Essence of Completion of Drug Dosages: A Review on Drug Resistance

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ABSTRACT

Antibiotic resistance happens when an anti-microbial agents has lost its capacity to adequately control or eliminate bacterial development; in other words, the bacteria are "resistant" and continue to multiply in the presence of therapeutic levels of an antibiotic. When antibiotic resistance occurs, antibiotics that previously would have killed the bacteria, or stopped them from multiplying, no longer work. Antibiotic resistance can result in extra medical expenses, prolong hospital stays and increased mortality rate. New resistance mechanisms are emerging and spreading globally, threatening our ability to treat common infectious diseases. The aim of the article is to review the antibiotic resistance, mechanism, diagnosis and prevention of antibiotic resistance.

Keywords: Antibiotics, Antibiotic Resistance, Infections.

INTRODUCTION

Infections can be caused due to multiple processes, microorganisms like bacteria, fungi, and viruses being one of them. Few of these micro organisms which result in infection under particular conditions are normal commensal organism of host. These associated commensal organisms may evolve to a pathogenic state in relation to diminished host immunologic defenses, which may occur in conditions like genetic defects, exposure to antimicrobial agents or immunosuppressive chemicals, exposure to ionizing radiation, cancer or as a result of an systemic diseases with immunosuppressive activity as human immunodeficiency virus or diabetes. Clinician should improve their knowledge of oral diseases and dentists must strengthen their understanding of general medicine, in order to avoid unnecessary risks for infection that originate in the mouth.[1]

In general, infections in the maxillofacial region are classified as either odontogenic or non-odontogenic. Odontogenic infections resulting from the infection of the tooth or adjacent tissues either remain localized to its origin or involve the surrounding areas. These infections are characteristically caused by bacteria resident in dental plaque. Microbial nature of odontogenic infection is polymicrobial with relatively less microbial specificity. These bacteria are not primarily pathogenic but may initiate and sustain infectious process if present in high level or in case of tissue invasion. Examples are periodontal and peri-apical infections.[2]

Non-odontogenic infections in maxillofacial region are associated with infections of surrounding orofacial structures like maxillary sinus, otological infections and other maxillofacial complex areas.[3] Non-odontogenic infections may include systemic infections with oral manifestations.

MICROBIAL FLORA OF ORAL CAVITY

Oral cavity is colonized by a species of bacteria, fungi and protozoa, of which only 10% are regularly, isolated using conventional culture techniques. Bacteria like coagulase-negative staphylococci, Gram-negative cocci of Neisseriaceae and Veillonellaceae, lactobacilli, spirochaetes, cornybacteria and mycoplasmas are also included as oral commensal flora. Bacteria with pathological virulence like Staphylococcus aureus, Enterococcus faecalis, S. pneumoniae, Streptococcus pyogenes, Neisseria meningitidis, members of the family Enterobacteriaceae, Haemophilus influenzae and actinomycetes may be found in oral cavity occasionally.[4]

The ecosystem of the oral cavity changes continuously throughout life. Under suitable conditions the commensal microorganisms may become virulent. Peptostreptococci, α-haemolytic streptococci, Gram-positive aerobic cocci and Gram negative anaerobes are frequently isolated from oral infections.[5]

ANTIBIOTIC USE IN DENTAL PRACTICE

In 1928 Alexander Fleming discovered the first antibiotic, Penicillin which was later introduced to clinical application in 1940 by Florey.[6]

In dental practice antibiotic prescription is empirical, i.e., the clinician does not know what microorganism is responsible for the infection, since pus or exudates cultures are not commonly made. Based on clinical and bacterial epidemiological data, the germs responsible for the infectious process are suspected, and treatment is decided based on a presumptive basis with short term broad spectrum antibiotic therapy and use of limited antibiotics to avoid development of resistance.[7] Antibiotics are typically prescribed in dental practice for some of the following purposes:

a Acute odontogenic infections.
b Non-odontogenic infections.
c Prophylactic treatment for patients at risk.
d As prophylaxis against local infection and systemic spread in oral surgery.[8]

