Antibiotic stewardship in dentistry – review of evidence-based clinical recommendations on appropriate antibiotic prescribing in dental practice

Part 1: The antibiotic resistance crisis and the principles and practices of appropriate antibiotic prescribing

Johan Hartshorne[1]

Acknowledgements:
I thank the following individuals for their expertise and assistance in reviewing and revising the manuscript scientifically and technically: Dr Cameron Meyer, Group Clinical Officer, Intercare Group, Pretoria; Dr Carl de Villiers, Clinical Advisory Committee and General Dentist, Intercare Medical and Dental Centre, Glen Marais; Dr Linton Brown, Clinical Advisory Committee and General Dentist Intercare Parow Medical and Dental Centre, Parow; Dr Harry Vermeulen, Clinical Advisory Committee and General Dentist, Intercare Wilgeheuwel Medical and Dental Centre Wilgeheuwel.

Executive summary

Rational

- The efficacy of antibiotics is slowly being compromised by a growing number of antibiotic resistant strains due to inappropriate use of antibiotics.
- Antibiotics are used inappropriately in 75% of cases involving dental conditions.
- Subsequent infections caused by antibiotic resistant pathogens are difficult, and at times impossible, and costly to treat.
- Implementing antibiotic stewardship efforts in dental practice are an opportunity to improve antibiotic prescribing practices and to curb the pandemic issue of antibiotic resistance.

Key Points

- The key to reducing antibiotic resistance and the number of adverse drug reactions is by avoiding unnecessary and inappropriate antibiotic prescribing.
- Antibiotics should be only prescribed when indicated for prophylactic therapy such as infective endocarditis, presence of regional or systemic body manifestations, or to fight infections in patients with immune suppressed or immune compromised conditions.
- A proper dental and medical history and clinical assessment is fundamental in minimizing misdiagnosis leading to overuse of antibiotics, for appropriate antibiotic selection to improve efficacy of antibiotic therapy, and to prevent adverse events and drug interactions.
- Antibiotics should be used in conjunction with, but not as an alternative or replacement to other appropriate interventions, such as endodontic therapy, periodontal debridement, or surgical extraction of a tooth.

[1] Dr Johan Hartshorne
B.Sc, B.Ch.D., M.Ch.D., M.P.A., PhD. (Stell), FFPH. RCP. (UK)
Intercare Dental Clinical Advisory Committee and General Dentist
Intercare Tyger Valley Medical and Dental Centre, 43 Old Oak Rd., Tyger Valley, Bellville
Email: johan.laptop@intercare.co.za
Mobile No: 082 5512 993

Practical implications

- Narrow-spectrum antibiotics should be prescribed for the shortest duration possible until the clinical cure of the patient is obtained and to minimize disturbance of the normal gut flora.
- Recommend the use of a probiotic to prevent microbial disturbance when prescribing an antibiotic.
- Clindamycin should be used judiciously and with caution due to its high frequency of adverse effects.
- Safety and product cost should always be taken into consideration with antibiotic selection.
- In almost all situations where an oral infection shows signs of systemic spread, proper local management and initiating antibiotic use is of benefit and likely outweighs the risk.
- Every prescribing health care practitioner should have an authorative reference (e.g. MIMS) readily available.

Introduction

Antibiotics represent one of the most successful forms of therapy in medicine. However, the efficiency of antibiotics is slowly being compromised by a growing number of antibiotic resistant pathogens worldwide.[1,2] The overuse of antibiotics means that they are becoming less effective and has led to the emergence of "superbugs". These are strains of bacteria that have developed resistance to many different types of antibiotics. Antibiotic resistance is increasing at an alarming rate whilst a growing list of infections are becoming harder and at times impossible to treat due to antibiotics becoming less effective. [3]

Antibiotic resistance does not mean the body is becoming resistant to antibiotics; it is the bacteria that have become resistant to antibiotics designed to kill them.

The implications of antimicrobial resistance are that microbial pathogens are not killed and continue to grow and exchange genes through horizontal transfer and mutate.[4] Subsequent infections caused by antibiotic resistant pathogens are difficult, and at times impossible to treat.[5,6]

Antibiotic resistance can affect people at any stages of life, as well as healthcare, veterinary, and agricultural industries, making it one of the world's most urgent public health problems.[5,6]

Every time a new antimicrobial is introduced, drug resistance to that antimicrobial occurs swiftly, for antibiotics, antivirals and antifungal therapies.[7] Antimicrobial treatment places selective pressure on the organisms, favouring the emergence of drug resistant strains.

In the USA alone, at least 2 million people are infected with antibiotic resistant bacteria, and at least 23000 people die as a result every year. [5,6] No one can avoid the risk of resistant infections, but some people are at greater risk than others e.g., people with chronic illnesses (i.e. periodontitis, diabetes, COPD, cancers, Alzheimer's disease, autoimmune diseases), immune-suppressed individuals, immune-compromised conditions, frail and elderly.

If antibiotics lose their effectiveness, then we lose the ability to treat infections and to control public health threats.

