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The Chemical Essence of life Antibiotics

Sana Munir[1], Rentha Fathima M[1], Anil Melath[2], Subair Kayakool[3] and Arjun MR[4]*

[1]Final year student, Mahe Institute of Dental Sciences and Hospital, India

[2]HOD, Professor and Principal, Mahe Institute of Dental Sciences and Hospital, India

[3]Professor, Dept of Periodontics and Implantology, Mahe Institute of Dental Sciences and Hospital, India

[4]Reader, Dept of Periodontics and Implantology, Mahe Institute of Dental Sciences and Hospital, India

*Corresponding author
Arjun MR, Reader, Dept of Periodontics and Implantology, Mahe Institute of Dental Sciences and Hospital, India.

Introduction
Antibiotics: These are substances produced by microorganisms, which selectively suppress the growth of or kill other microorganisms at very low concentrations. This definition excludes other natural substances which also inhibit microorganisms but are produced by higher forms (e.g., antibodies) or even those produced by microbes but are needed in high concentrations (ethanol, lactic acid, H_2O_2) [1].

Antibiotics are medicines that fight bacterial infections in people and animals. They work by killing the bacteria or by making it hard for the bacteria to grow and multiply.

Antibiotics can be taken in different ways:
• Orally (by mouth): This could be pills, capsules, or liquids.
• Topically: This might be a cream, spray, or ointment that you put on your skin. It could also be eye ointment, eye drops, or ear drops.
• Through an injection or intravenously (IV): This is usually for more serious infections [2].

The successful use of any therapeutic agent is compromised by the potential development of tolerance or resistance to that compound from the time it is first employed. This is true for agents used in the treatment of bacterial, fungal, parasitic, and viral infections and for treatment of chronic diseases such as cancer and diabetes; it applies to ailments caused or suffered by any living organisms, including humans, animals, fish, plants, insects, etc. [3]

Antibiotics have revolutionized medicine in many respects, and countless lives have been saved; their discovery was a turning point in human history. Regrettably, the use of these wonder drugs has been accompanied by the rapid appearance of resistant strains. Medical pundits are now warning of a return to the pre antibiotic era; a recent database lists the existence of more than 20,000 potential resistance genes (r genes) of nearly 400 different types, predicted in the main from available bacterial genome sequences [4]. Fortunately, the number existing as functional resistance determinants in pathogens is much smaller.

Antibiotics are a crucial line of defense against bacterial infections. Nevertheless, several antibiotics are natural products of microorganisms that have as yet poorly appreciated ecological roles in the wider environment. We isolated hundreds of soil bacteria with the capacity to grow on antibiotics as a sole carbon source. Of 18 antibiotics tested, representing eight major classes of natural and synthetic origin, 13 to 17 supported the growth of clonal bacteria from each of 11 diverse soils.

Bacteria subsisting on antibiotics are surprisingly phylogenetically diverse, and many are closely related to human pathogens. Furthermore, each antibiotic-consuming isolate was resistant to multiple antibiotics at clinically relevant concentrations. This phenomenon suggests that this unappreciated reservoir of antibiotic-resistance determinants can contribute to the increasing levels of multiple antibiotic resistance in pathogenic bacteria [5].

History
The first antibiotic, salvarsan, was deployed in 1910. In just over 100 years antibiotics have drastically changed modern medicine and extended the average human lifespan by 23 years. The discovery of penicillin in 1928 started the golden age of natural product antibiotic discovery that peaked in the mid-1950s. Since then, a gradual decline in antibiotic discovery and development and the evolution of drug resistance in many human pathogens has led to the current antimicrobial resistance crisis.

Here we give an overview of the history of antibiotic discovery, the major classes of antibiotics and where they come from. We argue that the future of antibiotic discovery looks bright as new technologies such as genome mining and editing are deployed to discover new natural products with diverse bioactivities. We also report on the current state of antibiotic development, with 45 drugs currently going through the clinical trials pipeline, including

several new classes with novel modes of action that are in phase 3 clinical trials. Overall, there are promising signs for antibiotic discovery, but changes in financial models are required to translate scientific advances into clinically approved antibiotics [6].
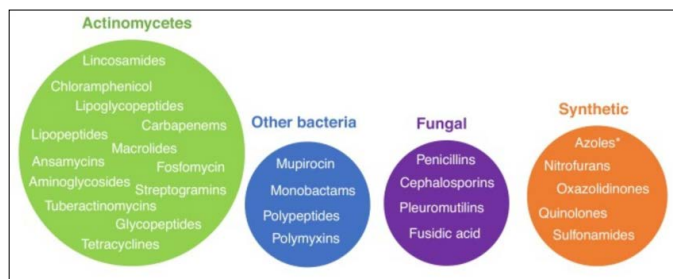
Since the introduction in 1937 of the first effective antimicrobials, namely, the sulfonamides, the development of specific mechanisms of resistance has plagued their therapeutic use. Sulfonamide resistance was originally reported in the late 1930s, and the same mechanisms operate some 70 years later [7].

Antibiotics in clinical use and modes of resistance [8]

Antibiotic class	Example	Mode of resistance
Beta lactams	Penicillins (ampicillin) Cephalosporins (cephamycin) Penems (meropenem) Monobactams (aztreonam)	Hydrolysis Efflus Altered target
Macrolides	Erythromycin Azithromycin	Hydrolysis Glycosylation Phosphorylation Efflux Altered target
Aminoglycosides	Gentamicin Streptomycin Spectinomycin	Phosphorylation Acetylation Nucleotidylation Efflux Altered target
Rifamycins	Rifampin	ADP-ribosylation Efflux Altered target
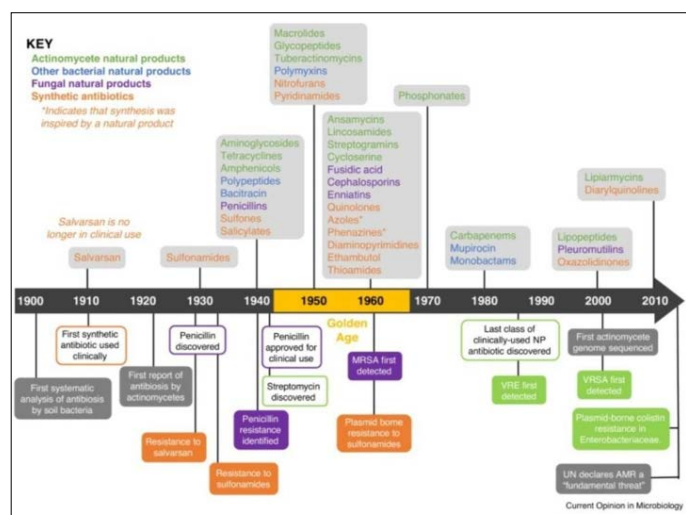
Classification