THERAPEUTIC ANTIBIOTIC PRESCRIBING

Sixteen years ago, in Manchester dentists in a teaching hospital preferred to prescribe antibiotics over performing surgical procedures. In this study indications for antibiotic prescribing were based on guidelines published by Cawson and Spector.[9] Penicillin V being the most frequent antibiotic prescribed (60%

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of total prescription); and 14% erythromycin, 12% amoxicillin and 8% Metronidazole were used less frequently. Amoxicillin was preferred for prophylactic treatment accounts for 66% and tetracycline was not used.[10]

In 1998 an analysis of a random 10% of prescriptions written by dentists in Scotland revealed evidence of poor prescribing practices. Amoxicillin, Metronidazole and penicillin V were prescribed in 90% cases since 1987.[10]

Palmer *et al*. conducted a study in England which showed that 5.6% of prescriptions account for combinations of antibiotics among which amoxicillin along with Metronidazole was most frequently used in clinical practise.[11] According to Commission of the Federation Dentaire Internationale, the combination therapy should be avoided whenever possible in dentistry. The Commission of the FDI recommended that tissue concentration of the therapeutic antibiotic prescribed during an infection should be more than the minimum inhibitory concentration for the pathogenic organisms. Though the antibiotic duration should be sufficient to treat the infection but short duration therapy are preferred to avoid antibiotic resistance.[12]

PROPHYLAXIS ANTIBIOTIC PRESCRIBING

Amoxicillin, penicillin V and Metronidazole are mostly preferred for prophylactic treatment.[13] According to the guidelines the antibiotic used for prophylaxis should reach an appropriate serum concentration during the surgical procedure and should be maintained until after surgery. The same guidelines recommend a single high dose that is not to be continued after surgery.[14]

In 1999 the Commission of the FDI stated the importance of prophylaxis prior to dental surgical procedures in patient prone to infective endocarditis for example those with prosthetic heart valves.[12] Other conditions indicated for antibiotic prophylaxis are patients with facial fractures, immunocompromised patients undergone radiotherapy, compound skull fractures or cerebral rhinorrhoea, prosthetic hips, ventriculoarterial shunts or bone grafts.[10]

According to the study conducted by Palmer et al most dentists would prescribe prophylaxis for patients with cardiac conditions undergoing this procedures.[13] According to American Heart Association prophylactic treatment is required in cardiac patients at the risk of infective endocarditis only during surgical procedures like dental extractions, periodontal surgery and scaling.[14]

TYPE OF ANTIBIOTIC RESISTANCE

Centers of Disease Control and Prevention stated that resistant bacteria are recommended on the basis of infection control program, current state, regional or national recommendations and significance of clinical and epidemiological aspects.[15]

If the microorganism can withstand the static and cidal properties of the antimicrobial agent and continue to survive and multiply; it's known as antibiotic resistance.[16]

There are two types of antibiotic resistance i.e. "endogenous" resistance and exogenous or "positive-function" resistance.[17]

Endogenous resistance

The endogenous type of resistance can arise as a change or loss of function and is generally genetically recessive. Mutations that afford endogenous resistance to particular antibiotic can be harmful as it may alter the target of the antibiotic, like an essential enzyme or structure, or modify the permeability to the class of molecule including the antibiotic, thus minimizing the amount of essential nutrients that enter the organism.

The antibiotics which are in broad clinical use (penicillin, cephalosporin, tetracycline, macrolides-lincosamide and chloramphenicol, amino glycoside, and glycopeptides classes) are generally does not cause high-level endogenous resistance because of a loss or change of normal function. Use of other natural products such as rifamycins, novobiocin, orfusidic acid leads to significant development of high level endogenous resistance generally via mutation of the antibiotic target. Hence they are developed for narrow spectrum or in combination therapy instead of using as a single agent.[18]

Exogenous resistance

It originates either through horizontal transmission of exogenous, evolved or genetically dominant functions. Exogenous resistance often known as positive function resistance may be more stable than endogenous resistance in the absence of selection; instead of producing conformational changes in enzyme or structures it indulges in addition of functions like formation of antibiotic-detoxifying enzyme. This type of resistance is more commonly seen in minimum inhibitory concentration for 50-90% of isolated tested for pathogenic species and tested in antibiotic susceptibility pattern of the pretreatment isolate.[18]

MECHANISM OF BACTERIAL RESISTANCE

The bacterial organism in order to produce antimicrobial resistance should interfere with some of the crucial step for effective action of antimicrobial agent. The intended modes of action of antibiotics may be counter-acted by bacterial organisms via several different means as summarized in table 1.

