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Antibiotic resistance in general dental practice—a cause for concern?

Louise C. Sweeney[1], Jayshree Dave[1,2], Philip A. Chambers[3] and John Heritage[1]*

[1]School of Biochemistry and Microbiology, University of Leeds, Leeds LS2 9JT, UK; [2]Department of Microbiology, The General Infirmary at Leeds, Leeds LS1 3EX; [3]Mutation Detection Facility, Cancer Research UK, Ashley Wing, St James's University Hospital, Leeds LS9 7TF, UK

This review examines the contribution dental prescribing makes to the selection of antibiotic resistance in bacteria of the oral flora. The antibiotics commonly used in dental prescribing in the UK are discussed, together with the problems of resistance in members of the oral flora. The antibiotic prescribing habits of general dental practitioners are then reviewed with respect to therapeutic prescriptions and those drugs that are prescribed prophylactically. Not all antibiotic prescriptions for dental problems are written by dentists; prescribing outside the dental profession is also considered. The review then considers the support available to dentists from clinical diagnostic microbiology laboratories. It concludes that better use of diagnostic services, surveillance and improvements in dental education are required now to lessen the impact of antibiotic resistance in the future.

Keywords: dental prescribing, oral flora, prophylaxis, diagnostic laboratories

Introduction

In 1998, the Standing Medical Advisory Committee (SMAC) published *The Path of Least Resistance*. In it, it stated that dentists account for 7% of all community prescriptions of antimicrobials. This may not seem much; nevertheless, dentists dispensed 3.3 million prescriptions for antibiotics in 1993, and by 1996 this figure had increased to 3.5 million prescriptions.[1] According to the British Dental Association, there are 22 000 general dental practitioners in the UK. This means each practitioner could be prescribing, on average, 159 antibiotic courses each year, an average of three prescriptions a week, implying a greater antibiotic usage by dentists than might be thought initially.

The relationship between antibiotic use and resistance is complex. A population genetics study demonstrated that the volume of drug use can influence the selection pressure for antibiotic resistance, but a quantitative relationship between these two factors was not demonstrated.[2] Reduction in antibiotic resistance can only occur following a significant reduction in antibiotic use. It has been argued that the time required for a drop in the prevalence of antibiotic resistance to occur will be more than the time required for resistance to develop under a constant selective pressure.[2]

An important factor influencing the emergence of resistance in a bacterial population is the selective pressure applied by antibiotics. Exposure of oral bacteria to low concentrations of minocycline has led to the emergence of strains that show reduced susceptibility to this drug.[3] Thus, the concentration that antibiotics can achieve in the oral cavity may be critical in selecting resistant bacteria within the oral flora. Making a choice of antibiotic to treat oral infections taking into consideration the concentrations that various drugs may achieve, however, is not straightforward. Many β-lactam antibiotics achieve very low concentrations in saliva in comparison with the concentration that is attained in serum, but the level of susceptibility for oral streptococci is such that the low saliva concentration does not cause problems.[4,5] Similarly, erythromycin does not reach as high a concentration in saliva as in serum.[6,7] In contrast, the concentration of azithromycin found in saliva is significantly higher than is found in serum,[8,9] but in the management of dental infection, azithromycin has been shown to depress concentrations of a non-steroidal anti-inflammatory drug in periodontal tissue, administered for pain relief.[10] Thus, the choice of which antibiotic to prescribe is not simply a matter of picking the drug with the greatest antimicrobial activity.

In medical practice, a low correlation between community prescribing and antibiotic resistance to urinary coliforms and *Streptococcus pneumoniae* was illustrated in a cross sectional study involving 405 general practices in southwest and northwest England.[11] However, that study used overall prescriptions as a crude measure for population exposure; social interactions were not examined. General medical practitioners are responsible for 80% of antimicrobial prescribing in the UK.[1] It has been demonstrated that most of the antibiotics are prescribed in the community and that the majority of prescribing was for conditions including otitis media, upper respiratory tract infection, bronchitis, pharyngitis and sinusitis.[12] These are infections associated with microorganisms found in the oropharynx. The majority of prescriptions written in the community are written by general medical practitioners, and the drugs prescribed will have a significant impact on the selection of resistance among bacteria in the oral flora. Nevertheless, the role of dental prescribing in the selection

*Corresponding author. Tel: +44-113-343-5592; Fax: +44-113-343-5638; E-mail: j.heritage@leeds.ac.uk

of resistant bacteria is an area that has received relatively little attention. This review seeks to address this deficit.

The oral flora

The oral cavity is colonized by a diverse range of microorganisms.[13–15] These comprise ~300–500 species of bacteria, fungi and protozoa, of which only ~10% are regularly isolated using conventional culture techniques. In a recent study, ~40% of the bacteria identified using 16S rRNA amplification methods were of novel phylotypes, and presumably many of these represent bacteria that cannot be isolated using conventional culture methods.[16] Of the bacteria that are easily recovered upon routine culture, the α-haemolytic streptococci are among the most frequent isolates. This is a group for which the taxonomy is still the subject of debate.[17] Other bacteria found in the oral commensal flora include coagulase-negative staphylococci, Gram-negative cocci belonging to the families Neisseriaceae and Veillonellaceae, lactobacilli, spirochaetes, corynebacteria and mycoplasmas. Bacteria that are potentially pathogenic and that are sometimes found in the oral cavity include *Staphylococcus aureus*, *Enterococcus faecalis*, *S. pneumoniae*, *Streptococcus pyogenes*, *Neisseria meningitidis*, members of the family Enterobacteriaceae, *Haemophilus influenzae* and actinomycetes.