Antimicrobial drugs can be classified on the basis of many characteristics:

A. Chemical structure

1. Sulfonamides and related drugs: Sulfadiazine and others, Sulfones—Dapsone (DDS),Para Aminosalicylic acid (PAS).
2. Diaminopyrimidines: Trimethoprim, Pyrimethamine.
3. Quinolones: Nalidixic acid, Norfloxacin, Ciprofloxacin, Prulifloxacin, etc.
4. β-Lactam antibiotics: Penicillins, Cephalosporins, Monobactams, Carbapenems.
5. Tetracyclines: Oxytetracycline, Doxycycline, etc.
6. Nitrobenzene derivative: Chloramphenicol.
7. Aminoglycosides: Streptomycin, Gentamicin, Amikacin, Neomycin, etc.
8. Macrolide antibiotics: Erythromycin, Clarithromycin, Azithromycin, etc.
9. Lincosamide antibiotics: Lincomycin,Clindamycin.
10. Glycopeptide antibiotics: Vancomycin,Teicoplanin.
11. Oxazolidinone: Linezolid.
12. Polypeptide antibiotics: Polymyxin-B,Colistin, Bacitracin, Tyrothricin.
13. Nitrofuran derivatives: Nitrofurantoin, Furazolidone.
14. Nitroimidazoles: Metronidazole, Tinidazole,etc.
15. Nicotinic acid derivatives: Isoniazid, Pyrazinamide, Ethionamide.
16. Polyene antibiotics: Nystatin, Amphotericin-B,Hamycin.
17. Azole derivatives: Miconazole, Clotrimazole, Ketoconazole, Fluconazole.
18. Others: Rifampin, Spectinomycin, Sodium.fusidate, Cycloserine,Viomycin, Ethambutol,Clofazimine, Griseofulvin.

B. Type of organisms against which primarily active
1. Antibacterial: Penicillins,Aminoglycosides,Erythromycin, Fluoroquinolones, etc.
2. Antifungal: Griseofulvin, Amphotericin B,Ketoconazole, etc.
3. Antiviral: Acyclovir, Amantadine, Zidovudine, etc.
4. Antiprotozoal: Chloroquine, Pyrimethamine, Metronidazole, Diloxanide, etc.
5. Anthelmintic: Mebendazole, Pyrantel, Niclosamide, Diethylcarbamazine, etc.

C. Spectrum of activity
1. Narrow-spectrum: Penicillin G, Streptomycin, Erythromycin
2. Broad-spectrum: Tetracyclines, Chloramphenicol

The initial distinction between narrow and broad-spectrum antibiotics is no longer clearcut. Drugs having all ranges of intermediate band width, e.g., extended spectrum penicillins, newer cephalosporins, aminoglycosides, fluoroquinolones are now available. However, the terms 'narrow-spectrum' and 'broad-spectrum' are still popular.

D. Type of action
1. Primarily bacteriostatic; Sulfonamides, Erythromycin, Tetracyclines, Clindamycin, Chloramphenicol, Linezolid, Ethambutol
2. Primarily bactericidal: Penicillins, Cephalosporins, Aminoglycosides, Vancomycin, Polypeptides, Fluoroquinolones, Rifampin, Metronidazole, Isoniazid, Cotrimoxazole, Pyrazinamide

Some primarily static drugs may become cidal at higher concentrations (as attained in the urinary tract), e.g. erythromycin, nitrofurantoin. On the other hand, some cidal drugs, e.g., cotrimoxazole, streptomycin may just be static under certain circumstances.

E. Natural sources of antibiotics
1. Fungi: Penicillin, Griseofulvin, Cephalosporin
2. Bacteria: Polymyxin B, Tyrothricin, Colistin, Aztreonam, Bacitracin
3. Actinomycetes: Aminoglycosides, Macrolides, Tetracyclines, Polyenes, Chloramphenicol [1]

Antibiotics in Periodontics

Periodontitis is an infection caused by bacteria residing in biofilms at or below the gingival margin. Destructive periodontal disease appears to be caused by subgingival infection by specific microbial agents. Traditional therapy for this disease has involved elimination or suppression of subgingival microbial complexes by mechanical debridement like scaling and root planning or surgical procedures. However, the pathogenic microbiota becomes more complex over time, so systemic administration of antibiotics may be required as an adjunct in controlling bacterial infections [9].

It has been demonstrated that once bacteria attach to a tooth surface and reside within a mature biofilm structure, they have reduced susceptibility to antimicrobials compared to planktonic or free-floating bacteria [10].

Therefore, mechanical debridement is considered critical to disrupt the biofilm when using systemic antibiotics to treat periodontitis. The rationale for use of adjunctive systemic antimicrobials is to further reduce the bacterial load, enabling resolution of the inflammation in the periodontal pocket. Antibiotics may be prescribed for periodontal patients who do not respond to conventional mechanical therapy, for patients having acute periodontal infections associated with systemic manifestations, for prophylaxis in medically compromised patients, and as an adjunct to surgical and non-surgical periodontal therapy. Application of antibiotic periodontal therapy focuses on the pathogenic microbiota, the patient, and the choice of drug [11].

Periodontal Pathogens

The most effective use of antibiotics for the treatment of periodontitis presupposes knowledge of the pathogenic microbiota. Most putative pathogens are indigenous to the human oral cavity, but possible super infecting organisms (enteric Gram-negative rods, pseudomonas, staphylococci, and yeasts) may also inhabit periodontal pockets. Most putative periodontal pathogens are Gram-negative anaerobic rods.

