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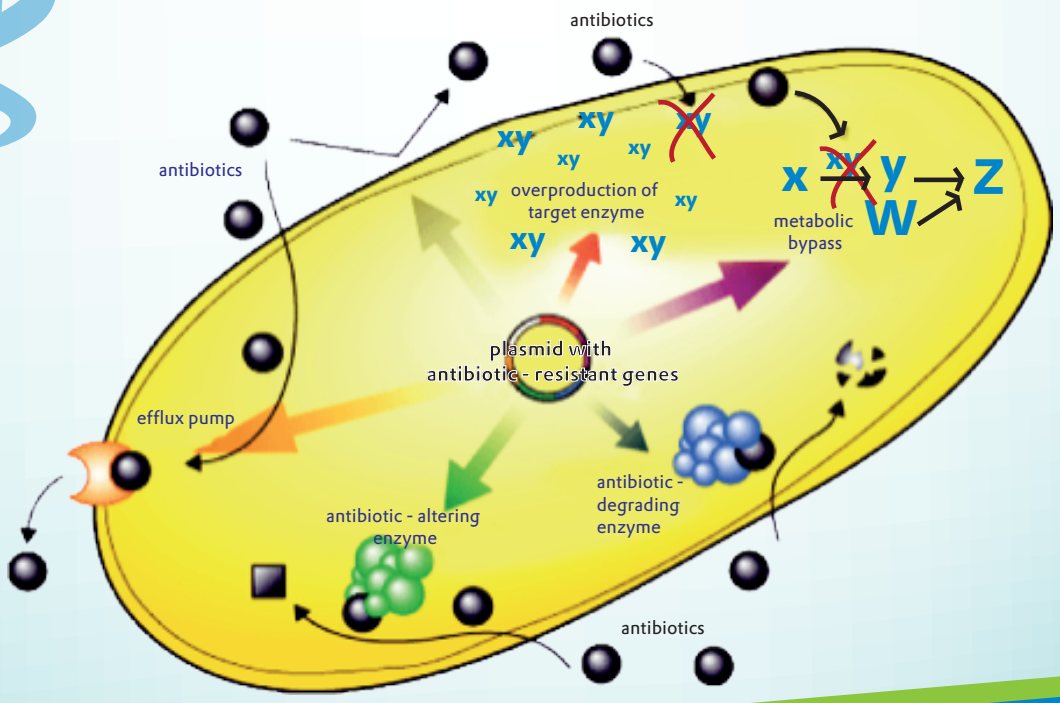

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Chettinad Health City
MEDICAL JOURNAL

Contents

GLYCOMET GP

D RISE

Editorial

Vanakkam.

This issue of the journal focuses on "Drug Resistance" – both microbial and non microbial.

Discovery of antibacterials has been an epoch of the 19th /20th centuries. Development of resistance to antibacterial by the microbes has been the major realization of the mid, late 20th & 21st century. The reason for this is not difficult to discern. Indiscriminate, inadvertent and inappropriate use of antibacterial has led to microbial drug resistance. A review article describes the mechanism of microbial drug resistance.

Tuberculosis has existed since time immemorial. Drugs for tuberculosis were discovered in the 20th century. From single drug chemotherapy, soon evolved multidrug chemotherapy of tuberculosis. The *Mycobacterium tuberculosis,* probably more ancient than mankind, seems to have outwitted mankind. The emergence of Multi Drug Resistance Mycobacterium tuberculosis is discussed in a review article.

A human being is a trillion celled organism. In the human body each cell (except those programmed for apoptosis) tries to survive and resist any change in its milieu. Human beings therefore also develop resistance to several pharmacological agents. This is described in a review article as Non Microbial Drug Resistance.

An original article deals with the impact of dental caries and dental fluorosis on the Quality of Life of 12- year old children in Tamil Nadu. Case reports feature interesting articles from the departments of surgery, paediatrics and dentistry.

An ancient Sanskrit sloka humorously describes the doctor as Yamaraja's brother[1].

vaidhyarAja namaH tubhyaM yamarAjasahodara |
yamaH tu harati prANAm vaidhyarAjaH dhanAni cha ||

वैध्यराज नमः तुभ्यं यमराजसहोदर ।
यमः तु हरति प्राणाम् वैध्यराजः धनानि च ॥

O Doctor, I salute you! You are the brother of Yama Raja!

While Yama only takes the life, the doctor takes the money too!

The attire/ensemble of Yamaraja's brother seems to have changed over the centuries. The article from the pages of history describes Medical fashion over the centuries.

An article highlights the Nobel Prize for medicine in 2013.Medical updates and an intriguing ECG adds to an interesting read.

We look forward to your valuable suggestions and comments.

Dr. N. Pandiyan
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1) Yamaraja's Brother: The Autobiography of Dr. M.K. Mani. Bharatiya Vidya Bhavan, 1989

Original Article

Impact of Dental Caries and Dental Fluorosis on the Quality of Life of 12- year old Children in Tamil Nadu, India.

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Abstract

Background Dental caries and fluorosis are the two common childhood oral diseases which are attributed to variations in exposure to fluorides. Epidemiological studies have shown the prevalence of dental caries and fluorosis in India. There is a lack of evidence to show the impact of these conditions on the quality of life of children in India. Hence the aim of this study is to assess the impact of dental caries and dental fluorosis on the quality of life of 12 year old children in Tamil Nadu, India.

Materials and Methods This cross-sectional study was conducted in Sriperumbudur taluk, Kanchipuram district, India among 220 twelve year old children. Dental caries was recorded using DMFT Index by Klein, Palmer and Knutson; Dental fluorosis was recorded using Dean's fluorosis index and the quality of life of children was assessed using a Tamil version of the Child Perception Questionnaire CPQ.

Results Dental caries is present among (88) 40% of the study population and dental fluorosis affected 131 (60.6%) of the study population. CPQ used to assess the impact of dental caries and dental fluorosis on quality of life showed an increase in mean scores across each domain and overall score, with the increase in severity of dental caries and dental fluorosis. One way ANOVA showed significant difference between groups categorized based on the severity of dental caries and fluorosis.

Conclusion Dental caries and fluorosis had a considerable impact on the quality of life of children. With the increase in severity of the disease there is an increased impact on the quality of life of children.

Key words : Caries onset, Caregiver behaviour, Caries prevention, Epidemiology in school children.

Chettinad Health City Medical Journal 2013; 2(3): 74-79

Background

Oral diseases and disorders during childhood can have a negative impact on the life of children and their parents. For example, dental caries can lead to toothache, which can be distressful and worrying for the affected children and their parents and dental fluorosis is regarded as a condition that may impact on the self-esteem and self-confidence of individuals at very early stages of life. Conversely, good oral health can have positive benefits for children. Children's confidence and self-esteem can be enhanced by the appearance of their teeth, reflecting the childrens perception of the shape and colour of teeth and their occlusion[1].

Oral disease and disorders are measured in population studies using clinical measures recorded by dental clinicians during oral examinations such as the decayed, missing, and filled index for caries or the Thylstrup and Fejerskov (TF) Index for fluorosis. These indices indicate the presence and severity of an oral condition. However, they do not consider individuals' perception of dental appearance and the possible impact of fluorosis on psychosocial well-being, which is also considered as an important factor in the comprehensive definition of health[2].

Since 1990s, there has been more studies on aesthetic perceptions as psychological indicators of oral health, and they have been shown to be powerful indicators of perceived need for dental care[3,4,5]. However, children are rarely asked about their perception of dental fluorosis and the impact it may have on activities conducted daily such as smiling and interacting with other children[6].

While fluorides provide a protective benefit against dental caries, fluoride consumed in greater amounts in early childhood can have the adverse effect of causing dental fluorosis, a developmental disorder of dental enamel. There exists, therefore, the potential for a clinical trade off in oral health with differing levels and timing of exposure to fluorides. Further, variation in the presence and severity of caries and fluorosis may be associated with a consequent trade-off in the impact of those clinical conditions on the oral health related

quality of life (OHRQoL) of children. On the one hand, there is potential for exposure to fluorides to reduce caries experience, and therefore to reduce negative impacts of dental caries on OHRQoL. Conversely, there is potential for excessive exposure to fluorides to cause dental fluorosis, which may change the appearance of teeth and cause negative impacts on OHRQoL[1].

The incidence of dental caries has declined worldwide[7] and it has been mainly attributed to the use of fluorides. However in developing countries like India, about 50% of school children are suffering from dental caries[8]. India lies in a geographical fluoride belt, which extends from Turkey upto China and Japan through Iran, Iraq and Afghanistan. Of the 85 million tons of fluoride deposits found on earth's crust, 12 million tons are in India[9]. Fluorosis is an endemic condition prevalent in 22 states of India[10]. Out of six lakh villages in India atleast 50% have fluoride content in drinking water exceeding 1.0ppm[11]. Endemic fluorosis also increases the risk of developing dental caries and it becomes aesthetically objectionable[12].

The magnitude of the prevalence of dental caries and dental fluorosis is high in India. Studies conducted in India have shown the prevalence of dental caries, dental fluorosis and its relation to fluoride levels in drinking water[13-17]. A better understanding of the oral health status of the patient is achieved when perceptions of oral health are reported by those individuals who experience the condition[18]. There is a lack of evidence to show the impact of these conditions on the quality of life of children in India. Hence this study was conducted with the aim to assess the impact of dental caries and dental fluorosis on the quality of life of 12 year old children in Sriperumbudur taluk, Kanchipuram district of Tamil Nadu, a fluoride endemic area in India.

Materials and methods

This cross-sectional study was conducted in Sriperumbudur taluk, Kanchipuram district, Tamil Nadu, a fluorosis endemic area in India. The sample size for the present study was estimated to be N = 202, 12-year old children based on the prevalence of caries free children from fluorotic area in the study conducted by Doc LG and Spencer A[1]. Inclusion criteria are 12 year old children who were permanent residents of that region since birth, children with good general health and children who were present on the day of examination. Children who were excluded are children with developmental defects of teeth like enamel hypoplasia, children under fixed orthodontic treatment and children with past history of professional topical fluoride therapy. Prior to the start of the study ethical approval was obtained from Institutional ethics committee. Approval was also obtained from the concerned school authorities and informed consent was obtained from parents or guardian of the children.

The survey instrument consists of a self- administered questionnaire, containing demographic information on name, age, gender, class, section and name of the school followed by assessment of impact of dental caries and dental fluorosis on the quality of life using Child Perception Questionnaire (CPQ) which addresses the frequency of events occurring during the previous three months. The questionnaire is composed of 37 items distributed among 4 domains:

- Oral symptoms (6 questions),
- Functional limitations (10 questions),
- Emotional well-being (9 questions) and
- Social well-being (12 questions).

A 5-point Likert scale was used with the following options:

- 'never' = 0,
- 'once/twice' = 1,
- 'sometimes' = 2,
- 'often' = 3, and
- 'every day/almost every day' = 4.

The CPQ[11–14] scores for each domain are computed by adding all of the item scores under that domain. The total score can vary from 0 to 148, with a higher score denoting a greater impact on QoL[19]. Children filled the questionnaire themselves, followed by clinical examination for recording dental caries using DMFT index by Klein, Palmer and Knutson (1938)[20] and dental fluorosis using Dean's fluorosis index – Modified given by Dean HT (1942) [21] .

Validation of the questionnaire was done after translating it to the native language (Tamil). A single examiner performed the clinical examination was trained through a series of clinical sessions. Intra-examiner reliability was assessed using Kappa statistics, by re-examining the DMFT scores of the first 20 patients examined in the day and the intra examiner reliability was found (= 0.86).

The data collected was analyzed and tested for significance using statistical software package, SPSS software for windows (version 17.0). Frequency tables were computed. ANOVA test was used to assess the impact of varying degrees of dental fluorosis and prevalence of dental caries on quality of life of children assessed using the CPQ.

Results

Among the 220 study subjects 115 (52.3%) were male and 105 (47.7%) were female. 60% of the study population were caries free and only 40% of the study population had normal enamel, Table – 1 shows the distribution of study subjects according to gender, prevalence of dental caries and dental fluorosis, mean DMFT of the study population is 0.97±0.46. Child Perception questionnaire was used to assess the impact of dental caries and dental fluorosis on quality of life of 12 year old children. Table – 2 shows the mean domain score and CPQ overall score for oral health related quality of life based on dental caries status. The scores increased with the severity of dental caries with the mean overall score for caries free children was least at 8.58 ± 5.175 and for children with ≥ 5 – DMFT the mean score was 22.86 ± 5.127. One way ANOVA showed significant difference across groups categorized based on dental caries status.

Table – 3 shows the mean domain score and CPQ overall score for oral health related quality of life based on dental fluorosis status, the scores increased with the severity of dental fluorosis with the mean overall score for children with normal enamel was least at 8.88 ± 5.98 and for children with moderate fluorosis the mean score was[16].76 ± 6.119. One way ANOVA showed significant difference across groups categorized based on dental fluorosis status.

The impact of dental caries and dental fluorosis on day to day life events was assessed using the global ratings of the extent to which overall life was affected. Figure -1 shows the global ratings of the extent to which overall life was affected based on dental caries status. 42.8% of children with DMFT- ≥ 5 indicated that their life was affected very much because of the oral condition and 70.4% of the caries free children indicated that they were not at all affected. Figure -2 shows the global ratings of the extent to which life overall was affected based on dental fluorosis status. 28% of children with moderate dental fluorosis indicated that their overall life was affected very much by the presence of dental fluorosis, only 60.6% children with normal enamel indicated that their life was not at all affected.

