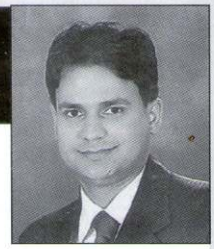
RECENT TRENDS IN ANTIBIOTIC THERAPY



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ORAL & MAXILLOFACIAL SURGEON

Introduction

In 1928 Penicillin was discovered. The Golden era of antimicrobial chemotherapy began with clinical use of it in 1941. Over last 60 years the "miracle drugs" revolutioned the health care. Clearly these drugs have eliminated or greatly reduced the morbidity and mortality of infection. Several important infections, diseases had been so well controlled that many young physicians and dentists know them only through their text books.

But is it the end of our problems??? The answer unfortunately is NO.....!!

By now we all know the world has a problem with bacteria that are resistant to all known forms of Antibiotics. In spite of recent advances in antibiotic therapy, infectious diseases are on a gradual increase. The threat of microbial diseases was believed to be controlled by 1980's, but since then antibiotic resistant streptococci, multi-drug resistant pseudomonas, methicillin resistant staphylococci and vancomycin resistant enterococci; made difficult to control infection in ICUs. The emergence of penicillin resistant anaerobes have become common in odontogenic infection. Most recently appearance of super microbes/super bugs, vancomycin resistant staphylococci have rung a worldwide wake up calls.

How can this be?

For more than a decade most pharmaceutical research companies diverted their attention from antibiotics to anti-inflammatory drugs, antidepressants, anti cancer drugs and other medication considering expense of developing and testing of new drugs. These companies are cautious about investing large sums of money in such ventures. With the result of all of above factors, there are few new clinically tested antibiotics. No antibiotics with a new mechanism of action are on the horizon. The recent new antibiotics have been modification of previous antibiotics like penicillins, cephalosporins and erythromycin.

How did this situation get so bad?

The answer is complex and resides with the bacteria, the patient and the doctor. The bacteria are nearly infinitely adaptable and can become resistant if given sufficient sub lethal exposure to an antibiotic. When this resistance is achieved by even a few bacteria, it can easily be passed on to other bacterial cells by several different methods. Bacteria can transfer genetic information via three mechanisms Transformation, Transduction, Conjugation. This genetically altered resistant organisms may continue to be well ahead of our efforts to control infectious diseases.

There are recent cover stories in leading newspaper of America about super bugs and end of "antibiotic era". Let us hope that this is just "hype" not real.

Considering above situation it is appropriate that we reassess antibiotics value and time has come to consider rational antibiotic therapy. This article presents an overview of usefulness of older antibiotics compared with the newer one, with emphasis on spectrum of activity, side effects and cost. To provide a contemporary view of the drug-verses-bug relationship, also covered principles of anti-microbial therapy; review of interesting articles and also about what is future in research of anti-microbial.

Penicillins

- Most valuable AMA available for the treatment of orofacial infections, whether of odontogenic, traumatic or post surgical origin.
- Pencillins are bactericidal have excellent distribution throughout body tissues and exhibit relatively low toxicity. It is the standard against which newer antibiotics or its own derivatives are measured.
- The appearance of penicillinase producing staphylococci in late 1940s to this wonder drug led to the research and development of pencillinase resistant penicillins (Ex: Methicillins, Oxacillin and naficillin). These agents has acryl side chain which prevented disruption of pencillin's B-lactam ring by lactamase.
- Synthesis of aminopencillin provided extended antimicrobial activity to include E-coli, Haemophilus Proteus mirabilis, shigella and salmonella.
- Later to meet the challenge of Pseudomonas and Enterobacteria resistance to AMA Carboxypenicillins (Ticaricillin, carbencillin) uriedopenicillins (Piperacillin, mezlocillin) were developed.
- Addition of B lactamase inhibitor like clavulanic acid/sulbactam to an aminopenicillin, ticarcillin, enhanced usefulness and spectrum of activity.

