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# Do No Harm or Harm Reduction: The Ethical Dilemma

Medical profession is a noble profession, which comes with lot of responsibilities. The relationship between the doctor and patient is a fiduciary relationship and doctors must adhere to the principles of medical ethics (autonomy, non-maleficence, beneficence and justice), rules (fidelity, confidentiality, privacy and veracity) and virtues (compassion, kindness, respect, etc.) in their interactions with the patients, which have been laid down by various professional bodies and associations as professional codes of conduct and standards for doctors. The Hippocratic Oath, the oldest of these codes of ethics, still holds true today.

Let's take a look at different codes of ethics and the principles therein.

In the **Hippocratic Oath,** the aspect that is instructive and serves as guide to physicians in respect of non-maleficence states that: *"I will follow that system of regimen, which, according to my ability and judgment, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous. I will give no deadly medicine to anyone if asked, nor suggest any such counsel."*

In the **Declaration of Geneva**, and as amended in Sydney 1968, physicians were expected and indeed mandated to: *"…maintain the utmost respect for human life from the time of conception; even under threat, ... not [to] use medical knowledge contrary to the laws of humanity."*

**The International Code of Medical Ethics** states that: *"A doctor must always bear in mind the obligation of preserving life."*

In India, at the time of registration with the Medical Council, the doctors are given a declaration as per the Appendix 1 of **Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002** which is reproduced hereunder:

> ***"A. DECLARATION***
>
> *At the time of registration, each applicant shall be given a copy of the following declaration by the Registrar concerned and the applicant shall read and agree to abide by the same:*
>
> 1) *I solemnly pledge myself to consecrate my life to service of humanity.*
> 2) *Even under threat, I will not use my medical knowledge contrary to the laws of Humanity.*
> 3) *I will maintain the utmost respect for human life from the time of conception.*
> 4) *I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient.*
> 5) *I will practice my profession with conscience and dignity.*
> 6) *The health of my patient will be my first consideration.*
> 7) *I will respect the secrets which are confined in me.*
> 8) *I will give to my teachers the respect and gratitude which is their due.*
> 9) *I will maintain by all means in my power, the honor and noble traditions of medical profession.*

10) *I will treat my colleagues with all respect and dignity.*

11) *I shall abide by the code of medical ethics as enunciated in the Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002."*

The **World Medical Association in its Medical Ethics Manual** has stated that:

*"Beneficence - literally, 'doing good'. Physicians are expected to act in the best interests of their patients.*

*Non-maleficence - literally, not doing wrong. Physicians and medical researchers are to avoid inflicting harm on patients and research subjects."*

**United Nations Educational, Scientific and Cultural Organization in Universal Declaration on Bioethics and Human Rights** which addresses ethical issues related to medicine, life sciences and associated technologies as applied to human beings, taking into account their social, legal and environmental dimensions. The relevant articles of the said Declaration are reproduced hereunder:

***"Article 4 - Benefit and harm:***

*In applying and advancing scientific knowledge, medical practice and associated technologies, direct and indirect benefits to patients, research participants and other affected individuals should be maximized* ***and any possible harm to such individuals should be minimized.***

***Article 5 - Autonomy and individual responsibility:***

*The autonomy of persons to make decisions, while taking responsibility for those decisions and respecting the autonomy of others, is to be respected. For persons who are not capable of exercising autonomy, special measures are to be taken to protect their rights and interests.*

***Article 8 - Respect for human vulnerability and personal integrity:***

*In applying and advancing scientific knowledge, medical practice and associated technologies, human vulnerability should be taken into account. Individuals and groups of special vulnerability should be protected and the personal integrity of such individuals respected.*

***Article 10 - Equality, justice and equity:***

*The fundamental equality of all human beings in dignity and rights is to be respected so that they are treated justly and equitably.*

***Article 11 - Non-discrimination and non-stigmatization:***

*No individual or group should be discriminated against or stigmatized on any grounds, in violation of human dignity, human rights and fundamental freedoms."*

**Indian Council of Medical Research** in 2000 in its book titled as "**Ethical Guidelines for Biomedical Research on Human Participants** has stated that:

*"All the research involving human participants should be conducted in accordance with the* ***four basic ethical principles, namely autonomy (respect for person/ participant) beneficence, non-maleficence (do no harm) and justice****. The guidelines laid down are directed at application of these basic principles to research involving human participants."*

**International Ethical Guidelines for Biomedical Research Involving Human Subjects** prepared by the **Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)** provides the general ethical principles as:

*"GENERAL ETHICAL PRINCIPLES*

*All research involving human subjects should be conducted in accordance with three basic ethical principles, namely respect for persons, beneficence and justice. It is generally agreed that these principles, which in the abstract have equal moral force, guide the conscientious preparation of proposals for scientific studies. In varying circumstances they may be expressed differently and given different moral weight, and their application may lead to different decisions or courses of action. The present guidelines are directed at the application of these principles to research involving human subjects.*

*Respect for persons incorporates at least two fundamental ethical considerations, namely:*

*a) respect for autonomy, which requires that those who are capable of deliberation about their personal choices should be treated with respect for their capacity for self-determination; and*

*b) protection of persons with impaired or diminished autonomy, which requires that those who are dependent or vulnerable be afforded security against harm or abuse.*

***Beneficence refers to the ethical obligation to maximize benefits and to minimize harms.*** *This principle gives rise to norms requiring that the risks of research be reasonable in the light of the expected benefits, that the research design be sound, and that the investigators be competent both to conduct the research and to safeguard the welfare of the research subjects. Beneficence further proscribes the deliberate infliction of harm on persons; this aspect of beneficence is sometimes expressed as a separate principle, non-maleficence (do no harm).*

*Justice refers to the ethical obligation to treat each person in accordance with what is morally right and proper, to give each person what is due to him or her. In the ethics of research involving human subjects the principle refers primarily to distributive justice, which requires the equitable distribution of both the burdens and the benefits of participation in research. Differences in distribution of burdens and benefits are justifiable only if they are based on morally relevant distinctions between persons; one such distinction is vulnerability.*

*"Vulnerability" refers to a substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternative means of obtaining medical care or other expensive necessities or being a junior or subordinate member of a hierarchical group. Accordingly, special provision must be made for the protection of the rights and welfare of vulnerable persons."*

**Obligation of non-maleficence: moral dilemma in physician-patient relationship by Peter F Omonzejele in his book - A Peer-review Journal of Biomedical Sciences, June 2005 Vol. 4 No. 1 pp. 22-30:**

> *"The principles and rules of medical ethics are derived from the Hippocratic oath and various declarations (Declaration of Geneva as amended in Sydney 1968, Declaration of Tokyo 1975, Declaration of Oslo 1970, Declaration of Helsinki 1975, etc.) regulating medical practice. Despite the Hippocratic oath and various declarations, a certain aspect (non-maleficence) of the oath and declaration is sometimes breached in what seems to be in the "interest" of patients in circumstances that constitute moral dilemmas.*
>
> *The physician-patient relationship is fiduciary. The patient believes and trusts that the physician would apply his professional expertise in his/her (the patient's) interest and benefit. Even more importantly, the patient believes that his/her physicians (based on the principle of non-maleficence) would do nothing to harm him/her. The principle of non-maleficence runs through from the Hippocratic oath to current versions and amendments of medical ethics.*
>
> *Non-maleficence in general, and medical non-maleficence in particular, recommends that one ought not to inflict evil or harm."*

Not only has medicine undergone tremendous advancements over the years, the social milieu has changed and the patients have changed as well, which is reflected in the doctor-patient relationship; from "*paternalism*", where doctors were "*parent figures*" taking medical decisions on behalf of their patients to the current "*patient-centric*" where the patient is an "*equal partner*".

Regardless, the core values of the practice of medicine are still based on the principles of non-maleficence, derived from the doctrine of "*primum non-cere*", which means "first do no harm" and its natural corollary, beneficence or "do good", which means doing the right thing for the patient.

Harm reduction is now a new term in non-maleficence. The basic ethical duty of the doctor is to treat on the principle "first do no harm". But doctors will often end up with social determinants of health where they will have to choose between the two devils and in that situation the answer is to choose the lesser devil and this is what is called a harm reduction strategy.

It has been recognized as a public health strategy since the 1980s, when it was first used as an alternative to abstinence-only interventions for adults with substance abuse disorders who were unwilling to quit.

Harm reduction is an umbrella term for interventions aiming to reduce the problematic effects of behavior. Harm reduction has a human rights agenda in that it is committed to bringing effective treatment to groups that have traditionally been denied quality care. It is scientific in that it is committed to the discovery and implementation of evidence-based interventions.

Doctors practice harm reduction every day. To list a few:

- Rational use of drugs and investigations is a harm reduction approach. It requires that "*patients receive medications appropriate to their clinical needs, in doses that meet their individual requirements, for an adequate period of time, and at the lowest cost to them and their community*" (WHO 1985).

  The 'Five Rights' of safe medication administration by the Institute of Healthcare Improvement also promote rational use of drugs: Right patient, Right drug, Right time, Right dose and Right route. Four more 'Rights' have been added to this: Right documentation, Right action (reason for prescribing the medication), Right form and the Right response.
- Antimicrobial stewardship programs, which are being advocated to curb the rising prevalence of antimicrobial resistance.
- The "Choosing Wisely" campaign, an initiative of ABIM (American Board of Internal Medicine Foundation) launched in 2012 encourages a dialogue between the doctor and the patient about *"what is appropriate and necessary treatment"* and helps patients to choose care that is: *Supported by*

*evidence, not duplicative of other tests or procedures already received, free from harm and truly necessary."*

- To reduce prescription errors, the Medical Council of India (MCI) has issued guidelines that require a doctor to write in capital letters.
- Vaccination is an established harm reduction strategy.
- Maintaining basic hygiene and hand washing are also ways of harm reduction.

No doctor practices medicine to harm the patient. Yet, patients are exposed to some potential harm.

There are risks of side effects with the prescribed medications; there are implied risks in every intervention or procedure. While a major surgery may be uneventful, sometimes unanticipated accidents can occur even in a minor surgery, despite all care. This makes medicine "a double-edged sword".

Would this be a violation of the principle of non-maleficence?

The **"principle of double effect"** differentiates intended and non-intended effects of an action. The intended effect is good and primary; however, associated with the intended effect is the necessary but bad and unintended (secondary) effect. To be morally justifiable, it must satisfy certain conditions: (JMBR. 2005;4(1):22-30).

- "*The action itself (independent of its consequences) must not be intrinsically wrong (it must be morally good or at least morally neutral).*
- *The agent must intend only the good effect and not the bad effect. The bad effect can be foreseen, tolerated and permitted but must not be intended; it is therefore allowed but not sought.*
- *The bad effect must not be a means to the end of bringing about good effect, that is, the good effect must be achieved directly by the action and not by the way of the bad effect.*
- *The good result must outweigh the evil permitted, that is, there must be proportionality or favorable balance between the good and bad effects of the action.*"

Harm is inflicted when the doctor has a duty of care towards the patient, there is a breach of the said duty and the patient has suffered harm as a consequence of a breach of that duty. This is liable for medical negligence or malpractice claim.

Difference of opinion, error of judgment, medical errors and medical accidents are not medical negligence. Experiencing a bad outcome does not always mean medical negligence. This has also been the position of the Supreme Court of India in its various judgments.

Harm reduction has often invited criticism as seemingly, it is seen to allow subjects to continue with the harmful behavior.

But, harm reduction accepts, without being judgmental, that some individuals are unwilling or averse to the idea of quitting risky health behaviors such as smoking or use of drugs and so takes the view that it is better to reduce the associated harm by some means, rather than pressurizing them to abide by total abstinence.

According to the National Health Care for the Homeless Council (2010*), "harm reduction is not at odds with abstinence; instead it includes it as one possible goal across a continuum of possibilities… Harm reduction neither condones nor condemns any behavior. Instead, it evaluates the consequences of behaviors and tries to reduce the harms that those behaviors pose for individuals, families and communities."*

Harm reduction currently accommodates a vast array of interventions. It is best exemplified by needle exchange programs for the injection drug users, which aim to prevent HIV transmission and other blood-borne infectious diseases, as well as prevent overdose, including naloxone distribution and opiate substitution treatment (methadone, buprenorphine).

Other examples are prioritizing less risky drinking habits for underage drinkers to reduce the risk of alcohol poisoning, encouraging safe sex and replacing binge eating with healthier alternatives. More extreme interventions would be, for example, providing clean razors for those engaged in self-injurious behavior, or educating intravenous femoral vein injectors how to inject drugs to safer sites.

Some harm reduction techniques have already become a norm (e.g., opiate substitution treatment), while others remain highly controversial (e.g., educating injecting users on how to properly inject drugs in order to minimize health consequences).

India is the world's second largest consumer and third largest producer of tobacco. According to WHO, India is home to 12% of the world's smokers. Tobacco is an important "modifiable" risk factor for non-communicable diseases. India also has the highest oral cancer rates globally. Tobacco therefore is a major preventable cause of premature morbidity and mortality. Around 9 lakh people die every year due to diseases attributable to tobacco use *(Press Information Bureau, March 1, 2016).* This makes tobacco

a major public health issue and tobacco control of great importance. Hence, harm reduction strategy should also be applied to tobacco.

While the duty and obligations of physicians to their patients remain unequivocally that of beneficence and non-maleficence, patient autonomy has now come to the forefront. The patients' choices about their treatment should be respected as should be their right to make decisions about their health. This also forms the basis of "informed consent", which is not only an ethical, but also a legal requirement today.

The Revised Declaration of Geneva adopted on October 17, 2017, now called the "Physician's Pledge" also puts the patients' interests and well-being foremost and in keeping with the changing times, has emphasized on patient autonomy.

- *"THE HEALTH AND WELL-BEING OF MY PATIENT will be my first consideration;*
- *I WILL RESPECT the autonomy and dignity of my patient;*
- *I WILL SHARE my medical knowledge for the benefit of the patient and the advancement of healthcare"*

Doctors should also respect the principle of justice in health care, where justice means fairness of access to treatment.

"Do no harm" is a utopian concept as medicine is not an exact science; it is an art based on science. No two patients are alike and clinical decisions are tailored to individual patients. Probability and uncertainty are part of the practice of medicine where complications are bound to occur and accidents are inevitable.

In a Guest Editorial published in the journal *Advances in Chronic Kidney Disease*, Kellerman PS writes, "*On a daily basis, we physicians weigh the benefits against the risks in almost everything we do, both diagnostically and therapeutically*" (*Adv Chronic Kidney Dis*. 2012; 19(3):127-8).

As Harvard Health Publishing also writes in its Blog *"The fact is that when difficult, real-time decisions must be made, it's hard to apply the "first, do no harm" dictum because estimates of risk and benefit are so uncertain and prone to error."*

While quitting the harmful behavior is the optimal goal, the patient ought to be given the option of harm reduction.

But, despite the apparent conflict between "Do no harm" and "harm reduction"and the ethical dilemma it poses, it is important to remember that doctors should act in the best interest of the patient i.e., *"Salus aegroti suprema lex"*.

■■■■

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# Heart Care Foundation of India Consensus Statement on Tobacco Harm Reduction and Vaping

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It is a well-known fact that tobacco products, primarily combustible cigarettes, are the single greatest cause of tobacco-related diseases and kill about 7 million people worldwide each year. The tobacco epidemic in India has also reached alarming levels. As per the latest estimates, there are nearly 106 million people in India who smoke tobacco and 32 million who smoke as well as chew tobacco. There are ~270 million people who use tobacco in India. India is home to roughly 11.2% of the smokers in the world and 1.35 million people in the country die every year due to tobacco-related illnesses.

The indirect and direct costs of tobacco-related illnesses and deaths in India are also staggering. As per a Report by the Ministry of Health and Family Welfare, Government of India, the total economic costs attributable to tobacco usage related diseases in India, in the year 2011 for people aged between 35-69, was Rs. 1,04,500 crores (around US $22.4 billion). In recent times, many smokers have transitioned to vaping products in their efforts to quit combustible smoking or reduce harm created by the same. Vaping products contain heated nicotine extracted from tobacco, as well as a variety of flavorings and other additives.

It is important to note here that vaping is not the same as smoking as there is no combustion that is taking place. Combustion from smoking generates significant level of tar, carbon monoxide and other chemicals out of which 69 are known carcinogens. Combustible cigarettes accelerate cancer caused by the released chemicals. Second-hand smoking or passive smoking from combustion not only increases the risk of coronary heart disease by 25-40% (almost the same level as a smoker), but also causes numerous health problems in infants and children, including more frequent and severe asthma attacks, respiratory infections, ear infections and sudden infant death syndrome. Vaping products, on the other hand, do not result in combustion that results in nicotine delivery and as a result do not generate harmful chemicals to the level of conventional cigarettes.

## SCIENTIFIC SUMMARY

There is significant scientific evidence that suggests that vaping products seem to be a reduced harm alternative to combustible cigarettes.

- In its independent evidentiary review, **Public Health England** (PHE) has categorically concluded that "*Vaping poses only a small fraction of the risks of smoking and switching completely from smoking to vaping conveys substantial health benefits over continued smoking. The previous estimate that, based on current knowledge, vaping is at least 95% less harmful than smoking remains a good way to communicate the large difference in relative risk unambiguously so that more smokers are encouraged to make the switch from smoking to vaping.*" It has further observed that "*To date, the levels of metals identified in e-cigarette aerosol do not give rise to any significant safety concerns, but metal emissions, however small, are unnecessary.*" On assessment of exposure to harmful constituents, PHE has observed that "*biomarkers of exposure assessed to date are consistent with significant reductions in harmful constituents and for a few biomarkers assessed... similar levels to smokers abstaining from smoking or nonsmokers were observed.*"
- **The Royal College of Physicians** has also opined that "*Toxin levels inhaled from vaping products under*

*normal conditions are likely to be well below prescribed threshold limit for occupational exposure, which make the probability of significant long-term harm unlikely.*"

- **The National Academies of Sciences, Engineering and Medicine (NASEM)** has concluded in relevant part that "*there is conclusive evidence that completely substituting e-cigarettes for combustible tobacco cigarettes reduces users' exposure to numerous toxicant and carcinogens present in combustible tobacco cigarettes" and there is substantial evidence that completely switching from regular use of combustible tobacco products to vaping results in reduced short-term adverse health outcomes in several organ systems.*"

  As such, NASEM has concluded that "*e-cigarettes pose less risk to an individual than combustible tobacco cigarettes*" and "*complete switching from combustible tobacco cigarettes to e-cigarettes would be expected to reduce tobacco-related health risk.*" Lead authors of the NASEM report on vaping, Dr Eaton and St Helen, also published a follow-on Evidence to Practice article, which recommended that, "*if a smoker's initial treatment has failed or not been tolerated, or if the smoker refuses to use approved medications and counseling and wishes to use e-cigarettes to aid quitting, physician should encourage the smoker to switch completely to e-cigarettes. We agree with PHE that behavioral support should be provided to smokers who want to use e-cigarettes to help them quit smoking, and that health professionals should receive education and training in use of e-cigarettes in quit attempts.*"
- **The American Cancer Society** has issued a statement that stipulates basis the available scientific evidence that the use of vaping is less harmful than smoking cigarettes. It has further observed that despite clinical advice, many smokers "*…will not attempt to quit smoking cigarettes and will not use FDA approved cessation medications. These individuals should be encouraged to switch to the least harmful form of tobacco product possible; switching to the exclusive use of e-cigarettes is preferable to continuing to smoke combustible products.*"
- **The American Heart Association** has observed that "*E-cigarettes either do not contain or have lower levels of several tobacco-derived harmful and potentially harmful constituents compared with cigarettes and smokeless tobacco. In comparison with nicotine replacement therapies (NRTs), e-cigarette use has increased at an unprecedented rate, which presents an opportunity for harm reduction if smokers use them as substitutes for cigarettes.*"
- **David B Abrams from the College of Global Public Health**, New York University, writes in the April 2018 issue of *Annual Review of Public Health:* "*A diverse class of alternative nicotine delivery systems (ANDS) has recently been developed that do not combust tobacco and are substantially less harmful than cigarettes. ANDS have the potential to disrupt the 120-year dominance of the cigarette and challenge the field on how the tobacco pandemic could be reversed if nicotine is decoupled from lethal inhaled smoke. ANDS may provide a means to compete with, and even replace, combusted cigarette use, saves more lives more rapidly than previously possible.*"

Based on currently available evidence, using current generation vaping products is less harmful than smoking cigarettes, but the health effects of long-term use are not known. The Heart Care Foundation of India (HCFI) and undersigned medical practitioners recognize their responsibility to continue monitoring and evaluation of emerging scientific evidence in relation to vaping products and will always strive to promptly inform policy makers, public and medical practitioners of these findings.

## CLINICAL RECOMMENDATIONS

The undersigned medical practitioners and HCFI have always supported smokers in their efforts to quit smoking regardless of the approach giving paramount importance to their health and well-being. To help smokers quit, HCFI and the undersigned medical practitioners recommend clinicians to advise their patients to use available smoking cessation products coupled with behavioral counseling.

However, we also note that many smokers are increasingly using vaping products to quit smoking or reduce the harm caused by combustible smoking. To this end, we recommend that the best option is to quit smoking altogether but if a smoker finds it tough, they should use vaping products. It is important to note here that all individuals/patients should be consistently advised to quit using any form of tobacco products or related products completely. We further caution against the concurrent use of vaping products and combustible cigarettes.

## POLICY RECOMMENDATIONS

The undersigned medical practitioners and HCFI would encourage the Government of India to frame policies and regulations of vaping products that addresses:

- Marketing and Advertisement

- Youth access: Such products should only be available to smokers above the age of 21
- Safeguarding pregnant women from initiation and use through awareness campaigns
- Labeling
- Quality control over manufacturing
- Standards for contaminants.

Further, such regulations should allow adults to access quality-controlled products in their efforts to stop the use of combustible smoking with the objective to reduce harm.

It is also recommended that the Government of India should allocate funds for independent and continued research on the health effects of vaping products and guide their policies from time to time basis such evidence. There should be consistent guidance from regulatory authorities on product and ingredient standards with a view to further reduce toxicity and addictiveness of any tobacco product and related harm reduction products. Importantly, with respect to vaping products, manufacturers should be disallowed from making any unproven health claims unless the same has been approved by a relevant authority of the Ministry of Health and Family Welfare, Government of India.

It is our strongest recommendation to refrain from initiation of consumption of any tobacco product and related harm reduction product. However, transitioning to a related harm reduction product presents an important and critical public health opportunity for existing smokers and must be encouraged through appropriate regulations and support from clinicians.

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# A Systematic Review and Meta-analysis on the Health and Safety Implications of Electronic Nicotine Delivery Systems

SAMBUDDHA DAS*, YASHMIN CHOUDHURY*, S THANGMINLAL VAIPHEI†, RN SHARAN‡


## ABSTRACT

**Objectives:** Cigarette smoking is a proven and avoidable cause of adverse health implications to smokers and by-standers accounting for about 6 million deaths every year. Despite the knowledge and legal measures adopted to discourage cigarette smoking, the global trend is otherwise. Various less harmful avenues of nicotine delivery claiming to be devoid of toxins, including electronic nicotine delivery systems (ENDS), have therefore emerged as a measure of tobacco harm reduction (THR). **Study design:** A systematic review and meta-analysis of published scientific literature was performed based on the principle of PICOSL in order to compare the toxicities of nicotine, other chemicals and metal ions produced during cigarette smoking vis-à-vis ENDS use, and to evaluate the health and safety aspects of ENDS. **Methods:** Research articles relevant to the use of ENDS among smokers and nonsmokers were retrieved through various databases and published articles from other sources. **Results:** Toxic chemicals such as the class 1 carcinogens and carcinogenic metal ions were found to be present in significantly higher quantities in conventional cigarette smoke than in ENDS vapor. ENDS usage was found to be 4.13-fold higher among former smokers than nonsmokers ($p < 0.05$), while the prevailing use of ENDS was 7.53-fold higher among current smokers than nonsmokers ($p < 0.05$). **Conclusion:** Our study establishes that new generation ENDS may serve as an efficient means of meeting the nicotine demand of a person addicted to smoking, without the grave health consequences of conventional cigarettes. While the cessation of smoking would undoubtedly reduce the associated risks significantly, ENDS may serve as an effective aid to smokers in their efforts to quit smoking, thus acting as a valuable tool of THR. Rational policies are required to extend the benefits of ENDS to smokers, while preventing their misuse, especially by adolescents.


