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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/13133
DOI URL: http://dx.doi.org/10.21474/IJAR01/13133

RESEARCH ARTICLE

ANTIBIOTIC RESISTANCE: "A COMMON CHALLENGE IN DENTISTRY.''

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Manuscript Info

Manuscript History
Received: 10 May 2021
Final Accepted: 14 June 2021
Published: July 2021

Key words:-
Antibiotic, Antibiotic Resistance, Dentistry

Abstract

The discovery and subsequent clinical introduction of antibiotics is one of the most important game changers in the history of medicine. Antibiotics are widely used in dental practice both for therapeutic and prophylactic reason. Unfortunately, in recent years the use of antibiotics has been accompanied by the rapid emergence of antimicrobial resistance causing a major threat to healthcare system**.** Solid guideline or recommendation is often lacking regarding prescription of antibiotic in dentistry.Issuing antibiotic prescribing guidelines, antibiotic stewardship program, addressing 'over the counter' sale of antibiotics,education programmes can be considered useful for curbing antibiotic abuse. To highlight the severity of the issue, several international declarations have been published to call upon the government around the globe to take action on antibiotic resistance.

Introduction:-

One of the central themes of success in human therapeutics in the 20th century was the discovery and development of antibiotics and antibacterial agents for the treatment of bacterial infections1.Antibiotics are either cytotoxic or cytostatic to the micro-organisms allowing the body's natural defences such as the immune system to eliminate them.To combat against infection or microbes, antibiotics are undoubtedly a blessing to human civilization that have saved lives of millions of people.

Millions of metric tonnes of newer classes of antibiotics have been produced in the last 60 years since its inception. Increased demand for antibiotics across many sectors has allowed for less expensive and off label uses of drugs.Conversely, due to the enormous and irresponsible use of antibiotics has contributed significantly to the advent of the resistant strains2.

India occupies first position among all countries in the world in regard of antibiotic consumption for human use3. Dentists prescribe 1 in 10 antibiotic prescriptions and are the top specialty prescriber for antibiotics in the United States4.Antibiotic overuse and misuse is a major contributor towards antibiotic resistance. The emerging resistance to antibiotics is a major threat to healthcare system.

Solid guideline or recommendation can be considered in streamlining the clinician's decision process regarding antibiotic utilization5.

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This review tries to highlight and find out antibiotics that can still be considered effective in the treatment of different odontogenic infections, systemic conditions where antibiotic prophylaxis is recommended, antibiotic resistance mechanism of some useful antibiotics and finally strategies on antibiotic prescription in order to curb unnecessary use of antibiotics and future directions.

Antibiotics commonly used in dental practice:

Antibiotics are typically prescribed in the practice of dentistry for some of the following purposes: a) as treatment for acute odontogenic infections b) as treatment for non-odontogenic infections c) as prophylaxis against focal infection in patient at risk (endocarditis and joint prosthesis) and as prophylaxis against local infection and systemic spread in oral surgery6 .

Asodontogenic infections are often polymicrobial in nature, hence antibiotics should have both aerobic and anaerobic coverage. Although amoxicillin clavulanic acid is the most preferred antibiotic in the field of dentistry, emerging beta- lactamase producing bacteria is rendering it less effective.

Clindamycin is a broad-spectrum antibiotic which is effective against aerobic, anaerobic bacteria as well as beta-lactamase producing bacteria.

The most common amoxicillin clavulanic acid dose is 625 mg thrice daily for 5-7 days.Amoxicillin clavulanic acid (875mg/125mg) twice daily and clindamycin (150 mg four times daily) in the treatment of acute odontogenic infection with or without abscess was assessed in a randomised, parallel group , comparative , observer blind study 7.The study concluded that amoxicillin clavulanic acid (875mg/125mg) was administered twice daily for 5-7 days and was comparable to clindamycin (150 mg) administered four times daily. A higher percentage of pain and swelling reduction (49.5% and 43.6%) was achieved withamoxicillin clavulanic acid group compared to the clindamycin group (45.6% and 39.6%) after two days of treatment.

Doxycycline is highly effective but underappreciated antimicrobial with a broad spectrum, exceptional bio availability and very little evidence of serious adverse events. Doxycycline is cheap and most popular tetracycline derivative currently available. Tetracycline class effect led to the classification of doxycycline as a category D drug by the USA food and drug administration (FDA) pregnancy category based on A,B,C,D,X categories. Consequently , its use has been limited especially in two vulnerable patient groups- pregnant women and children. Multiple studies conducted in different animal species between 1967-1980 found no teratogenic effect of doxycycline in pregnancy. Mouse and rabbit studies showed that there was no increase in congenital anomalies in animals treated upto six times the maximal human therapeutic dose (3.33 mg/kg) but increase of skeletal anomalies and decrease of fetal weight were observed at doses > 17 times the human therapeutic dose. No teratogenicity was observed upto 100 times the maximal therapeutic dose in rats and monkeys8,9.