Some facts regarding Penicillin's

a) Most mild to moderate odotogenic infections in the non-compromised host and non-hospitalised host respond to penicillin.

b) The addition of metronidazole to penicillin covers bacteroids that are resistant to penicillin and this combination has proved to be excellent empiric regimes at low cost and relatively low toxicity.

c) Side effects of penicillin are common, with allergy (up to 15%) being the most feared. The most common allergy is a maculo- papular rash, followed by urticaria, drug fever, bronchospasm, serum sickness, exfoliative dermatitis and least common is anaphylaxis and angioedema.

d) Anaphylaxis is less common with oral than parenteral administration, and only one third of patients who succumb to anaphylaxis have a history of prior penicillin allergy.

e) Ampicillin and Amoxicillin cause the highest incidences of skin eruptions (10%).

f) Severe, even fatal hyperthermia may occur with parenteral administration of large doses of penicillin G potassium.

MACROLIDS

- Erythromycin introduced in 1952 used in dental therapeutics as the primary alternative antibiotic for patients with a history of severe and immediate allergic reaction to penicillin.
- Erythromycin unlike penicillin considered as a bacteriostatic agent at therapeutic doses, its anti-microbial action is based on intribition of protein synthesis within bacterial ribosome.
- Similar to Pencillin V, its anti-microbial spectrum includes the viridans streptococci associated with endocarditis as well as the common oral gm +ve cocci associated with odontogenic infection.
- Two synthetic erythromycin derivatives have been developed and marketed in the last decade-Azithromycin and Clarithromycin. Recently a third agent dirithromycin also was approved for use in the United States.
- The therapeutic advantages of these newer agents include longer duration of action, enhanced acid stability and improved tissue distribution.
- The anti-microbial activity of these agents, for the most part similar to that of erythromycin, but found to have a somewhat broader anti-microbial activity than erythromycin.
  a) Azithromycin has better activity against Haemophilus influenza than does erythromycin.
  b) Clarithromycin has shown better activity against streptococci viridans, group A streptococci, and streptococcus pneumonia and Helico bacter pylori than erythromycin.
  c) Dirithromycin is more active in vitro against camphylobacter jejuni than erythromycin.
  d) In the 1990's clarithromycin was shown to be effective as erythromycin, penicillin, ampicillin, amoxicillin and the cephalosporins for the treatment of many upper and lower respiratory tract infections. By the late 1990's, however increasing resistance to clarithromycin was reported, especially with the influenzae and S.pneumonia.
  e) A comparison of erythromycin, clarithromycin and azithromycin reveals that none is as effective as penicillin V, administrated orally against the most common pathogons of Odontogenic infection.
  f) Clarithromycin and dirthromycin are unusual antibiotics because they are prodrugs; the majority of their anti-microbial activity is provided by one of their active metabolite
- Larger elimination half like of these synthetic agents reduce dosing requirements to once daily or twice a day regimen and also permits the maintenance of more constant blood and tissue concentrations.
- These long acting macrolide appears to have favourable tissue distribution and capable of reaching the site of infection.
- The distribution and accumulation of azithromycin within human neutrophils, as well as its prolonged half-life may augment its anti-microbial activity.
- Azithromycin, a newer macrolide, has the distinct advantage over erythromycin and clarithromycin of not creating drug-drug interactions. Azithromycin has azalide ring rather than macrolide ring not compete for similar hepatic enzyme.
- In the treatment of streptococcal pharyngitis and tonsillitis, azithromycin has been shown to be a clinically superior in therapy for 5 days than penicillin for 10 days.
- The utility of erythromycin for treating for dental and respiratory infections has been limited by side effects, the most common being abdominal cramps, nausea and vomiting. Prolonged use of estolate form of erythromycin associated with cholestatic hepatitis.
- For Clarithromycin and Azithromycin there is a paucity of clinical research, which might prove their superiority to penicillin in odontogenic infection.
- They cannot be recommended for Odontogenic infections except as substitute for penicillin in the allergic patient, when other antibiotics are contraindicated, if drug-drug interactions are potential threat (clarithromycin).
- These newer macrolides are however, recommended by AHA as alternatives to penicillin in endocarditis prophylaxis for dental patients. They replaced erythromycin in 1997 because of their increased bioavailability, tissue penetration and long duration of action.
- In spite of all these advantages high price of these newer drugs limits their routine use