**Keywords:** Cigarette, electronic nicotine delivery system, nicotine, smoking, vaping, tobacco harm reduction

An electronic nicotine delivery system (ENDS), popularly known as 'electronic cigarette' or simply 'e-cigarette', is a patented device used for the delivery of nicotine to users, thus also serving as a substitute for cigarettes. It comprises sequentially interconnected air inlet, atomizer, an aerosol passage and a mouth piece with an atomizer and liquid supply containing only nicotine.[1] The nicotine in ENDS is dissolved in propylene glycol or vegetable glycerine with or without different flavoring agents. This solution is heated by a battery operated heating element, producing a nicotine-containing aerosol which appears like vapor, and is inhaled by the user.[2] Hence, users call this habit 'vaping'. In a conventional cigarette, combustion of tobacco produces inhalable nicotine accompanied with smoke, carbon monoxide and tar - a complex mixture of an estimated 4000 chemicals, including carcinogens and toxins.[3] Since there is no combustion in ENDS,[2] the delivered nicotine is claimed to be either poor in or free from the toxic chemicals found in abundance in combustible, tobacco-based cigarettes.[4,5]

Tobacco smoking via conventional cigarettes continues to rise and is estimated to result in about 6 million deaths globally every year.[6] Nicotine replacement therapies (NRTs) such as nicotine patches and oral medications have proved ineffective in meeting the desired targets of smoking cessation across the globe.[6] In a worldwide survey of 19,414 users of ENDS,

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81% of former smokers reported complete substitution of smoking while current smokers had reduced smoking from 20 to 4 cigarettes per day. Participants also reported significant benefits in physical status and improvement in pre-existing disease conditions, including respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). Furthermore, the study revealed that ENDS can be effective as a smoking cessation tool even in highly dependent smokers. Majority of respondents used high levels of nicotine at initiation and tried to reduce nicotine consumption subsequently, while a small minority (3.5%) used non-nicotine liquids.[7] Hence, a group of scientists, social activists, policy makers and governments view ENDS as a potential tobacco harm reduction (THR) avenue and project it as a safe alternative to the highly deleterious cigarette smoking habit.[2,6] On the other hand, another group claims that THR tools, including ENDS, are not effective since all aspects of their health implications and safety have not been scientifically explored.[8]

Thus, while the serious health implications of tobacco-based conventional smoking are unambiguously accepted, the effectiveness of ENDS as a less harmful smoking cessation alternative and its role in THR efforts have become a matter of intense debate, with no conclusive information available in current literature.

In this study, we have undertaken a systematic review followed by a meta-analysis of published scientific literature in order to test the hypothesis that the use of ENDS does not contribute to significant health risk to a user vis-à-vis the use of conventional cigarettes and that ENDS can effectively aid a smoker's efforts to cease smoking.

## METHODS

### Literature Search

Research articles relevant to the use of ENDS among smokers and nonsmokers were retrieved through "Google Scholar", "PubMed", "PubMed Central", "Elsevier Science Direct" using the search terms "e-cigarettes", "ENDS", "Nicotine delivery systems", "risk of e-cigarette", "disadvantages of e-cigarettes", "world smoking report", "tobacco report", "smoking toxicants", "ENDS and smoking cessation". In addition, we also included some literature related to the above-mentioned search terms from sources other than the internet, and articles on the techniques used for systematic reviews and meta-analyses.

### Inclusion and Exclusion Criteria

Criteria for inclusion and exclusion were formulated on the basis of the principle of PICOSL (**P**opulation, **I**ntervention, **C**omparison, **O**utcome, **S**tudy-design, **L**anguage),[9] and are enlisted in Table 1.

### Statistical Analyses

For the meta-analysis, risk ratio (RR) with 95% confidence interval (CI) was calculated using unconditional logistic regression with the help of Review Manager (RevMan)

**Table 1.** Inclusion and Exclusion Criteria Based on the PICOSL Principle

| PICOSL principle | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **P**opulation | Cigarette smokers, users of traditional burnt tobacco, former cigarette smokers, cigarette nonsmokers, only ENDS users, former smokers who used ENDS for quitting, quitline callers, respondents of surveys on ENDS | Users of chewing tobacco, users of NRTs such as nicotine patches and oral medications |
| **I**ntervention | Exposure to cigarette smoking and/or ENDS | Combined exposure to cigarette smoking, ENDS and NRT |
| **C**omparison | Comparison of smokers with nonsmokers, smokers with former smokers, smokers with ENDS users, populations of countries with restrictions on ENDS with populations of countries where use of ENDS is not restricted | Placebo studies, surveys comparing ENDS users and nonusers with inconclusive findings |
| **O**utcome | Exposure to toxins and carcinogens, disease risk, health implications, bioavailability of nicotine, smoking cessation, public opinion and perception on ENDS | No effects, no health implications, no opinion |
| **S**tudy design | Case-control, surveys with conclusive findings, epidemiological findings, studies on public opinion regarding ENDS, all types of research articles, reviews, reports, letters, etc. pertaining to ENDS and/or conventional cigarette | Articles advertising ENDS, studies on specific brands of ENDS, articles dealing with the ethics of ENDS use, articles not on ENDS or conventional cigarettes, duplicate articles |
| **L**anguage | Studies in English | Studies in languages other than English |

statistical software (version 5.3.5). All findings were considered significant at $p < 0.05$. To determine the heterogeneity across studies, Cochran's Q statistics was used, which was considered significant at $p < 0.05$.[10] The random effect model (DerSimonian and Laird method) was used to calculate the pooled RR in case of significant heterogeneity.[11] Otherwise, the fixed effect model (Mantel-Haenszel method) was used.[12] Box-plots were plotted using SPSS (version 16.0) for comparison of the tobacco smoking population of different countries with respect to income level and ENDS regulations.

## RESULTS

### Included Articles

A total number of 299 articles relevant to the study were retrieved and screened from May 2016 to 21st August 2018 and 59 articles were found to meet the inclusion criteria. Among these, 35 articles were used for retrieval of qualitative information regarding ENDS, conventional cigarettes, NRT, THR, policies regarding ENDS, surveys regarding ENDS use, public perception of ENDS, smoking cessation and techniques of meta-analysis; 16 studies (4, 13-15, 20, 21, 42, 44-46, 49, 55-59) were used for quantitative analysis of relative chemical and metal ion content of ENDS vapor and conventional cigarette smoke, relative abundance of nicotine in blood plasma and urine of ENDS and conventional cigarette users, and the prevalence of cigarette smoking in different countries; and, 8 articles (34-41) were used for meta-analysis in order to evaluate the prevalence of ENDS usage among smokers and nonsmokers, and also among current smokers and nonsmokers (Fig. 1).

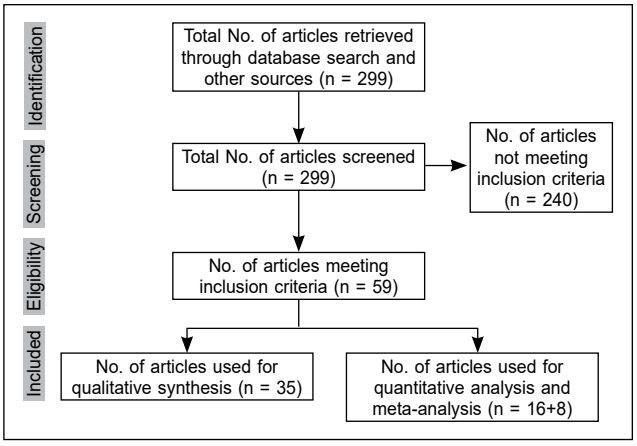



**Figure 1.** Flow chart showing the procedure of literature selection.

### Health Implications

#### Toxicity of nicotine

The amount of nicotine delivered to the blood plasma of users by second-/third-generation ENDS was compared to the amount of nicotine delivered by conventional cigarettes.[13,14] The physiological amounts of nicotine delivered to users of both ENDS and conventional cigarette were found to be nearly identical (Fig. 2A), but the amount of nicotine excreted in the urine of traditional cigarette smokers was about 0.5-fold higher in comparison to that of ENDS users (Fig. 2B).[15]

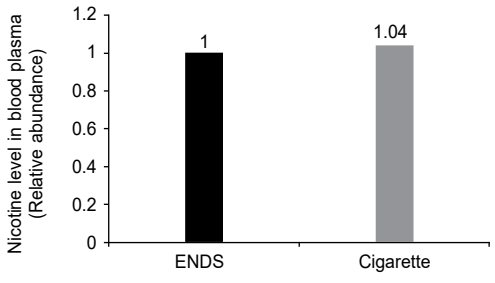
#### Toxicities of other constituents

Various studies comparing the toxic contents of cigarettes with those of ENDS have often used different units, posing difficulties in direct comparison of data. Data from these studies were therefore collected and recalculated where possible, to represent them in terms of fold difference (Table 2). Where it was not possible, we have indicated the average values of contents in cigarette smoke in comparison to the average contents in ENDS vapor (Table 2). The classification of chemicals as 'carcinogen' is based on the International Agency for Research on Cancer (IARC), Lyon.[16] The classification of other 'toxicant' is based on Food and Drug Administration (FDA), USA.[17]

A number of toxic chemicals were found to be significantly more abundant in conventional cigarette smoke than in ENDS vapor (Table 2). These include the Class 1 carcinogens (CA-1) and some possible carcinogens (CA-2b) (Table 2). Furthermore, some probable as well as possible carcinogens are found in conventional cigarette smoke, but their presence in ENDS vapor has not been reported (Table 2). Respiratory toxicants (RT), cardiovascular toxicants (CT) and reproductive or developmental toxicants (RDT) were also several fold more abundant in cigarette smoke than in ENDS vapor (Table 2). Notable among them is carbon monoxide (CO), a product of partial combustion of tobacco in cigarettes and a recognized CT, which is not produced in combustion-free ENDS.[18]

While metal ions play vital roles in cellular and subcellular physiology and metabolism,[19] heavy metal ions could also be toxic, causing serious health and pathophysiological conditions. We have therefore compared the metal ion content of conventional cigarette smoke with that of ENDS vapor (Table 3).

We observed that most metal ions were abundant in cigarette smoke as compared to ENDS vapor (Table 3). Notable among them are (a) cadmium, a potent CA-1, RDT as well as RT, and lead, a CA-2b. The seemingly nontoxic lanthanum is also several hundred-folds

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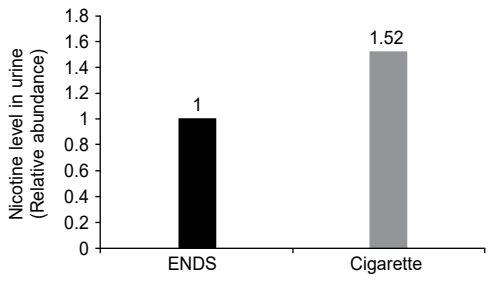
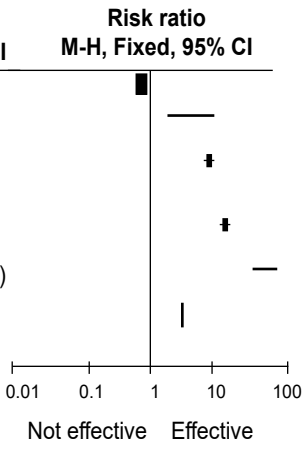



B

| Study or Subgroup | Former smokers Total | Nonsmokers Total | Weight | Risk ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| Dockrell et al (2013) | 4473 | 5866 | 60.9% | 0.76 (0.63, 0.92) |
| Czoli et al (2014) | 74 | 708 | 1.7% | 3.62 (2.05, 6.38) |
| Krishnan-Sarin et al (2014) | 423 | 4024 | 18.5% | 5.94 (5.27, 6.71) |
| Hughes et al (2015) | 803 | 9699 | 17.4% | 10.35 (9.26, 11.57) |
| Jiang et al (2016) | 1899 | 37740 | 1.5% | 46.78 (35.13, 62.30) |
| **Total (95% CI)** | **7672** | **58037** | **100.0%** | **4.13 (3.87, 4.41)** |

Heterogeneity. $\chi^2 = 894.95$, df = 4 ($p < 0.00001$); $I^2 = 100\%$

Test for overall effect : Z = 42.45 ($p < 0.00001$)

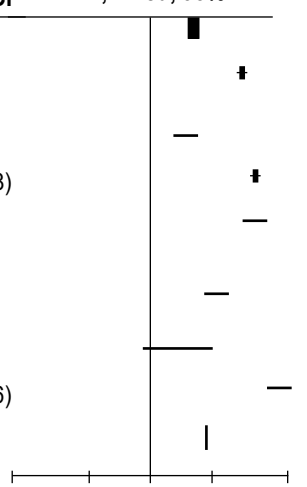



C

| Study or Subgroup | Current smokers Total | Nonsmokers Total | Weight | Risk ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| Dockrell et al (2013) | 4390 | 5866 | 49.5% | 2.92 (2.56, 3.34) |
| Krishnan-Sarin et al (2014) | 333 | 4024 | 12.2% | 8.80 (7.96, 9.73) |
| Czoli et al (2014) | 406 | 708 | 5.3% | 2.87 (1.95, 4.25) |
| Hughes et al (2015) | 1469 | 9699 | 24.6% | 14.93 (13.60, 16.38) |
| Babineau et al (2015) | 151 | 430 | 1.6% | 15.84 (9.62, 26.09) |
| Leventhal et al (2016) | 151 | 2933 | 4.1% | 5.90 (4.71, 7.38) |
| Gmel et al (2016) | 808 | 57 | 1.5% | 2.17 (0.83, 5.66) |
| Jiang et al (2016) | 1894 | 37740 | 1.1 | 58.61 (44.23, 77.66) |
| **Total (95% CI)** | **9402** | **61457** | **100.0%** | **7.53 (7.11, 7.99)** |

Heterogeneity: $\chi^2 = 659.95$, df = 7 ($p < 0.00001$); $I^2 = 99\%$

Test for overall effect: Z = 67.99 ($p < 0.00001$)




D

**Figure 2.** Bar diagram plots showing the relative abundance of nicotine absorbed in blood plasma **(A)** and excreted in urine **(B)** measured following ENDS vaping and cigarette smoking. Forest plot and data of risk ratio (RR) at 95% confidence interval (CI) showing **(C)** the existing level of ENDS usage was 4.13-fold higher among former smokers than nonsmokers making ENDS an effective means of nicotine inhalation and **(D)** ENDS vaping was 7.53-fold more popular alternative to cigarette smoking among current smokers as compared to nonsmokers suggesting that while ENDS vaping was a popular alternative to cigarette smoking primarily among former smokers, it was poorly inculcating the habit of vaping among nonsmokers.

more abundant in cigarette smoke than in ENDS vapor (Table 3). In contrast, some other metal ions, such as sodium, iron, aluminum, copper, nickel and silver were found to be marginally more abundant in ENDS vapor (Table 3). Among these, nickel is of concern since it is a weak CA-2b and a toxin (Table 3).

## Safety Implications

### Risk of acute toxicity from direct ingestion of nicotine

Acute ingestion of about 60 mg (range 30-60 mg) of nicotine could be fatal to humans.[20] Oral ingestion of 60 mg of pure nicotine would cause a blood plasma concentration of 0.18 mg nicotine $l^{-1}$ of blood, which is about 5% of actual toxic level. Such high acute concentration of nicotine in blood is possible only by accidental or intentional (e.g., to commit suicide) ingestion of nicotine and not due to smoking or vaping. Indeed, a cigarette with 10-15 mg nicotine in tobacco delivers only 1 mg of nicotine in blood[4] and equivalent ENDS vaping is likely to deliver about the same amount.[20,21] However, with an increase in the popularity of ENDS, the risk of accidental ingestion of nicotine is also likely to rise. Nicotine content in the ENDS refill ranges from 160 to 1,000 mg. These quantities of nicotine could be fatal if ingested accidently.[21]

### Risk of ENDS use during pregnancy

E-cigarette conditioned media is reported to significantly reduce trophoblast invasion and tube formation in HTR-8/SVneo cells, suggesting that an evaluation of the safety of e-cigarette use during pregnancy is urgently required.[22]

### Risks from the physical make-up of the nicotine delivery device

With the increased production and sale of ENDS, manufacturers have introduced various advanced designs for increasing user satisfaction, leading to a rapid evolution from the first-generation to the third-generation of ENDS devices ('mods'). The 'mods' have larger tank size for refills which make exposure to higher doses of nicotine possible. They also have longer lasting rechargeable batteries which pose risks similar to other electronic devices. Although uncommon, ENDS may be used, with or without modification, for pulmonary administration of banned substances such as, narcotics, marijuana, steroids and tetrahydrocannabinol (THC).[21] In fact, respondents of an internet survey perceived vaping cannabis through e-cigarettes or e-vaporizers as healthier and more discrete than smoking it.[23]

Poor materials and build quality, lack of quality control and improper use of ENDS can give rise to a condition called "thermal runaway" in lithium rechargeable batteries. This can potentially lead to explosion or fire hazard, though the risk may not be as high as that associated with burning cigarette butts. Technological advancements with thermal power cut-offs, overcharging protection circuits and other safety features in ENDS have by and large overcome these concerns.[24]

### General perception regarding safety of ENDS

Kamat and Van Dyke, 2017, reported that there is insufficient evidence of ENDS as a smoking cessation aid, and that it is too soon to assess the long-term health consequences of ENDS use.[25] They also emphasized that while the premise of ENDS as a harm reductionism avenue may be valid among adults, it should not be applied to children's experimentation with and use of ENDS. Adolescents between the ages of 14 and 17 years from deprived, mixed and affluent urban areas in Scotland and England supported strict regulation of the age-of-sale, marketing and public use of e-cigarettes.[26] Shantakumari et al, 2015, recommended that the existing restrictions on conventional cigarettes should also be imposed on e-cigarettes, with emphasis on monitoring advertising, product placement, celebrity endorsement and other marketing approaches in order to prevent promotion of e-cigarettes, particularly among children and non-smokers.[27] Kaur and Rinkoo, 2017, expressed the apprehension that weak regulation of ENDS might contribute to the expansion of the ENDS market - in which tobacco companies have a substantial stake - potentially negating years of tobacco control efforts. They recommend banning ENDS in the South East Asian region until sound scientific evidence regarding ENDS as a tobacco cessation tool is available.[28] There is also emphasis on the need for well-designed randomized controlled trials (RCTs) to draw concrete conclusions regarding the impact of ENDS and/or electronic non-nicotine delivery system (ENNDS).[29] Another worker contends that while there are no data showing increased prevalence of serious diseases or health consequences in people using ENDS, the problems related to nicotine dependence such as compulsion to smoke and limited freedom, still remain.[30]

On the contrary, Hall et al, 2015, argue that prohibiting ENDS infringes on smokers' autonomy to use a less harmful nicotine product while inconsistently

allowing individuals to begin and continue smoking cigarettes.[31] They also insist that lack of access to ENDS disadvantages smokers who want to reduce their health risks, and propose that ENDS be sold in ways that allow smokers to reduce the harms of smoking while minimizing the risks of deterring quitting and increasing smoking among youth.[31] Vickerman et al, 2017, reported that quitline callers who used ENDS experience confusion and misinformation about ENDS, and suggest that quitlines should impart improved education about ENDS, in order to facilitate the process of smoking cessation.[32] Vasconcelos and Gilbert, 2018, reported that despite uncertainty about the components, e-cigarettes were mostly viewed as healthier by smoker respondents in North London. However, the lack of reliable information and strong evidence for both the effectiveness and the safety of e-cigarettes acted as a barrier to their use as an aid to quitting smoking.[33]

### ENDS as a Substitute for Tobacco-combustion Based Conventional Cigarettes

A meta-analysis was performed in order to determine the efficacy of ENDS as an effective avenue of quitting cigarette smoking. The analysis used data pertaining to the use of ENDS and cigarette in different population groups, including nonsmokers, former smokers and current smokers.[34-41] Forest plot with combined pooled RR was plotted to determine the effectiveness of ENDS as a substitute for conventional cigarettes.

ENDS usage was found to be significantly ($p < 0.05$) higher among former smokers (RR = 4.13; 95% CI = 3.87-4.41) than among nonsmokers, by 4.13-fold, indicating that ENDS may be a useful tool in the smoking cessation efforts of smokers (Fig. 2C). We also addressed the question of whether ENDS may become a means of inculcating the habit of vaping among non-smokers. Our results indicate that the prevailing use of ENDS is significantly ($p < 0.05$) higher among current smokers (RR = 7.53; 95% CI = 7.11-7.99) than among nonsmokers by 7.53-fold (Fig. 2D).

We further analyzed available data from the World Health Organization (WHO) on the patterns of cigarette smoking and ENDS vaping in about 90 countries.[42] Box plot analysis shows that irrespective of the income level of the country (high, medium or low), the prevalence of smoking was virtually the same in majority of the population (median, 2nd and 3rd quartiles) in the countries analyzed, making cigarette smoking habit a deep rooted social behavior across all financial strata and cultures of society (Fig. 3A). However, the cigarette smoking population exhibited a trend to decline in those countries where ENDS was freely available and its usage was not regulated as compared to countries where it was regulated (Fig. 3B).

## DISCUSSION

Davis et al (2009)[43] reported that nicotine administered to immunocompetent mice at doses of 1 mg/kg$^{-1}$ body weight thrice weekly by intraperitoneal injection, or 25 mg/kg$^{-1}$ body weight daily by transdermal patches, had limited capacity to initiate tumor formation, but could promote metastasis and tumor growth. They also reported that nicotine could promote cellular invasion and epithelial-mesenchymal transition in lung, breast and pancreatic cancer cells *in vitro*. Significantly, the doses of nicotine used in the study were much higher than the average intake of smokers which is reported to range between 27.3 and 42.6 mg,[44] amounting to a calculated intake of 0.546 mg/kg/day to 0.852 mg/kg/day by an adult with an average body weight of 50 kg. It is, therefore, likely that nicotine itself may not be carcinogenic at the low doses obtained by smokers or ENDS users.

The European Union has set the maximum permissible limit of nicotine in ENDS liquids to 20 mg/mL$^{-1}$.[45] The nicotine content in a typical cigarette made of tobacco varies between 10 and 15 mg.[4] This amount of nicotine from a tobacco-based cigarette is estimated to deliver in the blood of a smoker (average 10 puffs/cigarette), a systemic dose of approximately 1-2 mg of nicotine per cigarette smoked depending on the puffing regimen.[4] The systemic dose of nicotine in blood after an ENDS vaping (ENDS with 10 mL cartridge of 24 mg/mL$^{-1}$ nicotine delivering on average 300 puffs per cartridge[46] is estimated to be about 0.8 mg, which is close to the value in cigarette smoking.[13,45] The nicotine delivery to a user by vaping using older generation ENDS device was relatively poor compared to smoking. However, over time, the new generation ENDS devices have become very efficient with nicotine delivery levels matching those of conventional cigarettes (Fig. 2A). The detection of more nicotine in the urine of conventional cigarette users in comparison to that of ENDS users could indicate faster metabolism of nicotine in cigarette smokers than ENDS vapers (Fig. 2B). Notwithstanding the minor difference in these two studies,[13,14] it may be concluded that new generation ENDS devices are capable of delivering comparable amounts of nicotine almost free of the tobacco-related damaging chemicals present in higher quantities in conventional cigarette smoke (Tables 2 and 3). Shahab et al, 2017,[47]

**Table 2.** Comparison of Toxicities of Main Chemical Components of ENDS Vape with Conventional Cigarette Smoke in Terms of Ratio or Amount Present (Where Data Pertaining to ENDS Emission were not Available/Possible/Detected). The Classification of Some of the Chemicals as Toxins, Shown in the Table, is Based on FDA (2012)[17] and IARC (2016).[16] Figure in Bold Indicates Dominance of the Chemical Entity.

| Chemical/Toxicants | Classification of chemical/toxicant* | Average relative (Ratio) or absolute quantity | | Reference |
|---|---|---|---|---|
| | | ENDS vape | Cigarette smoke | |
| Acetaldehyde | CA-2a, RT, AD | 1 | **91.17** | Goniewicz et al (2013),[54] Schripp et al (2013)[55] |
| Acrolein | CA-2b, RT, CT | 1 | **15.11** | |
| Formaldehyde | CA-1 | 1 | **8.31** | |
| Toluene | CA-2b, RT, RDT | 1 | **53.07** | |
| Carbon monoxide | CT | 1 | **2.71** | Czogala et al (2014)[56] |
| 1-Hydroxy-2-propanone | - | 1 | **62** | Schripp et al (2013)[55] |
| 1,2-Propanediol | CA-2a | 1 | **112** | |
| 2-Butanone (MEK) | - | 1 | **19** | |
| 2-Furaldehyde | - | 1 | **21** | |
| 2-Methylfuran | - | 1 | **19** | |
| 2,3-Butanedione | - | 1 | **21** | |
| 2,5-Dimethylfuran | - | 1 | **5** | |
| 3-Ethenyl-pyridine | - | 1 | **24** | |
| Acetic acid | - | 1 | **5.37** | |
| Acetone | RT | 1 | **3.2** | |
| Benzene | CA-1, CT, RDT | 1 | **22** | |
| Isoprene | CA-2a | 1 | **17.76** | |
| Limonene | - | 1 | **21** | |
| m,p-Xylene | CA-2b | 1 | **18** | |
| Phenol | CA-2b, RT, CT | 1 | **15** | |
| Propanal | - | 1 | **60** | |
| Pyrrole | - | 1 | **61** | |
| Benzo(a)pyrene | CA-2a | ND | 281.7 ng h-1 | Saffari et al (2014)[57] |
| Benzo(b)fluoranthene | CA-2a, CT | ND | 307.2 ng h-1 | |
| Benzo(e)pyrene | CA-2b | ND | 105.6 ng h-1 | |
| Benzo(g,h,i)perylene | CA-2b | ND | 187.0 ng h-1 | |
| Benzo(k)fluoranthene | CA-2a, CT | ND | 130.4 ng h-1 | |
| Chrysene | CA-2b, CT | ND | 213.3 ng h-1 | |
| Indeno(1,2,3-cd)pyrene | CA-2a | ND | 270.2 ng h-1 | |
| 4-(methylnitroso-amino)-1-(3-pyridyl)-1-butanone | CA-1 | 1 | **92.12** | Goniewicz et al (2013)[54]; Cho and Shin (2015)[58]; Farsalinos et al (2015)[49] |
| N'–nitrosonornicotine (NNN) | CA-1 | 1 | **978.1** | |

*CA-1 = Class 1 potent carcinogen; CA-2a = Class 2a probable carcinogen; CA-2b = Class 2b possible carcinogen (IARC, 2016)[16]; AD = Addictive substance; RT = Respiratory toxicant; CT = Cardiovascular toxicant, RDT = Reproductive or developmental toxicant (FDA, 2012)[17]; ND = Not determined.