Table 1: Distribution of study subjects according to gender, prevalence of dental caries and dental fluorosis

Characteristics	N	%
Gender		
Male	115	52.3
Female	105	47.7
Dental caries		
0 - DMFT	132	60
1 -2 - DMFT	44	20
3 - 4 - DMFT	30	13.6
≥ 5 DMFT	14	6.4
Total DMFT (Mean±SD)	0.97±0.46	
Dental Fluorosis		
Normal	89	40.4
Questionable	12	5.4
Very mild	57	26
Mild	37	16.8
Moderate	25	11.4
Severe	0	0

Table 2: Mean Domain Scores and CPQ[11-14] overall score for oral health related quality of life based on dental caries status

Domain	Oral symptoms* Mean ± SD	Functional limitations* Mean ± SD	Emotional well-being* Mean ± SD	Social well-being* Mean ± SD	CPQ (11-14) Overall score* Mean ± SD
0 - DMFT*	3.06 ± 1.823	2.13 ± 1.324	1.83 ± 1.604	1.73 ± 1.497	8.58 ± 5.175
1-2 – DMFT*	4.93 ± 1.946	3.05 ± 1.478	2.55 ± 1.486	2.02 ± 1.422	12.55 ± 5.346
3-4 – DMFT*	5.87 ± 1.613	4.07 ± 1.413	3.43 ± 1.135	3.13 ± 1.833	16.57 ± 4.023
≥ 5 – DMFT*	7.93 ± 2.556	5.93 ± 2.018	4.64 ± 1.277	4.00 ± 1.881	22.86 ± 5.127
F - value	31.618	33.27	14.309	9.23	32.94
p - value	0.00	0.00	0.00	0.00	0.00

***One-way ANOVA, d.f = 219**

Table 3: Mean Domain Scores and CPQ (11-14) overall score for oral health related quality of life based on dental fluorosis status

Domain	Oral symptoms* Mean ± SD	Functional limitations* Mean ± SD	Emotional well-being* Mean ± SD	Social well-being* Mean ± SD	CPQ (11-14) Overall score* Mean ± SD
Normal*	3.55 ± 2.159	2.21 ± 1.585	1.67 ± 1.521	1.39 ± 1.571	8.88 ± 5.98
Questionable*	4.08 ± 2.234	2.58 ± 1.240	2.08 ± 1.24	1.58 ± 0.900	10.58 ± 5.534
Very mild*	4.25 ± 2.565	2.81 ± 1.977	2.21 ± 1.359	1.91 ± 1.106	11.16 ± 5.903
Mild*	4.73 ± 2.479	3.19 ± 2.132	3.38 ± 1.622	2.95 ± 1.290	14.30 ± 6.119
Moderate*	5.04 ± 2.150	3.36 ± 1.630	3.84 ± 1.841	4.28 ± 1.768	16.76 ± 6.119
F - value	2.982	3.265	14.746	24.369	11.230
p - value	0.020	0.013	0.000	0.000	0.000

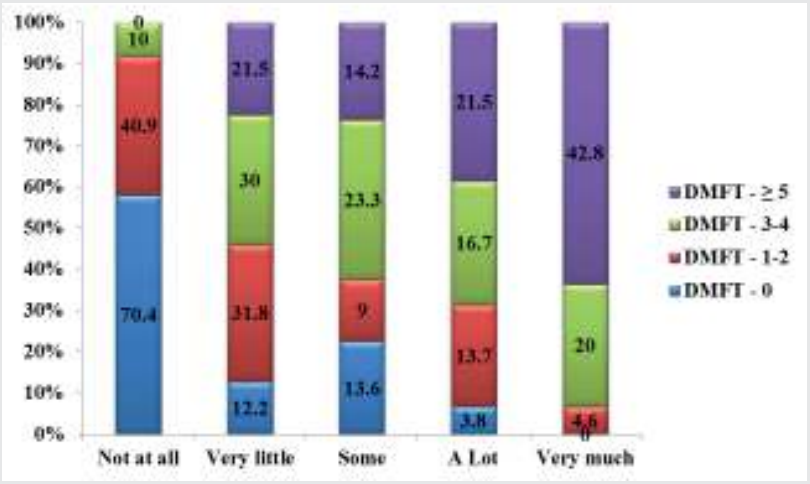

Fig 1: Global ratings of the extent to which life overall was affected based on dental caries

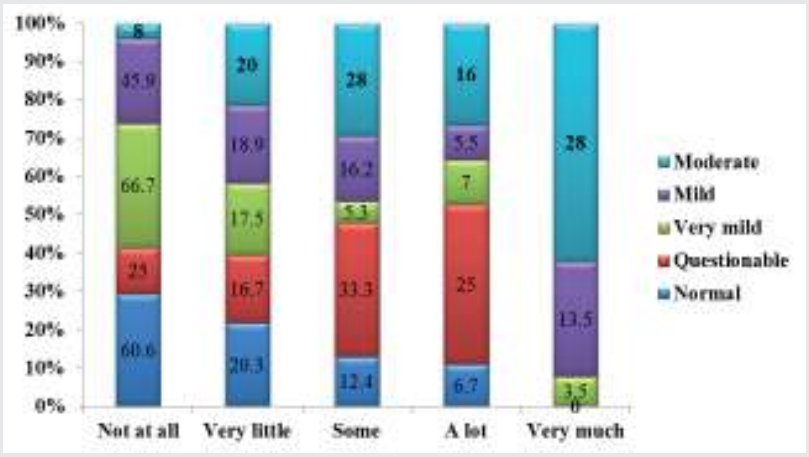

Fig 2: Global ratings of the extent to which life overall was affected based on dental fluorosis

Discussion

Dental caries and dental fluorosis are the two oral conditions associated with the usage and exposure to fluoride in early life[1]. It is well established that fluoride protects against dental caries[22]. However clinical trade-offs between caries and dental fluorosis may exist with varying levels and timing of exposure to fluorides increasing the risk of dental fluorosis without having a fully protective effect against dental caries[1]. Epidemiological studies have collected data regarding the prevalence of dental caries and dental fluorosis, however the impact of these oral diseases on quality of life is yet unknown. This cross- sectional study was conducted to assess the prevalence of dental caries, dental fluorosis and its impact on the quality of life of 12-year old children.

All over the world dental caries is the most common oral disease affecting children. In the present study dental caries was present among 40% of the study population with the mean DMFT – 0.97 lower than the studies by J Moses et al (2011)[23], Goyal A et al (2007)[24], Dhar V et al (2007)[25] conducted in other parts of India. As the children in the present study were exposed to higher levels of fluoride in drinking water since childhood, which had contributed for the decline in dental caries among the study population.

Fluoride level in drinking water though resulted in a decline in dental caries among the study population, dental fluorosis is found to affect 59.5% of the study population. In the present study the children are not exposed to any professionally applied topical fluorides or any other fluoridation programmes, however most of the children used fluoridated dentifrices on a regular basis. High prevalence of dental fluorosis among the study population is attributed mainly to the natural high fluoride levels in drinking water[26]. Prevalence of dental fluorosis in the current study was higher than the studies by Dhar V et al (2007)27 and JK Baskardass et al (2008)[17]. Current study reported none of the study subjects with severe dental fluorosis, in contrast to the study conducted by Sudhir KM et al (2009)[15] at Nalgonda a fluoride endemic area in Andhra Pradesh, India where 35% of the 12 year old children had severe dental fluorosis, this was due to the difference in fluoride concentration in drinking water sources.

From the epidemiological data it is clear that the fluoride levels in drinking water both benefited and

harmed the study population. Child perception Questionnaire was used to assess the impact of dental caries and dental fluorosis among the study population. In the present study there is an increase in the CPQ overall score and the mean scores across various domains like 'oral symptoms', 'functional limitations', 'social and emotional well-being' with the increase in severity of dental caries and dental fluorosis; similar to the studies by Loc DG et al (2007)[1] and Vargas Ferreria et al (2011)[28].

Dental caries and fluorosis have a measurable impact on the quality of life of affected children. This was evident from the results obtained from the study population and it was similar to the studies by Loc G Do et al (2007)[1], Vargas Ferreria et al (2011)[28], Tellez M et al (2012)[29]. Caries experience was found to have a plausible link to oral symptoms and functional limitations, as dental caries can cause symptoms like pain and discomfort affecting the functions like mastication and sometimes even being absent from the school. In the present study presence of dental fluorosis was associated with the lower caries experience; this was in accordance to the findings by Loc G Do et al (2007)[1].

Persons with attractive appearance are assumed to possess more socially desirable personalities, and are happier and more successful than others who are less attractive. Oral cavity is an important area for the appearance of a person, so the dental diseases could not only affect the physical health of patients, but also influence the psychological health, which could impact their day-to-day living or life quality in turn[30]. Social and emotional well-being is an important component of overall health. Dental fluorosis affected the social well-being of the children as fluorosis affecting the anterior teeth had an esthetic impact on the quality of life of the children; this was in accordance with the study by Williams DM et al (2006)[31].

Further studies are required to analyse the association of other oral health disorders affecting childhood, the quality of life of children and to find the perception of parents of the children affected with dental caries and dental fluorosis.

Conclusion

Dental caries and dental fluorosis are the two common oral diseases during childhood which are mainly affected by fluorides during tooth development. This study was conducted to assess the prevalence of dental caries.

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Review Article

Antimicrobial Resistance – an Overview

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Chettinad Health City Medical Journal 2013; 2(3): 80-84

Introduction

We may soon be facing the end of the "antibiotic era." The initial and seemingly unstoppable success of antibiotics, the fruit of human ingenuity, has been countered by an escalation of resistance mechanisms in bacteria. This crisis has been described as an "unwinnable war." The statistics compiled as a result of surveillance efforts illustrate the emergence of many genera of bacteria that are resistant to all antibiotics.

Antibiotics are compounds that are literally against life. Typically antibacterial drugs interfere with some structure or process that is essential for bacterial growth or survival without harm to the host harboring the infecting bacteria. We live in an era where antibiotic resistance has spread at an alarming rate[1-4].

What are antibiotics? Where do they come from? How do they work? How do they become resistant to bacteria? How do we find new antibiotics? Can we slow down the development of antibiotic resistant super bugs? (Super bugs are multidrug resistant bacteria, that are difficult to treat with limited drugs available) - these are the questions that arise in our minds.

Bactericidal drugs kill the organism but bacteriostatic drugs only nullify the growth. Most antibiotics in human use are natural products, elaborated by one species of microbe (bacteria or fungi). Over the past 60 - 70 years most antibiotics have been discovered by screening of soil samples for natural products that kill pathogenic bacteria, first on culture plates and then in animal infections[5].

These include Penicillins , Cephalosporins from fungi and Streptomycin, Erythromycin, Tetracycline and Vancomycin from different strains of filamentous bacteria like Streptomyces. Semi synthetic modifications have produced second and third generation Betalactams of both Penicillin and Cephalosporin classes where as total synthesis has created the second generation - Erythromycin, Clarithromycin and Azithromycin. Fluroquinalones like Ciprofloxacin are purely synthetic antibacterial drugs[5].

Antibiotics can be classified into broad spectrum and narrow spectrum antibiotics. For example, Tetracycline, a broad spectrum antibiotic, is active against Gram positive and Gram negative bacteria, where as Penicillin which has relatively narrow spectrum, can be used mainly against Gram positive bacteria. Other antibiotics such as Pyrazinamide have an even narrower spectrum, and can be used merely against *Mycobacterium tuberculosis*.

Targets for main classes of antibacterial drug

Antibiotics fight against bacteria by inhibiting certain vital processes of bacterial cells or metabolism. Based on these processes, we can divide antibiotics into five Major classes

(1) inhibitors of bacterial cell wall biosynthesis, example - Penicillin and Vancomycin

(2) inhibitors of bacterial protein synthesis, example - Amino glycosides

(3) inhibitors of nucleic acid synthesis, such as Fluroquinalones which inhibits DNA synthesis, and Rifampicin, which inhibits RNA synthesis.

(4) Antimetabolites such as sulfa drugs.

(5) Antibiotics that can damage the membrane of the cell, such as Polymyxin B, Gramicidin and Daptomycin[6].

What is antimicrobial resistance?

Antibiotic resistance occurs when an antibiotic has lost its ability to effectively control or kill bacterial growth; in other words, the bacteria are "resistant" and continue to multiply in the presence of therapeutic levels of an antibiotic. Antibiotic resistance evolves naturally via natural selection through random mutation, but it could also be engineered by applying an evolutionary stress on a population[6].

Antimicrobial resistance is resistance of a microorganism to an antimicrobial medicine to which it was originally sensitive. Resistant organisms (they include bacteria, fungi, viruses and some parasites) are able to withstand attack by antimicrobial medicines, such as antibiotics, antifungals, antivirals, and antimalarials, so that standard treatments become ineffective and infections persist, an increasing risk of spread to others. The evolution of resistant strains is a natural phenomenon that happens when microorganisms are exposed to antimicrobial drugs,

and resistant traits can be exchanged between certain types of bacteria (Table.1). The misuse of antimicrobial medicines accelerates this natural phenomenon. Poor infection - control practices encourages the spread of antimicrobial resistance[7].

Emergence of MRSA occurred in 1961 followed by emergence of ESBL producing gram negative bacilli in 1983. Vancomycin resistant enterococci (VRE) was reported in 1986. In 2000s emergence of carbapenem resistance was reported[8].

Bacterial survival strategies to combat antibiotics

Wide spread use of a effective antibiotic reduces its lifespan. Clinically significant resistance appears in periods of months to years. A principal mechanism for the rapid spread of antibiotic resistance genes through bacterial populations is that such genes get collected on plasmids[9] that are independently replicated within and passed between bacterial cells & among species. Furthermore some of these genes that reside on plasmids, may be further segregated within transposons[10] that can actively cut themselves out of one DNA locale, promiscuously moving their antibiotic resistance – conferring genetic cargo. The various mechanisms of antibiotic resistance are listed below (Fig.1)

Table 1. Evolution of Resistance to antibiotics

Antibiotic	Year deployed	Resistance observed
Sulfonamides	1930s	1940s
Penicillin	1943	1946
Streptomycin	1943	1959
Chloramphenicol	1947	1959
Tetracycline	1948	1953
Erythromycin	1952	1988
Vancomycin	1956	1988
Methicillin	1960	1961
Ampicillin	1961	1973
Cephalosporins first generation	1960s	Late 1960s
Cephalosporins second generation	1974	1980
Cephalosporins third generation	1980	1983
Quinalones	1983	1990
Carbapenem and monobactun	1984	2000s