A complex ecosystem is formed in the oral cavity, and it changes constantly throughout life. Many commensal microorganisms will cause disease if provided with appropriate conditions. Gram-positive aerobic cocci, α-haemolytic streptococci, peptostreptococci and Gram-negative anaerobes are frequently isolated from oral infections.[18] The role of general dental practitioners in selecting and maintaining antibiotic resistance is unclear. Thus, general dental practitioners may be unsure how to attend to this potential problem.

Resistance to amoxicillin, penicillin and metronidazole in the oral flora

The antibiotics prescribed most commonly by dentists are amoxicillin, penicillin and metronidazole.[19–22] These drugs have the potential to select for resistant bacteria within the commensal flora. Other antibiotics are used less frequently by dentists.

Aminopenicillins

Aminopenicillins are one of the three antibiotic types most commonly prescribed in dentistry.[23] Amoxicillin resistance has been described in *Veillonella* spp. and *Prevotella denticola* isolated from root canals. In one study, all 34 strains of facultative anaerobic bacteria isolated from the same root canals were susceptible to amoxicillin, as were 52 of 54 (96%) strains of obligate anaerobes.[24] The NCCLS agar dilution method was used and the breakpoint for amoxicillin was 8 mg/L. The results of this study suggest that resistance to amoxicillin is not widespread among anaerobes that inhabit deeper sites in the oral cavity. Fosse *et al.*[25] demonstrated susceptibility of Gram-negative bacilli such as *Prevotella* to amoxicillin when combined with clavulanic acid, although this group did report that at least one *Prevotella* sp. strain producing β-lactamase was found in 53.2% of patients and 39.4% of the periodontal pockets that they investigated. These reports are inconclusive, and further study is required to clarify the prevalence of resistance to aminopenicillins. This may prove problematic to achieve because of the difficulties associated with antimicrobial susceptibility testing for anaerobes. There are no standardized methodologies agreed, and reproducible results are difficult to achieve.

Penicillins

In 1986, streptococci producing β-lactamase were isolated from the subgingival plaque of adults with periodontitis.[26] Production of β-lactamase is, however, uncommon for most streptococci, where resistance is typically mediated by alterations to the penicillin-binding proteins.[27–29] Susceptibility tests on 207 isolates of nine species of α-haemolytic streptococci, including *Streptococcus mutans*, *Streptococcus salivarius*, *Streptococcus oralis* and *Streptococcus mitis*, found that only *S. mutans* was universally susceptible to penicillin.[30] Potgieter *et al.*[31] report four blood culture isolates of *S. mitis* that were resistant to penicillin (MICs 16–32 mg/L); they were also resistant to the aminoglycosides gentamicin, kanamycin and tobramycin. *S. mutans* is cariogenic, and several studies have reported on its susceptibility to penicillin and other antimicrobials.[32–35]

In a study investigating the susceptibility of 424 isolates of *S. mutans* taken from 116 children and students, all bacteria were found to be susceptible to penicillin, as well as to amoxicillin, trimethoprim, tetracycline and erythromycin.[35] In another study, 839 isolates of *S. mutans* from 209 patients were equally susceptible to penicillin in patients exposed and not exposed to dental amalgam fillings.[33] Mercury in dental amalgam did not select for antibiotic resistance.[36,37] Ninety-four percent of 41 strains of *S. mutans* isolated from patients with endocarditis had MICs of ≤0.08 mg/L for penicillin, only 68% had minimum bactericidal concentrations (MBCs) of penicillin ≤0.08 mg/L. High-level penicillin resistance (MIC ≥ 4 mg/L) was shown in 8% of *S. salivarius* strains, 20% of *S. mitis* strains and 35% of *S. oralis* strains.[30] Compared with other studies, however, this level of resistance is low. MICs of benzylpenicillin for *S. oralis* and *S. mitis* range from 32 to 64 mg/L.[38,39] *S. oralis* and *S. mitis* show the highest penicillin resistance amongst the α-haemolytic streptococci. Although the degree of resistance is variable, it is consistently present in bacteria isolated from the oral cavity.