**Table 3.** Comparison of Toxicities of Main Metal Ionic Components of ENDS Vape with Conventional Cigarette Smoke in Terms of Fold Differences. The Classification of Some of the Metal Ions as Toxins, Shown in the Table, is Based on FDA (2012)[15] and IARC (2016)[14]. Figure in Bold Indicates Dominance of the Metal Ions

| Metal ion | Average relative (Fold) content | | References |
|---|---|---|---|
| | ENDS vape | Cigarette smoke | |
| Aluminum | **1** | 0.55 | Williams et al (2013)[59]; Saffari et al (2014)[57] |
| Boron | 1 | **24.5** | |
| Cadmium† | 1 | **1369.37** | |
| Chromium‡ | 1 | **13.71** | |
| Copper | **1** | 0.93 | |
| Iron | **1** | 0.08 | |
| Lanthanum | 1 | **575.07** | |
| Lead‡ | 1 | **12.02** | |
| Magnesium | 1 | **1.06** | |
| Manganese | 1 | **1.5** | |
| Nickel# | **1** | 0.25 | |
| Potassium | 1 | **139** | |
| Silver | **1** | 0.7 | |
| Sodium | **1** | 0.31 | |
| Zinc | 1 | **57.74** | |

†Class 1 carcinogen (CA-1), respiratory toxicant (RT) and reproductive and developmental toxicant.
‡Class-2a probable carcinogen (CA-2a).
#Class 2b possible carcinogen (CA-2b) (IARC, 2016[16]; FDA, 2012[17]).

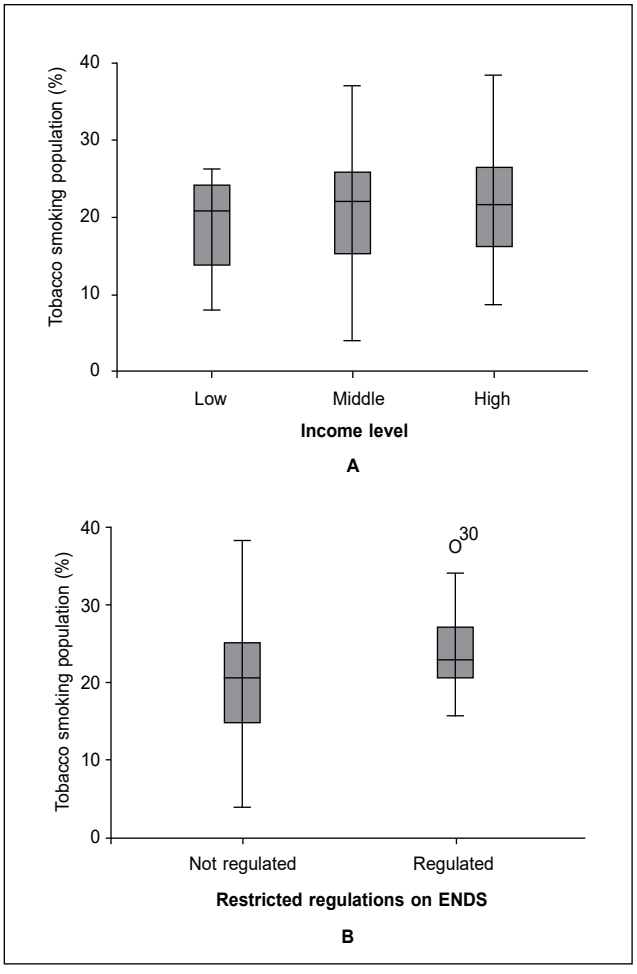



**Figure 3.** Box diagram plot showing **(A)** the prevalence of cigarette smoking habit in the populations of low, medium and high income countries (data from 90 countries; see WHO, 2015).[29] The median as well as 2nd and 3rd quartiles show nearly similar prevalence of cigarette smoking habit among people in all financial strata cutting across cultures. The data is suggestive of cigarette smoking habit being not significantly influenced by factors such as price or level of awareness, etc. **(B)** The declining trend of cigarette smoking populations in those countries where ENDS was freely available and not regulated or banned as compared to countries where ENDS was banned and tightly regulated (data from 90 countries; see WHO).[29] The decline was apparent on the median as well as on the 2nd and 3rd quartiles. The data is suggestive of ENDS being able to help quit cigarette smoking habit in population provided it is available as a choice.

also reported that former smokers with long-term e-cigarette-only or NRT-only use may obtain roughly similar levels of nicotine, and are exposed to lower levels of carcinogens and toxins when compared with smokers of combustible cigarettes only.

While ENDS produce fewer harmful chemicals than conventional cigarettes, it was reported that increasing the voltage of e-cigarettes from 3.2 to 4.8 V resulted in an increase in formaldehyde, acetaldehyde and acetone to the range of levels found in tobacco smoke.[48] Nickel may originate in ENDS vapor (Table 3) from the batteries and the nickel-coated parts (nichrome heating wire) used in the construction of atomizers in first-generation ENDS.[49] The origin of other metal ions in ENDS vape could also lie in the materials used. Thus, the design of the ENDS device is vital in reducing associated risks. In a risk assessment analysis, Farsalinos et al reported that smokers switching to ENDS were unlikely to have any significant health hazards from the amount of metals emitted from ENDS.[45] Moreover, newer generation ENDS use pyrex glass and stainless steel parts instead of nickel. While it was observed that conventional cigarette smoke contains significantly higher levels of lead than ENDS vapor (Table 3), one study reported that quantifiable levels of lead (25.2-838.4 ppb) are present

in certain commercially available disposable e-cigarette devices, and recommends that lead testing should be incorporated in chemical analyses of ENDS devices.[50] Thus, more research is desirable to further ascertain and control these emissions even at minute levels in ENDS vapor.

Our meta-analysis indicates that while ENDS is able to help smokers shift to vaping easily, it does not inculcate significant vaping habit among nonsmokers, allaying fears that it may act as an avenue for introducing nicotine dependence among nonsmokers (Fig. 2C and 2D). Our results also indicate that the cigarette smoking habit is not significantly influenced by factors such as price, awareness of harmful effects of smoking or nutritional level of the population, but ENDS may act as a useful mode of NRT to decrease the harmful effects of cigarette smoking (Fig. 3). Indeed, it has been proposed that given their harm-reduction potential, warnings for e-cigarettes should increase awareness about potential e-cigarette risks and discourage e-cigarette use among never smokers while not discouraging use among current and former smokers interested in e-cigarettes for smoking cessation or maintaining abstinence.[51]

The American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) recommended key policies including supporting federal, state and local regulation of ENDS; requiring manufacturers to register with the FDA and report all product ingredients, requiring childproof caps on ENDS liquids and including warning labels on products and their advertisements; prohibiting youth-oriented marketing and sales; prohibiting child-friendly ENDS flavors; and prohibiting ENDS use in places where cigarette smoking is prohibited.[52]

## CONCLUSIONS

Within the limits of available information, our study indicates that ENDS pose minimal health and safety concerns when compared to conventional cigarettes. These findings are supported by two recent reports.[53,54] Our study also establishes that newer generation ENDS are an efficient means of meeting nicotine demand, and can thus aid the cigarette smoking population in quitting smoking. The need of the hour is for THR activists and scientists to join hands and further investigate the implications of ENDS on human health. There is also a need for rational policy-making with the objective of maximizing benefits and minimizing potential risks by extending the benefits of ENDS to smokers who choose to use them as smoking cessation tools, while preventing the misuse of ENDS by never smokers, adolescents and children.

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**Competing interests:** None declared.

**Ethical Approval:** This study is a systematic review and meta-analysis based on information/data collected from published literature. Hence, no ethics approval is required.

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■■■■

## Baby Cough Syrup is Recalled after Bacterial Contamination

The CNN reported that makers of DG/health Naturals baby Cough Syrup + Mucus have issued a recall of the product in the US due to a bacterial contamination.

Some of the symptoms include vomiting and diarrhea. Infants, young children and others with weakened immune systems are the most at risk if exposed. The bacteria was found after audit testing showed that one in 10 bottles showed low levels of *Bacillus cereus*, the FDA said. Production has been suspended while the FDA and the company continue their investigations as to the source of the problem.

The children's cough syrup comes in a 2-ounce bottle in a carton labeled DG™/health baby Cough Syrup + Mucus. The product is distributed nationwide in Dollar General retail stores and has the potential to put children at risk for two forms of gastrointestinal illness… (*CNN*)

Bacterial Infection

Inflammation

Mixed Skin Infection

Fungal Infection

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+ Beclomethasone Dipropionate 0.025% w/w)

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# Seroprevalence of Scrub Typhus and Clinical Profile of Children with Scrub Typhus Presenting to a Tertiary Care Hospital in a Rural Setting

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## ABSTRACT

**Introduction:** Rickettsial infections were commonly recognized as an important cause of fever and central nervous system infections throughout Southeast Asia. Only in the recent years, it has been recognized to be an important cause of morbidity and mortality. **Objective:** To know the seroprevalence and clinical profile of children with scrub typhus presenting to a tertiary care hospital. **Methodology:** It was a cross-sectional study conducted in a tertiary health care center over a period of 1 year. Children presenting with fever for 5 days or more who were diagnosed negative for other causes of fever, like malaria and enteric fever, were considered as study population. A positive immunoglobulin M (IgM) ELISA (enzyme-linked immunosorbent assay) for scrub typhus was considered as primary outcome variable. Age, gender parameters were primary explanatory variables. Institutional ethical clearance was obtained. IBM SPSS version 22 was used for statistical analysis. **Results:** A total of 340 subjects were included in the final analysis. Among the study population, 241 (70.88%) children were aged >48 months. Male participants were 187 (55%) and remaining 153 (45%) were females. Out of 340 subjects, 48 (14.12%) participants were positive for scrub typhus. The common clinical features seen were fever, abdominal pain, cough, vomiting and hepatosplenomegaly in the decreasing order of frequency. **Conclusion:** The seroprevalence of scrub typhus rickettsial infection was 14.12%, which was quite high. Fever and abdominal pain were the prominent clinical features observed. Knowledge about scrub typhus fever may help in its early diagnosis and treatment and prevention of adverse outcome.


**Keywords:** Scrub typhus, prevalence, IgM ELISA

The infection caused due to Rickettsia normally presents as fever and is considered as one of the most significant central nervous system infections throughout Southeast Asia. Rickettsial infections are zoonotic infections. The transmission of rickettsial diseases is mainly through bites of arthropods like fleas, mites, etc. Rickettsia has three main serological groups of agents; scrub typhus is one of them. They are caused due to the serogroup *Orientia tsutsugamushi* and now there is newly discovered *Orientia chuto*, which is also known to cause scrub typhus fever. Scrub typhus is infectious in nature and trombiculid mites or chigger mites are mostly known for its transmission. The prevalence of scrub typhus infections is seen in areas of dense scrub vegetation. Hence, the name "scrub typhus" came into existence. Scrub typhus is endemic and is mainly found in the geographical region known as "tsutsugamushi triangle". The region majorly lies in Asia, Australia, islands in the Indian and Pacific Oceans. The triangle runs from northern part of Japan via Russia in the north, to Pakistan and Afghanistan in the west, and via the territories around India into northern Australia in the south. However, currently, the scrub typhus is widespread and is occurring in locations that were not previously thought to be endemic.

The typical characteristic feature that differentiates scrub typhus fever from other infections is the necrotic black lesion called "eschar", which is seen at the site of the mite bites. This helps in diagnosis of scrub typhus. The other signs and symptoms that are observed in scrub typhus cases include fever, chills, myalgia, headache,

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*IJCP SUTRA 832: "The recommended sodium intake is 5-6 g of salt per day (around a teaspoon)."*

vomiting, diarrhea and rash. The complications may lead to acute renal failure, hepatitis, acute respiratory distress syndrome, meningitis, circulatory collapse and multiple organ dysfunctions.

Scrub typhus represents a major cause of treatable febrile illness across Asia. The prevalence of scrub typhus has been reported worldwide but the true incidence of the disease is still unknown. The extent of the disease is mainly seen in East and Southeast Asia such as Japan, Taiwan, China, South Korea, Nepal, Indonesia and Australia. A study by Balaji et al showed that 40% fever cases were positive for scrub typhus in Tamil Nadu and in another study, S Kanagasabai et al noted that 15% of the study subjects were positive for scrub typhus. The data on the prevalence of scrub typhus is scarce.

Scrub typhus with considerable morbidity and mortality has now been well-documented in several states in India and neighboring countries. Most studies in India are retrospective in nature or based on adult population. Hence, this study was carried out to know the seroprevalence and clinical profile of children with scrub typhus presenting to a tertiary care hospital in a rural Indian setting.

## MATERIAL AND METHODS

### Study Site

This study was conducted at the Dept. of Pediatrics of a tertiary care teaching hospital in a rural setting.

### Study Population

Children up to 18 years of age, presenting with fever for 5 days or more and diagnosed negative for other causes of fever, like malaria and enteric fever, were considered as study population.

### Study Design

The current study was a prospective cross-sectional study.

### Sample Size

Sample size was calculated by assuming the expected prevalence of scrub typhus among the suspected cases as 56.42%, as per the previous published literature. The other parameters considered for sample size calculation included 10% absolute precision and 95% confidence level.

### Sampling Method

All the eligible subjects were recruited into the study consecutively by convenient sampling till the sample size was reached.

### Study Duration

The data collection for the study was done for 1-year period between July 2017 and June 2018.

### Inclusion Criteria

Children aged less than 18 years, presenting with fever for 5 days or more.

### Exclusion Criteria

- Adults aged above 18 years.
- Confirmed cases of malaria, enteric fever, leptospirosis.

### Data Collection Tools

All the relevant parameters were documented in a structured study proforma.

### Methodology

#### Statistical Methods

Scrub typhus immunoglobulin M (IgM) status was considered as primary outcome variable. Age, gender parameters were considered as primary explanatory variables.

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables.

The association between age, gender and scrub typhus IgM status was assessed by cross tabulation and comparison of percentages. Chi-square test was used to test statistical significance.

P value of <0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

## OBSERVATIONS AND RESULTS

A total of 340 subjects were included in the final analysis. Among the study population, 11 (3.24%) children were aged up to 12 months, 21 (6.18%) children were aged 13-24 months, 67 (19.71%) children were aged 25-48 months and 241 (70.88%) children were aged >48 months. Out of 340 children, male participants were 187 (55%) and remaining 153 (45%) were females.

Among the study population, 48 (14.12%) participants had positive results (Table 1).

Out of 11 participants aged up to 12 months, 1 (9.090%) participant had positive result; of 21 participants aged

**Table 1.** Seropositivity (IgM by ELISA) in Study Population (n = 340)

| Result | Frequency | Percentage (%) |
|---|---|---|
| Positive | 48 | 14.12 |
| Negative | 292 | 85.88 |

**Table 2.** Comparison of Scrub Typhus Positivity with Age of the Study Population (n = 340)

| Age group (in months) | Result | | Chi-square | P value |
|---|---|---|---|---|
| | Positive | Negative | | |
| Up to 12 (n = 11) | 1 (9.090%) | 10 (90.90%) | 3.337 | 0.343 |
| 13-24 (n = 21) | 1 (4.761%) | 20 (95.23%) | | |
| 25-48 (n = 67) | 7 (10.44%) | 60 (89.55%) | | |
| >48 (n = 241) | 39 (16.18%) | 202 (83.81%) | | |

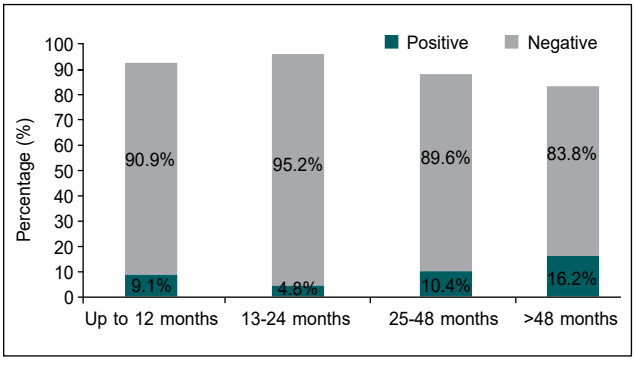


**Figure 1.** Stacked bar chart of scrub typhus positivity with age of the study population (n = 340).

13-24 months, 1 (4.761%) participant had positive result. Out of 67 participants aged 25-48 months, 7 (10.44%) participants had positive result and among 241 participants aged >48 months, 39 (16.18%) participants had positive result (Table 2 and Fig. 1). The difference in the proportion of results across different age groups was statistically not significant (p value 0.343).

The majority of participants had fever. The proportion of patients with abdominal pain and cough was 79.17% each, and for vomiting, hepatosplenomegaly (HSM), headache and myalgia was 47.92%, 39.58%, 31.25% and 31.25% (Table 3). Among the study population, 85 (25%) participants had fever up to 5 days and 255 (75%) participants had fever >5 days.

**Table 3.** Descriptive Analysis of Clinical Features in Study Population

| Clinical Features | Frequency | Percentage (%) |
|---|---|---|
| Fever | 48 | 100 |
| Abdominal pain | 38 | 79.17 |
| Cough | 38 | 79.17 |
| Vomiting | 23 | 47.92 |
| HSM | 19 | 39.58 |
| Headache | 15 | 31.25 |
| Myalgia | 15 | 31.25 |
| Hepatomegaly | 12 | 25.00 |
| Poor appetite | 10 | 20.83 |
| Nausea | 10 | 20.83 |
| Rashes | 9 | 18.75 |
| Lymphadenopathy | 9 | 18.75 |
| Cool peripheries | 8 | 16.67 |
| Breathing difficulties | 8 | 16.67 |
| CRT >3 SEC | 6 | 12.50 |
| Conjunctival congestion | 5 | 10.4 |
| Splenomegaly | 4 | 8.33 |
| Jaundice | 4 | 8.33 |
| Seizure - I episode GTCS lasted for about 5 minutes | 4 | 8.33 |
| Melena | 4 | 8.33 |
| Oliguria | 4 | 8.33 |
| Cardiovascular dysfunction (shock) | 4 | 8.33 |
| Eschar | 8 | 16.67 |
| Crepts and crackles | 2 | 4.17 |
| Petechiae | 2 | 4.17 |
| Neck stiffness | 2 | 4.17 |
| High-colored urine | 2 | 4.17 |
| Hematemesis | 2 | 4.17 |

## DISCUSSION

In the current study, a total of 340 subjects were included in the final analysis. The study population varied in different studies. A study done in 2017 included only 96 participants, while a study done in 2018 had 964 patients.

### Age

In the current study, 11 (3.24%) children were aged up to 12 months, 21 (6.18%) children were aged 13-24


IJCP SUTRA 834: "Traditional wisdom has long suggested drinking 1.5-2 liters (3-4 pints) of water per day."

months, 67 (19.71%) children were aged 25-48 months, 241 (70.88%) children were aged >48 months. In one study, the age ranged from 1 day to 18 years with the maximum number of children aged between 1 and 5 years (49.7%). In a study conducted in 2016, 13 (37%) subjects were aged between 1 and 5 years, 21 (60%) were aged >5-10 years and 6% were >10 years old. Various other studies reported the mean age as 8.97 ± 65.17, 7.3 ± 3.9, 3.2 ± 2.5 and 5.6 years.

In the current study population, 48 (14.12%) participants had positive results and 292 (85.88%) were negative for scrub typhus. The seroprevalence in our study was found to be 14.12%. The seroprevalence varied from 0.63% to 9.2% in various Indian studies.

### Clinical Features in Study Population

A study in 2017 found that all the patients had fever. Other findings were also in accordance with our study where 56% of the participants had myalgia and 50.5% children experienced vomiting. Pallor was present in 48% of children, abdominal pain in 26% of the participants, headache in 28% children, facial puffiness in 15% participants and seizures in 8.7% participants. Other common signs were hepatomegaly in 29%, splenomegaly in 28%, hypotension in 24%, edema in 21%, oliguria in 17%, maculopapular rash in 10%, meningeal signs in 10.4% and conjunctivitis in 3% of the participants. Thrombocytopenia was seen in 67% participants, anemia in 51%, pleural effusion in 23%, shock in 16%, hepatitis in 23%, acute kidney injury in 17%, meningoencephalitis in 10%, myocarditis in 7% and acute respiratory distress syndrome in 7%.

A study done in 2009 found that the primary clinical symptoms included fever (100%), cough (50%), eschar (50%), rash (35.7%), poor appetite (42.9%), lymphadenopathy (42.9%), headache (39.3%) and hepatomegaly (35.7%). All these were in accordance with our study.

### Eschar

In the current study, eschar in axilla was seen in 14.4%. In another study, eschars were often on the axilla/groin in 24.9% participants, followed by 23.4% in the abdominal region and waist area and 18.3% in the head and neck region.

### Fever (in Days)

Among the study population, 85 (25%) participants had fever up to 5 days and 255 (75%) participants had fever for >5 days. In a study, 18 (27%) patients had fever <7 days, 39 (59%) had fever for 7-14 days and 9 (14%) had fever for >14 days. A study done in 2017 reported the mean days of fever to be 8.856 ± 3.18.

## LIMITATIONS

- The present study was conducted only in pediatric population and was conducted at a single center. Hence, the study cannot be generalized to the rest of the population.
- Purposive sampling technique was employed for the study which is not a true representation of the general population. This may lead to selection bias.
- The study was hospital-based leading to Berksonian bias.

## RECOMMENDATIONS

Given that there was high prevalence of scrub typhus rickettsiosis in our study, the clinicians and general practitioners must be aware of the clinical profile related to scrub typhus fever. Rickettsial fever must be considered when the symptoms don't fit into the profile of any other diseases causing fever (dengue, malaria, etc.). Timely recognition of complications may help prevent the adverse outcome.

It is recommended to conduct a large multicentric population-based study to know the true prevalence of scrub typhus.

## CONCLUSION

The seroprevalence in our study was found to be 14.12% which was quite high when compared to previous studies.

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### Blood Pressure Control Reduces Dementia Risk in Mid-life AF Patients

Dementia risk in mid-life patients with atrial fibrillation (AF) can be reduced by controlling high BP, according to a study presented at EHRA 2019, a congress of the European Society of Cardiology (ESC). The study also found that lowering BP in patients older than 70 years old may not have as big of an impact on dementia risk.

### No Evidence that Calcium Increases Risk of AMD, Says Study

Eating a calcium-rich diet or taking calcium supplements does not appear to increase the risk of age-related macular degeneration (AMD), according to the findings of a retrospective analysis of data from the Age-Related Eye Disease Study (AREDS) published in *JAMA Ophthalmology*.

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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

RAM AVTAR*, RAVIKANT JAIN†


## 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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*IJCP SUTRA 838:* "Drugs like ibuprofen are known to cause kidney damage, if taken regularly."

**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.

**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.

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.

**Figure 2.** Wound after VAC.

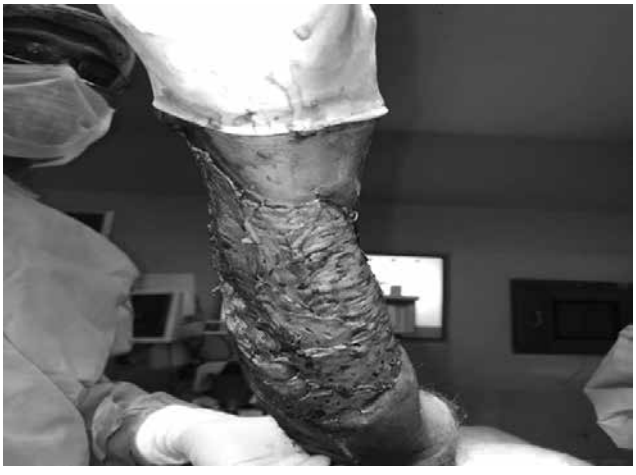

**Figure 3.** Wound after skin grafting.

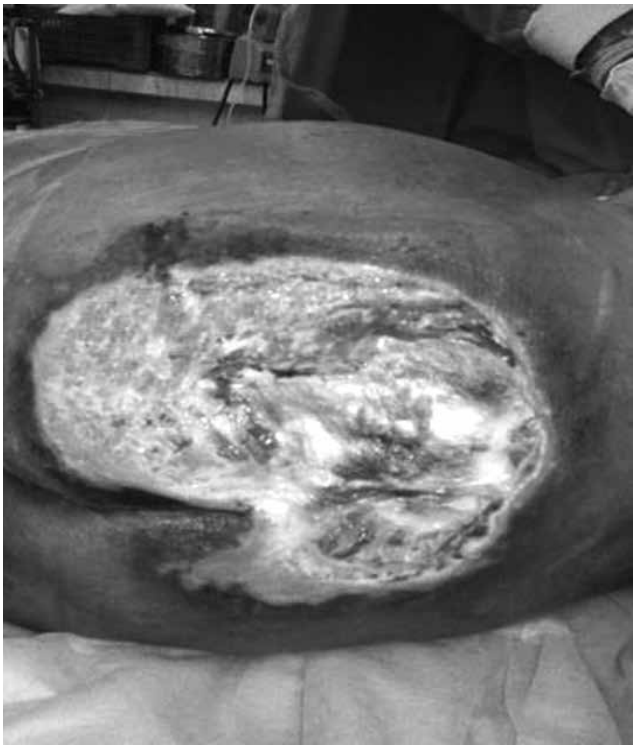

**Figure 4.** Wound before VAC.

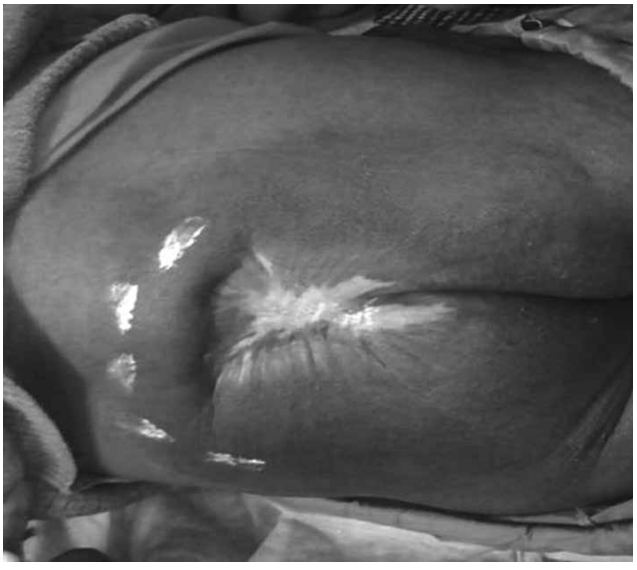

**Figure 5.** Wound after VAC.

## 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.


*IJCP SUTRA 840: "Malaria mosquitoes grow in fresh water collected in the house."*

## 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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### More Children Killed by Unsafe Water, Than Bullets

A lack of safe water is far deadlier for children than war in more than a dozen conflict-affected countries, the UN Children's Fund (UNICEF) said recently, in a report launched to coincide with World Water Day, marked on 22 March. UNICEF's 16-nation study into how water supplies effect children caught up in emergencies, also shows that children under-five are on average more than 20 times more likely to die from illnesses linked to unsafe water and bad sanitation, than from conflict.

