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Dr KK Aggarwal
Group Editor-in-Chief, IJCP Group

"Superbug"... Moving from Bacteria to Fungus

The fungus, *Candida auris* is an emerging "superbug" and is fast becoming a global health threat. The Centers for Disease Control and Prevention (CDC) has added drug-resistant *C. auris* to a list of germs, which are considered as "urgent threats".

C. auris has been reported from South Korea, India, Pakistan, Kuwait, Israel, Oman, South Africa, Colombia, Venezuela, the United States, Canada and Europe, including the United Kingdom, Norway, Germany and Spain (*Clin Microbiol Rev.* 2017;31(1). pii: e00029-17). A total of 617 cases have been reported in the US till March 29, 2019.

Last year, an elderly man died due to *C. auris* infection after an abdominal surgery in Mount Sinai Hospital in New York City. The New York Times reported, "The man at Mount Sinai died after 90 days in the hospital, but *C. auris* did not. Tests showed it was everywhere in his room, so invasive that the hospital needed special cleaning equipment and had to rip out some of the ceiling and floor tiles to eradicate it. Everything was positive—the walls, the bed, the doors, the curtains, the phones, the sink, the whiteboard, the poles, the pump," said Dr Scott Lorin, the hospital's president. "The mattress, the bed rails, the canister holes, the window shades, the ceiling, everything in the room was positive." (*New York Times*. April 6, 2019)

C. auris is a deadly infection; immunocompromised persons are more vulnerable to develop this infection. People who recently had surgery, live in nursing homes or who have breathing tubes, feeding tubes or central venous catheters are especially at higher risk.

Patients can remain colonized with *C. auris* for a long time and the fungus can survive on hospital surface for long duration. This facilitates spread of *C. auris* between patients in health care facilities.

C. auris can cause different types of infections, including bloodstream infection, wound infection and ear infection. The symptoms of *C. auris* infection are not easily identifiable as the patients are already critically ill.

According to the CDC, infection with *C. auris* is of concern because:

- It is often multidrug-resistant.
- It is difficult to identify with standard laboratory methods, and it can be misidentified in labs without specific technology, which can lead to inappropriate management.
- It has caused outbreaks in health care settings. For this reason, it is important to quickly identify *C. auris* in a hospitalized patient so that health care facilities can take special precautions to stop its spread.

(Source: CDC)

■■■■

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The Prospects of e-cigarettes in India: Overview of Evidence, Opportunities and Challenges Based on Experience in Western Countries

KONSTANTINOS FARSALINOS*, CHRISTOPHER RUSSELL†, RAJESH SHARAN‡

ABSTRACT

India represents a highly complex public health landscape in terms of smoking and tobacco use. Tobacco use involves not only smoking boxed tobacco cigarettes but also other local forms (e.g., bidis, hookah, chilam, etc.) as well as use of highly toxic smokeless tobacco products. Approximately 1 million people die every year from tobacco-related disease in the country. While India is facing substantial challenges in combating smoking and tobacco use, a new challenge for public health authorities is the availability of e-cigarettes. Appropriate regulation should be based on current evidence so that benefits are maximized and unintended consequences are avoided. Awareness and use of e-cigarettes has grown exponentially in several regions in the world, and this has generated an intense and controversial debate about their public health effect. E-cigarettes have been available in Western countries for many years, and they have been the focus of intense research. In this paper, we provide an overview of the currently-available evidence on the major determinants of the public health impact of e-cigarettes (risk profile, smoking cessation efficacy and unintended use by nonsmokers and youth) and conclude on the regulatory steps that authorities in India could follow in order to maximize the public health effect and minimize public health harm.

Keywords: Smoking, tobacco use, e-cigarettes, tobacco harm reduction, India

Tobacco smoking is one of the biggest public health threats in the world. The World Health Organization (WHO) estimates that there are more than 1 billion smokers globally[1] and predicts billion premature smoking-related deaths during the 21st century. For every person who dies from a smoking-related disease, there are around 20 people living and suffering from a smoking-related disease.[2]

In Southeast Asia, the prevalence of smoking is particularly high,[3] with prevalence varying from 24.3% (in India) to 63% (in Indonesia) for men and from 0.4% (in Sri Lanka) to 15% (in Nepal) for women.[4] Additionally, 10% of all adult deaths in this region is attributable to tobacco.[5]

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SMOKING AND TOBACCO USE IN INDIA

India, the fastest growing large economy[6] and the 2nd most populous country of the world with 65% of its over 1.34 billion strong population under the age of 35 years,[7] displays a unique situation in the region due to prevalence of a complex, 'rainbow' landscape of tobacco use. This country is not only home to an estimated 12% of world's cigarette smokers, it also has a larger section of the population indulging in (a) either smoking tobacco in its alternative or local forms (e.g., bidis, hookah, chilam, etc.), (b) chewing or masticating it in form of smokeless tobacco (SLT) such as khaini, zarda, gutkha, etc. or (c) both (mixed users). Therefore, India represents a highly complex public health challenge stemming from not only tobacco smoking in different forms, but also from the use of harmful SLT products, due to which approximately 1 million people die annually.[8] Global Adult Tobacco Survey (GATS)-2 data shows that India has the 2nd largest tobacco consuming population (over 300 million) in the world where 48% of men and 20% using tobacco in any form.[9] In spite of enforcement of conventional tobacco control measures in India, which does show some positive changes from GATS-1 to GATS-2

period (absolute reduction in tobacco prevalence of 6% and increase in initiation age by an average of 1 year), the GATS-2 data shows that the age of initiation to tobacco in any form is still earlier in India (18.3 years in males and 17.2 years in females) as compared with the average 20 years in other GATS-2 countries. It is interesting to note that despite high prevalence of knowledge about the serious health consequences of tobacco smoking or chewing in India, GATS-2 reports that only about 50% intended and about 40% attempted to quit. Ironically, India also has the lowest quit rates among the GATS-2 countries surveyed (followed by Indonesia). And this is corroborated by the fact that in the overlapping period, the disease demography of India has undergone a significant change with two medical conditions largely attributable to tobacco, ischemic heart disease and chronic obstructive lung disease, being ranked in positions 1 and 2 in 2016 from positions 6 and 8, respectively, in the 1990s.[10] It should be noted that the disease burden associated with smoking is predicted to rise further in low- and middle-income countries (LMICs), which includes India and many countries of South and Southeast Asia.[11] This clearly shows that smoking and tobacco use is a public health priority in India, with urgent and effective measures needed to reduce the burden to society and the health care system.

TOBACCO CESSATION ENVIRONMENT AND SERVICES IN INDIA

India is a member of the WHO Framework Convention on Tobacco Control (FCTC) and follows the MPOWER policy recommendations to reduce demand for tobacco. The core principles of the MPOWER are to Monitor tobacco use and prevention policies, to Protect people from tobacco smoke, to Offer help to quit tobacco use, to Warn about the dangers of tobacco, to Enforce bans on tobacco advertising, promotion and sponsorship, to Raise taxes on tobacco. However, several problems exist in implementing these guidelines effectively, relevant to the complexity of the tobacco use environment in the country and the large number of people using tobacco products.

Tobacco cessation clinics (renamed 'Tobacco Cessation Centers, TCCs, in India in 2005) are the first-line of defense available to current smokers and SLT users alike, and perhaps the most immediate avenue, to contain the morbidity and mortality related to tobacco. In 2014, it was estimated that appropriate counseling and behavioral interventions with or without nicotine or other pharmacological aids would be capable of potentially saving at least 180 million additional tobacco-related deaths in India by 2020 if 50% users successfully quit tobacco.[12] But the records available in public domain indicate that this powerful intervention strategy remains largely neglected in India. With 13 TCCs, the Ministry of Health and Family Welfare of Government of India, in collaboration with WHO, started providing formal cessation services in India in 2002. The number of such facilities was increased to 19 subsequently.[12] According to one report, in the first 5-year period, the TCCs could register only 34,741 subjects across India and baseline data were available for 23,320 subjects with short-term (6 weeks) and long-term (up to 9 months) follow-up.[13]

The majority of the subjects were SLT users and the minority were smokers. Of these cases, the 6-week outcome was available for 10,471 subjects (44.9% of total registered), which showed that 3,255 (31.1%) subjects had quit tobacco and 5,187 (49.5%) had reduced tobacco consumption by 50% while 2,029 (8.9%) reported no change in the status. The authors summed up to show that 36% of all registered subjects at TCCs exhibited 'improved' outcome (14% quitters + 22% with 50% reduced harm category). The long-term follow-up (3 x 3 months totaling to 9 months) data was available for 12,813 subjects. Among these, 26%, 21% and 18% subjects exhibited improvement (quit + reduced tobacco harm) after 1st, 2nd and 3rd follow-up cycle, respectively.

It is obvious that properly trained and empowered clinicians, medical professionals as well as para-medics, psychiatrists, counselors and infrastructures, including resources, have significant roles to play in tobacco cessation efforts and their outcomes. However, a recent study showed that a large majority of medical professionals in India have reported having insufficient experience to offer cessation assistance.[14] Additional barriers for smoking cessation include deeply ingrained cultural habits, tobacco use by health care professionals and limited motivation of physicians to document tobacco use and provide appropriate consultation.[15]

Considering the enormous diversity of India coupled with the prevalent 'rainbow' usage pattern of tobacco and the huge burden of aging current tobacco user population groups, it appears like a huge and mounting challenge to create an appropriate ecosystem for tobacco cessation service in India with trained human resources and required infrastructure facilities to increase the spread and reach of TCCs in the country. In light of the fact that India is home to over 300 million tobacco

users, the data on (a) number of TCCs available today, (b) number of people seeking tobacco cessation help in such centers, (c) number of trained professionals capable of offering them cessation service and (d) the infrastructure to sustain and intensify the efforts, appear disappointing.

All these strongly point out that additional avenues of smoking and SLT cessation must be made available to the current tobacco users in India in order to reduce the health burden of the country.

TOBACCO HARM REDUCTION AND E-CIGARETTES

Tobacco harm reduction (THR) policies aim to prevent or reduce harm by promoting substitution of combustible tobacco with less hazardous noncombustible sources of nicotine to smokers who are unable or unwilling to quit smoking in response to conventional tobacco control measures. While the concept of harm reduction was initially introduced for intravenous opiate use, it is in fact a strategy used in common daily activities such as the use of seatbelts and helmets to reduce the risk of injury and death from road accidents. Electronic cigarettes (e-cigarettes) – hand-held devices that use battery power to heat a solution of propylene glycol, glycerol and often flavorings and nicotine, to produce an aerosol that the user inhales – are, in many Western countries, rapidly growing in popularity among adults as an alternative to smoking conventional cigarettes.[16,17]

Yet the role of e-cigarettes in tobacco control and THR continues to be the focus of intense and controversial debate.[18] There are concerns that e-cigarettes may have adverse public health effects, focusing on their potential health risks, their efficacy as smoking substitutes and their use by nonsmokers and youth. While research is continuously evolving, it is important to use currently available evidence to determine the most appropriate regulatory framework for e-cigarettes that would maximize public health benefits for smokers and SLT users while minimizing harm for nonusers.

DETERMINANTS OF THE PUBLIC HEALTH IMPACT OF E-CIGARETTES

Determining the public health impact of e-cigarettes is a complex task. The main factors that need to be assessed are the safety/risk profile of the products, their smoking cessation/reduction efficacy, and their use by population subgroups, including youth.[19]

Their public health impact can be represented with the following formula:[19]

$$\textit{Public health impact}_{EC} = (\textit{hazard}_{\text{SM-EC}} \times \textit{smoking cessation}) - (\textit{hazard}_{EC} \times \textit{use among nonsmokers}) - (\textit{hazard}_{SM} \times \textit{smoking initiation})$$

Where EC: Electronic cigarette; SM: Smoking; SM-EC: Difference in hazard between smoking and electronic cigarette use; hazard_{SM}: Refers to smoking initiation due to e-cigarettes (gateway to smoking effect).

It is well-established that smoking cessation is effective in the primary and secondary prevention of smoking-related disease.[20,21] Therefore, the assessment of the safety/risk profile of e-cigarettes (and any other smoking substitute) in relation to smoking is critical. However, the absolute risk of the products (relative to non-use of any other inhalational habit) is also important considering the possibility that never smokers could initiate e-cigarette use. Since e-cigarettes are intended (from a public health perspective) to be used as THR products and smoking substitutes, their efficacy in smoking cessation is an important determinant of their public health impact. While smoking reduction might also be beneficial for health,[22] it is difficult to accurately quantify sustained reduction in consumption and the subsequent change in disease risk.[19] Finally, use of e-cigarettes by different population subgroups, particularly nonsmokers and youth, is important in understanding whether the products are used as intended from a public health perspective (i.e., as smoking substitutes).

SAFETY/RISKS OF E-CIGARETTES

Tobacco cigarette smoke contains thousands of chemicals, many of which are classified as carcinogenic while others have established cardiovascular, respiratory and genetic toxicity. Some compounds, such as tobacco-specific nitrosamines and heavy metals, are present in cured tobacco leaves,[23] while others, such as polycyclic aromatic hydrocarbons, are present in tobacco cigarette smoke due to combustion.[24] It is generally acknowledged; however, that a substantial proportion of the smoking-related health risk is derived from the combustion process, with temperatures of up to 900°C generated when taking a puff.[25] Several years ago, the statement "smokers smoke for nicotine but die from the tar" was mentioned in the literature, describing the crucial effect of the combustion process in the harm caused by smoking.[26]

E-cigarettes do not contain tobacco and do not involve combustion in their function, as shown by the absence of elevated exhaled carbon monoxide levels in e-cigarette users after using an e-cigarette.[27] The main ingredients used in e-cigarette liquids, with the exception of nicotine, are chemicals approved for use in food products, cosmetics and pharmaceuticals, that have established safety when ingested. Propylene glycol and glycerol, the main solvents of liquids, were approved for human consumption in 1982 and 1959, respectively and have well-established metabolic pathways when absorbed either orally or intravenously (for propylene glycol).[19] The same applies to food-approved flavorings. However, safety for ingestion does not necessarily ensure safety for inhalation. E-cigarettes introduce a new route of administration, through the respiratory tract, while they are used intermittently throughout the day and for a long time. This introduces some uncertainty, mainly for the local effects on the respiratory tract rather than on the systemic effects when absorbed.

There is limited but largely reassuring evidence on inhalation of propylene glycol and glycerol, mainly from animal studies. A study performed in the 1940s identified that propylene glycol inhalation had no adverse effects on any organ of primates.[28] Other studies in the same period found that propylene glycol (in aerosol form) had bacteriostatic and virostatic properties in both animals and humans.[29,30] More recent studies have not identified any substantial health concerns;[31,32] however, these studies evaluated only short-term exposure. Thus, more evidence is needed to establish the safety of these chemicals when inhaled. Examples of flavorings that could raise concern include diacetyl and acetyl propionyl. These compounds are safe when ingested but have been linked with the development of respiratory disease when inhaled.[33,34] A substantial proportion of sweet-flavored e-liquids from various manufacturers were found to contain either or both these compounds.[35] However, tobacco cigarette smoke also contains these compounds, at levels one to two orders of magnitude higher than in e-cigarettes.[35,36]

Various contaminants have been found in e-cigarette liquids and aerosol. Tobacco-specific nitrosamines, probably derived from nicotine extracted from tobacco, were found in liquids at very low levels that were comparable with pharmaceutical nicotine products.[37,38] Other compounds such as nitrates, phenols, aromatic amines and polycyclic aromatic hydrocarbons, major determinants of the risk related to smoking, are either absent or present in very low levels in e-cigarettes.[38-41]

Thermal degradation products, such as aldehydes, derived from the decomposition of e-cigarette liquid ingredients when subject to heat for evaporation,[42] have been found in e-cigarette aerosol. A limited number of studies reported levels of aldehydes that were several-fold higher than in tobacco cigarette smoke, raising serious health concerns about e-cigarette users.[43-45] These findings were not subsequently reproduced,[46,47] raising the possibility that unrealistic conditions were used during laboratory testing or of experimental error.[48-50] A recent systematic review on aldehyde emissions from e-cigarettes raised several methodological concerns, including the use of diverse puffing conditions, aerosol collection and analytical methods.[51] The review noted that newer-generation devices tested under realistic conditions emitted very low levels of aldehydes that were not only below smoking but also below commonly measured levels in the environment or occupational safety limits.[47,51,52] Metals have also been detected in e-cigarette aerosol.[39,53,54] However, a risk assessment analysis of data from two studies found that the levels emitted were below the upper limits set for inhalation medications and occupational safety levels.[55]

Toxicological studies in cell lines or in animals have identified potential mechanisms that could lead to adverse health effects such as cytotoxicity, inflammation, immunological modulation and oxidation.[56-58] However, the relevance of such studies is difficult to interpret. The *in vitro* or animal *in vivo* response depends mainly on the amount of exposure, and it is difficult to determine the dose that could be relevant to human effects. Thus, such studies are more valuable in comparing the effects of different exposures, mainly e-cigarette versus tobacco cigarette smoke exposure. Many such studies identified substantially lower adverse effects from e-cigarette aerosol compared to tobacco cigarette smoke.[59-62]

Long-term clinical epidemiological studies should be the cornerstone of evidence quantifying the level of risk or risk reduction of switching from smoking to e-cigarette use. However, considering that smoking causes disease after several years of use, it is too early to have such evidence for e-cigarette use. Additionally, the past smoking history of e-cigarette users would confer elevated risk even after complete smoking abstinence for several years. Limited clinical studies have been conducted on the health effects of e-cigarettes.

Few short-term studies, evaluating effects immediately post-use, have identified elevated blood pressure, heart rate and aortic stiffness.[63,64] Such effects have also been observed after using pharmaceutical nicotine nasal

spray, caffeine, after exercise or even after a meal and are related to the acute transient sympathetic stimulation caused by nicotine.[65-69] Limited long-term studies have shown improvement in spirometry measurements among asthmatics who partially or completely switch from smoking to e-cigarette use, lower blood pressure and improved hypertension control.[70-72] A recent study evaluated the effects of e-cigarette use in a small group of never smoking adults followed up for 3.5 years.[73] No adverse effects were observed in the respiratory and cardiovascular system. However, the follow-up duration was not long enough to substantiate that e-cigarettes are harmless. Studies on biomarkers of toxin exposure have shown substantially reduced levels of exposure to toxicants in e-cigarette users, which are similar to non-smokers or former smokers using nicotine replacement therapies (NRTs).[74,75]

In conclusion, currently available evidence raises little doubt that e-cigarettes are by far less harmful than smoking or other harmful forms of tobacco used in India. A recent risk assessment analysis of toxic emissions from e-cigarettes concluded that the carcinogenic risk of e-cigarettes is 0.4% that of smoking,[76] while another study calculated that the Excess Lifetime Cancer Risk (ELCR) is orders of magnitude lower in e-cigarette users compared to smokers and negligible in people exposed to e-cigarette aerosol as bystanders (second-hand exposure).[77] Several health organizations such as Public Health England, Royal College of Physicians, National Academies of Sciences, Engineering and Medicine and American Heart Association support that e-cigarettes are likely to be by far less harmful than smoking and that it would be reasonable to support an effort to quit smoking with their use among smokers who do not want to use or have failed to quit with approved medication.[78-81] Of course, all organizations acknowledge the lack of long-term epidemiological evidence. Considering the high prevalence of tobacco cigarette and SLT use in India, products that cause substantial health harm, e-cigarettes could represent an important harm reduction product choice for smokers and SLT users in India.

E-CIGARETTE USE AND SMOKING CESSATION

Quitting tobacco smoking at the soonest opportunity is the best action a smoker can take to improve his/her life expectancy and quality of life.[82] However, quitting smoking is notoriously difficult, often achieved only after many unsuccessful attempts.[83] Given that most of the 8 million smoking-related premature deaths annually that are projected to occur globally by 2030 will be among people who are currently smoking[84] and the large burden of disease and death in India, developing new and evermore effective ways of helping more people to quit smoking sooner is a public health imperative.

E-cigarettes are now the most popular method of assisted quit attempts in the United States, used in 35% of smokers' most recent quit attempts.[85] Data from multiple years of the US Current Population Survey-Tobacco Use Supplement (CPS-TUS) suggest that the substantial increase in e-cigarette use that has been observed in the United States between 2010 and 2015 is significantly associated with an increase in smoking cessation at the population level during these years.[86] The findings represent approximately 3,50,000 additional ex-smokers and the first significant increase in the smoking cessation rate at the population level in the US for the past 25 years. Obviously, this does not constitute undisputable evidence that the increase in smoking cessation rates was caused by e-cigarettes. However, smokers who used e-cigarettes in 2014-2015 were more likely to have attempted to quit smoking (65% vs. 40.1%) and more likely to have succeeded in quitting smoking for at least 3 months (8.2% vs. 4.8%) compared to smokers who had not used e-cigarettes. A recent analysis of the Population Assessment of Tobacco and Health (PATH) study reported that cigarette smokers who initiated e-cigarette use had 7.88 times the odds of 30-day cigarette cessation compared with nonusers of e-cigarettes, suggesting that regular use of e-cigarettes promotes smoking cessation.[87]

A similar effect has also been observed in England. A 2016 time-series covariate-adjusted analysis of population trends in e-cigarette use and smoking found that between 2006 and 2015, each 1% increase in use of an e-cigarette as part of a quit attempt was associated with a 0.058% increase in the rate of successful quit attempts at the population level.[88] E-cigarettes have also been shown to be approximately 60% more effective in producing smoking abstinence than nicotine replacement products or quitting without any formal help.[89] It has been estimated that 16,000-22,000 adult e-cigarette users quit smoking in England in 2014 who would not have quit had e-cigarettes not been available.[90] In total, there were an estimated 2,266,749 e-cigarettes users in Great Britain in 2014, of whom 908,432 (40.1%) were former smokers.[91] Importantly, a recent randomized controlled trial performed in the UK showed that e-cigarettes are twice as effective as NRTs in sustained smoking cessation after 1 year follow-up.[92]

The large number of additional quitters attributable to e-cigarette use also represents a large economic saving to

the United Kingdom (UK) society. The UK Department of Health estimates that every additional nonsmoker provides a net benefit to society of GBP 44,000.[93] The estimated 9,08,432 e-cigarette users in Great Britain in 2014 who had quit smoking therefore represent potential lifetime health benefits of GBP 39.9 billion. It has been suggested that no formal public health initiative for smoking cessation has had such reach - 2.3 million current e-cigarette users - or such impact - almost one million ex-smokers - in such a short space of time.[94] Additionally, because e-cigarettes are marketed in the UK as general consumer products, the switch of almost 1 million smokers to e-cigarettes has been achieved at virtually no cost to the UK taxpayer and the government financial resources, avoiding the public health spending required for organized smoking cessation services and subsidized pharmaceutical products.

There is also evidence that smokers who use an e-cigarette more frequently are significantly more likely to make a quit attempt and to succeed in that attempt. This is an expected finding considering that any intervention or smoking cessation aid should be used regularly in order to have any impact on the smoking habit. Data from the 2014-15 TUS-CPS show that smokers' frequency of e-cigarette use in the last month was positively related to both making a quit attempt and to succeeding in a quit attempt.[95] Approximately 32.6% of people who had used an e-cigarette on 25-30 of the past 30 days had quit smoking compared to 5.2% among those who had used an e-cigarette for 1-4 days of the past 30 days. Data from the 2014 and 2015 US National Health Interview Survey (NHIS) showed that over half (52%) of daily e-cigarette users had quit smoking in the last 5 years, with daily e-cigarette users being more than threefold more likely to have quit smoking compared to those who have never used an e-cigarette.[96] Evidence that regular e-cigarette use may help some smokers quit has been reported from other countries too. Recently, a population-representative study in Greece identified that current daily e-cigarette use increased the odds of being a recent former smoker by approximately 11-fold.[97]

Despite the above-mentioned evidence, meta-analyses of randomized controlled trials and cohort studies have shown mixed results. Two Cochrane reviews concluded that e-cigarettes help smokers to quit, but the confidence in the result was rated 'low' by GRADE standards.[98,99] Another systematic review found that e-cigarette use was associated with lower odds of quitting smoking.[100] A more recent study could not conclude on the effect of e-cigarettes on smoking cessation.[101] These inconclusive data are due to the inherent problems of many cohort studies; for example, many studies recruited subjects who had failed to quit smoking with the use of e-cigarettes at baseline, resulting in bias of the outcome being present at the start of the study.[102-104] Additionally, randomized controlled trials may be inappropriate for a behavioral intervention in which e-cigarettes are chosen by consumers based on self-preference,[105] unless they are performed in an "unconventional" way (e.g., by allowing participants to choose from different types of products).

YOUTH USE OF E-CIGARETTES

Another important consideration when assessing the likely population health impact of e-cigarettes is the extent to which e-cigarettes are used by youth and young adults, and the extent to which using an e-cigarette increases or decreases smoking prevalence in this population subgroup. Available data from multiple nationally representative surveys of US youth show that, while e-cigarette use was growing until 2016, the majority of use among US youth is infrequent and experimental.[106-110] For example, data from the 2015 National Youth Tobacco Survey indicate that 13.5% of middle school students had ever used an e-cigarette, 5.3% had used an e-cigarette at least once in the past 30 days, but only 0.6% had used an e-cigarette on ≥20 of the past 30 days.[106]

The prevalence of frequent e-cigarette use (i.e., use on ≥20 of the past 30 days) has remained very low among US youth between 2011 and 2015 and is largely confined among youth with a history of smoking. Frequent e-cigarette use among never-smoking youth is extremely rare.[109,110] Additionally, the majority of the small proportion of US youth who do use an e-cigarette frequently are actually using e-cigarettes that do not contain nicotine.[109,110] Characteristically, an analysis of the 2015 National Youth Tobacco Survey showed that only 0.3% of never smoking youth are using e-cigarettes frequently (≥20 of the past 30 days).[111] A recent development was the release of the 2018 National Youth Tobacco Survey data, which showed that e-cigarette use increased by 78% compared to 2017.[112] This represented a reversal of the trend for lower e-cigarette use among adolescents after 2016. The survey findings raised considerable concerns in the US, with the Food and Drug Administration (FDA) announcing the intention to ban the sales of flavored e-cigarettes (besides tobacco and menthol) in convenient stores or other places where minors can enter, and limit sales of these products to vape shops that do not allow access to youth. It should be noted that no information was released about

e-cigarette use according to the smoking status, which would determine whether e-cigarettes are attracting never smoking youth.

The greatest public health concern about e-cigarettes; however, is the rate at which youth use of e-cigarettes may increase rates of youth use of more harmful tobacco products (e.g., starting to smoke cigarettes). While studies show that e-cigarette use at baseline is associated with smoking at follow-up,[113,114] the reverse is also true.[113] While the transition from e-cigarette use initiation to ever or current smoking is established, it is difficult to substantiate the causal link when you consider the common liability model, in which people who are liable to use nicotine are more likely to use both e-cigarettes and cigarettes.[115] The common liability model is applicable not only to tobacco but also to other substance use disorders such as alcohol and marijuana.[116] It is reassuring that the increasing prevalence of experimental e-cigarette use between 2010 and 2015 among US youth and young adults has coincided with the sharpest declines ever recorded in smoking rates among youths and young adults. Between 2010 and 2015, a period in which the prevalence of experimental e-cigarette use grew rapidly among US young adults, the prevalence of smoking reduced by 54% among 18- to 19-year old males and by 64% among 18- to 19-year old females.[117] These reductions are 3 times and 5 times larger, respectively, than the reductions observed between 2005 and 2010, when the rate of e-cigarette use in these age cohorts was essentially zero. While the cross-sectional design of these surveys does not permit the conclusion that e-cigarette use has caused these sharp declines in smoking, they are at least reassuring that e-cigarette use is not decelerating, let alone reversing, the declining rate of youth smoking in the US. While monitoring e-cigarette use among youth is of high priority, any regulatory decisions should be based on the net public health effect, which includes an analysis of potential benefits and risks from e-cigarette use on the whole population as well as the evolution of smoking rates among youth. Characteristically, in the US in 2018, 3.2% of high school and 0.7% of middle school students were frequent users of combustible tobacco products.[118]

THE EUROPEAN UNION AND THE UNITED KINGDOM: A MODEL FOR REGULATING E-CIGARETTES IN INDIA

While evidence suggests that e-cigarettes can have a role as a harm reduction strategy in combating smoking, it is important for these products to be regulated. Regulation should ensure product quality, restrict marketing and promotion to intended, from a public health perspective, population subgroups (i.e., smokers), but also provide a competitive advantage against combustible tobacco cigarettes.

In deciding how to regulate e-cigarettes for the protection and benefit of public health, health authorities in India may wish to consider the United Kingdom's (UK's) relatively liberal e-cigarette regulatory framework. The UK is following the European Union regulatory framework on e-cigarettes, which includes quality standards, nicotine concentration limits, marketing restrictions and a defined process of registering all products that are available in the market.[119] Such a framework could in fact form the basis for regulation in any other country, with necessary adjustments to local characteristics and conditions. At the same time, several health organizations are endorsing e-cigarette use for smokers. While continuing to recognize complete cessation of all tobacco and nicotine use as the best course of action for a smoker, the UK Department of Health has pledged to support policies that maximize the availability of less harmful forms of nicotine delivery, such as e-cigarettes and NRTs, to adult smokers and to support smokers to switch to these less harmful nicotine products at the soonest opportunity.[120] This approach is based on evidence that e-cigarette use is the most popular method of quitting smoking in the UK; that e-cigarette use encourages quit attempts that would not otherwise have been made; and that using an e-cigarette can help smokers to quit. Prominent UK health organizations and charities - including Public Health England, the Royal College of Physicians, the Royal Society for Public Health, Cancer Research UK, and the British Lung Foundation, among others - also now support the position that millions of lives can be saved by widely promoting e-cigarettes as substitutes for smoking.[121]

The UK's relatively liberal approach to regulating e-cigarettes has coincided with a rapid, large increase in the prevalence of e-cigarette use among adult smokers, and record-breaking annual declines in the adult smoking rate, at 15.1% in 2017, the lowest adult smoking rate ever recorded in the UK.[122] Additionally, the strongest decline in smoking prevalence since 2011, by 25%, was observed among young adults (18-24 years old).[122] At the same time, the continuous monitoring of e-cigarette use among adolescents has consistently shown that most e-cigarette experimentation does not turn into regular use and levels of regular use in young people who have never smoked were very low.[123] This provides further reassuring evidence about the effects of e-cigarette appeal on smoking prevalence in youth. Recently, the UK Commons Science and

Technology Committee reviewed the available evidence on e-cigarettes and concluded that regulations should be further relaxed relating to e-cigarettes' licensing, prescribing and advertising of their health benefits relative to smoking.[124]

REGULATORY OPTIONS FOR INDIA

E-cigarettes are not risk-free products. However, current evidence strongly supports their harm reduction potential in terms of personal health risk compared to smoking tobacco cigarettes. While they could be associated with adverse public health effects (by being attractive to nonsmokers and serving as a gateway to smoking), current evidence shows no signs of such effects in countries where e-cigarettes have been available for several years, even in countries with no regulatory framework on e-cigarettes. The common liability model can easily explain the trends in e-cigarette use among youth, while at the same time smoking rates are rapidly declining. While more evidence is definitely needed, combating the tobacco problem in India is of very high priority, due to the high social and economic cost of smoking and SLT-related disease and death, and the lack of adequate resources to help tobacco users quit. Currently available evidence from Western countries, and relevant regulatory decisions, could help India create an appropriate framework to maximize the potential of e-cigarettes to serve as an additional, complementary tool in combating smoking and SLT use while minimizing adverse public health effects. In fact, a similar approach could be used for other harm reduction products such as snus, which could be used as substitute for the harmful SLT products available and used in India. An overview of the basic principles of a regulatory framework that could be applied in India is presented in Table 1. Such regulation should

Table 1. Basic Principles of a Regulatory Framework that could be Applied in India

Regulatory rules	Rationale - evidence	Benefit
Classification		
Different classification for e-cigarettes vs. tobacco cigarettes or other harmful SLT products.	E-cigarettes do not contain any tobacco. Nicotine has minimal adverse health effects. The lack of combustion is a main determinant of the risk difference between tobacco cigarettes and e-cigarettes.	It will be easier for smokers and SLT users to understand the difference in function and risk between the products.
Different restrictions on e-cigarette use vs. smoking.	Restrictions should be based on a risk continuum and be evidence-based. For example, while banning smoking in closed public places is scientifically justified, current evidence suggests no substantial health harm from second-hand exposure to e-cigarette aerosol.	Smokers and SLT users will better understand the difference in risk between products, and might be more motivated to quit by switching to e-cigarette use.
Product quality		
Reasonable quality standards for e-cigarette products.	While e-cigarettes do not involve combustion, this cannot justify the liberal use of any chemical without considering known and potential risks. Standards should be reasonable and easy to comply, to avoid creating a monopoly (e.g., by big tobacco companies). The European Union model of setting quality standards could be used as a basis.	Ensure product quality for consumers, further minimize potential risks. The European Union model of setting quality standards could be used as a basis.
Registration of all products through a transparent and clearly-defined process.	As any consumer product, regulation needs to clearly record the products that are available to consumers. The process will ensure compliance with all other regulatory decisions.	Avoid the creation of a "black market" and the marketing of products with questionable quality. Ensure that any new knowledge or information about problems or risks will be addressed through changes in the market (e.g., in case specific products need to be withdrawn from the market, for quality control, etc).