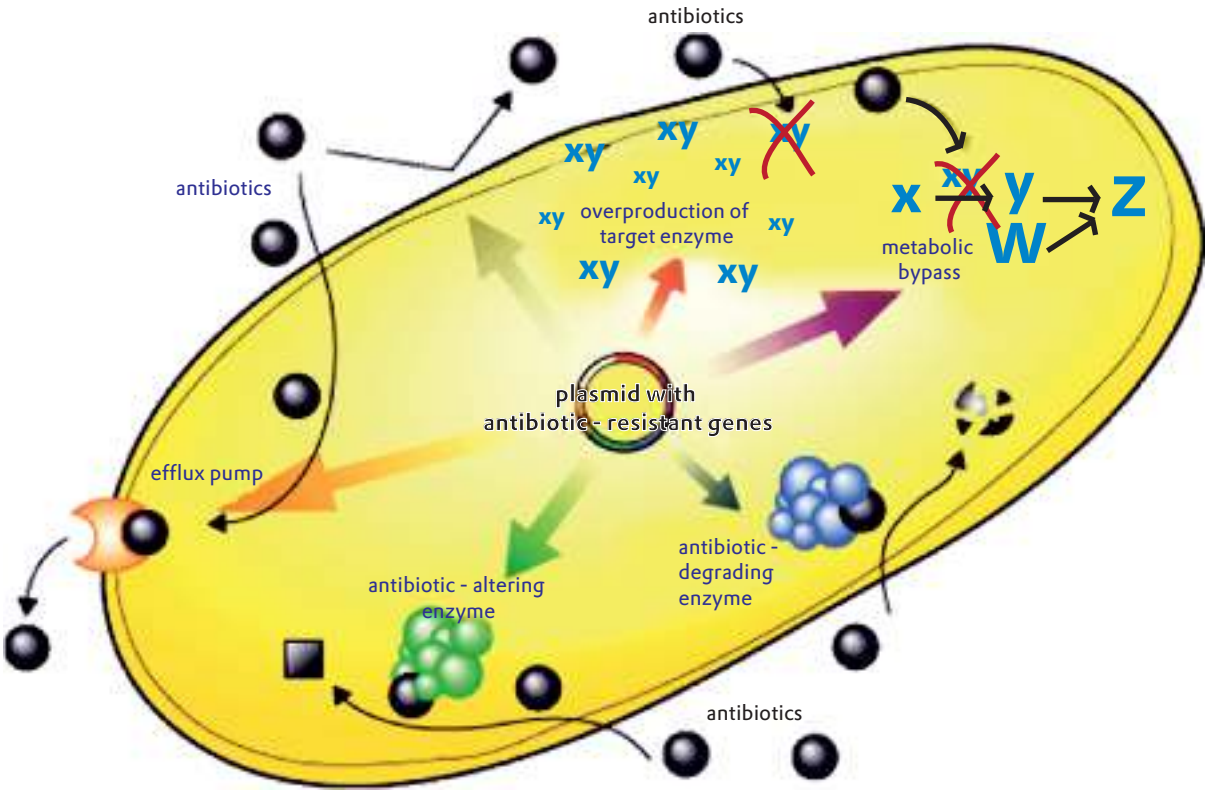

Fig 1: Mechanisms of antimicrobial resistance

Pump out the antibiotic

For antibiotics to be effective they must reach their specific bacterial targets and accumulate at concentrations that can act in some reasonable time frame. For example, the protein synthesis machinery is located in the cytoplasm, so antibacterials that inhibit protein synthesis must pass through the cell membrane. Both gram positive and gram negative bacteria that become resistant to Tetracycline's, commonly over produce related membrane proteins that act as an efflux pump for the drug[11,12]. As schematized in Fig.1, the drug is pumped out faster than it can diffuse in, so intra bacterial concentrations are kept low and ineffectual.

Reprogram the target structure

Another resistance strategy focuses not on removal or destruction of antibiotic, but on reprogramming of the target. An example of reprogramming strategy is used by Vancomycin Resistant Enterococci to escape from Vancomycin. In Vancomycin Resistant Enterococci the van_{HAX} genes encodes a new path way of enzymes that reduces pyruate to D-lactate.

Penicillin resistance can arise not only by β lactamase expression, but also by mutation of penicillin binding proteins (PBP) into new PBPs with low affinity for antibiotics. The acquisition by Staphylococcus aureus of the mec_A gene that encodes a PBP2′ protein with low affinity for all β-lactum antibiotics provides the molecular basis for the Methicillin resistant Staphylococcus aureus (MRSA) phenotype that is now widely disseminated.

Production of Enzymes

Extended-spectrum β - lactamases (ESBLs) are a rapidly evolving group of β - lactamases which share the ability to hydrolyze third - generation Cephalosporins and Aztreonam yet are inhibited by Clavulanic acid. The presence of ESBLs by Gram negative bacilli carries tremendous clinical significance. The ESBLs are frequently plasmid encoded. Plasmids responsible for ESBL production frequently carry genes encoding resistance to other drug classes (for example, Aminoglycosides). Therefore, antibiotic options in the treatment of ESBL-producing organisms are extremely limited. Carbapenems are the treatment of choice for serious infections due to ESBL-producing organisms, yet carbapenem-resistant isolates have recently been reported[4].

Carbapenems are β lactam antibiotics, as are Penicillins and Cephalosporins, but differ from these other classes in their exact chemical structure. Carbapenems are the sole lactam antibiotics with proven efficacy in severe infections due to ESBL producing bacteria and our last effective defense against multi-resistant bacterial infections.

NDM-1 stands for New-Delhi metallo beta-lactamase, an enzyme capable of destroying antibiotics, even powerful carbapenems. The enzyme NDM-1 is encoded for by sections of bacterial DNA known as plasmids, which can be transferred between types of bacteria, hence more than one type of bacteria can acquire this type of resistance. It is most often seen in *Klebsiella pneumoniae and E.coli*.

Most bacteria with the NDM-1 enzyme do remain susceptible to two types of antibiotics, neither of which are ideal for general use - these antibiotics are Colistin (an old and rather toxic antibiotic) and Tigecycline (a newer antibiotic than can only be used in some, not all types of infections). Otherwise bacteria with NDM are resistant to all antibiotics. A few isolates with NDM are completely resistant to antibiotics, including Colistin and Tigecycline.

Acenetobacter baumannii is a nonfermentative, gram-negative, nonmotile, oxidase-negative bacillus, whose natural reservoir still remains to be determined. Nevertheless, it is found in many health care environments and is a very effective human colonizer in the hospital. The combination of its environmental resilience and its wide range of resistance determinants renders it a successful nosocomial pathogen. As such, *A. baumannii* is emerging as a cause of numerous global outbreaks, displaying ever-increasing rates of resistance.

Acquired resistance

Several mechanisms are developed by bacteria in order to acquire resistance to antibiotics. All require either the modification of existing genetic material or acquisition of new genetic material from another source.

Vertical gene transfer

The spontaneous mutation frequency for antibiotic resistance is the order of about 108 – 109. This means one in every 108 - 109 bacteria in an infection will develop resistance through the process of mutation[7]. Once the resistance genes have developed, they are transferred directly to all bacteria's progeny during DNA replication. This is known as vertical gene transfer or vertical evolution, the process is strictly a matter of Darwinian evolution driven by principles of natural selection.

Horizontal gene transfer

Another mechanism beyond spontaneous mutation is responsible for the acquisition of antibiotic resistance. Horizontal gene transfer is a process whereby genetic material contained in small packets of DNA can be transferred between individual bacteria of the same species or even between different species. There are three possible mechanisms of horizontal gene transfer. These are transduction, transformation and conjugation (Fig 2 & 3).

Conjugation occurs when there is direct cell to cell contact between two bacteria and transfer of small pieces of DNA called plasmids takes place. Transformation is a process where parts of DNA are taken up by bacteria from external environment. This DNA is normally present in the external environment due to the death and lysis of another bacterium. Transduction occurs when bacteria specific viruses (bacteriophages) transfer DNA between two closely related bacteria.

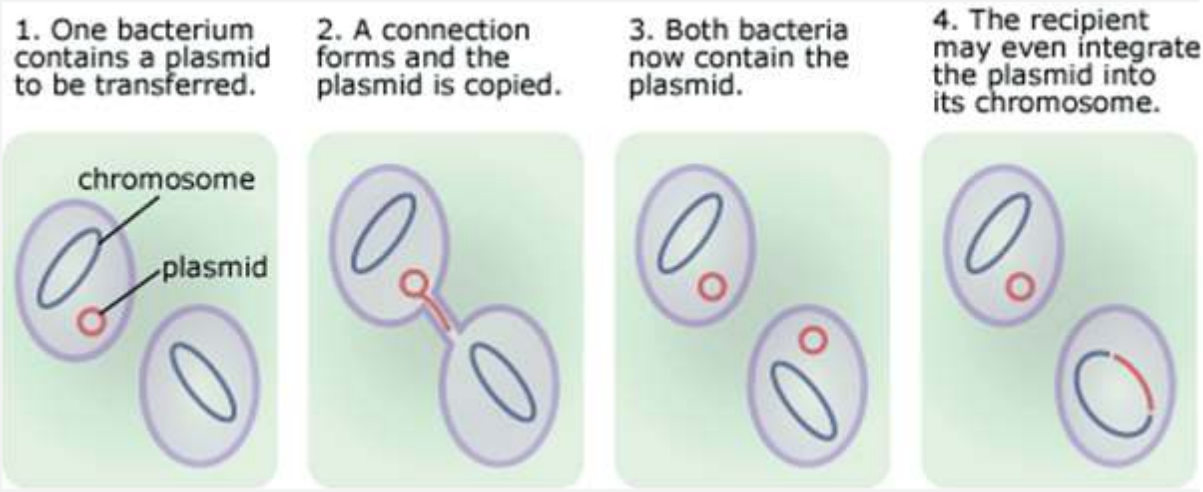

Fig.2 Gene transfer between bacteria by conjugation.

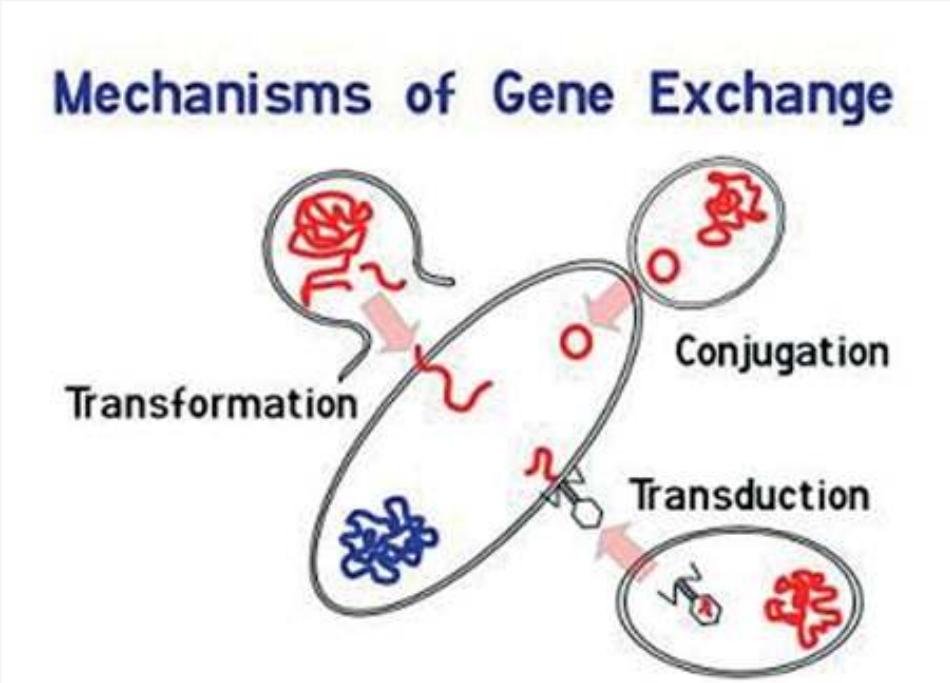

Fig.3 Various mechanisms of Gene transfer between bacteria

Indeed wider and more indiscriminate use of antimicrobial drugs could actually shorten the cycle time. After the advent of new mighty drugs the proper use of available antimicrobial agents, valuing them as precious and finite resources is essential. As well as efforts to minimize the spread of resistant bacteria through appropriate infection control measures in hospitals would be quite important and may represent a first step in solving the issue of resistant microorganisms[13].

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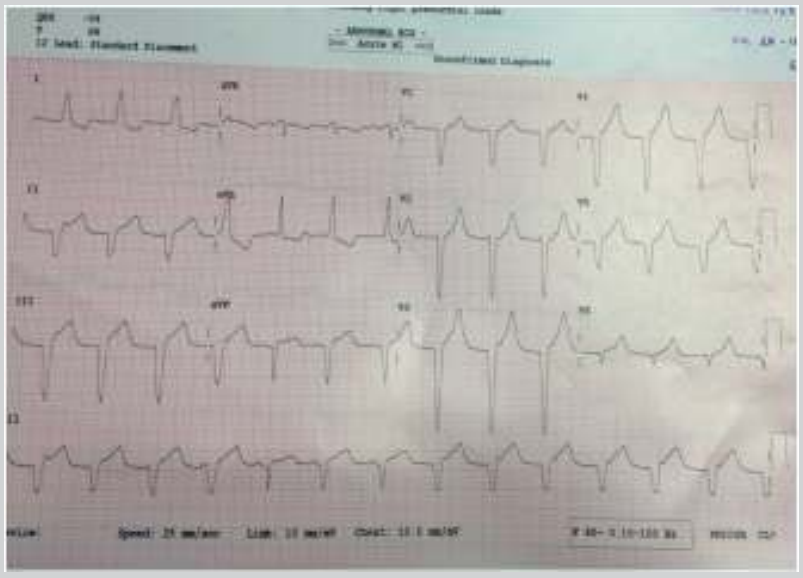
Diagnose the Condition

50 year old male admitted in the ICU complaints of chest pain and his first ECG showed features of acute IWMI. He was thrombolysed. Next day monitor showed arrhythmia and ECG was taken.



Answer in page: 104

-**Dr.M.Chokkalingam**, Consultant Cardiology, CSSH

Eat Chocolates to Stay Slim!

Several studies have already demonstrated the beneficial effects of eating chocolate, particularly in adults: staying slim and reduced risk of cardiovascular disease. Now in a new study published in Nutrition, researchers from Granada University's School of Medicine, report that similar benefit is also seen in teenagers. The study was carried out on 1458 adolescents from 9 European countries. The results showed that higher chocolate consumption was associated with lower amounts of total fat and fat around the waist regardless of other factors (including exercise). The beneficial effects are considered to be due to the presence of flavonoids, which exhibit antioxidant, anticlotting, anti-inflammatory and lipolytic effects. These benefits are seen with all types of chocolates and not only with dark ones. (Nutrition published online 21 October 2013; DOI: 10.1016/j.nut.2013.07.011; Abstract.)

- Dr. K. Ramesh Rao

Review Article

Non Microbial Drug Resistance

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Dr.A. Ruckmani, graduated from Madurai Medical College, earned her Diploma in Dermatology from Madras University and M.D in Pharmacology from Dr.MGR Medical University. She has been teaching Pharmacology from 1990 onwards. Her areas of research and interest include toxicology- snake bite poisoning, organo phosphorous poisoning, renal failure, anxiolytic & other CNS drugs, alternative systems of medicine and medical ethics. She received the INSA Fellowship award for the year 1999. She is currently Professor & Head, Dept. of Pharmacology, Chettinad Hospital & Research Institute.

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Introduction

When we think, talk or discuss about drug resistance we always refer to microbial drug resistance and it is the greatest challenge to mans' health. Of course it is one of the iatrogenic complications occurred mostly due to medication errors. It is natural for the microbes to learn to survive in the presence of its offenders. But are microbes alone capable of resisting the battle of drugs? It seems not. Every cell whether it is microbial or non microbial, human or non human, tries to protect itself against threats.