"The odds are already stacked against children living through prolonged conflicts - with many unable to reach a safe water source," said UNICEF Executive Director Henrietta Fore. "The reality is that there are more children who die from lack of access to safe water than by bullets."

According to the report, every year, 85,700 children under-15 die from diarrhea linked to unsafe water, sanitation and hygiene facilities (WASH), compared with 30,900 from conflict. Some 72,000 under-fives die annually from similar illnesses linked to WASH-access problems, compared to 3,400 from war-related violence. UNICEF studied data from Afghanistan, Burkina Faso, Cameroon, the Central African Republic, Chad, the Democratic Republic of the Congo, Ethiopia, Iraq, Libya, Mali, Myanmar, Somalia, South Sudan, Sudan, Syria and Yemen… (*UN*)

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# Platelet Distribution Width – Platelet Indices for Determining the Causes of Thrombocytopenia

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## ABSTRACT

**Background and aim:** Thrombocytopenia (TCP) is low platelets count. It can result from defective platelet production or due to increased platelet breakdown. The platelet number alone does not give a complete picture of platelet maturity and function. The platelet indices have become a subject of intensive study in recent years to find the causes of TCP. The platelet parameters are widely available as part of full blood count with no extra cost. Mean platelet volume (MPV) and platelet distribution width (PDW) are useful parameters in evaluating disorders of platelets. This study was undertaken to evaluate the effectiveness of PDW in diagnosing causes of TCP. **Material and methods:** Six hundred fifty cases of TCP and 500 individuals of control group with normal platelet count were included in the study. TCP was defined as platelet count below 1.5 lacs/mm$^3$. Hematological analysis was done on Sysmex XT-1800i automated hematology analyzer. Platelet counts of all the cases were rechecked by peripheral smear examination. Only those cases that had sufficient clinico-hematological work up and the causes of TCP had been reliably established were included in the study. **Results:** Hyperdestructive and abnormal pooling group constituted majority of the cases (446 [68.6%]), while hypoproductive group constituted 204 (31.4%) cases. The mean PDW was significantly higher in hyperdestructive group when compared with hypoproductive group and control group. The difference was statistically significant. **Conclusion:** PDW provides plenty of clinical information about the causes and pathophysiology of TCP and can be helpful to distinguish hyperdestructive from hypoproductive TCP.


**Keywords:** Thrombocytopenia, platelet indices, platelet distribution width, mean platelet volume

Thrombocytopenia (TCP) is not a disease entity by itself, but a finding that may result from a number of disease processes. There is subnormal number of platelets in the circulating blood and it is one of the most common causes of abnormal bleeding. Low platelet counts can have varied causes that can be grouped in three major categories as decreased production, increased destruction and splenic sequestration/abnormal pooling. Variation in the size, especially, large platelets, is seen on peripheral smear. This varying size of platelets was suggested to help in deciding the category of TCP long back. With the advancements in automated hematology analyzers, new platelet parameters are available, resulting in greater precision and faster processing of specimens. Some of these parameters include platelet indices: Plateletcrit (PCT), mean platelet volume (MPV) and platelet distribution width (PDW). However, despite being routinely available, these indices are generally considered as not interpretable and are rarely used by laboratories and physicians.

Clinically, platelet volume measurements have long been of interest to researchers concerned with platelet production. MPV correlates with platelet function and activation, whether measured as aggregation, thromboxane synthesis, beta-thromboglobulin release, procoagulant function or adhesion molecule expression.

There is evidence supporting that PCT, rather than platelet counts, predicts the risk of bleeding in patients with TCP. PDW is a quantitative assessment of platelet size and volume and is of limited usefulness in distinguishing between reactive thrombocytosis and essential TCP. PDW is increased in the presence of platelet anisocytosis.

MPV and PDW are increased in TCP. PDW represents the degree of heterogeneity of platelets. The changes

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*IJCP SUTRA 842: "If any utensil or container that stores water is cleaned properly once in a week, there are no chances of mosquito breeding."*

in PDW may be the result of recruitment of multiple ploidy classes of megakaryocytes. Each ploidy class contributes a set of platelets with different MPV. Several studies on these parameters have shown that they can be used to determine the cause of TCP and they have sufficient sensitivity and specificity in the diagnosis of TCP.

Osselaer et al, in their study, observed that PDW is certainly an important but forgotten platelet parameter. Hence, we have undertaken this study to ascertain the value of this forgotten parameter, PDW, in distinguishing various categories of TCP.

## MATERIAL AND METHODS

Thrombocytopenia was defined as platelet count <1.5 lacs/mm$^3$. Blood was collected in K-EDTA vacutainer and analysis was done by the Sysmex XT-1800i automated hematology analyzer within 2-6 hours of collection. Platelet count and platelet volume parameters of all the samples were noted. Each case of TCP was reassessed by peripheral smear examination and also by manual method, if necessary. Cases with discrepancy in counts by different methods were excluded from the study. Only the cases with sufficient clinical and hematological work-up were included in the study. The statistical data was finally analyzed by SPSS software.

## RESULTS

Total 650 cases of TCP were studied for the present study. Out of these, 416 (64%) were males and 234 (36%) were females with a male-to-female ratio of 1.78:1. A slight male preponderance was seen for the whole study and also in all age groups. Age ranged from 8 months to 84 years.

All cases were segregated into two groups based on the predominant underlying mechanism of TCP: Group A – Hyperdestructive TCP, Group B – Hypo-productive TCP. Group A constituted majority of the cases 446 (68.6%). This group was further subdivided into various categories based on the clinical diagnosis (Table 1). In Group A, bacterial infections accounted for the maximum number of cases, i.e., 114 (25.56%). All the categories in Group A had variable mean PDW with highest mean PDW in pregnancy (17.15 ± 1.05), while PDW was lowest in cardiac diseases (15.15 ± 0.5). Highest mean MPV was seen in cases of immune thrombocytopenia (ITP) (11.95 ± 0.45) and lowest (9.7 ± 0.3) seen in pregnancy (Table 1).

Group B constituted 204 (31.4%) cases. In this group also, PDW was variable with highest in aplastic anemia (13.6 ± 0.3) and lowest in leukemia (11.65 ± 0.85). Cases of leukemia showed the highest mean MPV (12 ± 0.8) while lowest mean MPV (7.9 ± 0.2) was seen in patients of megaloblastic anemia (Table 2).

Control group included 500 cases of normal platelet counts with 280 (56%) males and 220 (44%) females. The mean platelet count in control group was 1.72 ± 0.12 lacs/mm$^3$. In Group B, 0.105 lacs/mm$^3$ was the lowest platelet count, seen in patients of aplastic anemia, in Group B (Tables 1 and 2).

**Table 1.** Group A - Hyperdestruction of Platelets 446 (68.6%)

| Categories | No. of cases | Percentage (%) | Mean platelet count/mm$^3$ | Mean MPV (fl) (mean ± SD) | Mean PDW (fl) (mean ± SD) |
|---|---|---|---|---|---|
| Bacterial infections | 114 | 25.56054 | 0.710 | 10.30 ± 2.1 | 15.34 ± 1.5 |
| Cardiac diseases | 92 | 20.6278 | 0.896 | 10.45 ± 0.1 | 15.15 ± 0.5 |
| Renal diseases | 64 | 14.34978 | 1.110 | 10.70 ± 0.52 | 15.65 ± 0.35 |
| Liver diseases | 43 | 9.641256 | 0.625 | 10.42 ± 0.52 | 16.13 ± 0.08 |
| Dengue | 40 | 8.96861 | 0.224 | 10.92 ± 0.4 | 17 ± 0.14 |
| Malaria | 25 | 5.605381 | 0.785 | 10.22 ± 0.60 | 15.50 ± 0.05 |
| Pregnancy | 15 | 3.363229 | 0.740 | 9.7 ± 0.3 | 17.15 ± 1.05 |
| Viral infections | 12 | 2.690583 | 0.910 | 10.05 ± 0.15 | 16.10 ± 0.15 |
| ITP | 08 | 1.793722 | 0.256 | 11.95 ± 0.45 | 15.86 ± 0.14 |
| Sepsis | 06 | 1.345291 | 0.645 | 10.28 ± 0.82 | 16.14 ± 0.26 |
| Blood transfusion | 02 | 0.44843 | 0.840 | 10.20 ± 0.05 | 16.4 ± 0.1 |
| Miscellaneous | 25 | 5.605381 | 0.825 | 10.50 ± 0.70 | 15.55 ± 0.25 |
| Mean ± SD | | | 0.713 ± 0.24 | 10.47 ± 0.54 | 15.99 ± 0.59 |

**Table 2.** Group B - Hypoproduction of Platelets 204 (31.4%)

| Categories | No. of cases | Percentage (%) | Mean platelet count/mm$^3$ | Mean MPV (fl) (mean ± SD) | Mean PDW (fl) (mean ± SD) |
|---|---|---|---|---|---|
| Solid malignancy | 110 | 53.9215686 | 0.615 | 9.55 ± 1.05 | 12.55 ± 0.15 |
| Leukemia | 65 | 31.8627451 | 0.256 | 12 ± 0.8 | 11.65 ± 0.85 |
| Megaloblastic anemia | 21 | 10.2941176 | 0.455 | 7.9 ± 0.2 | 12.95 ± 0.15 |
| Aplastic anemia | 8 | 3.92156863 | 0.105 | 10.45 ± 0.85 | 13.6 ± 0.3 |
| Mean ± SD | | | 0.357 ± 0.19 | 9.97 ± 1.48 | 12.69 ± 0.71 |

## DISCUSSION

Thrombocytopenia is quantitative reduction in the platelet count and can be due to increased peripheral destruction, inadequate production or abnormal pooling. A confident assessment of mechanism cannot be made in individual cases on clinical grounds. Platelet indices are the measurements made on peripheral blood platelets and include MPV, PDW and platelet-large cell ratio (P-LCR). These parameters can be easily obtained from routine automated hematology analyzers but their role in application to clinical diagnosis is yet to be established. Measurement of platelet indices in automated analyzers has many advantages over manual estimation. It is simple, quick and inexpensive and it also eliminates the inter- and intraobserver bias. Moreover, in the manual method, the delay between collection of blood and smear preparation may change platelet morphology and cause artefactual increase in platelet diameter, due to increased adhesiveness with flattening of the platelets on the smears.

Platelet volume is a marker of platelet function and activation. In very general terms, increased MPV might be expected in "regenerative" TCP, i.e., that caused by increased peripheral loss, destruction or utilization of platelets and accompanied by increased production of platelets by marrow (megakaryocytic hyperplasia).

PCT, derived from platelet count and MPV, and PDW, derived from direct flow cytometric measurement of platelet cell volume, are less documented for their clinical roles.

The present study was carried out with the objective of studying platelet parameters in various clinical cases. We targeted 650 cases of TCP and their clinical features, platelet count and platelet parameters - MPV and PDW - were studied. Though we studied 1,000 cases of TCP, platelet parameters were given by cell counter in 650 cases. Analysis of the parameters was done in these 650 cases only and that constituted 65% of all. In control group, the same parameters were given in all 400 cases. In 350 (35%) cases, the platelet parameters were not given by the cell counter and in these cases, the platelet histogram showed deviation from the normal bell-shaped curve, leading to no output of values for platelet indices. This is a major limitation for platelet volume parameter studies in TCP and similar findings have been quoted by studies. All the cases were grouped according to most predominant mechanism.

We divided our study cases into two major groups on the basis of the predominant mechanism as Group A (Accelerated platelet destruction and pooling) and Group B (Impaired platelet production).

Group A - In hyperdestructive causes of TCP, marrow compensates actively for platelet loss. They release young platelets which are larger in size. There is a decrease in size during its 7-10 days life span. This group is constituted by disorders like immune and nonimmune cases of ITP, microbial infections, drugs, systemic lupus erythematosus (SLE) and neonatal TCP. Majority of our cases belonged to Group A (68.6%), suggesting the mechanism of accelerated destruction. We also included cardiac, renal, gestational TCP, neonatal TCP, post-transfusion cases and TCPs with shock and some other miscellaneous conditions in this group. The group had mild-to-moderate TCP except for the ITP category, which presented with relatively severe TCP.

The platelet count decreases proportionally and inversely to increasing spleen size. Approximately a third of total platelet mass is normally sequestered in spleen. Commonly, platelet counts of 50,000-70,000/mm$^3$ have been found in individuals with cirrhosis and associated splenomegaly. Our study accounted 9.6% cases in this group, with congestive splenomegaly suggesting abnormal platelet pooling with mean platelet count of 62,500.

Group B - There are several disorders with TCP secondary to inadequate platelet production from the

marrow such as chemotherapy for solid malignancies, acute leukemia, megaloblastic and aplastic anemia. Our study constituted 31.4% cases in this group, which included few dimorphic anemia in megaloblastic anemia. This category of patients had relatively moderate-to-severe TCP as compared to previous category.

The mean PDW in the present study for Group A was higher than that of control group, while value for Group B was similar to that of control group. Nelson et al noticed that patients with TCP due to loss or destruction of platelets have larger platelets, whether the loss is due to infection, hemorrhage or immune destruction. When TCP was due to lack of production, the platelet volume was similar to that seen in patients with normal blood cell counts. Babu et al noticed increased platelet heterogeneity in all TCP groups.

In normal subjects, MPV has an inverse, nonlinear relation with platelet count, while platelet volume heterogeneity has a direct, nonlinear relation with MPV. In comparison to the reference range established for normal subjects, patients with chronic lymphocytic leukemia, atherosclerotic heart disease, diabetes mellitus and chronic undifferentiated schizophrenia have been shown to have normal platelet volume mean and heterogeneity. Patients treated with cytotoxic chemotherapy for acute nonlymphocytic leukemia, patients with megaloblastic anemia and patients with aplastic anemia have been noted to have abnormally small platelets with increased heterogeneity. Patients with chronic myelogenous leukemia seem to have abnormally large platelets with increased heterogeneity.

Borkataky et al noticed high mean PDW values except for nonmegaloblastic subgroup of impaired production. Platelet size is heterogeneous even in normal persons. Its heterogeneity is; however, increased in patients with ITP, sepsis, disseminated intravascular coagulation (DIC), myocardial infarction and diabetes mellitus (accelerated destruction). The heterogeneity of platelet volume is considered to be due to aging of platelets or due to heterogeneous demarcation of megakaryocytes.

## SUMMARY AND CONCLUSIONS

Platelet distribution width is an important index in platelet parameters. PDW, along with other platelet indices, can give valuable information regarding the mechanism of platelet destruction. Increased variation in PDW indicates greater platelet heterogeneity along with destruction and splenic pooling. PDW varies inversely with platelet count. Further large studies with large number of cases in each subgroup are needed to explore the role of platelet indices in TCP and also to find the diagnostic role of platelet indices in various other diseases. The parameter P-LCR also needs to be worked upon to see for subtle changes, if any, and whether it could be explained by the mechanism of destruction of platelets.

## Acknowledgment

I take this opportunity to extend my gratitude and sincere thanks to all those who helped me to complete this study.

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*Am J Hypertens. 2003;16(5 Suppl):A129.*

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# Assessment of Cesarean Section Scar Strength: Still a Challenge?

URVASHI VERMA*, MUKESH CHANDRA†, ARUN NAGRATH‡, SAROJ SINGH#, RACHANA AGRAWAL*


## ABSTRACT

**Objective:** To assess the integrity (strength) of cesarean scar of uterus during interval period (nonpregnant state) by ultrasonography (USG), hysterography and hysteroscopy and their correlation. **Material and methods:** The study was conducted in the Dept. of Obstetrics and Gynecology and Dept. of Radiology, SN Medical College, Agra, Uttar Pradesh. Three hundred nonpregnant women with cesarean section in past were recruited to undergo USG, hysterography and hysteroscopy along with proper history and other routine examination. The thickness and appearance of anterior uterine wall, especially at scar area, were noted down during investigations. **Results:** The mean scar thickness was more (11.59 ± 1.33 mm) in women with only one cesarean section in comparison with women having more than one cesarean section (9.08 ± 9.2 mm). Healthy abdominal scar healed with primary intention correlated with good uterine strength. More breaking on hysterography was associated with thin scar on USG. When scar area was found irregular and wide on hysteroscopy, the thickness of scar was less on USG also. **Conclusion:** A prospective idea of uterine scar strength can be obtained by careful history taking, local examination of abdominal scar as well as per vaginal findings along with USG, hysterography and hysteroscopy in nonpregnant women. If findings are suggestive of weak scar, a lady can be counseled for planned cesarean section in her future pregnancy in spite of trial for vaginal birth after cesarean. Accordingly, if she can afford further risk and cesarean section, she should become pregnant otherwise should avoid further confinement in future.


**Keywords:** Cesarean scar integrity, ultrasonography, hysterography, hysteroscopy, interval period

Cesarean section is the most commonly performed surgical procedure involving the uterus in fertile women with low transverse incision being the most common type of uterine hysterotomy.[1,2] Every woman who has undergone cesarean delivery aborts the chances of normal vaginal delivery in future pregnancies. Almost all of us are very frequently asked by most of the women who have undergone cesarean section recently or in past, "Doctor, will I have a normal vaginal delivery (NVD) in future or not". It will be better, if we have some method, which could assess strength of uterine (cesarean) scar before a lady plans for her subsequent pregnancy/delivery. To seek an answer to this important and frequently asked question by almost every woman, this study was contemplated.

In women, who have undergone a cesarean section, a previous cesarean section casts a shadow over any future pregnancy, though under favorable circumstances, a repeat cesarean section may not be necessary. Today, a more up-to-date version of the old saying 'once a cesarean always a cesarean' would be 'once a cesarean always a hospital delivery'. Effort to encourage vaginal birth after cesarean (VBAC) appears to be the most productive approach to lowering the cesarean rate. Since, a fair number of cesarean sections are done for nonrecurring indications, the question of allowing a vaginal delivery in the future becomes a pressing problem in the mind of the Obstetrician, especially in developing countries like India.

Poidevin (1959) found that, on opening all uteri, which had previously been subjected to lower segment cesarean section (LSCS), a larger or smaller depressed scar would always be seen.[3] If the depression is not

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>5 mm deep, the scar can be relied upon not to give way. A defect within the lower uterine cavity in patients with a history of cesarean section has been described by Simpson et al on hysterosalpingography.[4] Ash et al described that patients who had a cesarean section will exhibit anatomic abnormality in lower uterine segment on ultrasonography (USG).[5]

## MATERIAL AND METHODS

This was a prospective study done on 300 women - 160 women had one cesarean section and 140 women had two cesarean sections - attending the OPD in Dept. of Obstetrics and Gynecology, SN Medical College, Agra, Uttar Pradesh. The age group varied from 15 to 45 years. Detailed obstetric history along with general, systemic and local examination was done along with urine pregnancy test. Women having recent pelvic infection and/or allergy to dye were excluded from the study.

Under local examination, any healing defect, scarring, pain, tenderness and any discharge from stitch line were noted. Genital tract examination was done to see the condition (mobility) of cervix, uterus and adnexal pathology. Every woman was subjected to USG, hysteroscopy and hysterography along with other routine investigations.

On ultrasound, scanning was done in serial longitudinal and transverse planes across the whole length of scar in postmenstrual phase with full bladder (Fig 1). Scar was identified as a hyperechoic small line or dots (equal sign) in lower part of uterus and its thickness was measured at various points by moving probe from side-to-side. Hysteroscopy (direct visualization of scar) was performed on 9th postmenstrual day or when bleeding stopped completely and whole of the anterior uterine wall was scanned up to internal os. Scar was identified as whitish and fibrotic area or line horizontally (Fig 2). The findings of scar area were compared with the findings by means of other methods. Hysterography (hysterosalpingography) was also performed on 9th postmenstrual day or when bleeding stopped completely and films in lateral view were taken (Fig 3). The depth of breaking/notching or filling defect was identified, measured and categorized in three groups (<1 mm, 1 mm and >1 mm). These findings were also compared with findings by means of other methods.

## RESULTS

As shown in Table 1, in women having only one cesarean section, the mean scar thickness was 11.59 ± 1.33 mm

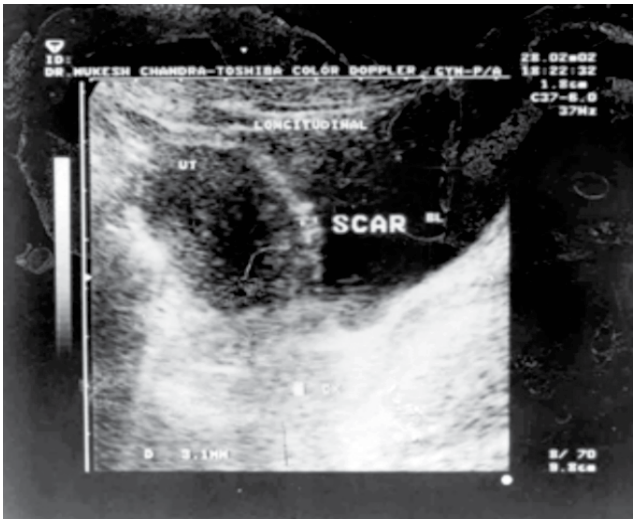


**Figure 1.** Anterior wall thickness at scar area (*white marker*) on USG.

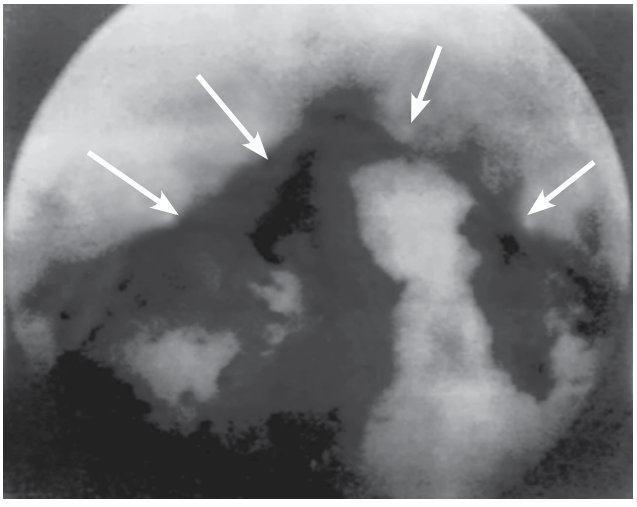

**Figure 2.** Hysteroscopic view of dehiscent scar (*white arrows).*

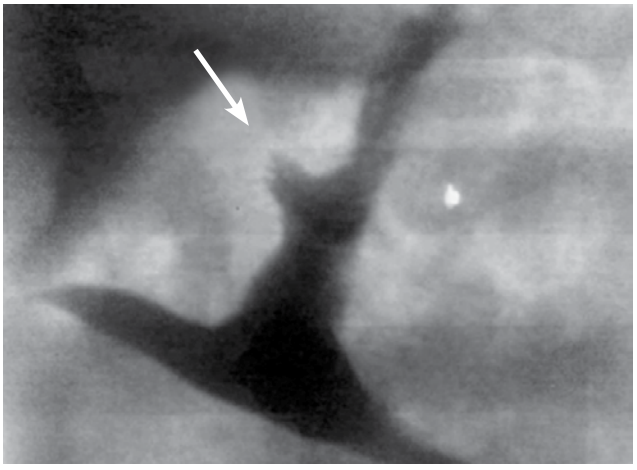

**Figure 3.** Hysterography after cesarean section reveal a wide and deep scar at the level of subisthemic incision (*white arrow*).

and in women having two cesarean sections, the mean scar thickness was 9.08 ± 9.2 mm; this is statistically significant. It was concluded that in women having more number of cesarean sections, the scar becomes thinner, which can also be proved by hysterography; the deformities shift to the larger type as the number of cesarean sections increase.