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Regulatory rules	Rationale - evidence	Benefit
Availability, accessibility and promotion		
Controlled (but not banned) marketing so that only smokers and SLT users are targeted.	E-cigarettes are intended to be used as smoking substitutes and not as a new "trendy" habit for anyone to adopt.	Ensure that e-cigarettes are appealing to smokers and SLT users only, and are not attractive to nonsmokers.
	Smokers and SLT users need to be informed about the availability of these products and their potential advantages compared to the products they currently use.	Allow smokers and SLT users to make informed decisions about their health.
	Deliver a clear message that the best approach is for people to quit smoking and SLT use without using any alternative product.	
	E-cigarettes should supplement (and not substitute) all other tobacco control efforts.	
Ban on sales to minors (<18 years old).	Ensure minimal access of youth to e-cigarettes.	Prevent e-cigarettes from being a new "trend" among youth.
Increased accessibility of e-cigarettes (e.g., allow online sales).	While tobacco cigarettes are available every where and are easily accessible, sales points for e-cigarettes are limited.	Accessibility to e-cigarettes will be facilitated, especially in remote areas.
	Prohibition of online sales will limit accessibility to a harm reduction product.	Accessibility to tobacco cigarettes and harmful SLT products should be limited.
	Such a prohibition unintentionally protects the sales of the most accessible and available product (i.e., tobacco cigarettes and other SLTs).	
Packaging/labeling warnings on e-cigarette products should be confined to the dependence potential of nicotine	Health warnings are scientifically justified for tobacco cigarettes (and other combustible products).	Smokers and SLT users will better understand the risk difference between products.
	There is no scientific evidence on the introduction of warnings about health risks in e-cigarette products.	People who do not want to develop dependence on nicotine will be warned against the use of nicotine-containing e-cigarettes.
	A warning about the dependence potential of nicotine is justified.	
Substantially reduced or (preferably) no taxation for e-cigarettes	Financial incentives should be used to convince more people to switch from tobacco cigarettes and SLT products to e-cigarettes.	Reduced price will allow more smokers and SLT users to afford e-cigarettes.
Facilitation of innovation and introduction of new products, including local production.	Product innovation over time has created safer and more effective and satisfying products for smokers.	Better-performing products that smokers like to use can increase smoking substitution rates.
	Product variability is needed because e-cigarette choice is based on self-preference.	Safer products will further minimize potential risks.
	Local production will likely reduce product cost.	Reduced product cost will enhance the accessibility of more smokers to e-cigarettes.
Promote research and monitoring of use - flexible regulatory framework that can adjust to new knowledge.	Population studies to identify the patterns of use among different population subgroups.	Regulatory decisions can change based on new knowledge.
	The main focus should be on sustained/regular/ frequent use rather than experimentation.	The true impact of e-cigarette use on public health must be monitored and calculated.
	Monitoring should assess effects on smoking and SLT use prevalence, as well as long-term health effects on users.	
	Technological evolutions and development of more effective and safer products should be allowed to enter the market and perhaps replace older technologies.	

clearly differentiate e-cigarettes from tobacco cigarettes or harmful SLT products, ensure availability, variability and accessibility of products, determine specific quality criteria, create a registration process for all marketed products and control marketing and promotion to intended populations (i.e., smokers and SLT users). Finally, smokers and SLT users should be motivated to switch to these products and be allowed to make informed decisions, without ignoring the undisputed fact that complete cessation without the use of any alternative is the best, but difficult to achieve by many, option. This approach is similar to the EU established regulation and appears to be reasonable for any country that allows the legal sales of combustible and other harmful tobacco products, giving the opportunity to the users of these products to switch to substantially less harmful alternatives if they are unwilling or unable to quit with approved methods.

While caution is justified and regulation needs to be flexible enough to adjust based on new developments, scientific information and local data, an approach of prohibiting e-cigarette sales or implementing regulations identical to tobacco cigarettes would be preliminary and unsupported by current evidence. It may in fact represent a missed opportunity to help a substantial proportion of smokers and SLT users in India by providing them with an alternative product at no cost to government resources. At the same time, a decision to ban e-cigarettes might unintentionally protect tobacco cigarette sales since e-cigarettes currently represent the biggest competitor to tobacco cigarettes globally.

CONCLUSION

Public health officials in India are facing a new challenge with the availability of e-cigarettes. Still, the focus of the authorities should remain on the substantial disease and death burden of smoking and SLT use, combined with the barriers to quitting. In that respect, e-cigarettes may present an important opportunity to supplement (and not substitute) all other tobacco control efforts. Therefore, public health authorities in India may wish to consider embracing a risk-proportionate framework for regulating e-cigarettes, as is the case in many Western countries, with the aim to eventually reduce smoking and SLT use and the accompanying disease and death burden.

Declaration of Conflicting Interests

In the past 36 months, CR's employer, the Centre for Substance Use Research (which was not involved in this work), has received funding from e-cigarette manufacturers to conduct research on THR, specifically, on the role of e-cigarettes in smoking cessation, initiation and relapse. KF and RS have no conflict of interest to report for the past 36 months.

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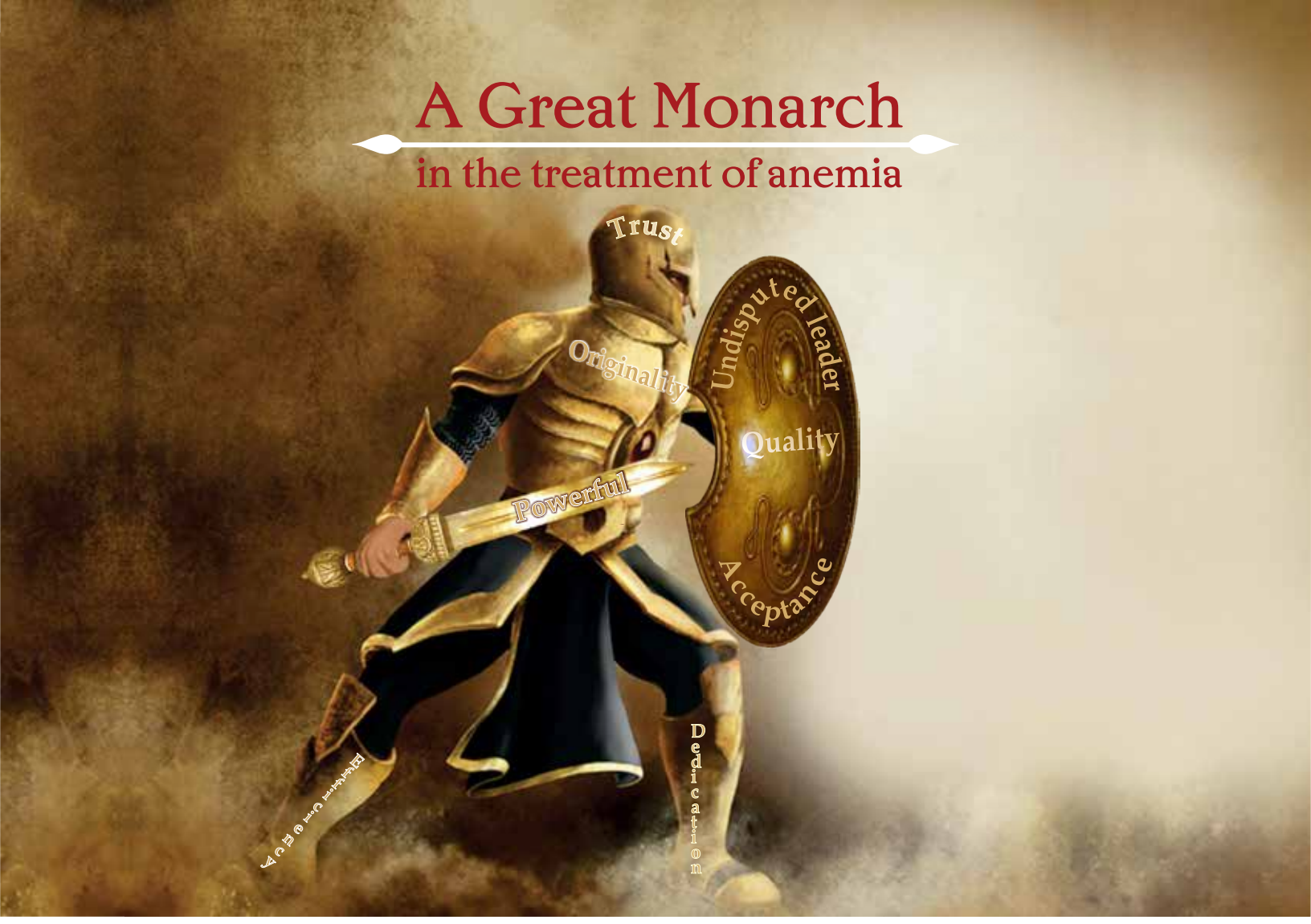

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A Comparative Study of Safety Profile and Efficacy of Acyclovir and Ganciclovir in Viral Corneal Ulcer

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ABSTRACT

Objective: The present study was conducted to evaluate the safety profile and efficacy of ganciclovir in cases of viral corneal ulcer and to compare it with acyclovir. **Material and methods:** It was a randomized controlled comparative study undertaken at the Regional Institute of Ophthalmology, Pt BD Sharma PGIMS, Rohtak, Haryana. The patients were divided into two groups of 25 each. Group I received acyclovir 3% ointment and Group II received ganciclovir 0.5% gel. Patients were followed-up weekly for 1 month. Efficacy of the drug was assessed in terms of visual acuity and extent of healing. Safety profile was assessed by development of ocular irritation, blurring of vision and iatrogenic diffuse punctate keratopathy. The observations were analyzed using unpaired and paired 't' test and Chi-square test. **Results:** By 14th day, 80% ulcers were healed in Group I while 88% were healed in Group II. The best corrected visual acuity after healing was also similar in the two groups (p = 0.730). The safety profile in terms of ocular irritation, blurring of vision and punctate keratopathy of both the drugs was found to be similar. **Conclusion:** The efficacy and safety profile of both the drugs was similar in the treatment of viral corneal ulcer.

Keywords: Acyclovir, ganciclovir, corneal ulcer

Viral keratitis is a common cause of blindness in both developing and developed countries. Even though both DNA and RNA viruses are responsible for keratitis, common corneal infections are caused by DNA viruses, the commonest ones being the herpes group viruses (Type 1, 2, 3 - varicella zoster virus [VZV]) and adenoviruses.

Congenital ocular herpes is rare. Primary ocular herpes is the first infection of a nonimmune subject with microdendrites and lymphadenopathy. Recurrent ocular herpes gets reactivated from sensory ganglia with triggering factors.

Diagnosis is mainly clinical and treatment is mostly symptomatic and with antiviral and cycloplegic drugs. Globally, there are 1,000,000 new cases each year. According to herpetic eye disease study (HEDS), herpes simplex virus (HSV) epithelial keratitis accounted for 47% of ocular herpes cases.

Previously, topical acyclovir was compared with trifluorothymidine, vidarabine and idoxuridine and with interferon.

The topical antiviral agents used in the treatment of herpetic viral keratitis include acyclovir ophthalmic ointment 3%, ganciclovir ophthalmic gel 0.15% and trifluridine ophthalmic solution 1%. Various studies have been conducted to asses and compare the efficacy, safety and tolerability of the drugs. Some of these trials have shown that acyclovir and ganciclovir are equally effective.

This study was conducted to evaluate and compare the efficacy and safety profile of ganciclovir as compared to acyclovir in viral keratitis.

MATERIAL AND METHODS

A single-blinded randomized control trial was carried out at the Regional Institute of Ophthalmology, PGIMS, Rohtak, Haryana over a period of 1 year.

Cases of acute viral corneal ulcer were included in the study. Patients with superadded bacterial infection and those appearing immune-mediated clinically were

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excluded. Patients were divided into two groups. Group I received topical acyclovir ointment 3% while Group II received topical ganciclovir gel 0.15%. Randomization was done using computer generated randomization table.

The sample size was calculated using the formula:

$$n = \frac{2(p)(1-p)(Z_B+Z_a/2)^2}{(P_1-P_2)^2}$$

where n is sample size, p is the prevalence of viral keratitis taken as 1.6%, Z_B is the desired power, i.e., typically 0.84, $Z_{a/2}$ is the desired level of statistical significance, i.e., typically 1.96 and (P_1-P_2) is the effect size taken as 0.01.

The size of each group came out to be 25, so the total sample size taken was 50. Detailed history was taken and on follow-up visits, ocular irritation and blurring of vision were assessed subjectively as 0-none, 1-mild, 2-moderate and 3-severe. The best corrected visual acuity was noted.

Corneal scraping was examined with Giemsa staining for multinucleated giant cells. Gram stain and potassium mount were used to rule out bacterial and fungal etiology. Follow-up was done on Days 1, 7, 14 and 21. Outcome was assessed in terms of safety profile and efficacy.

Assessment of safety profile

- Ocular irritation due to drug instillation.
- Blurring of vision due to drug instillation.
- Punctate keratopathy.

Assessment of efficacy

- Best corrected visual acuity (BCVA) after treatment.
- Mean ulcer healing time.
- Ulcer completely healed by Day 14 (%).

The treatment was given for 1 month with topical antiviral, lubricating eye drops, cycloplegic and antibacterial drops.

The quantitative variables were compared using unpaired 't' test between the two groups and paired 't' test for pair comparison. Qualitative variables were compared using Chi-square test. A 'p' value of <0.05 was considered statistically significant.

OBSERVATIONS AND RESULTS

The mean age of the subjects in the two groups was not significantly different (39.04 ± 16.59 years vs. 38.22 ± 14.25 years, p = 0.77). Viral corneal ulcer was found to be more common in males as compared to females (63.2% males vs. 34.6% females, p = 0.041).

The ulcer size in both the groups was not significantly different on Days 1, 7 and 14. The ulcers completely healed by Day 21 in both the groups. There was no significant difference in the ulcer size on the follow-up visits in the two groups (Table 1). By 14th day, 80% ulcers were healed in Group I while 88% healed in Group II. There was no significant difference in the time required for healing in the two groups. The ulcer healing time was almost similar in the two groups (Table 2).

The BCVA after healing was also similar in the two groups (Table 3). Blurring of vision after instillation of drug in both the groups was mild-to-moderate and similar, with p = 0.109 (Table 4). In both the groups, majority of the patients did not have ocular irritation (Table 5). The difference in the development of diffuse punctate keratopathy between the two groups was not statistically significant, with p = 0.156 (Table 6).

Table 1. Comparison of Ulcer Size on Different Follow-up Days with Unpaired *t*-test

	Group I Acyclovir (n = 25)		Group II Ganciclovir (n = 25)		P value
	Mean	SD	Mean	SD	
Day 1	4.2840	1.7804	4.3853	2.0546	0.771
Day 7	0.2800	0.4278	0.1344	0.2652	0.083
Day 14	0.0440	0.1321	0.0162	0.0824	0.447
Day 21	0.0000	0.0000	0.0000	0.0000	NA

Table 2. Comparison of Ulcer Healing Time in the Two Groups

	N	Mean (days)	SD	P value
Group I (Acyclovir)	25	10.8000	5.106	0.085
Group II (Ganciclovir)	25	7.9609	4.002	

Table 3. Comparison of BCVA (log MAR)

	Group I Acyclovir (n = 25)		Group II Ganciclovir (n = 25)		P value
	Mean	SD	Mean	SD	
Day 1	1.0650	0.4113	1.1700	0.4133	0.214
Day 7	1.0180	0.4265	1.0271	0.4411	0.420
Day 14	0.8010	0.4640	0.8825	0.4585	0.507
Day 21	0.7410	0.4658	0.7164	0.4651	0.730

Table 4. Comparison of Blurring of Vision due to Drug Instillation

Blurring of vision due to drug	Group I (n = 25)		Group II (n = 25)	
	No.	%	No.	%
None	4	16	9	36
Mild	8	32	10	40
Moderate	8	32	4	16
Severe	5	20	2	8

$\chi^2 = 5.853$; p = 0.109.

Table 5. Comparison of Ocular Irritation due to Drug Instillation

Ocular irritation due to drug	Group I (n = 25)		Group II (n = 25)	
	No.	%	No.	%
None	14	56	15	60
Mild	10	40	10	40
Moderate	1	4	0	0
Severe	0	0	0	0

$\chi^2 = 1.268$; p = 0.531.

Table 6. Comparison of Development of Diffuse Punctate Keratopathy in Two Groups

Diffuse punctate keratopathy	Group I (n = 25)	Group II (n = 25)
Absent	25 (100%)	24 (96%)
Present	0 (0%)	1 (4%)

$\chi^2 = 1.907$; p = 0.156.

DISCUSSION

In our study, the percentage of ulcers that completely healed by Day 14 was 80% in Group I and 88% in Group II. In a clinical trial, conducted in Europe, the rate of healing in ganciclovir 0.15% group was 83.3% and the rate of healing in acyclovir 3% group was 70.6%, but the difference was not statistically significant.

In another study, the healing rate of 71.05% with acyclovir and 86.1% with ganciclovir was also not statistically significant. In a multicentric study to see the relative efficacy of ganciclovir 0.15% and acyclovir 3%, there was no statistically significant difference detected in the rate of healing between the two groups (p = 0.8387).

Our findings are similar to these findings.

Mean BCVA was recorded on each follow-up and no statistically significant difference was found between the two groups (Table 3). No study could be found in literature where the BCVA was compared using these two groups. However, a clinical trial compared the effect of acyclovir and placebo with acyclovir and dexamethasone on visual acuity in herpetic disciform keratitis. The change in visual activity was similar for both the groups.

The blurring of vision due to drug instillation was graded subjectively depending upon severity as 0-none, 1-mild, 2-moderate and 3-severe. In the present study, the difference between the two groups was not found to be statistically significant (Table 4).

However, in other multicentric studies, average duration of blurring was significantly shorter in ganciclovir group when compared to acyclovir group. The difference in our study may be because of the fact that those studies are from western world and patients in our study are less literate and aware.

The ocular irritation due to drug instillation was graded subjectively from 0 to 3. Majority of the patients did not report any ocular irritation (56% in Group I vs. 60% in Group II). The difference in ocular irritation between the two groups was not statistically significant with p = 0.531 (Table 5).

In a multicentric trial, the frequency of punctate keratitis was half in ganciclovir group. Most of the previously conducted studies have shown the rates of superficial punctate keratitis to be similar in both acyclovir and ganciclovir group.

In another multicentric trial, stinging was significantly lower in ganciclovir group (p = 0.3) on 14th day. However, the duration of stinging and blurring was not statistically significant.

In this respect, some studies correlate while some do not correlate with or study.

CONCLUSION

Topical acyclovir 3% and topical ganciclovir 0.15% gel were equally effective in ulcer healing time. The ulcer healing time with topical acyclovir 3% was directly proportional to size of corneal ulcer.

The improvement of BCVA was similar in both the groups. The tolerance of the patients to topical acyclovir and ganciclovir was similar with respect to blurring of vision, ocular irritation and diffuse punctate keratitis. So, the safety profile of both the drugs (acyclovir and ganciclovir) was found to be similar.

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Stress, Overtime, Disease, Contribute to 2.8 Million Workers' Deaths per Year: UN

Stress, excessively-long working hours and disease, contribute to the deaths of nearly 2.8 million workers every year, while an additional 374 million people get injured or fall ill because of their jobs, the UN labor agency, ILO, said.

In a new report *"Safety and health at the heart of the future of work"* underlining ILO's message that no paid work should threaten your well-being, your safety or your life, the agency identifies several new or existing occupational risks of growing concern, that affect women more than men. These include modern working practices overall, world population growth, increased digital connectivity and climate change, which are believed to account for losses of almost 4% of the global economy.

The greatest proportion of work-related deaths (86%) come from disease, according to ILO, with some 6,500 people a day dying from occupational diseases, compared to 1,000 from fatal occupational accidents. The greatest causes of mortality are circulatory diseases (31%), work-related cancers (26%) and respiratory diseases (17%)…

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Indications, Patient Selection and Work-up Before Intrauterine Insemination

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ABSTRACT

Intrauterine insemination (IUI) is a common treatment for infertility. It involves the deposition of a good number of highly motile and morphologically normal sperms in the uterus near the fundus at the anticipated time of ovulation, bypassing factors which depend upon deposition of sperms in vagina and transport through the cervical mucus to the upper genital tract. This procedure is used for couples with unexplained infertility, minimal male factor infertility and women with cervical mucus problems. Despite its popularity, the effectiveness of IUI treatment is not consistent. Therefore, in spite of the fact that many a times the treatment is empirical, appropriate patient selection is very important and a complete work-up is required before taking up the patient for IUI. Patients should be counseled about the procedure involved, success rates, other options and risks associated.

Keywords: Intrauterine insemination, unexplained infertility, patient selection, work-up

Appropriate patient selection is the most important factor which determines success of any treatment. With intrauterine insemination (IUI), many a times the treatment is empirical, still it is possible to deduce a group of couples where the treatment will be actually beneficial. The rationale behind the treatment is to deposit a good number of highly motile and morphologically normal sperms in the uterus near the fundus at the anticipated time of ovulation, bypassing factors which depend upon deposition of sperms in vagina and transport through the cervical mucus to the upper genital tract. There are several indications of IUI which may be due to male factor, female factor or combined factors.

A complete work-up is required before taking up the patient for IUI. Any contraindications to the procedure must be ruled out. Patients should be counseled about the procedure involved, success rates, other options and risks associated.

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INDICATIONS OF IUI

Male Factors

Impotence/Ejaculatory dysfunction

This can be due to a number of causes:

- **Anatomical - Hypospadias:** Here deposition of semen occurs outside vagina or much away from the os. In such patients, semen is collected by masturbation for IUI.
- **Neurological:** This can be due to:
  - Spinal cord injury
  - Diabetes mellitus
  - Multiple sclerosis
  - Atherosclerosis
  - Damaged hypogastric nerves during surgeries like abdominoperineal resection of rectum, retroperitoneal lymph node dissection and aortoiliac surgery.

In these conditions, the sperm quality, especially its motility, is hampered despite high sperm density. Furthermore debris, inflammatory cells and quite often bacteria abound in these samples. The success of treatment depends upon sperm quality. Good results are obtained with samples where the progressive motility is more than 20-30%.

- **Retrograde ejaculation:** In this condition, there is reflux of semen backwards from the

posterior urethral valve and into the bladder at the time of ejaculation. The sperms lose their viability due to toxic effects and acidity of urine. It can be due to diabetes mellitus, multiple sclerosis, drugs like α-adrenergic blockers and phenothiazines and damage to innervation of bladder neck during surgeries like transurethral resection of the prostate (TURP) and retropubic prostatectomy. In retrograde ejaculation, urine is centrifuged and then washed to isolate sperms and IUI is then performed.[1]

The treatment for various causes of male infertility is summarized in Table 1.

- **Psychological conditions:** Such patients need sex-psychotherapy. Drugs such as sildenafil or papaverine may be given to bring about a good erection. Some patients benefit with the use of mechanical vibrators. Very occasionally, the patients may have to be subjected to general anesthesia and electroejaculation.
- **Drug-induced:** Drugs like sedatives, anti-depressants, antihypertensive agents, cimetidine, etc. can cause ejaculatory dysfunction.

Subnormal semen parameters

This includes:

- Oligozoospermia
- Asthenozoospermia
- Teratozoospermia
- Hypospermia
- Highly viscous semen.

The cause of infertility in such conditions is decreased availability of normal motile sperms for fertilization. As defined by the World Health Organization (WHO), a normal semen sample has a sperm count of more than 20 million/mL, with 50% or more of them showing forward progression and 30% or more having normal morphology.[2]

Table 1. Treatment for Various Causes of Male Infertility

Treatment
• Treat the cause
• Intracavernosal injection: Papaverine, phenoxybenzamine, phentolamine
• Surgical methods: Epididymal sperm aspiration, percutaneous vasal sperm aspiration
• Penile vibrator
• Electroejaculation

Mild male factor is defined as follows:

- Patient with only one abnormal male parameter
- Total motile sperm concentration of more than 5 million.

Ideally, a total motile pre-wash count of more than 10 million or a post-wash motile sperm count of 5 million is necessary to achieve a good pregnancy rate. Additionally, percentage motility of more than 40% in the final semen preparation correlates well with favorable outcome.

Patients with severe male factor infertility should go directly for *in vitro* fertilization or intracytoplasmic sperm injection (IVF/ICSI) or the use of donor sperms for insemination (artificial insemination with donor sperm - AID).

Other factors

The main treatment for obstructive azoospermia is percutaneous epididymal sperm aspiration (PESA) with ICSI. There is a recent report of achieving pregnancy after extracting sperm with PESA and performing IUI. Other conditions such as allergy to semen, vaginismus and other sexual dysfunctions may be treated with IUI.

Human immunodeficiency virus (HIV) infection: Sperm washing can significantly reduce the viral load.[3] Recently, insemination of HIV negative women with processed semen sample of HIV positive partners has been carried out to reduce the risk of transfer. However, prepared semen sample should be tested by polymerase chain reaction (PCR) before insemination.

Female Factors

Ovulatory dysfunction

It contributes to 30-40% of the female factors. In these cases, the first choice would be ovulation induction combined with timed intercourse or IUI. Many studies have shown that IUI gives better results as compared to timed intercourse.

Cervical factor

The cervix plays an important role in achieving successful pregnancy. It performs the following functions:

- Control of sperm entry into the upper genital tract
- Protection of sperms from vaginal acidity
- Nutrition of sperms
- Selection of sperms based on motility
- Sperm reservoir function
- Initiation of capacitation.

The following are some common causes of cervical factor infertility:

- Insufficient mucus production, which may be due to previous cauterization, surgery or rarely cystic fibrosis
- Altered quality of mucus
- Abnormal cervix: Stenosis, injury, malformation, infection, erosion
- Abnormal post-coital test (PCT) or hostile cervical mucus (the general consensus is that PCT has non-predictive value in terms of pregnancy).

IUI helps bypass these hostile factors. It has been observed that only 0.1% of the sperms placed in vagina are present in the cervical canal 1 hour after insemination.[4] Direct deposition of motile sperms in the uterine cavity can reverse this situation, and increase the chance of pregnancy. The use of IUI in patients with cervical factor of infertility yields very good pregnancy rates, in the range of 14-18%.

Endometriosis

IUI with ovulation induction can be tried in cases of mild endometriosis. Patients with mild-to-moderate endometriosis have good pregnancy rates between 7% and 18%. However, as the pregnancy rates (3-5%) are very low with severe endometriosis, it is best to opt for IVF/ICSI.

Common Factors

Immunological

Antisperm antibody can be found in both males and females. Causes in men are usually testicular trauma or obstruction to the male genital tract. In women, it can happen due to a break in the vaginal epithelium, peritoneal instillation, anal or oral intercourse. These antibodies prevent binding of sperm to zona pellucida and also impair the sperm movement. Various treatments like prolonged use of condoms, immunosuppression with steroids and laboratory procedures to wash sperm have been tried. However, all these have limited success.

Both IUI and IVF have shown to have high pregnancy rates in such patients. IUI helps to bypass these antibodies in cervical mucus.

Unexplained infertility

This diagnosis is made when a couple fails to conceive despite there being no obvious cause, even after subjecting the patient to a complete work-up. The diagnostic protocol should include an assessment of ovulation, evaluation of tubal patency and a normal semen analysis. The average incidence of unexplained infertility is around 10-15%.

Defects in folliculogenesis, gamete development, fertilization and embryo development may be the factors responsible. The rationale of empirical therapy is to bypass these causative factors. The managing principles are:

- Increasing availability of gametes by ovulation induction
- Improving gamete quality
- Bringing the gametes together by IUI or IVF.

The efficacy of various treatments in unexplained infertility is shown in Table 2.[5]

Insemination with husband's frozen semen

This is required in the following conditions:

- Absentee husband
- Antineoplastic treatment
- Vasectomy
- Poor semen parameters
- Drug therapy.

Insemination with donor sperms

It is now mandatory to use cryopreserved donor samples only, to minimize risk of HIV transmission. The indications for insemination with donor semen are:

- Azoospermia
- Severely subnormal semen parameters

Table 2. Efficacy of Various Treatments in Unexplained Infertility

Treatment	Combined pregnancy rate per initiated cycle (%)
No treatment	1.3
IUI	3.8
CC	5.6
CC with IUI	8.3
HMG	7.7
HMG with IUI	17.1
IVF	20.7

IUI = Intrauterine insemination; CC = Clomiphene citrate; HMG = Human menopausal gonadotropin; IVF = *In vitro* fertilization.

- Hereditary disease in father
- Persistent IVF/ICSI failures
- Rhesus isoimmunization
- Patient unable to afford IVF.

PATIENT SELECTION AND WORK-UP

An appropriate patient selection is the key to success for any treatment. A complete work-up including a detailed history is required before taking a patient for IUI. Many infertile couples have more than one contributory factor, which should be identified at the earliest. A scientific approach is warranted for a complete and efficient evaluation of female and male factors. More importantly, any contraindications to the procedure should be ruled out, as these can compromise the results (Table 3). Apart from a detailed history and physical examination, and routine investigations, certain specific tests for both the partners are required.

Evaluation of the Female Partner

Routine investigations: Complete blood count (CBC), erythrocyte sedimentation rate (ESR), sexually transmitted disease (VDRL, HBsAg, HIV), blood sugars, urine routine, bleeding and clotting time.

Anthropometric measurements such as body mass index (BMI) and waist-hip ratio (WHR) help identify subjects with central adiposity. These patients may require further evaluation of hyperandrogenism and hyperinsulinemia that may cause aberration in ovulation and cause luteal phase deficiency despite medication.

Table 3. Contraindications of IUI

Contraindications
• Bilateral tubal block
• Very severe oligoasthenospermia
• Genital tract infection
• Pregnancy contraindicated in female partners
• Unexplained genital tract bleeding
Relative contraindications
• Tubal pathology
• Genetic abnormality
• Pelvic mass
• Older women
• Multiple infertility etiologies
• Pelvic surgery
• Severe illness in one or both partners
• Recent chemotherapy or radiotherapy

Hormonal investigations:

- Serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) on Day 2/3 of cycle
  - FSH >10 mIU/mL and E2 >60 pg/mL indicates poor ovarian reserve
  - LH/FSH >2/1 indicates polycystic ovary syndrome (PCOS)
  - Low LH, FSH, E2 indicates hypogonadotropic hypogonadism
  - FSH >17 mIU/mL on Day 10 after clomiphene citrate indicates poor prognosis.
- In case of patients who are suspected to be poor responders, one can do these additional tests:
  - Serum inhibin-B test which is >45 pg/mL in poor responders.
  - Clomiphene citrate challenge test: Clomiphene citrate 100 mg/day from Day 5 to Day 9 and FSH on Day 10. A high FSH (>10 mIU/mL) indicates poor response and poor prognosis. This also points towards direct stimulation with gonadotropins, instead of clomiphene citrate.
  - Serum AMH (anti-mullerian hormone).
- Serum prolactin and triiodothyronine/thyroxine/thyroid-stimulating hormone (T3/T4/TSH)
- In case of patients with PCOS diagnosed by ultrasonography (USG), or symptomatology or having feature of androgenization, one can do the following tests:
  - Fasting serum insulin level (>10 mIU/mL is significant).
  - Fasting and postprandial blood sugars.
  - Dehydroepiandrosterone sulfate (DHEAS), androstenedione and testosterone.
  - In obese patients, a follicle phase 17-OHP level (to rule out congenital adrenal hyperplasia) and dexamethasone suppression test (to rule out Cushing's syndrome) should be carried out.
  - Rarely serum alanine transaminase level is done in patients who are intolerant to metformin treatment and who need to be placed on rosiglitazone.
  - In women with past history of renal disease on metformin treatment, serum creatinine and/or 24 hours creatinine clearance may have to be done.