However, some pathogens are Gram-positive facultative and anaerobic cocci and rods, and others are Gram-negative facultative rods [12].

Drugs

The pharmacological characteristics of antibiotics are critical in deciding their use, dosage, and routes and frequency of administration. Important pharmacological determinants include body weight, degree of absorption, rate of metabolism, and duration of effective antimicrobial levels at the site of infection.

The efficacy of periodontal antibiotic therapy is determined by the antimicrobial spectrum and the pharmacokinetic characteristics of the drug as well as by local environmental factors including [13, 14];
1. Drug binding to tissues
2. Protection of pathogens through binding, consumption, or degradation of the drug by non-target microorganisms
3. Subgingival plaque biofilm protecting the pathogens

4. Total bacterial load relative to the maximum achievable antibiotic concentration
5. Effectiveness of the host defenses
6. Pathogens in periodontal tissues, root surfaces, and extra-dental oral sites not affected by the therapy [15]

The antimicrobial agents used in periodontal therapy are tetracycline, macrolides, nitroimidazole compounds, quinolones, penicillins, and cephalosporins [11].

Oral antibiotic dosages [16]

Generic Name	Usual adult dosage	Length of treatment	Dosage suggestions
Amoxicillin/ clavul anic acid	250 or 500 mg, tid	10 days	Given without regard to meals
Amoxicillin plus metronidazole	375mg amoxicillin, tid, plus 250 metronidazole, tid 150-300mg, qid	7 days	Given without regard to meals
Clindamycin hydrochloride	150-300mg, qid	10 days	Given without regard to meals
metronidazole	250mg, tid or qid	10 days	Given without regard to meals
Tetracycline hydrochloride	250mg, qid	14-21days	Given 1 hour before or 2 hours after meal

Antibiotics in Surgery

In surgical practice, antimicrobial agents are administered in three types of situations: as prophylaxis, as an adjunct to operative treatment, and as therapy. Prophylactic antibiotics are given preoperatively to reduce the incidence of surgical site infection; adjunctive therapeutic antimicrobial agents are given in the setting of operative management of infections such as secondary peritonitis or necrotizing fasciitis; and antibiotics are used as primary therapy when operation is not performed, such as for cellulitis, or postoperative pneumonia. In the latter situation, antimicrobial actions and effects do not differ from those of other "medically treated" infections such as meningitis or uncomplicated urinary infection. Such antibiotic use as primary therapy will not be considered further. Here we will discuss "surgical infections", in which antimicrobial agents are given in association with operation or other types of drainage [17].

Appropriate use of antimicrobials is an integral part of good clinical practice. Clinicians should be aware of their role and responsibility for maintaining the effectiveness of current and future antibiotics.

Antimicrobial resistance AMR is one of the greatest threats to public health, sustainable development and security worldwide. Its prevalence has increased alarmingly over the past decades [18]. How to improve the management of infection in surgery [18]
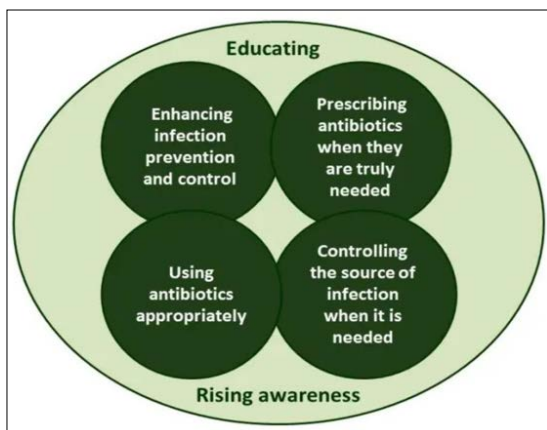
Antibiotics dosing in critically ill patients with sepsis and septic shock: A key component of the first-line management of critically ill patients is the administration of early and appropriate IV antibiotic therapy. An insufficient or otherwise inadequate antibiotic dosing is one of the variables more strongly associated with unfavorable outcomes in critically ill patients. The antibiotic dosing regimen should be established depending on host factors and properties of antibiotic agents. Antibiotic pharmacokinetics describes the fundamental processes of absorption, distribution, metabolism, and elimination and the resulting concentration-versus-time profile of an agent administered in vivo.

In patients with septic shock, administering an optimal first dose is probably as equally important as to the timing of administration. This optimal first dose could be described as a loading, or front-loaded dose and is calculated from the volume of distribution (Vd) of the drug and the desired plasma concentration. The Vd of hydrophilic agents (which disperse mainly in water such as beta-lactams, aminoglycosides and glycopeptides) in patients with septic shock may be altered by changes in the permeability of the microvascular endothelium and consequent alterations in extracellular body water. This may lead to lower-than-expected plasma concentrations during the first day of therapy resulting in sub-optimal achievement of antibiotic levels. In the setting of alterations in the volume of distribution, loading doses and/or a higher overall total daily dose of beta-lactams, aminoglycosides, or glycopeptides are often required to maximize the pharmacodynamics ensuring optimal drug exposure to the infection site in patients with sepsis or septic shock. Recommended dosing regimens of the most frequently used renally excreted antimicrobials according to renal function :Beta-lactams exhibit time-dependent activity and exert optimal bactericidal activity when drug concentrations are maintained above the MIC .antibiotics such as aminoglycosides exhibit concentration-dependent activity and should be administered in a once daily manner (or with the least possible number of daily administrations) in order to achieve high peak plasma concentrations [19].