Antibiotic resistance is implicated in elevated mobidity and mortality rates, require extensive and expanded medical care, as well as increased treatment costs, extended hospital stays, and sometimes requires toxic therapeutic alternatives, and is increasingly being recognized as an emerging global public health threat.[1,2,6] Appropriate antibiotic stewardship by dentists is urgently needed in view of the pandemic issue of antibiotic resistance.[8]

Currently, there is a challenge to accelerate the fight against antimicrobial resistance across the globe.[6] The emerging antibiotic resistance crisis has prompted the World Health organization (WHO) and the Centers for Disease Control and Prevention (CDC) to take action to protect the public.[1,6,9]

Global antibiotic resistance together with the lack of newly developed antibiotics represents an alarming signal for both human and animal healthcare worldwide. [10,11]

Reasons for the antibiotic resistance crisis

• Misuse and overuse of antibiotics

It is suggested that the overuse and misuse of antibiotics is the primary driver and cause of the evolution of bacterial resistance against antibiotics.[3,4,5,12,13]

Various studies have recently reported on the inappropriate use of antibiotics in dental practice.[14-22] Studies suggest that 30% to 50% of prescribed antibiotics are unnecessary or not optimally prescribed.[5,23] In another study it was reported that antibiotics are used inappropriately in 75% of cases involving dental conditions.[24] It is essential to understand that antibiotic therapy will fail if the source of infection is not removed. Primary dental and surgical procedures should always be the first line of care, with antibiotics serving as adjunctive therapy in indicated cases.[25,26] Antibiotics are not a replacement for surgical drainage or debridement.

Indications for the use of systemic antibiotics in dentistry are limited because most dental and periodontal disease is best managed by operative interventions and plaque control measures. The current use of antibiotics in dental practice is best characterized by empirical prescription based on

clinical and bacteriologic epidemiological factors resulting in the use of a very small range of broad-spectrum antibiotics for short periods of time. Prolonged use of antibiotics only serves the purpose of selecting resistant bacterial species.[27] This has contributed towards the development of antibiotic resistance in a wide range of bacteria and subsequent inefficacy of commonly used antibiotics.[28] The increasing antimicrobial resistance over recent years is probably related to the over- and misuse of broad-spectrum antibiotics.[28]

Consequently, there is a clear need for the development of evidence-based antibiotic prescribing guidelines. Educational and policy initiatives to encourage the rational and appropriate use of antibiotics in dentistry and oral medicine are also needed. This may help to curb the increasing incidence of antibiotic resistance and other adverse effects of antibiotic use, including gut microbial dysbiosis, *Clostridiosis difficile* (formerly Clostridium) (*C. difficile*) infection and allergies.

• *Bacterial genetic mutation and adaptation*

Antibiotic resistance occurs naturally through evolution characterized by genetic mutations, acquisition of genetic material or alterations of gene expression and metabolic adaptation through the process of horizontal gene transfer between bacteria.[4,29]Bacteria possess an enormous diversity of genes, which are constantly changing through horizontal transfer of genes allowing antibiotic resistance to be transferred among different species bacteria that allow them sooner or later to counteract the action of newly invented antibiotics.[1,4] In addition, antibiotics remove drug-sensitive competitors, leaving resistant bacteria behind to reproduce in a process of natural selection.[4] Every time a new antimicrobial is introduced, drug resistance to that antimicrobial takes place swiftly, and this occurs for antibiotics, antivirals and antifungal therapies.[7] Antimicrobial treatment thus places selective pressure on the organisms, favouring the emergence of drug resistant strains.

• *Diminishing pharmaceutical investment*

In addition to the overuse and misuse of antibiotics, the lack of new antibiotic development by the pharmaceutical industry, due to reduced economic incentives and challenging regulatory requirements have contributed towards the antibiotic resistance crisis.[2,9,30-36] Of the 18 largest pharmaceutical companies, 15 have abandoned the antibiotic field.[7,37] Antibiotic development is no longer considered to be profitable or an economically wise investment for the pharmaceutical industry.[37]

Until recently we have escaped the dire consequences of antibiotic resistance because there has been a stream of new antibiotics. However, over the last two decades the number of pharmaceutical companies investing in this area has diminished from 18 to 3, inevitably leading to stalled drug development.[7]

Principles and practices for optimal antibiotic prescribing in dentistry [38]

• *Core elements and objectives of antibiotic stewardship*

Antibiotic stewardship assists health care providers with judicious and appropriate use of antibiotics for patient use.

"Appropriate clinical decision-making with regard to antibiotic use requires the clinician to evaluate the needs of the individual patient and provide the best treatment for that patient. At the same time, the clinician should consider what is the best for the long-term sustainability of antibiotics as an effective means of patient care. This dual responsibility is at the core of antibiotic stewardship"[39].

[39]Antimicrobial stewardship has been defined by the Infectious Disease Society of America and the Society for Health Care Epidemiology of America as " an activity that included appropriate selection, dosing, route, and duration of antimicrobial therapy."[40] Although antibiotic stewardship concerns the development of resistant bacteria, the emerging evidence of the causal link between changes in the gut flora and the development of systemic disease makes the endeavour even more important and complex.[41]

The objectives of antibiotic stewardship are to improve prescribing habits with the intention to:

- Improve clinician prescribing and patient use so that antibiotics are only prescribed and used when needed.
- Minimize misdiagnosis leading to overuse of antibiotics.
- Ensure that the right drug, dose and duration is prescribed when an antibiotic is needed.[38,39]

1. Pre-treatment principles and practices

• Correctly diagnose oral bacterial infection

Oral bacterial infections have a predictable presentation in the oral cavity usually characterized by redness, pain, swelling in the tissues around the tooth; advanced infections will often be associated with an exudate (pus). The dental surgeon should take a detailed history and thorough systemic, local and radiographic examination to diagnose the disease as infection. In addition, one should also do a hematologic, serologic and other laboratory examination wherever necessary to diagnose and to evaluate the origin or severity of oral and maxillofacial infections.[42]

• Consider therapeutic management interventions

Therapeutic interventions, with primary focus on eliminating the pathology that led to the infection, may be sufficient to control a localized bacterial infection.