For screening and academic purposes, a C-peptide assay may be performed to pick-up latent diabetes.

- Tests for ovulation (ovulatory or anovulatory)
  - Basal body temperature
  - Serial vaginal ultrasound follicular scan in a spontaneous cycle
  - Serum progesterone on Day 21 of cycle >4 ng/mL indicates ovulation and >10 ng/mL indicates adequate luteal phase.

Pelvic sonography: This helps in evaluating uterus, uterine cavity and adnexae. Ovarian volume, antral follicle count and presence or absence of PCO pattern should be noted.

Hysterosalpingography (HSG): This is done on Day 8 of periods. It helps in evaluation of uterine cavity and to check the tubal patency.

Diagnostic laparoscopy and hysteroscopy may be required in certain cases to establish the exact diagnosis.

Pre-procedural work-up for IUI is summarized in Table 4.

Tests to rule out tuberculosis: These are especially important in developing countries (Table 5).

Table 4. Pre-procedure Work-up for IUI

Physical parameters	Clinical	Endocrinological
Anthropometry	**Transvaginal sonography**	**Day 2/3 hormones**
Weight (kg)	Evaluation of uterus and cavity	Serum LH, FSH, E2
Height	Measurement of ovarian volume	TSH, prolactin, SHBG, F. insulin
	No. of antral follicles, PCOS/non-PCOS	
Body mass index	**HSG** (to evaluate uterine cavity and tubal status)	
Waist-hip ratio	**Diagnostic laparoscopy and hysteroscopy** (if necessary): for evaluation of cervical, tubal, uterine and ovarian factors	**Day 21 hormones:** progesterone

PCOS = Polycystic ovary syndrome; LH = Luteinizing hormone; FSH = Follicle-stimulating hormone; E2 = Estradiol; TSH = Thyroid-stimulating hormone; SHBG = Sex hormone-binding globulin; HSG = Hysterosalpingography.

Evaluation of male partner

It involves evaluation of various clinical and laboratory parameters as shown in Table 6.

Pre-requisites for IUI

- Age less than 40 years.
- Patient capable of spontaneous or induced ovulation.
- At least 1 patent fallopian tube with good tubo-ovarian relationship.
- Sperm count of more than 10 million/mL pre-wash or a post-wash count of >3-5 million motile sperms with percentage motility of more than 40%.
- Easy access to the uterine cavity via a negotiable cervical canal.

Table 5. Tests to Rule Out Tuberculosis

- CBC with ESR
- Chest X-ray
- Mantoux test
- Endometrial biopsy
- TB ELISA IgG and IgM
- TB-PCR
- Bactec

CBC = Complete blood count; ESR = Erythrocyte sedimentation rate; TB = Tuberculosis; ELISA = Enzyme-linked immunosorbent assay; Ig = Immunoglobulin; PCR = Polymerase chain reaction.

Table 6. Evaluation of the Male Partner

Clinical parameters	Laboratory parameters: Investigations
Detailed history and examination	Semen analysis and culture
Hair distribution scoring	Normospermia: No further investigations
Examination of testis, vas, epididymis	Astheno/necrospermia: Antisperm antibody
Volumes of testis in case of azoospermia	Teratospermia: Check for DM
	Moderate oligospermia: Sperm function test
	Severe oligospermia: Vasogram, color Doppler scrotum
	Azoospermia: Testicular biopsy/ FNA testis
	Endocrine evaluation: LH, FSH, Testosterone, PRL, TSH

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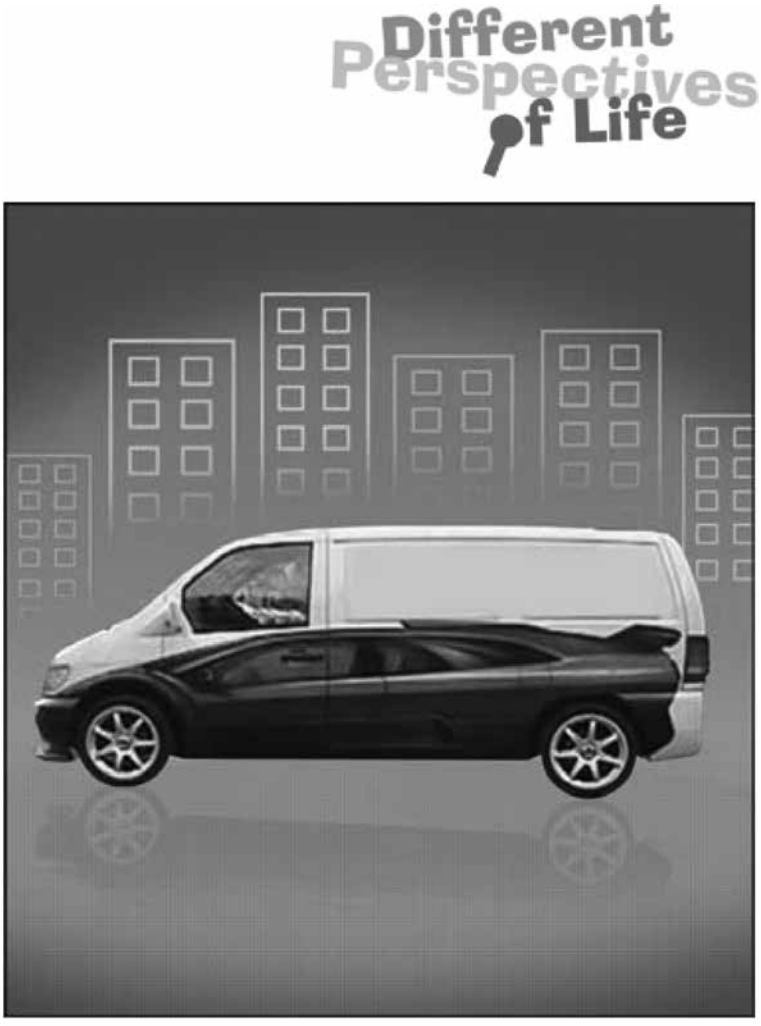

It appears as different vehicles but in reality there is only one vehicle.

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Micronutrient Bridge in Infectious Diseases and Its Immunological Role

SHANMUGAM A

ABSTRACT

Nutrition plays an important role in child health. Nutrition is an exogenous factor which plays a vital role in metabolism and growth. Micronutrients are the nutrients, which help promote the immunological function and help in maturation and proliferation of T-cells and B-cells. Here, we review the role of micronutrients in infectious diseases and their essentiality towards the concept of immunology.

Keywords: Nutrition, micronutrients, immunity, immunology

Nutrition plays an important role in child health. Nutrition is an exogenous factor which plays a vital role in metabolism and growth. Micronutrients are the nutrients which help promote the immunological function and help in maturation and proliferation of T-cells and B-cells. There are certain micronutrients, like iron, folic acid, vitamin A and vitamin B complex, copper and selenium that help in the maturation of T-cells and B-cells, which, in turn, increases the antibody response to fight against infections. The risk of common diseases and death is due to deficiency and depletions of micronutrients in the diet. So, each and every micronutrient has recommended dietary allowances (RDA) per weight in kilogram which is standardized by the World Health Organization (WHO). The appropriate RDA value of micronutrients should be given to the child to increase the immunity and phagocytic activity. According to the UNICEF, micronutrients are the nutrients which are not only responsible for physical growth and immune cell function but they also cater to the hormonal metabolism, biochemical mediators and sexual maturation. Micronutrient deficiency can cause serious health problems, such as reduced resistance to infectious diseases that can lead to death and mental retardation. Children with subclinical deficiencies of micronutrients and under nutrition are prone to day-to-day infections, leading to death. This paper reviews the role of micronutrients in infectious diseases and their essentiality towards the concept of immunology.

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ROLE OF MICRONUTRIENTS IN IMMUNE RESPONSES

Iron

Iron is the one of major micronutrients which plays a vital role in the human body for oxidation-reduction reactions. It is a component of oxygen carrying compounds hemoglobin and myoglobin. Iron deficiency serves as a cause of threatened infectious diseases. If iron deficiency is not corrected, it leads to anemia. More than 2 billion people are affected with iron deficiency. Iron deficiency anemia is common in the following situations:

- Social disadvantages such as poverty, poor housing and lower level of parental education
- Psychological disadvantage - It is due to insufficiency of iron and heme concentration in the blood, which leads to neurological lack of stimulation
- Biological disadvantage - There are certain situations where the biological disease leads to low birth weight, high infection rates and other nutritional deficiencies.

Iron deficiency is known to alter the emotional state of infants. Iron and folic acid can be obtained by consuming green leafy vegetables. Traditional food practices such as fermentation can improve the availability of iron in the diet. Deworming and breastfeeding will decrease iron deficiency anemia. Environmental sanitation plays a vital role in reducing the risk of infection.

Iron plays a vital role in the T-cell development which also generates some reactive oxygen and free radicals to kill the pathogens. The recommended supplementation of iron is 7-8 mg daily to overcome infections and leads to exaggerated immunity.

Zinc

Zinc is a vital nutrient. Zinc plays a key role in human metabolism and perpetuation of genetic materials for the enhancement of central dogma of molecular biology, which includes translation of ribonucleic acid (RNA) and transcription of proteins. The major source of zinc is through diet to enhance the immune function of the human body. Zinc is an important constituent of metalloenzymes and plays an important role in the synthesis of deoxyribonucleic acid (DNA) and RNA.

Zinc acts as a cofactor and enhancer for cell replication and intestinal mucosal cells regeneration. It is essential for wound healing and for epithelial cells turnover to maintain healthy skin. Zinc deficient children are prone to infections and cellular tissue damage. Zinc deficiency leads to regression of gene expression, alters the immunity level in the host, alters maturation and gonads development and pregnacy outcomes. Diarrhea is associated with increased amount of zinc excreted in feces. Dietary deficiency is common since the bioavailability of zinc is reduced by the co-existence of fiber and phytate in foods of vegetable origin. Zinc is an enhancer of T-cell production and subtypes switch. It stimulates the complement system leading to enhancement of both pathways of complement activation. Zinc plays a role in phagocytosis which leads to reduction in the risk of pneumonia, common cold symptoms and reduction in infectious diseases.

Selenium

Selenium is a mineral for the stimulation of antibodies. It is an antioxidant mineral. Selenium is incorporated into protein to make selenoproteins. These are important antioxidant enzymes called glutathione peroxidase. Antioxidants like vitamin C and E help to prevent cardiovascular disease, age-related disease, skin aging, ocular illness and cancer. Selenium is a good immune stimulant for several viral infections. Deficiency of selenium leads to loss of antioxidant host defense and decreased function of white blood cells and natural killer cell function.

Vitamin A

The deficiency of vitamin A leads to the development of impaired resistance to infection and diminished function of innate immunity along with loss of B- and T-cells.

Vitamin B Complex

Vitamin B1, otherwise called as thiamine, and vitamin B2, aid in antibody response. Vitamin B3 (niacin) and B5 (pantothenic acid) play a vital role in the production and release of antibodies. Pyridoxine helps in T- and B-cell production and maturation whereas biotin and folic acid help in the production and maturation of T-cells, which mediate the humoral immune response of the body. Cyanocobalamin increases the production and promotion of NK-cell activity and aids in T- and B-cell production.

Vitamin C

Vitamin C is an antioxidant which protects the cells from redox stress to control the infection. It has an antiviral activity which aids in the symptoms of common cold. Vitamin C improves innate and adaptive immune function. Vitamin C leads to collagen synthesis and it tends to help in the increase of free radical production.

Vitamin D

Vitamin D plays a vital role in the phagocytic activity, and inflammatory responses, which are promoted by specific T-cell subtypes. It is also important in wound healing process.

Vitamin E

Vitamin E deficiency - Immune issues: loss of phagocytic response and B-cell dysfunction. Vitamin E deficiency causes difficulty in controlling viral infection.

CONCLUSION

Micronutrients are very important for the growth and metabolism in child health and increase the immune function against infectious diseases. Each and every micronutrient should be supplemented by RDA and WHO guidelines. Nutrients supplementation improves the physical and immunological growth in children and adults. Healthy children ensure the optimal resource development of a country.

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Emerging Role of Combination of Doxofylline and Acebrophylline in the Managment of COPD

CHIRAG AMITBHAI GANGAJALIA

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide. Airway mucus hypersecretion has been observed in almost 50% of COPD patients. The outcome of the twin problems of airway mucus hypersecretion and air flow limitation in COPD patients accelerates the decline in lung function, which is typically associated with an increased rate of acute exacerbations of COPD induced by bacterial and viral infection and leads to increased rates of hospitalization. Current evidence indicates that doxofylline has comparable bronchodilator efficacy as theophylline but it is associated with a better safety profile than theophylline and has a favorable risk-to-benefit ratio. Acebrophylline is an airway mucus regulator with anti-inflammatory action. Acebrophylline modulates the pathology in obstructive airway disease at several steps in the pathogenesis of the disease. The role of doxofylline and acebrophylline in COPD has been proven.

Keywords: COPD, doxofylline, acebrophylline

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide. COPD affects the patients' ability to work and is associated with a negative impact on their quality of life and life expectancy. Airway mucus hypersecretion is now recognized to play an important role in the pathophysiological and clinical manifestations of COPD, bronchial asthma, bronchiectasis and other chronic inflammatory airway diseases. Emerging studies have demonstrated that inflammation and oxidative stress are key modulators in the pathogenesis of chronic inflammatory airway diseases and affect their clinical outcomes. They are postulated to trigger excessive mucus production and secretion by glands and goblet cells. The critical role of airway mucus hypersecretion in COPD must be fully recognized. Chronic cough and expectoration due to airway mucus hypersecretion, reduce airflow and exercise capacity and increase the risk of acute exacerbation, mortality and has a poor prognosis in COPD patients. The American Thoracic Society and European Respiratory Society have officially recognized that airway mucus hypersecretion plays an important role in common respiratory diseases.

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AIRWAY MUCUS HYPERSECRETION AND COPD

The chief feature of COPD is a persistent, progressive airflow limitation associated with chronic abnormal inflammatory responses to triggers such as harmful particles or gases in the respiratory tract and lungs. If a patient has airway mucus hypersecretion, the clinical manifestation would be chronic cough and expectoration. Individuals with such symptoms have three times higher likelihood of suffering from COPD than healthy individuals. These symptoms become manifest irrespective of smoking. In fact, paroxysmal cough is known to be an independent risk factor for COPD.

As compared to normal individuals, COPD patients have significantly greater number of goblet cells in the airway epithelium and these cells secrete significantly more mucoprotein. Airway mucus hypersecretion has been observed in almost 50% of COPD patients. The airways that are clogged by mucus reduce airflow and are postulated to play a role in the pathogenesis of COPD. A 3.5-fold greater risk of dying is postulated in COPD patients if they have airway mucus hypersecretion as compared to those COPD patients who do not have airway mucus hypersecretion.

The outcome of the twin problems of airway mucus hypersecretion and air flow limitation in COPD patients accelerate the decline in lung function, which is typically associated with an increased rate of acute exacerbations

of COPD induced by bacterial and viral infection, and leads to increased rates of hospitalization.

The processes involved in chronic cough and expectoration have been implicated in causing the accelerated dynamic lung hyperinflation. This may help explain why chronic cough and expectoration are considered to be independent risk factors for decreased exercise capacity in COPD patients. Patients with COPD who have chronic mucus hypersecretion (chronic bronchitis phenotype) have a greater deterioration in the quality of life than those without chronic mucus hypersecretion.

TREATMENT OF COPD PATIENTS WITH AIRWAY MUCUS HYPERSECRETION

The primary goals of COPD management are to improve the functional status of the patient and quality of life by improving symptoms, preserving optimal lung function and preventing recurrence of exacerbations. Most of the drugs used for the management of COPD are aimed to target the four potentially reversible causes of airflow limitation, namely bronchial smooth muscle contraction, bronchial mucosal congestion and edema, airway inflammation and increased airway secretions.

Bronchodilators are the cornerstone of any COPD treatment regimen. They dilate the airways and result in a decrease of airflow resistance. This increases airflow and decreases dynamic hyperinflation. A lack of response in pulmonary function testing should not prevent their use. Bronchodilators primarily provide symptomatic relief but have no effect on disease progression or mortality. The initial choice of bronchodilators remains a matter of debate. Conventionally, β_2-agonists were considered first-line and anticholinergics were added as adjunctive treatment options. Monotherapy with either agent or combination therapy with both are acceptable options. The adverse effect profile may help to guide therapy. The predictable adverse effects of β-agonists include tachycardia and tremors. Rarely, β_2-agonists may also precipitate a cardiac arrhythmia. Reported adverse effects of anticholinergics include dry mouth, dry eyes, metallic taste and prostatic symptoms. The Global Strategy for the Diagnosis, Management and Prevention of COPD (GOLD) guidelines include xanthines, such as theophylline, as bronchodilators in patients with stable COPD. Theophylline is one of the most widely prescribed drugs worldwide for the management of COPD. Theophylline leads to an improvement in both forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) in clinically stable COPD patients. It increases exercise tolerance, probably by reducing air trapping and has actions on the peripheral airways. This may be the reason why some patients with COPD have considerable symptomatic improvement even without any increase in spirometric values with theophylline. Another clinically relevant observation seen in severe COPD patients has been the significant clinical deterioration after withdrawal of theophylline despite therapy with other bronchodilators. This is indicative of the additional value of theophylline in COPD. In the long-term (over 12 months), theophylline seems more effective than placebo at reducing the frequency and duration of acute exacerbations of COPD. But, theophylline has several limitations as compared to the alternative xanthine drug doxofylline (Table 1). In many treatment guidelines, theophylline is considered to be a second- or third-line therapy owing to its narrow therapeutic window and propensity for pharmacological interactions. This makes its use challenging, particularly in elderly patients with comorbidities who are treated with multiple classes of drug.

Current evidence indicates that doxofylline has comparable bronchodilator efficacy as theophylline but it has a better safety profile than theophylline and a favorable risk-to-benefit ratio. Doxofylline could be an attractive alternative to theophylline in the treatment of patients with COPD. The use of an orally active drug that is safe such as doxofylline must be encouraged, especially in COPD patients, who find inhalers difficult to use or who do not get adequate relief of symptoms from other drugs.

A meta-analysis of 20 trials (n = 820) indicated that doxofylline administration induced a significant ($p < 0.001$) increase in FEV_1 of 8.20% (95% confidence interval [CI] 4.00-12.41; I^2 93%) and 317 mL (95% CI 19-439; I^2 87%) as compared with baseline. The GRADE analysis demonstrated a high quality of evidence for the effect of doxofylline on FEV_1 in COPD patients. Doxofylline has a better tolerability profile than theophylline owing to low secretagogue activity leading to superior gastric tolerability. Sleep architecture and quality remained minimally affected by doxofylline unlike theophylline. Another recent meta-analysis of patients of COPD treated with xanthines (14 studies and 998 COPD patients) indicated that doxofylline was superior to aminophylline, bamiphylline and theophylline. Doxofylline seems to be the best xanthine for the treatment of COPD.

Doxofylline does not increase myocardial oxygen demand. This fact is clinically relevant since many COPD patients suffer from cardiovascular comorbidities. Doxofylline does not affect atrial frequency or the

Table 1. Comparison of Doxofylline and Theophylline

	Doxofylline	Theophylline
Action and adverse effects	More selective in action. Doxofylline is postulated to have less affinity for the adenosine A1 and A2 receptors. Doxofylline has no significant effect on any of the known phosphodiesterase isoforms. Doxofylline appears to be both bronchodilator and anti-inflammatory. Unlike theophylline, doxofylline does not antagonize calcium channels and does not interfere with the influx of calcium into the cells, which probably reduces the cardiac side effects.	Theophylline is nonselective for the phosphodiesterase enzyme. Theophylline has an antagonistic action on the adenosine A1, A2a and A2b receptors. This is responsible for its cardiac and central nervous system (CNS) stimulatory side effects.
Metabolism and drug interactions	No significant effect on CYP1A2, CYP2E1 and CYP3A4 isoenzymes. No significant drug-drug interactions.	Interference with the cytochrome enzymes CYP1A2, CYP2A13, CYP1A1, CYP2E1. Interactions with many drugs, including cimetidine, phenytoin, macrolides, fluoroquinolones, calcium-channel blockers, fluconazole, rifampin.
Food interactions	No known food interactions.	High-protein diet has been demonstrated to increase theophylline clearance by 30%.
Gastric secretagogue action	Very low secretagogue activity.	Increased gastric acid secretion and smooth muscle relaxation.
Cardiac safety	Cardiac safety proved. No effect on sleep rhythm, gastric secretions, heart rate-rhythm and CNS functioning.	Adverse cardiac effects caused by adenosine antagonism. Sleep architecture and quality substantially and significantly disrupted.
Monitoring of patient	No monitoring of plasma levels necessary.	Theophylline has a narrow therapeutic index and hence monitoring of plasma levels is obligatory.

diastolic pressure unlike theophylline, which often causes hypotension.

Doxofylline demonstrates significant anti-inflammatory activity in the lung, which can result in significant steroid sparing activity. Doxofylline has been shown to improve pulmonary function tests as well as clinical symptoms and decrease the incidence of adverse effects and rates of use of emergency bronchodilators in clinical trials (Table 2).

ROLE OF MUCOLYTICS AND MUCOKINETICS

Mucolytic drugs are associated with diverse biological effects, such as reduction of airway inflammation, antioxidant and antiviral effects, reduction of mucin production and improvement of goblet cell hyperplasia.

Mucolytics have been administered to COPD patients not receiving inhaled corticosteroids since regular treatment with mucolytics may reduce exacerbations and modestly improve health status.

Mucolytics are useful in preventing COPD exacerbations as maintenance add-on therapy to patients with frequent exacerbations. The effectiveness of mucolytics is independent of the severity of airway obstruction and the use of inhaled corticosteroids. In a meta-analysis of 11 studies, mucolytics significantly reduced the rate of exacerbation versus placebo (odds ratio [OR] 0.51, 95% CI, 0.39-0.67; $p < 0.001$).

Acebrophylline is an airway mucus regulator with anti-inflammatory action. Acebrophylline modulates the pathology in obstructive airway disease at several steps in the pathogenesis of the disease. The acebrophylline molecule contains ambroxol which facilitates the biosynthesis of pulmonary surfactant. The resulting reduction in the viscosity and adhesivity of the mucus greatly improves cilliary clearance. Acebrophylline inhibits intracellular phosphodiesterase and facilitates bronchial muscle relaxation by increasing cyclic adenosine monophosphate (cAMP) levels. By diverting phosphatidylcholine towards

Table 2. Studies on Efficacy and Safety of Doxofylline versus Theophylline in Asthma

Study	Design and size	Study groups	Outcomes
Goldstein et al	Randomized controlled trial (n = 346; age: 35.5 ± 17.0 years)	Oral treatment with either doxofylline 400 mg t.i.d. (high-dose), doxofylline 200 mg t.i.d. (low-dose), theophylline 250 mg t.i.d. (active control) or placebo	Significant increase in FEV_1 in the doxofylline group when compared to placebo and theophylline groups. Significantly more number of patients treated with theophylline had to interrupt treatment due to adverse events (p = 0.001).
Melillo et al	Randomized controlled trial (n = 139; age: 17-77 years)	Doxofylline and theophylline	Both drugs significantly improved spirometric parameters and reduced salbutamol consumption. Doxofylline was better tolerated than theophylline.

surfactant synthesis, acebrophylline makes phosphatidylcholine unavailable for the synthesis of inflammatory mediators such as the leukotrienes and results in anti-inflammatory effect. Acebrophylline has been observed to reduce the frequency of episodes of bronchial obstruction and reduces the need for β_2-agonists and improves indexes of ventilatory function. Acebrophylline use is not associated with chest pain, palpitation, tremor, tachycardia, insomnia and sleep disturbance.

A total of 30 COPD patients (27 males and 3 females; mean age of 62.6 ± 3.9 years), were recruited in an open study to evaluate the clinical efficacy and the safety of a short-course of treatment with 100 mg acebrophylline, twice-daily for 14 days. There was a progressive improvement in signs and symptoms with auscultatory pattern and dyspnea. A significant improvement or normalization of the respiratory function indices was observed ($p < 0.01$) at the endpoint values when they were compared with baseline values. A significant increase of PaO_2 ($p < 0.01$) and a significant decrease of $PaCO_2$ values occurred at the end of the treatment ($p < 0.01$). Acebrophylline was well-tolerated by every patient.

CONCLUSION

COPD management requires a personalized approach because of heterogeneity observed in patients. The one-size-fits-all approach to only address the traditional symptoms and risk of exacerbations is now proving to be inadequate.

The therapeutic approach must take into account the COPD heterogeneity. A more relevant evidence-based approach to drug therapy such as combination of xanthenes, like doxofylline and mucolytic drugs, such as acebrophylline, can be used in an attempt to respond to unmet therapeutic needs in COPD patients. Secondly, since adherence to inhaled devices may be low, the use of orally active drugs that are safe and effective should be encouraged. The role of doxofylline and acebrophylline in COPD has been proven. Using these drugs together in COPD patients with mucus hypersecretion can help to address some of the prevailing issues of management in this patient population.

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A Prospective Study to Evaluate the Effectiveness of Negative-pressure Wound Therapy for Management of Acute Traumatic and Chronic Wound in Orthopedics

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ABSTRACT

Introduction: Acute and chronic wounds affect at least 1% of the population. Regardless of etiology, wounds are difficult to treat. Modern wound healing concepts have convincingly been shown to give higher wound closure rates compared with traditional wet gauze dressings. **Objectives:** To evaluate the results and benefits obtained from the use of negative-pressure wound therapy (NPWT) in patients with acute and chronic wounds in orthopedics. **Material and methods:** This was a prospective study of 26 patients (16 males and 10 females, mean age 41.76 years) with acute and chronic wounds treated using NPWT. The acute wounds were caused by trauma (road traffic accident [RTA], fall from height, crush injury). The chronic wounds stated in this study were from pressure sores in paraplegic patients. The treatment system used was VAC (vacuum-assisted closure, KCI, San Antonio, United States), applied to the wound in continuous mode from 100 to 125 mmHg. **Results:** The mean length of the use of NPWT was 20 days. The use of VAC led to a mean reduction of 37% in the wound area (157.12-120.57 cm^2; $p < 0.05$). Exposed tendons and bone were successfully covered with healthy granulation tissue in all cases. In all patients, coverage with granulation tissue was achieved and followed by a skin graft. No major complication occurred that was directly attributable to the treatment. **Conclusion:** NPWT eases the process of wound healing by formation of local infection free healing tissue in a short period of time and reduces hospital stay and morbidity.

Keywords: Negative-pressure wound therapy, wound healing, wounds and injuries, pressure sore

Dealing with wound is a matter of knowledge and experience. Different etiologies such as trauma and infection may lead to acute and chronic wounds. Regardless of etiology, wounds are difficult to treat if co-existing factors (e.g., infection or diabetes mellitus) prevent regular wound healing. Wounds represent a significant risk factor for hospitalization, amputation, sepsis and even death, and from the patient's perspective, wound therapy is often uncomfortable or painful. Modern wound healing concepts include different types of moist dressings and topical agents, although only a few of these treatments have convincingly been shown to give higher wound closure rates compared with traditional wet gauze dressings. Negative-pressure wound therapy (NPWT) is a newer noninvasive adjunctive therapy system that uses controlled negative-pressure, using vacuum-assisted closure (VAC) device, to help promote wound healing by removing fluid from open wounds, preparing the wound bed for closure, reducing edema and promoting formation and perfusion of granulation tissue.

Negative-pressure wound therapy, also known as VAC dressing, provides the following benefits: control of drainage of fluids, reduction of local edema, reduction of bacterial load and early development of granulation tissue by angiogenic stimulation. The aim of the present study is to evaluate the effect of NPWT in management of acute and chronic wounds in the orthopedic set-up.

MATERIAL AND METHODS

The present study was undertaken at ESI Hospital, Basai Darapur, New Delhi, India. Over a 1 year period, from July 2017 to July 2018, 26 patients (16 males and 10 females; Table 1) with acute and chronic wounds were treated with NPWT device (VAC, KCI, San Antonio, United States).

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Table 1. Patients Demographic Data

Sex	Number	Percentage (%)
Male	16	61.53
Female	10	38.46

The following inclusion criteria were adopted: Presence of positive culture, use of vacuum drainage for over 5 days, purulent local drainage and tissue necrosis.

Patient exclusion criteria included: Small-sized acute wounds with no comorbid conditions, age less than 15 years, mental disorders, systemic sepsis, malignancy and osteomyelitis.

All 26 patients were followed for minimum 6 months (mean 11 months, range: 6-18 months). Mean patient age was 41.76 years (range: 16-67 years). In all acute wounds, VAC was used when granulation tissue started to appear. In regard to chronic wounds, the lesion was debrided to refresh the bed and the edges before application of VAC. On average, wound was assessed every 4th day in term of the size, the defect and evolution of state of the wound. Final procedure after VAC therapy and complications related to the use of this therapy were evaluated. Patients were followed-up regularly in the OPD with minimum follow-up period of 6 months.

RESULTS

In the present study, 26 patients (16 males and 10 females) with mean age 41.76 years (16-67 years) were included. Out of the 26 patients, 20 patients had acute post-traumatic wound and 6 patients were having chronic wound. All patients were given a mean of 12 days of intravenous antibiotic therapy (8-42 days). The median duration of VAC therapy was 20 days (5-50); on average, the dressing was changed every 4th day.

A 37% mean reduction of wound area was observed, from 157.12 cm^2 to 120.57 cm^2 after VAC application. In all patients, coverage with granulation tissue was achieved and followed by a skin graft. Table 2 summarizes the results of VAC therapy.

Almost all patients achieved an improvement in the final appearance of the wound site, with infection eradication. No complications that could be directly attributed to the use of NPWT, such as deep bleeding or worsening local infection, were observed. Three patients had mild local itching, which was successfully treated with oral medication, allowing for the maintenance of treatment.

Figures 1-3 depict the wound before VAC, after VAC and after skin grafting, respectively. Figures 4 and 5 also depict a wound before and after VAC.

Table 2. Reults of VAC Therapy

Age	Area before VAC	Area after VAC	Days	VAC exchange	Procedure
16	25	18	10	3	Skin grafting
46	300	220	46	12	Skin grafting
25	12	5	12	3	Skin grafting
46	170	128	30	7	Skin grafting
36	89	76	36	10	Skin grafting
30	65	44	16	4	Skin grafting
32	68	49	16	4	Skin grafting
49	100	70	25	6	Skin grafting
53	129	119	20	5	Skin grafting
39	96	50	25	6	Skin grafting
58	10	7	22	5	Skin grafting
67	46	40	20	6	Skin grafting
39	280	130	25	4	Skin grafting
25	320	260	16	5	Skin grafting
32	26	22	20	5	Skin grafting
29	10	6	5	2	Skin grafting
60	128	96	30	5	Skin grafting
35	125	94	26	5	Skin grafting
62	430	310	50	12	Skin grafting
59	16	12	16	4	Skin grafting
39	280	264	18	5	Skin grafting
43	87	55	19	5	Skin grafting
49	432	380	30	6	Skin grafting
46	360	260	18	5	Skin grafting
39	320	255	18	5	Skin grafting
35	160	120	16	4	Skin grafting

Figure 1. Wound before VAC.