Antibiotics in surgery
1. Prophylaxis: Antibiotics to prevent infections
2. Empiric therapy: Antibiotics to treat clinically suspected infections
3. Targeted therapy: Antibiotics to treat bacteriologically confirmed infections [18]

7 Strategies for appropriate antibiotic prophylaxis in surgery
1. Antibiotics alone are unable to prevent surgical site infections. Strategies to prevent surgical site infections should always include attention to infection control and infection control and prevention strategies.
2. Antibiotics prophylaxis should be administered for operative procedures that have a high rate of postoperative surgical site infection or when foreign materials are implanted.
3. Antibiotics given as prophylaxis should be effective against aerobic and anaerobic pathogens most likely to contaminate the surgical site i.e., Gram-positive skin commensals or normal flora colonising the incised mucosae.
4. Antibiotic prophylaxis should be administered within 120 minutes prior to the incision. However the administration of the first dose of antibiotics beginning within 30-60 minutes before surgical incision is recommended for most antibiotics to ensure adequate serum and tissue concentration during the period of potential contamination.
5. A single dose is generally sufficient. Additional antibiotic doses should be administered intra operatively for procedures >2-4 hours or with associated significant blood loss.
6. There is no evidence to support the use of postoperative antibiotic prophylaxis
7. Each institution is encouraged to develop guidelines for the proper surgical prophylaxis [18].

10 Strategies for appropriate antibiotic therapy in surgery
1. The source of infection should always be identified and controlled as soon as possible.
2. Antibiotic empiric therapy should be initiated after a treatable surgical infection has been recognized and microbiological data (culture and susceptibility results) may not be available for up to 48-72 hours therapy.
3. In critically-ill patients empiric broad-spectrum therapy to cover the most likely pathogens should be initiated as soon as possible after a surgical infection has been recognized. Empiric antimicrobial therapy should be narrowed once culture and susceptibility results are available and/or adequate clinical improvement is noted.
4. Empirical therapy should be chosen on the basis of local epidemiology, individual patient risk factors for resistant bacteria and Candida spp., clinical severity, and infection source.
5. Specimens for microbiological evaluation from the site of infection are always recommended for patients with hospital-acquired or with community-acquired infections at risk for resistant pathogens and in critically-ill patients. Blood cultures should be performed before the administration of antibiotics in critically-ill patients.
6. Antibiotic dose should be optimized to ensure that PK-PD targets are achieved.
7. The appropriateness and need for antimicrobial treatment should be reassessed daily.
8. Once source control is established, short courses of antibiotic therapy are as effective as longer courses regardless of signs of inflammation.
9. Failure of antibiotic therapy in patients having continued evidence of active infection may require a re-operation for a second source control intervention.
10. Infection control and prevention measures, combined with antimicrobial stewardship programs should be implemented in surgical departments. These interventions and programs require regular, systematic monitoring to assess compliance and efficacy [18].

The 8 goals of antimicrobial stewardship programs
1. To educate healthcare workers.
2. To limit antimicrobial resistance.
3. To decrease adverse antibiotic events.
4. To reduce healthcare costs.
5. To decrease C. difficile infections.
6. To reduce inappropriate antibiotics use.
7. To improve patients' outcomes.
8. To increase adherence to guidelines [18].

Rational antibiotic therapy [18]
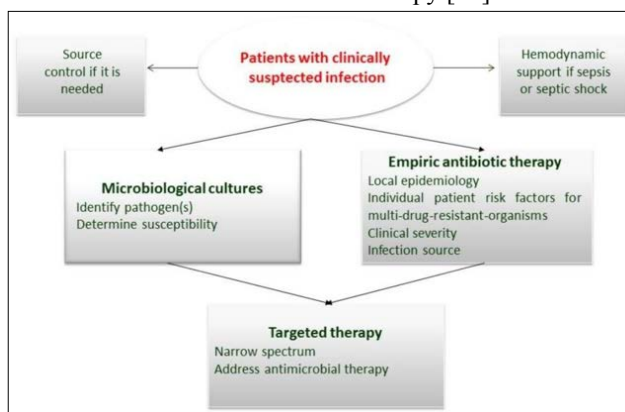
Antibiotics used in dental surgery

Amoxicillin and clindamycin were prescribed most frequently for infection prophylaxis (71.3% and 23.8% of antibiotic prescriptions, respectively).

The other antibiotics prescribed for dental procedures included amoxicillin-clavulanate (3.1%), azithromycin, metronidazole, and trimethoprim-sulfamethoxazole (each <1%) [20].

Antibiotics In Peadodontics

Recommended fluoroquinolone dosing in children [21]

Agent	Indication	Dosing	Adverse effects
Levofloxacin	Inhalational anthrax (in case of ciprofloxacin shortage)	(IV/oral) Infants >6 mo and children <5 y: 10 mg/kg/dose q12h; children >5 y:10 mg/kg/dose q24h	Dizziness, insomnia, rash, abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, increased LFT levels, rhinitis; fever, headache, restlessness (IV only)
Ciprofloxacin	Inhalation anthrax, cystic fibrosis, complicated UTV/pyelonephritis	18-40 mg/kg/day divided q8-12h; specific dosing varies by route, indication	Dizziness, insomnia, rash, abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, increased LFT levels, rhinitis; fever, headache, restlessness (IV only)

Recommended tetracycline dosing in children aged < 8 years [21]

Agent	Indication(s)	Dosing	Adverse effects
Doxycycline	Anthrax exposure, ehrlichiosis, RMSF	Weight <45 kg: 2-5 mg/kg/day in 2 divided doses;weight >45 kg:100 mg q12h (use adult dosing)	Nausea, vomiting, diarrhoea, esophagitis, rash, photosensitivity, nail discoloration, esophageal ulceration; hepatotoxicity, delayed bone growth (premature infants)

Drug related pharmacokinetic changes in neonate and young children [21]

Parameter	Drug	Effect	Mechanism
Absorption	Penicillin G	Increased bioavailability	Interaction between acid labile drug and elevated gastric ph
Distribution	Aminoglycosides (e.g., tobramycin) (water-soluble drugs)	Increased Vd of drug	Higher doses of water-soluble drugs needed owing to larger percentage of water in neonates
Metabolism	Phenytoin	Prolonged drug half-life that decreases as neonate ages	CYP2C9, responsible for biotransformation of phenytoin, not fully developed in neonates
Excretion	Aminoglycosides; concomitant administration of indomethacin, dopamine, betamethasone	Renal dysfunction; increased risk when administered with other drugs cleared renally	Maturation of renal function and tubular secretion not complete until early childhood; therefore, decreased drug clearance and prolonged renal exposure are possible

Antibiotics used for Coma Patients
Objectives: To determine the proportion of patients with documented bacterial aspiration pneumonia among comatose ICU patients with symptoms suggesting either bacterial aspiration pneumonia or non-bacterial aspiration pneumonitis

Patients: Prospective cohort of 250 patients admitted to the ICU with coma (Glasgow Coma Scale score ≤ 8) and treated with invasive mechanical ventilation [22].