Therapeutic interventions include periodontal debridement, endodontic treatment, tooth extraction, or incision drainage.

• Consider antibiotics when regional and/or systemic manifestations are present

According to a recent systematic review, antibiotics should only be prescribed when regional and/or systemic body manifestations are present within the previous 24 hours e.g., presence of pronounced oedema (cellulitis), limited mouth opening (trismus), increased heart rate (tachycardia), rapid respiration, lymphadenopathy, difficulty swallowing (dysphagia), general malaise, and fever (pyrexia) [26]

• Consider antibiotics when patients present with immune suppressed or immuno-compromised conditions

Antibiotics should be prescribed to fight infection when there is presence of a disease affecting the host defence system e.g. AIDS, cancer, autoimmune disease, patients on corticosteroid therapy, immune-compromised conditions, diabetes, chronic renal failure, patients who have undergone chemotherapy or radiation therapy or patients that have received organ transplants.[42]

Patients that are immune suppressed or immune-compromised are at higher risk of infection and are more likely to benefit from prophylactic antibiotics, because infections in this group are likely to be more frequent, associated with complications and may be more difficult to treat.[43]

• Weigh possible benefits and risks

All drugs have risks. Weigh the possible benefits versus risks (i.e. toxicity, allergy, adverse effects, *C. difficile* infection) of antibiotics before prescribing. Be aware of the risks of the primary antibiotics used to treat dental infections: penicillin's, azithromycin and especially clindamycin. *C. difficile* infection (pseudomembranous colitis) is often associated with clindamycin and other broad spectrum antibiotic use. This is the most common serious side effect of antibiotic use. Penicillin allergy is also a serious risk. Closely monitor patients with extensive medical problems and those taking multiple medications.

In almost all situations where an oral infection shows signs of systemic spread, proper local management and initiating antibiotic use is of benefit and likely outweighs the risk.

• Prescribe antibiotics only for patients on record and only for bacterial infections you have been trained to treat

Clinicians must know and understand the patient's medical history and be familiar with their dental history for safe and effective patient care.

Familiarity and experience with managing bacterial dental, periodontal and oral mucosal infections are essential for the best perspective and decision-making.

Consultation and referral with a specialist is appropriate when an infection shows signs that it is outside the clinician's area of training and experience, e.g. altered eye movement, suggesting infection has entered into the cranial space, or difficulty swallowing, suggesting that the infection is spreading into deep neck tissues.

• Do not prescribe antibiotics for viral and fungal infections, ulcerations related to trauma, or aphthae in the oral cavity

Viral infections manifest as blisters and constant pain at the site of the blister/ulcer.

Fungal infections usually present with redness and some white areas that can be rubbed off using gauze.

Ulcerations related to aphthous ulcers or autoimmune diseases such as lichen planus, pemphigoid and pemphigus, usually hurt when exposed to acid like orange or tomato juice and salty foods.

Traumatic ulcers incidents are generally recalled by the patient, are not an infection and do not commonly become infected unless the patient is immune-suppressed, or has a medical problem that compromise their ability to heal (i.e. diabetes).

• Implement antibiotic prophylaxis recommendations for the medical concerns for which guidelines exist

The American Heart Association and the American Dental Association have developed guidelines for the prophylactic use of antibiotics to prevent infective endocarditis, in patients with specific cardiac conditions.[44,45]

In most cases, prophylactic antibiotics are NOT recommended for patients with prosthetic joints. If in doubt, consult with the patient's surgeon or physician.

Severely immunosuppressed patients, such as those undergoing chemotherapy, corticosteroid therapy or patients with immune compromised diseases such as AIDS, cyclic neutropenia and uncontrolled diabetes, are at an increased risk of systemic infection from an oral source.[42,43] Clinicians may elect to be more aggressive in initiating antibiotic use in

such patients and may elect to use antibiotics prophylactically to prevent an infection if the intended dental or periodontal procedure may cause bacteremia.

• Assess medical history and conditions, pregnancy status, drug allergies, and potential drug interactions and adverse events that may impact antibiotic selection.

All medications have risks; the antibiotics commonly used in dentistry – penicillin's, clindamycin and azithromycin – are no exception.

A proper medical history should reveal any medications that may risk drug interactions. Primary antibiotics used for dental infections (penicillin's, clindamycin and azithromycin) are not commonly associated with such adverse drug responses. Drugs that inhibit liver cytochrome P450 enzymes are most commonly associated with drug interactions. In dentistry these are metronidazole and erythromycin (both antibiotics) and ketoconazole (an antifungal). Avoid using these drugs in patients taking specific medications that are metabolized in the liver.

The clinician should consult an authorative reference (MIMS), the patient's physician or pharmacists, before prescribing an antibiotic when there is any concern of drug interaction.