The four major bacterial strategies are:

1 By blocking the antimicrobial agent from reaching the target by minimizing its ability to penetrate the cell.
2 By expelling the antimicrobial agents from the cell through general or specific efflux pumps.
3 By deactivation of antimicrobial agents through modification or degradation.
4 By making conformational changes in antimicrobial target within the bacteria.[16]

1. By blocking the antimicrobial agent to reach to target by minimizing its ability to penetrate the cell

Modification in the frequency, size, and selectivity of cell membrane porin channels; prohibits the antimicrobial agents from crossing the bacterial outer membrane and reaching their intended targets. This strategy has been observed in:

- Pseudomonas aeruginosa against imipenem (a beta- lactam antibiotic).
- Enterobacter aerogenes and Klebsiella spp. against imipenem.
- Vancomycin intermediate-resistant S. aureus or VISA strains with thickened cell wall trapping Vancomycin.
- Many Gram-negative bacteria against aminoglycosides.
- Many Gram-negative bacteria against quinolones.[16]

2. By expelling the antimicrobial agents from the cell through general or specific efflux pumps

Some bacteria possess membrane proteins that act as an export or efflux pump for certain antimicrobials, extruding the

Antimicrobial class	Mechanism of resistance	Specific means to Achieve resistance	Examples
Beta-lactams Antibiotics	Enzymatic destruction	Destruction of beta-lactam rings by beta-lactamase enzymes leading to inability to bind to Penicillin binding proteins, and hinder cell wall synthesis.	Enterobacteriaceae resistant to penicllins, cephalosporins, and Aztreonam; Staphylococi resistant to penicillin
	Modification of target sites	Mutational changes in indigenous PBPs or addition of various PBP inhibit antibiotic binding to PBP and interfere with cell wall synthesis.	Staphylococci resistant to oxacillin and methicillin.
	Reduced uptake	Reduction in number or character of porin channels can decrease betalactam uptake as they cross the outer membrane at the porin channels to reach the PBP of gram negative bacteria.	Enterobacter aerogenes, Pseudomonas aeruginosa and Klebsiella pneumoniae resistant to imipenem.
Glycopeptides	Modification target sites	Changes in molecular structure of cell wall precursor components reduce the binding of vancomycin so that cell wall synthesis can continue.	Enterococci resistant to vancomycin
Aminoglyosides	Enzymatic changes	Enzymatic modification changes various sites on the aminoglycoside molecule which reduces or completely ends the ability of this drug to bind the ribosome and stop protein synthesis.	Gram-positive and Gram negative bacteria resistance against aminoglycosides
	Reduce uptake	Reduction in number or intrinsic properties of porin channels can decrease aminoglycosides uptake as they cross the outer membrane to reach the ribosome of gram negative bacteria.	Various Gram-negative bacteria resistant to aminoglycosides
	Modification of target sites	Changes in ribosomal proteins or of 16sRNA decrease the ability of aminoglycosides to bind and stop protein synthesis.	Mycobacterium species resistant to streptomycin
Quinolones	Reduced uptake	Modification of outer membrane reduces the uptake of drug and/or an "efflux" pump is activated that removes quinolones before Intracellular concentration is sufficient to inactivate DNA metabolism.	Gram negative and staphylococci (efflux mechanism only) resistant to various quinolones
	Modification of target sites	Modification of DNA gyrase subunits inactivates Quinolones to bind this enzyme and interfere with DNA processes.	Resistance of Gram negative and Gram positive to various antibiotics.

