistant to these drugs (29).

Many strains of oral bacteria like Prevotella denticola and Streptococcus viridans are resistant to fourth generation of cephalosporin (30). Increased rates of resistance to cephalosporins such as ceftriaxone, ceftazidime, cefpirome and cefepime have been reported among Streptococcus viridans in neutropenic cancer patients (31).

β- LACTAMASE INHIBITORS

The inactivation of amoxicillin by β-lactamases of gram negative anaerobic bacteria can be prevented by the addition of â-lactamase inhibitors such as Amoxicillin + Clavulanate, Ampicillin + Sulbactam, Piperacillin + Tazobactam and Ticarcillin + Clavulanate (32,33).

β - lactamase inhibitors are often used in recurrent oral infections. It has been found that many periodontal pathogens like P. gingivalis and P. intermedia are highly susceptible to amoxicillin+clavulanic acid (32,34). It is evident that many oral pathogens are susceptible to this combination (35) and hence it should be used exclusively for treatment of â lactum resistant infections and that too after confirming through culture and sensitivity tests.

LINCOSAMIDES

Clindamycin, a broad-spectrum antibiotic with activity against aerobic, anaerobic, and β-lactamase-producing pathogens is used as second line of drug after penicillin and cephalosporins which may be useful in penicillin-allergic patients but should be used after confirmation by culture and sensitivity tests. Clindamycin has been used for many years as prophylactic treatment during dental procedures to prevent endocarditis (36). Even though, resistance to clindamycin has been reported in Porphyromonas gingivalis and Bacteroides ureolyticus (37), it still has a strong antimicrobial activity on anaerobes.

MACROLIDES

The macrolides which include erythromycin, azithromycin, and clarithromycin are not routinely used in dental practice as they are bacteriostatic and cannot be used in acute infections (38). Azithromycin is less effective against gram-negative Cocci than erythromycin (39). The findings of a study reveal that erythromycin is ineffective against Streptococcus viridans and most of Fusobacterium species (24) and also has decreased activity against non pigmented Prevotella (22). A recent study suggested that Streptococcus oralis and Streptococcus mitis have developed resistance to macrolide group of antibiotics (40).

TETRACYCLINE

Tetracycline is a broad-spectrum antibiotic, used as an adjunct to mechanical periodontal therapy. Due to its irrational use in management of periodontal infections, many oral microorganisms have developed resistance (41). Tetracycline-resistant bacteria have been isolated from oral microbial flora in which most of the isolates carried tetracycline resistance genes out of which, the most common gene identified was tet(M), followed by tet(W), tet(O), tet(Q) and

tet(S) (42). The tet(M) containing strains was predominantly present in strains of Streptococci, mainly S. intermedius, S. oralis and S. sanguis. It was also detected in Actinomyces, Bifidobacterium, and Veillonella species, Prevotella and Bacteroides isolates (43,44). Newer strains like Streptococcus parasanguinis and Eubacterium saburreum are also reported to be resistant to tetracycline (45). Since tetracycline is used both in systemic as well as in local drug delivery systems, it enhances selection to these agents by oral microbes and hence decision to use antibiotics should be based on the merit of individual case.

NITROIMIDAZOLES

The nitroimidazole group of drugs is specifically anti-anaerobic in nature which includes metronidazole, nimorazole, tinidazole and ornidazole which has been proved to be efficacious in treating acute ulcerative gingivitis, chronic progressive periodontitis, pericoronitis, periapical infections, osteomyelitis and dry socket where anaerobes are implicated as pathogens (46). Serrano C *et al* (47) isolated eleven species which included Fusobacterium nucleatum, Prevotella intermedia and Prophyromonas gingivalis which were resistant to metronidazole. Aggregatibacter actinomycetem comitans and Porphyromonas gingivalis which are causative organisms of periodontitis are associated with resistance to metronidazole along with amoxicillin and clindamycin (34). Many Oral anaerobes are still susceptible to metronidazole (35) hence judicious use of it is necessary in management of periodontal diseases.