2. Prescribing principles and practices

• Ensure that an evidence-based antibiotic reference (i.e. MIMs – Monthly Index of Medical Specialities) is readily available during patient visits

While most clinicians are well versed in the antibiotic choices for oral bacterial infections, it is prudent for the clinician to have at least one of several recognized prescribing reference resources readily available.

• Avoid prescribing based on non-evidence-based historical practices, patient demand, convenience, or pressure from colleagues

Avoid any non-evidenced based pressures that may influence the clinician's decision making in situations where antibiotic use is not indicated. This may lead to inappropriate antibiotic use and result in a poor clinical outcome for the patient.

• Thorough documentation in the patient's file

Clear and complete documentation of the diagnosis of an oral bacterial infection, the treatment steps, and the rationale for antibiotic use (if prescribed) should be made in the patient's record.

• Prescribe only when clinical signs and symptoms of a bacterial infection suggest a systemic immune response, such as fever or malaise along with local oral swelling

A local oral bacterial infection is best and effectively managed through mechanical intervention (e.g. extraction, endodontic therapy, and cleaning and irrigation of the infected site) to eliminate the irritant or foreign body causing the infection. Once effective cleaning and removal of the irritation is accomplished, the body's immune system should clear up remaining infection. A good policy to teach is never to let the sun set on puss.

Antibiotic therapy however, is appropriate if there are signs and symptoms of a systemic immune response.

• Use the most targeted (narrow-spectrum) antibiotic for the shortest duration possible. (2-3 days after the clinical signs and symptoms subside)

Most bacterial organisms associated with oral infections are sensitive to penicillin's, making it the first drug of choice as follows:

Penicillin VK, 500 mg given 4X daily or Amoxicillin, 500mg given 3X daily.

If there is no response in 48 to 72 hours, then amoxicillin protected from beta-lactamase with clavulanic acid (e.g. Augmentin) can be tried, 1000mg 2X daily.

If the patient has a true IgE mediated allergy to penicillin's, then the drug of choice is Clindamycin 300mg given 4X daily.

Patients that are unable to take clindamycin may be prescribed Azithromycin, 500mg given 1X per day.

The number of tablets/capsules prescribed should be enough for 10 days and the patient should be instructed to take the antibiotic as prescribed for two to three days after the clinical signs and symptoms are gone. Antibiotics should be used for the shortest time possible until the patients' clinical cure is achieved.[26]

Consider the most appropriate route of administration. Topical>Oral>IM>IV

Use microbiome protection therapies (i.e. probiotics) for all cases.

Clinicians should urge disposal of unused antibiotics immediately upon completion of treatment.

The duration of antibiotic therapy influences resistant development. A meta-analysis of antimicrobial use in primary care concluded that longer treatment duration was associated with an increased risk of emergence of antibiotic resistance.[46]

• Revise empiric antibiotic regimens on the basis of patient progress and, if needed culture results

All patients taking antibiotics for an oral bacterial infection should be followed closely to make sure the infection is resolving and that there are no adverse effects.

A patient taking an antibiotic as prescribed following a proper incision and drain or mechanical intervention should start to see a positive response within 48 to 72 hours. Patients not improving in that time frame or who are experiencing adverse responses to the antibiotic should be re-evaluated and their antibiotic changed to the next drug of choice.

For poorly responding patients, a consultation with a specialist may be appropriate as well as a culture and sensitivity test to ensure the correct antibiotic has been chosen.

• Discuss antibiotic use and prescribing protocols with referring specialists

All clinicians managing a patient's care should utilize similar evidence-based protocols, including the first, second and third drug of choice, at the proper dosage for the proper duration.

The use of similar protocols improves the care of shared patients and decreases the risk of conflict for the clinicians and confusion for the patient.

3. Patient education

• Educate patients to take antibiotics exactly as prescribed, to take antibiotics prescribed only for them, and not to save antibiotics for future illnesses

Antibiotics are complex drugs with different absorption rates, half lives and elimination mechanisms, all of which influence the prescribed dosage.

Antibiotics must be taken as prescribed to be effective; many antibiotic failures can be traced back to the fact that the patient did not comply with the clinician's recommended dosage.

Clinicians should clearly and unequivocally inform patients of the need to take their medication as directed for two to three days after the clinical signs (fever, swelling, redness) and symptoms (pain) have resolved.

Clinicians should instruct patients to dispose of unused drugs immediately upon completion of treatment and provided guidance on drug disposal options.

Patients who refuse to take a prescribed antibiotic as directed, for any reason, must be instructed to immediately inform the prescribing clinician so an alternative treatment approach can be identified.

4. Staff Education

All members of the dental team should be educated about oral bacterial infections, the office treatment protocols, the rationale for the steps in the infection protocol and the criteria used to initiate antibiotic therapy.

Staff training improves the probability of patient compliance with antibiotic prescriptions.

Classification, characteristics and application of antibiotics commonly used in dental practice

Antibiotics are a subset of antimicrobials (Antimicrobials also include antivirals, antifungal, antiprotozoal). The most commonly used antibiotics in dental practice according to class of antibiotic are summarized in Table 1.