Methicillin Resistant Staphylococcus Aureus (MRSA), Multi Drug Resistant (MDR) &Total Drug Resistant (TDR) tuberculosis, Chloroquine resistant malaria and several other drug resistant microbes are well known. But resistance developed by human cells against drugs is not known as that of microbial resistance. This non microbial drug resistance is equally important as it also challenges man's health and this paper attempts to find out the extent, mechanisms and implications of human cell resistance.

Human cells like microbial cells resist the insults caused by xenobiotics. The term xeno is a Greek term meaning foreign, strange, guest and alien, biotics refers to "present in living organisms". Xenobiotics are chemical substances which are not naturally present in the living organism but derived from outside. These include all chemicals such as pesticides, various groups of drugs, industrial wastes and other pollutants which can affect the health of the humans causing cancer, infertility, obesity, diabetes and neurological impairment.

In this article some of the well known groups of drugs against which human cells have developed resistance are discussed.

Resistance to Anti Cancer Drugs

The cytocidal activity of anticancer drugs depend on many factors such as selective lethality to the cancer cells, ability of the drugs to enter into the cell, extent of cellular damage and apoptosis. The cancer cells in course of time learn to develop resistance to anti cancer drugs. The mechanisms of development of resistance includes

Altered influx of drugs: has been reported for methotrexate, cisplastin, vincristine[1]. concentration to act on the DNA and inhibit cell multiplication, hence the cancer cells multiply in the presence of these drugs

Efflux of drugs: the concentration of anticancer drugs like vinca alkaloids, doxorubicin and cyclosporin A is low in the brain due to the active efflux of drugs by P-glyco protein (P-gp) expressed at the luminal membrane of brain capillary endothelial cells[2]. resulting in reduced levels of drugs in the brain.

Insensitivity to apoptosis: Apoptosis is a protective programmed death of mutant cells so that mutant cells do not multiply. When apoptosis fails, mutant cells multiply and produce cancer. Some of the anticancer drugs facilitate apoptosis of cancer cells. Cancer cells can become insensitive to apoptosis induced by anti cancer drugs leading to multiplication and spread of cancer[3,4].

Resistance to Anti Epileptic Drugs

Resistance developed by the neuronal cells to anti epileptic drugs poses a great threat to treatment of epilepsy. The following mechanisms have been reported for the development of resistance to anti epileptics.

Drug efflux The cerebral cells express P glycoprotein 1 and 2 which can efflux the anti epileptic drugs[5].

Over expression of ATP-binding cassette transporters (ABC transporters) which rapidly eliminate the sodium channel blockers[6].

ABC transporters are transmembrane proteins which help in the transport of substrates such as drugs, sterols in and out of cell membrane using energy released during ATP hydrolysis. Over expression of these proteins causes efflux of drugs. The resistance to the anti epileptic drugs such as Phenytoin, carbamazepine, valproate in some of the patients develops due to such efflux of drugs.

Structural changes in target cells Change in target sites like receptor, enzymes so that drug can not bind with the target sites making the cell unresponsive to drugs[7].

Severity of epilepsy at the start of treatment If the number and severity of epileptic episodes are higher before the start of treatment response to therapy is less[7].

Polymorphism of drug metabolizing enzyme: CYP2C19 a polymorphic Drug Metabolizing Enzyme (DME) was shown to be associated with decreased clobazam response[8]

Resistance to Anti Hypertensive Drugs

Resistant hypertension is defined by the Joint National Committee 7 as "blood pressure that is above the patient's goal despite the use of 3 or more antihypertensive agents from different classes at optimal doses, one of which should ideally be a diuretic". The contributing causes for resistant hypertension are female gender, black race and comorbid disease like diabetes and obesity. Among these, diabetes associated with nephropathy contributes greatly to resistant hypertension[9]. The other causes include

Co administered drugs: Though the patients may take the antihypertensive drugs regularly, certain co administered drugs such as NSAIDs, steroids, oestro progestinic agents, immune suppressants, erythropoietin, inhibitors of angiogenesis and anti-HIV agents may blunt their actions and cause resistance to antihypertensive therapy[10]

Associated diseases: Diabetes with progressing kidney disease causes resistance to antihypertensive therapy[11]

Genetic mutations: Variants of the epithelial sodium channel gene E_{NaC} were found to be prevalent in resistant hypertension in a Finnish study. Variation in the allele of the enzyme CYP3A5 1 which metabolize the steroidal hormones of cortisol and corticosterone was reported to be present in black race[12].

Insulin Resistance

Insulin resistance is well known. It is defined clinically as "the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as much as it does in a normal population" [13].

Insulin resistance is reported in both type 1 and type 2 diabetes mellitus, more commonly in type 2 DM. The causes for insulin resistance are obesity, infections, genetic variation in proteins involved in cascade of insulin action, fetal mal-nutrition, steroidal therapy, smoking and physical inactivity[13]. At the cellular level, changes in the insulin receptor protein kinase have been identified as one of the major causes for insulin resistance[14].

Resistance to Antiemetics

Resistance has been reported to 5HT3 antagonists like tropisetron, ondansetron, or granisetron and single-nucleotide polymorphism (3435C>T) in the gene that codes for the drug efflux transporter adenosine triphosphate -binding cassette subfamily B member 1 (ABCB1) has been observed especially with granisetron[15].

Resistance to Anti asthmatics

Development of resistance to anti asthmatic drug, recognized in the present decade has made treatment of asthma a challenging one. Resistance can occur to the three major groups of drugs used clinically, Beta-2 agonists, muscurinic blockers and glucocorticoids. Long term use of Beta-2 agonist will cause down regulation of beta-2 receptors resulting in broncho constriction. Similarly repeated use of anticholinergic like Ipratropium can cause up regulation of muscurinic receptors causing broncho spasm. To overcome such long term effects, combination therapy with beta-2 agonist and glucocorticoid has been used. Glucocorticoid administration improves resistance to beta-2 agonists by increasing beta-2 receptor expression[16] but even resistance to glucocorticoids is also reported. Kobayashi Y, et.al stated that defective expression of protein phosphatase-2 (PP2a) contributes to glucocorticoids resistance and its over expression increases sensitivity to glucocorticoids[17].

Resistance to Anthelmintic Drugs

Resistance to anthelmintic drugs has been reported in animals and there are reports about the possibility of development of resistance in human helminths also. *Necator americanus, Ancylostoma duodenale, Schistoma mansoni* and *Onchocera volvulus* have been found to have developed resistance to Mebendazole, Pyrantel, Praziquntel and Ivermectin respectively[18]. Though the helminthic cells are not human cells the possibility of development of resistance to anthelmintics should be considered when we use these drugs in humans.

Discussion

The term drug resistance is synonymous with antimicrobial resistance. Bacteria, fungi and viruses develop several strategies to thrive in the presence of antimicrobials. The strategies they develop in general include,

Production of an enzyme that can inactivate the antimicrobial agent

Developing an alternative enzyme for the enzyme which is a target for the antimicrobial agent

A mutation in the target, which reduces the binding of the antimicrobial agent

Reduced influx of the antimicrobial agent

Efflux of the antimicrobial agent

Over expression or suppression of a gene that can inactivate/ metabolize the enzyme.

The mechanisms of resistance developed by human cells against anti cancer, antiepileptic and antiemetic drugs appear almost similar. In cancer and epilepsy the target cells are specific group of cells like cancer cells and neuronal cells. The target cells adopt several modes of resistance to reduce the effects of the drugs, by

reducing intracellular concentration, making the target sites unresponsive to drugs and also facilitating the repair mechanisms especially in cancer cells. Helminths also develop similar changes so that they can exist in the presence of anthelmintics.

Whereas the antihypertensive drugs target many types of cells like cardiac, vascular and renal. If the body has to develop resistance, changes should occur in all these type of cells which would be difficult and harmful to body homeostasis. It is found to be more of drug interactions and associated diseases that decrease the antihypertensive effect. Variation at the sodium ion channel level has been identified which might resist the ion transport across cell membrane.

With regard to antiasthmatics, drug resistance is mainly due to altered regulation of number of receptors like down regulation of beta-2 receptors.

These reports are evidence that whether the cell is microbial or non microbial, the cell learns to resist any insult that would challenge its survival. The microbial drug resistance results in refractory infective diseases threatening human health whereas the human cellular resistance also leads to refractory non infective diseases. When individuals develop resistance to antidiabetic and antihypertensive drugs, the two important diseases contributing cardiovascular morbidity and mortality will pose a major threat to human health.

The resistance to anti asthmatic drugs may result in the increased incidence of status asthmatics and treatment failure. Resistance to anticancer drugs will lead to untreatable cancers resulting in high mortality. Hence creating awareness and recognition of non microbial drug resistance and evolving strategies to prevent its occurrence is essential, similar to prevention of infections caused by MDR organisms. Hence both the types of drug resistance should be handled equally.

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Review Article

Tackling Antimicrobial Resistance in Tertiary Hospital, Antimicrobial Stewardship Programme (ASP)

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Dr. Rajasekaran has 40 years of professional experience in medicine with 9 years in rural service and over 30 years of teaching experience in medicine at premier institutes of Tamilnadu for both undergraduates and postgraduates. His original work on modified management of Acute copper sulphate poisoning, presented at Toxicon is quoted as reference in ISBN indexed toxicology Book and the same is accepted by Tamilnadu Health system projects for the copper sulphate poisoning. He has authored, presented and published several papers in national, state and city conferences and delivered lectures in national, state and district fora on various medical topics. He has a great passion for bedside teaching.

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Introduction

Global threat of antimicrobial resistance (AMR) is a big challenge which has to be tackled at the earliest. The use of antimicrobials, improved sanitation and vaccination has reduced the incidence of infectious disease mortality[1]. In the present day while more and more microbial resistance is being reported, the pharmaceutical companies are not showing interest in research to develop newer antimicrobials. This may lead us to "preantibitotic era" with no antibiotic available to manage the infections[2]. India has been named to be the source of NDM-1 (NewDelhi Mettalobetalactamase) producing super bugs which has created a panic among the health care industry[3]. This has increased the awareness of strict infection control and antibiotic stewardship across the country and the globe.

Around a year ago a joint meeting of representatives of medical societies and policy making bodies met to tackle the challenge of AMR. Consensus of this meeting is named as "Chennai Declaration". The aim of the declaration is to initiate a national policy to the rising AMR. The declaration in the executive summary has suggested to the government organisations such as Ministry of Health, Drug Controller of India, state health departments, and policy making bodies like Medical Council of India and National Accrediting Board for hospital (NABH) to play a vital role in controlling the AMR. The declaration has also requested to have an infection control team at every hospital, State Health Departments and have a task force to monitor the functions of the teams[4]. Tertiary hospital like Chettinad Health City needs definitely an infection control team and antimicrobial stewardship programme (ASP) to tackle the AMR.

Antimicrobial stewardship programme and members of the team (Fig.1.)

ASP may be defined as an ongoing effort by the health care institution to optimise antimicrobial use among the hospital patients in order to improve patient outcomes, ensure cost effective therapy and reduce adverse sequel of antimicrobial use including AMR. Members of the ASP should include infectious disease physician (IDP), clinical microbiologist, clinical pharmacist, infection control professionals, and institutional epidemiologist and information system specialists[5].

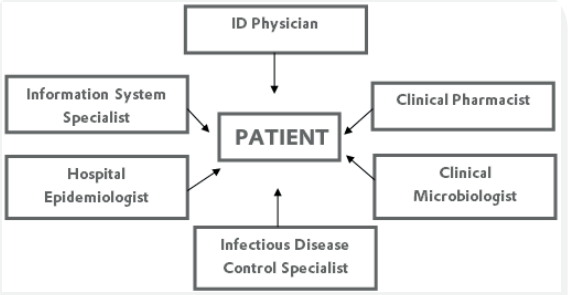

Fig 1: Antimicrobial stewardship team
- Adopted from 'Preserving bacterial susceptibility Implementing Antimicrobial Stewardship Programs' by Debra A. Goff,

Goals of ASP[6-7]

- Improve the cure rate, reduce the surgical infection and decrease the mortality and morbidity
- Reduce the unintended complications of antimicrobials
- Reduce the antimicrobial resistance
- Reduce the cost of management of the infections

Infectious disease physician (IDP) in ASP[8]

The IDP should have eight strategies namely education, formulary restrictions, pharmacy justification, pharmacy substitution, computer surveillance, laboratory item cost listing, purchase plans and multi disciplinary approach. He must develop an antimicrobial management program keeping the AMR in mind. Steps for IDP to apply for establishment of an antimicrobial management program[8]

1. Develop knowledge about the local antimicrobial budget and patterns of usage.
2. Collect the necessary data to publish a quarterly

prices of all formulary antimicrobials.

3. Gather baseline usage and cost data and attempt to compare them to those of equivalent institutions
4. Outline a structure for participation in the ASP team and estimate the annual costs for funding, including salary for the IDP.
5. Meet with administrators of hospitals and managed care companies to discuss implementation.
6. Focus on the most frequently used and most costly agents on the formulary.
7. Publish a manual, Guidelines for Antimicrobial Use, and provide appropriate educational or multimedia formats for educating the prescribing staff.
8. Ensure a fail-safe mechanism to resolve disagreements with the prescribing staff
9. Develop innovative educational methods including computerized interplay to explain the use of new antimicrobials, antivirals, and antiinfectious biologics.
10. Re-evaluate the ASP annually with quality assurance personnel and review the cost-effectiveness with the chief of staff, the president of the hospital, and the Vice President for Clinical Affairs.

Clinical pharmacist in the ASP[9]

Whenever the clinical pharmacist receives a restricted antibiotic prescription he must notify the prescriber about the requirement of the authorisation. He can also refer the list of restricted antibiotics prescribed for review with IDP or physician authorised for approval to maintain the proper prescription safety. Though this may lead to a wedge between the physician and pharmacist it should be realised that it is done in the interest of the patients and society. Clinical pharmacist can develop institutional guidelines on antimicrobials use and also conduct education programmes for the staff.

Clinical microbiologist and ASP

The clinical microbiologist and microbiology laboratory play a pivotal in the ASP. The early identification of the pathogenic microbes and their susceptibility test performance is very essential in the control of AMR[10]. The clinical microbiologist must report most appropriate and selective susceptibility pattern. He must abstain from reporting rare susceptibility pattern even if it is there to avoid inadvertent therapies[11].

The laboratory should be actively involved in the AMR surveillance. Periodic reporting of local common pathogen and their antibiotic susceptibility will enable the ASP team to decide on empirical antimicrobial therapy[12].

Infectious disease control staff and hospital epidemiologist

Infectious disease control staff should be well aware of the source of AMR and their mode of spread in the health centres[13]. They must also know the significance of the AMR in the patient and their prevention and spread. Organizing epidemiological surveillance, checking the efficacy of the methods of disinfection along with improving the hospital cleanliness are some of the essential duties that may be carried out by the infection control staff[14].