Azithromycin is a semi-synthetic,acid stable antibiotic and represents a prototype novel class of macrolide named azalides. It has a long half-life and good tissue penetration10.It has activity against anaerobic bacteria as well as gram-negative bacilli. It is effective against periodontal pathogens Aggregatibacteractinomycetemcomitans and P. gingivalis. Azithromycin has significantly less bacterial resistance to the subgingival microflora of chronic periodontitis compared to other commonly prescribed antibiotics11.

Tinidazole is a 5-nitro imidazole introduced into clinical medicine in 1969.Tinidazole is intracellularly reduced (mediated by ferredoxin system and low oxidation reduction potential) to active intermediates. Most aerobic micro-organisms do not generate low oxidation reduction potential explaining the selective activity of tinidazole against anaerobic micro-organisms.Tinidazole is rapidly bactericidal ,its activity is not affected by inoculum size and emergence of resistance during treatment is rare12.Hence tinidazole can be considered for treatment of periodontal infection along with doxycycline.

Moxifloxacin is a broad spectrum antibacterial agent and it is quite effective against both oral streptococci (macrolid sensitive/ resistant) and anaerobic pathogens13.Both amoxicillin and clindamycin are used for prevention of bacteraemia following dental extraction.Resistance to clindamycin has been reported among oral streptococci after dental extraction has been found14.

In a randomized control trial , comparative efficacy of amoxicillin, clindamycin and moxifloxacin in the prevention of bacteraemia following dental extraction was evaluated.

The study concluded that administration of a single oral dose of 400 mg moxifloxacin 1-2 hours before the procedure can be safer alternative to 2 grams amoxicillin or 600mg clindamycin for prevention of bacteraemia following dental extraction.

Depending on the nature of oral infection,antibiotics should be prescribed for 5-7 days15.Now a days short term antibiotic therapy is mostly preferred. In short-term antibiotic therapy,antibiotic of choice should have easy penetrability into tissues and effective at an optimal dose and optimal dosing regimen.

Antibiotic Prophylaxis:
In AHA's 2007 guideline, the AHA concluded that bacteraemia resulting from daily activity is much more likely to cause infective endocarditis than bacteraemia associated with dental procedure.

Revised A.H.A. guideline for prophylaxis of dental procedure is recommended only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from infective endocarditis [Table 1, table 2].Prophylaxis is no longer needed for routine anaesthetic injection through non infected tissue , dental radiograph , placement of orthodontic brackets , shedding of deciduous teeth/ bleeding from trauma to lips / oral mucosa16.

Table 1:- Cardiac conditions with the highest risk of adverse outcome from infective endocarditis and for which prophylactic dental procedures are recommended.

1. Prosthetic cardiac valve
2. Previous infective endocarditis
3. Congenital heart disease

-Unrepaired cyanotic congenital heart disease including palliative shunts and conduits
-Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure.
-Repaired congenital heart disease with residual defects at the site of a prosthetic patch or prosthetic device.(which inhibit endothelization)

- Cardiac transplantation with subsequent valvulopathy.

Table 2:- Prophylactic antibiotic regimens before a dental procedure.

Patient group	Antibiotic	Dose(single,30-60 minute before procedure)	
		Adults	Children
Able to take oral medication	Amoxycillin	2g	50mg/kg
Unable to take oral medication	Ampicillin Or Cefazolin or Ceftriaxone	2 g IM or IV 2g IM or IV	50 mg/kg IM or IV 50 mg/kg IM OR IV
Allergic to penicillin or ampicillin and able to take oral medication	Cephalaxin Or Clindamycin Or Azithromycin or Clarithromycin	2 g 600 mg 500 mg	50mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillin or ampicillin and unable to take oral medication	Cefazolin or Ceftriaxone Or Clindamycin	1 g IM or IV 600 mg IM OR IV	50 mg/kg IM or IV 20 mg /kg IM or IV

Antibiotic Resistance:
During the last two decades, there have increases in the levels of resistance to erythromycin among clinical as well as commensal isolates and these increases correlate with the increased use of this class of antibiotics17.