The high levels of resistance that are now being demonstrated in the α-haemolytic streptococci are a cause for concern. There is evidence to show that interspecies transfer of resistance determinants occurs between *S. pneumoniae* and other α-haemolytic streptococci.[38,39] The resistance determinants transferred from *S. pneumoniae* are mosaic genes, containing regions with nucleotide sequences very similar to those from strains susceptible to penicillin interspersed with regions of nucleotide sequence divergence, which confer resistance.[40] These related sequences have been identified in *S. sanguis*, *S. oralis* and *S. mitis*, indicating interspecies transfer.[40–43]

Porphyromonas gingivalis, *Prevotella intermedia* and *Prevotella nigrescens* are common isolates from oral infections. Antibiotic susceptibility testing of strains of these bacteria from patients in Spain found *P. gingivalis* strains producing β-lactamase have been isolated infrequently from periodontal pockets.[44,45] The occurrence of penicillin resistance is a more consistent finding in *Prevotella* spp.[46,47] No significant difference in the presence or degree of penicillin resistance has been demonstrated between pigmented and non-pigmented species in this genus.[44] Despite the small numbers reported by these authors, their studies indicate that surveillance of these species is important.[25,47]

Other oral anaerobes implicated in infection include members of the genera *Fusobacterium* and *Veillonella*; these bacteria have been associated with penicillin resistance.[39,48,49] In one study, 31% of fusobacteria isolated from odontogenic abscesses were found to produce

β-lactamase.[50] Other workers are recommending clindamycin for the first-line treatment of odontogenic infections because of the problems of β-lactamase production amongst the bacteria that cause this polymicrobial condition.[51] In that study, resistant bacterial strains were isolated more frequently from patients who had recently received penicillin treatment than from patients who had not received recent antibiotic treatment.

Metronidazole

Dentists are the most frequent prescribers of metronidazole.[1] However, the emergence of resistance to this drug may be slower than if it were used alone, because in order to target both aerobic and anaerobic organisms, metronidazole is used empirically in combination with one or more antibiotics, although resistance to the drug may be associated with mobile genetic elements, aiding spread.[52]

Possible mechanisms of resistance to metronidazole include mutations in the enzymes responsible for reduction of the drug to its active form, mutations resulting in decreased entry of the antibiotic into the cell and mutations to transporters causing efflux of the drug.[53] Roche & Yoshimori[54] found that eight out of 97 isolates from odontogenic abscesses were resistant to metronidazole. These included five isolates of *Lactobacillus* spp., two isolates of *Gemella morbillorum* and an isolate of *Actinomyces israelii*. All other anaerobes associated with odontogenic abscesses in this study were susceptible to metronidazole. These included *Prevotella* spp., *Peptostreptococcus* spp., *Bacteroides* spp. and *Porphyromonas* spp., all of which have been previously implicated in odontogenic disease. Lana *et al.*[24] isolated 54 obligate anaerobes from the root canals of Brazilian patients, and found 52/54 (96.3%) were susceptible to metronidazole. There were only two resistant isolates: *Clostridium butyricum* and a member of the genus *Veillonella*. *P. denticola* was resistant to every antimicrobial tested, with the exception of metronidazole. Of the facultative anaerobes tested 17/34 (50%) were inhibited by metronidazole when tested anaerobically. This is not surprising, owing to the heterogeneous behaviour of these microorganisms, being capable of metabolism under anaerobic and aerobic conditions; a crucial step in the activity of metronidazole is the reductive activation of the nitro group on the drug. This converts it from an inactive prodrug to a nitroso free-radical form, which is cytotoxic.

Eick *et al.*[50] determined the susceptibility of isolates from periodontal and odontogenic abscesses to a variety of antibiotics used in their treatment, including metronidazole. The capnophiles *Eikenella corrodens* and *Actinobacillus actinomycetemcomitans* were resistant to metronidazole, owing to an intrinsic resistance mechanism.[50] This observation is supported by Madinier *et al.*,[55] who studied the susceptibility of *A. actinomycetemcomitans* to various antimicrobials. This bacterium is an important factor in intractable periodontal disease, often leading to early loss of permanent teeth. Of 50 strains tested, 72% were resistant to metronidazole at the chosen breakpoint (16 mg/L). An MIC_{90} of 128 mg/L was recorded for their isolates.

The presence of, or potential for, metronidazole resistance has not been widely investigated. This is probably because the few studies that have been conducted have found a high prevalence of susceptibility to metronidazole among anaerobes, although there has been a report of subdural empyema caused by *Prevotella loescheii* with reduced susceptibility to metronidazole, the MIC of one isolate being 12 mg/L.[56] Increasing resistance to metronidazole among isolates of *Helicobacter pylori*[57] and the anaerobic protozoa[58] is being reported.

Resistance to other antimicrobial agents in the oral flora

Cephalosporins

As with penicillins, the α-haemolytic streptococci show high resistance to cephalosporins, with MICs as high as 128 mg/L for cefotaxime.[39] High MICs have also been reported for first- and second-generation cephalosporins. High-level cefotaxime resistance was easily transferred in the laboratory to less resistant *S. pneumoniae*, a process that is thought to occur in nature, although dental practitioners do not prescribe cefotaxime, since it is administered parenterally.[38] Changes in three penicillin-binding proteins accompanied the transfer of the high-level cefotaxime resistance determinant.[38] *Entercoccus* spp., isolated from root canal exudates of periodontal patients, have expressed high-level resistance to cephalosporins, more so than other isolates including Gram-negative bacteria.[59] Outside of the laboratory, the rate of transfer may be low, but there is a potential for greater transfer with increasing selection pressure due to more frequent antibiotic exposure.