Early-onset ventilator-associated pneumonia (EO-VAP) is the leading cause of morbidity and mortality in comatose patients. However, VAP prevention bundles focus mainly on late-onset VAP and may be less effective in preventing EO-VAP in comatose patients. Systemic antibiotic administration at the time of intubation may have a role in preventing EO-VAP. Therefore, we evaluated the effectiveness of systemic antibiotic administration in VAP prevention in comatose patients through a systematic review and meta-analysis. As a result Antibiotic prophylaxis in comatose patients reduced the incidence of EO-VAP and decreased the ICU stay slightly. Future trials are needed to confirm these [23].

Antibiotics used during Pregnancy
Pregnancy can be considered as the unique situation that two different organisms – mother and foetus – are exposed to the same drug. When prescribing over this special condition, the physician must remember that the prescription will affect two organisms and the drug must treat the mother without affecting the foetus. Beta-lactams having a long history of use without significant deleterious effects on the foetuses still are the safest choice during pregnancy. A careful risk-benefit evaluation must be established before the use of antibiotics during pregnancy, i.e., the benefit of the antibiotic must be greater than the risk to the foetus [24].

Transport across the placenta
The mechanism of drug transportation to the foetus blood is simple diffusion. This process is influenced by physicochemical factors of the antibiotic like molecular weight, lipid solubility, ionization rate and the plasmatic protein binding. The great majority of antimicrobial agents has highly lipid solubility and low molecular weight allowing a very easy diffusion across the placenta, quickly reaching the intrauterine compartment, exposing the foetus and decreasing the maternal antibiotic plasmatic concentration [25].

FDA categories
Category A: Controlled studies in women fail to demonstrate a risk to the foetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of foetal harm appears remote.
Category B: Either animal-reproduction studies have not demonstrated a foetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

Category C: Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal, or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the foetus.

Category D: There is positive evidence of human foetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Category X: Studies in animals or human beings have demonstrated foetal abnormalities, or there is evidence of foetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant [26].

Antimicrobial agents according to class, clinical use, adverse effects and FDA classification

Class	Clinical Indication in pregnancy	Adverse effects	FDA category
Penicillins	Puerperal sepsis Gonorrhoea Syphilis Community acquired	Allergy Skin rash Diarrhoea	B
	pneumonia Urinary tract infection Bronchitis		
Cephalosporins	S.aureus infections Surgical chemoprophylaxis Acute pyelonephritis Pelvic inflammatory disease Gram negative sepsis (ceftriaxone) P. aeruginosa sepsis (ceftazidime)	Cross allergy with penicillin	B
Other beta-lactams Carbapenems Imipenem Meropenem Ertapenem	Postpartum infections Severe pyelonephritis Perinatal infections	Diarrhoea Skin rash Nausea	CCB
Aztreonam	Aerobic gram-negative infections (alternative to aminoglycoside) Urinary tract infections Uncomplicated gonorrhoea	Nausea Gastrointestinal effects Eosinophilia	B
Vancomycin	MRSA infections C. difficile induced colitis	Ototoxicity Nephrotoxicity Red man syndrome	C
Teicoplanin	Gram positive infections	Injection site intolerance	Not been evaluated
Erythromycin	Legionella, Mycoplasma and Chlamydia infections T. pallidum	Hepatotoxicity (estolate) Gastrointestinal	B
Clarithromycin	Upper respiratory tract infections H. pylori eradication Mycobacterium avium complex prophylaxis in HIV positive patients	Gastrointestinal effects	C
Lincosamides	Postpartum metritis Anaerobic infections	Gastrointestinal effects Skin rash	B
Aminoglycosides Gentamicin Streptomycin Amikacin	(In general) Septicaemia and other severe infections of Gram negative aerobic infections	(In general) Nephrotoxicity Ototoxicity Neuromuscular blockade	CDD
Tetracyclines	Mycoplasma, Chlamydia and Spirochete infections	Hepatotoxicity Yellow-brown teeth discoloration	D
Chloramphenicol	Salmonellosis Rocky Mountain fever Typhoid fever	Haemolytic anaemia Grey Baby Syndrome	C
Metronidazole	Anaerobic sepsis Trichomonas vaginlis, Giardia lamblia and Entamoeba histolytica infections	Gastrointestinal effects Metallic taste Headache	B
Quinolones	Urinary tract infections (alternative to beta-lactams) Upper respiratory tract infection	Gastrointestinal effects Headaches Dizziness Eosinophilia	C
Sulfonamides	Toxoplasmosis Prophylactic protocols for pneumonia by Pneumocystis carinii in HIV positive pregnant women	Kernicterus (neonate) Allergic skin rash Stevens-Johnson syndrome Haematological effects	B
Polymyxin Colistin	Gram negative infections Prophylaxis in Caesarean section (Assoc. ampicillin)	Nephrotoxicity, neuromuscular blockade, ataxia, dizziness	C [24]

Advantages

Dentists use antibiotics for two main reasons. The first is for prophylaxis and the second is for control of infection.

4 D's of antimicrobial therapy
: right Drug
: right Dose
: De-escalation to pathogen-directed therapy,
: right Duration of therapy [27]

Antibiotics are, of course, most commonly used to control infection. In the dental field, the commonest indication is a dental abscess; this can arise either from a dead tooth or from the periodontium (the supporting structure of the tooth). On rare occasions osteomyelitis can occur. Other conditions that may call for the administration of antibiotics include acute ulcerative gingivitis or Vincent's disease, infections around erupting impacted wisdom teeth, salivary gland infections, infection from a tooth involving the maxillary antrum, and perforation of the antrum during extraction. Oral manifestations of a systemic disease like tuberculosis or syphilis should be treated with the appropriate antibiotic agent [28].