The prudent use of antibiotics requires an understanding of: (i) what is an antibiotic; (ii) why we should use an antibiotic; (iii) when we should use an antibiotic; and (iv) how we should use and antibiotic.[42]

Pathogenic microbial flora and antibiotic sensitivity patterns in odontogenic infections

The most common odontogenic infections are dental caries (99,4%), gingivitis (56,4%), periodontitis (38,4%), peri-apical; (6,4%) and peri-coronitis (3,8%).[47] Maxillofacial spaces, especially the buccal spaces are frequently involved (54%). Most odontogenic infections are caused by bacteria normally found within the oral cavity. Approximately 50% of odontogenic infections are caused by anaerobic bacteria alone, 44% by a combination of aerobic and anaerobic and only 6% by aerobic alone.[48] A recent study by López-Gongález and co-workers reported that bacteria associated with odontogenic infections were mainly anaerobic (65,3%) and aerobic (35,7%) and exibit a high resistance to antibiotics[49]

The efficacy of antibiotics against isolated organisms varies considerably: clindamycin (88%), metronidazole (79%), cefotaxime (72%), erythromycin (72%), amoxiclav (71%), ciprofloxacin 967%), vancomycin (65%), cefadroxil (59%), ceftazidine (59%), azithromycin 58%).[47]

López-Gongález and co-workers reported in their study that the majority of microorganisms (82%) were sensitive to amoxicillin/clavulinic acid.[49]

The main principle of treatment of odontogenic infections is to establish drainage of the abscess either through endodontic therapy or the removal of the tooth. Prescribing antibiotics should be considered an adjunctive therapy to surgical intervention.[50]

Table 1: Classification dosage, application and characteristics of commonly used antibiotics in dental practice

Class	Drug names	Dosage	Interval (hr)	Activity	Side-effects
Penicillin	Penicillin VK (NS) Ampicillin (NS) Amoxicillin (NS) *Amoxicillin/ Clavulanic acid (BS)	500mg 500mg 500mg 875	6 (qid) 6 (qid) 8 (tds) 12 (bd	Bactericidal Inhibits cell wall synthesis * Broad spectrum Aerobes Gm-ves Gm+ves	Minimum toxicity Diarrrhea, vomiting, Hypersensitivity allergic reactions
Cephalosporins	1st Generation Cefazolin (NS) Cephalexin (NS) 2nd Generation* Cefaclor (BS) Cefuroxime (BS) 3rd Generation* Cefixime (BS) Ceftriaxone (BS) 4th Generation* Cefpirome (BS) Cefipin (BS)	500mg	6 (qid)	Bactericidal Inhibits cell wall synthesis *Broad spectrum Aerobes Gm +ves Gm-ves	Diarrhea, nausea, vomiting, 5-10% cross reaction with penicillin – allergy Haematologic toxicity
Macrolides	Erythromycin (BS) Azithromycin (BS) Clarithromycin (BS)	500mg 250mg 500mg	6 (qid) 12 (bd) 24	Bacteriostatic Blocks protein synthesis Broad spectrum Gm+ves Gm-ves	Liver toxicity Diarrhea Nausea , vomiting Coumadin interaction
Lincosamide	Clindamycin (NS)	300mg	6 (qid) (max 1,8gm / day	Bacteriostatic Inhibits protein synthesis Gm- aerobes Gm+ aerobes & anaerobes	Pseudomembranous colitis; *C.difficili* Hypersensitivity reaction
Tetracycline	Doxycycline Minocycline (BS)			Bacteriostatic Blocks protein synthesis Gm+ & Gm-aerobes	Diarrhea, nausea, vomiting Tooth discoloration
Fluoroquinolones	Ciprofloxacin Moxifloxacin (BS)	500mg 400mg	12 (bd) 24	Bactericidal Inhibits DNA synthesis Broad spectrum Gm+ves Gm-ves	Avoid in pregnancy Toxic effect on chondrocytes, tendon fractures Inhibits fracture healing
Imidazoles	Metronidazole (NS)	500mg	6 (qid)	Bactericidal Narrow spectrum Inhibits RND synthesis Anaerobes Gm+ves Gm-ves C.difficile	Hepatotoxicity Body fluid discoloration Incompatible with alcohol

(NS = Narrow spectrum; BS – Broad spectrum)

Adverse reactions and unintended consequences associated with prescribing antibiotics in dental practice

Antibiotics are considered the keystone of modern medicine, but their excessive use continues to generate unwanted adverse effects around the world ranging from diarrhoea, to life threatening allergic reactions.[7]

A recent study on antibiotic prescribing in England revealed that the most commonly prescribed antibiotics ranked from least to most likely to cause adverse drug reactions were as follows: amoxicillin<cephalosporins< erythromycin<tetracyclin<azithromycin< metronidazole< amoxicillin+clavulinic acid<clarithromycin<penicillin V< clindamycin.[51] This study confirmed that amoxicillin, the most common prescribed antibiotic by dentists had the highest level of safety of all antibiotics prescribed by dentists. Of all the antibiotics prescribed by dentists, clindamycin was least safe presenting with 15 x greater likelihood to cause an adverse drug reaction and a 30x greater likelihood to cause a fatal adverse drug reaction.[51]

Another study quantified the most prevalent adverse events from antibiotic prescribing amongst adults in Emergency departments in the USA during the period 2011-2015[52], are summarized in Table 2.