Figure 2. Wound after VAC.

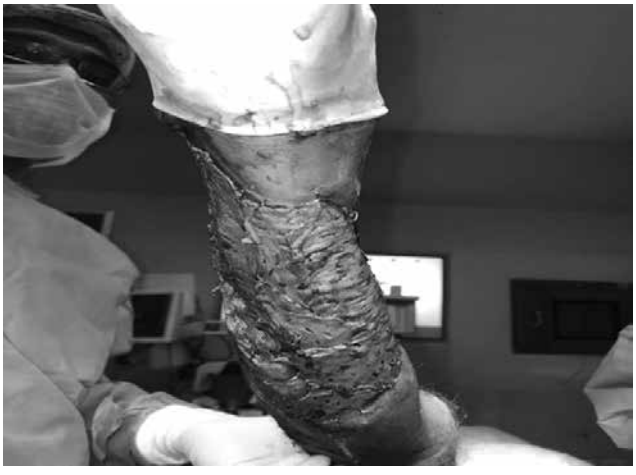

Figure 3. Wound after skin grafting.

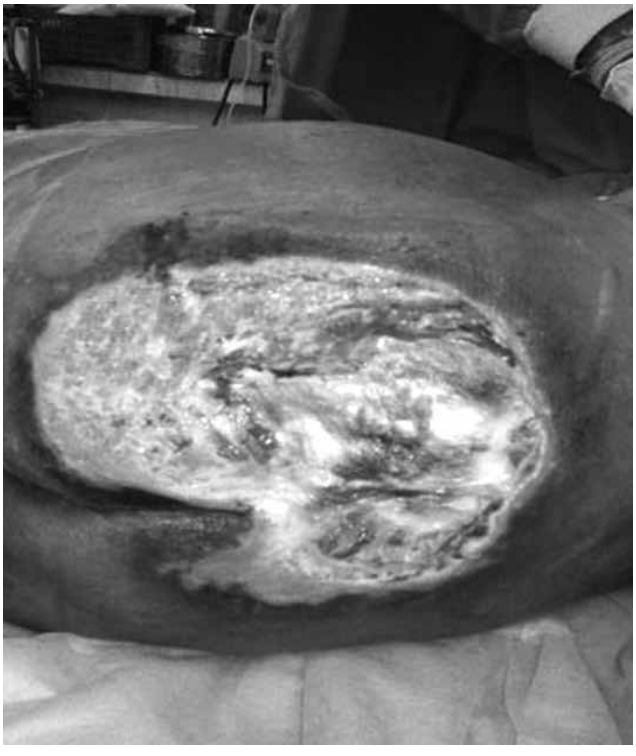

Figure 4. Wound before VAC.

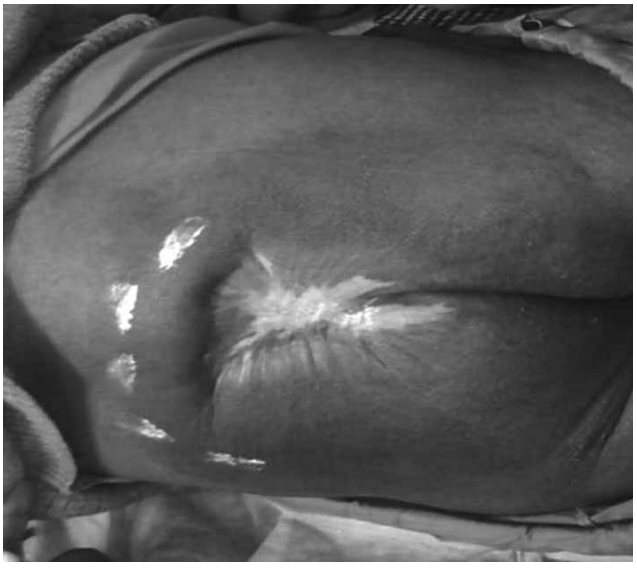

Figure 5. Wound after VAC.

DISCUSSION

Numerous papers have been published on VAC therapy, which suggest that the technique may have an important role to play in the management of chronic or infected wound. The topical use of NPWT has been widely studied in the literature over the past 20 years. A vast majority of clinical trials has shown the effectiveness of this therapy in the treatment of superficial wounds. The localized use of NPWT in infected wounds offers advantages such as wound drainage, angiogenesis stimulation, proteinase excretion and decreased local and systemic bacterial load.

In the present study, the mean time of VAC use was 20 days and the mean duration of intravenous antibiotic therapy was 12 days, in contrast with data in the literature indicating the use of intravenous antibiotics for 6 weeks for patients with infected wounds. In this treatment period, the dressing was changed every 4th day, providing comfort to the patient and the nursing staff, while maintaining a clean dressing without the need for daily changes.

In the present study, healthy infection-free granulation tissue was obtained in all patients, alongside a significant decrease in lesion size. These data are similar to those obtained by Gregor et al, who, in a systematic review to assess the effectiveness and safety of VAC compared to conventional therapies for complex wounds, observed a significant reduction of the lesion area for those treated with VAC, without significant adverse effects. In the present study, there were no major complications, such as hemorrhage, etc.

CONCLUSION

NPWT therapy adheres to DeBakey's principles of being short, safe and simple. The VAC system eases the process of wound healing in chronic and acute wounds with reduction in morbidity and hospital stay. NPWT facilitates the formation of a local infection-free healing tissue in a short period of time, which reduces the need for complex surgical procedures for the final coverage of important structures. From this present study, it is concluded that NPWT is a safe, effective and fast alternative to conventional dressing in the treatment of acute and chronic wounds. There is no significant complication associated with the use of NPWT. The main limitation of the present study, apart from the small sample size, was the lack of a control group, which did not allow for a direct comparison of patients treated in the same center with conventional method or NPWT. Future studies with large sample size and control group are needed to accurately assess the benefit of VAC therapy.

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UNICEF Launches #VaccinesWork Campaign to Inspire Support for Vaccines

UNICEF launched a new global campaign on 24 April to emphasize the power and safety of vaccines among parents and wider social media users.

The campaign ran alongside World Immunization Week from 24 to 30 April to spread the message that together communities, including parents, can protect everyone through vaccines. This year, UNICEF is partnering with the Bill and Melinda Gates Foundation, the WHO, and Gavi, the Vaccine Alliance to encourage even greater reach. The Bill and Melinda Gates Foundation will contribute USD$ 1 to UNICEF for every like or share of social media posts using the hashtag #VaccinesWork in April, up to USD$1 million, to ensure all children get the life-saving vaccines they need…

Indian Journal of Clinical Practice, Vol. 29, No. 12, May 2019

ALBI and Child-Pugh Score in Predicting Mortality in Chronic Liver Disease Patients Secondary to Alcohol: A Retrospective Comparative Study

NAGARAJA BS*, MADHUMATHI R*, SANJEET SB†

ABSTRACT

Background/Aims: The severity of liver dysfunction in chronic liver disease (CLD) is often estimated with Child-Pugh (CTP) classification or model for end-stage liver disease (MELD) score. The albumin-to-bilirubin (ALBI) score is a new model for assessing the severity of liver dysfunction, which is simple and more objective. In the present study, we aimed to retrospectively compare the performance of ALBI score with Child-Pugh score for predicting the mortality in patients with CLD. **Material and methods:** Data of patients with CLD, irrespective of etiology, were retrospectively reviewed. Child-Pugh score and ALBI score were calculated for the patients and results from receiver operating characteristic (ROC) curves were analyzed. **Results:** The study was conducted on 299 patients of CLD; age distribution was between 20 and 85 years with mean age of patients being 45.7 ± 10.94 years, sex ratio male: female 265:34 with mortality rate of 19.73%. The area under curves (AUC) of ROC of ALBI and Child-Pugh were 0.586 and 0.549, respectively. **Conclusion:** Ability of ALBI score for predicting mortality was comparable with that of Child-Pugh score but Child-Pugh score of >10 had better performance of predicting mortality as compared to ALBI score.

Keywords: Chronic liver disease, liver cirrhosis, alcoholic liver disease, Child-Pugh score, MELD score, ALBI score

The World Health Organization (WHO) estimates 2 billion people as consuming alcohol and 76.3 million as having alcohol use disorders. Thirty percent of Indian adults use alcohol, among which 4-13% are daily consumers. The alcohol consumption rose by 30% in 2015. An estimate of 14 million has been made as heavy consumers. Looking at this data, the burden of alcoholic liver disease on the community is obvious. Alcohol abuse leads to spectrum of liver diseases ranging from fatty liver, alcoholic hepatitis to cirrhosis and hepatocellular carcinoma. Liver cirrhosis is a common cause of death worldwide.[1,2] The accurate prognostification of liver cirrhosis is important in our daily practice. The most commonly used tool to predict the prognosis of liver cirrhosis is Child-Pugh score.[3] However, it has been established for a long time, and its components are selected primarily based on the surgeons' experiences. Model for end-stage liver disease (MELD) score is another tool for prognostic assessment of liver cirrhosis.[4,5] Until now, there is lots of controversy regarding the comparison of Child-Pugh versus MELD scores.[6-8] Of late, albumin-to-bilirubin (ALBI) score has been proposed as a novel, simple and readily available model calculated using mathematical formula $-0.085 \times (\text{alb g/L}) + 0.66 \times \log (\text{bil } \mu\text{mol/L})$.

The ALBI score, by combining serum albumin and bilirubin, is a new model for assessing the severity of liver dysfunction. Johnson and colleagues reported that the ALBI score more accurately predicts patients' mortality without requiring subjective determinants of liver failure, including ascites and encephalopathy, in patients with hepatocellular carcinoma.[9]

A retrospective study also investigated the prognostic significance of the ALBI score among patients with primary biliary cirrhosis.[10] It was found that the ALBI score seems to outperform other scores (such as Child-Pugh and MELD score) for predicting the occurrence of hepatic events in such patients. Furthermore, Chen et al[11] demonstrated that ALBI score had a significantly better performance for long-term survival prediction in patients with hepatitis B virus (HBV)-related cirrhosis than the Child-Pugh or MELD

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scores. Herein, we attempted to study the ALBI score for in-hospital death in alcoholic cirrhotic patients.

AIMS AND OBJECTIVES

- To calculate ALBI and Child-Pugh score in chronic liver disease (CLD) patients secondary to alcohol.
- To assess the utility of ALBI in predicting the mortality in CLD patients secondary to alcohol.
- To evaluate the discriminative abilities of ALBI and Child-Pugh score in predicting the in-hospital mortality in CLD patients secondary to alcohol.

MATERIAL AND METHODS

Study Design

The study was conducted at Bowring and Lady Curzon Hospital (Attached to Bangalore Medical College and Research Institute). Cirrhotic patients secondary to alcohol admitted in the hospital between January 2017 and December 2017 were retrospectively reviewed and the data of the patients were collected. Approval was obtained from the Institutional Ethical Committee.

Inclusion Criteria

- Age >18 years.
- Liver cirrhosis patients secondary to alcohol.

Exclusion Criteria

- CLD due to HBV, hepatitis C virus (HCV), malignancy, metabolic causes and autoimmune hepatitis.

Method of Collection of Data

Detailed history and clinical examination was done for all patients. Routine investigations like complete hemogram, renal function test, liver function test, serum electrolytes, human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), HCV, prothrombin time/International Normalized Ratio (PT/INR), activated partial thromboplastin time (APTT), ultrasonography (USG) abdomen and other relevant investigations were noted. Diagnosis of liver cirrhosis was established by USG abdomen with shrunken liver with altered echo texture.

ALBI score and Child-Pugh score (Table 1) were calculated and compared.

ALBI score = (–0.085 × [alb g/L] + 0.66 × log [bil μmol/L])

Table 1. Calculation and Comparison of ALBI and Child-Pugh Score

Parameter	Numerical score		
	1	2	3
Ascites	None	Slight	Moderate-to-severe
Encephalopathy	None	Slight-to-moderate	Moderate-to-severe
Bilirubin (mg/dL)	<2.0	2-3	>3.0
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (Prolonged in seconds)	1-3 s	4-6 s	>6.0

Child-Pugh Class A = 5-6 points; Child-Pugh Class B = 7-9 points; Child-Pugh Class C = 10-15 points.

Method of Statistical Analysis

All statistical analyses were performed using Medcalc software. Continuous data were expressed as the mean ± SD (standard deviation) and median with minimum and maximum. Categorical data were expressed as the frequency. The receiver operating characteristic (ROC) curve were performed to identify the discriminative ability of ALBI and Child-Pugh score in predicting in-hospital mortality. The area under the curve (AUC) were calculated and compared. The best cut-off value was selected as the sum of sensitivity and specificity was maximal. The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) were reported.

RESULTS AND ANALYSIS

The sample size in our study was 299 patients. The age distribution was between 20 and 85 years with mean age of patient being 45.7 ± 10.94 years. Two hundred sixty-five were males and 34 were females. Among 299 patients, 59 patients had in-hospital mortality and 240 were discharged with mortality percentage of 19.73%.

Comparison of In-Hospital Mortality with ALBI and Child-Pugh Scores

The in-hospital morality was 19.73%. The AUC of the ALBI score for predicting the in-hospital mortality was 0.586 (confidence interval [CI]: 95%; 0.528-0.642). The best cut-off value was –1.01, with sensitivity of 94.92%, a specificity of 32.5%, PLR of 1.406 and NLR 0.156 (Fig. 1).

The AUC of the Child-Pugh score for predicting the in-hospital mortality was 0.549 (CI 95%; 0.490-0.606). The best cut-off value of the Child-Pugh score was 10, with a sensitivity of 76.27%, a specificity of 34.58%, PLR of 1.165 and NLR of 0.686 (Fig. 2).

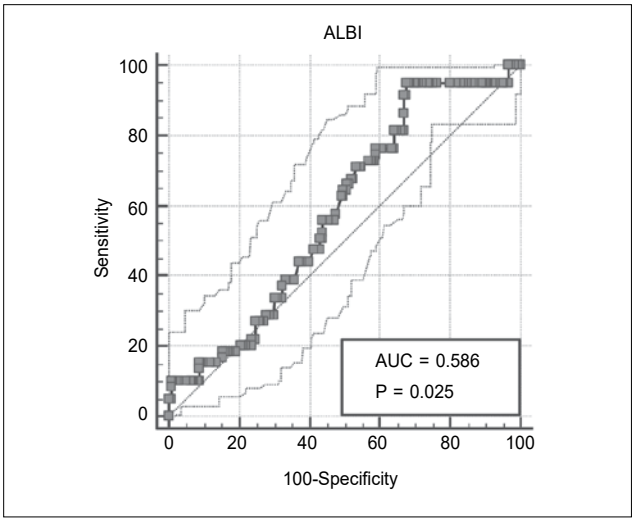


Figure 1. ROC curve of ALBI score for predicting in-hospital mortality.

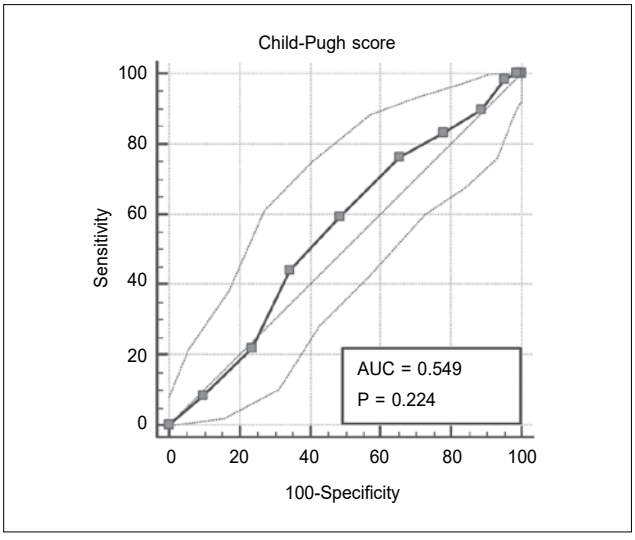


Figure 2. ROC curve of Child-Pugh score for predicting in-hospital mortality.

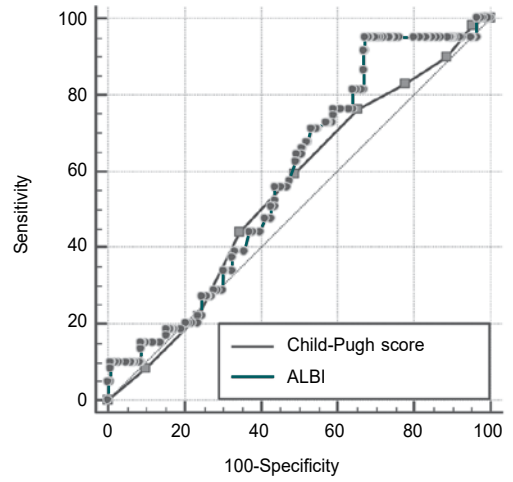
The AUC for predicting the in-hospital mortality was not significantly different between the Child-Pugh and ALBI scores. (Child-Pugh and ALBI: p = 0.4461) (Fig. 3).

The performance of Child-Pugh score is higher than ALBI score.

DISCUSSION

Child-Pugh score and MELD score have been studied extensively for their prognostic abilities and have shown good performance in predicting the mortality of cirrhotic patients. But, the cumbersome calculation of scores and the variables included in them have subjective variability that has led to the development of ALBI score.

Variable	AUC	SE	95% CI
Child-Pugh score	0.549	0.0401	0.490-0.606
ALBI	0.586	0.0382	0.528-0.642



Child-Pugh score ~ ALBI	
Difference between areas	0.0370
SE	0.0486
95% CI	–0.0582 to 0.132
Z statistic	0.762
Significance level	P = 0.4461

Figure 3. Comparison of ROC curves.

ALBI score involves only two variables and has already been studied in various liver disorders such as HBV, hepatocellular carcinoma, primary biliary cirrhosis and has shown to perform well and is comparable with the Child-Pugh and MELD scores. In our study, an attempt has been made to compare the discriminative ability of ALBI score with that of the Child-Pugh score in predicting the in-hospital mortality in alcoholic cirrhosis patients. ALBI score showed better performance compared to Child-Pugh score in predicting mortality, but there was no statistical difference between them.

In a study by Shao et al, ALBI score demonstrated similar ability as that of Child-Pugh and MELD score in predicting in-hospital mortality in cirrhosis. It also suggested that ALBI score can be readily used as prognostic model.[3]

Another study by Chen et al showed that the ALBI score determined on admission indicates the likelihood of survival of acute-on-chronic liver failure patients.[12]

In a study conducted by Zou et al, in patients with alcohol-related liver cirrhosis, ALBI score had the largest AUC, followed by the Child-Pugh and MELD scores, so they concluded that ALBI score has moderate-to-high prognostic performance.[13]

A study conducted by Peng et al showed that there was no significant difference among the three scores in predicting in-hospital mortality in cirrhotic patients.[14]

A retrospective study done by Xavier et al on 111 patients between January 2011 and November 2015, came out with the conclusion that ALBI score is particularly useful in the assessment of short-term outcomes, with a better performance than the most commonly used scores.[15]

The limitations of our study were that it was a retrospective study, the late mortality was not considered and follow-up was not done.

CONCLUSION

AUC of the ALBI score and the Child-Pugh score were comparable and there was no statistical difference between them. ALBI can be used in place of Child-Pugh score in peripheral centers to assess the prognosis of CLD patients secondary to alcohol in view of simple calculation, only two variables and no subjective variation of the score.

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Every citizen of India should have the right to accessible, affordable, quality and safe heart care irrespective of his/her economical background

HEART CARE FOUNDATION OF INDIA
A Not-For-Profit Organisation

Sameer Malik Heart Care Foundation Fund

An Initiative of Heart Care Foundation of India

E-219, Greater Kailash, Part I, New Delhi - 110048 E-mail: heartcarefoundationfund@gmail.com Helpline Number: +91 - 9958771177

"No one should die of heart disease just because he/she cannot afford it"

About Sameer Malik Heart Care Foundation Fund

"Sameer Malik Heart Care Foundation Fund" it is an initiative of the Heart Care Foundation of India created with an objective to cater to the heart care needs of people.

Objectives

- Assist heart patients belonging to economically weaker sections of the society in getting affordable and quality treatment.
- Raise awareness about the fundamental right of individuals to medical treatment irrespective of their religion or economical background.
- Sensitize the central and state government about the need for a National Cardiovascular Disease Control Program.
- Encourage and involve key stakeholders such as other NGOs, private institutions and individual to help reduce the number of deaths due to heart disease in the country.
- To promote heart care research in India.
- To promote and train hands-only CPR.

Activities of the Fund

Financial Assistance

Financial assistance is given to eligible non emergent heart patients. Apart from its own resources, the fund raises money through donations, aid from individuals, organizations, professional bodies, associations and other philanthropic organizations, etc.

After the sanction of grant, the fund members facilitate the patient in getting his/her heart intervention done at state of art heart hospitals in Delhi NCR like Medanta – The Medicity, National Heart Institute, All India Institute of Medical Sciences (AIIMS), RML Hospital, GB Pant Hospital, Jaipur Golden Hospital, etc. The money is transferred directly to the concerned hospital where surgery is to be done.

Drug Subsidy

The HCFI Fund has tied up with Helpline Pharmacy in Delhi to facilitate patients with medicines at highly discounted rates (up to 50%) post surgery.

The HCFI Fund has also tied up for providing up to 50% discount on imaging (CT, MR, CT angiography, etc.)

Who is Eligible?

All heart patients who need pacemakers, valve replacement, bypass surgery, surgery for congenital heart diseases, etc. are eligible to apply for assistance from the Fund. The Application form can be downloaded from the website of the Fund. http://heartcarefoundationfund.heartcarefoundation.org and submitted in the HCFI Fund office.

Important Notes

- The patient must be a citizen of India with valid Voter ID Card/ Aadhaar Card/Driving License.
- The patient must be needy and underprivileged, to be assessed by Fund Committee.
- The HCFI Fund reserves the right to accept/reject any application for financial assistance without assigning any reasons thereof.
- The review of applications may take 4-6 weeks.
- All applications are judged on merit by a Medical Advisory Board who meet every Tuesday and decide on the acceptance/rejection of applications.
- The HCFI Fund is not responsible for failure of treatment/death of patient during or after the treatment has been rendered to the patient at designated hospitals.
- The HCFI Fund reserves the right to advise/direct the beneficiary to the designated hospital for the treatment.
- The financial assistance granted will be given directly to the treating hospital/medical center.
- The HCFI Fund has the right to print/publish/webcast/web post details of the patient including photos, and other details. (Under taking needs to be given to the HCFI Fund to publish the medical details so that more people can be benefitted).
- The HCFI Fund does not provide assistance for any emergent heart interventions.

Check List of Documents to be Submitted with Application Form

- Passport size photo of the patient and the family
- A copy of medical records
- Identity proof with proof of residence
- Income proof (preferably given by SDM)
- BPL Card (If Card holder)
- Details of financial assistance taken/applied from other sources (Prime Minister's Relief Fund, National Illness Assistance Fund Ministry of Health Govt of India, Rotary Relief Fund, Delhi Arogya Kosh, Delhi Arogya Nidhi), etc., if anyone.

Free Diagnostic Facility

The Fund has installed the latest State-of-the-Art 3 D Color Doppler EPIQ 7C Philips at E – 219, Greater Kailash, Part 1, New Delhi.
This machine is used to screen children and adult patients for any heart disease.

Free Education and Employment Facility

HCFI has tied up with a leading educational institution and an export house in Delhi NCR to adopt and to provide free education and employment opportunities to needy heart patients post surgery. Girls and women will be preferred.

Laboratory Subsidy

HCFI has also tied up with leading laboratories in Delhi to give up to 50% discounts on all pathological lab tests.

Help Us to Save Lives

The Foundation seeks support, donations and contributions from individuals, organizations and establishments both private and governmental in its endeavor to reduce the number of deaths due to heart disease in the country. All donations made towards the Heart Care Foundation Fund are exempted from tax under Section 80 G of the IT Act (1961) within India. The Fund is also eligible for overseas donations under FCRA Registration (Reg. No 231650979). The objectives and activities of the trust are charitable within the meaning of 2 (15) of the IT Act 1961.

Donate Now...

About Heart Care Foundation of India

Heart Care Foundation of India was founded in 1986 as a National Charitable Trust with the basic objective of creating awareness about all aspects of health for people from all walks of life incorporating all pathies using low-cost infotainment modules under one roof.

HCFI is the only NGO in the country on whose community-based health awareness events, the Government of India has released two commemorative national stamps (Rs 1 in 1991 on Run For The Heart and Rs 6.50 in 1993 on Heart Care Festival- First Perfect Health Mela). In February 2012, Government of Rajasthan also released one Cancellation stamp for organizing the first mega health camp at Ajmer.

Objectives

- Preventive Health Care Education
- Perfect Health Mela
- Providing Financial Support for Heart Care Interventions
- Reversal of Sudden Cardiac Death Through CPR-10 Training Workshops
- Research in Heart Care

Heart Care Foundation Blood Donation Camps

The Heart Care Foundation organizes regular blood donation camps. The blood collected is used for patients undergoing heart surgeries in various institutions across Delhi.

Committee Members

Chief Patron

Raghu Kataria

Entrepreneur

President

Dr KK Aggarwal

Padma Shri, Dr BC Roy National & DST National Science Communication Awardee

Governing Council Members

Sumi Malik
Vivek Kumar
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Naina Aggarwal
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Dr Uday Kakroo
Harish Malik
Aarti Upadhyay
Raj Kumar Daga
Shalin Kataria
Anisha Kataria
Vishnu Sureka
Rishab Soni

This Fund is dedicated to the memory of **Sameer Malik** who was an unfortunate victim of sudden cardiac death at a young age.

- HCFI has associated with Shree Cement Ltd. for newspaper and outdoor publicity campaign
- HCFI also provides Free ambulance services for adopted heart patients
- HCFI has also tied up with Manav Ashray to provide free/highly subsidized accommodation to heart patients & their families visiting Delhi for treatment.

http://heartcarefoundationfund.heartcarefoundation.org

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A Snapshot of Patients on Hemodialysis in July 2018, GGH, Jamnagar: A Cross-sectional Study

AJAY C TANNA*, PRANAV I PATEL†

ABSTRACT

Noncommunicable diseases (NCDs) are the leading causes of premature death and morbidity. Chronic kidney disease is a major factor linked with poor health outcomes of major NCDs. A study was recently carried out at Guru Govind Singh Hospital, Jamnagar, Gujarat, among patients undergoing hemodialysis, to assess demographic data, comorbid conditions, determine common medical problems in patients on dialysis, reinforce diet patterns and water intake patterns, assess risk factors that lead to cardiorespiratory events, and awareness of the drug intake and schedule. This cross-sectional study revealed that hypertension, diabetes and liver parenchymal disease were the most common associated comorbidities. Cardiac, respiratory and cerebrovascular diseases were also the comorbidities in a significant number of patients, followed by hypothyroidism, fibrous bone dysplasia, hypopituitarism, mullerian agenesis syndrome. Most patients were found to have no idea about how much water they should drink. None of the patients were strictly following a diet. Additionally, none knew the exact amount of salt, protein and fat that they should take in a day. Awareness of drug intake was also low. The findings reinforce the importance of patient education and involvement of patients in their own treatment.

Keywords: Hemodialysis, chronic kidney disease, diet, water intake, comorbidities

Noncommunicable diseases (NCDs) are the leading causes of premature death and morbidity and significantly affect the healthcare costs, productivity and growth. Chronic kidney disease (CKD) is a major factor linked with poor health outcomes of major NCDs. CKD is associated with an increase in cardiovascular mortality and heightens the risk in patients with diabetes and hypertension. Early detection and treatment of CKD has the potential to slow or prevent progression to end-stage renal disease (ESRD).

A large number of dialysis patients have comorbid conditions such as diabetes. Additionally, patients with ESRD on long-term dialysis therapy have a high mortality, largely due to cardiovascular causes.

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A study was carried out at Guru Govind Singh Hospital, Jamnagar, Gujarat, among patients undergoing hemodialysis, with following aims and objectives:

- To assess demographic data
- To assess comorbid conditions
- To find common medical problems in patients on dialysis
- To find incidence of catheter related issues and promoting asepsis
- To reinforce diet patterns and water intake patterns
- To assess risk factors that lead to cardiorespiratory events
- To assess adherence to schedule of hemodialysis
- To assess awareness of the drug intake and schedule.

Figure 1 provides a glimpse of the hemodialysis unit.

METHODS

A proforma was made to assess above-mentioned aims in local language i.e., Gujarati. A single-blinded study (patients) was conducted with the only task given to patients as marking complaints and what food they eat even if they take it occasionally. Rest of the proforma

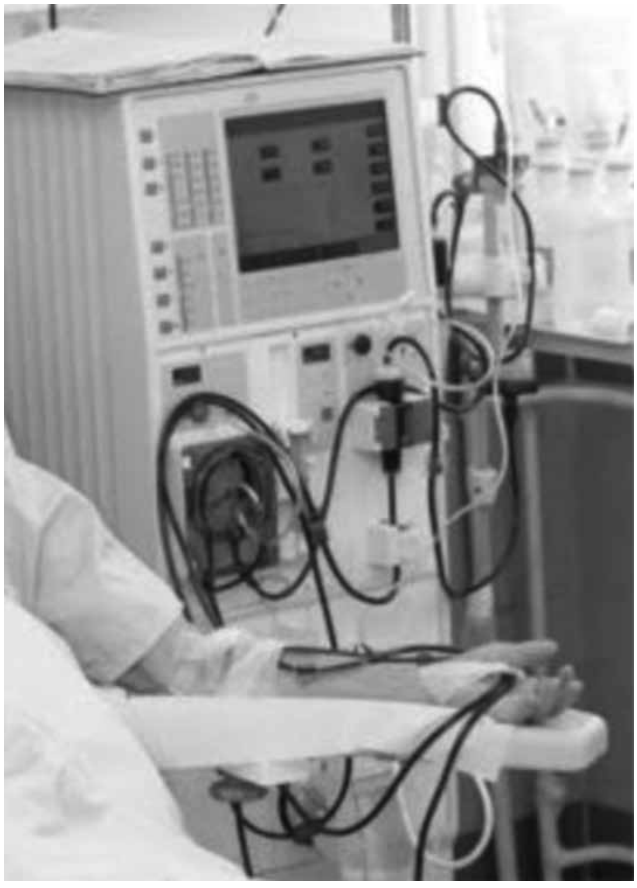

Figure 1. A glimpse of the hemodialysis unit.

was filled by personal interview with each patient and previously marked boxes were confirmed. In the diet, detailed list of various food products was used to identify commonly use but harmful food products in CKD patients. Patients were also taught about various techniques of water restriction and diet preparation.

STATISTICS

Population: Patients with CKD on dialysis.

Sample: Forty-four patients were randomly assessed at the end of the month.

There was no control group or comparison group and data was analyzed as a cross-sectional study only.

RESULTS

A total of 44 patients were analyzed in month of July, 2018. Out of these, 29 patients were males and 15 were females. Most patients had a functional arteriovenous (AV) fistula. None of the few patients with central-line *in situ* experienced bleeding or discharge from insertion site. Headache, fever, chills, rigors and nausea were common complaints from patients. Fifteen (30%) patients had a weight of more than 60 kg. Hypertension (40 patients-91%), diabetes (11 patients-25%) and liver parenchymal disease (10 patients-20%) were the most common associated comorbidities. Cardiac, respiratory and cerebrovascular diseases were also the comorbidities in a significant number of patients (total 11 patients had at least one of three-25%). Some other less common comorbidities found were hypothyroidism, fibrous bone dysplasia, hypopituitarism, mullerian agenesis syndrome, etc. In all, 6 patients had addictions. Only 15 (30%) patients were taking restricted amount of water. Rest had no idea about how much water they should drink. None of the patients had separate water container to measure total water intake for a day.