The hospital epidemiologist should monitor the guidelines compliance (regarding the AMR) of the hospital staff. They must also get the guidelines compliance data and use it to improve the impact of the ASP. They must have surveillance of AMR constantly to detect and investigate the outcome of the ASP[15].

Hospital administrators and management role in ASP[15]

The ASP members 'efforts should be recognised and endorsed by the administration and management. In addition to allotting required fund, the ASP team members should be given autonomy and a free hand in policy making for controlling the AMR.

"Front - end" and "Back - end" Strategies of the antibiotic stewardship[16]

In an analysis of antibiotic prescription pattern in India, it was noticed that new and costly drugs were used without ascertaining sensitivity pattern[26]. The goal of the ASP is to control the misuse of antimicrobials apart from taking care of the doses and appropriate use of them. To achieve this, antibiotic control strategies could be applied at the antimicrobial prescribing point (Front end) or after the antimicrobial is prescribed (Backend).

In 'Front end strategy' the control of antimicrobials is achieved by Formulary restriction, preauthorisation, an interactive discussion and guidelines. The back end strategy is carried out by the feedback audit, where the de-escalation, dosage optimisation and switching of the route of administration of antimicrobials are done.

Education and training[17]

One of the ways the physicians can be motivated to change their antimicrobial prescribing pattern is by 'academic detailing'. In academic detailing process, the baseline knowledge of antimicrobial prescribing pattern is assessed by interviews followed by programs for them and their opinion leaders. In these programs authoritative and unbiased sources of information are given presenting both sides of controversial issues.

The stake holders are allowed to take part in the interactive sessions at the end of which they are given essential messages by suitable educational materials. This educational strategy may be carried out by the clinical pharmacist or by the IDP periodically. These messages can also be spread by interactive educational sessions during the grand rounds in the large teaching hospitals.

Antimicrobial restriction strategies

To impose the ASP guidelines compliance for antimicrobial use by the physicians external control may

be implemented[18,19]. Only selected antimicrobials are freely dispensed in the pharmacy. Other antimicrobials are dispensed on 'criterion based strategies' which include 'prior authorization criterion' for which prior approval of the specialist physician is required or 'closed formulary strategies' where it may not be available at all.

Antibiotic cycling strategies

If an antibiotic is out of use or used minimally for certain period the resistance by the microbial decline theoretically[20]. Using this principle the drugs can be substituted on rotation especially for gram negative infections. However there are certain contradicting evidences[21] for this strategy, hence computer assisted strategy may be preferred.

Review and feedback

The guidelines are issued and daily review is done for the appropriateness of the antibiotic and to suggest an alternative antibiotic if necessary .This may educate the physician and not interfere with autonomy of their prescription[22].

Computer assistance[23]

The review and the feedback mentioned above are achieved using the information technology. The computer assistance may provide the patient specific data which are taken by expert systems to provide patient specific recommendations at the point of the patient care. The computer system should be flexible and reprogrammable according to the stewardship requirements[15].

Defining the priorities, and measuring the progress and success (Fig.2)

This can be achieved by the driver diagram[24]. The driver diagram has three or more levels. The diagram has 1) vision or goal 2) primary driver which is high level requirement to attain the goal 3) the activities required for the same. Each primary driver if they are very complex can have its own set of simple steps namely "secondary driver".

Conclusion

The key to the success of an ASP in a teaching hospital depends upon the management support, the multiprofessional ASP team, frequent evidence based institutional guidelines, education and training of the stakeholders, the effective communication system in the institution and above all the effective patient safety. Recommendations of the GARP[26] (global antibiotic resistance partnership) India aims at 1)reducing the need of antibiotics 2) antibiotic targeting 3) avoiding antibiotics in agriculture and 4) giving priority to national surveillance for AMR, while improving diagnostic laboratory capacity, setting up of ASP in the hospitals and restricted use antibiotic for non-therapeutic purposes. If these are strictly followed the AMR in India and across the Globe may show a marked decline.

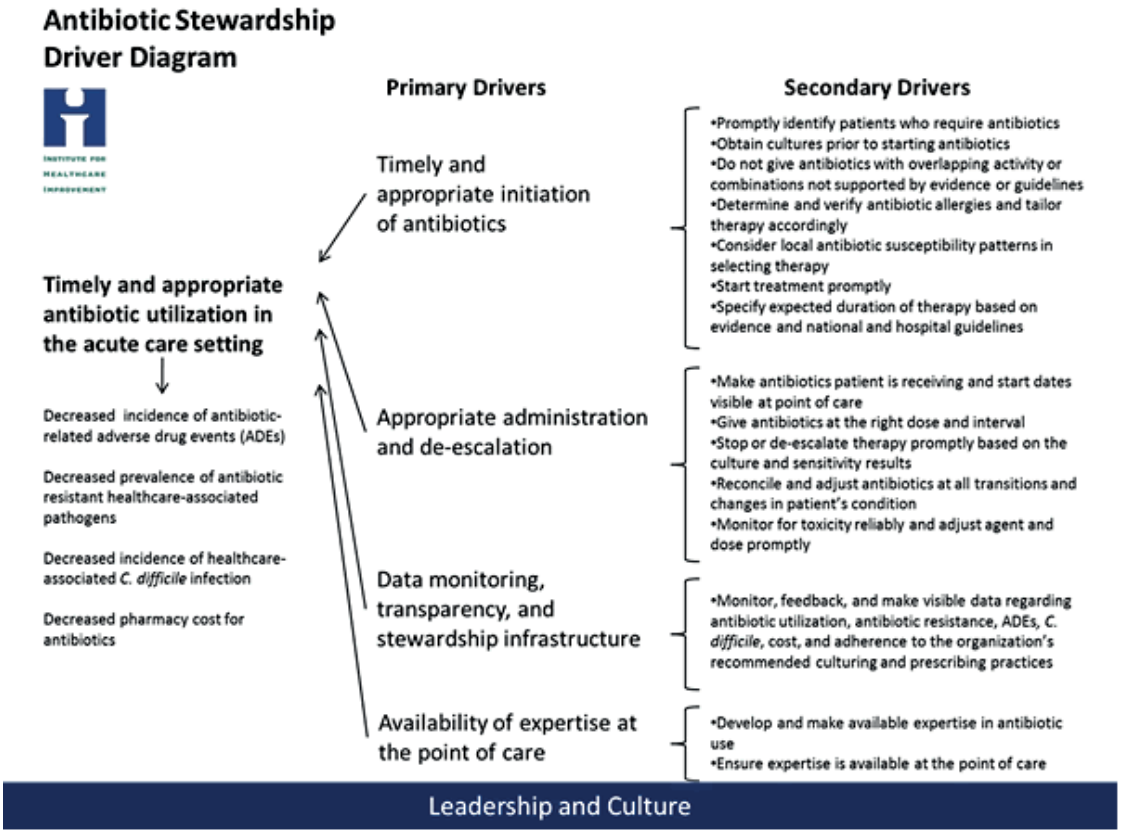

Fig2: Antibiotic stewardship Driver Diagram (http://www.cdc.gov/getsmart/healthcare/images/driver-diagram.gif)

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Case Report

Schwannoma of Intercostal nerve- An Uncommon Localization

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Abstract

Schwannomas are benign slow growing tumors arising from Schwann cells that sheath the nerves. They can occur anywhere in the body, but generally found arising from cranial or spinal nerve roots. A rare case of 32 year old man presenting with a swelling in the left costal region diagnosed clinically as a benign soft tissue swelling is reported here. A possibility of intercostal nerve schwannoma was suspected on imaging and confirmed by histopathology following surgical resection.

Key words : Schwannoma, Intercostal nerve, Peripheral nerves

Chettinad Health City Medical Journal 2013; 2(3): 92-93

Introduction

Schwannoma is the commonest type of intraneural tumour. It typically comes from a single bundle (fascicle) within the main nerve and displaces the rest of the nerve. Peripheral nerve involvement are rare, 25 to 45% occurring in the head and neck region[1]. Involvement of chest wall is extremely rare of which less than 10% affects the intercostal nerve. Primary neural tumors of the chest mostly arise in the mediastinum, usually asymptomatic diagnosed incidentally on x-ray of chest[2].

Histologically two types of cellular pattern are noted. Antoni A, where there are well developed cylindrical structures which on cross section produce a palisading pattern of nuclei around a central mass of cytoplasm (Verocay body) and Antoni B, where there is a loosely arranged stroma in which the cells form no distinctive pattern.

Case Report

A 32 yr old male patient presented to the surgery outpatient department of a tertiary care hospital with complaints of a swelling in the left lateral chest wall for the past 10 years. The swelling gradually increased in size and was not associated with pain or fever. There was no history of trauma to the chest wall in the past. Clinical examination of the cardiovascular, respiratory, abdomen and nervous system were unremarkable. Local examination of the left chest wall revealed a subcutaneous swelling of 8cmx5cmx5cm dimensions over the regions of 9th and 10th ribs (Figure 1). It was not tender but firm in consistency with smooth surface and mobility was restricted in horizontal plane. His routine blood investigations were within normal limits.

Ultrasound revealed a large well defined 8x4.1x3.7cms size, mixed echogenic - predominantly hypo echoic mass along the lateral aspect of lower chest in the muscle plane and superficial to ribs suggestive of soft tissue tumor.

Fig1: Clinical picture of left chest wall swelling

CT scan of chest showed a 66mmx43mmx63mm (cc x rl x ap) well encapsulated, heterogeneously enhancing oval soft tissue density arising from lower left lateral chest within the intercostal muscle plane at level of lateral aspect of 9th and 10th ribs (Figure 2). Underlying bone and adjacent fat planes appeared normal. There was no evidence of intrathoracic or intra abdominal extension. Features suggestive of benign soft tissue tumor noted with possibility of intercostal nerve schwannoma was considered.

Under General anesthesia, skin incision was made and dissection was carried out. A single grey white soft tissue encapsulated mass measuring about 8x4x3.5cms was excised in toto (Figure 3) and sent for

histopathological analysis. Location of the lesion was consistent with the imaging studies. At one end of the lesion there was a small nerve tissue entering into the intercostal muscle plane. Suction drain was placed and removed during the third post op day. Post operative period was uneventful.

Histopathology examination of the specimen showed an encapsulated tumor composed of Antoni A and Antoni B areas consistent with Schwannoma. (Fig.4)

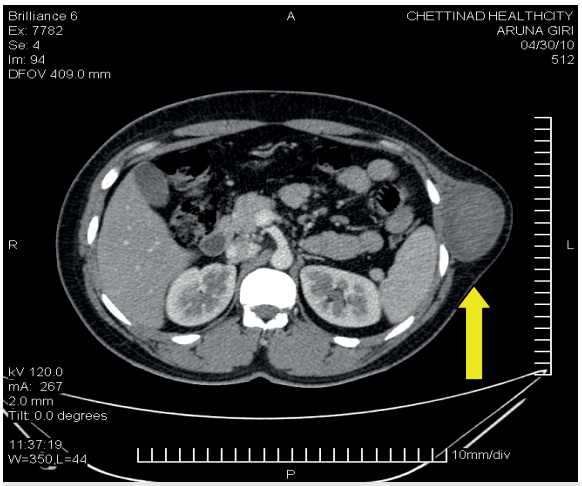

Fig 2: CT image showing an left extrathoracic swelling

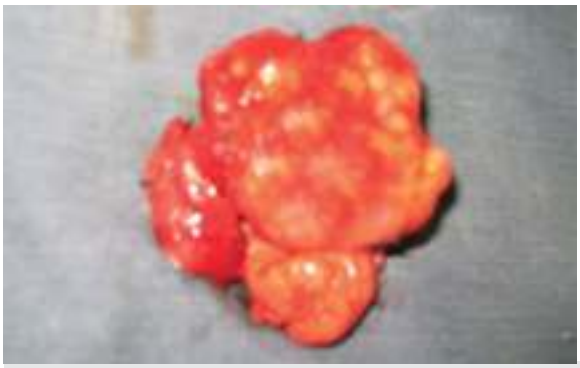

Fig 3: Gross specimen showing a well encapsulated mass

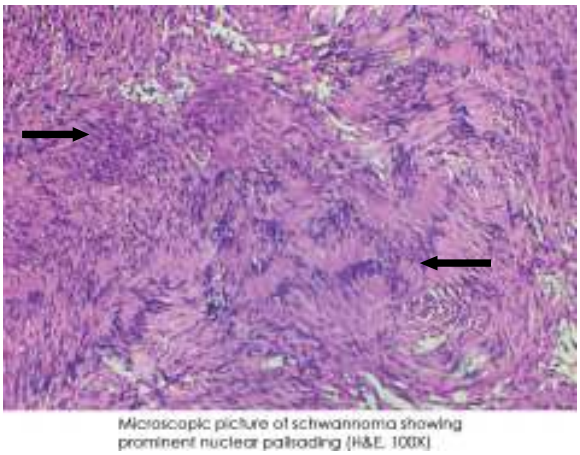

Fig 4: Histopathology showing Antoni A(⟶) & Antoni B (⟵)Bodies

Discussion

Schwannomas are commonly found in adult in association with the vestibulocochlear nerve. Results from three large case series of 328 cases of thoracic neural tumours concluded that 90 % of thoracic neurogenic tumors originate in the mediastinum, especially in the posterior mediastinum and only 5% from intercostal nerves. Schwannomas are considered to be the second common intrathoracic neural tumour[3,4]. However, in our case the lesion was presenting externally with no intrathoracic extension. Schwannomas are usually asymptomatic until they grow large enough to cause compressive lesions. When symptomatic, they cause pain along distribution of the nerve involved. In the present case discussed the tumour grew externally, hence remained asymptomatic and presented itself as a soft tissue swelling.

In conclusion, in patients presenting with a soft tissue swelling in the chest wall along the distribution of intercostal nerves, schwannoma should be considered as one of the differential diagnosis. Computed tomography to rule out or identify peripheral tumors of intercostal nerve should be considered when in doubt. Local excision is the treatment of choice in small lesions without internal extension[3].

Acknowledgements

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Case Report

Neonatal Cholera

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Abstract

Neonatal Cholera is one of the rare clinical presentations. Occurrence of cholera in a new born reflects the poor hygienic condition of the family and bad child rearing practices. As therapy is primarily aimed in treating this particular condition, the broader perspective is to impress upon the population about hazards of bottle feeding and good hygienic measures.

Key words : Neonatal Cholera, lower economic strata, bottle feeding.

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Introduction

Cholera is an acute debilitating diarrhoea disease causing morbidity and mortality among lower socioeconomic status people in tropical countries. It does occur in neonates, though rare. We report a 27 day old neonate who had clinical features consistent with cholera.