Most of the erythromycin resistant isolates with an identified resistance gene were streptococci and the most common resistance gene was ‘ mef’ followed by erm (B). The mef gene was detected in 67% of isolates with an identified erythromycin resistance gene. Additionally the mrs (A) efflux gene was identified in one staphylococcus sp. The methylase gene was found in 33% isolates with an identified erythromycin resistance gene, most of these isolates carried an erm(B) gene, however one erm (B) gene isolated from veillonella sp. for the first time. One isolate carried both erm (B) and mef genes and erm(F) was isolated from prevotella sp17.The presence of erythromycin resistance gene in oral streptococci is important because viridans group streptococci have been shown to cause systemic diseases and they can dessiminate the erythromycin resistance gene to other pathogenic bacteria such as streptococci pneumonia.

Low level resistance to nitro imidazole (metronidazole) is often ascribed to the nim gene18.The role of nim genes in metronidazole resistance is controversial. An explanation for conflicting results is that very high levels of nim proteins are required to confer metronidazole resistance and that other factors determine high level of metronidazole resistance.

Another emerging antibiotic resistance has been reported in community associated S. aureus.In 2004, a novel S.aureus clone designated ST 772 was isolated from hospitals in Bangladesh 19as well as from an Indian community setting20.This novel clone ST 772 has potential for infiltration into nosocomial environment21,22,23,24. ST 772 has shown resistance towardsaminoglycosides,b-lactums , fluoroquinolones , macrolides and trimethoprim24,25,26.

Possible mechanism for emergence of ST 772 strain has been identified as virulence factors, specific antibiotic resistance determinants and mutation coding regions27.Enterotoxin homologue ORF CM 14 were ubiquitous in ST 772, Pantom Valentine Leucocidin(PVL) genes and enterotoxin A gene are associated with ST 772.

Mutations of interest in ST-772 A strains are - the first mutation caused a non-synonymous change in fbpA (L55P) encoding a fibrinogen binding protein that mediates surface adhesion in S. aureus. The second comprised a non-synonymous change (L6 7V) in the plc gene ,encoding a phospholipase associated with survival in human blood cells and abscess environment in USA300. The third encodes a non- synonymous mutation (S 2 7 3G) in tet , an efflux pump promotes resistance to tetracycline as well as survival in abscess environments and skin colonisation28.

Members of genus Bacteroids and Prevotellashows the highest rates of penicillin resistance29,30.Viridans group streptococci, anaerobic streptococci and prevotella species show resistance to macrolides. The newer macrolides clarithromycin and azithromycin offer improved pharmacokinetic compared to erythromycin31,32.Erythromycin has adequate activity against the majority of odontogenic pathogens but upto 50%. Fusobacterium are resistant to erythromycin33,34.

Strategies to prevent overuse of antibiotics:

Irrational use of antibiotics in dentistry can be reduced by adopting following principles:

(i) Conservative use of antibiotics
(ii) Being responsible while prescribing antibiotics
(iii) Educating our patients

Measures required for curbing antibiotic abuse:

(i) Implementation of national action plan for antimicrobial resistance :Indian government had adopted the National action plan for containing antimicrobial resistance in April,2017. But more practical implementation is yet to be done.
(ii) Antibiotic stewardship program: Implementation of these programmesenhance the judicious use of antimicrobial by encouraging the selection of the optimal antimicrobial drug regimen, dose, duration of therapy and route of administration35.
(iii) Addressing ‘ over the counter’ sale of antibiotics
(iv) Education programmes
(v) Enhancing the role of primary health care in reducing antimicrobial resistance.

Solid guideline or recommendations can be considered cornerstone in streaming the clinician’s decision process regarding antibiotic utilization. Sweden has long tradition of strategic work against antibiotic resistance which is probably an important factor for favourable rates of antibiotic resistance seen in comparison to many other countries36.In Sweden national recommendation for antibiotic prophylaxis for antibiotic treatment in dentistry were

published in 2012 and 2014, respectively37.The decline in antibiotic prescription seen after 2007 may indicate an effect of mere educational efforts since it followed the formation of StramaDentwith the aim of counteracting antibiotic resistance in dentistry. The guideline strongly promote the use of narrow spectrum compounds as first choice of treatment. The results show that the reduction was largest among broad spectrum compound further supporting that observed decline in prescription is in fact a consequence of novel guideline5.

Discussion And Conclusion:-

Till now there is lack of basis for identification of specific problem areas which is necessary in order to pinpoint aberrant antibiotic utilization in dentistry as there is reason for concern regarding antibiotic resistance in dental practice. The installation of surveillance system accompanied by audit to ascertain the number of prescriptions written and their appropriateness , to highlight areas of prescribing knowledge that are lacking in the dental practice are recommended. Further investigation and education are required to attempt to slow down resistance development and lessen the future impacts on antibiotic prescribing in dentistry.