Most of the patients said that they followed diet but none of them were strictly following, when inquired further. Everyone told that they restricted salt intake but none knew the exact amount of salt that they should take in a day. Overall, 30 (68%) patients were taking fruits or dry fruits occasionally; 42 (95%) patients were taking salted products in one form or another, e.g., wafers, food packets, pickles, biscuits, popcorns, etc.; 9 patients were taking coffee. None of them knew how much protein and fat they should take.

Approximately half (48%) of the patients took tablets as given by their caretakers; only some of them could recall drug schedule and only very few could identify the tablets.

Most patients were regular in their dialysis schedule. Only 2 patients missed their dialysis schedule due to higher center visits. On further investigation, rain, outdoor visits, ill health of patient or relatives, death of known person, etc. were found to be other reasons for missing dialysis in past. Five patients died in July 2018 - 4 were due to cardiorespiratory events and one was due to cerebrovascular accident.

DISCUSSION

As we can see in Figure 2, major areas of concern were found to be diet restriction, monitoring hypertension, water restriction, knowledge of drugs, reduction of obesity, control of diabetes and liver disease in descending order.

On further inquiry, all patients told that they were explained about diet and water restriction at least once but majority of them forget it and lost the diet chart. Few were concerned about time in applying techniques and others were worried about cost. They were explained about importance of these restrictions and made aware about complications and prognosis if not followed. But

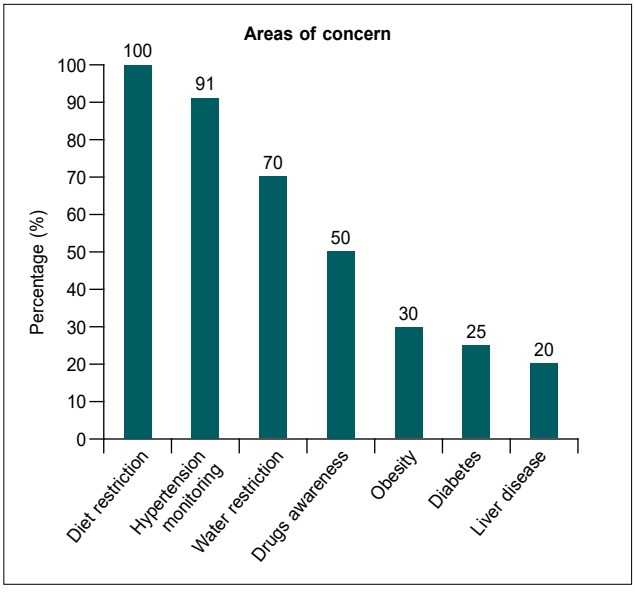

Figure 2. Key areas of concern.

from this experience, we can say that water restriction and diet must be repeatedly explained and must be reinforced at regular intervals by providing posters, charts, etc. in local language. Avoidance of harmful food products like fruits, dry fruits, coffee, salted products, etc. should be the first target. Diet adequacy can be determined by serum electrolytes, albumin and cholesterol and sugar levels. Serum albumin <4 g/dL indicates poor prognosis. Water intake can be monitored by determining serial weight of the patients. Certain bad practices like eating food products like wafers, while on active hemodialysis should be discouraged as it takes time for food to reach stomach and be processed. Opinion of a dietician and demonstration of some prepared diet dishes with explanation about how it was made would be of great help.

Blood pressure (BP) monitoring is vital. Monitoring of BP during hemodialysis is as important as before and after. BP should be monitored as frequently as possible as major variations were observed during this study. For instance, one normotensive patient became hypertensive within just 2 minutes of detaching the machine. Most of the time when patient complains of high BP, headache and fever and chills, BP is observed to be high. So if possible, at every incident, BP should be measured.

Patient should be taught to identify their drugs and remember the schedule. Obesity decreases efficacy of hemodialysis (as increase in volume of distribution in Kt/V formula). Weight reduction by proper diet and exercise should be advised.

Diabetes control is necessary as increase in blood sugar levels favors infection, increases thirst, impairs immunity, worsens kidney function, etc.

Patients with liver disease should be taken care of for extra risks of bleeding tendencies, glycemic control, risk of infection, control of liver disease itself, etc.

As cardiovascular events remain the most common cause of death, each patient on dialysis must be monitored by weight, blood sugar levels, ECG, Echo, digital X-rays, cholesterol levels, level of activity, etc. for risk factors.

CONCLUSION

As healthcare workers, from our side, we are moving towards following guidelines regarding repeated monitoring, proper techniques, using advanced technologies, separate disposable instruments and maintaining total asepsis, etc. But at the same time, patient education and involvement of patients in their own treatment is necessary to achieve maximum results. We shall not forget the importance of nonpharmacological measures as they are universal, e.g., in this study, by monitoring random blood sugar, we helped 25% patients; by monitoring BP, we helped 91% patients but by explaining and reinforcing diet and water restriction, we helped 100% of patients.

"The doctor can have a stronger impact on the patient than any drug." —Paracelsus

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Indian Journal of Clinical Practice, Vol. 29, No. 12, May 2019

Erythroderma: Epidemiology, Clinical Profile and Clinicopathological Correlation in 47 Patients

US AGARWAL*, ANSHUL MAHESHWARI†, SUNIL KOTHIWALA‡, KARUNA GUPTA#, ARPITA JINDAL#

ABSTRACT

Background: Erythroderma, or generalized exfoliative dermatitis, is a disease characterized by erythema and scaling of greater than 90% of the body's surface. There is paucity of Indian studies over the etiology, clinical profile and its histopathological correlation. **Aims and objectives:** To assess the demographic profile, clinical features and histopathological correlation in erythroderma patients. **Material and methods:** We registered all patients of erythroderma consecutively from January 2013 to December 2013. After a thorough history and clinical examination, a provisional clinical diagnosis was made. We performed biopsy from two representative sites of patient and it was sent for histopathological examination. The slides were examined by two pathologists and one dermatologist without any relevant clinical information. The clinical diagnosis was matched with the blinded microscopical diagnosis. **Results:** The mean age of onset was 54.1 years with a male-to-female ratio of 3.3:1. The most common causes were airborne contact dermatitis (53.2%) followed by psoriasis (21.2%), drug-induced erythroderma (12.7%), chronic actinic dermatitis (2.1%), atopic dermatitis (2.1%), endogenous dermatitis (2.1%), mycosis fungoides (2.1%), lichenoid dermatitis (2.1%) and idiopathic (2.1%). Histopathology was able to provide diagnosis in 32 (68%) patients. Out of these 32 patients, microscopical diagnosis was in accordance with clinical diagnosis in 28 patients. **Conclusion:** Most of the clinical features of erythroderma are overlapping. Specific and diagnostic features of disease are seen only in a few patients. Repeated evaluations, close follow-up and skin biopsy are recommended for a better clinical diagnosis and patient care.

Keywords: Erythroderma, generalized exfoliative dermatitis, erythema, biopsy, histopathological examination

Erythroderma or exfoliative dermatitis is an inflammatory disorder in which erythema and scaling occur in a generalized distribution involving more than 90% of the body surface. Because most patients are elderly and skin involvement is widespread, the disease implies an important risk to the life of the patient. The estimated annual incidence of erythroderma seems to be 1-2/1,00,000 patients. This disorder may represent a variety of cutaneous and systemic diseases, and therefore a thorough work-up is essential, which includes detailed history of triggering factors like drugs, occupation, sunlight exposure, pre-existing dermatoses, infections, malignancies, etc. It should be followed by a meticulous clinical examination for specific diagnostic clues to rule out its etiology. Histopathology can help in identifying the cause of erythroderma in up to 50% of cases, particularly by multiple skin biopsies.

Indian studies showed a higher prevalence of erythroderma than other studies. Sehgal and Srivastava recorded the incidence of erythroderma from the Indian subcontinent as 35/1,00,000 dermatologic outpatients. But, there are conflicting views over role of histopathology as some studies were unrewarding.

This study was performed to find out the causes of erythroderma in north-west part of India, to find out the epidemiological, clinical profile of these patients and histopathological correlation.

MATERIAL AND METHODS

The study was performed from January 2013 to December 2013. In this tenure, all cases of erythroderma attending skin outpatient department were included in the study. A thorough history which included duration, progression of disease, occupation,

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seasonal variation, precipitating factors, site of onset, other existing skin disease and other comorbidities like hypertension, atopy, etc. was taken from patient. It was followed by a thorough general physical and dermatological examination. Laboratory investigations such as complete hemogram, blood glucose, blood urea, serum creatinine, liver function tests, serum electrolytes and chest radiograph were performed. Abdominal ultrasound, peripheral smear, fine needle aspiration cytology (FNAC) of lymph nodes, CT scan, etc. were done only if required.

Four millimeter punch biopsy was performed in all patients from two representative sites. The slides were seen independently by two pathologists and dermatologist without relevant clinical information. Slides were examined by them independently for any specific diagnosis. The microscopical diagnosis was then correlated with clinical diagnosis.

RESULTS

Age of patients ranged from 14 to 86 years with median of 58 years and mean age of onset of 54.1 ± 17.8 years. Majority of patients belonged to age group of 51-60 years (Fig. 1). Male predominance was seen with male-to-female ratio of 3.3:1. The total duration of erythroderma in patients ranged from 10 days to 20 years with median of 2 years and mean of 4.1 ± 5.2 years. Exacerbation of disease ranged from 7 to 120 days with a mean of 43.3 ± 25.3 days. Majority of male patients were farmers (55.5%) followed by laborers (22.2%) and students (6.3%). Majority of female patients were housemakers (72.7%) (Table 1).

Most common aggravating factor was seasonal exacerbation seen in about 26 patients (55.3%) with summer exacerbation in 17 patients (36.1%). Seasons had no effects on disease in 21 patients (44.7%). History of atopy was present in 11 (23.4%) patients. Other aggravating factors were sunlight and dust, which were seen in 11 (23.4%) patients each. Drugs were responsible in 4 (8.5%) patients. History of pre-existing skin disease was present in 30 patients (63.8%). Other comorbidities, like hypertension was present in 17 patients (36.1%), diabetes in 4 patients (8.5%) and tuberculosis in 4 patients (8.5%). In 17 patients of hypertension, nine were already on antihypertensive medicine but 8 patients were diagnosed with hypertension for the first time. The site of onset of erythroderma was scalp and face in 20 patients (42.6%), extremities in 18 patients (38.3%), and trunk and abdomen in 8 patients (17.0%). Most common clinical finding was pruritus (100%) followed by lymphadenopathy (70.2%), edema (57.4%), nail changes (55.3%), fever (38.2%), palmoplantar keratoderma (21.2%), weight loss (14.9%) and loss of appetite (10.6%) (Table 2). Severe pruritus causing disturbance in sleep was present in 29 (61.7%) patients. Inguinal lymphadenopathy was present in 33 (70.2%) patients and axillary lymphadenopathy in one patient. Most common nail change was Beau's line followed by shiny nails, yellowish discoloration of nails, subungual hyperkeratosis, pitting and onycholysis. In 3 (6.3%) patients, 20 nail dystrophy was present. Pitting edema of the distal extremities was present in 21 (44.7%) patients. Generalized edema of pitting type was present in 4 (8.5%) patients. Histopathology was able to provide specific histopathological diagnosis e.g., psoriasis, dermatitis in 32 (68%) patients. Out of these 32 patients, clinical correlation occurred in 28 (87%) patients. Overall, in 28 (60%) patients, clinical diagnosis matched with histopathological diagnosis. Table 3 summarizes the clinicopathological correlation. Nonspecific biopsy was seen in 15 (32%) patients. Histopathology was most accurate in diagnosing drug reaction (100%), followed by mycosis fungoides (100%) and psoriasis (70%) (Fig. 2). The specific findings of biopsies are depicted in Table 4. The most common causes were airborne

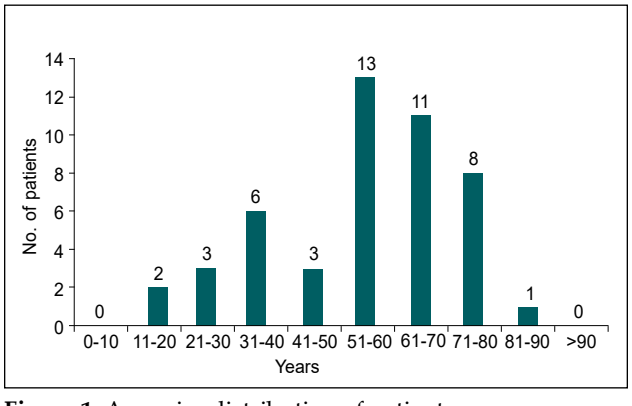

Figure 1. Age-wise distribution of patients.

Table 1. Occupational Profile of Patients

Occupation	No. of males	No. of females
Farmer	20	-
Laborer	8	-
Student	3	2
Housemaker	-	8
Carpenter	1	-
Sarpanch	1	-
Service	2	1
Army officer	1	-

Table 2. Clinical Profile of Patients

Symptom/disease	Airborne contact dermatitis (n = 25)	Psoriasis (n = 10)	Drug-induced erythroderma (n = 6)	Mycosis fungoides (n = 1)	Other (n = 5)
Pruritus	25	10	6	1	5
Fever	7	8	3	0	0
Loss of appetite	3	1	0	1	0
Weight loss	4	1	0	1	1
Edema	15	6	3	0	3
Lymphadenopathy	18	9	3	1	2
Nail changes	15	9	0	0	2
Palmoplantar keratoderma	4	6	0	0	0
Hypertension	14 6 ND	1 ND	1		1ND
Diabetes	3	0	0	0	1

ND: Newly diagnosed case.

Table 3. Clinicopathological Correlation

Clinical diagnosis	Histopathological diagnosis	Clinicopathological correlation
Airborne contact dermatitis (n= 25)	Dermatitis (n = 10) Psoriasis (n = 3) Nonspecific (n = 12)	40%
Psoriasis (n = 10)	Psoriasis (n = 7) Dermatitis (n = 1) Nonspecific (n = 2)	70%
Drug-induced erythroderma (n = 6)	Drug-induced (n = 6)	100%
Chronic actinic dermatitis (n = 1)	Dermatitis (n = 1)	100%
Endogenous dermatitis (n = 1)	Dermatitis (n = 1)	100%
Atopic dermatitis (n = 1)	Dermatitis (n = 1)	100%
Mycosis fungoides (n = 1)	Mycosis fungoides (n = 1)	100%
Lichenoid dermatitis (n = 1)	Lichenoid dermatitis (n = 1)	100%
Idiopathic (n = 1)	Nonspecific (n = 1)	-

contact dermatitis (53.2%) followed by psoriasis (21.2%), drug-induced erythroderma (12.7%), chronic actinic dermatitis (2.1%), atopic dermatitis (2.1%), endogenous dermatitis (2.1%), mycosis fungoides (2.1%), lichenoid dermatitis (2.1%) and idiopathic (2.1%) (Fig. 3).

DISCUSSION

The approach to patients with erythroderma depends on their previous dermatologic background. Patients with pre-existing dermatoses are easy to diagnose. Otherwise, erythroderma remains a diagnostic challenge, especially in those patients without history of dermatologic diseases and who deny having recently taken any medications.

In our study, age of patients ranged from 14 to 86 years with mean age of onset of 54.1 ± 17.8 years. This is in accordance with various previous studies. In this series, men outnumbered women in a ratio of 3.3:1. Similar findings were seen in other studies. In a study by Hulmani et al, male-to-female ratio was quite high at 14:1. As men are commonly involved than women

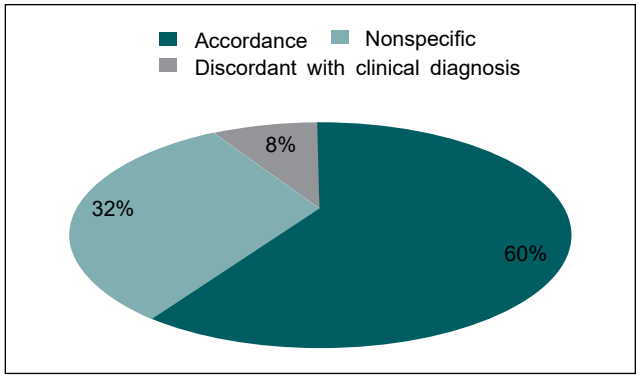

Figure 2. Clinical and histopathological diagnosis.

Table 4. Histopathological Findings

Psoriasis (n = 10)	
Hyperkeratosis	7
Parakeratosis	10
Munro microabscess	7
Granular layer absent	8
Acanthosis	7
Suprapapillary thinning	6
Dilated blood vessel	6
Perivascular lymphocytic infiltrate	9
Infiltrate having neutrophils	3
Drug-induced (n = 6)	
Hyperkeratosis	5
Parakeratosis	4
Necrotic keratinocyte	3
Basal cell vacuolization	5
Melanin incontinence	4
Lichenoid infiltrate	3
Perivascular lymhocytic infiltrate	5
Eosinophils in infiltrate	3
Dermatitis (n = 29)	
Hyperkeratosis	25
Parakeratosis	25
Acanthosis	24
Spongiosis	11
Perivascular lymphocytic infiltrate	27
Eosinophils in infiltrate	8

in outdoor activities, male-to-female ratio is quite high in this study.

Most common aggravating factor was seasonal variation seen in 26 patients. Summer exacerbation was seen in 17 patients. Dust and sunlight aggravated the condition in 11 patients each. This is in contrast to another study where winter season was aggravating

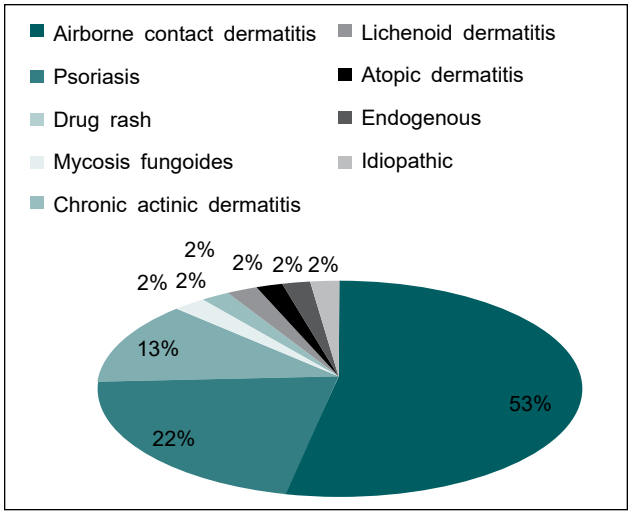

Figure 3. Etiology of erythroderma.

factor seen in 30% patients. In our study, most common cause of erythroderma was airborne contact dermatitis compared to Hulmani et al where most common etiology was psoriasis. This might be the cause of winter exacerbation in their study. Most of the clinical findings were in accordance with other studies. Lymphadenopathy was seen in 70% of our patients and was quite high. Some studies showed it as 19-33%. Others showed it to be around 55%. Nail changes were seen in 55% of patients. Nail changes were Beau's lines, shining in the nails, subungual hyperkeratosis, pitting, yellowish discoloration and onychodystrophy. Similar findings were present in other studies.

Histopathology was successful in determining the specific cause of erythroderma in 32 (68%) of the patients. So, overall clinicopathological correlation occurred in 60% of patients. As in our study, relevant clinical information wasn't provided to the pathologist but still they were able to match the clinical diagnosis in 28 (60%) patients. The percentage might push up higher with relevant clinical information. In a study by Rym et al, histopathological correlation was found in 74% of patients; in a study by Bandopadhyay et al, there was correlation in 52% of cases. Most common histopathological finding in our study was perivascular lymphocytic infiltrate.

The findings are comparable with slight differences from a study by Walsh et al. Comparison of our etiologic diagnosis with the previous studies is compiled in Table 5. In our case series, most common clinical diagnosis was airborne contact dermatitis. It is quite different from other studies where it constituted a minority group.

Table 5. Comparison of Different Etiology of Erythroderma in Various Studies

Study causes	Pal et al	Rym et al	Bandopadhyay et al	Sudho et al	Chaudhary et al	Hulmani et al	Our study
Psoriasis	37.8	51.25	33.33	32	40	33.33	21.2
Eczema	12.2	7.5	4	12	20	20	57.4*
Ichthyosis	7.8	0	1.33	0	0	0	0
Pityriasis rubra pilaris	2.2	5.25	1.33	0	0	3.33	0
Scabies	2.2	1.25	3.33	0	0	0	0
Pemphigus foliaceus	5.6	6.25	5.33	4	0	0	0
Lichen planus	0	1.25	0	0	0	0	0
Atopic dermatitis	0	0	13.33	8	6.66	6.6	2.1
Other dermatoses	6.6	3.75	0	8	0	0	2.1
Drug reaction	5.5	11.25	12	24	10	16.6	12.7
Malignancy	5.5	8.75	2.67	4	6.66	3.3	2.1
Idiopathic	14.6	7.5	21.33	08	16.6	16.6	2.1

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Delayed Cardioversion Noninferior to Early Cardioversion in Recent-onset AF

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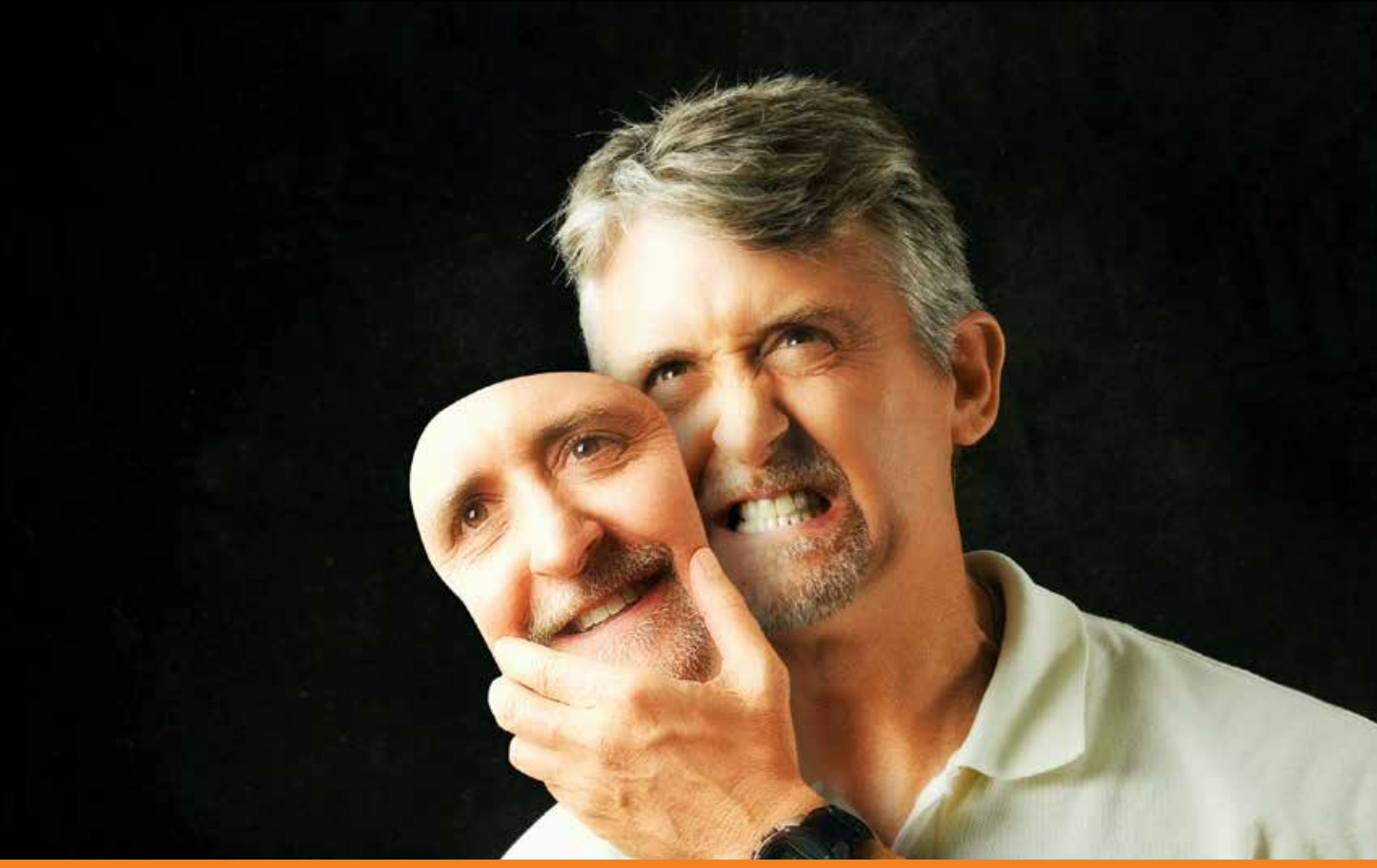

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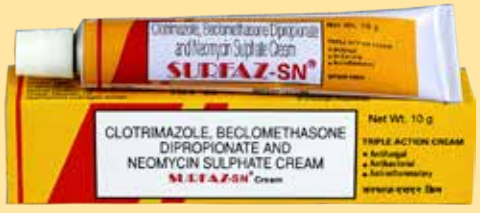

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Indian Journal of Clinical Practice, Vol. 29, No. 12, May 2019

Prophylactic Effect of Topical Besifloxacin and Moxifloxacin on the Bacterial Conjunctival Flora Before and After Intraocular Surgery

SHAIK MOHAMMAD ZAKIR*, ABHISHEK AGRAWAL†, SAIYID N ASKARI‡, SHAMIM AHMAD§

ABSTRACT

Aim: To study bacterial conjunctival flora before and after topical moxifloxacin or besifloxacin used as prophylactic agent in intraocular surgeries. **Settings and design:** Prospective randomized study. **Material and methods:** Conjunctival swabs of 100 patients undergoing intraocular surgeries were collected 2 days before the surgery without prior antibiotic use and inoculated on culture media for culture and antibiotic sensitivity tests. Patients were randomized into two groups (50 each). Patients of Group A and Group B received topical moxifloxacin 0.5% and besifloxacin 0.6% eye drop, respectively, to the assigned eye 6 hourly. Postoperatively, antibiotic eye drops were instilled 4 hourly for 10 days and then stopped. Topical anti-inflammatory and steroid drugs were continued for 6 weeks. Conjunctival swabs were repeated from operated eyes 20 and 40 days postoperatively. Statistical analysis was done using Chi-square and McNemar's tests. **Results:** Bacterial growth appeared in 27 cases (most commonly *Staphylococcus epidermidis* 51.85%) - 16 in Group A and 11 in Group B - and none of the isolate showed resistance to the assigned antibiotic. **Conclusions:** The antibacterial efficacy of topical moxifloxacin and besifloxacin in preventing postoperative infections is similar; hence, both may be equally effective for prophylaxis in intraocular surgeries.

Keywords: Conjunctival flora, moxifloxacin, besifloxacin, intraocular surgeries, prophylaxis

The term "normal conjunctival flora" refers to microorganisms that dwell within the eyes of healthy individuals. Predominant isolates recovered from the normal adult conjunctiva are *Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus* nonhemolytic and *Propionibacterium acnes*.

The knowledge of these organisms and their antibiotic sensitivity/resistance provides a better guide in choosing an appropriate antibiotic for prophylaxis of postoperative infections for which topical fluoroquinolones are commonly used. Due to antibiotic resistance, proper selection of antibiotic remains a challenge for ophthalmologists.

The present study was planned to ascertain normal conjunctival flora and its sensitivity/resistance to the new fourth-generation fluoroquinolones viz. moxifloxacin and besifloxacin.

MATERIAL AND METHODS

This prospective randomized study was conducted on 100 eyes of 100 patients who presented at Eye OPD in our institution from February 2014 to August 2015 for treatment of diseases requiring intraocular surgeries. The details of the procedures were explained to all the patients in their language and written consent was obtained. Ethical clearance for the study was granted by the Institutional Ethics Committee.

Patients with hypersensitivity to moxifloxacin and besifloxacin or any of the ingredients in the study medications were excluded from this study. Patients who had used any topical antibiotic drops 3 months prior to culture, taken systemic antibiotics 1 month before and during the study period, neonates, infants, pregnant and lactating females were also excluded.

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Moxifloxacin ophthalmic solution and besifloxacin ophthalmic suspension were used for the study.

After taking first preoperative conjunctival swab from the study eye, patients were randomly divided in two groups, A and B, with 50 patients each. Patients of Group A (Moxifloxacin Group) received topical moxifloxacin 0.5% eye drops and patients of Group B (Besifloxacin Group) received topical besifloxacin 0.6% eye drops to the assigned eye 6 hourly for 2 days preoperatively and continued postoperatively every 4 hours for 10 days, and then stopped. Topical anti-inflammatory and steroid eye drops were started from first postoperative day for 6 weeks. Conjunctival swabs were repeated from the operated eyes 20 and 40 days postoperatively and inoculated on culture media to look for bacterial growth.

Sterile cotton swabs with polypropylene stick were used for obtaining conjunctival swab from the eyes of patients. The swabs were inoculated on Blood Agar and Chocolate Agar and incubated at 37°C overnight. Positive cultures were processed for identification of organisms by studying Gram-staining, colony characteristics and several biochemical tests. Later on, antibiotic sensitivity was assessed for moxifloxacin using the commercially available disc containing 5 μg of the drug. Antibiotic discs of besifloxacin are not available commercially, and the sensitivity was assessed using self-made discs of sterile Whatman No. 41 filter paper of 5 mm diameter and eye drop besifloxacin 0.6%, finally achieving a concentration of 10 μg/disc. Antibiotic sensitivity testing was done by the Standard Disc Diffusion method described by Bauer et al (1966).

The results were analyzed statistically using Chi-square and McNemar's tests.

RESULTS

A total of 100 eyes of 100 patients (62 males and 38 females) were included in the study; majority (68%) were between the ages of 51 and 70 years. Maximum number of patients (85/100) underwent manual small incision cataract surgery (MSICS) with posterior chamber intraocular lens (PCIOL) implantation. Nine patients underwent trabeculectomy and 6 patients had combined trabeculectomy with MSICS with PCIOL implantation. Conjunctival swabs were obtained from 100 eyes (50 in moxifloxacin and 50 in besifloxacin group) and inoculated on bacterial culture media. Twenty-seven swabs yielded growth of bacteria (positive cultures) with no statistically significant difference between males and females as shown in Table 1.

The results of the study indicated higher positive cultures occurring in early summer season and also slightly higher in older patients (more than 50 years of age), although the difference was statistically insignificant. Out of 27 positive cultures, 23 (85.2%) cases were patients with mature and immature age-related cataract, 2 (7.4%) cases were with primary open-angle glaucoma and other 2 (7.4%) with co-existing cataract and glaucoma. The association of various diagnoses with positive conjunctival culture was statistically insignificant (p = 0.893). In our study, the most common organisms isolated were *S. epidermidis* (51.85%), *S. aureus* (29.63%), followed by *Streptococcus pyogenes* (11.11%) and *Corynebacterium xerosis* (7.41%) as shown in Table 2.

The intraocular surgery of the patients showing bacterial growth on culture plates was postponed and the designated antibiotic was continued for 5 days. Conjunctival swabs were obtained after a week of drug-free period and at this time, there was no bacterial growth in any of the 27 patients as the organisms were sensitive and therefore eliminated from the conjunctival sac. The same antibiotics were restarted 2 days before the surgery and rest of the procedure was followed as described for other patients. None of the patients included in the study developed postoperative endophthalmitis. The inhibition of bacterial growth was 100% in both the groups viz. moxifloxacin and besifloxacin and all the laboratory cultures showed no bacterial growth on second and third visits, revealing the sensitivity of organisms to be almost similar to both the test antibiotic eye drops as shown in Tables 3 and 4.

Table 1. Gender-wise Distribution of Positive Cultures among Patients

Gender	Positive culture n (%)	Negative culture n (%)	Total n (%)
Male	16 (25.81)	46 (74.19)	**62 (100)**
Female	11 (28.95)	27 (71.05)	**38 (100)**
Total	**27 (27)**	**73 (73)**	**100 (100)**
	$\chi^2 = 0.118$, df = 1, p = 0.731		

Table 2. Occurrence and Distribution of Isolated Organisms

Operated eyes	Total No. of eyes	Positive culture	Organisms isolated							
			SE		SA		SP		CX	
			No.	%	No.	%	No.	%	No.	%
RE	56	15	07	46.67	05	33.33	02	13.33	01	6.67
LE	44	12	07	58.33	03	25	01	8.33	01	8.33
Total	**100**	**27**	**14**	**51.85**	**08**	**29.63**	**03**	**11.11**	**02**	**7.41**

$\chi^2 = 0.506$, df = 3, p = 0.918

SE: *Staphylococcus epidermidis*; SA: *Staphylococcus aureus*; SP: *Streptococcus pyogenes;* CX: *Corynebacterium xerosis;* RE: Right eye; LE: Left eye.