A 27 day old female neonate born to G2P1 mother presented with history of loose stools and vomiting of 1 day duration. Loose stools were 15-20 times, watery, curdy white and had fishy odour. Baby had 5 episodes of non bilious vomiting. There was history of abdominal distension, reduced urine output for 10 hours duration, lethargy and refusal of feeds. Baby was being bottle fed with diluted cow's milk.There was no history of fever and seizures. There was a similar family history of loose stools in the older sibling and they were from poor socioeconomic background. On examination baby was irritable with sunken eyeballs, depressed anterior fontanelle and dry oral mucosa. There was reduced skin turgor prolonged capillary filling time and feeble peripheral pulses, HR-170/mt and RR-60/mt. There was abdominal distension and bowel sounds were heard.

Blood investigations showed evidence of neutrophilic leucocytosis and hyperglycemia. There was no azotemia and dyselectrolytemia. CRP and Blood culture were negative.

In view of acute onset of profuse watery diarrhoea with fishy odour along with signs of severe dehydration with the background history of bottle feeding and elder sibling with similar history, provisional diagnosis of neonatal cholera was made.

Stool sample was sent for hanging drop examination and culture. Stool examination showed darting motility on hanging drop method. Stool culture showed growth of *Vibrio cholerae* Ogawa type on Blood Agar/TCBS medium. (Fig.1) Baby was immediately resuscitated with Ringer Lactate. Baby was treated with erythromycin.

Discussion

Cholera is caused by *Vibrio cholerae* a gram negative nonspore forming curved rod with a polar flagellum. Vibrio cholera strains 01 and 0139 are the pathogenic strains. The two biotypes of vibrio cholera 01 are classic and eltor type[1].

Vibrio cholera has 2 major O antigenic type-Ogawa and Inaba and unstable intermediate type-Hikojima[2].

Cholera rarely occurs under two years of age[3]. Cholera diarrhoea is extremely rare in neonates. Colostrum may offer potent protection among breast fed neonates mediated by specific immunoglobulin IgA[7]. In India, Cholera is endemic and affects usually the 3 to 5 year old age group.There have been occasional reports in neonatal period with Vibrio Cholera 0139 in Bengal[4].

Vibrio cholerae once ingested in significant amount especially in an environment where gastric acidity is compromised, colonises upper small intestine. Here it produces enterotoxins –Cholera toxins which stimulates adenylate cyclase resulting in raised c-AMP levels causing decreased absorption of sodium and chloride by intestinal villi and increased active secretion of chloride by crypt cells, hence resulting in high voluminous diarrhoea[1].

The genome of Vibrio cholera O1 biotype Eltor comprises of two circular chromosomes, a large chromosome of 3 million bp and small chromosome of 1.07 million bp. The most important presenting feature in symptomatic patient is massive loss of fluids and electrolytes.The incubation period varies from 6 hours to 5 days.

Baby may present with low grade fever, vomiting and diarrhoea. Diarrhoea in severe cases is profuse, painless, rice water in consistency with fishy odour with occasional flakes of mucus. Babies present with tachycardia,tachypnea irritability, sunken anterior fontanellae, poor skin turgor and may even progress to stupor, circulatory collapse and renal failure.

Fluid loss may persist even upto 1 week. Laboratory investigations reveal neutrophilic leucocytosis, raised serum protein, elevated haematocrit, hyponatremia, hypokalemia and acidosis[5]. The clinical diagnosis is confirmed by stool for hanging drop method and stool culture which shows vibrio cholera growth in thiosuplate citrate bile sucrose medium and Tellurite taurocholate gelatin agar (TCBS). Rapid diagnostic technique with DNA based methods, ie polymerase chain reaction using primers for ctx A gene and outer membrane protein OmpW gene are described[2]. Treatment is done by immediate rehydration with parenteral fluids and oral rehydration salution to be initiated. The drugs used for specific treatment are tetracycline, Doxycycline, Trimethoprim-sulphamethoxazole, erythromycin, Furazolidone and quinolones.

Complications include seizure, dyselectrolytemia, acute tubular necrosis, hypokalemia, arrhythmia, paralytic ileus, hypoglycemia or hyperglycemia and even death[5].

Tellurite taurocholate gelatin agar (TCBS) & Blood Agar plates showing growth of vibrio cholera.

Diarrhoea in newborn should be investigated as the infection can cause bacteremia which has grave prognosis. Various studies have shown stormy clinical course including death if the neonate presents with bacteremia[7]. The newborns presenting with mild diarrhoea had a favourable outcome when treated with erythromycin and rehydration fluids[3]. The common risk factors associated with neonatal cholera are poor sanitary condition, bottle feeding, household exposure (sibling with diarrhoea) and hypochlorhydria. The early events of infection or invasion could have occurred before the first colostrum feed probably during birth from a mother with asymptomatic stool carriage[7].

Cholera can be prevented by phenol - killed bivalent cholera vaccine, but in tropical and developing countries personal and environmental hygiene is the only method to prevent this dreaded disease[2]. *Vibrio Cholerae* is not uncommon in neonates presenting with diarrhoea in cholera endemic countries[6].

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HPV Screening Challenges PAP Smear!

Ever since its introduction by Georges Papanicolau, PAP stain has remained unchallenged as the screening procedure for cervical cancer. However, now there appears to be a contender in the form of HPV screening. In a new study published in Lancet, the researchers analysed the data from more than 175,000 women, aged 20 to 64, who had been followed for an average of six and a half years after having one of these screening tests. The protection offered by both methods appeared to be similar for the first two and a half years of follow-up. But after that, HPV screening provided 60-70% better protection than PAP smear. This protection was particularly noticeable in women between the ages of 30 and 35. Besides that, HPV screening done once in 5 years provided the best protection in contrast to PAP smear, which must be repeated every three years to get similar degree of protection. (The Lancet, news release, Nov. 2, 2013).

- Dr. K. Ramesh Rao

Case Report

A Rare Combination of Aggressive Periodontitis with Multiple Impacted Supernumerary Teeth

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Abstract

Aggressive periodontitis (AgP) comprises a group of rare, often severe, rapidly progressive form of periodontitis mostly characterized by an early age of clinical manifestation and a distinctive tendency for cases to aggregate in families. Supernumerary teeth are an important cause of dental retention. Multiple supernumerary teeth without a syndrome is rare. Most of such cases are found in association with syndromes such as Gardner's syndrome, cleidocranialdysostosis and cleft lip and palate. It has been reported that the prevalence for non-syndrome multiple supernumerary teeth is less than 1%.We describe here, a case of a 20 year old patient presenting with multiple impacted supernumerary teeth with aggressive periodontitis, which is a unique presentation in the absence of any syndrome.

Key words : Supernumerary tooth, Impacted tooth; Aggressive Periodontitis.

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Introduction

Aggressive periodontitis (AgP) comprises a group of rare, often severe, rapidly progressive form of periodontitis mostly characterized by an early age of clinical manifestation and a distinctive tendency for cases to aggregate in families. AgP was characterized by: (1) noncontributory medical history; (2) Rapid attachment loss and bone destruction; (3) familial aggregation of cases; (4) lack of consistency between clinically visible bacterial deposits and severity of periodontal breakdown[1]. Based on specific clinical and laboratory features, special forms of AgP have been recognized: localized AgP (LAP) and generalized AgP (GAP). A diagnosis of LAP is done based on the evidence of circumpubertal onset and localized first molar/incisor presentation with interproximal attachment loss in at least two permanent teeth, one of which is a first molar and involving no more than two teeth other than first molars and incisors[2].

Supernumerary tooth is one of the developmental anomalies pertaining to the tooth morphology. A supernumerary tooth is that which is additional to the normal series and can be found in any region of the dental arch[3]. The occurrence of multiple Supernumerary teeth in a patient, in the absence of an associated systemic condition or syndrome is considered as a rare phenomenon. Wherever "multiple supernumerary teeth" is considered to mean five or more supernumerary teeth, the prevalence has been reported to be less than 1%[4]. Localized aggressive periodontitis has been associated with numerous dental anomalies such as fusion, talons cusp, root fusion, and developmental grooves[5]. Possible association of AgP with supernumerary teeth has been reported in the literature[6,7]. The purpose of this paper is to report a case of multiple impacted supernumerary teeth presenting with AgP in the absence of an associated systemic condition or syndrome and highlight the possibilities of a possible biological association.

Case Report

A female patient aged 20 years came to the Department of Periodontics, with the complaint of bleeding gums in the upper and lower arches since 6 months and mild pain in the left back teeth region. Family history and medical history were not significant. Hematological evaluation showed ESR (35mm/hr) and differential white blood cell count showed slight elevation in the percentage of neutrophils (77%). The systemic investigations were not suggestive of any disease or syndrome. Intraoral examination revealed clinical attachment loss of 5 to 6mm in all first molar region and around 6mm in upper incisors and lower anteriors, and generalized gingival inflammation with mild plaque and calculus present without gingival recession. Grade I mobility was seen in 31,32,41 and 42 region[8]. Subsequent radiological examination of the orthopantomogram [Fig.1] revealed multiple impacted supernumerary premolar teeth in relation to 14, 15, 24, 34, 44 and 45 region. The right maxillary and mandibular quadrant consisted of two impacted supernumerary teeth in the first and second premolar region whereas the left maxillary and mandibular quadrant consisted of one impacted supernumerary tooth in the first premolar region and all impacted supernumerary teeth mimicked the permanent teeth. The arc shaped bone loss seen in all

first molars and vertical bone loss in upper incisors was seen, whereas in mandibular anteriors, moderate horizontal bone loss was evident. The patient was educated about her oral condition and explained the treatment plan, which included thorough scaling and root planning (SRP) supplemented with antimicrobial agents. Systemic antibiotics (Doxycycline 100 mg once daily for 14 days after the initial loading dose of 200 mg on first day), were prescribed along with thorough SRP followed by a full mouth flap for access and osteoinductive bone grafting (Osseograft) was done in all first molars and no surgical removal of the multiple supernumerary impacted teeth was planned as it was clinically asymptomatic in nature. Post-operative instructions were given and the patient was advised for recall after 1 week, 2 weeks, 1 month and then every 3months once.

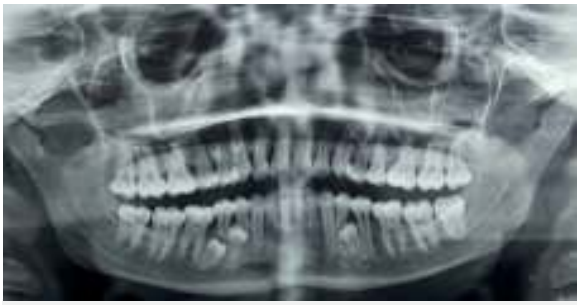

Fig 1. Orthopantomogram view

Discussion

The case described, represents unique characteristic of multiple impacted supernumerary teeth in a single patient with aggressive periodontitis. The supernumerary teeth present in various different forms mimic the permanent teeth. If they are similar to a natural tooth, they are called by the same name; for instance, supernumerary canine, otherwise, when its morphology is abnormal, it is just indicated as a supernumerary tooth located in a certain area. The presence of only one supernumerary tooth occurs in 76-86% of the cases, the presence of two in 12-23% and only 1% of the individuals have three or more supernumerary teeth[4]. Multiple supernumerary teeth can be associated with Gardner's syndrome, Fabry-Anderson syndrome, Ehlers-Danlos syndrome, or cleidocranial dysplasia[9,10]. Supernumerary teeth may lead to various pathological conditions. These include delayed eruption or non-eruption, displacement of permanent teeth, resorption or malformation of the adjacent roots and cystic formation[11]. The etiology of hyperdontia still remains unclear. Hattab et al[4] described hyperdontia as "a multifactorial inheritance disorder which originates from the hyperactivity of the dental lamina", while others suggested that supernumerary teeth were formed due to the dichotomy of the tooth bud[12]. Supernumerary teeth are generally thought to occur in the upper jaw ten times more frequently than in the lower jaw[13]. It is essential to enumerate and identify the teeth which are present clinically and/or radiographically, before a definitive diagnosis and proper treatment plan can be formulated, as supernumerary teeth can be an important cause of dental retention[14]. Localized aggressive periodontitis is characterized by severe attachment and angular bone loss, particularly in incisors and molars. Aggressive periodontitis is reported in various study populations - 0.1%, by Odell and Hughes[15] ; 0.32%, by Lopez et al[16]. ; and 0.76%, by Melvin et al[17]. So, both the entities, viz., aggressive periodontitis and supernumerary teeth, are uncommon conditions.

The first study recognizing the possible connection between supernumerary teeth and periodontitis was a case report by Eley in 1974[18]. In 1981, Rubin et al. described two identical Black twins with localized juvenile periodontitis, multiple supernumerary teeth and no dental caries. The authors hypothesized that all these three entities were due to genetic influence[19]. As Odell and Hughes reported in 1995, both aggressive periodontitis and supernumerary teeth are uncommon but have a familial tendency, and an association may be seen in a small minority of cases. Both entities show familial prevalence, but at the same time, both are consistent with multifactorial and multigenic etiology[15].

But in a retrospective study done by Gokhanet al. (2004), the association between aggressive periodontitis and supernumerary teeth was suggested to be random rather than a biologic one[7].

To conclude, one may think in terms of the correlation between aggressive periodontitis and multiple impacted supernumerary teeth as in this study. This does not mean that both entities have biological connection. However, association between these two entities is definitely a rare one. To prove such biological connection, further studies and genetic investigations are required to be carried out.

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If it is afternoon, bye-bye ethics!

If you don't like being taken for a ride while making a purchase or a business transaction,remember to do it in the morning. It appears that the people in general are more likely to be honest in the early hours of a day. As the day progresses, even the ones who are morally inclined, are likely to lie and cheat. This is the conclusion of a study conducted by researchers from Harvard University and the University of Utah. In a series of cleverly designed simple experiments involving students and adults, the researchers demonstrated that the tendency to lie and indulge in unethical acts became stronger in the afternoon. The researchers have called this "morning morality effect". Why there is loss of moral sense and self-control as the day progresses is not clear. But this study has important implications for human activities that rely on trust and ethical behaviour. It appears that individuals involved in such transactions need to be supervised carefully during the later part of the day. The results are published in the online version of Psychological Science. (http://pss.sagepub.com/content/early/2013/10/28/0956797613498099.abstract)

- Dr. K. Ramesh Rao

Class Room

Nanomedicine: Promising Tools in Biomedical Sciences

Dr.Agnishwar Girigoswami

Dept. of Medical Bionanotechnology, Chettinad Hospital and Research Institute (CHRI), Chennai, India.