Oral Prophylactic Regimens for Dental Procedure

Procedure	Drug	Dose
Standard Prophylaxis	Amoxicillin	Adult-2g Children 50 mg/Kg orally 1 hour before procedure
Allergic to Penicillin	Clindamycin	Adult-600 mg Children-20 mg/kg orally 1 hour before procedure
	Cephelexin or Cafadroxil	Adult-500 mg Children-15mg/kg orally 1 hour before procedure
	Azithromycin or Clarithromycin	Adult-500 mg Children-15mg/kg Oral 1 hour before procedure

Comparison of Macrolids

	Erythromycin	Clarithromycin	Azithromycin
GIT Disturbance	Yes	Less	Less
Food affects absorption	Yes	No	No
Prolonged Tissue Levels	No	Yes	Yes
Drug-Drug Interactions	Yes	Yes	No
IV Use	Yes	No	No

METRONIDAZOLE

- It is introduced in 1959 for treatment of Trichomonas vaginalis and later was used for infections caused by many anaerobic bacteria.
- It is rapidly and almost completely absorbed when given orally and inexpensive and can be used intravenously.

- It is bactericidal and although its spectrum of activity is confined to narrowly to anaerobes, it is useful against anaerobes of Odontogenic infection and effective when used together with penicillin.
- Although more than 90% obligate anaerobes are susceptible to metronidazole. Actinomyces and propionibacterium are not sensitive.
- Drug-drug interactions include alcohol, comadin and Phenobarbital.
- A metallic testing glossits and upper and lower GIT complaints may occur.

CLINDAMYCIN

- It is a chemical modification of lincomycin, when was first introduced in 1962.
- Specifically for use in polymicrobial oral infection, clinical success rate of clindamycin in Odontogenic infection is similar to penicillin.
- It is an ideal anti-microbial drug for Odontogenic infections and useful in the therapy or prophylaxis against skin organisms (Streptococcus, staphylococcus, Corynebactirium)
- Clindamycin's absorption, not affected by food in take, reaches 90% from GIT.
- Clindamycin moves rapidly from serum in to tissues, penetrates well into bone, joints, soft tissue and saliva and experimentally into abscesses.
- It potentiates opsonization and is actively transported into PMNs, which enhances phagocytosis and bacterial killing.
- Adverse reactions rash, fever, rarely anaphylaxis, peripheral neuropathy.
- Diarrhoea and colitis may occur with clindamycin (20%) (1:50,000 pts). These complications occur more commonly with oral rather than IV therapy.

NEW GENERTIONS OF QUINOLONES

The classification of quinolones into generations has been useful for general practitioners, since it is based on susceptible organism and evolution.

1st generation Quinolones:

Nalidixic acid, the 1st oral quinolone was primarily used for UTI. This drug and other 1st generation quinolones (oxalinc acid and cinoxin) have no value in therapy for common Odontogenic infections. Its serum and tissue concentration is low, no activity against gm +ve bacteria and aerobes.

2nd Generation Quinolones:

- It contains a fluorine ion, which enhance their antimicobial activity.
- Ciprofloxin is active against staphylococci and pseudomonas, but has no activity against anaerobes and has limited usefulness in Odontogenic infections despite its still frequent prescription for this purpose.

Ex : Norfloxin, Ofloxacin

3rd Generation Quinolones:

(Levofloxin 250 mg, 500 mg, Sporofloxin Tab 200 mg, 400 mg) are more useful against streptococci but are also ineffective against anaerobes.

- Sporfloxin may cause serious photosensitivity skin reactions (8%).

Two New Fluroquinolones:

- **Gatifloxin** has been approved for oral/IV use for once daily therapy at acute sinusitis, chronic bronchitis and community acquired pneumonia.
- **Maxifloxin** is now available in USA for oral use only. Both are more active than levofloxin against S. pneumonia and has less active against pseudomonas than ciprofloxin.