Table-1: Mechanisms of Resistance against Different Antimicrobial Classes[21,23]

antibiotic out of the cell. This leads to decreased intercellular concentration which is insufficient to obtain an effect. This strategy has been observed in:

- E.coli and other Enterobacteriaceae against tetracyclines.
- Enterobacteriaceae against chloramphenicol.
- Staphylococci against macrolides and streptogramins.
- Staphylococcus aureus and Streptococcus pneumoniae against fluoroquinolones.[19]

3. By Inactivation Of Antimicrobial Agents Via Modification Or Degradation

Bacteria can also destroy the active component of the antimicrobial agent for example the bacterial enzyme; beta lactamase causes hydrolytic deactivation of the beta-lactam ring in penicillins and cephalosporin. This can be observed in:

- Gram negative and Gram positive bacteria resistant against aminoglycosides (phosphorylation, adenylation, and acetylation).
- Resistance against chloramphenicol (acetylation) in Enterobacteriaceae.[20]

4. By making conformational changes in antimicrobial target within the bacteria

Few bacteria modify their essential target sites by reprogramming or camouflaging for developing resistance against certain antibiotics. Thus even in the presence of active antimicrobial compound these resistant bacteria survive and multiply and no binding or inhibition occurs. This can be observed in:

- Staphylococci resistant against methicillin and other beta-lactams (Changes in Penicillin Binding Proteins that ineffectively bind beta-lactams to inhibit cell wall synthesis).
- Mycobacterium spp. resistant against streptomycin (alteration of ribosomal proteins or of 16s rRNA).
- Enterococci resistant against Vancomycin (modification in cell wall precursor components to reduce binding of

Vancomycin).
- Quinolones resistance due to DNA gyrase mutation.
- RNA polymerase mutation leading in resistance to rifamycins.[21,22]

MOLECULAR MECHANISM OF RESISTANCE

The abilities of bacterial organisms to utilize the various strategies to resist antimicrobial compounds are all genetically encoded. There are two type of molecular mechanism of resistance:[16]

1. Intrinsic resistance
2. Extrinsic resistance

1. Intrinsic resistance: Intrinsic resistance is the intrinsic ability of a bacterial species to resist a particular antimicrobial agent through its inherent structural or functional characteristics. Such innate ability of resistance can be due to (table-2):

- Reduced affinity of the drug for the bacterial target.
- Inactivation the drug by innate enzyme production.
- Loss of drug accessibility drug into the bacterial cell.
- Removal of the drug by chromosomally encoded active exporters.

2. Extrinsic Resistance: Acquired resistance is said to occur when a particular microorganism which was previously susceptible to a particular antimicrobial agent now develops the ability to resist it. It occurs by changes in bacterial genome through mutation or horizontal gene acquisition (table-3).

TEST METHODS IN DETECTING ANTIMICROBIAL RESISTANCE

There are several antimicrobial susceptibility testing methods available today, and each one has their respective advantages and disadvantages. The antibiotic sensitivity testing methods are:

- Dilution method (broth and agar dilution method).
- Mechanism-specific tests like beta-lactamase detection test and chromogenic cephalosporin test.

Organism	Intrinsic resistance against	Mechanism involved
Anaerobic bacteria	Aminoglycosides	Absence of oxidative metabolism for effective uptake of aminoglycosides
Aerobic bacteria	Metronidazole	Inability to reduce the drug to its active form anaerobically
Gram-positive bacteria	Aztreonam (A beta-lactam)	Insufficient penicillin binding proteins (PBPs) that bind and inhibition by this beta lactam antibiotic
Gram-negative bacteria	Vancomycin	Inability of vancomycin to penetrate the outer membrane resulting in lack of uptake.
Klebsiella spp.	Ampicillin (a beta-lactam)	Enzymes formation (beta-lactamase) that destroy Ampicillin before the drug can reach the PBP targets
Stenotrophomonas. maltophila	Imipenem (a beta-lactam)	Production of enzymes (beta lactamase that terminates imipenem before the drug reach PBP targets.
Lactobacilli and Leuconostoc	Vancomycin	No appropriate cell wall precursor target for vancomycin to bind and inhibit cell wall synthesis
Pseudomonas aeruginosa	Sulfonamides, trimethoprim, tetracycline, or chloramphenicol	Antibiotics unable to reach Effective intracellular concentrations leading to lack of uptake.
Enterococci	Aminoglycosides	Insufficient oxidative metabolism for uptake of Aminoglycosides.
	All cephalosporins	insufficient PBPs that effectively bind and are inhibited by these beta lactam antibiotics.