Hypersensitivity reactions and cross-reactivity

The most common adverse event to antibiotics manifesting across all antibiotic classes, is sensitivity reactions.[52] (Table 3) They are usually mild and limited to rash or skin lesion in the head and neck region. Antibiotics, especially penicillin's, cause allergic reactions ranging from rash, skin reactions, Stevens-Johnson syndrome to breathing difficulty and anaphylaxis.[53] Life-threatening anaphylactic reactions have occurred in some highly sensitized individuals, but remain rare.[54]

The use of cephalosporins in patients with penicillin allergy has been a concern. The latest literature shows that cross reactivity between penicillin's and 3rd and 4th generation cephalosporins is negligible and it is therefore considered safe to administer a cephalosporin with a side chain that is structurally dissimilar to that of penicillin or to administer a 3rd or 4th generation cephalosporin.[55]

Dysbiosis of the gut microbiome and gastrointestinal conditions

Risks associated with the use of antibiotics include, nausea, vomiting, diarrhoea and stomach cramps because of disturbance of the gut microbiome.[53]

The gut microbiome contains around 100 trillion bacteria that support digestion and the immune system. Aggressive antibiotics can wipe out the good bacteria, whilst strengthening the bad bacteria. Key pathogens, such as *C. difficile* flourishing in the perturbed gut microbiome are immune to antibiotics, resulting in *C. difficile* diarrheal infections.[32] Patients who are more vulnerable to adverse effects include children, elderly, hospitalized, those with chronic inflammatory and/or immune compromised conditions. Recent studies indicate that antibiotic therapy can induce changes in the commensal flora is not always fully reversible and that may represent a risk for further colonization and dysbiosis- and infection with bacteria possessing antibiotic resistance.[56]

Other side effects include the development of fungal infections in the mouth or vagina resulting from an imbalance in the body's normal flora.

Table 2: The prevalence of adverse events following antibiotic prescribing amongst adults

Antibiotic class	Mild allergy	Moderate to severe allergy	Gastro-intestinal disturbances	Other
Penicillin	57,5	23	15,9	
Cephalosporins	59,3	21,7	14,7	
Macrolides	59,4	17,4	18,1	
Lincosamide	48,3	22,9	27,0	
Tetracycline	44,9	19,8	28,3	
Fluoroquinolones	47,6	15,8	25,4	
Imidazoles	43,2	26,2	19.6	6,0

(Adapted from: Geller, Lovegrove, Shehab et al, 2018)[52]

C. difficile infection (CDI)

C. difficile is spore forming, Gr-positive anaerobic bacillus found in the gut, that is the cause of 15-25% of all episodes of antibiotic associated diarrhoea.[6] CDI can result in pseudomembranous colitis, toxic megacolon, colon perforations, and sepsis. Clinical factors associated with increased risk of CDI include age older than 65yrs, and underlying systemic disease. Antibiotics associated with higher risk of CDI include clindamycin, cephalosporins and the fluoroquinolones.[57]

Studies have shown that more than 50% of antibiotics prescribed for children are for upper respiratory tract infection associated with common cold. Because the majority of common cold infections are viral, using antibiotics to treat such infections does nothing to stop the infection. Instead, it creates unwanted side effects. Studies have shown that children given antibiotics for routine upper respiratory tract infections are more susceptible to aggressive antibiotic resistant strains of bacteria commonly known as *Clostridiodes* (formerly *Clostridium) difficile*. *C. diffcile* associated diarrhea is responsible for 250000 infections in hospitalized patients and 14000 deaths every year among children and adults in the USA.[32]

Peripheral neuropathies

Isolated cases of peripheral neuropathies, leading to numbness or paraesthesia, have been reported with use of metronidazole. The medication should be discontinued instantly if such signs appear.[58]

Hepatotocicity

Some antibiotics are metabolized in the liver, e.g. erythromycin, clindamycin and metronidazole. In patients with liver failure use of such drugs should be restricted.[59]

Drug interactions

Almost all antibiotics can potentiate the effects of Warfarin by inhibiting intestinal flora that produce Vit. K, thus enhancing the anticoagulant effect and increasing the risk of bleeding. Antibiotics that inhibit Warfarin metabolism is ciprofloxacin, clarithromycin, erythromycin and metronidazole.[60]

Fluoroquinolone antibiotics are useful antibiotics in the management of infections. However, several agents, e.g. calcium, iron, magnesium and aluminium, can substantially reduce the absorption of fluoroquinolones thereby causing treatment failure. A good standard of practice is to obtain a full, current medication list from your patient before prescribing antibiotic regimens,[60] or use you MIMS reference guide. It should also be noted that many antibiotics may cause oral contraceptives to fail, leading to unwanted pregnancies.

Conclusion

Rapidly emerging resistant bacteria due to inappropriate use of antibiotics, bacterial mutations and genetic adaptations, and the lack of development of new antibiotic drugs is threatening the extraordinary health benefits that have been achieved with antibiotics over decades. Currently it is being considered as one of the biggest threats to global health, food security, and development.

Evidence from the literature suggests that knowledge regarding antibiotic resistance amongst health care professionals, patients, and the public is still limited. Therefore, the need for educating health care professionals, patients and the public at large is essential to optimize the use of antibiotics, and to curb antimicrobial resistance. Implementing antibiotic stewardship efforts in dental practice is an opportunity to improve antibiotic prescribing practices and to reduce antibiotic resistance.