CEPHALOSPORINS

- 1st introduced in 1960, these B-lactam antibiotics are broad-spectrum drugs with a low rate of toxicity and few barriers to administration.
- So many cephalosporins are available that are arbitrarily divided into four major categories or generations, based on their spectrum of activity.
- Differences in the antimicrobial activity and toxicity among the various semi synthetic cephalosporins result from modification of the cephalosporin C molecules produced from fungus cephalosporium acremonium.
- 1st generation cephalosporins have considerable activity against aerobic-gram positive cocci, including methicillin sensitive s.aureus and the streptococcus.
- 2nd generation cephalosporins have only variable activity against some gm- negative organisms.
- 3rd generation cephalosporins have little activity against gm +ve organisms such as staphylococci.
- **Progression from 1st to 3rd generation results in loss of effectiveness against gram-positive organisms.**
- 4th generation agents (cefepime) have proven activity against gram positive and gram-negative bacteria.
- So many cephalosporins are currently available often with similar names that distinguishing one from another can be difficult or even confusing.
- Although cephalosporins are adequate alternatives to penicillin for therapy of Odontogenic infections in noncompromised hosts, they generally lack activity against bacteriodes, except for cefoxitin and cefotetam.
- They remain popular in OMFS for use in facial trauma in which skin (staphylococci) and mucosal (aerobic and anaerobic, streptococci) organisms are anticipated as wound contaminants.
- Reports of cross-sensitivity with penicillin allergies ranges from 2% to 16%.
- If a patient presents a history of Ig E-mediated allergies, such as anaphylaxis angioedema or urticaria, to any of the penicillins, then cephalosporins use is not recommended.

RATIONAL ANTIBIOTIC THERAPY

Antimicrobials are valuable for us. **The concept of 'pill for every ill' is not true**, rather detrimental to our health when they are being over used, underused, wrongly used ... in other words irrationally used.

Successful chemotherapy must be a rational.

Definition Rational use of drugs is the process of providing essential/scientific drugs to those people who need them at the right time, in right dose and at right cost.

In other words, the physician must make the correct diagnosis and understand the pathophysiology of the disease before deciding whether to treat a patient with drug/AMAs. If the answer is affirmative, the physician should know enough about the AMA to select the right one and to administer it by the right route, in the right amount, at the right interval, for the right length of time.

Irrationalities in AMA's usage:

- Over prescribing
- Under prescribing
- In correct prescribing
- Use of ineffective/harmful drugs and combinations.
- Improper diagnosis which forms the base of most of these irrationalities.
- Rational AMA use is the art and science of prescribing the best suited AMAs to individuals who need then, not to those who merely want them.

The rational of antibiotic therapy constitutes

Regimen should be right.

Availability of AMA

Treatment of Choice should be correct

Inform patient about the treatment, drug and use of safe drugs.

Objectives of Treatment should be clear.

Need of drug should be ascertained

Acceptable quality

Low Cost

The two most important considerations in rational antibiotic therapy are the type of the patient (host factors) and the likely infecting organisms.

Host factors

- Age
- Renal and hepatic function.
- Pregnancy
- Site of infection
- Presence of prosthetic material
- Immune status
- Allergy

RESPONSIBLE USE OF ANTIBIOTICS IN DENTISTRY

Prescription for the future:

Microbes' were the primitive cells, but they are undeniable heavy weights in evolutionary process.

"Microbes were the 1st organisms to evolve on the earth and were sole inhabitants for billion of years ... only during last 0.01% of earth history have humans been arrived. Bacteria may still dominate our biosphere today in number of species, number of organisms or total mass".

Bruce Jackosky, Planetary Review July/August 1998.

The fight between men and microbes started with discovery of penicillin in 1928. Antibiotics cured or controlled tuberculosis, syphilis, pneumonia and other bacterial infections. New antibiotics released to use. The arrival of super microbes such as Vancomycin resistant staphylococcus, tilted balance of power towards microbe. This virulent strain appeared in a New York Hospital in 1998. There are no known antibiotics to control it. Its presence in the environment is evidence that antibiotics have not eliminated bacterial infections, an alarming call to all of us.

Clinician must understand the impact of antibiotics on patients and on the quality of public health. As health care provides we all understand above problem and write a safer and more effective prescription for the future.

Act Locally, Think Globally:

- **Antibiotic treatment is a double edged sword that alters the natural balance of organisms. Each time antibiotic used to eliminate bacteria other pathogens gain strength.**
- The bacteria are genetic overachievers; they reproduce expontially and meet challenging conditions with incredible ease and flexibility. One E-coil can create 20 generations, more than one million pogency in about 7 hours. To put microbial population in to perspective, consider that more bacteria occupy one foot of human intestine than there are people on earth.

