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Antibiotic Over-Prescription –

Drug Abuse Or Abusing The Xenobiotic Metabolism?

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ABSTRACT

Antibiotics are prescribed by doctors and dentists for treatment as well as prevention of infection. As such, the indications for the use of systemic antibiotics in dentistry are very limited. Most dental and periodontal diseases are best managed by operative intervention and oral hygiene measures. Due to a number of factors ranging from inadequate knowledge to social factors, unnecessary antibiotic

prescribing practices by dentists is very common & prevalent. Unfortunately, the prescription practices of dentists are inadequate and this is manifested by over-prescribing. A few recommendations to improve antibiotic prescribing practices have been presented by us below in an attempt to curb the increasing incidence of antibiotic resistance and other side effects of antibiotic abuse.

HISTORY

An antibiotic is a chemical produced by a micro-organism that kills or inhibits the growth of another micro-organism. The word antibiotic came from the word antibiosis a term coined in 1889 by Louis Pasteur's pupil Paul

Vuillemin, which means the process by which life could be used to destroy life. Selman Waksman suggested the word “antibiotic” (coined in 1889 by P. Vuillemin). Let us look at the timeline of various antibiotics:

- 1928 – Penicillin discovered by Fleming
- 1932 – Sulfonamide antimicrobial effect by Ehrlich
- 1943 – Drug companies begin mass production of penicillin
- 1948 – Emergence of cephalosporin precursors
- 1952 – Erythromycin derived from *Streptomyces erythreus*
- 1956 – Vancomycin introduced for penicillin-resistant *Staphylococcus*
- 1962 – Quinolone antibiotics first discovered
- 1970s – Linezolid discovered but not pursued
- 1980s – Fluorinated quinolones introduced, making them clinically useful
- 2000 – Linezolid introduced into clinical practice

PRELUDE with Statistics

Antibiotic over-prescription is most prominent in OPD set ups like clinics and emergency departments all over the world. In Europe, approximately 80% to 90% of antibiotic prescriptions are written by general practitioners. Rates of outpatient prescription are similar in the United States and the CDC estimates that at least 30% of outpatient antibiotic prescriptions are

unnecessary. Most inappropriate use of antibiotics in outpatient facilities occurs when antibiotics are prescribed for viral respiratory infections, such as viral bronchitis, otitis and sinusitis. Other examples of inappropriate use include prescribing a non-first-line antibiotic or an antibiotic with excessively broad-spectrum activity for a susceptible infection or an infection that may be

treated with a narrow-spectrum drug. The CDC estimates that more than 70% of the bacteria responsible for the 2 million infections acquired in US hospitals each year are resistant to at least one commonly used antibiotic and 20% to 50% of antibiotics prescribed in United States of America's acute-care hospitals are unnecessary or inappropriate. Examples of interventions to prevent overuse or over-prescription of antibiotics in hospitals, including intensive care units, include use of rapid diagnostics

and community or hospital-based resistance data to determine appropriate empiric treatment, avoidance of administering unnecessary broad-spectrum antibiotics, shortening the duration of therapy whenever possible, and basing treatment on pharmacokinetic and pharmacodynamic characteristics of the patient and his or her infection. We, the dentists account for 7% of all prescriptions of antimicrobials all over the world, in general and around 9% in India, in specific.

POSSIBLE PROBLEMS

Problems that can possibly occur with the injudicious use of antibiotics:

- Toxicity
- Hypersensitivity
- Drug
- Resistance
- Super infections
- Nutritional
- Deficiencies
- Masking of an infection.

REVIEW

Antibiotic indications for the use of systemic problems in dentistry are very limited, since most dental and periodontal diseases are best managed by operative intervention and oral hygiene measures. However, evidence of inadequate prescribing practices by dentists is there, possibly due to varied factors which range from inadequate knowledge to social stigmas. The main reasons for injudicious antibiotic prescribing are social factors only or say, lack of patient acceptance to dental treatment without any medicines. Let us first discuss the Drug metabolism mechanism.