Antibiotics useful in Dental Practice

Antibiotic used	Cidal/Static	Important characteristic
Amoxicillin	Cidal	- Better oral tolerance. - Less chances of toxicity. - Most odontogenic infections still respond to this drug.
Amoxicillin+clavulanate	Cidal	Similar to amoxicillin having additional Beta lactamase resistance
Metronidazole	Cidal	Active against obligate anaerobes but no activity against facultative anaerobes like Streptococci. Useful in stage of abscess formation
Cephalosporins	Cidal	Useful in selective cases of penicillin allergy and have good activity against most oral pathogens but should not used in cases of patients showing Type I hypersensitivity to penicillin group of drugs
Clindamycin	Static	Useful in penicillin allergic patients and has a wide spectrum of activity including anaerobes. Useful in penicillin allergic infections. Risk of superinfection.
Tetracyclines	Static	High concentrations achieved in bone and gingival tissues. Topical formulations available for use in periodontology
Aminoglycosides	Cidal/static	- Injectable drugs - Active against gram negative odontogenic infections - Used in combination with other drugs in severe odontogenic infections - Ototoxicity and hepatotoxicity
Macrolides antibiotics	Static	Rapid antimicrobial resistance develops with these newer antibiotics and so they must be avoided in dental settings when better choices are available [29]
Fluoroquinolones	Cidal	Moxifloxacin has been found to be active against most odontogenic micro-organisms [30]. Useful in minor infections in penicillin allergic patients, but better alternatives are available and hence not recommended for routine use.

Tetracyclines also have many additional properties other than their antimicrobial action, such as the inhibition of mammalian collagenases, which prevent tissue breakdown, and the inhibition of clastic cells, which results in anti-resorptive activity [34]. Inflammatory diseases such as periodontitis include an excess of tissue collagenases, which may be blocked by tetracyclines, thus leading to enhanced formation of collagen and bone [31-35].

Disadvantages
Common side effects of selected antimicrobial agents

Antimicrobial	Side effects
Penicillins	hypersensitivity reactions (contraindicated in patients having history of penicillin or cephalosporin allergies) gastrointestinal discomfort, nausea, vomiting, diarrhea pseudomembranous colitis (ampicillins) vaginitis.
Erythromycin	gastrointestinal discomfort, nausea, vomiting avoid in patients having renal dysfunctions.
Tetracyclines	gastrointestinal discomfort, nausea, vomiting, diarrhea photosensitivity, rash, onycholysis intra- and extraoral fixed drug eruptions vertigo (especially with minocycline) vaginitis benign intracranial hypertension (pseudotumor cerebri) permanent tooth discoloration in children up to 8 years of age (all tetracyclines) permanent tooth and alveolar bone discoloration in adults (minocycline only) exacerbates systemic lupus erythematosus avoid during pregnancy and in patients having renal dysfunctions tetracyclines are contra-indicated in expectant mothers and children up to 12 years of age, and in patients having actual or incipient renal failure.[28]
Clindamycin	gastrointestinal discomfort, nausea, vomiting, diarrhea pseudomembranous colitis maculopapular rashes and urticaria avoid in patients having renal dysfunctions or gastrointestinal disease, especially colitis
Ciprofloxacin	gastrointestinal discomfort, nausea, vomiting unpleasant taste central nervous system stimulation leading to restlessness, dizziness, headache, tremor, confusion photosensitivity joint stiffness vaginitis avoid in children, adolescents or pregnant women (causes arthropathy in immature animals) and in patients having central nervous or seizure disorders (i.e., epilepsy)
Metronidazole	gastrointestinal discomfort, nausea, vomiting, diarrhea dizziness, vertigo, irritability, insomnia unpleasant metallic taste and dry mouth furred tongue peripheral neuropathy and convulsive seizures (long-term doses only) avoid during pregnancy and in patients having central nervous system disorders
Cephalexin	hypersensitivity reactions (contraindicated in patients having history of penicillin or cephalosporin allergies) dizziness, fatigue, headache pseudomembranous colitis vaginitis avoid in patients having renal dysfunctions [36]

Contraindications

1. Age may affect kinetics of many AMAs, and certain AMAs produce age-related effects. Conjugation and excretion of chloramphenicol is inefficient in the newborn: larger doses produce grey baby syndrome. Sulfonamides displace bilirubin from protein binding sites— can cause kernicterus in the neonate because their blood-brain barrier is more permeable. The t½ of aminoglycosides is prolonged in the elderly and

2. they are more prone to develop VIII nerve toxicity. Tetracyclines deposit in the developing teeth and bone— discolour and weaken them— are contraindicated below the age of 6 years.

3. Renal and hepatic function: Antimicrobials needing dose reduction/ avoidance in renal failure -Drugs to be avoided are: Nalidixic acid

4. Talampicillin; Nitrofurantoin Tetracyclines (except doxycycline). Antimicrobials in liver disease- Drugs to be avoided- Erythromycin estolate Tetracyclines Pyrazinamide Nalidixic acid Talampicillin Pefloxacin

5. Drug allergy History of previous exposure to an AMA should be obtained. If an AMA has caused an allergic reaction—it has to be avoided in that patient, e.g. drug of choice for syphilis in a patient allergic to penicillin is tetracycline. β-lactams, sulfonamides, fluoroquinolones and nitrofurantoin frequently cause allergies.

6. Pregnancy All AMAs should be avoided in the pregnant woman because of risk to the foetus 5. Genetic factors Primaquine, nitrofurantoin, sulfonamides, chloramphenicol and fluoroquinolones carry the risk of producing haemolysis in G-6-PD deficient patients [1].

Side effects of antibiotics
- Allergic reactions: Every year, there are more than 140,000 emergency department visits for reactions to antibiotics. Almost four out of five emergency department visits for antibiotic-related side effects are due to an allergic reaction. These reactions can range from mild rashes and itching to serious blistering skin reactions, swelling of the face and throat, and breathing problems. Minimizing unnecessary antibiotic use is the best way to reduce the risk of side effects from antibiotics. You should tell your doctor about any past drug reactions or allergies.

- C. difficile: C. difficile is a type of bacteria (germ) that causes diarrhea linked to at least 14,000 American deaths each year. When you take antibiotics, good bacteria that protect against infection are destroyed for several months. During this time, you can get sick from C. difficile. The bacteria can be picked up from contaminated surfaces or spread from the healthcare environment. People, especially older adults, are most at risk who take antibiotics and also get medical care. Take antibiotics exactly and only as prescribed.