In the presence of threat, bacteria either render the attack harmless or make them less vulnerable. Mutation and genetic transfer are the processes that enable cells to adapt or change. Once a mutation is present all offspring generally acquire the new trait.

- The transfer of genetic material among bacteria is a much more effective survival mechanism. Antibiotic resistant genes can be passed among every species of bacteria. When one organism dies, another may absorb some of its genes.
- Antibiotic resistance has even been found in species of bacteria living in the open ocean. These microbes have never been exposed directly to antibiotics produced by human.
- The longer a population of bacteria is subjected to an antibiotic, the more resistant the survivors become. As vulnerable m.o. die, the number of surviving microbe increasingly makes each successive generation better equipped to meet future antibiotic challenge. Beneficial microbes that might have helped to curb the growth of pathogenic microbes are also killed. Eventually bacterial strains are created that may resist available antibiotic regimes.
- Antibiotic resistant bacteria preserved in animal, plants, milk, eggs and meals also.
- Only about 158 antibiotics are currently available and strains of bacteria resistant to each of these antibiotics

identified. It takes million dollars and many years to develop a new antibiotic. Few new drugs are under development because bacteria can render an antibiotic useless with a single shuffle of genetic material. The day may be rapidly approaching when even the most powerful antibiotics will be ineffective against pathogens now considered harmless.

- Health care providers all over the world undoubtedly contribute to this problem.
- **Researchers estimate that approximately 1/3 of all out patient antibiotic prescriptions are unnecessary.**
- Antibiotic are one of the few kinds of drugs that affect not only a single patient but entire populations of individuals through their collective effects on microbial ecology.
- Antibiotics have an impact that extends far beyond clinician and his/her patient. By stimulating the developments of resistant strains of bacteria, these medications permanently alter the microbial environment. In an era where travel to every point of the globe is possible in less than 24 hours; drug resistant pathogens are easily transmitted.
- Dentist, physicians and patients have a serious responsibility to understand why antibiotics must be administered with caution and adhere to principles that govern their appropriate use.

Kill the bug without drugs!

- **Pulpitis, Apical periodontitis, draining sinus tract or localized swelling can usually be treated endodontically without antibiotics.**
- The circulation within the pulp is compromised in the presence of inflammation/infection. Because an antibiotic is carried by vascular system, its ability to reach bacteria in a therapeutic conc. will be limited. This environment diminishes the efficiency of the antibiotic.
- Endodontic treatment/access opening of tooth and removing the bacteria and their by products thoroughly debriding the root canal system-effectively eliminates the infection, curtails the inflammation and promotes healing.
- Swelling can be drained through the tooth/through soft tissue incision.

When defences are down antibiotics are sound:

Patient with compromised immune systems are at a higher risk of developing bacteraemia may rapidly progress to overwhelming septicaemia.

1. Patient undergoing chemotherapy antibiotic prophylaxis considered for invasive dental procedure.
2. Patient with AIDS, in the absence of bacterial infection does not generally require antibiotic prophylaxis.

   Antibiotics are considered in cases where more chances of bacteraemia may occur (In case of extraction of teeth with abscess).
3. Insulin dependent, with poorly controlled Diabetic mellitus antibiotic coverage recommended for invasive dental procedure.

   Antibiotics generally are not required for those who are not dependent on insulin therapy.
4. AHA/ADA reconsiders use of antibiotic coverage for chronic intravenous drug abusers and for patients who have undergone splenectomy.

Drainage stimulates healing, relieves pressure, improves circulation and eliminates bacteria.

- Remove the cause when possible.

When we need the drugs to kill the bugs?

Pain alone/localized swellings do not require antibiotic treatment.

- Patient in poor health/who are immune compromised are more likely to need antibiotics.
- Swelling/fever that escalates within 24 to 72 hours period may indicate that an infection is spreading. A useful indicator for the use of antibiotics is elevation of temperature by 1.5° C.
- A large, diffuse swelling may require antibiotics as well as surgical drainages.
- Patients who have cellulites/extra oral swelling, lymphadenopathy, elevated body temperature, malaise/unexplained fever usually require antibiotic therapy and surgical drainage.
- Antibiotics can safely be discontinued after 2 to 3 days provided that satisfactory drainage has been achieved, the temperature returned to normal and the swelling is resolving.
- For periodontal surgery antibiotics are indicated for most patients with compromised immune system.
- When the defence are down antibiotics are sound.
- Antibiotics are an adjunct to treatment. The patient's own immune system provides cure.
- Antibiotic prophylaxis in orthogenetic surgery is justified by recent study.
- The use of antibiotic prophylaxis during placement of implant is controversial. But antibiotic prophylaxis in 3rd molar removal (infection rare is 1%) has no value as shown by Indian study unless the immune system compromised.