Drug metabolism is the metabolic breakdown of drugs by

living organisms, usually through specialized enzymatic systems. More generally, xenobiotic metabolism (from the Greek xenos "stranger" and biotic "related to living beings") is the set of metabolic pathways that modify the chemical structure of xenobiotics, which are compounds foreign to an organism's normal biochemistry, such any drug or poison. These pathways are a form of biotransformation present in all major groups of organisms, and are considered to be of ancient origin. These reactions often act to detoxify poisonous compounds (although in some cases the intermediates in xenobiotic metabolism can themselves cause toxic effects).

DRUG METABOLISM

The study of drug metabolism is called pharmacokinetics. The metabolism of pharmaceutical drugs is an important aspect of pharmacology and medicine. The rate of metabolism determines the duration and intensity of a drug's pharmacologic action. Drug

metabolism also affects multi-drug resistance (MDR) in infectious diseases and in chemotherapy for cancer, and the actions of some drugs as substrates or inhibitors of enzymes involved in xenobiotic metabolism is a common reason for hazardous drug interactions.

These pathways are also important in environmental science, with the xenobiotic metabolism of microorganisms determining whether a pollutant will be broken down during bioremediation, or persist in the environment. The enzymes of

xenobiotic metabolism, particularly the glutathione S- transferases are also important in agriculture, since they may produce resistance to pesticides and herbicides.

Drug metabolism is divided into three phases:

1. In phase I, enzymes such as cytochrome P450 oxidases introduce reactive or polar groups into xenobiotics.
2. These modified compounds are then conjugated to polar compounds in phase II reactions.

3. These reactions are catalysed by transferase enzymes such as glutathione S-transferases.

4. Finally, in phase III, the conjugated xenobiotics may be further processed, before being recognised by efflux transporters and pumped out of cells.

Drug metabolism often converts lipophilic-compounds into hydrophilic products that are more readily excreted.

ETIOLOGY

Antibiotic overuse and over-prescription in outpatient care especially in DENTISTRY can usually be attributed to -

1. Dentists prescribing antibiotics before test results confirm a bacterial infection (if done at all),

2. Patient pressure to receive an antibiotics prescription from their dentist to resolve acute symptoms first and rest all things later,

3. Patients taking antibiotics they have purchased online through information and knowledge

provided by the ever-intelligent ‘Google Baba’,

4. Patients taking antibiotics after self-diagnosing a bacterial illness or

5. Patients taking antibiotics left over from a previous prescription.

ANTIBIOTIC PRESCRIPTION and DENTISTRY

The most effective way to manage pain of dental or oral origin is to remove the underlying cause.

The gold standard for all dental diseases is the worldwide accepted funda of ‘3-Ds’ to manage dental pain viz.:

1. Diagnosis,
2. Drug (if required), and

3. Dental treatment.

The rationale use of anti-microbials is based upon three variables:

1. A defined indication,
2. The appropriateness of the anti-microbial and
3. Adverse effects associated with the drug.

The DENTAL BAMBOOZLEMENT

The major concern of superfluous usage of antibiotics is the emerging resistant strains of micro-organisms. Microbial resistance is usually the unresponsiveness of micro-organism to

an antimicrobial agent. Resistant organisms can be drug tolerant, drug destroying, drug impermeable or rapid ejection of drug. Fig. 1 (below) shows the antibiotic resistance process:

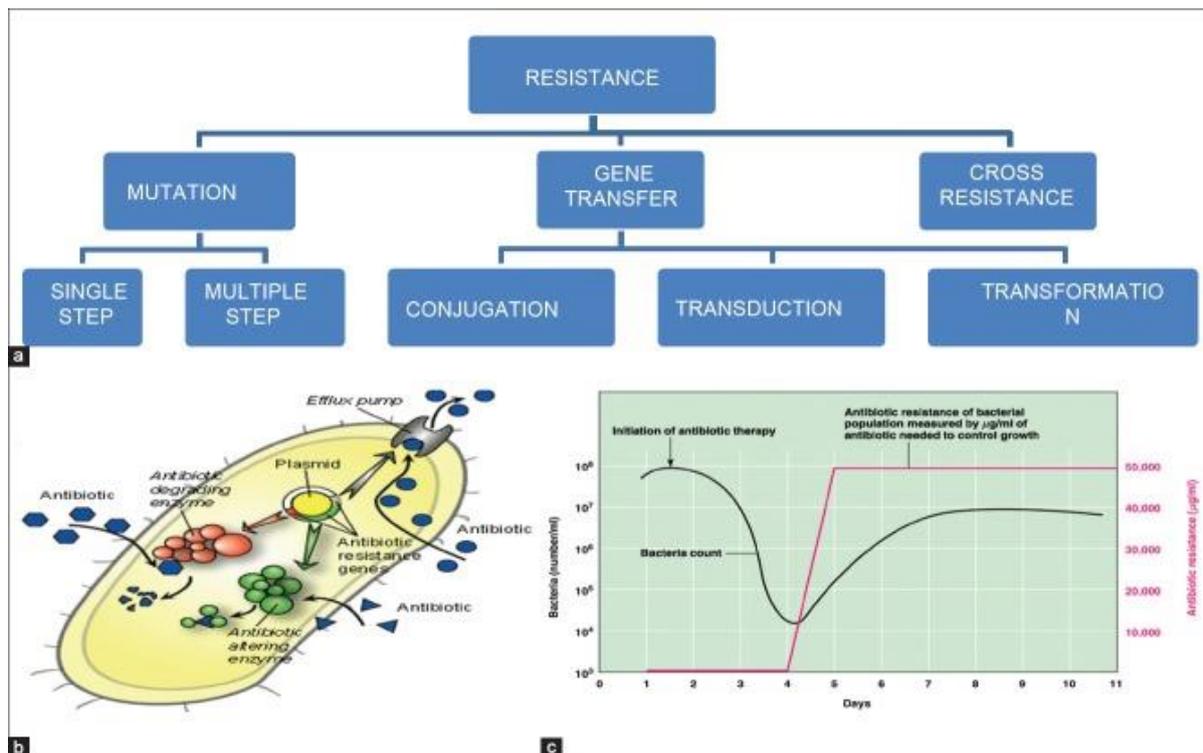


Fig. 1 – The Antibiotic Resistance Process

(Image Courtesy: Google)

Resistance to amoxicillin, penicillin, and metronidazole in the oral flora has been reported very commonly. Amoxicillin resistance has been described in *Veillonella* spp. and *Prevotella denticola* isolated from root canals. Many dentists prescribe antibiotics for pulpitis, abscess and chronic inflammatory periodontal conditions etc. We all should know that pulpitis can't be treated with anti-microbials as it is inherently inflammatory in nature and only, local

treatment can relieve the pain and infection in that tooth. We all know, the pulp of a tooth is enclosed in a “closed chamber” and when it becomes necrotic, anti-microbials cannot penetrate or be effective in such a situation; despite this, antibiotics are often prescribed without any other active intervention. Acute or chronic pulpitis can be treated successfully by either endodontic therapy or extraction (usually, the former) and anti-microbials are not required or indicated

for the same (in a vast majority of the cases). When the periapical tissues become involved and an abscess is formed, the treatment is drainage by simple I & D (Incision and Drainage) or a simple excision. Antimicrobials in such cases are simply, an adjunct to the treatment and are used to limit swelling and also prevent metastasis of the infection to vital organs. Chronic inflammatory periodontal conditions are also not indicated for antibiotics and systemic anti-microbials should

only be used in periodontal conditions where drainage or debridement is impossible; where a local spread of the infection or a systemic upset has occurred. Sub-microbial dose of doxycycline is widely used in periodontal therapy as an adjunct to mechanical therapy, although resistance is not reported if taken for a short period but there are studies which have reported doxycycline resistance if sub-microbial dose of doxycycline is prescribed for a prolonged period.

LITERATURE

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. In 1986, streptococci producing β -lactamase were isolated from the subgingival plaque of adults with periodontitis. Potgieter *et al.* report four blood culture isolates of *Streptococcus mitis* that were resistant to penicillin (minimum inhibitory concentrations 16–32 mg/L);

they were also resistant to the aminoglycosides gentamicin, kanamycin, and tobramycin. *Streptococcus mutans* is cariogenic and several studies have reported on its susceptibility to penicillin and other antimicrobials. Roche and Yoshimori 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*.