Table-2: Examples of intrinsic resistance and their respective mechanisms[23,24]

Acquired resistance via	Resistance observed	Mechanism involved in the resistance
Mutations	Resistance of Mycobacterium tuberculosis to rifamycins	the rifampin-binding region of rpoB shows point mutation
	Various clinical isolates to fluoroquinolones shows resistance.	The quinolone-resistance-determining-regiont (QRDR) of GyrA and ParC/GrlA shows mutation predominantly.
	Resistance of E.coli, Hemophilius influenzae to trimethoprim	Mutations involved in the chromosomal gene specifying dihydrofolate reductase
Horizontal gene transfer	Resistance of Staphylococcus aureus for methicillin (MRSA)	Through addition of mecA genes which is on a mobile genetic element called "staphylococcal cassette chromosome" (SCCmec) which codes for penicllin binding proteins (PBPs) that insensitive to ß-lactam inhibition
	Many pathogenic bacteria resistant against sulfonamides	Mediated by the horizontal transfer of foreign folP genes or parts of it.
	Resistance of Enterococcus faecium and E. faecalis against vancomycin.	Through addition of few associated gene clusters VanA and Van B, which code for enzymes that modify peptidoglycan precursor, result in resistance against vancomycin.

Table-3: Examples of acquired resistance through mutation and horizontal gene transfer.[25]

- Disk-diffusion method.
- Automated methods
- E-test.
- Genotypic methods such as PCR and DNA hybridization methods.[26]

HOW TO MINIMIZE ANTIBIOTIC RESISTANCE

Various strategies are followed to reduce antibiotic resistance:

1. Appropriate Antibiotic Prescribing

Since the resistance to the first commercial antimicrobial agent (penicillin) was identified in 1948, most of the bacterial pathogen has developed resistance to some of the other antibiotic in clinical use.[27] As antibiotic-resistant pathogens are observed almost concurrently with the use of new antibiotics in hospitals, there is a maximum probability that with the increasing use of antibiotics in clinical practice, resistance will inevitably follow. Unfortunately, development of novel antibiotic has dramatically declined over last 30 years though antibiotic resistance has been continuously rising.[28] Therefore, to prevent the return of the pre-antibiotic era, one must use existing antibiotics more cautiously.[29]

2. Antimicrobial Stewardship Programs (ASP)

These days many institutions are conducting Antimicrobial Stewardship Programs (ASPs) to optimize antimicrobial therapy, control treatment-related cost, better clinical outcomes and safety, and limit antimicrobial resistance.[30]

ASPs are based on few factors primarily on education, "front-end" interventions (e.g., restricting the availability of selected antimicrobial agents) or the "back-end" interventions (e.g., analyzing broad-spectrum empirical therapy and then based on antimicrobial susceptibility testing (AST) results and clinical response streamlining or terminating the therapy).[31] The "front-end" interventions includes the following aspects. (i) the development of situation-specific treatment guideline; (ii) AST; (iii) educating the prescribers; (iv) identification of accurate organism; (v) minimizing the effect of antibiotics on the microbiota and host immune homeostasis; (vi) knowledge of pharmacokinetic (PK) and pharmacodynamic (PD) properties of drugs which helps selecting optimal dose and duration of antibiotics; and (vii) formulary restriction and preauthorization.[29] Two crucial points for determining the optimal dosing regimen with minimal induction of resistance, are minimum inhibitory concentration (MIC) and mutant prevention concentration (MPC).[32] By proper implication of PK/PD concepts and the MPC strategy, the antibiotics potency can be optimized and the selection of resistant mutants limited. The "back-end" interventions includes the following aspects: (i) clinical decision support; (ii) post-prescription review and feedback; (iii) the development of protocols for de-escalation of therapy on the basis of AST and clinical response; (iv) diagnostic testing using biomarkers like procalcitonin or C-reactive protein (CRP); (v) determination of therapy length; and (vi) antibiotic heterogeneity (cycling and mixing).[29]