In a recent study, staphylococci from the oral cavity were all found to be susceptible to cephalosporins,[60] although an older study reported the presence of methicillin-resistant *S. aureus* in the oral cavity,[61] and this bacterium is notably difficult to eradicate from the oropharynx.[62] Peptostreptococci have also shown susceptibility to cephalosporins.[44] Kuriyama *et al.*[44] found that bacteria of the genus *Porphyromonas* and of the genus *Fusobacterium* showed susceptibility to cephalosporins, although fourth-generation cephalosporins were found to have higher MIC_{50}s and MIC_{90}s than older cephalosporins. This suggests that cephalosporins may be used inappropriately. Conversely, Eick *et al.*[50] found the nearly one-third of *Fusobacterium* spp. and one-third of *Veillonella* spp. were resistant to cefoxitin. Kuriyama *et al.*[44] found that a range of *Prevotella* species were resistant to a range of cephalosporins.

Resistance to β-lactams such as penicillins and cephalosporins is found in the oral flora, but the prevalence and degree of resistance is unclear. The potential to pass high-level resistance to *S. pneumoniae* makes it particularly important that the prevalence is determined with greater accuracy than is currently the case.

Tetracyclines

Mechanisms by which bacteria resist tetracycline include the synthesis of efflux proteins, production of ribosome protection proteins and enzymatic modification of the antibiotic. Tetracycline resistance is encoded by *tet* genes, of which 27 have currently been described, most of which are found in oral species.[53]

Antibiotic profiling of α-haemolytic streptococci isolated from the oropharynx of healthy Greek children showed 23% of isolates were resistant to tetracycline;[63] the majority of isolates were *S. mitis*. Konig *et al.*[39] also found two high-level tetracycline-resistant isolates of *S. mitis*.

Okamoto *et al.*[64] studied the prevalence of black-pigmented anaerobes of the genus *Porphyromonas* and of *Prevotella* spp., and the distribution of the *tet*(Q) gene amongst them. Of *P. nigrescens*, 46/167 (27.5%) isolates harboured *tet*(Q), as did three of 47 (6.4%) isolates of *P. intermedia*. In a separate study, 21% of *P. intermedia* isolates carried the *tet*(Q) gene, whereas only 15.2% of *P. nigrescens* carried the *tet*(Q) gene.[65] Contrary to the previous study, three of five (60%) *P. gingivalis* isolates also carried *tet*(Q), but this was in combination with the erythromycin resistance determinant *erm*(F).

Carriage of both *tet*(Q) and *erm*(F) is common.[66–68] Chung *et al.*[69] found 34 isolates of black-pigmented anaerobes, including *Bacteroides fosythus*, carrying both genes. Tetracycline resistance is also a frequent co-marker in penicillin-resistant oral strains.[70,71] Fosse *et al.*[25] found resistance to tetracycline frequently associated with β-lactamase production, with 50% of Gram-negative oral anaerobes isolated resistant both to tetracycline and to penicillins. Madinier *et al.*[55] found 4% of *A. actinomycetemcomitans* strains tested were resistant to tetracycline at the breakpoint of 8 mg/L; the MIC_{90} of tetracycline was 4 mg/L.

Tetracycline resistance is widespread. Furthermore, tetracyclines are used infrequently in dental practice because of the side-effects associated with this family of drugs, which can affect tooth colour.[72] Association of resistance to tetracyclines with penicillin and erythromycin resistance makes the high prevalence of tetracycline resistance potentially dangerous. Its presence may facilitate the dissemination of other resistance determinants.[65,73–75]

Macrolides and related antibiotics

Resistance to erythromycin is most commonly due to the acquisition of one of 21 *erm* genes. These code for rRNA methylases that bring about methylation of adenine residues in 23S rRNA, preventing the binding of macrolides to the 50S ribosomal subunit. Other mechanisms by which bacteria express macrolide resistance include drug inactivation by an enzyme encoded by *mph*, and efflux of macrolides by an ATP-binding transporter encoded by *msr*A found in *S. aureus*.[53] Low-level macrolide resistance in the oral flora may also be associated with the expression of genes in the *mef* family, encoding another efflux pump.[76,77]

Ioannidou *et al.*[63] studied macrolide resistance in oral α-haemolytic streptococci in healthy Greek children. Of 200 isolates, 77 (38.5%) were resistant to erythromycin, the macrolide most commonly used in dentistry, and 67 (33.5%) isolates were resistant to clarithromycin. Although the prevalence of resistance to each drug was similar, the MIC_{90} for erythromycin was twice that of clarithromycin. With 53% of isolates being resistant, *S. oralis* isolates showed the highest prevalence of resistance to erythromycin, followed by *S. salivarius* and *S. sanguis*, with 48% and 44% of isolates resistant to this drug, respectively.