Table 3. Group A: Effect of Topical Moxifloxacin on Bacterial Conjunctival Flora

Before use		After use			
1st Conjunctival swab (Preoperative)		2nd Conjunctival swab (Postoperative Day 20)		3rd Conjunctival swab (Postoperative Day 40)	
Positive	Negative	Positive	Negative	Positive	Negative
16	34	00	50	00	50

McNemar's $\chi^2 = 5.78$, df = 1, p = 0.016

Table 4. Group B: Effect of Topical Besifloxacin on Bacterial Conjunctival Flora

Before use		After use			
1st Conjunctival swab (Preoperative)		2nd Conjunctival swab (Postoperative Day 20)		3rd Conjunctival swab (Postoperative Day 40)	
Positive	Negative	Positive	Negative	Positive	Negative
11	39	00	50	00	50

McNemar's $\chi^2 = 14.58$, df = 1, p < 0.001

DISCUSSION

Prevention of infections following intraocular surgeries is one of the areas of maximum concern to all ophthalmic surgeons. This is especially true because recent reports suggested that though the incidence of postoperative endophthalmitis has decreased significantly in present era, the emergence of resistance among bacterial isolates to routinely used prophylactic antibiotics is a matter of great concern for eye specialists world over. In view of the possible role of conjunctival flora in the causation of any postoperative infections following intraocular surgeries along with an emergence of multidrug-resistant organisms, an understanding of the sensitivity of such flora to appropriate antibiotics is of fundamental importance. Certainly, such type of studies might guide the ophthalmologists when using a prophylactic antibiotic before performing a surgery.

Therefore, the present study aims to assess the normal conjunctival flora and possible role of two newer fourth-generation fluoroquinolones (moxifloxacin and besifloxacin) as one of the preventive measures against postoperative infections. The study was done on 100 patients admitted for various intraocular surgeries; majority of them comprised of age-related cataract (85/100), 11 being mature and 74 being immature age-related cataracts. This is because of the fact that cataract continues to be the leading cause of ocular morbidities requiring intraocular surgeries. In the present series, majority of the admitted patients (85 out of 100) underwent MSICS with PCIOL implantation followed by trabeculectomy and combined trabeculectomy with MSICS with PCIOL implantation.

McNatt et al (1978) reported that out of the 184 eye cultures, 112 (60.9%) contained at least one microorganism. Herde et al (1996) reported that out of 686 conjunctival swab cultures, 126 (18.4%) showed bacterial growth. Our study demonstrated only 27 positive bacterial growths out of 100 cases (27%) as shown in Table 1. This variable incidence could be due to variable environmental and individual factors.

In the present study, the bacterial conjunctival flora observed was almost the same in either sex (25.81% in males and 28.95% in females) as shown in Table 1. Rao and Rao (1972) also did not observe any difference in conjunctival bacterial flora of either sex (22.5% in males and 18.2% in females). They also studied the variation of conjunctival bacterial flora in relation to weather and observed a higher rate of positive bacterial cultures during summer season. Our results too indicated higher positive cultures occurring in early summer season, highest being in the month of April. The incidence of positive bacterial culture was observed to be slightly higher in older patients (>50 years of age), although the difference was statistically insignificant. Singer et al (1988) reported similar results in their study.

There was no association of various diagnoses with positive conjunctival culture. de Kaspar et al (2004) also found no relationship between the conjunctival flora and the ocular morbidities (83% positive in eyes undergoing cataract surgery and 77% in those undergoing glaucoma surgery; p = 0.2246).

Many researchers have studied the composition of normal conjunctival flora. Nema et al (1964) found coagulase-negative staphylococci as the most common organism isolated from conjunctiva. The other isolated organisms included Diphtheroids, coagulase-positive staphylococci, streptococci, pneumococci, Gram-positive spore bearing bacilli and various Gram-negative coliform bacilli. Gritz et al (1997) isolated *S. epidermidis* in 54.8% and Diptheroids in 9.5% subjects in conjunctival swabs. In our study, we noticed *S. epidermidis* (51.85%) as the most common organism isolated from conjunctiva, followed by *S. aureus* (29.63%), *S. pyogenes* (11.11%) and *C. xerosis* (7.41%) as shown in Table 2.

A number of other studies have revealed *S. epidermidis* to be the most frequently isolated organism from the conjunctival sac. This organism, being a part of normal bacterial flora of conjunctiva remains nonpathogenic among healthy individuals but can cause severe infections in the eye, including endophthalmitis, in altered conditions. Therefore, all the conjunctival organisms, including staphylococci harbored by human conjunctiva, need attention before performing any intraocular surgery in order to prevent any postoperative infection.

O'Brien et al (2007) found that moxifloxacin had potent and rapid bactericidal activity against most of the Gram-positive pathogens causing postoperative endophthalmitis, and had excellent ocular penetration after topical administration. Scoper (2008) also reported that fourth-generation fluoroquinolones (moxifloxacin and gatifloxacin) had increased potency against Gram-positive bacteria compared with third-generation fluoroquinolones (levofloxacin), while maintaining similar potency against Gram-negative bacteria.

In our study, bacterial growth was seen in 16 preoperative conjunctival swabs in moxifloxacin group and all of these isolates were found to be sensitive to moxifloxacin on performing *in vitro* antibiotic sensitivity tests and complete eradication of bacteria, as evidenced by conjunctival swab culture, was obtained after pre- and postoperative use of this antibiotic as depicted in Table 3.

Moshirfar et al (2006) first reported 2 cases of bacterial keratitis-resistant to fourth-generation fluoroquinolones after laser *in situ* keratomileusis (LASIK) and photorefractive keratectomy (PRK). Yin et al (2013) also found that repeated use of topical moxifloxacin after intravitreal injection significantly increased antibiotic resistance of ocular surface flora and recommended not to use prophylactic antibiotics routinely after intravitreal injections. Oldenburg et al (2013) isolated 89 *Pseudomonas aeruginosa* isolates during 2007, 2008 and 2009 in "The Steroids for Corneal Ulcers Trial" (SCUT) and reported an increase in the proportion of resistant isolates to moxifloxacin from 19% in 2007 to 52% in 2009. An increase in resistance to the fourth-generation fluoroquinolones was detected for both methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA) by Chang et al (2015).

In spite of reports of emergence of resistance against widely used moxifloxacin, no bacterial strain isolated in our study showed resistance to the drug. Similarly, it remained effective in the moxifloxacin receiving group as suggested by negative bacterial cultures taken 20 and 40 days postoperatively. One of the reasons for not detecting resistance to the drug might be attributed to the low prevalence of organisms with resistance to moxifloxacin in the studied population.

The other group of patients, comprising of 50 subjects undergoing various intraocular surgeries, received topical besifloxacin eye drop (0.6%). In May 2009, besifloxacin, a fluoroquinolone, was approved by the Food and Drug Administration (FDA) as a topical agent for the treatment of bacterial conjunctivitis. The results of a study conducted by Haas et al (2010) have confirmed that besifloxacin has potent *in vitro* activity against bacterial isolates including *S. aureus, S. epidermidis* and *S. pneumoniae.* Similar type of antibacterial activity against some of the isolates resistant to other fluoroquinolones was also evident

in a study that evaluated the antibacterial spectrum of besifloxacin against as much as 40 Gram-positive and Gram-negative species (Haas et al, 2009).

In our study, the prophylactic potential of besifloxacin was examined *in vitro* against only Gram-positive organisms as no Gram-negative organism could be recovered in the bacterial conjunctival flora of the patients included. All the organisms isolated from Group B patients were sensitive to besifloxacin because no bacterial growth was seen in postoperative microbiological examination as shown in Table 4. Sanders et al (2009) also demonstrated that besifloxacin was significantly more effective than gatifloxacin and moxifloxacin in reducing the number of MRSA in the rabbit cornea 16 hours after infection.

Both the fluoroquinolones under study (moxifloxacin and besifloxacin) seemed to be highly effective in *in vitro* sensitivity test conducted against all the bacterial isolates recovered from the patients undergoing various intraocular surgeries. Further, the *in vivo* use in pre- and postoperative period in the eyes of as much as 100 patients before undertaking intraocular surgeries and postoperatively at Day 20 and Day 40 revealed their effective potential as possible prophylactic agents in ophthalmic surgeries (Table 3 and 4).

CONCLUSION

On comparing the activity against the bacterial isolates, no significant difference was observed and both the antibiotics (moxifloxacin and besifloxacin) showed an effective antibacterial potential. Thus, these antibiotics can be used in ophthalmology as effective antibacterial prophylactic agents among the patients undergoing various intraocular surgeries.

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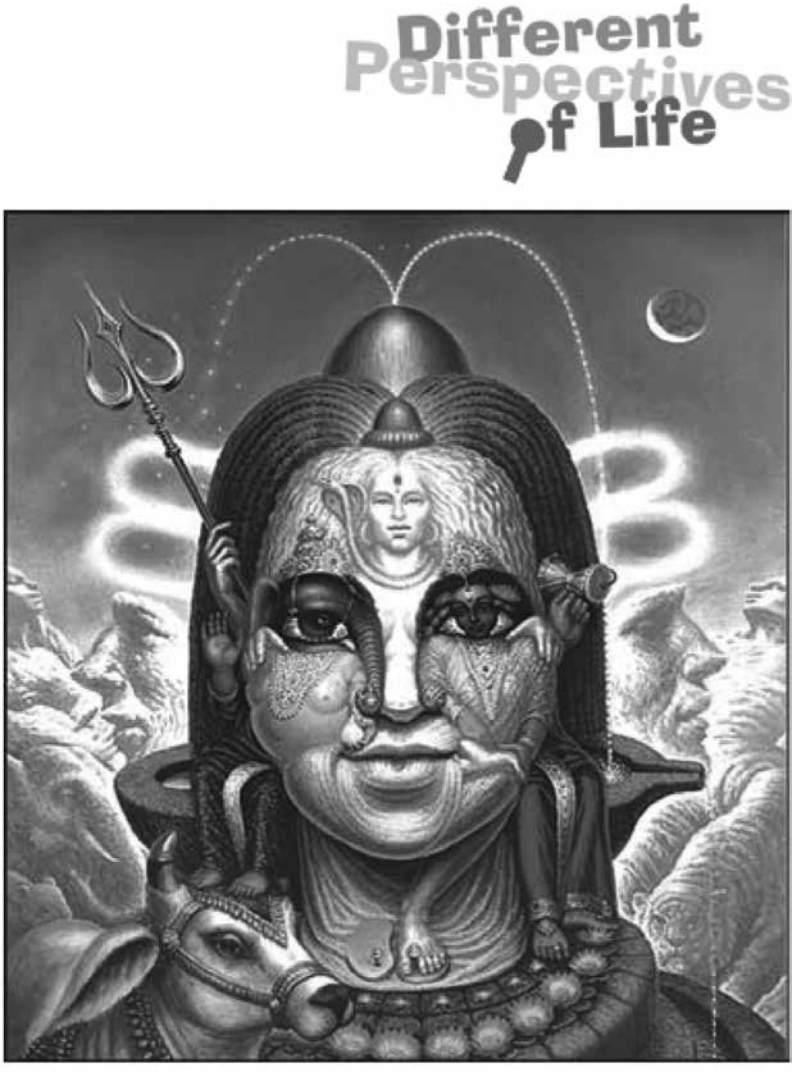

Different perceptions of Lord Shiva – multiple faces.

Indian Journal of Clinical Practice, Vol. 29, No. 12, May 2019

Uterine Didelphys with Pregnancy and Obstructed Labor: Intrapartum Course Complicated by a Rare Uterine Anomaly

SHASHIDHAR B*, HEMALATHA M SHETTI†

ABSTRACT

Mullerian duct anomalies (MDAs) are congenital anatomic abnormalities of the female genital tract that arise from non-development or nonfusion of the mullerian ducts or failed resorption of the uterine septum, with a reported incidence of 0.1-10.0%. MDAs are clinically important because they are associated with an increased incidence of impaired fertility, menstrual disorders and obstetric complications. We hereby report a case of a primigravida with full-term pregnancy with obstructed labor referred from a primary health center. During the course of examination, she was found to have congenital abnormality of uterus and vagina. She underwent an emergency cesarean section with good perinatal outcome. Women with uterus didelphys belong to a high-risk group, although pregnancy outcome is comparatively good.

Keywords: Mullerian duct anomalies, congenital anatomic abnormalities, obstructed labor, uterus didelphys

The true incidence of congenital uterine anomalies in the general population and among women with recurrent pregnancy loss is not known accurately. Although incidences of 0.1-10% have been reported, the overall data suggest an incidence of 1% in the general population and 3% in women with recurrent pregnancy loss and poor reproductive outcome. Female genital tract develops from 3 sites, ovaries from the germ cells that migrate from the yolk sac into the mesenchyme of the peritoneal cavity and develop into ova and supporting cells; lower third of vagina develops from the ascending sinovaginal bulb; and uterus, fallopian tubes and upper two-thirds of vagina develop from the fusion of two mullerian ducts. Incomplete fusion of the mullerian or paramesonephric ducts results in the most common types of uterine malformation: uterus didelphys, uterus bicornis bicollis, uterus bicornis unicollis, uterus subseptate, uterus arcuatus and uterus unicornis. Uterus bicornis bicollis is characterized by double or single vagina, double cervix and two single-horned uterus which show partial fusing of their muscular walls with duplication running right down to the uterine orifice. Congenital anomaly of the mullerian duct system can result in various urogenital anomalies including uterus didelphys with blind hemivagina and ipsilateral renal agenesis.[1]

The diagnosis of this condition is usually made after menarche, but its rarity and variable clinical features may contribute to a diagnostic delay for years after menarche.[2] With timely and accurate diagnosis, appropriate management is likely to provide the best possible outcome for all such patients.

CASE REPORT

A 20-year-old primigravida, wife of a farmer, who was referred from a primary health care center, reported to labor room on 31st May 2009 at 09:13 pm with a history of 9 months of amenorrhea and leak per vagina since 3 days and pain abdomen since 3 days. She was married for 1 year.

General examination was unremarkable. On abdominal examination, uterus was term size and cephalic presentation and there was an unusual contour of abdomen on right side. Fetal heart sound was localized

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Figure 1. Per speculum examination showing right and left hemi vagina with complete vertical vaginal septum.

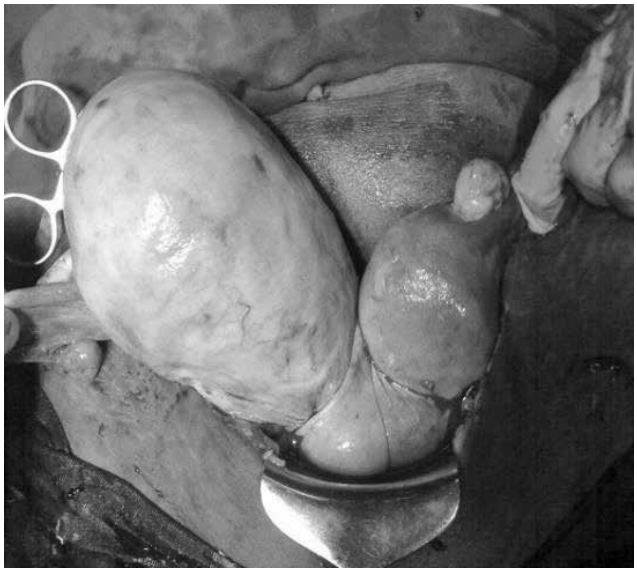

Figure 2. Anterior view of gravid right hemi uterus with incision on the lower segment and nongravid left hemi uterus.

in the right iliac fossa and was 146 bt/min. Per speculum examination revealed complete vertical vaginal septum (Fig. 1) and bulging of vaginal fornices in right hemivagina, active clear liquor leak demonstrated on the blade of speculum in right hemivagina. Internal examination revealed right cervix was partially effaced and 2 cm dilated and presenting part at minus three station, and in left hemivagina cervix was uneffaced and os closed.

On clinical examination, the pelvis was found to be grossly contracted. A decision for emergency cesarean

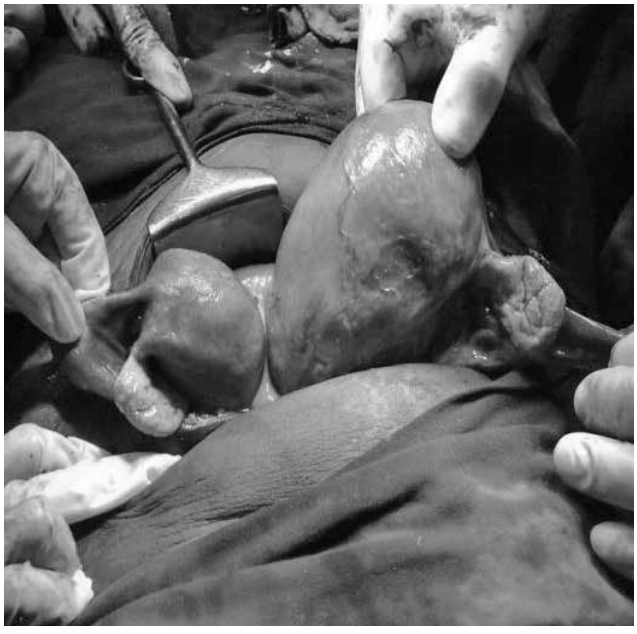

Figure 3. Posterior view of didelphic gravid hemi uterus.

section was made. She underwent an emergency cesarean section on 01/06/09 at 12:30 am; a full-term male baby of weight 3.2 kg was extracted who cried after delivery. Uterus was found to be bicornis bicollis and pregnancy was found in the right hemi uterus (Figs. 2 and 3). Postoperative stay was uneventful and sutures were removed on 7th postoperative day and the patient was discharged the same day.

DISCUSSION

Mullerian anomaly rate is reported between 0.1-1% in general population with significantly higher rates associated with infertility and reproductive wastage. Uterus didelphys is one of the least common anomalies, representing approximately 5-7% of müllerian defects. The reproductive outcomes are slightly better than those of women with unicornuate uterus. Acién reported that poorest viability results were found in the bicornuate (40%), arcuate (45%) and septate uterus groups (59%) and rates of children surviving for more than 7 days were around 70% in the bicornis bicollis, didelphys, unicornuate and subseptus uterus groups.[3] Maneschi et al reported live birth rate of 81% and suggested that reproductive and gestational performances of women with uterus didelphys are preserved. In patients with infertility complaints, associated causes must be ruled out before surgical correction. If these are present, their correction must be attempted as first therapeutic step, and term pregnancy with live baby is the rule.[4] Interestingly, pregnancy has been observed consistently in right horn.[5]

In case of single pregnancy, it is in the right uterus in uterus didelphys. Even in this present case, pregnancy has been found in the right hemi uterus. Heinonen and colleagues observed a cesarean section rate of 82% and fetal survival rate of 67.5% and premature delivery of 21%.[6] All the patients also had a longitudinal vaginal septum.

Three-dimensional sonography has contributed the most and has become the investigation of choice in units where available. Raga et al and Wu et al reported that three-dimensional sonography offered a 100% specificity and is reproducible and reliable noninvasive diagnostic procedure for the exclusion of uterine anomalies and was able to differentiate between the different anomalies.[7,8] Magnetic resonance imaging (MRI) is the most sensitive imaging modality for congenital anomalies.

CONCLUSION

Congenital uterovaginal anomalies can have adverse effects on pregnancy outcome. Early diagnosis and an aggressive evaluation of any patient presenting with mid-trimester abortion, premature labor, malpresentation, prevent additional pregnancy wastage and maternal morbidity and are likely to provide the best possible outcome for all such patients.

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Vitamin D Deficiency – A Reversible Cause of Proximal Myopathy

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ABSTRACT

A 22-year-old married Hindu female, vegetarian, with lower socioeconomic status, presented with an insidious onset progressive bilateral lower limb symmetrical proximal muscle weakness without sensory and bladder and bowel involvement, from last 2 years. Bone scan reports were suggestive of mineral and bone disease. Vitamin D deficient osteomalacia was diagnosed based on elevated serum alkaline phosphatase levels, raised intact parathyroid hormone levels, decreased 25-hydroxyvitamin [25(OH)D] levels. Patient's symptoms improved after oral active vitamin D and calcium administration. The present case highlights the importance of considering vitamin D deficiency in patients presenting with musculoskeletal symptoms and a routine evaluation for vitamin D deficiency should be considered in all patients.

Keywords: Vitamin D deficiency, proximal myopathy, hypocalcemia, osteomalacia

Although the prevalence of vitamin D deficiency is common worldwide, it is often under-estimated. It is estimated that vitamin D deficiency or insufficiency affects around 1 billion population worldwide.[1] According to the previously published study reports, the prevalence of varying degrees of vitamin D deficiency with low dietary calcium intake in Indian population is extensive (50-90%).[2] However, the exact incidence of myopathy in individuals with hypovitaminosis D is unknown. Proximal myopathy has been reported to be present in 60-75% of patients with vitamin D deficiency.[1]

The weakness usually occurs in proximal muscles and it is often minimal and subclinical. Osteomalacia, by definition, means that osteoblasts have laid down a collagen matrix, but there is a defect in its ability to be mineralized. In children, a defect in the mineralization of the osteoid in the long bones and the failure or delay in the mineralization of endochondral new bone formation at the growth plate leads to the classic skeletal deformities of rickets. However, in adults, the mineralization defect takes on a different character due to the failure of mineralization of newly formed osteoid at sites of bone turnover of periosteal or endosteal apposition. Here, we present a case of severe muscle weakness with osteomalacia due to vitamin D deficiency, which rendered the patient wheel chair bound.

CASE REPORT

A 22-year-old female visited our outpatient clinic with weakness of bilateral lower limbs, which was gradually progressive from last 2 years. The patient, who was wheel chair bound from past 3 months, complained of bilateral lower limb pain, backache, severe fatigue and inability to walk without support and to get up from squatting position and slight difficulty in combing of hair and lifting of weight from last 3 months. There was no history of any trauma/steroid intake/periodic paralysis/chronic diarrhea/carpopedal spasm/hematuria/neck swelling/palpitations/tremors/jaundice/height loss/fragility fracture/antiepileptic intake/antitubercular intake. Patient had history of recent blood transfusions and was currently on oral iron and multivitamins supplements.

On examination, patient was conscious, well-oriented, had pallor with slight dark complexion. Her vitals

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were: blood pressure (BP) - 120/80 mmHg, pulse - 84 bpm, respiratory rate (RR) - 16/min, body mass index (BMI) - 19.4 kg/m^2. She had regular bowels, bladder habits and sleep cycle. Her cardiovascular, respiratory and abdominal examinations were normal.

Central nervous system (CNS) examination revealed symmetrical proximal muscle weakness in bilateral lower limb with power of 3/5 at hip joint and in upper limb with power of 4/5 at shoulder joint and brisk deep tendon reflexes (DTR), and there was no sensory involvement. Skeletal examination revealed tenderness over lower back, hip and shin. Rest of the examination was normal.

Lab investigations revealed hemoglobin (Hb) - 10.4 g/dL, total leukocyte count (TLC) - 4,500, differential leukocyte count (DLC) - $P_{68}L_{28}M_2E_2$, platelet count - 4.2 lac. Kidney and liver function tests were normal. Patient had low serum calcium - 8.0 mg/dL, low serum phosphate - 1.8 mg/dL, raised serum alkaline phosphatase (ALP) - 874 IU/L and serum albumin level of 3.8 g/dL. Serum intact parathyroid hormone (PTH) level was 93.06 pg/mL (normal: 10-65 pg/mL) and serum 25-hydroxyvitamin D [25(OH)D] level was 18.68 nmol/L (normal: 75-100); immunoglobulin A anti-tissue transglutaminase antibodies (IgA-tTG) level was normal. The urine was negative for urinary albumin and glucose and pH was 6.0; 24-hour urinary calcium was 49.3 mg/day (100-300 mg/day). Antinuclear antibodies (ANA), thyroid function test and total creatine phosphokinase (CPK) level were normal. The bone mineral density (BMD) T-score and Z-score, as measured by dual-energy X-ray absorptiometry, was -2.7 and -2.5 at the lumbar spine and -2.8 and -2.0 at the femoral neck, respectively, indicating a low BMD for her chronological age.

Radiographic images revealed a pseudo-fracture in the right radial shaft and lower end of left femur (Fig. 1), bilateral superior pubic rami (Fig. 2), and first, second and fifth metatarsal bones along with diffuse osteopenia in B/L tarsals, metatarsals and phalanges (Fig. 3). Bone scan (technetium 99m-methyl diphosphonate [^{99m}Tc-MDP]) showed abnormal increased uptake by skull bone, scapula and upper limb bones, multiple ribs and vertebrae, pelvic bone, lower end of left femur and multiple metatarsal bones (Fig. 4). Electrophysiological study was suggestive of myopathy.

On the basis of examination and investigations, patient was diagnosed as a case of vitamin D deficiency with secondary hyperparathyroidism. The patient was treated with once weekly doses of cholecalciferol 60,000 IU along with calcium carbonate 500 mg twice-daily.

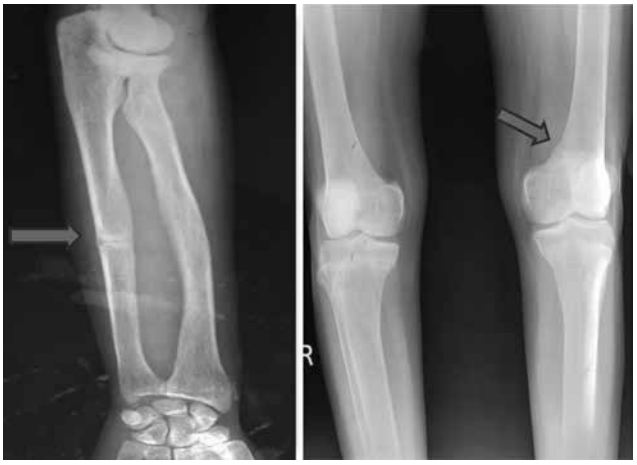

Figure 1. X-ray right forearm and lower end of left femur shows looser zone.

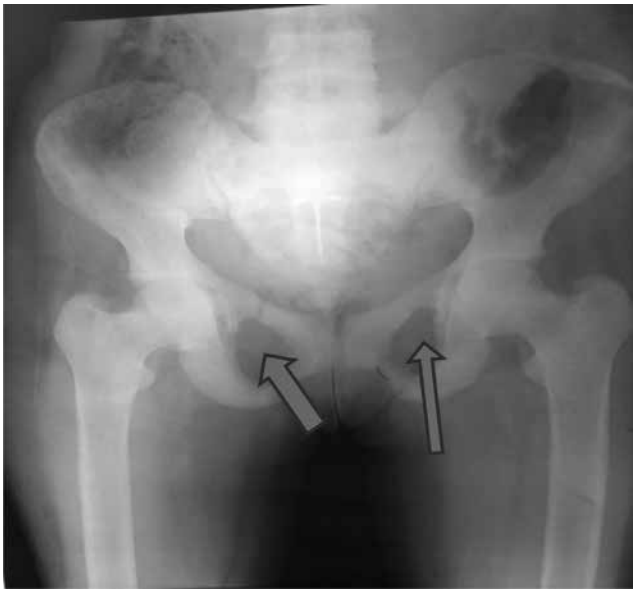

Figure 2. X-ray pelvis shows pseudo-fracture.

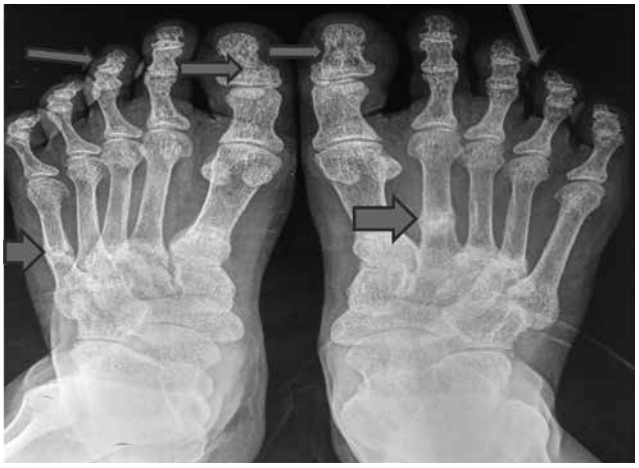

Figure 3. X-ray shows looser zone (*thick arrows*) and diffuse bone resorption (*thin arrows*).

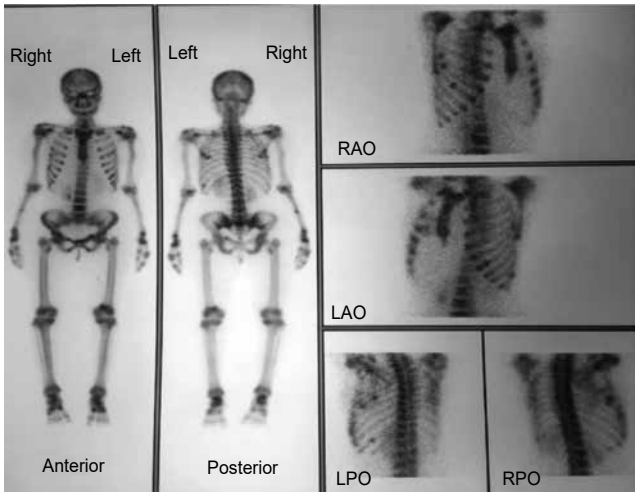

Figure 4. Bone scan.

Follow-up conducted at 4 weeks showed a gradual improvement in her symptoms. She was able to get up from chair and move without support and got significant relief in pain and fatigue. Levels of serum calcium and phosphorus were normalized but serum alkaline phosphatase (ALP) levels were still high (814 IU/L). At 3-month follow-up, pain, muscle weakness and gait disturbance had been completely alleviated and she resumed her routine daily activities. Biochemical parameters showed normal serum calcium, phosphorus as well as serum PTH and ALP. Patient is now on regular follow-up.

DISCUSSION

It has been estimated that over 1 billion people worldwide have vitamin D deficiency.[3] Vitamin D deficiency leads to decreased intestinal absorption of calcium and phosphorus, causing hypocalcemia and hypophosphatemia. Consequently, PTH secretion increases to overcome hypocalcemia which ultimately causes bone demineralization and osteomalacia in adults. In adults, osteomalacia usually does not present with any overt skeletal signs. However, patients with osteomalacia complain of throbbing, aching bone discomfort. Bone discomfort is worse when sitting or lying in bed. This is usually associated with proximal muscle weakness and aching in muscles.[4-6] Pressing on the skeleton resulting in discomfort is consistent with a trigger point that can lead to the misdiagnosis of fibromyalgia. In many cases, these patients are suffering from periosteal bone discomfort consistent with osteomalacia.

Several studies have shown an association between vitamin D deficiency and proximal myopathy. In most of the patients, muscle weakness, which is usually minimal, is revealed mostly on detailed history and physical examination. In infants, myopathy is evident from muscle weakness and hypotonia.[7] Adults may present with predominant proximal muscle weakness with difficulty in getting up from squatting position or climbing stairs. Other clinical characteristics of the disease include uniform generalized muscle wasting with preservation of sensation and DTR, and waddling gait.[8] Bone pain may also be present.