Although there seems to be a correlation between introduction of governmental strategies to reduce antibiotic usage in dentistry and declining antibiotic prescription, there is further need for improvement of antibiotic stewardship in odontology and to clarify effective measures to disseminate information.5

This review tries to highlight the impact of antibiotic resistance as a potential, global health threat and focus its effects to improve this complex problem.

References:-

1.Christopher T Walsh,GerryWright,AntibioticResistance,ChemicalReviews,vol 105,(2),2005.
2.Sojib Bin Zaman et al,A Review on AntbioticResistance:Alarm bells are ringing,Cureus,9(6)1403,2017.
3.TanejaN , Sharma M, Antimicrobial resistance in the environment : The Indian scenario. Indian J Med Res,149, 119-28,2019.
4.Hicks LA et al. US outpatient antibiotic prescribing variation according to geography,patient population and provider specialty in 2011,Clin. Infect Dis ,60(9),2015.
5.Bodil Lund, Andreas Cederlund , Margareta Hultin and Frida Lundgren, Effect of governmental strategies on antibiotic prescription in dentistry, ActaOdontologica Scandinavica,2020
6.RafaelPovedaRoda et al,Antibiotic use in dental practice:Areview,Med Oral Patol oral Cir bucal,E,186-92,2007
7.Archiel Launch Tancawan, Maria Noemi Pato, KhamizaZainolAbidin ,Amoxycillin /clavulanic acid for the treatment of Odontogenic infections: A randomized study comparing efficacy and tolerability versus clindamycin, International Journal of dentistry,1-9,2015
8.CahenRL ,FaveA,Absence of teratogenic effect of 6-alpha deoxy-5 oxytetracycline,FedProc Fed Am SocExp Biol,31,238,1972.
9.DelahuntCS,Toxicology of vibramycin,ToxicolApp Pharmacol,10,402,1967.
10.Schentag JJ, BallowCH,Tissue directed pharmacokinetics,Am J Med,91, 5S-11 S,1991.
11.VanWinkelhoff AJ et al,Antibiotic resistance in sub-gingival microflora in patients with adult periodontitis, A comparative survey between Spain and the Netherlands (in Dutch), 106,290-294,1999.
12.NordCE,Microbiological properties of tinidazole: spectrum , activity and ecological considerations. J antimicrob chemother,10,Suppl A : 165-72,1982.
13.P. Diz Dios et al,Comparative Efficacies of Amoxycillin , Clindamycin and Moxifloxacin in prevention of bacteraemia following dental extractions,Antimicrobial agents and chemotherapy,50(9) 2996-3002,2006.
14.Tomas I et al ,In vitro activity of moxifloxacin compared to other antimicrobials against streptococci isolated from iatrogenic oral bacteraemia in Spain .Oral Microbiol. Immunol,19, 331-335,2004.
15.Punithavathy Ramachandran et al,Implication of overprescription of antibiotics. J Pharm BioalliedSci.11(suppl 2): S434-S 437,2019.
16.David K. Lam,George K.B. Sandor, Cameron M.L. Clokie,Prevention of infective endocarditis : Revised guideline from American heart association and implications for dentists,JCDA,74(5),449-453,2008
17.A. Villedieu et al, Genetic basis of erythromycin resistance in oral bacteria,Antimicrobial agents and chemotherapy,2298-2301,2004.
18.Trinh S, ReyssetG,Mutagenic action of 5- nitroimidazoles: in vivo induction of GC-CG transversion in two BacteroidFragilis reporter genes,Mutat Res, 398,55-65,1998