Prophylactic Antibiotic Prescription

Prophylactic antibiotics, taken prior to a number of dental procedures, have been advocated to reduce the likelihood of post-operative local complications, like infection, dry socket, or serious systemic complications like infective endocarditis. The evidence for antibiotics acting to prevent infection from surgical wounds in the mouth is poor to non-existent, indicating that pre-operative antibiotic prophylaxis for routine third molar surgery in medically fit patients is unwarranted. It is also very interesting to note that a single dose of metronidazole is ineffective in preventing the development of dry socket. For most dento-alveolar surgical procedures in fit, non-medically compromised patients, antibiotic prophylaxis is not required or recommended. In the case of sub acute bacterial endocarditis (SABE) or infective endocarditis (IE), the absolute risk rate after dental treatment, even in at-risk patients, is considered very low. This is consistent

with recent guidelines from the British Society for Antimicrobial Chemotherapy, and the American Heart Association, which recommend that only patients in the high risk category require an antibiotic cover. The basis for this recommendation is:

1. There is no consistent association between having an intervention, dental or non-dental, and the development of SABE and IE.
2. Regular tooth brushing almost certainly presents a greater risk of SABE or IE than a single dental procedure because of repetitive exposure to bacteraemia with oral flora.
3. The clinical effectiveness of antibiotic prophylaxis is not proven.
4. Antibiotic prophylaxis against SABE or IE for dental procedures may lead to a greater number of deaths through fatal anaphylaxis than would a strategy of no

antibiotic prophylaxis as well as the antibiotic prophylaxis against SABE or IE was costly.

Antibiotic prescription may also be associated with unfavourable side effects ranging from gastrointestinal disturbances to fatal anaphylactic shock and development of resistance. The increasing resistance problems of recent years are probably related to overuse or misuse of broad-spectrum agents such as cephalosporins and fluoro-quinolones. We have now entered an era where some bacterial species are resistant to the full range of antibiotics presently available, with the methicillin-resistant *Staphylococcus aureus* being, the most widely known example of extensive resistance. These serious complications associated with antibiotics use have encouraged studies investigating antibiotic prescribing practices of dentists. A considerable percentage of dental pain originates from acute and chronic infections of

pulpal origin, which necessitates operative intervention, rather than antibiotics. Non-indicated clinical cases for antibiotic use include acute periapical infection, dry socket and pulpitis. Chronic inflammatory periodontal conditions are also not indicated for antibiotics; systemic antimicrobials should only be used in acute periodontal conditions where drainage or debridement is impossible, where there is local spread of the infection or where systemic upset has occurred. In addition to the proper dosing regimens and professionally responsible prescribing practices, the general public needs to be educated about the importance of restricting the use of antibiotics to only cases of severe infection. Patients have become accustomed to being given an antibiotic for a range of medical and dental complaints. Unfortunately, patients presenting at dental surgeries also routinely expect an antibiotic for the treatment of 'toothache'.

RISKS of antibiotic overuse

Risks of antibiotic over-prescription include not only increase in antibiotic resistance, but increase in disease severity, disease length, health complications and adverse effects, risk

of death, healthcare costs, re-hospitalization and need for medical treatment of health problems that previously may have resolved on their own.

Factors promoting antimicrobial resistance:

1. Exposure to suboptimal levels of micro-organisms.
2. Exposure to microbes carrying resistant genes.
3. Prolonged period of drug regimen

ACTIVE INTERVENTION

Some active interventions to prevent antibiotic over-prescription in a Dental OPD include:

1. Patient and Dentist education;
2. Excellent diagnostics to establish the exact cause of problem;
3. Development of processes, protocols and guidelines aimed at reducing inappropriate antibiotic use; and
4. Review of prescription by a physician with appropriate feedback to the prescribing dentist.

Some Good Practices to avoid Antibiotic Resistance:

1. Antibiotics are medicines that treat bacterial infections only. They do not cure infections caused by viruses, such as the common cold or flu. Taking antibiotics when you do NOT need them can prevent them working when you DO need them.