FLUOROQUINOLONES

Ciprofloxacin is one of the fluoroquinolone group of antibiotics which can be used in combination with metronidazole for the treatment of mixed anaerobic periodontal infections when the patient has an allergy to beta-lactam antibiotics (48). Findings of an in vitro study reported that F. nucleatum and P. gingivalis exhibited resistance to ciprofloxacin (49). Antimicrobial activity is also reported against third generation of fluroquinolones that is levofloxacin. The oral pathogens such as Streptococcus viridans, P. gingivalis and Prevotella species demonstrated resistance (21,37).

ANTIFUNGALS

The incidence of oral candidiasis is increasing in the world largely due to HIV infection where in a combination of antimicrobial drugs are used to manage variety of infections arising due to immuno-compromised state. Due to this, Candida albicans has developed resistance to azole group of antifungals. Resistance has been observed to amphotericin B, nystatin, cotrimazole, fluconazole which makes the dentists left with very little option due to which prognosis becomes poor. The multidrug resistance of C. albicans is due to MDR-1 and CDR-2 genes (50-52).

CARBAPENEMS

Carbapenem is the last group of antibiotics which include drugs like meropenem, imipenem and faropenem, are usually reserved for the life threatening infections. Even though report suggests that all oral microbes are susceptible, it should not be considered because of risk of development of resistance (30,37). In a few conditions like children undergoing treatment for cancer, meropenem resistance among alpha-hemolytic streptococci was observed (53).

RESISTANCE OF ORAL MICROBES TO ANTISEPTIC MOUTH RINSES AND DENTIFRICES

Dentifrices and mouth rinses contain therapeutic agents which are effective in preventing dental plaque and controlling gingival inflammation. Even though, dentifrices are used daily, there is less chance of development of resistance by oral bacteria. The antiplaque or antiseptic formulations which contain chlorhexidine, triclosan, cetylpyridinium chloride, sodium benzoate, povidone-iodine, hydrogen peroxide and essential oils are topically used as mouth rinses. They are bactericidal when used undiluted and bacteriostatic if diluted with water. Since, chemical antiplaque agents are topical in nature and often mixed with water in 2:1 ratio, the risk of development of resistance is low (54). It has been reported that long term use of antiplaque agents available in dentifrices and mouth rinses does not lead to selection of resistant strains or significantly affect the structure of microbial oral flora. There is also no evidence of colonization of pathogenic or opportunistic microorganisms and hence can be used daily for prevention of periodontal diseases (55,56).

CHLORHEXIDINE MOUTH RINSES

Chlorhexidine gluconate is still considered a gold standard for antiplaque mouth rinses, which is used for short duration after periodontal therapy. The development of resistance is probably less compared to antibiotics or biocides containing quaternary ammonium compounds (57) but still resistance of Streptococcus sanguis has been reported against chlorhexidine (58). Due to limited number of investigations, it is difficult to arrive at a conclusion but nevertheless chlorhexidine should be prescribed only for a short duration to prevent adverse effects associated with long term usage and also the risk of resistance.

TRICLOSAN MOUTH RINSES

Triclosan is a biocide, widely used in mouth rinses, dentifrices, cosmetics and common household products which enhance the risk of selection of less susceptible organisms (59). Triclosan mouth rinse is favoured over chlorhexidine due to its decreased side effects but rapid widespread daily use of triclosan in many forms may present a potential public health risk in regard to development of resistance. Even though, there is no scientific evidence regarding the use of triclosan mouth rinses and bacterial resistance, but considering the fact that it is used widely in many cosmetic products, daily mouth rinsing with triclosan should be limited to only special cases who are unable to perform mechanical oral hygiene practices and patients who are immunocompromised (60,61).

PREVENTION OF ANTIMICROBIAL RESISTANCE IN DENTISTRY

Dentists can make a difference by using antimicrobials judiciously by prescribing correct antibiotic regimen only when indicated; keeping a track record of the pre-

scribed antibiotics and signs of resistance among patients must be identified and documented. The practice of prudent use of antimicrobials is referred as "Antimicrobial stewardship" and can be put in to practice when they prescribe for antibiotic prophylaxis and for therapeutic purposes (62).