Dr. Agnishwar Girigoswami, Associate Professor, Department of Medical Bionanotechnology, CHRI, has earned his Ph.D. from University of Kalyani in 2004. In the course of PhD, he explored fluorescence probing techniques to understand the biological phenomenon. In 2006, he joined the Korea Advanced Institute of Science & Technology (KAIST), South Korea as Postdoctoral Researcher with a prestigious Government (Brain Korea) fellowship. There, he developed a novel DNA/PNA-chip for genetic diagnosis coupling microarray technology and nanotechnology along with specific enzymatic reactions. Later he joined Jadavpur University, Kolkata; JIS College of Engineering, Kalyani; RKVM Girls College, Kolkata for research and teaching before joining CHRI in 2010. His 14 years research and 10 years teaching have brought many publications in peer reviewed journals.

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Lately nanotechnology is acquiring interest with rapid pace in biomedical sciences. This growing interdisciplinary field provides enormous technological platform for application in several areas like molecular diagnosis, imaging, nano-based therapeutics etc[1]. The nanotechnology is developed by the combination of science and technology for designing, synthesis and manipulation of materials with smallest functional unit confines in nanometer scale to attribute specific function at the supramolecular level. Classically, nanotechnology refers to the particle size ranging from 1 to 100 nm but it can be extended to below 1 μm to obtain ordered structure for useful application[2]. The key feature of nanomaterials is its excellent physicochemical properties that differ from their bulk due to the high surface to volume ratio (fig. 1). These unique physicochemical properties frame them to be excellent candidates for screening, imaging, diagnosis, treatment of diseases and altogether it is known as 'nanomedicine'.

Nanomedicine is defined as the "monitoring, repair, construction, and control of human biological systems at the cellular, molecular, and atomic levels using engineered nanodevices and nanostructures"[3]. National Institute of Health states another definition of nanomedicine for the medical research as "an offshoot of nanotechnology, which refers to highly specific medical interventions at the molecular scale for curing disease or repairing damaged tissues, such as bone, muscle, or nerve"[4]. The cutting edge technological field nanomedicine deals with five major disciplines in medical and biological sciences namely, analytical tools, nanoimaging, nanomaterials and nanodevices, novel therapeutics and drug delivery systems, and regulatory & toxicological issues in relation with clinical practices[4]. The ultimate goal of nanomedicine is to understand the mechanism of action of biological machinery inside the living cells at nanoscale and based on these information, it is possible to redevelop new engineering technology to treat disease conditions.

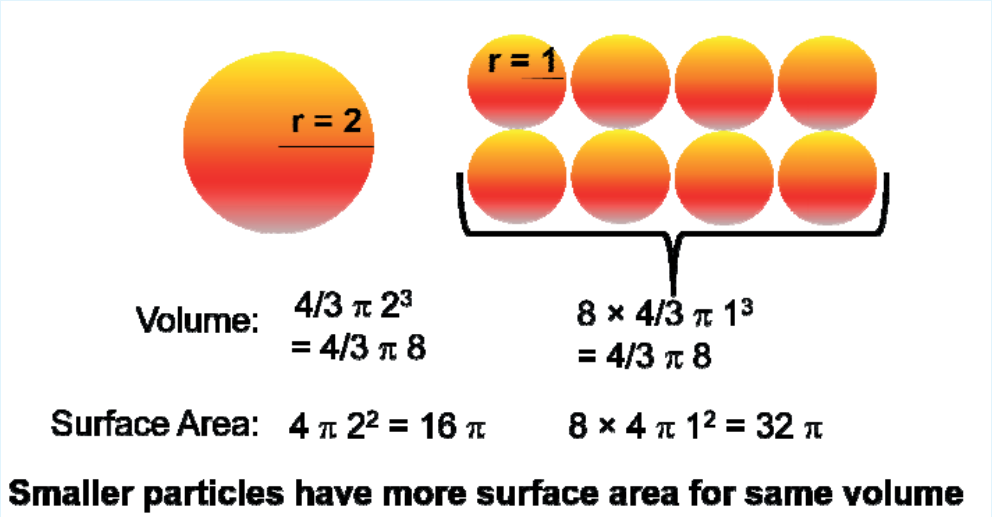

Fig 1: Schematic diagram to show the effect of particle size on the surface area to volume ratio. The surface to volume ratio increases with the reduction of particle size.

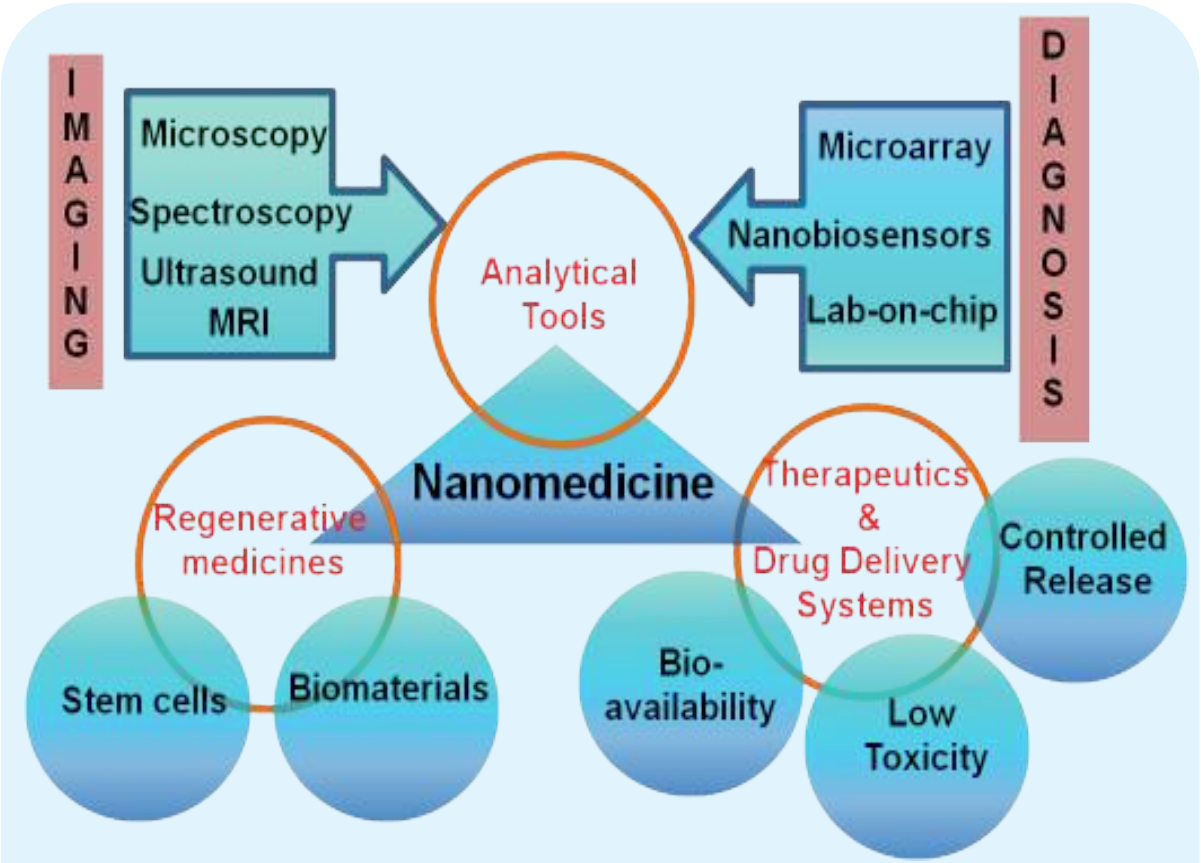

Fig 2: Schematic representation of different fields of application of nanomedicine.

The impact of nanomedicine in biology can be seen mainly in diagnostic & imaging methods, drug release kinetics and regenerative medicines which are summarized in figure 2.

Nanomedicine in Diagnostics

Recent developments in nanomedicine have made it possible to analyze biological systems at cellular and sub-cellular levels for the development of medical diagnosis and therapy. Nanomedicine based diagnostics basically concerns in vitro and in vivo models that help to quantify and visualize the expression of targeted biomolecules. To satisfy the huge demand in analyzing and scrutinizing the behavior of the human diseases and related treatment, researchers are continuously developing new nanoscale devices like micelles, liposomes, dendrimers, core-shell nanoparticles, quantum dots, polymer, inorganic nanoparticles etc. (figure 3). Currently, fluorescent labeled or radio-labeled molecules are widely used in biomedical laboratories for the diagnosis purpose, with lots of difficulties regarding sample volume, toxicity, sensitivity, specificity, detection time etc. In contrary, nanotools are most promising to overcome all these limitation of conventional methods due to their high surface to volume ratio, high reactivity, tunable size and inherent optical properties[5].

The major application of nanomedicine is improved fluorescent marker for the purpose of diagnosis and screening. In this connection, quantum dots are well known nanometer-sized inorganic semiconductor[6]. Due to the unique size dependent quantum confinement effect, these inorganic chromophores show broad absorption band along with a specific and sharp fluorescence emission. The high quantum yield, excellent chemical and photo stability and tuneable size dependent optical properties make them good candidate in single molecule tracking, in vivo imaging, fluorescent cell sorting, etc over conventional organic fluorophores.

Advances in nanotechnology have led to engineer super paramagnetic nanoscale material which is an excellent promising tool for in vitro as well as in vivo MR imaging. The effectiveness of traditional contrast agents is limited due to the lack of specificity and sensitivity. These contrast agents are not effective in determining early stage of metastatic tumour where as nanomedicine based contrast material like super paramagnetic iron oxide (SPIO) nanoparticles can overcome these issues related to solubility, specific targeting, toxicity, immunological responses etc[7]. Magnetic resonance imaging signal is basically the precession of hydrogen nuclei of water molecule in an applied magnetic field. The contrast agents are used to shorten the spin-lattice relaxation time (T_1) and spin-spin relaxation time (T_2). Paramagnetic nanoscale materials such as gadolinium (Gd) and manganese (Mn) with higher relaxivities give stronger contrast enhancement for T_1-weighted MRI and super paramagnetic contrast agents like SPIO give T_2-weighted MRI[8, 9].

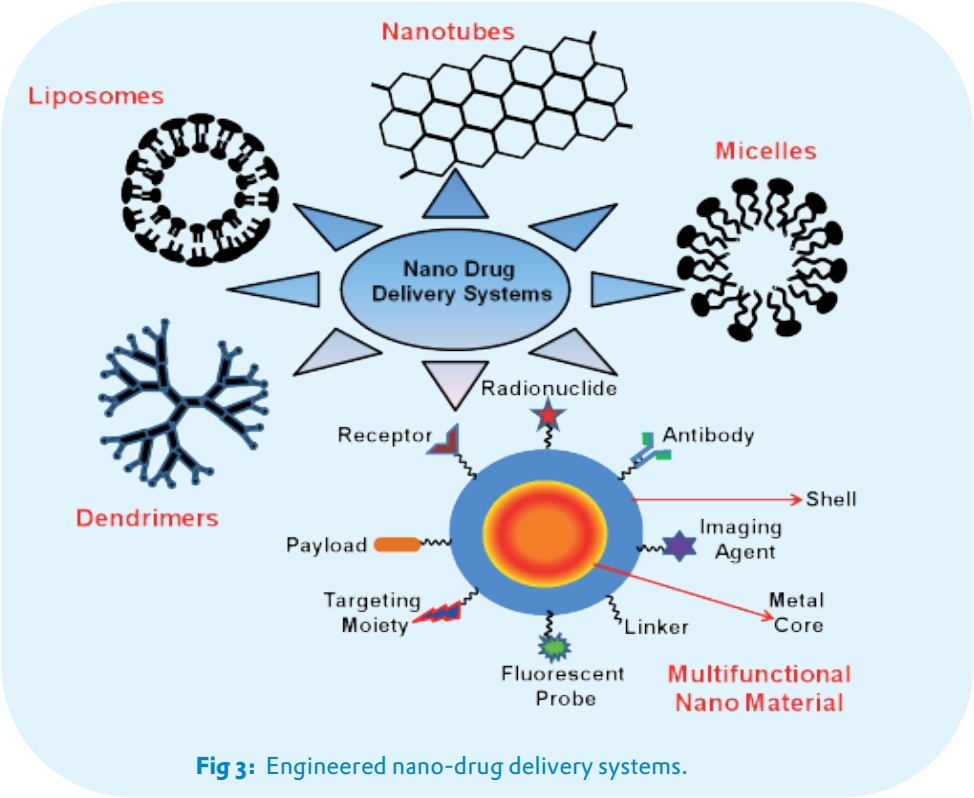

Fig 3: Engineered nano-drug delivery systems.

Nanomedicine in Therapeutics

Nanoparticles are popular for their biomedical applications due to their ability to overcome different biological barriers and to target specific tissues with sustained release of drugs. The non-specific action of chemotherapeutic anti-cancer drugs causes significant side effect in cancer patients. Engineered nanoparticles drug carriers can deliver drugs to the specific tumour tissues and enhanced permeability and retention (EPR) effect allows accumulation of anticancer drugs in cancerous tissues with reduced drug toxicity. These nanoscale drug delivery systems include polymer-based nanoparticles, polymeric micelles, dendrimers, liposomes etc. These engineered nanocarriers can be made slowly degradable, pH sensitive, temperature sensitive, and targeted by conjugating them with specific monoclonal antibodies or macromolecules like folic acid, sugar, etc. The surface functionalization of nano carriers with ligands that are selectively recognized by the receptors on the cancer cell surface facilitate active tumour cells targeting strategy. For passive targeting mechanism, the nanomedicine reach tumour cells through the leaky vasculature of the blood capillaries and the enhanced vascular permeability of tumour tissues causing accumulation of chemotherapeutic agents in tumours (figure 4).

Another advantage of nanocarriers is continuous release of drug with controlled rate to the specific targeted site. Various biodegradable polymer nanoparticles, liposomes, dendrimers have been used in drug delivery research as they can efficiently deliver the drug to the specific site with therapeutic benefit minimizing the side effect. Such nanodevices are formulated by dissolving, attaching, encapsulating or entrapping the pharmacologically active agent to nanoparticles matrix. The major goal in designing these devices are sustained release of therapeutic agents to the specific site of action with the therapeutically optimal rate and reduced toxicity[10].

Challenges in Nanomedicine

It was expected that the nano-invention would improve the quality of life, upgrade the diagnostics and therapeutics with reduced cost and it is. But, there are lots of issues regarding the potential health effects associated with exposure to man-made nanomaterials. Due to the lack of information for the prediction of impact of engineered nanomaterials on the environment and human health, there is a need for additional research. Presently, numerous regulatory agencies concerned with nanomedicine, insurance companies, and public health groups are raising questions for the implementation of nanomedicine in routine clinical practice[11].

Sanhai et al recently addressed possible seven challenges for nanomedicine in Nature Nanotechnology[12]. Most important challenge is the determination of the distribution of nanomaterials in the human body after systemic administration through possible routes and understanding the transport of these materials across compartmental boundaries in the body. Other challenges are the development of new mathematical and computer models for predicting risk and benefit parameters through a 'periodic table of nanoparticles'. Success on these issues urgently needs collaborative effort from all government and non-government agencies.