Killing with Penicillin and its substitutes

- Penicillin VK is effective against most aerobic and anaerobic bacteria that are commonly present in the oral environment.
- Amoxicillin, a derivative, has a broader spectrum of activity and is a good choice for immune compromised patient. However, treatment with amoxicillin increases likelihood of inducing antibiotic resistance.
- Clindamycin is an appropriate substitue if the patient is allergic to penicillin. It is a B-lactamase inhibitor highly effective against orofacial infections.

- Erythromycin, which is commonly prescribed for penicillin allergic patients, has been shown to be ineffective against most of the anaerobes associated with orofacial infections. Other antibiotics are now preferred.
- Clarithromycin is another acceptable penicillin substitute. It has some advantage over erythromycin. It is effective against facultative anaerobes and some of the obligate anaerobes.
- Metronidazole is a synthetic antibiotic that is highly effective against obligate anaerobes but is not effective against facultative anaerobic bacteria. If penicillin is ineffective after 48 to 72 hours, metronidazole is a valuable anti-microbial agent for combination antibiotic therapy.
- Proper dosage and selection of an antibiotic with the right spectrum of activity are equally important. Treatment regimens should be short and aggressive to minimise the development of resistant bacteria and to achieve a therapeutic concentrations. The patient must understand clearly that adherence to the dosing schedule is critical to eliminate the infection. A loading dose of 1000 mg of penicillin VK should be followed by 500 mg every 6 hours for five to seven days. Consider contacting the patient 24 hours after administration of antibiotics to assess the patient condition. If there is no improvement after 48 hours, penicillin can be supplemented with a dosage of metronidazole. The recommended oral dosage of metronidazole is 250 mg (500 mg loading dose every 6 hours).
- The usual adult dose of clindamycin begins with a loading dose of 300 mg followed by 150 mg every 6 hours.
- Clarithromycin may be given in a dose of 250 500 mg every 12 hours.

Principles of antibiotic dosing for Orofacial Infections:

1. Use high dose for a short duration for dose dependent AMA's.

   Antibiotic success depends on monitoring the blood and tissue concentration above MIC for the target organism, are more critical with the dose dependent AMA's. [Ex: B-lactoms, Amino glycosides, Metronidazole and quinolones]. It is more critical with the B-lactom prolonged dosing beyond, which is necessary only increases antibiotic toxicity, allergy, and antibiotic resistance. The bacteriostatic agents including macrolides, tetracycline and clindamycin act at any reasonable concentrations.
2. Achieve blood level of antibiotic 2 to 8 times of Minimum Inhibitory Concentration (**MIC**).

   Such blood levels are necessary to compensate for the tissue barriers that impede antibiotic penetration to the site of infection, as one has to consider variabilities in gender, age, sex etc.
3. Use an oral antibiotic loading dose.

   Without loading dose it takes 6 to 12 hour to achieve maximum thereapeative blood and tissue levels via oral route.
4. The AMA's are terminated when the host defences have gained control of the infection.

Future of Antibiotics

- Researchers believe that studying of bacterial function at the molecular level holds the key to rapid new drug development.
- Future antibiotics may "customized" to disarm bacteria genetically and prevent development of resistant strains.
- Scientists are using high tech tools such as super computers x-ray crystallography to study enzymes that promote bacterial resistance. Over 100 naturally occurring antibacterial peptides have been identified. Eventually peptides may form new category of antibiotic that not only kills bacteria, but also neutralizes enzymes that make bacteria resistant.

  Genetic is another promising area of exploration. Scientists discovered how the genetic trigger works for diphtheria. Antibiotics preventing this trigger/virulence could be developed.
- Techniques to enhance host immune response are also the promising area.

Review of Literature

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