A study by Sefton[78] in 1999 demonstrated the presence of resistant flora and the changes in the oral flora on administration of macrolides to patients with periodontal disease. Periodontal patients were subdivided into a treatment group and placebo group. The treatment group received the azalide, azithromycin. The total number of organisms recovered during sampling remained constant throughout the study but, as was shown in a similar study using tetracycline,[74] this was due to the replacement of susceptible organisms with a resistant population. Resistant streptococci increased significantly compared with the placebo group, and remained at raised levels for up to 3 months after treatment. These bacteria also showed cross-resistance to other macrolides.[78] This shows longer lasting effects compared with a similar study performed in the laboratory with tetracycline, where high level resistance was maintained for only 8 h.[74]

Macrolide resistance in oral anaerobes often occurs in conjunction with tetracycline resistance. Sanai *et al.*[65] investigated the antibiotic resistance of *P. gingivalis*, *P. intermedia* and *P. nigrescens*. Carriage of erythromycin resistance genes alone and tetracycline resistance genes alone was similar in all of the strains. An equal proportion of *P. intermedia* isolates carried *erm*(F) alone or *tet*(Q) alone (21% each, respectively). This is also seen in other *Prevotella* species.[65]

The recent study on the effect on oral biofilms of a single pulse of tetracycline demonstrated the relationship between tetracycline and erythromycin resistance.[74] Of the isolates resistant to tetracycline, 67% were also resistant to erythromycin. A single pulse of tetracycline selected for erythromycin-resistant isolates, as shown by the increase in the proportion of such isolates in the biofilms from 5% to 28%.[74]

Andres *et al.*[47] were able to link erythromycin and tetracycline resistance and β-lactamase production in Gram-negative anaerobes, concluding that they were associated with conjugative elements in oral *Prevotella* species. The co-transfer of resistance determinants to these three antibiotic classes occurs frequently within this genus, although the mechanism by which this happens has not been elucidated fully.

Chlorhexidine

Chlorhexidine is used widely by dentists and doctors as an antibacterial agent. Reports of *S. aureus* and *Streptococcus sanguis* using *in vitro* studies suggest problems with potential use owing to the emergence of resistance, which may be plasmid mediated.[79–81] Susceptibility testing *in vitro* of chlorhexidine against 141 isolates of *S. mutans* demonstrated that the MIC of chlorhexidine was ≤1 mg/L.[35] Resistance to chlorhexidine in *S. mutans* and *Streptococcus sobrinus* was absent following the application of chlorhexidine for 1 week; three different chlorhexidine applications, chlorhexidine varnish, chlorhexidine fluoride varnish and chlorhexidine fluoride gel, were given to 58 individuals, and the MIC of chlorhexidine against 863 isolates of *S. mutans* was ≤1 mg/L and against 53 isolates of *S. sobrinus* was ≤2 mg/L.[34]

Antibiotic prescribing by general dental practitioners

Because of the limitations imposed by the Dental Practitioners' Formulary, there is little variation in the class of antibiotic that dentists prescribe, although there is variation in the amount of antibiotics that practitioners prescribe.[82,83] Thus, it is important to establish the presence or potential presence of strains within the flora that express resistance to antibiotics. Particular attention should be paid to those antibiotics that are used most frequently in dental practice.

Therapeutic antibiotic prescribing

Sixteen years ago, dentists in a teaching hospital in Manchester were found to be giving too many prescriptions and performing too few surgical procedures.[84] In that study, indications for antibiotic prescribing were based on guidelines published by Cawson & Spector.[85] These guidelines required the proven presence of infection with a bacterial rather than a viral aetiology, which was thus likely to respond to antibacterial chemotherapy. The infection itself had to be severe enough to justify treatment. Alternatively, treatment would be justified if its use would prevent a serious infection, such as bacterial endocarditis. Lastly, the guidelines stated that antibiotics should only be used where no alternatives, including surgery, were available. In the Manchester study,[84] 153/192 patients (80%) were prescribed antibiotics as treatment for dental and oral infections, and 39/192 (20%) for prophylaxis. The most frequent antibiotic prescribed for infection was penicillin V (60% of total prescriptions); erythromycin (14%), amoxicillin (12%) and metronidazole (8%) were prescribed less frequently. Tetracycline was not prescribed. Amoxicillin accounted for 66% of prescriptions for prophylaxis.

Most dental infections can be treated successfully by removal of the source.[84,86] The majority of patients are, nevertheless, treated with antibiotics. A tendency to use antimicrobial treatment before resorting to dental extraction has been found. Only 25% of the 192 patients studied by Barker & Qualtrough[84] were treated first by dental extraction.

Results from subsequent studies have not challenged these conclusions. An analysis of a random 10% of prescriptions written by dentists in Scotland between May and October 1998 revealed evidence of poor prescribing practices.[20] Amoxicillin, metronidazole and penicillin V accounted for 90% of prescriptions, showing no great change in antibiotic choice since 1987. A range of 17 different antibiotics was prescribed. The doses were in accordance with recommendations in the Dental Practitioner's Formulary,[83] but there was wide variation in the frequency and duration. For example, prescriptions of amoxicillin in capsule formulation, which represented 73% of amoxicillin prescriptions, ranged from 2 to 20 days treatment. Only 39.1% of tetracycline prescriptions were correctly prescribed, at 250 mg.