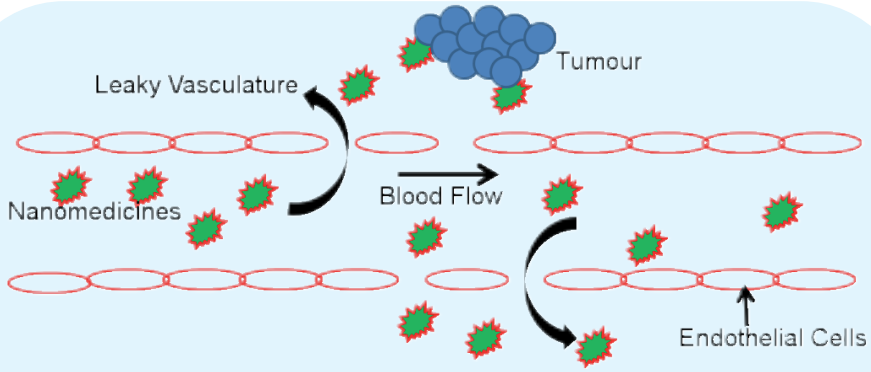

Fig 4: Diagram shows the delivery of drugs to the tumour through leaky vasculature of the blood capillaries

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Smoke, if you are eager to age quickly!

Reputations of marijuana, red wine and chocolates have been redeemed recently by the discovery of hidden benefits associated with their use. But no such luck for cigarettes; each new study damns it further. In a new study carried out on 79 pairs of identical twins, in whom one sibling is a smoker, the researchers compared the faces for the effects of aging. A panel of three plastic surgeons analysed the twin's facial features and graded the aging using standard assessment tools. The smoking twin, when compared to his non-smoking sibling, had worse scores for baggy eyes, baggy cheeks, smile lines and wrinkles along upper and lower lips. The cigarette induced damage affected mainly the lower two thirds of the face. Smoking for even five years appeared to make a significant difference. Smoking induces damage by depriving the cells of oxygen and by disrupting the collagen and elastin. Apart from its other effects, smoking is really bad for one's appearance. The study is published in the November 2013 issue of Plastic and Reconstructive Surgery

- Dr. K. Ramesh Rao

Nobel prize in Physiology / Medicine -2013

Dr.G. Arun Kumar

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Chettinad Health City Medical Journal 2013; 2(3): 103-104

The Eukaryotic cell has a very dynamic machinery that performs specialised functions in the system. This cell has highly organised compartments that perform various cellular activities. One of the central activities of the cell is Protein Synthesis that is essential for the function and survival of the cell. More than 20,000 known protein-coding genes are present in the human genome. A cell at any given point of time produces numerous proteins. Each protein that is synthesised in the cell needs to be transported to its target compartment within the cell or to other cells.

The protein synthesis takes place in the rough endoplasmic reticulum with the help of ribosomes. The protein that is synthesised is then transported to the golgi apparatus, where it is subject to chemical modifications like glycosylation and phosphorylation. From the golgi apparatus, the mature protein is packed and transported to its destination. Given the large amount of proteins being synthesised in the cell, it was a puzzle how the protein reached its destination. This transport has to be highly precise in spite of the complexities of diverse number of proteins being synthesised and diverse number of target destinations. The destination could be both within the cell (eg: nucleus, endoplasmic reticulum, etc) or can be to other cells (eg: delivery of hormones, cytokines, neurotransmitters etc).

This year Nobel Prize in Physiology or Medicine was awarded to Dr.Randy Schekman, Dr.James Rothman and Dr.Thomas Südhof: the three scientists who gave insights into how this delivery of the synthesised protein takes place with utmost accuracy. They discovered the key role played by a specialised compartment of the cell called as vesicles, which organised the transport system both within and between the cells. The vesicle is a small membrane bound organelle that is of three types (Figure-1)

(i) Cop II coated vesicles that transport proteins from Endo Plasmic Reticulum to the Golgi Apparatus.

(ii) Cop I coated vesicles that do a reverse transport from Golgi Apparatus to the Endo Plasmic Reticulum.

(iii) Clathrin coated vesicles that transport the proteins from the Golgi Apparatus to the Lysosome or Plasma Membrane. The Clathrin coated vesicles are the most common type of vesicles that are involved in protein transport between the cells.

The specificity of the transport system is achieved by means of specific receptors present on the membrane of the vesicles. This receptor has specific ligands in the target cell/organelle and the interaction between the vesicular receptor and the ligand determines the specificity of the transport.

Dr. Randy Schekman identified genes that are involved in vesicular fusion in the yeast. His group defined a set of *sec* genes in the yeast by developing temperature sensitive mutants of these genes. The organism that was mutant to the *sec* genes had accumulation of proteins in the cell. Further, a set of 23 sec genes were identified that were involved in the vesicular fusion with different organelles of the cell[1,2].

Dr.James Rothman identified the specific vesicular membrane receptor that was essential for the fusion of the vesicle to the target organelle. His team first discovered a protein called as N-ethylmaleimide Sensitive Factor (NSF) that is a key receptor involved in vesicular fusion. His group further characterized Soluble NSF Attachment Protein (SNAP) in the vesicles and their receptor called SNAP Receptor (SNARE) that determine the specificity of the vesicular fusion with the target[3,4].

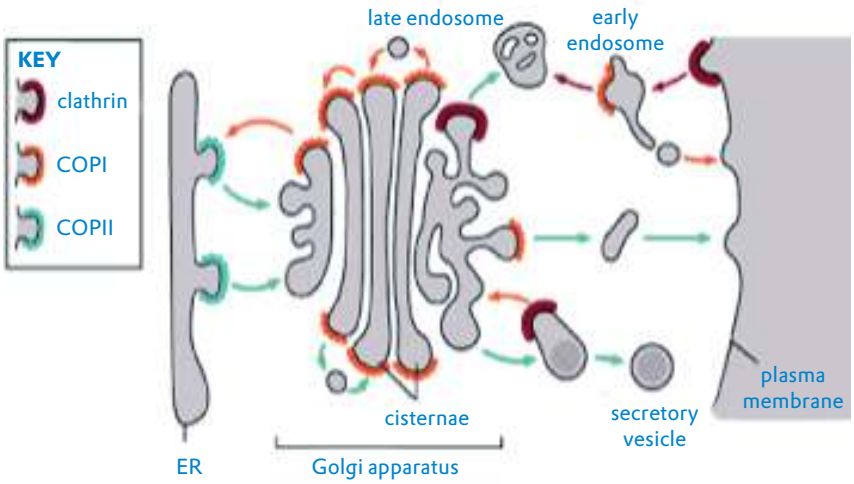

Fig 1: Types of Vesicles in an Eukaryotic Cell

Dr.Thomas Südhof gave insights into the control of vesicular fusion. Using Neuron cell as a model his team identified specific proteins called as synaptotagmin-1 that interacts both with the Phoshpholipid bilayer and Ca2+ ions. It is known that Ca2+ ion concentration was critical in determining the neuronal signal.

Identification of the synaptotagmin-1 molecule described that the release of the vesicular package was mediated by synaptotagmin-1 molecule in response to Ca2+ concentration thus controlling the timing of the vesicular fusion[5,6].

About the Nobel Laureates
(Adapted from the press release of The Nobel Assembly at Karolinska Institute)

James E. Rothman was born 1950 in Haverhill, Massachusetts, USA. He received his PhD from Harvard Medical School in 1976, was a postdoctoral fellow at Massachusetts Institute of Technology, and moved in 1978 to Stanford University in California, where he started his research on the vesicles of the cell. Rothman has also worked at Princeton University, Memorial Sloan-Kettering Cancer Institute and Columbia University. In 2008, he joined the faculty of Yale University in New Haven, Connecticut, USA, where he is currently Professor and Chairman in the Department of Cell Biology.

Randy W. Schekman was born 1948 in St Paul, Minnesota, USA, studied at the University of California in Los Angeles and at Stanford University, where he obtained his PhD in 1974 under the supervision of Arthur Kornberg (Nobel Prize 1959) and in the same department that Rothman joined a few years later. In 1976, Schekman joined the faculty of the University of California at Berkeley, where he is currently Professor in the Department of Molecular and Cell biology. Schekman is also an investigator of Howard Hughes Medical Institute.

Thomas C. Südhof was born in 1955 in Göttingen, Germany. He studied at the Georg- August-Universität in Göttingen, where he received an MD in 1982 and a Doctorate in neurochemistry the same year. In 1983, he moved to the University of Texas Southwestern Medical Center in Dallas, Texas, USA, as a postdoctoral fellow with Michael Brown and Joseph Goldstein (who shared the 1985 Nobel Prize in Physiology or Medicine). Südhof became an investigator of Howard Hughes Medical Institute in 1991 and was appointed Professor of Molecular and Cellular Physiology at Stanford University in 2008.

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Answer to : **Diagose the Condition**

This ECG shows wide QRS complex with ventricular rate of around 85/min. The P waves are seen just after QRS complex. But in the long strip of lead II, fifth and seventh QRS complexes are narrow and were preceded by a normal P wave. There is a slight difference in the morphology in such a way that fifth complex is narrower than seventh complex. Fifth beat is called a CAPTURE BEAT and seventh beat is a FUSION BEAT.

This is a classical ACCELERATED IDIOVENTRICUALR RHYTHM. AIVR is a reperfusion arrhythmia common after acute MI. AIVR needs no specific treatment and it usually resolves spontaneously.

-**Dr.M.Chokkalingam,** Consultant Cardiology, CSSH

From the Pages of History

Medical Fashion – A Brief Look at its Evolution

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For the last hundred years or so, the medical professionals have been identified by the distinctive attire they wear. That distinctive piece of clothing has been the White Coat. What was a physician's garb before that? Hippocrates did not prescribe any dress code. But he stated that a doctor should be 'clean in person, well-dressed, and anointed with sweet smelling unguents that are beyond suspicion'. So, in earlier times, a physician was expected to dress well. If he did so, he was likely to be compensated far more handsomely for his services than a poorly dressed one. It did not matter that his treatment more often than not hastened the demise of his patients. Medicine was not yet a science. It was full of superstitious beliefs, speculations and some untested empirical observations. Of course, there were "barber surgeons" and "witch doctors" in some societies. They were distinctively clothed. In fact, the witch doctor's attire was so egregiously designed as to scare away even the most evil of spirits (!); and it might have even scared most patients enough to stop them from complaining.

By the nineteenth century, the physicians were mostly seen in black dress, much like priests and undertakers. It was appropriate, since a visit to the physician was frequently followed by visits from the other two. The surgeons still performed surgeries without masks or gloves but with an apron (an oversized pinafore) over their regular dresses. These aprons were made out of canvas and were heavily stained with dried blood and fluids from past surgeries. They were rarely, if ever, washed. The sight of the surgeon and his assistants walking into OT wearing those aprons must have evoked visions of hell in the minds of unanaesthetised patients about to be operated. Miraculously, the mortality was not 100 per cent and some patients came out of this ordeal alive.

Introduction of anaesthesia only emboldened these surgeons to become even more adventurous. Undistracted by screams of agony, they performed some truly gruesome surgery.

Things began to change in the later part of 19th century. The Germ Theory of disease was beginning to make an impact. The ideas of Joseph Lister and Ignaz Semmelweis about antisepsis were being gradually accepted. In 1890, William Halstead introduced gloves. Around the same time, Paul Berger was popularising the use of masks in France. The medicine was at last becoming science and was beginning to make good on its original promise. Buoyed by the success, the medical profession was eager to symbolically reinforce the impression that its major concerns were cleanliness and purity (freedom from disease). The white coat, introduced by Canadian surgeon, George Armstrong, appeared to do just that. Thus, it, along with white gown and drapes became apparels of medical profession. But white colour in OT proved to be less than ideal. It exaggerated the blood stains and worsened the glare while operating. As green colour appeared to overcome these shortcomings,it became the colour of choice.

By the middle of 20thcentury, a new uniform made its appearance. It consisted of draw-string pants and loose fitting short sleeved top. This outfit, known as Scrubs, has since become the de facto dress code for most of the healthcare professionals. Although green is still the most popular colour, scrubs are available in a variety of colours, sizes and trims. The emphasis is here is on functionality, comfort and elegant simplicity and not on symbolism.

In the meantime, the venerable white coat has lost some of its whiteness. Apart from well-known "white-coat Hypertension", its use has been conclusively linked to increased incidence of nosocomial infections (MRSA and C. difficile). This has led to banning of its use in certain countries (particularly in UK and in paediatric wards worldwide).

The Medical Profession has come a long way: from its humble beginnings as a purveyor of therapeutic mumbo-jumbo to a highly organised scientific discipline capable of providing leading-edge solutions to the patient's problems. It can now survive on the strength of its capabilities. It does not require the trappings of sartorial or tinctorial symbolism.

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Hey, I Look Good in a Blurry Group Photograph!

If we are to go by the conclusions of a recent study, we should surround ourselves with people if we want to look attractive. Apparently we look better when we are in small groups than when we are alone. The study was conducted in University of California, San Diego, on 130 undergraduate students. These participants were shown photographs of individuals shot alone and in small groups and were asked to rate their attractiveness. In most cases, participants rated the individuals as more attractive when they were in groups than when they were alone. In addition, they found blurry faces more attractive. The researchers have called the former "Cheerleader Effect" and the latter, "benefit of doubt effect". They propose that the uneven features of individual faces get averaged out when seen in a group. It seems the average faces are more attractive. So, be in a good company and insist on unfocussed photograph! The study is published in Psychological Science (2013; DOI:10.1177/0956797613497969).

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Hold not thy breath whilst thou sleepeth!

Interrupted breathing during sleep (obstructive sleep apnoea -OSA) has long been suspected to be a risk factor for cardiovascular disease. In a new study published in American Journal of Respiratory and Critical Care Medicine, the researchers link OSA to increased risk of subclinical myocardial injury. The study was done on 1645 subjects free from heart disease and were followed up for a median period of 21.4 years. All the subjects underwent polysomnography to stratify the OSA into none, mild, moderate and severe grades. Their blood samples were also analysed for high sensitivity troponin T (hs-TnT) which is a sensitive predictor of both coronary heart disease and heart failure. During the follow-up period, 222 subjects died, 212 had coronary heart disease and 122 developed heart failure. Analysis of the results revealed significantly elevated hs-TnT in subjects with OSA and its levels correlated with severity of OSA. The authors suggest that monitoring hs-TnT in individuals with OSA may have a prognostic value and may help predict the occurrence of a cardiovascular event. (http://www.atsjournals.org/doi/abs/10.1164/ rccm.201309-1572OC#.UmoTfFzIVCo)

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