- Antibiotic resistance: The use of antibiotics may increase the risk of bacteria becoming resistant to them. Antibiotic-resistant infections can be very serious and difficult to treat [37].

Rationale Combinations

Fixed dose combinations (FDCs) is a combination product of two or more active pharmacological ingredients (APIs) in a single dosage form. FDCs enhance the efficacy of individual drugs, decrease the chance of drug resistance, improve patient compliance and also decrease the pill burden on the patients [38].

Antimicrobials (amoxicillin + clavulanic acid) were the most commonly prescribed FDCs (60%), followed by diclofenac and paracetamol combination (42%) [39].

Some of the other common combinations are of amoxicillin and metronidazole, penicillin and metronidazole, metronidazole and clindamycin, amoxicillin with metronidazole and penicillin, amoxicillin with clindamycin, and amoxicillin with penicillin [40].

Improved efficacy and enhancement of the drug effect were the most common advantages of FDCs. But, according to World Health Organization (WHO) guidelines there are a number of other advantages like decreased chances of adverse drug reactions,

improvement in patient compliance, convenience of prescribing [41].

Titration of doses to suit the needs of individual patients, incompatible pharmacokinetics, drug interactions, and potential quality problems are the disadvantages of using FDCs [41].

Combinations of antibiotics are only indicated in the treatment of severe infections, with the DPF recommending phenoxymethylpenicillin (or erythromycin) with metronidazole [42].

Tetracyclines are typically used in conjunction with corticosteroids and these combinations have anti-inflammatory, antibacterial and anti-resorptive properties, all of which help to reduce the periapical inflammatory reaction including clastic-cell mediated resorption [43].

Clindamycin and a combination of three antibiotics (metronidazole, ciprofloxacin and minocy-cline) have also been reported to be effective at reducing bacterial numbers in the root canal system of infected teeth [43].

The First reported local use of an antibiotic in endodontics was in 1951 when Grossman used a polyantibiotic paste known as PBSC (a mixture of penicillin, bacitracin, streptomycin and caprylate sodium), peni-cillin targets Gram-positive organisms, bacitracin for penicillin-resistant strains, streptomycin for Gram-neg-ative organisms and caprylate sodium to target yeasts. Later, Nystatin replaced caprylate sodium as an anti-fungal agent in a similar medicament, known as PBSN [44].

The Combination That Appears to be most promising consists of metronidazole, ciprofloxacin and minocycline evaluated the potential of this mixture to kill bacteria in the deep layers of root canal dentine in situ [45, 46].

List of FDCs included in the WHO essential drug list [47]

Drugs	Form	Strength
Neomycin + Bacitracin	Ointment	5 mg+500 IU
Amoxicillin + Clavulanic acid	Tablet	500 mg+125 mg
Rifampicin + Isoniazid	Tablet	150 mg+75 mg 300 mg+150 mg
Rifampicin + Isoniazid + Pyrazinamide	Tablet	150 mg+75 mg + 400 mg
Rifampicin + Isoniazid + Ethambutol	Tablet	150mg+75mg+275mg
Rifampicin + Isoniazid + Ethambutol + Pyrazinamide	Tablet	150mg+75mg+275mg+ 400mg
Zidovudine + Lamivudine	Tablet	300mg+150mg
Sulfadoxine + Pyrimethamine	Tablet	500 mg+25 mg
Levodopa + Carbidopa	Tablet	100 mg + 10 mg 250 mg+25 mg
Sulfamethoxazole + Trimethoprim	Tablet Oral	100 mg+20 mg 400 mg+80 mg
	Liquid Injection	200mg+40mg/15ml 80 mg+16 mg/ml (in 5 ml ampoule)

Commonly prescribed FDCs in various dental departments [39]
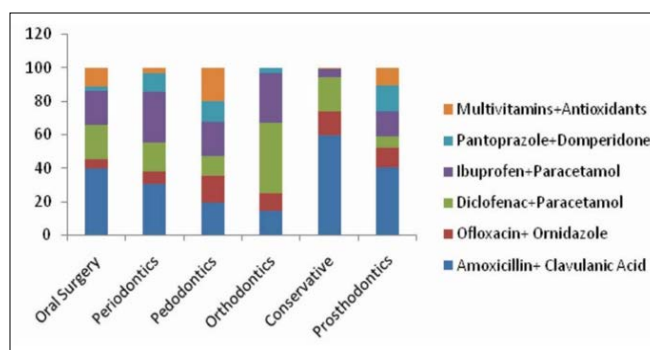
Analysis of knowledge of clinicians on rationality of commonly prescribed FDCs in dentistry [39]

FDCs	Rational	Irrational
Amoxicillin+Clavulanic Acid	76 (98.7%)	1 (1.3%)
Ampicillin+ Cloxacillin	70 (90.9%)	70 (90.9%)
Ofloxacin+Ornidazole	60 (77.9%)	17 (22.1%)
Multivitamin+Antioxidants	60 (77.9%)	17 (22.1%)
Pantoprazole+Domperidone	50 (64.9%)	27 (35.1%)
Nimesulide+Paracetamol	24 (31.2%)	53 (68.8%)
Nimesulide+Diclofenac	20 (26%)	57 (74%)
Diclofenac+Paracetamol+ Serratiopeptidase	48 (62.3%)	29 (37.7%)

Irrational Combinations

The most commonly prescribed irrational FDC was diclofenac + paracetamol combination, 42% residents and 41% dental clinicians and residents believed that regular Continuous Medical Education (CMEs) stressing upon rational use of medicine could reduce the magnitude of this problem [39].

Treating a particular ailment with effective, safe and good quality drugs is the basic aim of drug therapy [34]. Irrational drug therapy use can lead to reduction in quality of drug therapy, increased risk of side effects, drug resistance [48, 49].