The case presented here had disabling muscle weakness and was not able to walk independently. Her serum calcium level was low-normal with low serum phosphorus with secondary hyperparathyroidism and elevated serum ALP. Normal serum levels of calcium and phosphorus in healthy individuals are achieved predominantly through interaction between the two hormones: PTH and calcitriol. In patients with vitamin D deficiency, secondary hyperparathyroidism causes release of calcium stored in bone and reabsorption of calcium by kidneys to maintain normal serum calcium till bony calcium is available. Hence, mild-to-moderate vitamin D deficiency is usually accompanied by normal blood levels of calcium, high-normal or elevated levels of PTH, elevated levels of ALP, a low 24-hour urine calcium excretion rate. Overt hypocalcemia and/or hypophosphatemia may appear only in patients with severe and long-standing vitamin D deficiency.[9]

While the exact cause of the muscle weakness and bone discomfort is not fully understood, it is believed that because the major cause of osteomalacia is vitamin D deficiency and because skeletal muscle has a vitamin D receptor (VDR), the lack of 1,25-dihydroxyvitamin D [1,25(OH)2D] interacting with the skeletal muscle VDR increases muscle weakness.[10]

Metabolic myopathies may be often accompanied by secondary hypovitaminosis D. Biopsies can help in differentiating hypovitaminosis D myopathy (HDM) from other myopathies, but this is rarely performed in current clinical practice due to its invasiveness and better availability of noninvasive biochemical and radiological markers.

The mechanism of HDM remains controversial, and it is still not clear whether vitamin D deficiency itself or in association with secondary hyperparathyroidism is the primary cause of muscle tissue and functional abnormalities. PTH production, induced by low vitamin D levels, may confer direct effects on skeletal muscles.

It is important to evaluate vitamin D deficiency as a cause of myopathy in suspected cases. Severe vitamin D

deficiency is easily treatable. Generally, advocated strategy is to prescribe a loading dose (50,000 IU of oral vitamin D once a week for 2-3 months or three times weekly for 1 month). A previous analysis of multiple loading algorithms indicated that a minimum total dose of 6,00,000 IU best predicted an end-of-treatment 25(OH)D concentration >30 ng/mL. For mild-to-moderate deficiency (11-25 ng/mL), a shorter term treatment or lower dose may be effective. In cases with recurrent deficiency, maintenance daily dose of 800-2,000 IU or more will be required. Treatment using high-dose vitamin D for 6 months or more may be essential for full normalization of HDM.

The present case highlights the significance of considering treatable causes first in patients presenting with musculoskeletal symptoms. A routine test for hypovitaminosis D should be considered in patients with musculoskeletal symptoms such as bone pain, myalgia and generalized weakness; as there is an increased chance for misdiagnosing hypovitaminosis D-associated symptoms as fibromyalgia, chronic fatigue, age-related weakness or depression.

CONCLUSION

It is always worthwhile to look for common and treatable factors causing metabolic bone disease. HDM is a common cause for proximal muscle weakness and osteomalacia. Raised ALP and PTH levels should always be worked up to diagnose vitamin D deficiency, which is easily treatable. Myopathy linked to vitamin D deficiency is completely reversible.

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EXID, A Rare Paradoxical Response to ART

Scientists have identified a rare, paradoxical response to antiretroviral therapy (ART) known as extreme immune decline or EXID. Five individuals evaluated at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, experienced a significant decline in CD4+ T cell levels despite suppression of HIV below detectable levels for more than 3 years, according to a report published online April 18, 2019 in *JCI Insight*.

Exercise in the Morning to Gain Better Results

A new study published April 18, 2019 in *Cell Metabolism* has found that exercising at the correct time of day - around mid-morning - results in more oxygen in the cells and a more rejuvenating effect on the body. These results suggest daily timing as a critical variable for metabolic benefits from exercise and implications in chronobiology-based exercise therapy for patients with metabolic disorders.

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Indian Journal of Clinical Practice, Vol. 29, No. 12, May 2019

Malignant Peripheral Nerve Sheath Tumor Arising in a Neurofibroma

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ABSTRACT

Malignant peripheral nerve sheath tumor (MPNST) is a rare variety of soft tissue sarcoma of ectomesenchymal origin. These tumors present diagnostic difficulties in differentiating from other high-grade spindle sarcomas. This is a case of a 45-year-old lady who presented with pain and swelling in the groin for past 4 months, which on excision and histopathology revealed an MPNST in a neurofibroma.

Keywords: Malignant peripheral nerve sheath tumor, soft tissue sarcoma, ectomesenchymal, neurofibroma

Malignant peripheral nerve sheath tumor (MPNST) is a malignant neurogenic tumor that occurs with high frequency (8-13%) in association with neurofibromatosis type 1 (NF-1), arising either *de novo* or in transition from neurofibroma.[1] It either develops from peripheral nerves, pre-existing benign neurofibromas or schwann cells. NF-1 patients are more frequently diagnosed with MPNST in the third or fourth decades of life, whereas the sporadic form of MPNST is most frequently diagnosed in the sixth or seventh decades of life.

CASE REPORT

A 45-year-old female developed pricking type of pain in the right groin extending to right knee for a duration of 4 months. There was also a history of fever on and off for 1 month. She gave a history of neurofibromatosis for 35 years. On local examination, a large neurofibroma was seen in the right inguinal region. Neurofibromas were also seen on the knee and arms (Figs. 1 and 2).

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On ultrasound, there was a well-defined heterogeneous mass involving predominantly deep subcutaneous and muscular planes of proximal right thigh measuring 9.7 × 5.7 × 5.8 cm. Fine needle aspiration cytology (FNAC) of the same lesion showed fibrocytes, mature adipocytes, a few spindle-shaped cells with sharp ends suggestive of wavy nerve fibers. She had history of excision of the swelling in the same region 2 years ago, which was histologically proved to be a neurofibroma.

In the same region, the patient presented with the present swelling. On excision of the mass, histologically it showed an undifferentiated pleomorphic sarcoma (Fig. 3), which was confirmed on immunohistochemistry

Figure 1. Single, small neurofibroma seen on lateral aspect of the left knee.

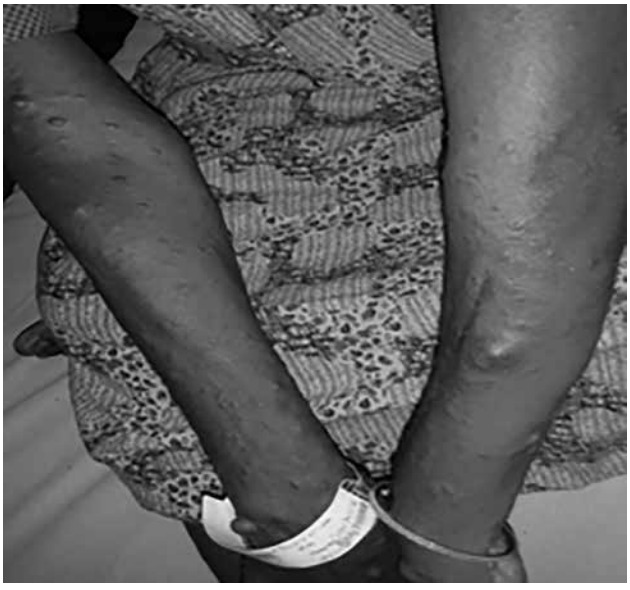

Figure 2. Both arms showing multiple neurofibromas of varying sizes.

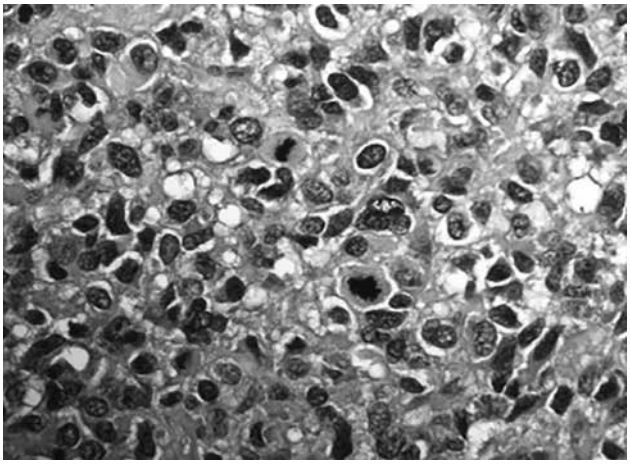

Figure 3. Pleomorphic tumor cells with mitotic figures (H&E x400).

Figure 4. S-100 positivity in the tumor cells (IHC x100).

to be positive for vimentin and S-100 (Fig. 4) suggesting a neural origin. The tumor cells were markedly pleomorphic with increased mitosis, many of them being atypical. Thus, a diagnosis of MPNST in a neurofibroma was given. Patient was referred to a radiation oncologist for further management.

DISCUSSION

MPNST is a rare malignant tumor with poor prognosis accounting for 3-10% of all soft tissue sarcomas. It is the second most common variety of soft tissue sarcomas seen. A combination of gross and microscopic findings along with immunohistochemical studies is commonly used to diagnose a case of MPNST.

These tumors occur in equal frequency in males and females and some series have shown a female preponderance. The majority of these tumors are seen involving the extremities; although tumors were also seen in unusual sites, such as the pelvis, retroperitoneum and infratemporal fossa. Imaging is routinely performed to assess the extent of the disease and plan surgical resection. However, it does not reliably determine the malignant transformation from neurofibroma to MPNST. Magnetic resonance imaging (MRI) is the investigation of choice because it can reveal the nerve of origin. Grossly, the tumor size ranges from 4 to 24 cm in greatest dimension.[2]

Histologically, following criteria are used for the diagnosis of MPNST: a) Gross fusiform tumors in relation to nerves; b) microscopic feature of spindle cell with fascicular pattern and varying degrees of mitosis, necrosis and tumor calcification; c) presence of associated benign neurofibroma or schwannanian cells and d) positive immunohistochemical staining for S-100 protein, neuron-specific enolase and others like actin, cytokeratin, smooth muscle actin and vimentin to differentiate from other spindle cell sarcomas. The tumors are classified as low-grade and high-grade on the basis of their cellular differentiation, mitotic count, tumor necrosis and expression of MIB-1 proliferation marker.[2,3]

However, it is not always possible to demonstrate the origin from a nerve, especially when it arises from a small peripheral branch. This point was exemplified in a series by Nambisan et al, in which nerves could not be identified in 61% of cases of MPNST[4] and in the series by Bilgic et al, in which nerve origin could be identified only in 45-56% cases.[5] Still, there are several other distinct features, such as proliferation of tumor in the subendothelial zones of vessels with neoplastic cells

herniating into vessel lumen and proliferation of small vessels in the walls of the large vessels, which are very characteristic features of MPNST. Syndromes that are associated with MPNST are NF-1 and NF-2.

Histologically, strict morphologic criteria must be applied to distinguish the spectrums of MPNSTs from cellular schwannoma, atypical and malignant meningioma and from a variety of rarely occurring intracranial sarcomas, such as high-grade pleomorphic sarcoma "malignant fibrous histiocytoma" fibrosarcoma, synovial sarcoma and leiomyosarcoma. On the benign side of the spectrum, cellular schwannoma is another tumor to be distinguished from MPNST. This tumor is particularly prone to be mistaken for malignancy, given the presence of hypercellularity, mitotic activity, and occasional locally aggressive growth. Strong S-100 protein as well as collagen IV/laminin immunoreactivity is the rule in this tumor. With respect to separating MPNST from benign nerve sheath tumors, p53 may be useful, strong immunostaining being seen in the majority of MPNSTs.[6] Ten percent of MPNSTs exhibit focal divergent differentiation, either mesenchymal (rhabdomyosarcoma, chondrosarcoma, osteosarcoma, angiosarcoma) or epithelial (mucin-producing, neuroendocrine or squamous type).

CONCLUSION

MPNSTs are aggressive, high-grade, therapy-resistant and associated with poor prognosis. A combination of clinical, pathological and immunohistochemistry helps in diagnosing these tumors. Proliferation marker (MIB-1) can be a good adjunct to grade and tailor the treatment in MPNST. Sex and cellular differentiation are the new adverse prognostic factors for survival of the patients. Postoperative radiotherapy has a definitive role in both disease-free and overall survival. Though multimodality therapy, including surgical resection and adjuvant radiotherapy, is available, the prognosis remains dismal. Modern clinical studies and the development of effective targeted chemotherapy are needed to gain control of the disease.

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Preschool Children with Chronic Constipation are Often Picky Eaters

In the first study of its kind in the US, researchers found that normally developing preschool children with chronic constipation have underlying sensory issues that contribute to their difficulties with toileting behaviors. These children are often picky eaters who might be overly sensitive to food textures, tastes or odors. They also might have an exaggerated response to noises, bright lights or other sensory stimuli. These findings are published in the *Journal of Pediatrics*.

AAP Updates Clinical Advice on Treating Children with Neurofibromatosis Type 1

The American Academy of Pediatrics (AAP) and the American College of Medical Genetics and Genomics have published updated guidelines on neurofibromatosis type 1, online April 22, 2019. Children often are identified when they develop multiple flat patches of the skin "café-au-lait spots" that are darker than the surrounding area. Periodic monitoring for scoliosis, signs of early puberty, and school difficulties is recommended as more signs and symptoms emerge with age, including benign tumors along the nerves in the skin and other parts of the body.

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Dreaded Complication of Free Flap Failure Managed Intelligently

ASHOK SHARMA*, SANJIV K GOYAL*, SANDEEP SINGH MAAVI†, VIJAY JAGAD‡, AMITABH KUMAR UPADHYAY#

ABSTRACT

Salvage surgery in head and neck carcinoma is often followed by dreaded postoperative complication. Reconstruction with free flap is usually the ideal treatment option. Here, we present the case of a 46-year-old man with necrosis of free flap in post-radiotherapy carcinoma buccal mucosa. The flap was thus taken down and was replaced by a large pectoralis major myocutaneous flap to cover the intraoral defect and part of the facial defect. The area in front of ear was left bare, to be reconstructed after stabilization of the patient. Later, the patient was taken up for surgery and posterior auricular flap was used to cover the defect anterior to the ear. Astute knowledge of local flap with preserved blood supply is thus needed in post-radiotherapy cases with failure of free flap.

Keywords: Head and neck carcinoma, free flap, salvage surgery

Salvage surgery in head and neck carcinoma is often met with dreaded postoperative complication. Reconstruction with free flap becomes the ideal intervention as it gets new blood supply to the area and hence theoretically improves the chances of viability of flap. In case of necrosis of free flap, very little options are left for the cover of the defect. Here, we are presenting the case of necrosis of free flap in post-radiotherapy carcinoma buccal mucosa. After multiple surgeries, patient received adequate cover of the defect with local flaps but with poor functionality.

CASE REPORT

A 46-year-old man presented to us with history of ulcer in left buccal mucosa and severe trismus for past 3 months. In past, patient had undergone surgery and radiation for carcinoma left buccal mucosa 1½ year back.

On examination, patient had severe trismus Grade IV and the lesion was seen starting from left anterior commissure; due to severe trismus, posterior extent of the lesion was not assessable. Magnetic resonance imaging (MRI) scan of the face and neck revealed irregular thickened lesion involving whole of left buccal mucosa extending from upper alveolus to the lower gingivobuccal sulcus. Biopsy from the buccal mucosal lesion revealed squamous cell carcinoma. In accordance with the extent of lesion and the post radiotherapy status of the neck skin, we planned for wide excision and cover with free flap.

Patient underwent wide excision with left hemimandibulectomy, left upper alveolectomy and cover with anterolateral free flap. Post-op on second day, the free flap became dusky and revision surgery was planned (Fig. 1). The flap was taken down and was replaced by a large pectoralis major myocutaneous (PMMC) flap to cover the intra-oral defect and part of the facial defect. The PMMC flap did not cover the defect completely and the area in front of left ear was left open (Fig. 2). Patient was managed conservatively and later

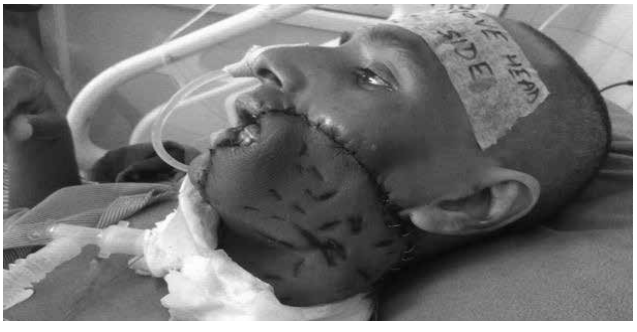

Figure 1. Free flap getting dusky at post-op Day 2.

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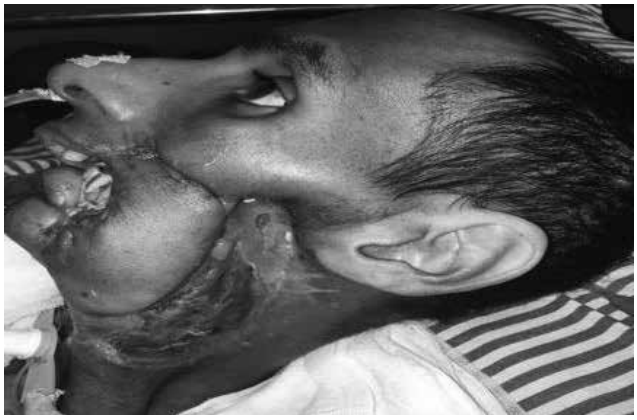

Figure 2. PMMC flap covering part of the defect after taking down the free flap, preauricular area still left uncovered.

Figure 3. Complete cover of the defect after using posterior auricular flap.

after complete recovery, posterior auricular flap was used to cover the defect anterior to left ear (Fig. 3).

DISCUSSION

Post-radiotherapy recurrent tumors in head and neck regions are taxing for surgeons to deal with. These cases are met with maximum postoperative complication due to reduced vitality of the tissue. The tissue, after radiotherapy, undergoes fibrosis with severe contractures and reduced blood supply. Reconstruction of the defect after full thickness excision is another challenge. The option of local rotation flap is not viable due to extensive radiotherapy effect and associated contracture. Plastic surgeon needs to bring viable tissue from nonirradiated area to the site of defect and anastomose to it. This can be best done by myofasciocutaneous free flap. Still postoperative complication rate of infection, fistula formation, flap necrosis remains high in these cases.

An ideal free flap which suits best for the defect and has least complication is not derived yet. One has to choose according to the site and size of the defect for optimal functional and cosmetic rectification. This patient of ours had lesion involving left buccal mucosa right from anterior commissure to the retromolar trigone and also the left lower gingivobuccal sulcus. The left cheek was puckered post-radiotherapy, but frank invasion of tumor into the skin was not there. In view of extensive buccal mucosal involvement and thick nonpliable cheek skin, we planned for complete full thickness excision and reconstruction with free flap. Anterolateral thigh flap was used for reconstruction of inner buccal mucosal lining and for the outer skin coverage.

On post-op Day 2, flap became dusky and on stroking the flap no prompt bleeding was noted. Plan was made to take down the flap and for local flap cover. Patient's left side face and neck was irradiated and hence there were minimal options for local flap. PMMC flap was used to cover the defect, intraoral lining was covered completely but the face was partly covered. The area in front of ear was left bare for reconstruction after stabilization of the patient. After 2 weeks, he was taken up for surgery and posterior auricular flap was used. Patient was discharged after complete take up of the flap. Astute knowledge of local flap with preserved blood supply must be there in post radiotherapy cases with failure of free flap.

CONCLUSION

Free flaps are the best to cover the defect after salvage surgery in head and neck carcinoma. Free flap failure leads to bad functional as well as cosmetic aspect of head neck region. A redo surgery with cover from local flaps is difficult and that compromises the final outcome of the patient.

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Newer and Emerging Topical Therapies in Dermatology

SATISH DA*, RADHIKA VK†, APARNA AD†

Some newer and emerging topical therapies in dermatology in recent times are discussed here.

FENTICONAZOLE

Fenticonazole is an imidazole antifungal agent used to treat fungal infections of the vagina (Vulvovaginal candidiasis). It is active against a range of organisms including dermatophytes, *Malassezia furfur* and *Candida albicans*. It is not recommended for usage in pregnancy and lactation. Side effects include local reactions like burning sensation, itching and rash, which are rare. Fenticonazole nitrate is available for topical use as a 2% cream. Fenticonazole acts by inhibition of the synthesis of aspartate (acid) proteinase, a virulence enzyme of *C. albicans* correlated with the adherence of the yeast to epithelial cells.

HYDROGEN PEROXIDE 40%

It is a proprietary formulation of a stabilized high concentration hydrogen peroxide solution that is the first and only US Food and Drug Administration (FDA) approved topical treatment for raised seborrheic keratoses. It acts by direct oxidation of organic tissues, local lipid peroxidation and generation of reactive oxygen species as well as generation of local concentrations of oxygen that are toxic to seborrheic keratoses cells. It is available as a 40% solution.

TRIFAROTENE 0.005% CREAM

Cellular effects of retinoids are mediated by two types of nuclear receptors: the retinoic acid receptor (RAR) and the retinoid X receptor (RXR), both of which are present in three isoforms (alpha, beta and gamma). Trifarotene is a fourth-generation topical retinoid, a potent and a selective RAR-gamma receptor agonist. This results in better efficacy and a favorable safety profile in acne and ichthyotic disorders. It has completed phase 3 trials in acne vulgaris in November 2017.

ATROPINE SULFATE

It is an anticholinergic agent and antimuscarinic agent (parasympatholytic). It is indicated in primary axillary hyperhidrosis, symptomatic eruptive syringomas and multiple eccrine hidrocystomas. Mechanism of action: Tumor cells differentiate towards dermal duct cells. Cells could get activated during cholinergic stimulation and atropine would antagonize the above action completely. The agent is available as atropine sulfate 1% ointment.

TIMOLOL MALEATE

It is a beta-blocker medication. It has been used in superficial and small infantile capillary hemangiomas and pyogenic granuloma. It causes constriction of the blood vessels, and reduces blood flow, resulting in reduction in size of cells, making the vessels softer. It is available as 0.5% gel.

THYMOL LOTION

Thymol is found in oil of thyme, extracted from *Thymus vulgaris* (plant). Mechanism of action: It alters the hyphal morphology, causes hyphal aggregates which results in lyses of the hyphal wall. It is indicated in Tinea infections and Candidal paronychia.

INDIRUBIN

It is an active ingredient in Indigo naturalis (Chinese medicine). It is a chemical compound (oily extract) produced as a by-product of bacterial metabolism. Lindioil is a refined formulation of Indigo naturalis. Mechanism of action: Indigo naturalis extract regulates proliferation and differentiation of epidermal keratinocytes, restores the epidermal barrier function and inhibits inflammatory reactions. It reduces subungual hyperkeratosis and onycholysis. It acts as an anti-inflammatory and as an antiangiogenic agent. Indications: Psoriasis.

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TOPICAL AGENTS IN THE PIPELINE FOR ACNE

Agents Targeting Sebum Production

- Topical antiandrogens:
  - Cortexolone-17 alpha-propionate (CB-03-01) is a monoester of cortexolone which has anti-androgen actions with no systemic side effects.
  - ASC-J9 cream causes degradation of the androgen receptor. It also causes reduction in the sebum production.
  - NVN-1000 (SB204) is a gel that causes release of nitric oxide with topical application. It decreases cutaneous androgen levels by inhibiting cytochrome P450, reduces 5-alpha reductase activity, thereby reducing sebocyte proliferation. It also exhibits antibacterial effects.
- Melanocortin receptor antagonists: JNJ 10229570, a melanocortin receptor 1 and 5 antagonist, reduces the size of sebaceous glands and the production of sebaceous lipids.
- Insulin-like growth factor 1 inhibitors: Epigallocatechin-3 gallate (EGCG), is a polyphenolic constituent in green tea. It inhibits 5-alpha reductase 1 activity, limiting dihydrotestosterone-dependent sebum production. It also exerts antimicrobial activity against *Propionibacterium acnes*.
- Acetylcholine inhibitors: Botulinum toxin inhibits the presynaptic acetylcholine release, reducing sebum production, pore size and skin oiliness.
- Acetyl coenzyme A carboxylase (ACC) inhibitors: They reduce synthesis of triglycerides, increasing oxidation of fatty acids. DRMO1 7.5% gel is under trial.

Agents that Normalize Abnormal Keratinization within the Pilosebaceous Unit

- Retinoic acid metabolism blocking agents: Talarozole inhibits cytochrome CYP26, increasing levels of retinoic acid, causing normalization of follicular epithelium, reducing comedo formation. 0.35% and 0.7% talarozole gel is formulated that causes less irritation.
- Monoclonal antibodies and anti-interleukin (IL)-1 alpha: RA-18C3, an IL-1 alpha monoclonal antibody is used to treat moderate-to-severe acne. Subcutaneous injections of 100 mg/200 mg of RA-18C3 are given on days 0, 21 and 42 for a total of 3 injections, showing significant improvement.

Agents that Work by Modulating the Inflammatory Response

Phosphodiesterase (PDE) inhibitors, inhibitors of IL-1 beta-mediated inflammatory response - Gevokizumab, Vitamin D analogs, Dapsone gel 5%.

BEXAROTENE GEL

Bexarotene gel 1% is effective in treating mild-to-moderate plaque psoriasis as monotherapy and in combination with narrow band ultraviolet B (NB-UVB). Mechanism of action: It selectively binds to nuclear retinoid X receptor.

EOSIN AND OIL OF CADE

Topical preparation of 2% eosin alone or in combination with oil of Cade is effective in the treatment of flexural/napkin psoriasis in children.

IVERMECTIN 1%

Cream formulation is effective in treating papulopustular rosacea and in periorificial dermatitis in children. In 2014, the US FDA approved this medication for the treatment of rosacea in adults. Ivermectin is efficacious in reducing inflammatory lesion counts and erythema. Mechanism of action: Ivermectin is a topical antiparasitic agent, a macrocyclic lactone with broad-spectrum activity against multiple parasitic organisms. Ivermectin eradicates Demodex mites that reside in the pilosebaceous units of patients with papulopustular rosacea. Anti-inflammatory effects of ivermectin are achieved through reducing neutrophil phagocytosis and chemotaxis, inhibition of inflammatory cytokines and upregulation of anti-inflammatory cytokine.

BRIMONIDINE TARTRATE (0.33% GEL)

It is the first topically effective agent for the treatment of facial erythema of rosacea having a rapid onset, sustained duration of effect for 12 hours, and good tolerability. It is applied once a day. Mechanism of action: It is a highly selective alpha-2 adrenergic receptor agonist and is 1000-fold more selective for the alpha-2 adrenergic receptor than the alpha-1 adrenergic receptor. It is a potent vasoconstrictor of the subcutaneous vessels, acts as an anti-inflammatory agent by reducing edema associated with rosacea. It is metabolized by the liver, and the major route of elimination is urinary excretion.

TAZAROTENE GEL (0.1%)

It has now been recommended in the treatment of moderate-to-severe facial atrophic acne scars.

NEWER TOPICAL AGENTS FOR ATOPIC DERMATITIS

Targeting Janus Kinase

Tofacitinib inhibits JAK1 and JAK3, and inhibits TH2 signalling pathways. It also inhibits cytokines such as IL-4, attenuating JAK-STAT signalling in keratinocytes. It has a good safety profile, early onset of effect and local tolerability, with the most common adverse event being self-limited infections, (nasopharyngitis) and application site pain and pruritus. Ruxolitinib, a JAK1/JAK2 inhibitor, is currently under a phase 2 study in adult atopic dermatitis patients.

PDE4 Inhibitors

Crisaborole - It is a boron-based (phenoxybenzoxaborole), nonsteroidal, topical anti-inflammatory, PDE4 inhibitor, identified through the development and screening of various benzoxaborole derivatives. It is a small molecule, the first in its class to be approved by the FDA. Mechanism of action: Inhibition of PDE4 causes increase in the levels of cyclic AMP, thereby controlling inflammation. Once crisaborole reaches systemic circulation after topical application, it is metabolized to inactive metabolites thus limiting systemic exposure to crisaborole and systemic PDE4 inhibition. It is available as a 2% topical ointment. It is used in the treatment of mild-to-moderate atopic dermatitis in children 2 years and older.

Benvitimod

It is a nonsteroidal, anti-inflammatory molecule that was originally derived from the metabolites of nematodes. It causes reduced expression of pro-inflammatory cytokines, inhibition of T-cell viability and infiltration, thus diminishing skin inflammation. Adverse events are folliculitis, contact dermatitis and headache. Two phase 2 trials have been completed and published on the safety and efficacy of topical benvitimod treatment.

BIMATOPROST

It is a synthetic prostamide F2a analog. It exerts its effects by stimulating the prostamide receptor. Eyelash hair follicles are higher in the telogen phase, which supports the effectiveness of bimatoprost for hypotrichosis of the eyelashes. The US FDA approved the use of bimatoprost ophthalmic solution 0.03% in December 2008. The recommended application of bimatoprost 0.03% ophthalmic solution is one drop daily for 16 weeks. Indications: FDA-approved - Eyelash hypotrichosis; Other off label uses - Eyebrow hypotrichosis, androgenetic alopecia, alopecia areata; Others with minimal evidence - Vitiligo.

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Maintenance and Preservation of Medical Records

KK AGGARWAL*, IRA GUPTA†

Hon'ble Member Dr SM Kantikar, of Hon'ble National Consumer Disputes Redressal Commission in the case "**Sri Ramachandra Hospital versus Suryanarayana & Others", vide judgment dated 17.12.2015** has stated:

"So, unsurprisingly, the content of medical records may be fundamental to the success of potential medical negligence case. A trained, experienced vigilant person is necessary to ensure this, which although it may be a time-consuming and costly process. Ultimately, the Patient records can help or tarnish a doctor in medical negligence cases....!!"

INTRODUCTION

Medical records are documentary evidences, which are of immense help not only in medicolegal cases but also in defending the doctor in cases of negligence suits or allegations against him/her. There are many cases/instances, which are decided in favor of doctors only on the grounds of well-kept and well-reproduced records in consumer courts. However, doctors because of their busy schedule, either don't maintain records or records are kept very brief, incomplete, cryptic, which are of no use in court matters.

Hon'ble Supreme Court and the National Consumer Commission in various judgments have held hospitals/doctors liable for medical negligence for non-production of medical record and for non-maintenance of medical records.

DUTY OF THE DOCTOR TO MAINTAIN MEDICAL RECORD

It is the duty of doctor or hospital to preserve, maintain the medical record for certain specified period under different laws like Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002, Limitation Act, Consumer Protection Act, the Directorate General of Health Service (DGHS), Prenatal Diagnostic Test Act, 1994, the Clinical Establishments (Registration and Regulation) Act, 2010 (Central Act No. 23 of 2010). These records are required in medical negligence, accident, insurance claims and in criminal cases and also in the Labor Courts.

The **Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002** (hereinafter **MCI Code of Ethics)** provides that:

*"**Duties and responsibilities of the Physician in General:***

1.3 Maintenance of medical records:

1.3.1 Every physician shall maintain the medical records pertaining to his/her indoor patients for a period of 3 years from the date of commencement of the treatment in a standard proforma laid down by the Medical Council of India (MCI) and attached as Appendix 3.

1.3.2 If any request is made for medical records either by the patients/authorized attendant or legal authorities involved, the same may be duly acknowledged and documents shall be issued within the period of 72 hours.

1.3.3 A Registered medical practitioner shall maintain a Register of Medical Certificates giving full details of certificates issued. When issuing a medical certificate, he/she shall always enter the identification marks of the patient and keep a copy of the certificate. He/She shall not omit to record the signature and/or thumb mark, address and at least one identification mark of the patient on the medical certificates or report. The medical certificate shall be prepared as in Appendix 2.