Palmer *et al.*[21] conducted a similar study in England and found that 5.6% of prescriptions were for combinations of antibiotics, the most frequent combination being amoxicillin and metronidazole. This is not surprising, because of the polymicrobial nature of many dental infections. Recent guidelines published by the Commission of the Federation Dentaire Internationale, however, recommend that combination therapy should be avoided whenever possible in dentistry.[87] This recommendation was prompted by the wide variation in frequency and duration of antibiotic course and dose, with only 8.2% of prescriptions for penicillin V as recommended by the Dental Practitioner's Formulary[21] for most infections.

The Commission of the Federation Dentaire Internationale recommends that therapeutic antibiotics be given at a dose that will produce tissue concentrations higher than MIC for the pathogenic organisms implicated in the infection being treated.[87] The duration of treatment should be sufficient to eliminate the pathogens, although it is now argued that short-duration therapy is the most effective method to prevent development of resistance.[87] The choice of antibiotic for treatment must be based either on the likely pathogens and their probable susceptibility, or the susceptibility of pathogens cultured from the infection.[87] Other measures of antibiotic efficacy may also need consideration when choosing appropriate therapy. These include consideration of the ratio of the peak antimicrobial concentration at the site of infection to the MIC of the drug, the time that the concentration of drug at the site of infection is higher than its MIC against the pathogen(s) and the AUC/MIC ratio.[88]

Prophylactic antibiotic prescribing

The use of antibiotic prophylaxis is contentious in dental practice. Were infections to be caused by pathogens from the oral flora that are resistant to therapeutic agents, even if these occurred at sites that are remote from the oral cavity such as in cases of endocarditis, this would compromise management. This problem is now more than a theoretical possibility; Lonks *et al.*[89] report a case of endocarditis caused by an isolate of *S. mitis* resistant to penicillin and cefotaxime, although it remained susceptible to vancomycin. The patient in this case had recently undergone several dental procedures and was given amoxicillin for prophylaxis. The occurrence of resistance determinants encoding high-level resistance is increasing in the α-haemolytic streptococci; these provide an important gene pool that not only affects the oral flora, but also may complicate management of extra-oral infections.[38,90,91]

The antibiotics used for prophylaxis mirror those used for treatment. Amoxicillin, penicillin V and metronidazole are the most popular choices.[22] Guidelines recommend using an antibiotic prior to surgery that will attain a high serum concentration by the time that surgery begins, and that will be maintained until after surgery.[92,93] The same guidelines recommend a single high dose that is not to be continued after surgery.

The Commission of the Federation Dentaire Internationale published new guidelines in 1999, stating that prophylaxis before dental surgery is appropriate for patients at risk of infective endocarditis, for example those with prosthetic heart valves.[87] Other conditions for which prophylaxis is considered appropriate include patients with facial fractures, compound skull fractures or cerebral rhinorrhoea, immunocompromised patients, patients who have recently received radiotherapy to head and neck, and patients who have prosthetic hips, ventriculoarterial shunts or bone grafts. When questioned, only 21.8% of practitioners consider prophylaxis necessary for patients who have recently undergone radiotherapy to the head and neck,[22] but guidelines recommend prophylaxis in these cases since the blood supply is diminished following radiotherapy, making patients more susceptible to infection.[93] Dentists should work under the guidance of cardiologists or other specialists in the determination of valvular dysfunction with 'at risk' patients of this type.

Over 50% of dentists surveyed in England would seek specialist advice before administering prophylaxis to patients with HIV infection, although it is thought that they are no more at risk of complications following dental infection than the immunocompetent.[22] Most guidelines recommend considering each case individually, assessing the patient and the procedure and balancing benefits and risks.[87,93,94]

There is controversy surrounding the use of antibiotics for dental prophylaxis. For example, there is little or no evidence that oral microorganisms are significantly responsible for infections in prostheses other than cardiac prostheses.[94] The Working Party of the BSAC does not support the use of prophylaxis in these cases.[95] Of 891 dentists surveyed in England, however, 25.2% said they would prescribe prophylaxis for patients with prosthetic joints.[22]

The American Heart Association recommends prophylaxis against infective endocarditis in cardiac patients only in dental procedures associated with significant bleeding.[92] Such procedures include dental extractions, periodontal surgery and scaling. Reassuringly, the majority of dentists surveyed by Palmer *et al.*[22] would all prescribe prophylaxis for patients with cardiac conditions undergoing these procedures. High-risk patients include those with prosthetic heart valves, previous bacterial endocarditis or complex cyanotic congenital heart disease. Patients with a past history of rheumatic fever without valvular dysfunction are at negligible risk of infective endocarditis. Of dentists surveyed, however, 40% said they would give prophylaxis to these patients.[22]

Infective endocarditis occurs in up to 50 people per million per year, and 40% exhibit no known risk factors.[94] It has also been noted that cases of endocarditis involving oral microorganisms are related infrequently to dental treatment.[96] Additionally, Longman & Martin[93] affirm that the rate of post-surgical infection in dentistry is low. Are dentists, therefore, being unnecessarily cautious? Such caution may be necessary in this litigious era.[93] The guidelines drawn up by the American Heart Association have been based on experience and relevant literature rather than randomized or controlled human trials.[92] The use of prophylaxis is therefore based on careful prediction. Such

prediction is not sufficiently accurate to prevent infectious complications. It is not surprising that dentists opt to err on the side of caution.