19.Afroz S ,Kobayashi N , Nagashima S , Alam M , Hossain B , Rahman A, Islam R, Lutfor AB, Muazzam N, Khan AH, Paul SK, Shamsuzzaman K, Mahmud C, Musa K, Hossain A, Genetic characterization of Staphylococcus aureus isolates carrying Panton-Valentine leucocidin genes in Bangladesh, Jpn J Infect Dis ,61, 393-396,2008.
20.Goering RV, Shawar RM, Scangarella NE , O'Hara FP, Amrine-Madsen H, West JM , DalessandroM,Becker JA, Walsh SL, Miller LA , Van Horn SF, Thomas ES, Twynholm ME, Molecular epidemiology of methicillin resistant and methicillin susceptible staphylococcus aureus isolates from global clinical trials,J ClinMicrobiol,46,2842-2847,2008.
21.D' Souza N , Rodrigues C ,Mehta A,Molecular characterization of methicillin-resistant staphylococcus aureus with emergence of epidemic clones of sequence type(ST)22 and ST 772 in Mumbai ,India, J ClinMicrobiol ,48, 1806-1811,2010
22.Nadig S, Velusamy N, Lalitha P, Kar S, Sharma S,ArakereG,Staphylococcus aureus eye infections in two Indian hospitals : emergence of ST772 as a major clone,ClinOphthalmol,6, 165-173,2012
23.ManoharanA , Zhang L, Poojary A, Bhandarkar L, Koppikar G, Robinson DA,An outbreak of post-partum breast abscesses in Mumbai , India caused by ST22-MRSA-IV : genetic character and epidemiological implication infect ,140,1809- 1812,2012.
24.Blomfeldt A, Larssen KW, MoghenA,GabrielselC,Elstrom P, Aamot HV, Jorgensen SB, Emerging multidrug resistant Bengal –Bay Clone ST -772 MRSA –V in Norway,molecular epidemiology 2004-2014, European J ClinMicrobiol Infect Dis ,36, 1911-1921,2017.
25.Chakrakodi B, PravakaraS , Nagaraj S,Etienne J ,ArakereG.High prevalence of ciprofloxacin resistance in community associated Staphylococcus aureus in a tertiary care Indian Hospital , AdvMicrobiol 4, 133-141,2014
26.Steinig EJ, Andersson P, Harris SR , Sarovich DS , Manoharan A , Coupland P, Holden MT , Parkhill J, Bentley SD , Robinson DA,Tong SY, Single molecule sequencing reveals the molecular basis of multidrug-resistance in ST 772 methicillin –resistant Staphylococcus aureus. BMC Genomics ,16,388,2015
27.Eike J. Steinig, Sebastian Duchene, D. Ashley Robinson , Stefan Monecke, Maho Yokoyama, MaisemLaabei, Peter Slickers, PatiyanAndersson et al, Evolution and Global Transmission of a multidrug -resistant community associated methicillin resistant Staphylococcus aureus lineage from the Indian subcontinent, 10(6), e 1105-19,2019
28.Balakuntla J ,Pravakara S, Arakere G. Novel rearrangements in the staphylococcal cassette chromosome mec type V elements in Indian ST772 and ST672 methicillin resistant Staphylococcus aureus strains ,Plos One 9:e 94293,2014
29.Snydman DR , Jacobus NV , McDermott LA , Golan Y, Goldstein EJ, HarrelL,Update on resistance of Bacteroidfragilis group and related species with special attention to carbapenems 2006-2009,Anaerobe,17,147-51,2011
30.Snydman DR , Jacobus NV , McDermott LA ,Ruthazer R, Golan Y, Goldstein EJ , National survey on the susceptibility of Bacteroidfragilis group: Report and analysis of trends in the United States from 1997 to 2004, Antimicrob Agents Chemother, 51, 1649-55,2007
31.Kuriyama T, Karasawa T, Nakagawa K, Saiki Y, Yamamato E, Nakamura S,Bacteriologic features and antimicrobial susceptibility in isolates from orofacial odontogenic infections,OralSurg Oral Med Oral Pathol Oral RadiolEndod, 90,600-8,2000
32.Soares GM , Figueiredo LC, Faveri M , Cortelli SC, Duarte PM, Feres M, Mechanism of action of systemic antibiotics used in periodontal treatment and mechanisms of bacterial resistance to these drugs, J Appl Oral Sci, 20, 295-309,2012
33.Karlowsky J, Ferguson J ,Zhanel G, A review of commonly prescribed oral antibiotics in general dentistry, J Can Dent Assoc,59,292,1993
34.Senhorinho GN, Nakano V, Liu C, Song Y, Finegold SM, Avila –Campos MJ,Occurrence and antimicrobial susceptibility of porphyromonas spp. and Fusobacterium spp. in dogs with and without periodontitis, Anaerobe, 18, 381-5,2012
35.Dellit TH, Owens RC, McGowan JE, Gerding DN, Weinstein RA , Burke JP. Infectious diseases society of America and Society for healthcare epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship, Clin Infect Dis,44,159-77,2007
36.Swedres- Svarm, Consumption of antibiotics and occurrence of resistance in Sweden and National Veterinary Institute, 2018
37.Le Corvoisier P, Renard V, Roudot – Thoraval F et al, Long- term effects of an educational seminar on antibiotic prescribing by GPs: a randomised control trial, Br J Gen Pract,63(612),e-455-e464,2013
38.Sanchez GV, Fleming Dutra KE, Roberts RM et al, Core elements of outpatient antibiotic stewardship ,MMWR Rocomm Rep, 65(6),1-12,2016.