References

1. Lin J, Nishino K, Roberts MC, et al. Mechanisms of antibiotic resistance. Front Microbiol 2015; 6: 34. https://doi:10.3389/fmicb.2015.00034

2. Ventola CL. The antibiotic crisis. Part 1: Causes and threats. Pharm Ther 2015; 40(4): 277-283.

3. Zaman SB, Hussain MA, Nye R, et al. A review on antibiotic resistance: alarm bells are ringing. Cureus 2017; 9(6): e1403. https://doi:107759/cureus.1403

4. Read AF, Woods RJ. Antibiotic resistance management. Evol Med Public Health 2014, 2014(1): 147. https://doi:10.1093/emph/eou024

5. Centers for Disease Control, Office of Infectious Disease. Antibiotic Resistance threats in the United States, 2013. April 2013. https://www.cdc.gov/drugresistance/threat-report-2013.

6. CDC, Centers for Disease Control and Prevention. Antibiotic / Antimicrobial resistance. US Department of Health and Human Services, 2019.

7. Shallcross LJ, Davies SC. Antibiotic overuse, Br J Gen Prac 2014; 12: 604-605 https://doi:10.3399/bjgp14X682561

8. Ramasamy A. A review of use of antibiotics in dentistry and recommendations for rational antibiotic usage by dentists. Int Arabic J Antimicrob Agents 2014; 4(2): 1 https://doi:10.3823/748

9. World Health Organization. Antibiotic resistance. 5 February 2018. https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance

10. Spellberg B, Powers JH, Brass EL et al. Trends in

antimicrobial drug development: implications for the future. Clin Infect Dis 2004; 38(9):1279-1286.

11. Cheng G, Dai M. Ahmed S etal. Antimicrobial drugs fighting against antimicrobial resistance. Front Microbiol 2016; 7: Art 470/ https://doi.org/10.3389/fmicb.2016.00470

12. Nosanchul JD, Lin J, Hunter RP, Aminov RI. Low-dose antibiotics: current status and outlook for the future. Front Microbiol 2014; 5: 478. https://doi:10.3389/fmicb.2014.00478

13. Fluent MT, Jacobsen PL, Hicks LA. Considerations for responsible antibiotic use in dentistry. JADA 2016; 147: 683-686.

14. Karibasappa GN, Dujatha A. Antibiotic resistance – A concern for dentists? J Dent Med Sci 2014; 13(2): 112-118.

15. Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotics prescriptions among US ambulatory care visits, 2010-2011. JAMA 2016; 315(17): 1864-1873.

16. Oteri G, Panzarella V, Marcianò A, et al. Appropriateness in dentistry. A survey discovers improper procedures in Oral medicine and Surgery. Int J Dent 2018; Art ID: 3245324. https://doi.org/10.1155/2018/3245324

17. Bolfoni MR, Pappen FG, Preira-Cenci T, Jacinto RC. Antobiotic prescription for endodontic infections: a survey of Brazilian endodontists. Int Endod J 2018; 5(2): 148-156.

18. Stein K, Farmer J, Singhal S, et al. The use and misuse of antibiotics in dentistry: A scoping review. J Amer Dent Assoc 2018; 149(10): 869-884.

19. Teoh L. Marino RJ, Stewart K, McCullough MJ. A survey of prescribing practices by general dentists in Australia. BMC Oral Health 2019; 19: Article No: 193.

20. Ramachandran P, Rachuri NK, Martha S, et al. Implications of over prescription of antibiotics: A cross-sectional study. J Pharm Bioallied Sci 2019; 11(Suppl 2): S434-S437.

21 Vasaduvan S, Grunes B, McGeachie J, Sonis AL. Antibiotic prescribing patterns among dental professionals in Massachusetts. Pediatri Dent 2019; 41(1): 25-30.

22. Suda KJ, Calip GS, Zhou J, et al. Assessment of the appropriateness of antibiotic prescriptions for infection prophylaxis before dental procedures, 2011-2015. JAMA Netw Open 2019; 2(5): e193909. https://doi:10.1001/jamanet-workopen.2019.3909

23. Demirjan A, Sanchez GV, Finkelstein JA et al. CDC Grand Rounds: getting smart about antibiotics. MMWR Morb Mortal Wkly Rep 2015; 64(32): 871-873.

24. Marra F, George D, Chong M, et al. Antibiotic prescribing by dentists has increased JADA 2015; 147(5): 320-327.

25. Swift JQ, Gulden WS. Antibiotic therapy: managing odontogenic infections. Dent Clin North Amer 2002; 46: 623-633.

26. Martins JR, Chagas OL. Velasques BD, et al. The use of antibiotics in odontogenic infections: What is the best choice? A systematic review. J Oral Maxillofac Surg 2017; 72(12): 2606e1-2608e11.

27. Pallasch TJ. Pharmacokinetic principles of antimicrobial therapy. Periodontol 2000 1996; 10: 511.

28. Oberoi SS, Dhingra C, Sharma G, Sardana D. Antibiotics in dental practice. Int Dent J 2015; 65: 4-10.

29. Tent PA, Juncar RI, Onisor F, et al. The pathogenic microbial flora and its antibiotic susceptibility pattern in odontogenic infections. Drug Metab Rev 2019; 51(3): 340-355.

30. Gould IM, Bal AM. New antibiotic agents in the pipeline and how they can overcome microbial resistance. Virulence 2013; 4(2): 185-191.

31. Sengupta S, Chattopadhyay MK, Grossart HP. The multifaceted roles of antibiotics and antibiotics in nature. Front Microbiol 2013; 4: 47.