Evidence in the literature suggests that antibiotic prescribing by dentists is often inappropriate. The Dental Practitioner's Formulary limits the number of antibiotics that dentists can prescribe to 13.[83] The choice of antibiotic that a dental practitioner makes, because the range of options is limited, is less likely to be inappropriate. It may therefore be the dose, duration or frequency of antibiotic prescription that is inappropriate. Yet the development of resistance in the oral flora is not due solely to the prescribing habits of dentists, who are responsible for only a small proportion of the total prescription of antibiotics.

Dental prescribing by practitioners outside the dental profession

Patients may choose to seek treatment from medical practitioners before consulting a dentist, and general medical practitioners are more likely to prescribe antibiotics than are dentists for acute dental problems.[97] A prospective cross-sectional study in May 1994 found this was the case in 41% of 500 consecutive patients attending the examination and emergency department of Cardiff Dental Hospital. Sixty of the 500 patients in that study were already receiving antibiotics when they attended the dental hospital.[19] Of these, general dental practitioners prescribed for 55% of cases, general medical practitioners prescribed for 33% and hospital doctors prescribed for 8%. Thus, even for dental infections, prescribing is not the exclusive domain of dental practitioners; others are also prescribing antibiotics, which in turn adds to the selective pressure for resistance.

Use of diagnostic microbiology laboratories by general dental practitioners

Diagnostic microbiology laboratories can provide information to assist in therapeutic decisions, resistance surveillance and the development of local policies and guidelines.[98] The evidence of inappropriate prescribing by dentists suggests that the facility is underused by the dental profession. Between 1993 and 1997, the number of specimens received from general dental practitioners by the microbiology laboratory of Glasgow Dental Hospital decreased by ~60%, from 45 samples to 17 per year.[98] It seems that bacteriological sampling only occurs where empirical therapy has failed. A questionnaire was developed by Palmer *et al*.[99] to assess the prescribing knowledge of dental practitioners in England and Scotland. A number of respondents, not specified by the authors, felt that when short of time it was acceptable to prescribe antibiotics without further investigation.[99] It was also felt that antibiotics could be prescribed if a definitive diagnosis could not be made or if treatment had to be delayed.[99] The immediate relief of the patient seems to be an important factor when considering treatment. This may also be fuelled by patient expectation. SMAC also cites patient expectation as a contributing factor to the frequency of antibiotic inappropriate prescribing.[1] Dentists would rather give antibiotics, and therefore give rapid relief to the patient, than take what may be a long time to process a bacterial sample in order to diagnose and treat the infection correctly. From the laboratory perspective, there are also logistical difficulties when processing dental specimens, owing to the lack of standard methodologies and the need to preserve the integrity of small specimens containing diverse populations of anaerobic bacteria during transport to the laboratory. Overall, the literature reveals a lack of communication between general dental practitioners and diagnostic microbiology laboratories.[84,98,99] More information about the service these laboratories can provide and information on the correct procedures for clinical sampling and transport would enable greater awareness and use of these facilities.

Discussion

The resistance data reviewed above demonstrate that the presence of resistance in oral flora is an international problem. Studies have been performed in countries including Germany,[50] Taiwan[30] and Brazil.[100] Nearly all have found a degree of antibiotic resistance present in particular oral commensals, often those associated with specific dental infections. The α-haemolytic streptococci and Gram-negative anaerobes, such as members of the genus *Prevotella*, appeared in the majority of studies reviewed, showing strains resistant to a range of antibiotics used commonly in dentistry.[30,38,54,63] Most strains tested show penicillin resistance, and there is only one antibiotic, metronidazole, to which the oral flora has yet to show significant resistance. Antibiotic resistance is not uniform within all strains, but even a low prevalence can change rapidly through a combination of the action of transferable resistance determinants and frequent exposure to antibiotics.

The literature suggests a significant contributing factor in the selection of resistance may be an unnecessary use of antibiotic prescriptions in dentistry. Studies conducted by Barker & Qualtrough,[84] Thomas *et al*.,[19] Roy & Bagg[20] and Palmer *et al*.[21,22,99] suggest inappropriate prescribing by dental practitioners. Although dental undergraduates are taught that most oral infections may be treated by surgical or mechanical means without the use of antibiotics,[84] dentists are prescribing millions of pounds worth of antibiotics every year.[82] The therapy used is typically empirical, employing broad-spectrum antibiotics. Furthermore, culture and susceptibility testing to aid diagnosis and the rational choice of antibiotic often do not precede prescription for dental infection.[98] This means that antibiotics are being prescribed for a range of dental infections for which they may not be required. This inappropriate prescribing results in frequent exposure to broad-spectrum antibiotics, predisposing to selection of resistant strains. It is therefore hardly surprising that resistance is present in the oral flora, and has the potential to pose real problems in terms of morbidity, cost of care and future treatment choice.