2. Antibiotics target bacteria, killing or weakening them and helping you to fight off infections. Your body does not develop resistance to antibiotics; it is the bacteria which becomes resistant to antibiotics through genetic changes. This means that if you get an antibiotic-resistant bacterial infection, the usual antibiotics used to fight it will no longer be effective. A less accessible or last resort antibiotic will then need to be used, and in some cases options for potential active antibiotics could run out.
3. Antibiotics are given to humans, animals, fish and crops. Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause. Antibiotic-resistant bacteria spread through contact with humans, animals, food or environment that is carrying them. You can help to prevent the spread of infections by regularly washing your hands, covering your nose and mouth when you cough or sneeze, and practising safer sex.
4. Antibiotic resistance is happening everywhere in the world, affecting people of all ages. It is one of the biggest threats to public health today. Antibiotic resistant infections can take longer to treat, may require more frequent doctor visits, possible hospital stays, more severe side effects and expensive treatments. It is damn serious, dare we say that.
5. While antibiotic resistance occurs naturally over time, the misuse and over-use of antibiotics in plants, animals and humans has accelerated this process to dangerously high levels, but it's not too late to reduce the impact of antibiotic resistance and we all have a part to play in preserving the effectiveness of antibiotics.

COMBATING Anti-microbial resistance:

1. Speedy development of new antibiotics.
2. Track resistance data nationwide.
3. Restrict antimicrobial use.
4. Use narrower spectrum antibiotics (by conducting sensitivity tests).
5. Use anti-microbial cocktails.

Alternatives to conventional antibiotics:

1. Resistance-modifying agents
2. Phage therapy
3. Bacteriocins
4. Biotherapy
5. Vaccines
6. Chelation
7. Probiotics
8. Anti-sense agents
9. Broad spectrum antibiotics from plants and animals.

SUMMARY

Appropriate use of antibiotics is necessary to target drug-resistant bacterial infections and prevent further bacterial resistance from emerging. Generally speaking, there are very few indications for anti-microbials in dentistry and they should be used very judiciously. In the absence of signs and symptoms of infections, practitioners should refrain from prescribing

antibiotics for relieving pain. No one can deny the value of antibiotics in the management of oro-facial infections. But it should be kept in mind that it has to be used as an adjunct and not a substitute for a definite treatment. Much of the pressure to prescribe comes from patient pestering, the fear of medical litigation, getting rid of the walk-in patient (firstly) to treat the appointment

patient or just simply poor clinical decision making. Recommendations to improve antibiotic prescribing practices are basically an attempt to curb the increasing incidences of antibiotic resistance and other side effects of antibiotic abuse. The clinician should first determine whether an antimicrobial therapy is really warranted for a given patient. The following things should always be kept in mind before prescribing any antibiotic:

1. Is the antimicrobial agent indicated on the basis of clinical

findings? Or is it prudent to wait until such clinical findings become apparent?

2. Have appropriate clinical specimens been obtained (if indicated) to establish a microbiological diagnosis?
3. What are the likely etiological agents for the patient's problem?
4. Is there clinical evidence that antimicrobial therapy will confer clinical benefit to such a patient?

CONCLUSION

Dental patients not only pressurize their dentist to get an antibiotic prescription, they also self-medicate badly. Self-medication with antibiotics is alarmingly high in many developing countries like India. Also in Europe, self-prescription of antibiotics has been widely reported. The prescribing practices of dentists can be improved by increasing awareness among dental practitioners for the recommended guidelines along with the importance of

initiating awareness programs among the general public. Dentists should voluntarily, limit the injudicious use of antibiotics. Superfluous and injudicious use of antibiotics can be prevented by either using it as an adjunct and not alone as a treatment option along with using antibiotic sensitivity tests and using infection specific antibiotics coupled with the use of narrow spectrum antibiotics instead of broad spectrum ones. There should always be

an inherent intention to limit prophylactic antibiotic prescription as this has always been a subject of debate. Limiting prophylactic antibiotic prescription in healthy individuals with those having no underlying systemic diseases or no immuno-compromised

conditions is highly recommended. We are entering into an era where cures may be few due to increasing microbial resistance, so the biggest force for change will be possible, if all practicing dentists looked at their prescription making it a bit more rational.

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