Ampicillin/Amoxicillin are effective only against gram negative bacilli but not against beta lactamase producing staphylococci. while cloxacillin is antistreptococcal penicillin with no effect on gram negative bacilli, since both these infections rarely co-exist, so combining them is irrational [50, 51]. Adding paracetamol to another nonsteroidal anti-inflammatory drug (NSAID) like diclofenac, aceclofenac, and ibuprofen does not offer additional benefit, but increases the chances of nephrotoxicity [52].

Serrati peptidase is a proteolytic enzyme supposed to relieve inflammation. This claim is not based on controlled clinical trials and FDCs containing this compound with NSAIDs offer no additional anti-inflammatory advantage except higher cost to the patient [53].

Combinations of NSAIDS/analgesics with antispasmodic agents are irrational and they can result in dangerous elevation of the body temperature. As per WHO guidelines, the combination of vitamins is part of nutrition, and vitamin combinations should not be used indiscriminately [50]. H2 blockers and proton pump inhibitors are effective in peptic ulcer and it is irrational to combine these drugs with an antiemetic as peptic ulcer is not always associated with vomiting.

FDCs of cardiovascular drugs like Ramipril + Telmisartan are associated with more adverse events without any additional benefit [54]. Likewise combining two antihypertensives affecting the same pathway (Enalapril + Losartan) is irrational as it does not add to efficacy. In FDCs of cough and cold remedies such as cetirizine + phenylpropanolamine + dextromethorphan; phenylpropanolamine is a banned drug due to its potential to cause stroke. Phenylpropanolamine can also aggravate diabetes, glaucoma and prostate enlargement.

There is no justification in combining mucolytic agent (Ambroxol) with antibacterial (Ciprofloxacin or Cefadroxil or Roxithromycin), as thick secretions in the respiratory tract are not always because of respiratory infections. Also, the antibacterial therapy always does not require an associated dose of mucolytic agent. Hypolipidemic drugs such as atorvastatin and nicotinic acid in fixed dose combinations have increased probability of myopathy [55].

In the year 2005 the committee banned the use of xed dose combination of Amoxicillin and Cloxacillin, and Ampicillin and Cloxacillin in the hospital. Similarly, the DTC has also banned several multivitamins and B-complex preparations containing multiple combinations [56].

The most imperative concern with irrational FDCs is that they expose patients to unnecessary risk of adverse drug reactions, antibiotic FDCs are responsible for increasing the chances of resistance [41].

List of some banned FDC products [57]

Banned FDC	Year of banning
Combination of vitamins with tranquilizers and / or anti-in ammatory agents	1984
Combinations of antihistamines with antidiarrheals or with antiamoebic drugs.	1984
Combinations of vitamins with analgesics.	1984
Combinations of vitamins C with tetracycline	1984
Phenformin and its Combinations	1991
Phenylbutazone in Combination with other Drugs	1991
Amphetamine and its Combinations	1991

List of some commonly used IFDCs [57]

Combination products	Examples	Reasons for being termed irrational
Combination of antipyretic and analgesic	Ibuprofen 200 mg + paracetamol 325 mg	Both these drugs have the same mechanism of action. So there is no synergism. NSAID combinations are known to cause direct damage to the kidney.
Combination of ampicillin with cloxacillin. (Amoxicillin with cloxacillin)	Mega pen	Both of the combination belongs to same class namely Beta lactamase acting at the same site by the same mechanism offering no synergism or additive effects when combined. Moreover, combining two antibiotics acting through the same mechanism cannot be justified
Combination of Codeine with other medicines	Codeine sulphate 10 mg + Paracetamol 500 mg	Combination can cause excessive sedation which can be dangerous. Need further examination
Expectorants with central cough suppressants, antihistamines, bronchodilators and mucolytics	Bromhexine Hydrochloride 8 mg + Terbutaline sulphate 2.5 mg + Guaifenesin 100 mg + Menthol 5 mg	Using a combination of expectorants is a costlier way of helping a condition which is often self - resolving. Expectorant given in effective doses are often not tolerated and produce adverse drug reaction
Multivitamin preparations	Combinations of several vitamins	Multivitamin combination is considered to be irrational. Excessive use may leads to several side effects.

Recent Advances

A remarkable and often overlooked fundamental of antibiotics is that they have biological activities beyond microbial killing. The host modulatory aspects of macrolides, tetracyclines, and beta-lactams are reviewed by Aminov (2013a) underscoring how, for example, macrolides such as azithromycin are routinely used for immunomodulation in patients with chronic pulmonary disease rather than for an antimicrobial effect. Azithromycin is also used as a tool by Imperi et al. to detail how non-conventional thinking about regulating virulence factors or modifying host inflammatory cascades are useful to combating major pathogens such as Pseudomonas aeruginosa (Imperi et al., 2014). Along this line, Morita and colleagues carefully detail the pleiotropic responses of P. aeruginosa to sub-therapeutic levels of several antibacterial and propose avenues to pursue to combat this pathogen, such as developing efflux pump inhibitors (Morita et al., 2014) [58].

Plenty of new antimicrobial agents with new targets have been marketed recently, while few are still awaiting Food and Drug Administration (FDA) approval.

Some of the new agents are in clinical development phase are listed below [59]

Name of drug	Class of drug	Year of FDA approval / phase of trial	Spectrum of activity
Marketed agents Daptomycin Telithromycin Tigecycline Retapamulin Doripenem Telavancin Ceftaroline Fidaxomicin	Lipopeptide Ketolide Glycylcycline Pleuromutilin Carbapenems Glycopeptides Cephalosporins Macrocyclic	2003 2004 2005 2007 2007 2009 2010 2011	Gram+ve bacteria Gram+ve and -ve Gram+ve and -ve Gram+ve and -ve Gram+ve Gram+ve Gram+ve Gram+ve
Awaiting FDA approval. Iclaprim Ceftobiprole	DHFR inhibitor Cephalosporin	Approval awaited Approval awaited	Gram+ve Gram+ve
Agent in clinical development Torezolid Radezolid Solithromycin Cethromycin Dalbavancin Oritavancin	Oxazolidinones Oxazolidinones Ketolides Ketolides Glycopeptide Glycopeptide	Phase II Phase II Phase II Phase III Phase III Phase III	Gram+ve Gram+ve Gram+ve Gram+ve Gram+ve Gram+ve

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