32. CDC. Centres for Disease Control and Prevention, Nearly half a million Americans suffered from Clostridium difficile infections in a single year. US Department of Health and Human Sevices. February 25, 2015. https://www.cdc.gov/media/releases/p0225/clostridium-difficile

33. Lushniak BD. Antibiotic resistance: a public health crisis. Pub Health Rep 2014; 129(4): 314-316.

34. Gross M. Antibiotics in crisis. Curr Biol 2013; 23(24): R1063-R1065.

35. Piddock LJ. The crisis of no new antibiotics – what is the way forward? Lancet Infect Dis 2012; 12(3): 249-252.

36. Michael CA, Dominey-Howes D, Labbate M. The antibiotic resistance crisis: causes, consequences, and management. Front Public Health 2014; 2: 145.

37. Bartlett JG, Gilbert DN, Spellberg B. Seven ways to preserve the miracle of antibiotics. Clin Infect Dis 2013; 56(10): 1445-1450.

38. Centers for Disease Control and Prevention. Core elements of outpatient antibiotic stewardship, 2016 https://www.cdc.gov/antibiotic-use/community/pdfs/16_268900-A_CoreElementsOutpatient_508.pdf

39. Jacobsen PL. The core elements of antibiotic stewardship in Dentistry. CDA J 2018; 46(12): 757-765.

40. Dellit TH, Owens RC, McGowen JE, et al. Infectious Disease Society for Health Care Eipdemiology of America; Society for Healthcare Epidemiology of America. Infectious Disease Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007; 44(2): 159-177.

41. Glick M. Antibiotics The good, the bad, and the ugly. JADA 2016; 147(10): 771-773.

42. Shivanand S, Doddawad VG, Vidya CS, et al. The current concepts in the use of antibiotics in dental Practice. Int J App Eng Res 2018; 13(5): 2959-2964.

43. Lodi G, Figini L, Sardella, et al. Antibiotics to prevent complications following tooth extractions. Cochrane database Syt Rev 2012; 11: CD003811. https://doi:10.1002/14651858.CD003811.pub2

44. Wilson W, Taubert KA, Gewitz M. Prevention of infective endocarditis: Guidelines from the American Heart Association – A guideline from the American Heart Association Rheumatic Fever, Endocarditis and Kawasaki Disease Committee, Council on cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and anaesthesia. Circulation 2007; 116(15): 1736-1754.

45. Wilson W, Taubert KA, Gewitz M et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anaesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. J Amer Dent Assoc 2008; 13 Suppl: 3S-24S.

46. Costelloe C, Metcalfe C, Lovering A et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: a systematic review and meta-analysis. BMJ 2010; 340: c2096.

47. Vishnoi N, Bishnoi RS, Gupta MK. Clinical appearances, microbiological findings and antimicrobials susceptibility patterns to orofacial infections of odontogenic origin in relation to cytokine analysis. J Drug Delivery Ther 2019; 9(3-s): 589-574.

48. Brook I, Frazier EH, Gher ME. Aerobic and anaerobic microbiology of the periapical abscess. Oral Microbiol Immunol 1991; 6(2): 123-125.

49. López-Gongález E, Vitales-Noyola M, González-Amaro AM et al. Aerobic and anaerobic organisms and antibiotic sensitivity to odontogenic maxillofacial infection. Odontol 2019; 107(3): 409-417.

50. Hajek G, Goldberg MH, Ferneini EM. In: Ferneini EM, Goldberg MH (eds) Odontogenic infections. Evidence-Based Oral Surgery, Springer, Cham 2019.

51. Thornhill MH, Dayer MJ, Durkin MJ, et al. Risk of adverse reactions to oral antibiotics prescribed by dentists. J Dent Res 2019; 1-7 Article in Press.

52. Geller AI, Lovegrove MC, Shehab N, et al. National estimates of emergency department visits for antibiotic adverse events among adults – United States 2011-2015. J Gen Int Med 2018; 33(7): 1060-1068.

53. American Association of Endodontists. AEE guidance on the use of systemic antibiotics in endodontics. AAE Position Statement. 2017

54. Cunha-Cruz J, Hujoel PP, Maupome G, saver B. Systemic antibiotics and tooth loss in periodontal disease. J Dent Res 2008; 87(9): 871-876.

55. Campagna JD, Bond MC, Schabelman E, Hayes BD. The use of cephalosporins in penicillin-allergic patients. A Literature review. J Emerg Med 2012; 42: 612-620.

56. Stewardson AJ, Huttner B, Harbarth S, At least it won't hurt: the personal risks of antibiotic exposure. Curr Opin Pharmacol 2011; 11(5): 446-452.

57. Rupnic M, Wilcox MH, Gerding DN. Clostridium difficile infection: new developments in epidemiology and pathogenesis. Nat Rev Microbiol 2009; 7(7): 526-536.

58. Bendesky A, Menedez D, Ostrosky-Wegman P. Is metronidazole carcinogenic. Mutat Res 2002; 511(2): 133-144.

59. Roda RP, Bagán JV, Bielsa JMS, Pastor EC. Antibiotic use in dental practice. A review. Med Oral Patol Circ Bucal 2007; 12: E186-192.

60. Ament PW, Bertolino JG, Liszewski JL. Clinically significant drug interactions. Am Fam Physician 2000, 61(6): 1745-1754.