According to Table 2, on hysterography it was evident that 70 patients had depth of beak >1 mm and mean scar thickness of 8.86 ± 1.36 mm, and equal number of patients had a beak of 1 mm and mean scar thickness of 10.00 mm. There were 160 women who had <1 mm deep beak and mean scar thickness of 10.75 ± 1.25 mm. On comparing the two groups, <1 mm and >1 mm deep beak, scar thickness was found to be statistically significant ($p < 0.05$). It was concluded that if scar was found to be thin on USG, there will be more beaking in anterior uterine wall (scar area) on hysterography.

On hysteroscopy, interior of uterine cavity was seen and classified into two groups according to the regularity and irregularity of scar area and again, whether it was wide or linear. If uterine outline, anteriorly at scar area, was found irregular or wide, both conditions indicate a weak scar. It was further confirmed by USG as well as by hysterography (Table 3).

As seen in Table 3, 230 cases had fine linear abdominal scars and mean scar thickness of uterus by USG was 10.24 ± 0.9 mm while 40 cases had wide puckered scar over abdomen and mean scar thickness of uterine scar was 9.50 ± 1.12 mm. There were only 30 cases having keloid/hypertrophic scar formation over abdomen and mean uterine scar thickness of 8.67 ± 1.2 mm on USG. The values are statistically significant ($p < 0.05$). Table 4 summarizes the distribution of cases and their scar thickness by USG according to hysteroscopic findings.

**Table 1.** Distribution of Cases and their Ultrasonography Findings According to Number of Cesarean Section

| No of cesarean section | Scar thickness by USG (mean ± SD in mm) | No. of women |
|---|---|---|
| 1 | 11.59 ± 1.33 | 160 |
| 2 | 9.08 ± 0.92 | 140 |
| **Total** | **10.37 ± 1.2** | **300** |

't' = 2.181; $p < 0.05$

**Table 2.** Distribution of Cases According to Hysterographic (Isthmographic) Findings and its Correlation with USG Findings

| Depth of beak on hysterography (mm) | No. of cases | Scar thickness by USG (mean ± SD in mm) |
|---|---|---|
| >1 mm | 70 | 8.86 ± 1.36 |
| 1 mm | 70 | 10.00 ± 0.00 |
| <1 mm | 160 | 10.75 ± 1.25 |
| **Total** | **300** | **10.37 ± 1.20** |
| >1 vs. 1 | 't' 0.272 | p >0.05 |
| <1 vs. >1 | 3.531 | <0.05 |
| 1 vs. >1 | 2.567 | <0.05 |

## DISCUSSION

Although not many studies are available regarding uterine scar status especially in nonpregnant condition, Alfred Warionch in his study in 1967, using hysterography concluded that as the number of cesarean sections increases, the scars become thinner.

Osser et al also found that myometrial thickness at the level of isthmus uteri decreases as the number of cesarean sections increases; the frequency of the large scar defect increases.[6] This was also found in our study. Now many surgeons have started practicing excision of scar area after identifying it as fibrosed, nonvascular thinned portion during cesarean section in a hope to get a healthy and good strength scar in future.

During hysterocervicography, a steep oblique or lateral view may be helpful in better defining this particular cesarean section scar because certain defects can be obscured on a frontal view.[7] Though, in the interpretation of hysterosalpingography, awareness of the appearance of cesarean scar defect is important in avoiding misdiagnosis of the scar for underlying pathology or normal variant such as prominent cervical glands, post myomectomy diverticulum, synechiae and focal adenomyosis.[4,8]

On hysterosalpingography, the defects were categorized by location (lower uterine segment, uterine isthmus,

**Table 3.** Distribution of Cases According to the Abdominal Wall Scar Status and its Relation to the Uterine Scar Thickness on USG

| Abdominal scar on per abdomen examination | No. of cases | Uterine scar thickness on USG (mean ± SD in mm) |
|---|---|---|
| Fine/Linear (FL) | 230 | 10.24 ± 0.9 |
| Wide/Puckered (WP) | 40 | 9.50 ± 1.12 |
| Hypertrophic/Keloid (K) | 30 | 8.67 ± 1.2 |
| **Total** | **300** | |
| FL vs. WP | 't' 2.463 | p <0.05 |
| FL vs. K | 3.610 | <0.05 |
| WP vs. K | 0.926 | >0.05 |


IJCP SUTRA 849: "Create a sleep sanctuary. Reserve your bedroom for sleep."

**Table 4.** Distribution of Cases and their Mean Scar Thickness by USG According to Hysteroscopic Findings

| Uterine outline on hysteroscopy | No. of cases | Scar thickness on USG (mean ± SD in mm) | 't' test | P value |
|---|---|---|---|---|
| Regular | 250 | 10.68 ± 0.93 | 3.965 | <0.05 |
| Irregular | 50 | 8.80 ± 1.17 | | |
| Wide | 90 | 9.44 ± 1.17 | 3.262 | <0.05 |
| Linear | 210 | 10.76 ± 0.97 | | |

upper endocervical canal), side (right, left, bilateral, small midline) and size by Surapaneni and Silberzweig.[7]

In comparison with hysterosalpingographic diagnosis of cesarean scar defect, Regnard et al detected a similar rate of cesarean section scar (57.5%) via saline contrast sonohysterography.[9] Fabres et al suggested that the defect may be related to the suture material used, the suturing technique itself or a combination of both.[10] It is presumed that the most ischemic technique and slowest reabsorbable suture would be the worst combination and thus most likely to produce a cesarean scar defect.[10]

In the study by Surapaneni and Silberzweig, out of 148 women with history of cesarean section and technically adequate hysterosalpingography, 89 (60%) were found to have anatomic defect.[7] In a study by Ofili-Yebovi on USG lower segment, uterine scars were detected in 321/324 women with a history of previous cesarean section; 63 women had evidence of deficient cesarean scar.[11]

## CONCLUSION

If we want to avoid more and more encounters with impending dehiscence and uterine rupture following cesarean section, we have to be alert since the beginning of the story. We have to correct anemia before a lady gets pregnant and during her pregnancy. During labor, we should be alert for warning signs and should shift the patient in time. Nonabsorbable or slow absorbing sutures and very tight stitching (ischemic technique) should be avoided. Postoperative anemia and infections must be avoided.

The integrity of scar is affected by various factors like general condition of woman at the time of cesarean section, technique of stitching, type of suture material, preoperative, peroperative or postoperative infections as well. If the thickness of scar area is <10 mm on USG or depth of beak on hysterography is >1 mm or if it looks wide and irregular on hysteroscopy, all are indicative of a weaker uterine scar.

This procedure can be done during the interval period and the patients accordingly counseled with regard to their chances of achieving their subsequent reproductive goals. Repeat elective cesarean section, then, is chiefly indicated in case of established weak/deficient scar found by above mentioned method and investigations as in disproportion and after a classical operation.

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# Guillain-Barré Syndrome – Sensory Ataxic Variant

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## ABSTRACT

Guillain-Barré syndrome (GBS) is an acute inflammatory polyradiculoneuropathy characterized by rapidly evolving areflexic motor paralysis, with or without sensory disturbance. GBS is manifested as multiple nerve root and peripheral nerve injury. Demyelination is the main electrophysiological and pathological feature of this disease. Cerebrospinal fluid (CSF) analysis will show albuminocytological dissociation. Here we report a rare case of sensory ataxic variant of GBS in a 50-year-old male with no other comorbidities who presented to us with complaints of unsteadiness while walking and tingling sensation over both legs (below knee) for 6 days followed by both upper limbs (below elbow) for 2 days. On examination, deep tendon reflexes were absent in all four limbs with bilateral flexor plantar response. Sensory examination revealed impaired fine touch, vibration and joint position sense up to bilateral knee and elbow with normal pain and temperature sensations. Gait was sensory ataxic type with positive Romberg's test. CSF examination showed normal cell count with elevated protein level. Nerve conduction study showed sensory demyelinating patterns with normal motor component in upper and lower limbs. He was treated with intravenous immunoglobulin for 5 days and recovered completely after 2 weeks.


**Keywords:** Guillain-Barré syndrome, sensory ataxic variant, albuminocytological dissociation, intravenous immunoglobulin

Guillain-Barré syndrome (GBS) is an acute inflammatory polyradiculoneuropathy characterized by rapidly evolving areflexic motor paralysis with or without sensory disturbance. GBS is manifested as multiple nerve root and peripheral nerve injury. The usual pattern is an ascending paralysis that may be first noticed as rubbery legs accompanied by tingling dysesthesia in the extremities and progressively involves the trunk, the upper limbs and finally bulbar muscles with difficulty in handling secretions and maintaining the airway. Deep aching pain in weakened muscles may present initially. Weakness typically evolves over hours to a few days, often reaching a peak at the 4th week. Subtypes of GBS are acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN) and Miller-Fisher syndrome (MFS). Autonomic involvement may occur in some patients. Demyelination is the main electrophysiological and pathological feature of this disease. Cerebrospinal fluid (CSF) analysis shows albuminocytological dissociation. It often presents with single-phase self-limiting course for which intravenous immunoglobulin and plasmapheresis are effective. Some patients with sensory neuropathy may exhibit sensory GBS.[1-4] A case report of sensory ataxic variant of GBS is discussed here.

## CASE REPORT

A 50-year-old male presented to us with complaints of unsteadiness while walking and tingling sensation over both legs (below knee) for 6 days followed by both upper limbs (below elbow) for 2 days. There were no other comorbidities. Patient had fever 12 days prior to the onset of the above symptoms for which he was treated in a private hospital as an outpatient. There was no history of limb weakness, bowel and bladder disturbances or speech disturbances. There was no history suggestive of cranial nerves, cerebellar, extrapyramidal system involvement. Additionally, there was no history of trauma, neck pain or of addictive habits.

On examination, patient was conscious, oriented, well-built and nourished. Higher mental functions, speech, cranial nerves, motor system and cerebellar examination were normal. Deep tendon reflexes were absent in all four limbs with bilateral flexor plantar response. Sensory

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*IJCP SUTRA 851: "Taking a nap at the peak of sleepiness in the afternoon can help to supplement hours missed at night."*

examination revealed impaired fine touch, vibration and joint position sense up to bilateral knee and elbow with normal pain and temperature sensations. Gait was sensory ataxic type with positive Romberg's test. Ophthalmological examination was normal. Routine investigations were normal. Vitamin $B_{12}$ assay and retroviral test were normal. Magnetic resonance imaging (MRI) brain with cervical screening was normal. CSF examination showed normal cell count, glucose level and elevated protein level. Nerve conduction study showed sensory demyelination pattern in upper and lower limbs with normal motor component.

Based on above examination findings and investigations, a diagnosis of sensory ataxic type of GBS was made. He was treated with intravenous immunoglobulin at a dose of 2 mg/kg for 5 days. Patient showed improvement and ataxia and tingling sensation recovered after 2 weeks.

## DISCUSSION

Criteria for diagnosing sensory GBS are:[4,5]

- Acute symmetrical sensory loss
- A peak in symptoms at 4 weeks
- Absent tendon reflexes
- Normal muscle strength
- At least two pieces of evidence for nerve demyelination in electrophysiological examination
- Single-phase course
- Exclusion of other neurological diseases
- No family history
- Increase in protein levels in the CSF in the acute phase.

Since the patient fulfilled all the above-mentioned diagnostic criteria, the diagnosis of sensory ataxic type of GBS was made. To date, only a few cases of pure sensory GBS have been reported.[6] Thus, the clinical and pathological features of sensory variant of GBS have not been well characterized and reduced awareness of these features has resulted in delayed diagnosis and treatment.

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■■■■

### Drug-resistant Strains could Become the Dominant form of TB in Europe

The latest WHO/European Centre for Disease Prevention and Control (ECDC) report, "Tuberculosis surveillance and monitoring in Europe 2019 (2017 data)", shows that the European Region is struggling to make sufficient progress to finally end TB. Challenges in timely detection, which result in ongoing transmission and inadequate treatment are driving resistance. Despite an overall decline in cases, TB remains a major public health issue that is causing patients suffering and perpetuating poverty.

With 30 people diagnosed with TB every hour in the European Region, both patients and health systems are paying a high price. The eastern part of the Region has become the world's drug-resistant TB hot spot. Of the 2,75,000 new diagnoses and relapsed cases, an estimated 77,000 patients are suffering from difficult-to-treat multidrug-resistant TB (MDR-TB). Almost 7,000 patients are battling extensively drug-resistant TB (XDR-TB), an even more extreme form of the disease… (*WHO Europe*)

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.

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**Raghu Kataria**

Entrepreneur

**President**

**Dr KK Aggarwal**

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

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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

Indian Journal of Clinical Practice, Vol. 29, No. 11, April 2019

# Imaging Diagnostic Dilemma of Large Subchorionic Hematoma

PS BALDAWA


## ABSTRACT

Vaginal bleeding in first-half of pregnancy occurs in one-fourth of all pregnant women. This case report mainly highlights the occurrence of large subchorionic hematoma (SH) in first trimester. Usually, large SHs occur in second trimester, are associated with pregnancy loss but are relatively uncommon in first trimester. This case describes a 32-year-old woman, $G_2P_1L_1$, who presented with complaints of vaginal spotting, was misdiagnosed to have threatened abortion with twin gestation. Later, the diagnosis was confirmed to be a large SH. Patients with large SH are at greater risk for eventual fetal death, hence the need for serial scanning to determine final outcome of their gestation.


**Keywords:** Hypoechoic mass lesion, subchorionic hematoma, twin gestational sac

Subchorionic hematoma (SH) may be detected sonographically in the first trimester by the presence of a crescent-shaped echo-free area outlining the intact gestational sac. But at times, this sonographic appearance may not be echo-free, which is why it needs to be differentiated from other differential diagnoses. This case report identifies such a diagnostic dilemma.

## CASE REPORT

A 32-year-old lady presented to Gynecology OPD with complaints of spotting per vaginum. Her obstetric history was $P_1L_1$. She had a full-term normal vaginal delivery 1 year ago. She was still lactating and had amenorrhea since last year. On clinical examination, she was afebrile; the vital parameters were stable with pulse rate of 88/min and blood pressure of 120/80 mmHg. On examination, abdomen was nontender, nondistended, with normal bowel sounds. The uterus was not palpable. There was no rebound tenderness or guarding or rigidity. On pelvic exam, the cervical os was closed and scant altered dark blood was noted in the vaginal vault. No active bleeding was present. The patient had a positive Chadwick's sign. Bimanual exam revealed neither masses nor cervical motion tenderness. The remainder of the physical exam was unremarkable. Her laboratory tests revealed hemoglobin of 10.2 g/dL, total white blood cell (WBC) count of 5,600/$mm^3$; urine pregnancy card test was weakly positive. She was sent for ultrasound imaging (Figs. 1-4).

A diagnosis of threatened abortion with twin gestation was made and the patient was managed conservatively with bed rest and progesterone injections. But 2 days later, the patient had profuse bleeding and repeat scanning revealed the image as shown in Figure 5. Due to excessive bleeding, conservative management was aborted and emergency dilation and curettage (D&C) was done. During curettage, the products of conception were removed but still no grating sensation could be felt. Hence, an intraoperative ultrasound was performed that revealed the disrupted hematoma still within the uterine cavity. An old organized clot (dark-brown colored) of ~4 × 4 cm was removed piecemeal and sent for histopathology. The histopathology report confirmed it to be just a hematoma with no traces of any vanishing or reduced twin gestational sac or chorionic tissue.

## REVIEW OF LITERATURE

Bleeding per vaginum in the first-half of pregnancy occurs in approximately one-fourth (25%) of women

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*IJCP SUTRA 853:* "If you need to nap, limit it to 20-30 minutes."

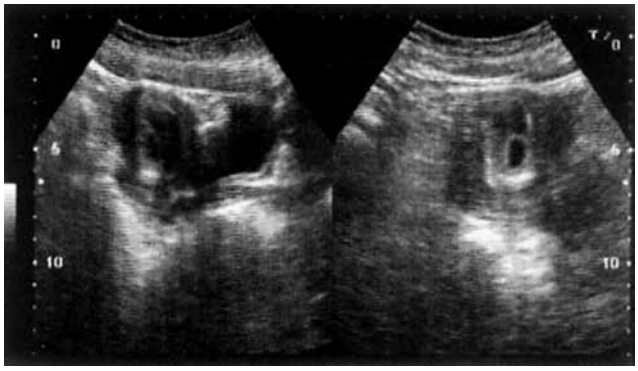

**Figure 1.** Transabdominal scan showing two hypoechoic intrauterine areas appearing as ? twin gestational sacs.

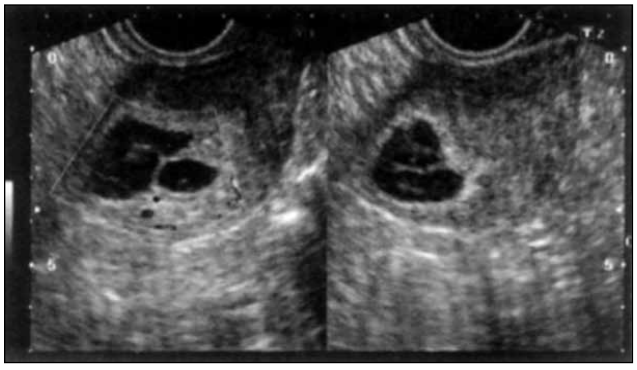

**Figure 2.** Transvaginal scan showing one gestational sac with yolk sac within it but no fetal pole and the other ? gestational sac with some hyperechoic areas within it ? fetal parts.

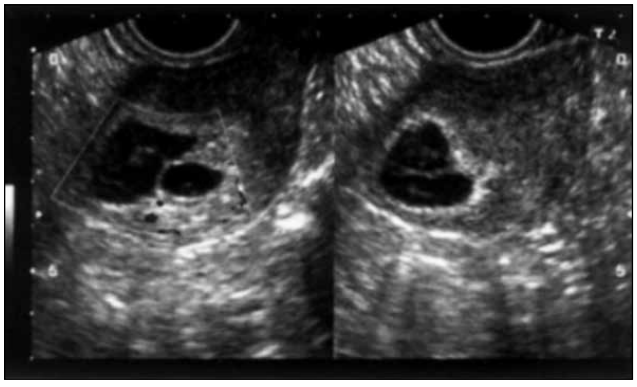

**Figure 3.** The gestational sac with the yolk sac had mean diameter of 13.7 mm corresponding to 5 weeks 2 days and the other hypoechoic area measured 4.2 x 3.5 cm = 14.7 $cm^2$ and was surrounding 50-60% of the gestational sac (as seen on transabdominal scan - Fig. 1).

and about half of these pregnancies terminate in abortion. The main reasons for vaginal bleeding in early gestation are SH and rupture of a marginal placental sinus. Its etiology is largely unknown, although uterine malformations, history of repeated abortions and infection have been suggested as possible predisposing factors. The size of the hematoma is graded according to

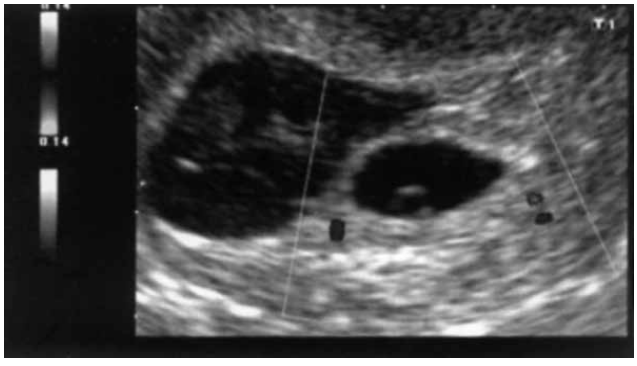

**Figure 4.** Color Doppler revealed no vascularity in the hypoechoic mass and very poor vascularity of gestational sac.

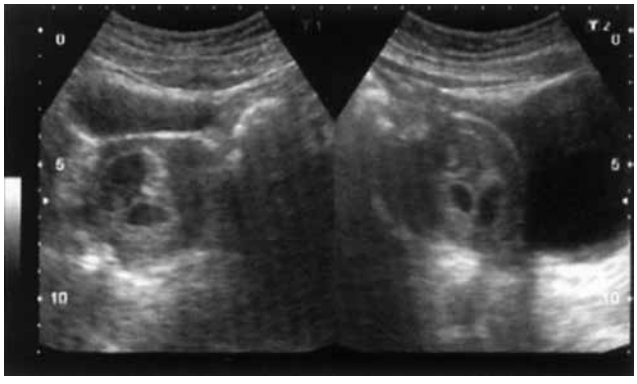

**Figure 5.** Transabdominal scan showing that the upper hypoechoic area had become more isoechoic, suggesting it was a large SH which had now become organized and the patient had developed a second SH at the lower pole of the gestational sac.

the percentage of chorionic sac circumference elevated by the hematoma as follows:

- Small indicates less than one-third of the chorionic sac circumference elevated by hematoma.
- Moderate indicates one-third to one-half of the chorionic sac circumference elevated by hematoma.
- Large indicates one-half to two-thirds or greater of the chorionic sac circumference elevated by hematoma.

Bennett et al showed that there was little difference in the rates of spontaneous abortion between pregnancies with small and moderate-size separations (7.7% and 9.2%, respectively), but the rate nearly doubled when the separation was large (18.8%). Kahn et al have described a similar case report of a 24-year-old $G_3P_1A_1$ Hispanic woman who presented to the Emergency Department (ED) at 6½ weeks POG by date with vaginal bleeding of 1-day duration. She underwent a bedside endovaginal ultrasound in the ED. The emergency physician identified a live

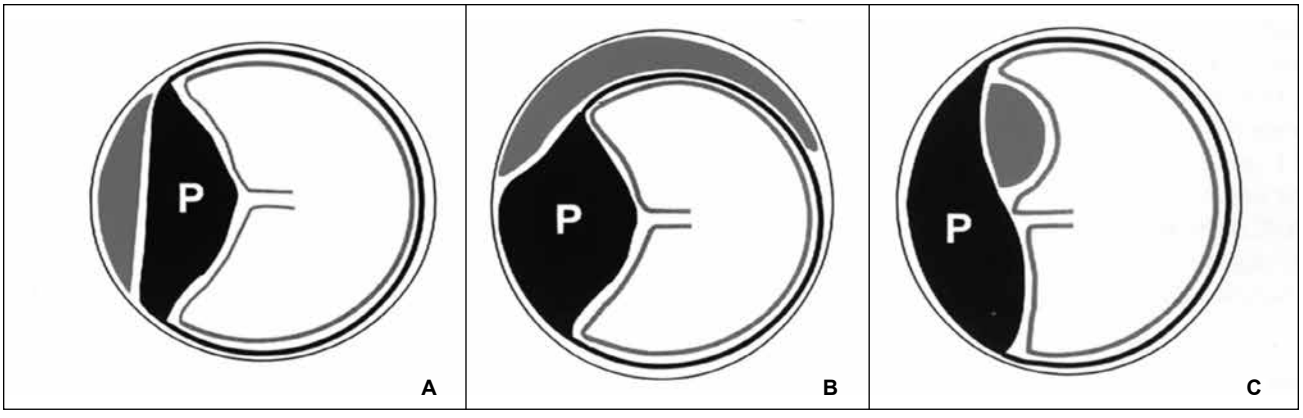


**Figure 6.** Line diagram for classification of hematomas in and around placenta.

P: Placenta, Orange color: Hematoma, Grey line: Amnion, Black line: Chorion
A: Retroplacental bleeding is found behind placenta.
B: Subchorionic bleeding dissects chorion and endometrium. When such bleeding involves the margin of placenta, it is called marginal SH.
C: Subamniotic hemorrhage is contained within the amnion and chorion and thus extends anteriorly to placenta but is limited by reflection of amnion on placental insertion site of umbilical cord. Subamniotic bleeding is rare.

intrauterine pregnancy (IUP) with another structure that appeared to be a second gestational sac. The patient subsequently had an endovaginal ultrasound in the radiology department, 46 minutes later. The attending radiologist described one live IUP and an SH. Comparison of the ED and radiology ultrasound showed that the second structure, identified as SH, had significantly decreased in size.

Endovaginal ultrasound in the evaluation of possible ectopic pregnancy is a useful bedside tool in the ED. They have discussed a pitfall that can occur with endocavitary ultrasound when a twin gestation is presumed. Hence, it is worthwhile knowing the differential diagnosis of SH, which include a twin gestational sac, uterine leiomyoma (fibroid), focal myometrial contraction, chorioamniotic separation, prominent retroplacental veins. SHs should also be distinguished from retroplacental hematoma and subamniotic hematoma (Fig. 6). SHs are usually described as crescentic anechoic collections lifting the chorionic membrane. But as described by Trop et al and Nyberg et al in their articles, depending on the time elapsed since the bleeding, the collection will have variable echotexture; it will be hyperechoic initially, with decreasing echotexture over time. Twin sac has an echogenic rim of chorionic tissue, which distinguishes it from an SH.

An SH may be present in conjunction with multiple pregnancy and it is important not to confuse it with a vanishing or spontaneously reduced twin. Unlike a gestational sac, the size and shape may be variable and may contain low level internal echoes. Although, they occur frequently in multiple pregnancies, till date only a single case series reports on SH in multiple pregnancy. Investigators retrospectively analyzed the incidence of SH and embryonic death in both singleton and twin pregnancy. Interestingly, 50% of twin pregnancies had an SH. The detection of a large SH on ultrasound increases the risk for miscarriage, stillbirth, placental abruption and preterm labor. Patients with SH are at greater risk for eventual fetal death even if signs of fetal life are present initially on sonography. We recommend that these patients be scanned serially to determine the final outcome of their gestation.