1.3.4 Efforts shall be made to computerize medical records for quick retrieval."

NONMAINTENANCE OF MEDICAL RECORD IS A PROFESSIONAL MISCONDUCT

If the doctor does not comply with the provisions of MCI Code of Ethics, then the doctor is liable for disciplinary action. One of the act or omission on the part of doctor, which can invite disciplinary action against the doctor is nonmaintenance of medical record. The provisions of MCI Code of Ethics are as follows:

"7. Misconduct: The following acts of commission or omission on the part of the physician shall constitute

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professional misconduct rendering him/her liable for disciplinary action–

> *7.2 If he/she does not maintain the medical records of his/her indoor patients for a period of 3 years as per regulation 1.3 and refuses to provide the same within 72 hours when the patient or his/her authorized representative makes a request for it as per the regulation 1.3.2."*

Whether it is Government hospital or private, under whatsoever name may be, or the clinical establishments covered by Section 2 (c) of 2010 Act or the MCI Act, shall be liable to maintain the medical record and provide to patient or their attendants. Regulation 1.3 of the Regulations framed by the MCI (supra) requires that medical record shall be provided within 72 hours as and when demanded. The provision contained in Regulation 1.3 is applicable equally to all clinical establishments, private or State sponsored, like individual medical professionals, hospitals, medical colleges, nursing homes, universities, etc. Even if 2010 Act has not been applied, the definition of clinical establishment contained in 2010 Act, may be borrowed for the purpose of implementation of Regulation 1.3 framed by the MCI (**Judgment dated 12.09.2014 Hon'ble High Court of Allahabad, Lucknow Bench in the matter of "Sameer Kumar versus State, Misc. Bench No. 11289 of 2013).**

Importance of Maintaining Good Medical Records

Good medical records:

- Communicate vital information about a patient's history and health status.
- Act as basis of planning and continuing medical treatment.
- Serve as source of information about the quality of care rendered to patient.
- Are a record of consent, refusal, referrals, etc.
- Serve as a source of information for mediclaim (insurance) related cases.
- Serve as a source of research and education.
- Provides evidence on whether care rendered met the professional standard of care.

Essential Ingredients of a Good Medical Record

Medical records should be maintained serially in a chronological order with dates and they should preferably contain the following entries in them:

- General particulars of the patient e.g.; Name, age, sex, address, emergency contact number, who brought him/her [with details], etc.
- Consent form duly filled and signed or thumb impression taken.
- Dates and timings of examination/admission and discharge - inpatients.
- Dates and timings of all visits and consultation.
- Details of the complaints - in a chronological order.
- Personal and past history.
- Physical and laboratory/investigation findings (reports enclosed).
- Treatment given/surgical procedures in detail (immediate entry not later).
- Day-to-day prognosis.
- In case of death; precise cause of death, date and time of death.
- Details of consultation by other doctors and their opinion.
- In medicolegal cases police need to be informed both at the time of admission as well at the time of discharge.
- Inpatients - details of discharge, cause of discharge – cured/referred to other center/discharge on request or against medical advice (DMMA), etc.
- Any other special findings which you feel noteworthy.

GUIDELINES FOR PREPARATION AND MAINTENANCE OF MEDICAL RECORD

Doctors should prepare and maintain medical records in the following manner:

- Maintain different registers for specific purposes in their office or place of practice.
- Maintain a separate register for the medical certificates issued, wherein all details must be entered. Every certificate must include two identification marks, if not, at least one identification mark of patient, his signature/left thumb impression should be taken in the space meant for that. Certificates are to be prepared in duplicate and one copy must be kept in the records as office copy which should contain the receipt signature of the patient or the legal representative.
- All medical records including certificates must be prepared in a prescribed performa.
- All medical records should be written in a legible way or type written e.g., writing diagnosis or prescription in capital letters is a better way. Scribbling must be avoided.
- Medical records must be accurate, up to date, placed in order and complete in all respects. Incomplete or altered records create room for suspicion.

- Any alterations in the medical record made must be initialled without obliterating the original entry. E.g., drawing a single line over the sentence/word.
- The doctor must take some time/spend some time to prepare the patient's details in documentary form or get them prepared by a trained competent assistant (in western countries trained medical clerks are used by the doctors).
- Sincere efforts should be made to computerize the data, so that we can minimize the errors and the paper work can be brought down. (Facts of Medical Record Keeping - The Integral Part of Medical and Medicolegal Practice. *Gurudatta. S. Pawar, **Jayashree G. Pawar)

Patient has the Right to Obtain Medical Records

The Hon'ble National Consumer Disputes Redressal Commission in the matter titled as "**Dr. Paramjit Singh Grewal vs. Charanjit Singh Chawla", vide judgment dated 19 October, 2006 held that:**

> *"It is high time that Doctors write correct notes in the operation record and discharge summary. These documents should be made available to the patient at any time without any hue and cry. When information is given orally, it becomes a matter of debate as to who is telling the truth. It is patients right to know how his case has been dealt with by the treating Doctor. It will also enable him to follow the treatment prescribed for future and, if required, sometimes, even to take a second opinion of an expert. It is the duty of the Doctor to state in the record all the details of the treatment given, medicines which are prescribed and the follow up advice, if any, and give it to the patient for his reference. Patient has a right to get the medical record pertaining to him and he cannot be denied the same when he paid the Doctor/ Hospital for his treatment and hired the services."*

Even as per Clause 1.3.2 of the **MCI Code of Ethics,** it is the duty of the doctor to provide the medical record to the patient or his/her authorized representative. The provision is reproduced hereunder:

*"**Duties and responsibilities of the Physician in General:***

> *1.3.2. If any request is made for medical records either by the patients/authorized attendant or legal authorities involved, the same may be duly acknowledged and documents shall be issued within the period of 72 hours.*

If the patient or any of his/her authorized representatives makes a request for the medical record and the doctor refuses to provide the medical record to the patient within a period of 72 hours (i.e., 3 days) then the doctor is liable for professional misconduct. The provisions of MCI Code of Ethics are as follows:

"7. Misconduct: The following acts of commission or omission on the part of the physician shall constitute professional misconduct rendering him/her liable for disciplinary action:

> *7.2 If he/she does not maintain the medical records of his/her indoor patients for a period of 3 years as per regulation 1.3 and refuses to provide the same within 72 hours when the patient or his/her authorized representative makes a request for it as per the regulation 1.3.2."*

In case of **Dr Shyam Kumar v Rameshbhai, Harmanbhai Kachiya I (2006) CPJ 16 (NC), the Hon'ble National Commission of Consumer Disputes Redressal** said that not producing medical records to the patient prevents the complainant from seeking an expert opinion and it is the duty of the person in possession of the medical records to produce it in the court and adverse inference could be drawn for not producing the records.

The **Hon'ble Central Information Commission** in the matter titled as "**Mrs Anita Singh vs. Gnctd,** CIC/SA/A/2015/001894 order dated **16 March, 2016 observed** that three enactments, RTI Act, Consumer Protection Act and Medical Council Act, provided the appellant a strong and undeniable right to information to the patient of his/her own medical record. The Right of patient to Information to his/her own medical record is not only guaranteed under above three legislations but also rooted in Article 19 and 21 of the Constitution of India, 1950. This right is not limited to records held by public authorities alone but extends to all hospitals including private or corporate hospitals; also to individual doctors, who treat patients.

CONCLUSION

Medical records are an integral part of medical practice as these records are important for the doctor, hospital, patient, patient's relative and society in general. These records are useful in situations like medical emergencies, medical negligence cases, medical researches, etc. Maintaining and preserving good medical record is the responsibility of the doctor/hospital. The medical record should not only be maintained and preserved, it should be complete. Incomplete medical record illustrates that care was incomplete, noncompliance of standards, organizational policies, supports allegations of negligence, etc. Honest, best and well-maintained medical records will always save the doctor and also the hospital from all types of crises and claims at all times.

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News and Views

WHO Says Ebola not an International "Health Emergency" But Risks Spreading Across DR Congo Border

The Ebola outbreak in the Democratic Republic of the Congo (DRC) "does not constitute a public health emergency of international concern", according to a statement issued by the World Health Organization (WHO).

But acknowledging the potential risk that the disease may spread to neighboring countries, WHO Director-General, Tedros Adhanom Ghebreyesus, expressed on behalf of the International Health Regulations (IHR) Emergency Committee, "deep concern" over a recent surge in the transmission of the virus in specific areas, namely North Kivu and Ituri provinces, both of which are heavily populated by armed groups.

Latest data as on indicated April 12, 2019 a total of 1,206 confirmed and probable cases of Ebola in this latest deadly outbreak in DRC which began last August, with 764 deaths, making the outbreak - which is endemic in the DRC - the worst in the country's history. (*UN*)

Health Care Professions Condemn New Brunei Laws

The World Health Professions Alliance has condemned new laws, recently put in place by the Brunei, which it considers to be inhumane and discriminatory, and in breach of international human rights agreements. The new penal code, introduced on 3rd April, imposes death by stoning for adultery and gay sex, as well as amputations for theft and public flogging for abortion.

"International Council of Nurses (ICN) joins our colleagues in the health professions in strongly condemning discrimination against and violence towards vulnerable groups, and considers the death penalty to be cruel, inhuman and unacceptable", said Howard Catton, Chief Executive Officer of the ICN. "We call on the government of Brunei to uphold the human rights of all".

Dr Otmar Kloiber, Secretary General of the World Medical Association, said "The World Medical Association warns all physicians in Brunei that participating in such punishments, even advising or preparing for, would constitute a gross violation of medical ethics."

DTAB Proposes Notifying All Medical Devices as 'Drugs'

The Drugs Technical Advisory Board (DTAB) has recommended notifying all medical devices as 'drugs' and make it mandatory for them to follow regulatory norms such as registration, testing of products as well as reporting of adverse reactions.

Devices like equipment, analyzers, instruments, etc. used in various health care facilities for diagnosis, treatment, mitigation do not come under the purview of Drugs and Cosmetics Act at present. Only 23 medical devices have been notified as 'drugs'. The Health Ministry has notified 12 other products including blood pressure monitoring device, MRI equipment and CT scan equipment as 'drugs' in different phases in effect from 2020… (*ET Health*)

The First Targeted Therapy for Metastatic Bladder Cancer

The US Food and Drug Administration (FDA) has granted accelerated approval to erdafitinib, a treatment for adult patients with locally advanced or metastatic bladder cancer that has a type of susceptible genetic alteration known as FGFR3 or FGFR2, and that has progressed during or following prior platinum-containing chemotherapy. Patients should be selected for therapy with erdafitinib using an FDA-approved companion diagnostic device.

Duodenoscope Contamination Rates Continue to Remain High, Finds FDA

Postmarket surveillance studies examining the percentage of clinically used duodenoscopes which remain contaminated with viable microorganisms after use of labeled reprocessing instructions continue to show higher than expected levels of contamination. Hence, in a safety communication issued April 12, 2019, the US FDA has again reminded facilities of the importance of following duodenoscope reprocessing instructions.

Countries and Civil Society Push for Greater Transparency and Fairer Prices

At a global forum on fair pricing and access to medicines, delegates from governments and civil society organizations called for greater transparency

around the cost of research and development as well as production of medicines, to allow buyers to negotiate more affordable prices.

The forum, co-hosted by the WHO and the Government of South Africa, aimed to provide a global platform for frank discussion among all stakeholders - including governments, civil society organizations and the pharmaceutical industry - in order to identify strategies to reduce medicine prices and expand access for all.

CDC Issues Food Safety Alert for Multistate Outbreak of Salmonella Infections Linked to Pre-cut Melons

The Centers for Disease Control and Prevention (CDC) has issued a food safety alert about a multistate outbreak of Salmonella infections linked to pre-cut melons supplied by Caito Foods, LLC. On April 12, 2019, Caito Foods, LLC, recalled pre-cut watermelon, honeydew melon, cantaloupe and fruit medley products containing one of these melons that were produced at the Caito Foods, LLC, facility in Indianapolis, Indiana.

A total of 93 people infected with the outbreak strain of Salmonella have been reported from nine states; 23 people have been hospitalized. No deaths have been reported … (*CDC*)

AIIMS to Start Registry of All Orthopedic Implant Surgeries

The All India Institute of Medical Sciences (AIIMS), Delhi, will start a registry of all orthopedic implant surgeries done at the hospital to keep track of surgical outcomes such as revision procedures, infection rate, etc. It could act as a reference point for a national registry that the Union Health Ministry began considering after the Johnson & Johnson's faulty hip implants controversy, which highlighted the need for documenting the results of all surgeries across the country where implants were being used… (*Hindustan Times*)

Short Rest Periods Improve Learning New Skills

In a study of healthy volunteers, National Institutes of Health researchers found that our brains may solidify the memories of new skills we just practiced a few seconds earlier by taking a short rest. The improvements made during the rest periods added up to the overall gains the volunteers made that day. Moreover, these gains were much greater than the ones seen after the volunteers returned the next day to try again, suggesting that the early breaks played as critical a role in learning as the practicing itself. These results are published in the journal *Current Biology*.

Diesel Exhaust Filtered of its Tiny Particles may Worsen Allergy-induced Lung Impairment

A study published in the *American Journal of Respiratory and Critical Care Medicine* has shown some surprising results. It found that air pollution from diesel engines may worsen allergy-induced lung impairment more when tiny particles are filtered from the exhaust than when they are not. The effects of filtered diesel exhaust on lung function and on white blood cells were more pronounced in those participants who were genetically susceptible to oxidative stress.

"A Global Measles Crisis" is Well Underway, Say UNICEF and WHO

Noting a 300% surge in the number of measles cases during the first 3 months of this year, compared to the same period last year, two UN agency heads declared that we now stand "in the middle of a global measles crisis".

"Cases have soared across the world, including in places where measles had previously been eliminated, like the United States", asserted Henrietta Fore, Executive Director of the UN Children's Fund (UNICEF) and Tedros Adhanom Ghebreyesus, Director-General of the WHO.

Following 2 years of consecutive increases, the DRC, Ethiopia, Georgia, Kazakhstan, Kyrgyzstan, Madagascar, Myanmar, Philippines, Sudan, Thailand and Ukraine, are all in the midst of current outbreaks. It is also spreading fast among clusters of people, who are resisting vaccination, in countries with high overall vaccination rates, including the United States, Israel, Thailand and Tunisia… (*UN*)

Researchers 3D-print Heart from Human Patient's Cells

Researchers have 3D-printed a heart using a patient's cells, providing hope that the technique could be used to heal hearts or engineer new ones for transplants.

"This is the first time anyone anywhere has successfully engineered and printed an entire heart replete with cells, blood vessels, ventricles and chambers," Professor Tal Dvir of Tel Aviv University's School of Molecular Cell Biology and Biotechnology and senior author of the research, said in a statement. The research is published in the journal *Advanced Science*.

The process of printing the heart involved a biopsy of the fatty tissue that surrounds abdominal organs. Researchers separated the cells in the tissue from the rest of the contents, namely the extracellular matrix linking the cells. The cells were reprogrammed to become stem cells with the ability to differentiate into heart cells; the matrix was processed into a personalized hydrogel that served as the printing "ink". The cells and hydrogel were first used to create heart patches with blood vessels and, from there, an entire heart.

"At this stage, our 3D-heart is small, the size of a rabbit's heart," Dvir said. "But larger human hearts require the same technology." (*CNN*)

Canagliflozin shown to be Renoprotective in Type 2 Diabetes Patients with CKD

In patients with type 2 diabetes and stage 2 or 3 kidney disease, the risk of kidney failure and cardiovascular events was lower with once-daily oral canagliflozin 100 mg than with placebo at a median follow-up of 2.62 years, according to the results of the phase III CREDENCE trial (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial presented at the 2019 World Congress of Nephrology in Melbourne, Australia and simultaneously published in the *New England Journal of Medicine*.

Many Heart Attack Patients do not Need ICU Care, Suggests Study

Many patients who suffer a type of heart attack known as an ST-elevation myocardial infarction (STEMI) are treated in the intensive care unit (ICU), despite a relatively low risk of developing a complication requiring ICU care, according to analysis of data from the Chest Pain-MI Registry published in *JACC: Cardiovascular Interventions*.

Esophageal Reflux is Common Post Sleeve Gastrectomy

Findings of a new systematic review and meta-analysis reported in the *Annals of Surgery*, show a 19% overall increase in the prevalence of esophageal reflux after sleeve gastrectomy and a 23% increase in rates of new-onset reflux.

The long-term prevalence of esophagitis was 28% and Barrett's esophagus was 8%. Four percent of all patients required conversion to Roux-en-Y Gastric Bypass (RYGB) surgery for severe reflux.

A Mobile Phone App that Discovers Disease and Saves Lives in Africa

What if a mobile phone could prevent a health epidemic? It may sound like science fiction, but the WHO Polio Geographic Information System (GIS) Technology is doing just that in 43 countries in Africa.

The idea is simple: Health workers visit remote villages to check if local inhabitants have any symptoms of a range of life-threatening infectious diseases, including polio and measles. Then, with the mobile app, they quickly and easily alert WHO. The system allows WHO and health ministries to monitor in real time the visits that people and caregivers make to the most remote areas and to make sure that people most in need are being reached.

"This is one of the most exciting things that is happening in the WHO regional office in Africa," Dr Matshidiso Moeti, WHO Regional Director for Africa, told participants during the GIS session, which took place on the last day of the second African Health Forum in Praia, Cabo Verde … (*WHO Africa*)

CALF Now a National Reference Lab for Milk

The Food Safety and Standards Authority of India (FSSAI) has recognized CALF, an Anand-based laboratory of the National Dairy Development Board (NDDB), as a national reference laboratory (NRL) for dairy and dairy products. With FSSAI's latest order, CALF has become the only NRL in the country for milk and milk products. CALF was so far a referral lab of FSSAI for milk and milk products for various analyses. In total 13 accredited laboratories across the country have been accorded the status of national reference laboratories in specific areas. Of this, eight are from government sector while the rest five are from private sector… (*TOI-FSSAI*)

Labeling Added Sugars Content on Packaged Foods and Beverages could Lower Risk of Heart Disease and Diabetes

A label showing added sugars content on all packaged foods and sugary drinks could have substantial health and cost-saving benefits in the United States over the next 20 years, according to a new study published in the journal *Circulation*. The researchers predict that between 2018 and 2037, the added sugars label would prevent more than 3,54,000 cardiovascular disease cases and lead to almost 6,00,000 fewer cases of type 2 diabetes. The estimated reduction in net health care costs would be more than $31 billion, after policy costs have been

factored in, and not including societal costs, such as lost productivity.

Sleeping Pills Linked to Increase in Use of Antihypertensive Medications in Older Adults

A prospective cohort study published in *Geriatrics and Gerontology International* has shown an association between the use of sleeping tablets by older hypertensive adults and subsequent increase in use of antihypertensive medications.

Diabetes is a Risk Factor for Fragility Fractures in the Frail

Participants with type 2 diabetes were significantly frailer than individuals without diabetes. Frailty increases the risk of fragility fracture and enhances the effect of diabetes on fragility fractures. Particular attention should be paid to diabetes as a risk factor for fragility fractures in those who are frail, suggests a study published in the April 2019 issue of *Diabetes Care*.

"Cancerous and Addictive" - WHO Issues Betel Nut, Tobacco Warning

The combination of betel nut and tobacco is heightening dangers to health because both substances contain cancer causing agents and are addictive, WHO says. A technical officer at the WHO in Fiji, Ada Moadsiria, said some people chewed betel nut with tobacco while others smoked soon after chewing the nut, which has psychoactive properties.

Co-use raised the danger to health, Dr Moadsiria said. The nicotine in the tobacco is already an addictive substance but then arecoline, which is found in betel nut, is actually also causing dopamine release and therefore dependence on this product," she said. "So, not only is it increasing risk of cancer but it's also increasing risk of addictiveness." (*Radio New Zealand*)

FDA Stops Sale of All Surgical Mesh Products for Transvaginal Repair of Pelvic Organ Prolapse

The US FDA has ordered the manufacturers of all remaining surgical mesh products indicated for the transvaginal repair of pelvic organ prolapse (POP) to stop selling and distributing their products in the US immediately. The order is the latest in a series of escalating safety actions related to protecting the health of the thousands of women each year who undergo surgery transvaginally to repair POP. The FDA has determined that the manufacturers, Boston Scientific and Coloplast, have not demonstrated a reasonable assurance of safety and effectiveness for these devices, which is the premarket review standard that now applies to them since the agency reclassified them in class III (high risk) in 2016… (*FDA*)

USPSTF does not Recommend Screening for Elevated Blood Lead Levels in Childhood and Pregnancy

The US Preventive Services Task Force (USPSTF) does not recommend screening for elevated blood lead levels in childhood and pregnancy in its latest guidelines published in *JAMA*. For pregnant women and children 5 years and younger, *"the USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for elevated blood lead levels in asymptomatic pregnant persons."*

FDA Approves Hydrogel Capsules for Weight Management

The FDA has cleared hydrogel capsules for weight management in adults with a body mass index (BMI) of 25-40 kg/m^2, when used together with diet and exercise. The prescription device is a capsule containing hydrogel particles that expand in the stomach after they are ingested but are not systemically absorbed, making the user feel full. They are taken twice daily with water before meals.

TRANSFORM LDL-C Risk, a New Study to Identify High-risk Patients with Established ASCVD

The American College of Cardiology has joined hands with Sanofi and Regeneron to conduct a new national study - TRANSFORM LDL-C Risk - to identify high-risk patients with atherosclerotic cardiovascular disease (ASCVD) and optimizing their access to the latest evidence-based treatments for low-density lipoprotein cholesterol (LDL-C) lowering and cardiovascular event risk reduction.

Missing Breakfast + Late-night Dinner is a Deadly Combination

People who skip breakfast and eat dinner near bedtime have worse outcomes after a heart attack, suggests a new research published in the *European Journal of Preventive Cardiology*. People with the two eating habits had a 4-5 times higher likelihood of death, another heart attack, or angina within 30 days after hospital discharge for heart attack. The study author recommends a minimum 2-hour interval between dinner and bedtime.

Indian Journal of Clinical Practice, Vol. 29, No. 12, May 2019

What is the Importance of Silence?

KK AGGARWAL

True silence is the silence between the thoughts and represents the true self, consciousness or the soul. It is a web of energized information ready to take all provided there is a right intent. Meditation is the process of achieving silence. Observing silence is another way of deriving benefits of meditation. Many yogis in the past have recommended and observed silence now and then. Mahatma Gandhi spent one day in silence every week. He believed that abstaining from speaking brought him inner peace and happiness. On all such days he communicated with others only by writing on paper.

Hindu principles also talk about a correlation between mauna (silence) and shanti (harmony). Mauna Ekadashi is a ritual followed traditionally in our country. On this day, the person is not supposed to speak at all and observes complete silence all through the day and night. It gives immense peace to the mind and strength to the body. In Jainism, this ritual has a lot of importance. Nimith was a great saint in Jainism who long ago asked all Jains to observe this vrata. Some people recommend that on every ekadashi one should observe silence for few hours, if not the whole day.

In his book, The Seven Spiritual Laws of Success, Deepak Chopra talks in great detail about the importance of observing silence in day-to-day life. He recommends that everyone should observe silence for 20 minutes every day. Silence helps to redirect our imagination towards self. Even Swami Sivananda, in his teachings, recommends observation of mauna daily for 2 hours. For ekadashi, take milk and fruits, study one chapter of Bhagwad Gita daily, do regular charity and donate one-tenth of your income in the welfare of the society. Ekadashi is the 11th day of Hindu lunar fortnight. It is the day of celebration, occurring twice a month, meant for meditation and increasing soul consciousness.

Vinoba Bhave was a great sage of our country known for his Bhoodaan movement. He was a great advocator and practical preacher of mauna vrata.

Mauna means silence and vrata means vow; hence, mauna vrata means a vow of silence. Mauna was practiced by saints to end enmity and recoup their enmity. Prolonged silence as the form of silence is observed by the rishi munis. Silence is a source of all that exists. Silence is where consciousness dwells. There is no religious tradition that does not talk about silence. It breaks the outward communication and forces a dialogue towards inner communication. This is one reason why all prayers, meditation and worship or any other practice where we attune our mind to the spiritual consciousness within are done in silence. After the death of a person, it is a practice to observe silence for 2 minutes. The immediate benefit is that it saves a tremendous amount of energy.

Silence is cessation of both sensory and mental activity. It is like having a still mind and listening to the inner mind. Behind this screen of our internal dialogue is the silence of spirit. Meditation is the combination of observing silence and the art of observation.

(Disclaimer: The views expressed in this write up are my own).

Group Editor-in-Chief, IJCP Group

■■■■

Study Shows Association Between Visit-to-visit Variability in Fasting Glucose and Systolic Dysfunction

Visit-to-visit fasting plasma glucose variability is an important risk factor for long-term changes in left cardiac structure and systolic dysfunction in patients with type 2 diabetes as reported in a study published in the journal *Cardiovascular Diabetology*. This association was independent of mean glucose control status and other conventional risk factors.

Positive Thinking

Jerry was the kind of guy you love to hate. He was always in a good mood and always had something positive to say. When someone would ask him how he was doing, he would reply, "If I were any better, I would be twins!"

He was a unique manager because he had several waiters who had followed him around from restaurant to restaurant. The reason the waiters followed Jerry was because of his attitude. He was a natural motivator. If an employee was having a bad day, Jerry was there telling the employee how to look on the positive side of the situation.

Seeing this style really made me curious, so one day I went up to Jerry and asked him, "I don't get it! You can't be a positive person all of the time. How do you do it?" Jerry replied, "Each morning I wake up and say to myself, Jerry, you have two choices today. You can choose to be in a good mood or you can choose to be in a bad mood." I choose to be in a good mood. Each time something bad happens, I can choose to be a victim or I can choose to learn from it. I choose to learn from it. Every time someone comes to me complaining, I can choose to accept their complaining or I can point out the positive side of life. I choose the positive side of life. "Yeah, right, it's not that easy," I protested.

"Yes it is," Jerry said. "Life is all about choices. When you cut away all the junk, every situation is a choice. You choose how you react to situations. You choose how people will affect your mood. You choose to be in a good mood or bad mood. The bottom line: It's your choice how you live life."

I reflected on what Jerry said. Soon thereafter, I left the restaurant industry to start my own business. We lost touch, but often thought about him when I made a choice about life instead of reacting to it. Several years later, I heard that Jerry did something you are never supposed to do in a restaurant business: he left the back door open one morning and was held up at gunpoint by three armed robbers. While trying to open the safe, his hand, shaking from nervousness, slipped off the combination. The robbers panicked and shot him. Luckily, Jerry was found relatively quickly and rushed to the local trauma center. After 18 hours of surgery and weeks of intensive care, Jerry was released from the hospital with fragments of the bullets still in his body. I saw Jerry about six months after the accident. When I asked him how he was, he replied, "If I were any better, I'd be twins. Wanna see my scars?"

I declined to see his wounds, but did ask him what had gone through his mind as the robbery took place. "The first thing that went through my mind was that I should have locked the back door," Jerry replied. "Then, as I lay on the floor, I remembered that I had two choices: I could choose to live, or I could choose to die. I chose to live."

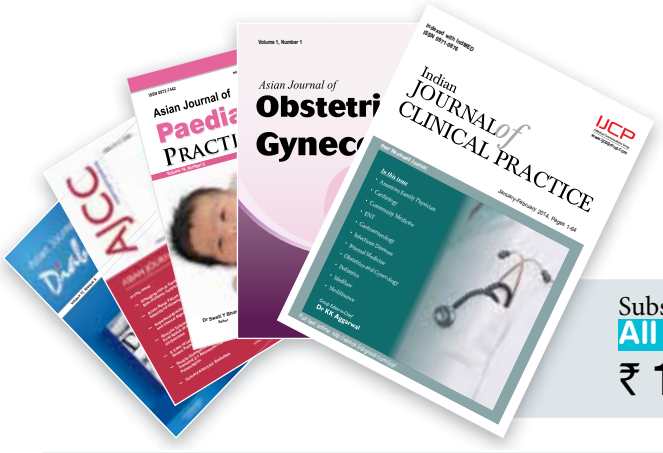
"Weren't you scared? Did you lose consciousness?" I asked. Jerry continued, "The paramedics were great. They kept telling me I was going to be fine. But when they wheeled me into the emergency room and I saw the expressions on the faces of the doctors and nurses, I got really scared. In their eyes, I read, 'He's a dead man.' I knew I needed to take action."

"What did you do?" I asked.

"Well, there was a big, burly nurse shouting questions at me," said Jerry. "She asked if I was allergic to anything". 'Yes,' I replied. The doctors and nurses stopped working as they waited for my reply… I took a deep breath and yelled, 'Bullets!' Over their laughter, I told them, "I am choosing to live. Operate on me as if I am alive, not dead."

Jerry lived thanks to the skill of his doctors, but also because of his amazing attitude. I learned from him that every day we have the choice to live fully. Attitude, after all, is everything.

■■■■



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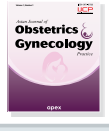
Asian Journal of Obs & Gynae Practice 	4	1,500/- ☐	550/- ☐
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Lighter Side of Medicine

HUMOR

10 GUINNESS IN 10 MINUTES

An American walks into an Irish pub and says, "I'll give anyone $100 if they can drink 10 Guinness in 10 minutes."

Most people just ignore the absurd bet and go back to their conversations. One guy even leaves the bar.

A little while later that guy comes back and asks the American, "Is that bet still on?" "Sure," he says.

So, the bartender lines 10 Guinness up on the bar and the Irishman drinks them all in less than 10 minutes.

As the American hands over the money he asks, "Where did you go when you just left?" The Irishman answers, "I went next door to the other pub to see if I could do it."

I KNOW, DOC

A man swallowed a mouse while sleeping on the couch one day. His wife quickly called the doctor and said, "Doctor, please come quickly. My husband just swallowed a mouse and he's gagging and thrashing about."

"I'll be right over," the doctor said. "In the meantime, keep waving a piece of cheese over his mouth to try to attract the mouse up and out of there."

When the doctor arrived, he saw the wife waving a piece of fish over her husband's mouth. "Uhh, I told you to use cheese, not fish, to lure the mouse."

"I know, doc," she replied, "but first I've got to get the darn cat out of him."

THINK ABOUT ME

Think big, Think smart,

Think positive, Think beautiful,

Think great, I know this is too much for you, so here is a shortcut.

Just think about ME…

IS MR SMITH THERE?

A law firm receptionist answered the phone the morning after the firm's senior partner had passed away unexpectedly.

"Is Mr Smith there?" asked the client on the phone. "I'm very sorry, but Mr Smith passed away last night," the receptionist answered.

"Is Mr Smith there?" repeated the client. The receptionist was perplexed. "Perhaps you didn't understand me. I'm afraid Mr Smith passed away last night."

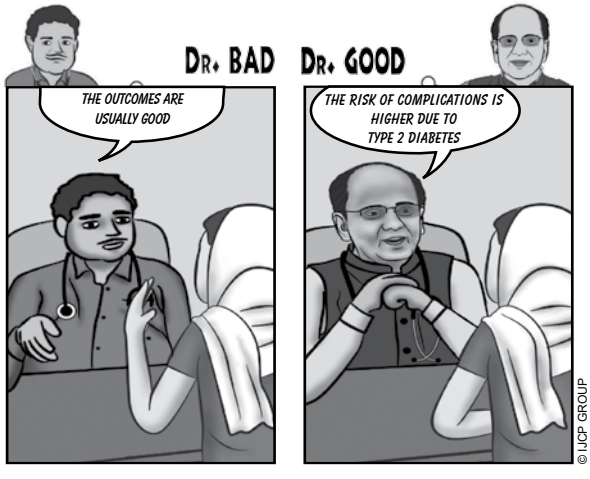
"Is Mr Smith there?" asked the client again.

"Ma'am, do you understand what I'm saying?" said the exasperated receptionist. "Mr Smith is DEAD!"

"I understand you perfectly," the client sighed. "I just can't hear it often enough."

Dr. Good and Dr. Bad

SITUATION: A 46-year-old female with type 2 diabetes had recently undergone mastectomy.



LESSON: A retrospective study showed that females with type 2 diabetes who undergo surgical breast cancer procedures are more susceptible to comorbidity, in-hospital complications, risk factors and advanced cancer presentations in contrast to their counterparts who do not have type 2 diabetes.

BMJ Open. 2017;7(11):e017676.

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Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol. 1955;40:89-111.

Books

Stansfield AG. Lymph Node Biopsy Interpretation Churchill Livingstone, New York 1985.

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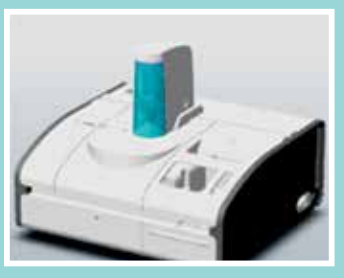

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Digital
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