ANTIBIOTIC PROPHYLAXIS

Prophylactic antibiotics are prescribed to prevent metastatic spread of pathogenic oral bacteria leading to infections such as infective endocarditis (63). According to a Cochrane systematic review, there remains no evidence, whether penicillin prophylaxis is effective or ineffective against bacterial endocarditis in people at risk who are about to undergo an invasive dental procedure (64). Antibiotic prophylaxis is essential in some of the conditions and it is advised to follow updated recommendations of American dental association (ADA) and American heart association (AHA) (65,66), to prevent antibiotic resistance in cardiac conditions and guidelines of American association of orthopedic surgeons (AAOS) in patients with total joint replacements (67). Guidelines of the respective countries should also be considered if available.

THERAPEUTIC PRESCRIPTIONS

Many studies conducted among dentists in Belgium (17), Australia (68), Kuwait (69), suggested over use or misuse of antibiotics which were associated with poor understanding of pathological processes involved in pulp and periapical diseases, lack of knowledge regarding indications for effective antibiotic use, whenever there is uncertainty of diagnosis, for convenience, expectation of patient and lack of time to treat immediately. There is lack of uniformity in the rationale for antibiotic use among dental practitioners and this can be solved by formulation of guidelines by national dental associations. The formulation of evidence-based guidelines will prevent misuse of antibiotics by dentists which has become a global problem (69).

Creating awareness among dentists is of utmost importance and educational initiatives to promote rational use of antibiotics in dentistry can be organised at the local, national and at international level. Regular workshops and continuing dental education programs (CDE) to update the knowledge on application of antibiotics should be initiated on priority basis (70).

GUIDELINES OF RATIONAL USE OF ANTIBIOTICS IN DENTISTRY

Indications (15, 71, 72)

- Evidence of systemic spread
- Facial cellulitis and / or dysphagia
- Aggressive periodontitis
- Necrotising ulcerative periodontal diseases
- Pericoronitis
- Acute periodontal conditions where drainage is impossible
- Space infection of the head and neck after pus drainage
- In acute situations of odontogenic infection of pulpal origin but as a complement to root canal treatment

When antibiotics are not required (15,72)

- Chronic marginal gingivitis
- Chronic periodontitis
- Dry socket
- Irreversible pulpitis with or without acute periapical periodontitis
- Necrotic pulp with or without acute periapical periodontitis
- Necrotic pulp with chronic periapical periodontitis without swelling
- Necrotic pulp with a draining sinus tract

General Principles (73,74)

- Making an accurate diagnosis.
- Using appropriate antibiotics and proper dosing schedules.
- Considering narrow-spectrum antibacterial drugs in simple infections to minimize disturbance of the normal microflora, and preserve the use of broad-spectrum drugs for more complex infections.
- Using a loading dose to rapidly achieve therapeutic blood levels.
- Avoiding combinations of bacteriostatic and bactericidal drugs.
- Avoiding unnecessary use of antibacterial drugs in treating viral infections.
- Obtaining thorough knowledge of the side effects and drug interactions of an antibiotic before prescribing it.
- Educating patients regarding proper use of antibiotics and stressing the importance of completing full course of therapy.
- Generic drugs are as effective compared to branded ones which also reduce cost.

Control of antimicrobial resistance through inter-sectoral coordination (9)

Responsible actions are to be taken to ensure appropriate use of antibiotics where ever necessary such as at the local, national, and international levels.

- Improvement of diagnostic services through capacity building measures particularly in developing countries.
- Development of standard infection control protocols in all health care set ups.
- Practice of antibiotic stewardship among all health care practitioners including veterinarians.
- Education and motivation of the public regarding proper antibiotic use.
- Building and enhancing surveillance programs;
- Financial resource mobilization to undertake research activities with regard to developing new drugs.
- Regulating over the counter sale of antibiotics and central prescribing restrictions along with advertising curbs.
- International cooperation and assistance.
- Controlling and improving the quality of generic antibiotics.

CONCLUSIONS

Antimicrobial therapy is an invaluable and life-saving adjunctive therapy but inappropriate and indiscriminate use, has led to wide-spread development of multidrug resistant strains which are associated with increased mortality in the world. Dentists are one among the global prescribers of antibiotics, so prudent and judicious use of antibiotics among them is necessary for combating bacterial resistance. There is an urgent need to formulate guidelines for treatment and educational initiatives to

promote rational use of antibiotics. General public should also be educated regarding proper use of antibiotics and the sale of over the counter antibiotics should be banned. All these efforts will translate in to slowing the development of resistance by microbial pathogens and also save the antibiotics for our future generation also.

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