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A different perception used for amusement of children.

Indian Journal of Clinical Practice, Vol. 29, No. 11, April 2019

# Asymptomatic Hypercortisolism

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## ABSTRACT

The diagnosis of Cushing's syndrome presents great challenges in determining the etiology of cortisol excess. It must be emphasized that iatrogenic hypercortisolism is the most common cause, the second common cause being pituitary corticotrope adenoma and Carney's syndrome is one of the rarest of causes.


**Keywords:** Cushing's syndrome, primary pigmented nodular adrenocortical disease, lentigines, bilateral adrenalectomy

Cushing's syndrome presents clinically with central obesity, hypertension, glucose intolerance or diabetes mellitus, moon facies, purple striae, proximal muscle weakness, hirsutism and psychological disturbances. Presented here is the case of a patient who was asymptomatic except for moon facies and family history of Cushing's syndrome. He was admitted for an unrelated symptom.

## CASE HISTORY

Mr Kalpesh, an 18-year-old male was investigated for short stature. He was asymptomatic otherwise.

**Family history:** Sister was diagnosed to have primary pigmented nodular adrenocortical disease (PPNAD) for which bilateral adrenalectomy was done and she was put on steroid replacement therapy.

**Physical examination:** Patient had short stature, moon face, multiple lentigines on face (freckles) but patient was not anemic.

**Blood pressure:** 120/80 mmHg in right arm.

**Cardiovascular system:** S1/S2 +.

**Respiratory system:** Bilateral vesicular breath sounds heard.

**Abdomen:** Soft, no organomegaly.

A clinical diagnosis of Cushing's syndrome was made.
**Investigations:** Complete blood count (CBC) profile: Hemoglobin (Hb) - 10.9 g/dL; packed cell volume (PCV) - 37.1; total count (TC) - 6,600 cells/$mm^3$; differential count (DC) - $P_{67}L_{30}M_3$; platelet count - 2,76,000; mean corpuscular volume (MCV) - 65.7; mean corpuscular hemoglobin (MCH) - 19.3 and mean corpuscular hemoglobin concentration (MCHC) - 29.4. Blood group: B-positive.

**Diabetic profile:** Fasting blood sugar - 74 mg/dL; random blood sugar - 129 mg/dL.

**Renal function tests:** Serum creatinine - 0.7 mg/dL; blood urea - 28 mg/dL.

**Thyroid function tests:** Serum $T_3$ - 130 ng/dL (normal 81-178 ng/dL); serum $T_4$ - 11.6 ng/dL (normal 4.5-12.5 ng/dL); serum thyroid-stimulating hormone (TSH) - 1.46 μIU/mL (normal 0.4-4 μIU/mL).

**Liver function tests:** Serum alkaline phosphatase (ALP) - 262; serum albumin - 4.9 g/dL; serum glutamic-oxaloacetic transaminase (SGOT) - 32 IU/L; serum glutamic-pyruvic transaminase (SGPT) - 14 IU/L; serum calcium - 9.2 mg/dL; serum phosphorus - 3.6 mg/dL.

**Hormone profile:** Serum follicle-stimulating hormone (FSH) - 3.34 μIU/mL (normal 2.5-10 μIU/mL); serum luteinizing hormone (LH) - 1.82 μIU/mL (normal 2.5-10 μIU/mL); serum prolactin - 8.18 ng/mL (normal 5-25 ng/mL); basal adrenocorticotropin (ACTH) - 10.3 pg/mL (0-46 pg/mL); basal cortisol - 12.64 μg/mL (normal 5-25 μg/mL); MN cortisol - 13.39 μg/mL. Dexamethasone suppression test: Serum cortisol - 12.64 μg/dL.

**Electrocardiogram:** Within normal limits.

**Chest X-ray PA view:** Within normal limits.

**X-ray of left hand and wrist (for bone age):** 16-17 years.

**CT scan neck to pelvis:** NAD.

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†Professor (Head of Unit)
‡Assistant Professor
#Senior Resident
$Resident
Medical Dept., MP Shah Medical Collage, Jamnagar, Gujarat

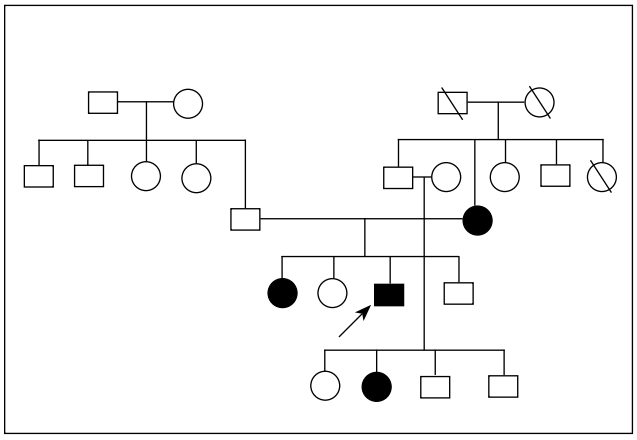
**DEXA scan of bone:** Showed osteoporosis.

**Sexual maturation rating:** B1P4.

**TV:** Bilateral 15 mL.

**SPL:** Adult size.

### Pedigree Analysis



Evaluation of investigations showed ACTH independent endogenous hypercortisolism with nonsuppressed overnight dexamethasone suppression (ODS) cortisol. Rest of hormone profile was normal. CT scan neck to pelvis was done to know the source of ACTH, which was normal. Clinical diagnosis of Carney's complex was made in view of PPNAD in sister and lentigines on the face, which is a feature of Cushing's syndrome. He was evaluated for other components of Carney's complex including 2D-Echo, which was normal. Bilateral laparoscopic adrenalectomy was done. He was then given steroid replacement therapy. The biopsy result confirmed the diagnosis of PPNAD.

## DISCUSSION

Carney's complex is an autosomal dominant disorder. It is also known as LAMB syndrome (Lentigines, Atrial myxomas, Mucocutaneous myxoma and Blue nevi) or NAME syndrome (Nevi, Atrial myxoma, Myxoid neurofibroma and Ephelides).

Other than these predominant skin lesions, patients may have Cushing's syndrome, acromegaly, peripheral nerve schwannomas or testicular tumor. These patients frequently have mutations in the tumor suppression genes *PRKARIA*. Cushing's syndrome is due to adrenal tumor and acromegaly is due to pituitary adenoma. This is an ACTH independent Cushing's syndrome diagnosed in children and young adults. There is bilateral adrenal cortical micronodular hyperplasia. It is otherwise known as PPNAD. The adrenals contain small brown-black nodules up to 0.5 cm in diameter with large eosinophilic cells laden with lipofuscin nodules. Carney's complex has been classified in mixed syndromes of MEN 1 or 2. Some patients have gynecomastia due to excess estrogen production.

A correct diagnosis permits a potentially life-threatening disorder to be treated.

## CONCLUSION

This case has been presented for its rarity as a hereditary cause of Cushing's syndrome. In addition, the tell tale clinical features of hypercortisolism were missing and patient was asymptomatic. Only a detailed family history helped us to suspect the diagnosis and investigations proved it. Patient is doing well with steroid replacement therapy.

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### Solriamfetol Approved for Obstructive Sleep Apnea

The US FDA has approved solriamfetol to improve wakefulness in adults with excessive daytime sleepiness associated with narcolepsy (75 mg, 150 mg) or obstructive sleep apnea (37.5 mg, 75 mg, 150 mg). It is the first and only dual-acting dopamine and norepinephrine reuptake inhibitor approved by the FDA for this indication and is to be taken orally once-daily.

Indian Journal of Clinical Practice, Vol. 29, No. 11, April 2019

# Acinic Cell Carcinoma of the Parotid

EASWERAN SV*, LOKESH†, RAGHVENDRA U‡, YUVRAJ#, MANJULA¶


## ABSTRACT

Acinic cell carcinoma, also known as acinar/acinous cell carcinoma is a rare salivary gland cancer (6-10%). Around 3-13% malignancies involve the parotid. It can also arise from other glands, namely submandibular, minor salivary gland. It may also present in the pancreas and lung, where it usually metastasizes. Acinic cell carcinoma usually occurs bilaterally and it presents in younger median age. It is a slow growing, painless tumor. It affects females more than males. Facial nerve is spared. If it metastatizes, it does so to the lung, bone, central nervous system, mediastinum, liver and brain.


**Keywords:** Acinic cell carcinoma, parotid gland

Acinic cell carcinoma is a rare salivary gland cancer. In the past, the malignant nature of this cancer was disputed and hence it was classified as an 'acinic cell tumor'/benign 'adenoma'; later due to high potential to recur and metastatize, it came to be known as a malignant carcinoma (WHO). Acinic cell carcinomas are typically slow growing, low-grade (highly differentiated) neoplasms. Recurrences (8-60%) and metastasis (7-29%) after 3-10 years are common. Patients with lung metastasis have poor prognosis.

## CASE REPORT

A 25-year-old male presented to the ENT OPD with history of swelling of the left side of the cheek since 2-3 years, which gradually kept on increasing to attain the present size (Fig. 1 a and b). Patient had no evidence of facial nerve abnormality.

### On Examination

Swelling was present on the left side of the cheek; soft to firm on palpation, mobile; no rise of local temperature; facial nerve was normal.

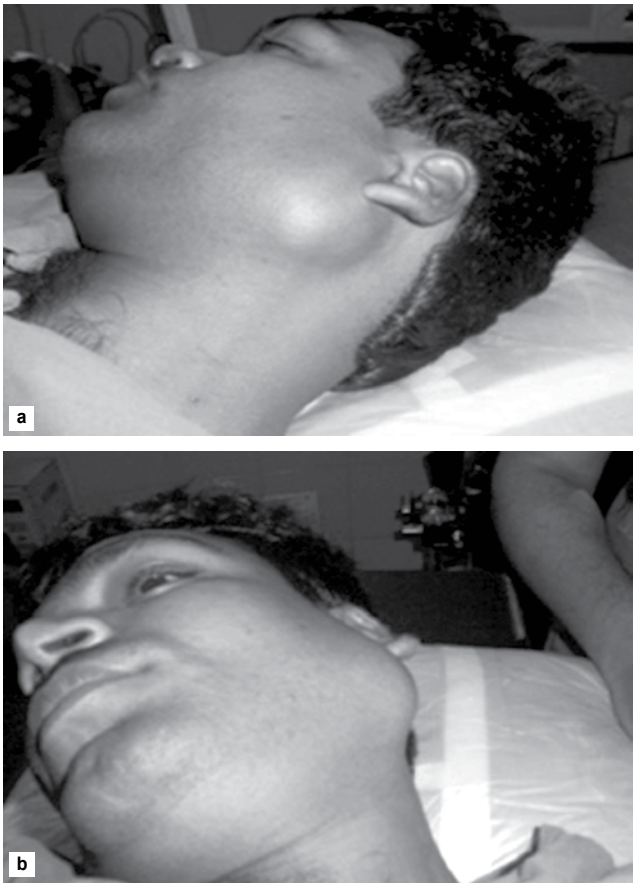


**Figure 1 a and b.** Swelling on the left side of the cheek.

### Investigation

#### Blood Examination

Hemoglobin (Hb): 9.2 g/dL, WBC - TC: 5,100 cells/mm$^3$, DC: N-50%, L-40%, E-8%, M-2%, erythrocyte sedimentation rate (ESR)-31 mm/1st hour, BT-1 minute

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#Radiologist
¶Pathologist
Sirsi Scan Center, North Karnataka



*IJCP SUTRA 859:* "Cover your mouth with a tissue when you cough, sneeze or laugh."

30 seconds, CT-3 minute 15 seconds, RBS-122 mg/dL, HIV-negative, HBS-negative.

### Ultrasound

A well-defined, rounded, predominantly cystic lesion of size 4.3 × 2.7 cm was seen involving left parotid gland with internal solid component and internal septae (Fig. 2 a and b). It seemed to be soft tissue cystic neoplasm involving parotid gland, possibly benign.

### FNAC

- **Gross:** 3 mL of slight reddish fluid aspirated.
- **Microscopy:** Blood-stained smears showed many scattered lymphocytes, few neutrophils and ductal epithelial cells, few acini and cystic macrophages on background of proteinaceous material.

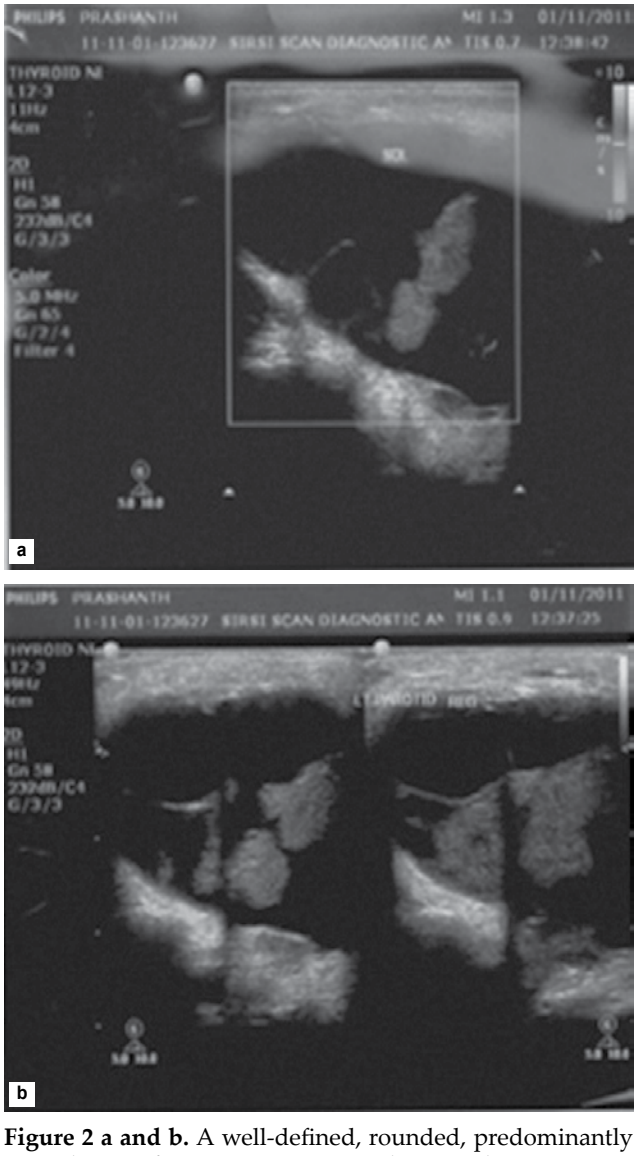


**Figure 2 a and b.** A well-defined, rounded, predominantly cystic lesion of size 4.3 × 2.7 cm on ultrasound.

### Steps of Surgery

Patient was intubated. Part was cleaned and draped. A lazy S incision was taken on the affected side after giving local as infiltration. Layers were dissected, and a cystic swelling was identified in the matter of superficial part of the parotid. Swelling and the superficial parotid gland were excised and sent for histopathology. Facial nerve was identified and preserved. Branch of the greater auricular nerve was inadvertently cut. Suturing was done in layers (Fig. 3 a-c). Drain was kept at the operated site for the next 3 days. Patient tolerated ID

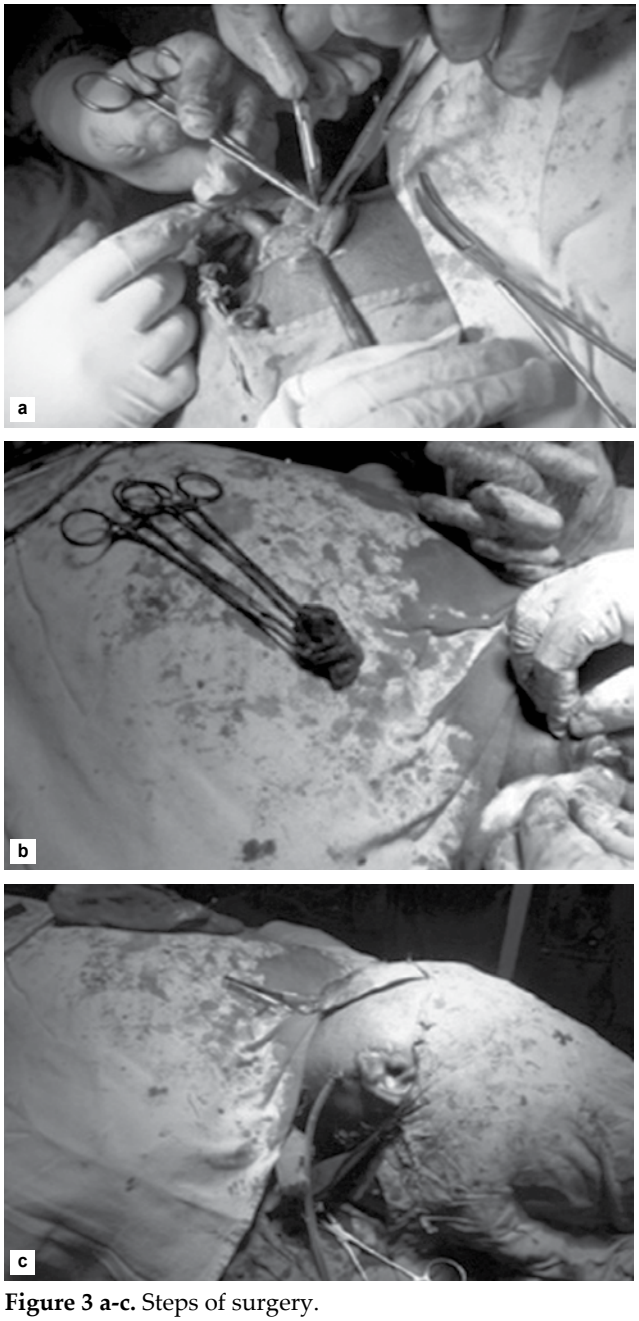


**Figure 3 a-c.** Steps of surgery.

gland tumor procedure well. Postoperatively, patient was put on injectable antibiotics, painkillers and antacids. Patient was discharged on 4th postoperative day.

## Histopathological Report

- **Gross:** Partly opened cystic mass, measuring 4 × 3 × 0.4 cm with bosselated surface. The cut surface revealed focally irregular thickened and small cystic spaces containing blood clot. No evidence of solid areas.

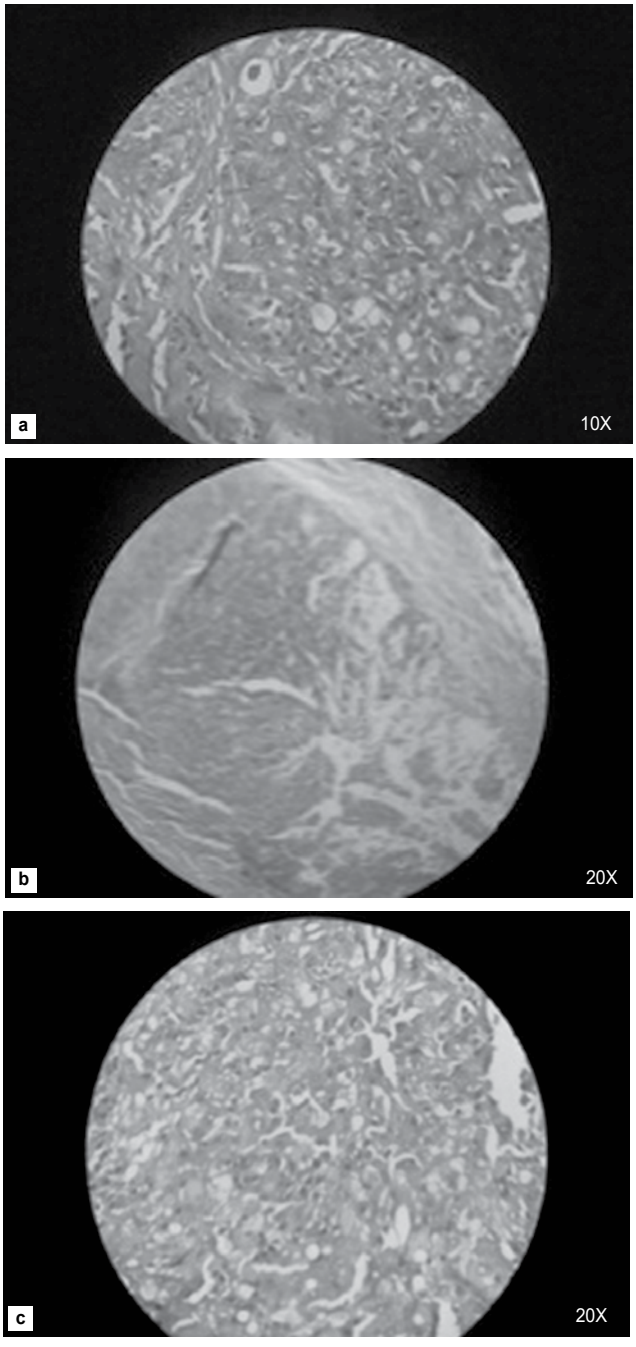


**Figure 4 a-c.** Histopathological finding of the tumor mass.

- **Microscopy:** Multiple sections showed parotid tissue with focally microcystic and papillary cystic glands lined by acinic cells displaying granular cytoplasm and focally clear, vacuolated cells, surrounding stroma containing lymphoid aggregates, hemorrhage and hemosiderin pigments. Few areas showed laminated concretions like psammoma bodies within the lumina (Fig. 4 a-c). There was 0-1 mitotic activity/hpf.

## Impression

Features were suggestive of acinic cell cacinoma with marked cystic degeneration.

## Follow-up

Patient has been following-up since 2 months post-discharge (Fig. 5 a and b). Patient was advised follow-up for first 3 months and then at 3-6 month intervals.

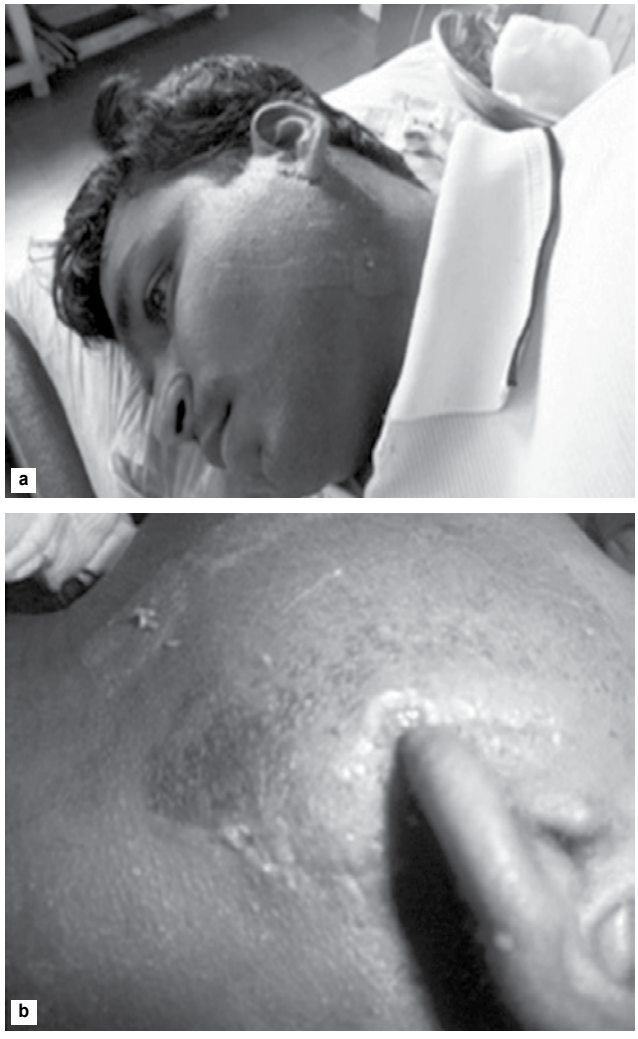


**Figure 5 a and b.** Patient at 2 months follow-up post-discharge.

## DISCUSSION

Acinic cell carcinoma is a rare salivary gland cancer accounting for 6-10% of all salivary gland carcinomas and 3-13% of all malignant parotid gland tumors. It arises more frequently in the parotid gland; other sites may include submandibular gland, minor salivary gland. It is usually seen bilaterally. On rarer occasions, it also presents in the pancreas and the lung and if it does, it usually metastasizes. It is seen in the younger age group. It is a slow-growing tumor, is painless and spares the facial nerve.

The sites of its metastasis are lungs, bone, central nervous system and liver. In the past, it was considered a benign lesion; however, now it is considered by World Health Organization (WHO) as malignant due to its recurrence potential and metastases; recurrences and metastasis after 3-10 years are common. Lung metastasis has poorer prognosis.

Acinic cell carcinoma is the least aggressive of salivary gland cancers. High-grade variants of acinic cell carcinoma are papillocytic carcinoma or carcinomas with undifferentiated cells in medullary pattern. It belongs to the family of adenocarcinomas. Pancreatic form of acinic cell carcinoma is a rare subtype of exocrine pancreatic cancer, which includes ductal and acinar cell tumors, seen commonly in males.

Treatment comprises of surgery and/or postoperative radiation. Complete and total removal is a must to avoid recurrence; incomplete excision is associated with lower chance of survival. If complete and total tumor removal is not achieved then radiation using fast neutron beam is given. Conventional radiation is used to treat high-grade and residual disease after surgery. Chemotherapy has been considered ineffective and is used only for pain relief. Acinic cell carcinoma is considered chemo-resistant in literature. Its pancreatic version is treated using intra-arterial infusion chemotherapy.