This issue is contentious. The American Dental Association suggested that dentists are responsible prescribers of antibiotics and are unlikely to play a major role in the global problem of antibiotic resistance.[101] The UK Department of Health take a different view: SMAC's *Path of Least Resistance*[1] lists dentists as contributors to the problem, along with medical practitioners, veterinarians and those involved in agriculture.

Further investigation is required to confirm the results that patients attending dental hospitals have already been prescribed antibiotics by their general practitioners.[34] Examining prescriptions and prescribing practices of dentists alone, however, may not be sufficiently informative. The prescribing of antibiotics by medical practitioners has already been found to contribute to resistance development in a range of pathogenic and commensal organisms, including those in the oral flora.[1] If doctors are consulted frequently regarding dental infections, and are therefore prescribing for these infections, the effect of dental prescribing on the development of antimicrobial resistance in the oral flora may be less significant than the evidence suggests. Furthermore, as the antibiotics that dentists prescribe are used for treatment of infections other than those associated with the oral cavity, the prescribing of these drugs by medical practitioners

will provide a further selective pressure for resistance. Additionally, as medical practitioners are not expert in the treatment of dental problems, it would not be surprising to find them prescribing inappropriately for dental infections that may only require surgical or mechanical intervention. Guidelines and education regarding prescribing for dental infections may well need to be targeted to medical practitioners as well as dentists.

The problem of antibiotic resistance in the oral flora requires further investigation. More audits of antibiotic prescribing practice may be helpful, although it must be remembered that prescriptions are an indirect measure of antibiotic consumption and are not a measure of the rate of resistance emergence, which is multifactorial.[102] Palmer *et al*.[103] examined the potential of audits to alter prescribing habits. The results were encouraging; the number of prescriptions for antibiotics declined by 42.5% after the initial 6 weeks of the audit. In the first period, 2316 prescriptions were issued; this fell to 1330 after educational meetings half way through the process. Thus, there was a significant change in the appropriateness of prescribing during the study.[103] The audit and the resulting guidelines, and educational meetings addressing the problems revealed by the audit, were therefore found to be effective, at least in the short term.

In May 1997, Health Canada and the Canadian Infectious Disease Society held a national conference in Montreal entitled 'Controlling antimicrobial resistance: an integrated action plan for Canadians'. The aim was to develop a plan to limit the development of antimicrobial resistance and its spread.[104] Dental practitioners were represented at the conference and a number of recommendations were made, to be implemented by all practitioners prescribing antibiotics. One was the establishment of a surveillance system to determine the extent of resistance and to monitor the use of antibiotics.[104] Currently, there is no surveillance system in the UK that monitors resistance in the oral flora. Surveillance may be used to monitor the susceptibility of microorganisms and to detect any changes in that susceptibility.[105] It may also provide information that will allow the formulation of strategies to combat antimicrobial resistance, including policy changes, formulary changes and alteration of prescribing practices. It may also be used to assess the impact of any strategies on resistance selection and transmission. Resistance trends, including the most prevalent mechanisms of resistance and their transmission, may also be determined from surveillance data.[105–107]

The diagnostic microbiology laboratory has a significant role to play in surveillance, through identification of organisms with a pathogenic role in infection, and their subsequent susceptibility testing. It is therefore important to establish better awareness and communication between general dental practitioners and diagnostic microbiology laboratories. Information obtained from microbiological testing must be collated and disseminated rapidly to health care professionals and other appropriate groups for it to be employed usefully. Local surveillance networks are most important for guiding clinicians in the use of empirical therapy and managing resistant infections.[108] It is important to include all health professionals in such networks.

Strains of bacteria resistant to antibiotics are present within the oral flora in sufficient quantities to warrant further investigation. There is evidence that inappropriate prescribing by dental practitioners may be contributing to the development of this resistance. If so, then the dental profession must take steps to prevent the problem from becoming worse. Comprehensive undergraduate and postgraduate education on the subject is required. Further studies and establishment of a surveillance system are also to be recommended. Clear guidelines and prescribing policies need to be developed to attempt to limit resistance within the oral flora. Antibiotic use by dentists affects flora that exist beyond the oral cavity, since, during therapy, antibiotics become distributed throughout the body. Antibiotics prescribed by medical practitioners also have similar broad effects. If dentists, along with medical practitioners, can reduce the number of antibiotic prescriptions, the rate of resistance development may be slowed.

There is reason for concern regarding antibiotic resistance in dental practice. The installation of a surveillance system, accompanied by audit to ascertain the numbers of prescriptions written and their appropriateness, to highlight areas of prescribing knowledge that are lacking in dental practice are recommended. Further investigation and education are required to attempt to slow resistance development and lessen the future impact on antibiotic prescribing in dentistry. The emergence of antibiotic-resistant bacteria within the oral flora will have an impact on the prescribing of antibiotics in dentistry. Action must be taken now to lessen this impact in the future.

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