Antibiotic heterogeneity, like antibiotic cycling (also known as "antibiotic rotation") or antibiotic mixing (also known as "antibiotic diversity"), continues to be a questionable subject, although many investigators with the help of clinical investigations or theoretical models have studied its effects on antibiotic resistance.[33-35] Antibiotic cycling includes the exchange of one class of antibiotics with those of a different class possessing a similar spectrum of activity, but different mechanisms of antibiotic resistance (e.g., β-lactams, aminoglycosides, and fluoroquinolones).[34]

3. Appropriate knowledge

To optimize antibiotic use in clinical practice, the prescribers should have appropriate knowledge of general medicine, microbial virulence, immunological and genetic host factors, pharmacokinetic and pharmacodynamic properties of drugs and basic knowledge of epidemiology. But this responsibility of the clinicians towards the future patients and public health in preserving the efficiency of antibiotics and minimizing antibiotic resistance, is sometimes ignored.[29]

4. Infection control and hygiene

To prevent hospital-acquired infections appropriate hospital disinfection and personal hygiene of healthcare workers is required. Guidelines for preventing nosocomial transmission of MDR bacteria in hospitals are offered by The Centers of Disease Control and Prevention (CDC) and SHEA.[36] One of the most common cause for Transmission of healthcare-associated pathogens is through the hands of healthcare workers particularly. In addition to hand hygiene; disinfection of gloves, gowns, uniforms, and plastic aprons should also be considered.[37]

5. Veterinary medicine

Since the first commercial antibiotic, penicillin became available for the treatment of human diseases antibiotics have also been used in veterinary medicine.[38] Although some antibiotics are developed specially for veterinary use, most of the antibiotics being used in veterinary medicine belong to the same antimicrobial classes as those being used for human diseases.[27] Recent reports about antibiotics, which is crucial for human therapy, are frightening, the report states that the presence of ESBL-producing and carbapenemase-positive *Enterobacteriaceae* strains in food animals, and MRSA in various food animal species and food products, as well as plasmid-mediated quinolone resistance in food animals and food products.[39,40]

Because stress in crowded environments debilitates the immune system in food animals and antibiotics can prevent bacterial infections, antibiotics are considered useful for intensive breeding of animals. But, the use of antibiotics in veterinary medicine, aquaculture, and agriculture needs to be reduced. Antibiotic resistance in human gene will not be overcome until the introduction of resistance genes into human through food animals is not restricted. Therefore, new methods to manage infectious diseases in animal husbandry are required to prevent the emergence and transfer of antibiotic resistance in food animal.[29]

6. The evolution of novel antibiotics

Antimicrobial drugs such as antibiotics are a unique class of drugs that affect the growth of invading pathogens and commensal microbiota instead of directly targeting the human biochemical processes. Bacteria can easily adapt to their environmental changes and develop antibiotic resistance through several mechanisms, including mutation and horizontal gene transfer within and between species.[41] therefore, new weapons

are always indispensable for combating bacterial infections.[29] Therefore development of a new mechanism of action or a new target is necessary which can be achieved by systematic administration of new active substances. Although, based on actual data, four of them are known to have an activity against MDR Gram-negative bacteria; none of them has any new mechanism of action.[29]

For discovering new classes of antibiotics, novel strategies for rational design and screening-based approaches are required. New strategies are also presented for the treatment of microbial diseases, such as host defense peptides, immunoglobulins, bacteriophages, vaccines, and probiotics.[42]

CONCLUSION

Resistance of common bacteria to antibiotics has reached alarming levels in many parts of the world. The major risk of antibiotic resistance is that treatable illnesses could become incurable. This would put a greater economic and emotional burden on families and on our healthcare system. Healthcare professionals play an important role in limiting the spread of antibiotic resistance. Optimizing the use of antibiotics can also to help reduce antibiotic resistance. Antibiotic stewardship should always be practiced whenever antibiotics are used.

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