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### Back-scratch Test: 8-Foot Up-and-Go Purpose

- Assesses agility/dynamic balance, which is important in tasks that require quick maneuvering, such as getting off a bus in time or getting up to attend to something in the kitchen, to go to the bathroom or to answer the phone.
- Method: Number of seconds required to get up from a seated position, walk 8 feet (2.44 m), turn and return to seated position.
- Risk zone: More than 9 seconds.

The standard required for driving is the ability to read a car number plate at 20 m.

Indian Journal of Clinical Practice, Vol. 29, No. 11, April 2019

# Superficial Brachial Artery: Its Embryological and Clinical Significance

MEENAKSHI KHULLAR


## ABSTRACT

The principal arteries of the upper limb show a wide range of variations that are of considerable interest to orthopedic surgeons, plastic surgeons, radiologists and anatomists. We present here a case of bilateral superficial brachial artery found during the routine dissection of the upper limbs of a 50-year-old female cadaver. In both the limbs, the third part of the axillary artery divided into superficial brachial and deep brachial arteries; denominated according to their relation to the median nerve. The superficial brachial artery continued in the arm without giving any branches and ended in the cubital fossa dividing into radial and ulnar arteries. The deep brachial artery gave rise to anterior circumflex humeral, posterior circumflex humeral and profunda brachii arteries. Earlier superficial brachial artery has been reported with a prevalence rate varying from 0.2% to 25% but bilateral variation is extremely rare. The great variability of this arterial pattern may be attributed to the failure of regression of some paths of the embryonic arterial trunks. The embryological and clinical significance of this variant are also discussed in detail.


**Keywords:** Axillary artery, superficial brachial artery, deep brachial artery

Axillary artery (AA) is a continuation of the subclavian artery from the outer border of the first rib. It ends at the inferior border of the teres major and continues in the arm as brachial artery. According to textbooks, an AA penetrates the dorso-ventral divisions of the brachial plexus by passing between the lateral and medial roots of the median nerve. Rarely, an aberrant AA is unable to penetrate the brachial plexus. In this case, the AA is positioned superficial to the brachial plexus and then, this is known the superficial brachial artery (SBA).

The SBA has been reported by many authors because of its relatively high frequency in comparison with other vascular variations. It is necessary; however, to pay attention to the branches originating from the aberrant AAs, in addition to the various courses of the AA, in order to understand their morphogenesis.

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## CASE REPORT

During the routine undergraduate dissections on the upper limbs of a 50-year-old female cadaver, it was observed that on both the sides, the third part of the AA, after giving the subscapular artery, bifurcated into an SBA and a deep brachial artery. The SBA descended superficial to the lateral root of the median nerve, did not give any branch in the arm and continued as the brachial artery proper. Finally, on reaching the cubital fossa, it terminated by dividing into radial and ulnar arteries. The deep brachial artery passed deep to the medial root of the median nerve and gave anterior and posterior circumflex humeral branches of AA and profunda brachii branch of brachial artery. Then it terminated by giving twigs to the muscles of arm (Fig. 1).

## DISCUSSION

Variations in the arterial pattern of the upper limb are common and have been reported by several investigators. The presence of an SBA and the usual pattern of its branching in the upper arm or forearm have also been reported.

The definition of the SBA was set for the first time by Adachi in 1928 and runs as follows: "The SBA is the one that runs superficial to the median nerve." It may replace the main trunk or may be accompanied by an



*IJCP SUTRA 863: "Cut down on unnecessary calories from sweets, sodas, refined grains like white bread or white rice, unhealthy fats, fried and fast foods and mindless snacking. Keep a close eye on portion sizes, too."*

**Table 1.** Incidence of the SBA in Various Studies

| Name of Author | % of cases with SBA |
|---|---|
| Quain | 0.2 |
| Gruber | 0.4 |
| Muller | 1 |
| Adachi | 3.1 |
| Miller | 3 |
| McCormack et al | 0.12 |
| Skopakoff | 19.7 |
| Fuss et al | 17 |
| Rao and Chaudhary | 4.2 |
| Rodriguez-Niedenführ et al | 4.9 |
| Patnaik et al | 6 |
| Kachlik et al | 5 |

equally important, less important or more important trunk running deep to median nerve. Table 1 shows the prevalence of SBA as observed by different authors from time-to-time.

## ONTOGENY

The embryological background of these variations in the vasculature of the upper limb may be explained as abnormal deviations in the normal vascular patterns. Arey and Jurjus mentioned six explanations for the variations observed:

- The choice of unusual paths in the primitive vascular plexus
- The persistence of vessels which are normally obliterated
- The disappearance of vessels which are normally retained
- An incomplete development
- The fusion and absorption of parts which are normally distinct
- A combination of factors leading to an atypical pattern normally encountered.

Ontogenic basis of the present case can be easily made out if we look at Singer's five stages of development of the brachial artery (Fig. 2):

- **Stage I:** Originally, the subclavian artery extends to the wrist, where it terminates by dividing into terminal branches for the fingers. The distal portion of the artery becomes the interosseous artery of the adult.

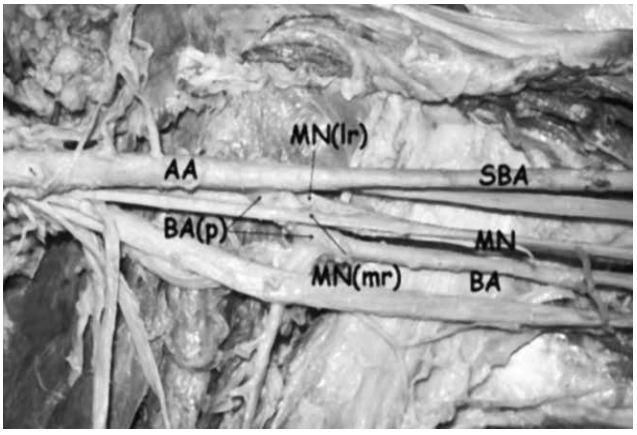


**Figure 1.** The third part of the axillary artery (AA) dividing into the superficial brachial artery (SBA) and the deep brachial artery [BA(p)]; MN(lr) - (lateral root of median nerve), MN(mr) - (medial root of the median nerve), MN (median nerve).

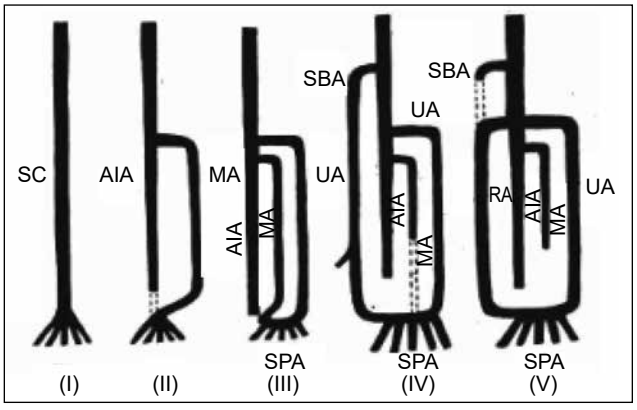


**Figure 2.** Stages of development of arteries of upper arm.

SC = Subclavian artery; MA = Median artery; AIA = Anterior interosseous artery; SBA = Superficial brachial artery; UA = Ulnar artery; SPA = Superficial palmar arch; RA = Radial artery.

- **Stage II:** The median artery arises from the interosseous artery and becomes larger while interosseous artery subsequently undergoes retrogression. During this process, the median artery fuses with the lower portion of interosseous artery and ultimately forms the main channel for the digital branches becoming the principle artery of the forearm.
- **Stage III:** In embryos of 18 mm, the ulnar artery arises from brachial artery and unites distally with the median artery to form superficial palmar arch. Digital branches arise from this arch.
- **Stage IV:** In embryo of 21 mm length, the SBA develops in the axillary region and traverses the medial surface of the arm and runs diagonally from the ulnar to the radial side of the forearm to the

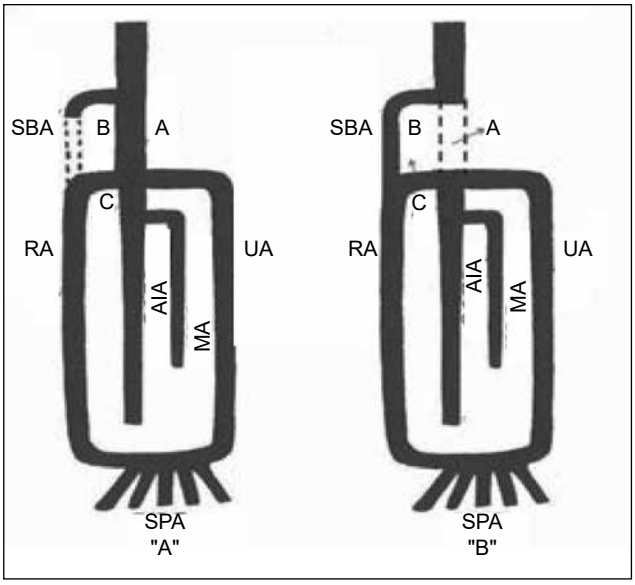


**Figure 3.** Normal development of the brachial artery ("A") and that in the present case ("B").

SBA = Superficial brachial artery; RA = Radial artery; UA = Ulnar artery; MA = Median artery; AIA = Anterior interosseous artery; SPA = Superficial palmar arch.

posterior surface of the wrist. There it divides over the carpus into branches for the dorsum of the thumb and index finger.

- **Stage V:** Finally three changes occur. When the embryo reaches the length of 23 mm the median artery undergoes retrogression becoming a small slender structure, now known as 'arteria nervi mediani'. The SBA gives off a distal branch, which anastomoses with the superficial palmar arch already present. At the elbow, an anastomotic branch between brachial artery and SBA becomes enlarged sufficiently to form with the distal portion of the latter, the radial artery, as a major artery of the forearm; the proximal portion of the SBA atrophies correspondingly.

In the present case, it seems that in Stage III of Singer, ulnar artery came from brachial artery as usual. SBA continued as radial artery and anastomosis between SBA and brachial artery developed normally (See Fig. 3). However, brachial artery between origin of SBA and ulnar artery ('A' in Fig. 3) retrogressed and lost its communication with common interosseous artery.

The SBA failed to retrogress and continued to supply radial artery. The anastomosis between SBA and brachial artery ('B' in Fig. 3), which usually forms proximal part of radial artery now formed proximal part of ulnar artery, thus giving appearance that ulnar artery and radial artery are terminal branches of SBA and common interosseous artery ('C' in Fig. 3) came as a branch of ulnar artery.

## CLINICAL SIGNIFICANCE

Gonzalez-Compta highlighted the diagnostic, interventional and surgical significance of such a vascular variation. Diagnostically, it may disturb the evaluation of angiographic images. Interventionally, accidental puncture of superficially placed arteries may occur while attempting venipuncture. Surgically, it is vulnerable in both orthopedic and plastic surgery operations. Hence, the anatomic knowledge of the vascular patterns of upper limb is of crucial importance not only for neurosurgeons, but for all those involved in radiodiagnostics, particularly in cases involving traumatic injuries, as improved knowledge would allow more accurate diagnostic interpretation and surgical treatment.

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■■■■

# Make sure

## DURING MEDICAL PRACTICE

**SITUATION:** A 38-year-old woman with BP between 130-139 mmHg and 85-89 mmHg since 3 months came for follow-up.


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**LESSON:** Treatment of prehypertension with candesartan is well-tolerated and reduced the risk of incident hypertension in the Trial of Preventing Hypertension (TROPHY). Over the 4 years of the study period, stage 1 hypertension developed in nearly two-thirds of patients with untreated prehypertension.

*N Engl J Med. 2006;354(16):1685-97.*

Indian Journal of Clinical Practice, Vol. 29, No. 11, April 2019

# Law on Euthanasia in India

KK AGGARWAL*, IRA GUPTA†

Life and death as concepts have invited many thinker, philosopher, writer and physician to define or describe them. **Swami Vivekananda** expects one to understand that life is the lamp that is constantly burning out and further suggests that if one wants to have life, one has to die every moment for it. One may like to compare life with constant restless moment spent in fear of extinction of a valued vapour; and another may sincerely believe that it is beyond any conceivable metaphor. Death is complicated and life is a phenomenon which possibly intends to keep away from negatives that try to attack the virtue and vigour of life from any arena.

In spite of all the statements, references and utterances, be it mystical, philosophical or psychological, the fact remains, at least on the basis of conceptual majority, that people love to live - whether at eighty or eighteen - and do not, in actuality, intend to treat life like an—autumn leaf.

The perception is not always the same at every stage. There comes a phase in life when the spring of life is frozen, the rain of circulation becomes dry, the movement of body becomes motionless, the rainbow of life becomes colorless and the word life' which one calls a dance in space and time becomes still and blurred and the inevitable death comes near to hold it as an octopus gripping firmly with its tentacles, so that the person shall rise up never.

The **ancient Greek Philosopher, Epicurus**, has said, although in a different context:

*Why should I fear death?*

*If I am, then death is not.*

*If death is, then I am not.*

*Why should I fear that which can only exist when I do not?*

But there is a fallacy in the said proposition. It is because mere existence does not amount to presence. And sometimes, there is a feebleness of feeling of presence in semi-reality state when the idea of conceptual identity is lost, quality of life is sunk and the sanctity of life is destroyed and such destruction is denial of real living.

The society at large feel that a patient should be treated till he breathes his last breath.

Every doctor is supposed to take specific oath that he will make every attempt to safe the life of the patient whom he/she is treating and who is under his/her treatment. This oath, thus, puts a moral and professional duty upon a doctor to do everything possible, till the last attempt, to save the life of a patient.

The **Medical Council of India (MCI) Code of Ethics rejects Euthanasia** (deliberately ending a patient's life at his/her own request or at the request of close relatives).

*"6.7 **Euthanasia: Practicing euthanasia shall constitute unethical conduct**. However, on specific occasion, the question of withdrawing supporting devices to sustain cardio-pulmonary function even after brain death, shall be decided only by a team of doctors and not merely by the treating physician alone. A team of doctors shall declare withdrawal of support system. Such team shall consist of the doctor in-charge of the patient, Chief Medical Officer/Medical Officer in-charge of the hospital and a doctor nominated by the in-charge of the hospital from the hospital staff or in accordance with the provisions of the Transplantation of Human Organ Act, 1994."*

If that is so, would it not be against medical ethics to let a person die by withdrawing medical aid or, even for that matter, life supporting instruments.

Medical scientists have been, relentlessly and continuously, experimenting and researching to find out better tools for not only curing the disease with which human beings suffer from time to time, noble attempt is to ensure that human life is prolonged and in the process of enhancing the expectancy of life, ailments and sufferings therefrom are reduced to the minimal. There is, thus, a fervent attempt to impress the quality of life.

It is this very advancement in the medical science which creates dilemma at that juncture when, in common perception, life of a person has virtually become unlivable but the medical doctors, bound by their

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IJCP SUTRA 867: "Eat mindfully. Emphasize colorful, vitamin-packed vegetables and fruits; whole grains; fish, lean poultry, tofu and beans and other legumes as protein sources plus healthy fats."

**Hippocratic Oath and medical ethics** want to still spare efforts in the hope that there may still be a chance, even if it is very remote, to bring even such a person back to life.

The Hippocratic Oath taken by a doctor and the MCI Code of Ethics may make him feel that there has been a failure on his part and sometimes also make him feel scared of various laws. There can be allegations against him for negligence or criminal culpability.

There is a **distinction between the administration of lethal injection or certain medicines to cause painless death and non-administration of certain treatment,** which can prolong the life in cases where the process of dying that has commenced is not reversible or withdrawal of the treatment that has been given to the patient because of the absolute absence of possibility of saving the life. To explicate, the first part relates to an overt act whereas the second one would come within the sphere of informed consent and authorized omission. The omission of such a nature will not invite any criminal liability if such action is guided by certain safeguards. The concept is based on nonprolongation of life where there is no cure for the state the patient is in and he, under no circumstances, would have liked to have such a degrading state.

In the landmark judgment **Common Cause versus Union of India, 2018 (5) SCC 1, the Hon'ble Constitution Bench of 4 Judges of Supreme Court** held that **Euthanasia** is basically an intentional premature termination of another person's life either by direct intervention **(active euthanasia)** or by withholding life-prolonging measures and resources **(passive euthanasia)** either at the express or implied request of that person **(voluntary euthanasia)** or in the absence of such approval/consent **(nonvoluntary euthanasia)**.

**Active euthanasia** also includes physician-assisted suicide, where the injection or drugs are supplied by the physician, but the act of administration is undertaken by the patient himself. Active euthanasia is not permissible in most countries.

**Passive euthanasia** occurs when medical practitioners do not provide life-sustaining treatment (i.e., treatment necessary to keep a patient alive) or remove patients from life-sustaining treatment. This could include disconnecting life support machines or feeding tubes or not carrying out life-saving operations or providing life-extending drugs. In such cases, the omission by the medical practitioner is not treated as the cause of death; instead, the patient is understood to have died because of his underlying condition.

Further, In **Gian Kaur versus State of Punjab, (1996) 2 SCC 648**, the Hon'ble Constitution Bench of Apex Court expounded that the **word "life" in Article 21** has been construed as life with human dignity and it takes within its ambit the **"right to die with dignity"** being part of the **"right to live with dignity"**. As part of the right to die with dignity in case of a dying man who is terminally ill or in a persistent vegetative state, only passive euthanasia would come within the ambit of Article 21 and not the one which would fall within the description of active euthanasia in which positive steps are taken either by the treating physician or some other person. That is because the right to die with dignity is an intrinsic facet of Article 21.

In **Aruna Ramachandra Shanbaug versus Union of India, 2011 (15) SCC 480**, Hon'ble Supreme Court has observed that **autonomy means the right to self-determination where the informed patient has a right to choose the manner of his treatment.** To be autonomous the patient should be competent to make decisions and choices. In the event that he is incompetent to make choices, his wishes expressed in advance in the form of a Living Will, or the wishes of surrogates acting on his behalf ('substituted judgment') are to be respected.

Thus, **all adults with the capacity to consent have the common law right to refuse medical treatment and the right of self-determination.** Doctors would be bound by the choice of self-determination made by the patient who is terminally ill and undergoing a prolonged medical treatment or is surviving on life support, subject to being satisfied that the illness of the patient is incurable and there is no hope of his being cured.

In "**Common Cause versus Union of India, 2018 (5) SCC 1,** the Constitution Bench of Hon'ble Supreme Court held that **Advance Medical Directive** would serve as a fruitful means to facilitate the fructification of the sacrosanct right to life with dignity. The said directive will dispel many a doubt at the relevant time of need during the course of treatment of the patient. That apart, it will strengthen the mind of the treating doctors as they will be in a position to ensure, after being satisfied, that they are acting in a lawful manner. However, Advance Medical Directive cannot operate in abstraction. The Hon'ble Court in the said judgment has enumerated various safeguards and procedure of advance medical derivatives and also in cases where there is no advance medical derivatives which will remain enforced till Parliament makes a law on Advance Medical Derivatives.

Indian Journal of Clinical Practice, Vol. 29, No. 11, April 2019

# Medtalks with Dr KK Aggarwal

- **Smoking and heart burn:** Smoking can irritate the entire gastrointestinal tract. In addition, frequent sucking on a cigarette can cause you to swallow air. This increases pressure inside the stomach, which encourages reflux. Smoking can also relax the lower esophageal sphincter (LES).
- The Centers for Disease Control and Prevention (CDC) released a report about a boy who contracted tetanus in Oregon back in 2017. It was the first tetanus case in the state in over thirty years. Very few physicians in the US know how to manage tetanus because it's so rare. The CDC says the boy's parents spent about 800 thousand dollars on medical expenses. The average tetanus shot costs around 30 dollars.
- If the disability percentage is below 80 with the use of an assisted device, a candidate will be eligible to apply to study medicine. It will be applicable to UG and PG courses. The Board of Governors-Medical Council of India (BoG-MCI) approved the proposal.
- Eating a low-calorie diet that mimics fasting can help reduce intestinal inflammation and repair the gut, and help treat inflammatory bowel disease (IBD). Researchers from the University of Southern California found that a "fasting mimicking diet" caused a reduction in intestinal inflammation and an increase in intestinal stem cells in part by promoting the expansion of beneficial gut microbiota.
- Preliminary research suggests a possible association between consumption of sugar-sweetened beverages (SSBs) and higher disability in patients with multiple sclerosis (MS). In a cross-sectional study, MS patients who reported drinking two cans of SSBs per day were far more likely to have severe disability than those who seldom consumed these drinks. (*Elisa Meier-Gerdingh, MD, of St. Josef Hospital in Bochum, Germany*)
- Exposure to second hand smoke is linked with the development of chronic kidney disease (CKD) among nonsmokers, according to a large cohort study published online in the *Clinical Journal of the American Society of Nephrology*.
- Crohn's disease involves inflammation of the digestive tract. But new research into its causes is focusing on fungi commonly found on the skin. These microscopic fungi, called Malassezia restricta, are linked to dandruff. They're found in oily skin and scalp follicles, but they also end up in the gut. However, it's not known how they get there or what they do.
- An echocardiographic substudy of the COAPT trial failed to identify any baseline echo characteristics to differentiate patients with heart failure (HF) and secondary mitral regurgitation (MR) that would or would not benefit from the MitraClip.
- The US Food and Drug Administration (FDA) has issued a safety alert regarding cyber security vulnerabilities in telemetry systems in certain medtronic lines of CareLink programers and monitors used with many of its defibrillator implant systems.
- Amid an ongoing series of tainted sartan drug recalls, the US FDA announced that it will not object to temporary distribution of losartan that contains the impurity N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) above the interim acceptable intake limit of 0.96 parts per million (ppm) and below 9.82 ppm until it can be eliminated.
- Immediate coronary angiography may offer no survival advantage over a delayed-angiography approach in adults resuscitated but unconscious after out-of-hospital cardiac arrest with no sign of ST-segment elevation myocardial infarction (STEMI), suggests a randomized trial with more than 500 patients. Survival at 90 days, the Coronary Angiography After Cardiac Arrest Trial (COACT) primary end point, was similar at about 66% in both the immediate- and delayed-cath groups.
- Long-term follow-up of stabilized patients with infective endocarditis in the left side of the heart shows no delayed treatment failure with a change from intravenous to early oral antibiotic treatment, sparing them weeks of in-hospital treatment. The results, a post hoc exploratory analysis of the POET trial, were presented at the ACC 2019 Scientific Session (ACC. 19), and published online March 17 as Correspondence in the *New England Journal of Medicine.*
- More early research into a possible male contraceptive pill was presented at ENDO 2019:

The Endocrine Society annual meeting. The results suggest that this pill, a modified testosterone which combines two hormonal activities in one, will decrease sperm production while preserving libido (Christina Wang, MD, of the Clinical and Translational Science Institute at the Los Angeles Biomed Research Institute Torrance, California).

- From the academic session 2019-20, students admitted to MBBS course would be having new curriculum designed after 21 years by Board of Governors of MCI. Apart from other changes, the major ones are - clinical exposure to begin from the first year, and a month-long foundation course. Till now students used to have clinical exposure from second year. Curriculum has introduced new system of elective subjects with which students can pick subjects of their choices.
- The MCI has ruled that National Eligibility cum Entrance Test (NEET) for aspirants who wish to pursue medicine abroad is mandatory, according to official Gazette notification by the MCI. Students have a reason to rejoice as MCI has extended the validity period of NEET scores to 3 years. Every year, around 7,000 students opt to take up medical courses abroad and go to China, Bangladesh, and Russia to study medicine.
- New European guidelines support the use of multiparametric magnetic resonance imaging (MRI) before performing a prostate biopsy. Fast MRI can detect clinically significant prostate cancers with a similar degree of specificity to multiplane, multiparametric or standard biparametric approaches.
- A report in the *BMJ* in 2017 found GPs and their staff are increasingly facing violence, harassment and threatening behavior in their surgeries. It found, in the space of a year, a 9% rise across the UK in the overall number of crimes committed at GP surgeries and health centres. There were 1974 in 2015-2016 compared with 2147 in 2016-17. The report showed an increase in assaults, harassment and a 90% rise in public order offences like threatening behavior. General practitioners (GPs) can remove a patient from their practice list immediately if the person is violent, aggressive or behaves in a way that makes the GPs fear for their safety or the safety of their staff.
- **Building on the ACA to Achieve Universal Coverage:** US universal coverage can be achieved by expanding Medicaid in all states, increasing assistance for buying coverage in the marketplace, ensuring that people enroll in affordable coverage for which they're eligible, and addressing coverage for undocumented immigrants.
- Testing for *Helicobacter pylori*, either directly on biopsy specimens or by means of stool antigen or urea breath testing, is recommended in persons at increased risk for this infection. Treatment choice depends on whether there is penicillin allergy, previous exposure to macrolides, and macrolide resistance. Testing for cure is recommended after treatment.
- **Changes in Practice after Malpractice Claims:** In analyses of a national database of paid malpractice claims from 2003 through 2015, 89% of physicians had no claims, 9% had one claim, and the remaining 2% had two or more claims and were responsible for 39% of all claims. Physicians with multiple claims were not more likely to relocate geographically, but they were more likely to switch to smaller practices (*N Engl J Med.* 2019).
- Mucinous ovarian cancer accounts for 3% of epithelial ovarian cancers and must be distinguished from mucinous carcinomas that have metastasized to the ovary. Most cases manifest as large, localized masses; resection is associated with a good prognosis.
- In persons with rifampicin-resistant tuberculosis that was susceptible to fluoroquinolones and aminoglycosides, a short regimen was noninferior to a long regimen with respect to the primary efficacy outcome and was similar to the long regimen in terms of safety. (Funded by the US Agency for International Development and others; Current Controlled Trials number, ISRCTN78372190; ClinicalTrials.gov number, NCT02409290.
- All institutions conducting biomedical and health research are now required to have an ethics committee, according to the new rules specified by the Indian Council of Medical Research (ICMR). These committees have to be constituted in line with the ICMR's National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017. The idea is to "safeguard the safety, rights and welfare of research participants".
- The United States will follow suit with the World Health Organization's recommendation for artesunate as a first-line treatment for severe malaria. Clinical studies have shown that intravenous (IV)

artesunate is safe, well-tolerated and can be administered to infants, children, and pregnant women in their second and third trimesters, as well as during lactation, according to the CDC. In the first trimester of pregnancy, the benefits of IV artesunate treatment outweigh the risk of death and poor outcomes due to severe malaria.

- How you can reverse mild cognitive impairment (MCI): Certain types of medications can cause memory problems. Your doctor may be able to offer you a different drug therapy that won't affect your memory. Depression is also linked to MCI. It may be possible to alleviate symptoms of MCI by treating the depression.
- **FDA approves device for treating moderate-to-severe chronic heart failure:** The US FDA has approved the Optimizer Smart system for treating patients with chronic, moderate-to-severe heart failure who are not suited for treatment with other heart failure devices such as cardiac resynchronization therapy to restore a normal timing pattern of the heartbeat.

  The FDA gave the device a Breakthrough Device designation because it treats a life-threatening disease and addresses an unmet medical need in patients who fail to get adequate benefits from standard treatments and have no alternative treatment options.
- As per a British study, a high-sensitivity cardiac troponin 1 (hs-cTnI) assay to diagnose myocardial infarction (MI) may lead to overdiagnosis with resulting inappropriate therapies. (University Hospital Southampton).
- US FDA is proposing a rule for breast cancer screenings that would require doctors to give women more information about the risks associated with dense breasts. FDA wants doctors to ensure patients understand how dense breasts, which don't have a lot of fatty tissue, can skew the accuracy of mammograms and present a higher risk of developing breast cancer later in life. About 12 percent of all women are diagnosed with breast cancer at some point in their life. Given that more than half of women over the age of 40 in the US have dense breasts, helping to ensure patient access to information about the impact that breast density and other factors can have on the risk for developing breast cancer is an important part of a comprehensive breast health strategy. Mammograms are considered the best way to detect breast cancer. However, they're not as reliable in dense breasts, characterized as those with not as much fat and more fibrous or glandular tissue, according to the American Cancer Society. Dense tissue makes it harder for doctors to see cancer, meaning the tests can be less accurate. Mammograms of dense breasts can be difficult to interpret because the dense tissue can obscure signs of breast cancer and lower the sensitivity of the image. Dense breasts have also been identified as a risk factor for developing breast cancer.
- The US FDA has approved oral testosterone undecanoate to treat men with hypogonadism resulting from Klinefelter syndrome or tumors that have damaged the pituitary gland.
- The CDC once again issued a warning to pet owners that recent cases of Salmonella have been linked to pet hedgehogs, and the agency is warning pet owners to take precautions to avoid infection.

### Statin Muscle-related Adverse Events

- Statin muscle-related adverse events are relatively uncommon. Myalgias and myopathy occur with a frequency of 2 to 11%. However, severe myonecrosis and clinical rhabdomyolysis are much rarer (0.5% and less than 0.1%, respectively). Patients can experience statin-induced myalgias without an elevation in serum creatine kinase (CK) concentration.
- The risk of muscle injury is substantially higher when taking a statin that is extensively metabolized by cytochrome P450 3A4 (CYP3A4; lovastatin, simvastatin, atorvastatin) together with a drug that interferes with CYP3A4.
- Pravastatin, fluvastatin, rosuvastatin, and pitavastatin are preferred when given to a patient receiving another drug that is a strong inhibitor of CYP3A4.
- Grapefruit juice inhibits CYP3A4; however, daily consumption of 8 oz or less of grapefruit juice or one-half of a grapefruit or less is unlikely to increase the risk of an adverse interaction or muscle injury.
- Enhanced susceptibility to statin-associated myopathy occurs in patients with acute or chronic renal failure, obstructive liver disease, and hypothyroidism.
- Muscle symptoms and/or signs usually begin within weeks to months after starting statins. Myalgias, weakness, and serum CK concentrations usually return to normal over days to weeks after drug discontinuation.


*IJCP SUTRA 871: "High blood pressure is also the most common cause of kidney damage."*

- Angiotensin II receptor blockers (ARBs) are recommended for the treatment of hypertension, heart failure, and CKD, with more than 61 million prescriptions written for valsartan, losartan, and irbesartan in the United States in 2016. Ongoing US FDA recalls — all in generic ARB-containing products — began last July when the probable carcinogen N-nitrosodimethylamine (NDMA) was detected in the valsartan active pharmaceutical ingredient (API) supplied by Zhejiang Huahai Pharmaceutical (ZHP), Linhai, China.

  Within months, the rolling recalls had extended to irbesartan- and losartan-containing products. A second probable carcinogen, N-nitrosodiethylamine (NDEA), was identified last fall and a third, N-nitroso-N-methyl-4-aminobutyric acid (NMBA), in February.
- A petition filed before the Delhi High Court has sought directions to the Centre and the MCI to ensure that doctors prescribe generic medicines. The petition filed in public interest by advocate Amit Sahni contends that the Pradhan Mantri Bhartiya Janaushadhi Pariyojana (PMBJP) was introduced to lower health care costs by providing quality generic medicines at affordable prices.
- Traditionally, experts have recommended not exercising at night as part of good sleep hygiene. Now a new study, published in *Sports Medicine*, suggests that you can exercise in the evening as long as you avoid vigorous activity for at least one hour before bedtime.

## Does My Patient have Hyponatremia?

Hyponatremia or sodium (Na) <135 mEq/L represents a relative excess of water in relation to Na.

Hyponatremia can be acute or chronic:

- Acute: <48 hours. Results from parenteral IV administration in postoperative patients (who have ADH hypersecretion associated with surgery) and from self-induced water intoxication (as in, for example, competitive runners, psychotic patients with extreme polydipsia and users of ecstasy).
- Chronic: >48 hours.

Hyponatremia can be categorized as mild, moderate or severe:

- Mild hyponatremia: 130-134 mEq/L
- Moderate hyponatremia: 120-129 mEq/L
- Severe hyponatremia: Na <120 mEq/L.

The symptoms of mild-to-moderate hyponatremia are relatively nonspecific and include headache, fatigue, lethargy, nausea, vomiting, dizziness, gait disturbances, forgetfulness, confusion and muscle cramps.

The symptoms of severe hyponatremia include seizures, obtundation, coma and respiratory arrest.

How do I know that my patient has hyponatremia? Look for the following:

**Is hyperglycemia present?** Corrected serum Na. The sodium level will fall by 2 mEq/L for every 100 mg/100 mL rise in glucose level.

**Rule out pseudohyponatremia:** Lipemic serum, severe obstructive jaundice or a known plasma cell dyscrasia.

**Rule out lab artefact:** Na measured with flame photometry.

**Recent prostate surgery:** Utilizing large volumes of electrolyte-poor irrigation fluid (or intrauterine procedures).

**Recent drugs:** Mannitol, glycerol or IV immune globulin (isotonic or hypertonic hyponatremia).

**Hypotonic hyponatremia:** Severely reduced glomerular filtration rate (GFR) and thiazide (or thiazide-type) diuretics.

**Is edema or ascites present?** Advanced heart failure or cirrhosis.

**Nonedematous patients with hypotonic hyponatremia:** Euvolemic or hypovolemic.

### Treatment

Patients with acute hyponatremia, most patients with severe hyponatremia (<120) and most patients with symptomatic hyponatremia should be treated in hospital settings that allow frequent assessments of the patient's neurologic condition.

**Four treatment goals** to prevent further declines in the serum Na concentration, to decrease intracranial pressure in patients at risk for developing brain herniation, to relieve symptoms of hyponatremia and to avoid excessive correction of hyponatremia in patients at risk for osmotic demyelination syndrome.

- Goal of initial therapy: Raise Na by 4 to 6 mEq/L in a 24-hour period.
- Acute hyponatremia or severe symptoms: This goal in <6 hours.

- Chronic, severe hyponatremia, the maximum rate of correction should be 8 mEq/L in any 24-hour period.

## Clinical Situations

- Asymptomatic acute hyponatremia Na <130 mEq/L: 50 mL bolus of 3% hypertonic saline to prevent the serum sodium from falling further. Remeasure Na hourly to determine the need for additional therapy. Do not give these patients hypertonic saline if the hyponatremia is already autocorrecting due to a water diuresis.
- Symptomatic acute hyponatremia Na <130 mEq/L: Symptoms that might be due to increased intracranial pressure (seizures, obtundation, coma, respiratory arrest, headache, nausea, vomiting, tremors, gait or movement disturbances, or confusion) with a 100 mL bolus of 3% saline, followed, if symptoms persist, with up to two additional 100 mL doses (to a total dose of 300 mL) over the course of 30 minutes.
- Chronic hyponatremia and Na <130 mEq/L.

*Severe symptoms of hyponatremia or in those with known intracranial pathology (such as recent traumatic brain injury, recent intracranial surgery or hemorrhage, or an intracranial neoplasm or other space-occupying lesion):* Treat with a 100 mL bolus of 3% saline followed, if symptoms persist, by up to two additional 100 mL doses (to a total dose of 300 mL).

*Asymptomatic or have mild-to-moderate symptoms and who have moderate hyponatremia (120-129 mEq/L):* Take only those measures that are broadly applicable to all hyponatremic patients (identify and discontinue drugs that could be contributing to hyponatremia; identify and, if possible, reverse the cause of hyponatremia; and limit further intake of water).

*Asymptomatic or have mild-to-moderate symptoms and who have severe hyponatremia (<120 mEq/L):* Give IV 3% saline beginning at a rate of 15-30 mL/hour. In addition, among those with reversible causes of hyponatremia who are likely to develop a water diuresis during the course of therapy, or in those who are at high risk of developing osmotic demyelination syndrome (ODS), desmopressin (dDAVP) should be initiated simultaneously to prevent overly rapid correction.

### Follow-up

- Hypertonic saline should be discontinued once the daily correction goal of 4-6 mEq/L has been achieved.
- Fluid restriction to below the level of urine output is indicated for the treatment of symptomatic or severe hyponatremia in edematous states (such as heart failure and cirrhosis), syndrome of inappropriate ADH (SIADH), advanced renal impairment and primary polydipsia. In patients with a highly concentrated urine (e.g., 500 mOsmol/kg or higher), fluid restriction alone may be insufficient to correct hyponatremia.
- Depending upon the etiology: Loop diuretics, oral salt tablets, urea, K supplementation or vasopressin receptor antagonists (tolvaptan for up to 30 days, not in liver disease).

### Oral salt

Nine grams of oral salt provides a similar quantity of sodium as 1 L of isotonic saline (154 mEq) but without any water; 1 g of oral salt is equivalent to 35 mL of 3% saline. Oral salt tablets should not be given to edematous patients (e.g., those with heart failure, cirrhosis).

- A new paper in the *New England Journal of Medicine* offers a blueprint for how doctors can use artificial intelligence to help them diagnose diseases. The authors outline the benefits of machine learning to reduce physician error and streamline the health care system. They also highlight the challenges of using AI in medicine — cautioning that even machines can't be perfect.
- Ketamine's rapid antidepressant effects and its recent approval by the US FDA has clinicians and patients alike buzzing with excitement.
- The US Surgeon General's office estimates that more than 20 million people have a substance use disorder.
- In a long-term prospective study of more than 8000 British civil servants followed for almost 25 years, investigators found no significant association between following a healthier diet in midlife and a lower risk for incident dementia or cognitive decline

■■■■

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Indian Journal of Clinical Practice, Vol. 29, No. 11, April 2019

# ESICON 2018: 48th Annual Conference of Endocrine Society of India

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## EVOLVING LANDSCAPE OF DPP-4i CVOTs WITH CARMELINA IN FOCUS

**Dr Sanjay Kalra, Haryana**

- Linagliptin is a single-dose dipeptidyl peptidase-4 inhibitors (DPP-4i) with established clinical efficacy and safety. It is the only globally available DPP-4i excreted mainly via gut/bile. The drug requires no dose adjustment.
- The CARMELINA trial was designed to evaluate the cardiovascular (CV) and kidney safety of linagliptin in patients with type 2 diabetes mellitus (T2DM) vs. placebo. Primary endpoints included CV death, nonfatal myocardial infarction (MI) and nonfatal stroke. Key secondary endpoint included sustained estimated glomerular filtration rate (eGFR) decrease by ≥40%, progression to sustained end-stage kidney disease (ESKD) and death due to kidney disease. Patients included in the trial had established cardiovascular disease (CVD), kidney disease or both. Patients with T2DM were randomized to oral treatment with linagliptin or placebo on top of standard of care.
- The trial included a broad group of kidney disease patients.
- The trial showed no increased risk for hospitalization for heart failure (HF) even in high-risk patients with pre-existing HF.
- Event rate of hospitalized HF was 2.8 times higher in patients with eGFR <45.
- The long-term kidney safety profile of linagliptin was confirmed in the first prespecified adjudicated kidney outcome data with DPP-4i.
- The number of patients who had ≥1 new glucose-lowering medication introduced post-baseline was significantly lower with linagliptin compared to placebo.
- With linagliptin, fewer patients initiated or increased insulin dose.
- Overall, linagliptin did not increase the risk of hypoglycemia.
- The trial showed a reassuring long-term kidney safety profile. It fills a data gap as it included patients across the full range of kidney function.
- With CARMELINA, linagliptin showed a reassuring CV safety profile and a robust and reassuring HF safety.

## DIABETIC KIDNEY DISEASE AND ROLE OF SGLT-2i

**Dr Mathew John, Trivandrum**

- Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) act by inhibiting SGLT-2 in the proximal tubule of the kidney, thereby increasing natriuresis and glucose excretion.
- They have beneficial effects on weight, systolic BP and glycated hemoglobin (HbA1c).
- Large cardiovascular outcomes trials (CVOTs) have found reductions in composite major adverse cardiac events (MACE), HF hospitalization, CV death and various composites of CV outcomes.
- Most of the data regarding the long-term effects on the kidney are derived from the CVOTs: EMPA REG OUTCOME, CANVAS and DECLARE TIMI.
- About 70-90% of subjects enrolled in CVOTs of SGLT-2i did not have diabetic kidney disease (DKD).
- Mechanisms of renal protection with SGLT-2 blockers - Restoring tubuloglomerular feedback; reducing renal hypoxia; changes in renal substrate utilization; improvements in BP; improvements in glycemia; improvements in weight and reducing uric acid levels.
- Key benefits of SGLT-2i in DKD - Retard the progression of eGFR in subjects with proteinuric DKD; retard the progression of microalbuminuria to macroalbuminuria; retard the progression of macroalbuminuria to ESRD; reduce the risk of new-onset albuminuria; reduce various CV outcomes in subjects with DKD.



*IJCP SUTRA 874:* "Eat healthy and keep your weight in check."

## MANAGEMENT OF NEUROENDOCRINE TUMORS

**Dr Karel Pacak, USA**

- Classification of neuroendocrine tumors (NETs) - Carcinoids and gastroenteropancreatic tumors (GEPs); Chromaffin cell tumors; Multiple endocrine neoplasia (MEN)1-, MEN2-, neurofibromatosis (NF)1-related NETs; Medullary thyroid carcinoma (MTC); Poorly differentiated small cell carcinoma; NETs of unknown origin.
- Early accurate diagnosis leads to better prognosis.
- NETs - Specific characteristics: Take up hormone precursors; Synthesize, store and release hormones; Express specific transporters and receptors; Have specific metabolomic profiles; They are immunogenically cold.
- Endoscopic methods in NETs negative on imaging - Capsule endoscopy; Double balloon enteroscopy.
- The North American Neuroendocrine Tumor Society (NANETS) recommendation for NETs - *Surgery*: 50% recurrence rate; surveillance should continue beyond 5 years, not clear if 10 years but recommended, especially for young patients and those with positive LNs. *Surveillance*: Every 6-12 months, CT/MRI abdomen, initially Octreoscan or $^{68}$Ga-DOTATATE recommended.
- A study evaluated the efficacy and safety of lutetium-177 ($^{177}$Lu)-DOTATATE in patients with advanced, progressive, somatostatin-receptor-positive midgut NETs. The treatment led to markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide long-acting repeatable (LAR) (Strosberg J, et al. *N Engl J Med.* 2017;376(2):125-35).

## DIGITAL DIABETOLOGY: DAILY PRACTICALITIES

**Dr AG Unnikrishnan, Pune**

- Trust your patient, but do not let that stop you from verifying records if a discrepancy is noted.
- Rule out other causes of false rise in HbA1c.
- Consider the possibility of malfunctioning glucometer.
- Calibrate or change the device. In our setting, make sure that the glucometer is used by a single person.

## IN-HOSPITAL MANAGEMENT OF DIABETES MELLITUS

**Dr Arpan Dev Bhattacharyya, Bengaluru**

- Diabetes control in hospital is important.
- The target needs to be clear.
- Insulin is certainly the agent of choice.
- TEAM approach is the KEY to success.
- Regular audit of our own work helps to improve the quality of care we provide.
- Glycemic targets that can be recommended in different patient populations - Not recommended: <110 and >180 mg/dL; May be appropriate: 110-140 mg/dL and Recommended: 140-180 mg/dL.
- Criteria of good control - Good: 80% or more; Suboptimal: 40-80% and Poor: <40% (in the target range).
- A survey at the Manipal Hospital suggested that increased attention needs to be paid to improving glycemic control in patients hospitalized for reasons other than diabetes. Using subcutaneous insulin, glycemic control was good in 48%, suboptimal in 15% and poor in 37% of patients. The corresponding numbers while on intravenous insulin were 45%, 11% and 46%, respectively (Deepak PJ, et al. *Postgrad Med J*. 2003;79(936):585-7).

## ENDOCRINE MANAGEMENT OF GENDER INCONGRUENT PERSON

**Dr Mala Dharmalingam, Bengaluru**

- Individuals should be treated with the lowest effective hormone doses, and the focus of treatment should be based on the individual's response and not just hormone levels.
- Patient safety is of utmost concern.
- Side effects should be monitored.

## DIAGNOSIS AND MANAGEMENT OF MENOPAUSE

**Dr Ganapathi Bantwal, Bengaluru**

- Hormone therapy (HT) is the most effective treatment for vasomotor symptoms (VMS) and genitourinary syndrome of menopause (GSM).
- The concept of "lowest dose for the shortest period of time" may be inadequate or even harmful for some women.
- A more fitting concept is "appropriate dose, duration, regimen and route of administration."
- Decision on duration requires individualization.
- Given the more favorable safety profile of estrogen alone, longer durations may be more appropriate.
- Risk stratification by age and time since menopause is recommended (<10 years from menopause or <60 years).

- Transdermal or lower doses of HT may decrease risk of VTE and stroke.
- Micronized progesterone is a safer alternative when use of progesterone is considered.

## HEART FAILURE - AN ELEPHANT IN THE ROOM: MANAGEMENT IN THE ERA OF SGLT-2i

**Dr Sundar Mudaliar, California**

- Cardiovascular disease is more than MACE (MI, CVA, CV death).
- HF is an important component of CVD.
- HF is quite prevalent in patients with diabetes; occurs in >1 in 5 patients aged over 65 years.
- Patients with both diabetes and HF have a poor prognosis, with a median survival of ~4 years.
- Diabetes can lead to HF through both atherosclerotic-mediated and atherosclerotic-independent mechanisms.
- In a network meta-analysis, the use of SGLT-2i or glucagon-like peptide (GLP)-1 was associated with lower mortality in patients with T2DM.
- SGLT-2i have moderate benefits on atherosclerotic MACE in patients with established atherosclerotic cardiovascular disease (ASCVD). Additionally, they have robust benefits on reducing hospitalization for HF and progression of renal disease regardless of existing ASCVD or a history of HF.

## ADA-EASD 2018 CONSENSUS: IN INDIAN CONTEXT

**Dr Awadhesh K Singh, Kolkata**

- Sulfonylureas (SUs) and thiazolidinediones (TZDs) remain the cornerstone of therapy in a developing country where the patient has to pay from his pocket.
- Alpha-glucosidase inhibitors (AGIs) are not included in ADA-EASD consensus as they are not used in the USA, but are still useful in Indians.
- GLP-1 receptor agonists (GLP-1RAs) and SGLT-2i should be used in established CVD, given the data we have.
- SGLT-2i have data suggestive of prevention of hospitalization for HF in T2DM and thus should be used if patients can afford.

## ADRENAL INSUFFICIENCY IN CHILDREN

**Dr David Torpy, Australia**

- Adrenal insufficiency refers to low plasma cortisol, often confirmed by adrenocorticotropic hormone (ACTH) stimulation testing.
- Majority of adrenal insufficiency cases in children (primary/secondary) have a genetic etiology. Testing is based on AI category and associated features. Precise diagnosis may assist in prognosis/management and may assist with family counseling/prenatal diagnosis.
- Adrenal crisis is an acute deterioration in health associated with hypotension. Resolution occurs following parenteral glucocorticoid administration.
- Adrenal insufficiency treatment in children (chronic) - Treatment with hydrocortisone in 2 or 3 divided doses (total daily dose 8-12 mg/m$^2$ body surface area [BSA], 0.2-0.3 mg/kg) over other types of glucocorticoids replacement therapies; In children with primary adrenal insufficiency, synthetic, long-acting glucocorticoids should be avoided; In confirmed aldosterone deficiency, fludrocortisone can be given; In infants, sodium chloride supplements should be given.
- Adrenal crisis treatment in children - Hydrocortisone IV doses (<3 years - 25 mg; 3-12 years - 50 mg; >12 years - 100 mg; OR Hydrocortisone 100 mg/m$^2$ BSA); Bolus D5 normal saline 20 mL/kg over 1 hour, further infusion based on standard resuscitation guidelines.
- Adrenal insufficiency in children is rare. Suspect if there is fatigue, weight loss, upper gastrointestinal distress, hypotension, especially if chronic or subacute.
- Clinical assessment of BP, especially for postural hypotension is useful.
- Hypoglycemia, and hyponatremia are common; hyperkalemia and pigmentation are not reliably present.
- Around 50% have congenital adrenal hyperplasia (CAH), 30% autoimmune, adrenal insults, ACTH resistance and other genetic causes follow. Associated features are key to establishing genetic cause.
- Adrenal insufficiency challenges - Glucocorticoid dosing: There is no reliable biochemical marker of tissue glucocorticoid sufficiency; Adrenal crises are frequent (6-8%/year) and the current preventive strategies not fully effective; Impaired well-being in 40% treated adults (?children).

## COMBINATION OF EMPA AND LINA: A LEAP TOWARDS HOLISTIC DIABETES MANAGEMENT

**Dr Sujoy Majumdar, Kolkata**

- Empagliflozin/linagliptin fixed-dose combination (FDC) offers high efficacy with convenience of a single tablet, thereby reducing the pill burden.

- There are 2-4 times higher odds of patients reaching the goal HbA1c compared to individual agents. It is associated with early achievement of glycemic goal with durable efficacy.
- The combination offers extraglycemic benefits like weight reduction, BP control, overall CV and renal safety, etc.
- There is absence of any additional safety concerns, or drug interactions.
- To summarize, Empa/Lina combination till date remains one of the best steps towards holistic management of diabetes mellitus.

## TENELIGLIPTIN: RECENT EVIDENCES

**Dr Sujoy Ghosh, Kolkata**

- Teneligliptin is a specific DPP-4i with dual excretion through hepatic and renal routes.
- No dose adjustment is required in hepatic (mild and moderate) or renal plasma dysfunction. It can be administered irrespective of meals.
- Once a day dosing is possible and the drug has low potential for drug-drug interactions.
- Treatment with teneligliptin results in significant reduction in HbA1c, fasting plasma glucose (FPG) and postprandial plasma glucose (PPG). It is weight neutral and has low risk of hypoglycemia.
- The drug is generally well-tolerated.
- Teneligliptin has been found not to cause detectable increase in CV risk in Japanese and Indian studies. The drug had no clear effect on the occurrence of CV adverse events, vital signs, ECG or lipid parameters.

## MAKING CHOICES: DPP-4i, SGLT-2i OR BOTH IN TAKING NEXT STEP AFTER METFORMIN

**Dr JJ Mukherjee, Kolkata**

- Combination of DPP-4i and SGLT-2i results in greater improvement in glycemic control than each individual component alone.
- SGLT-2i/DPP-4i vs. DPP-4i alone yields greater reductions in HbA1c and FPG.
- SGLT-2i/DPP-4i vs. SGLT-2i alone - additional reductions in HbA1c and FPG are less marked.
- HbA1c reduction due to SGLT-2i/DPP-4i combination vs. DPP-4i alone seems to be directly proportional to baseline HbA1c.
- In contrast, additional HbA1c reduction due to SGLT-2i/DPP-4i combination vs. SGLT-2i alone seems modest regardless of baseline HbA1c.
- While the combination of SGLT-2i and DPP-4i results in a clinically meaningful reduction in HbA1c and FPG with low risk of hypoglycemia, the additional glucose control is significant when SGLT-2i is combined with or added to DPP-4i, but not the other way round.
- Action of SGLT-2i is unlikely to be affected by combined use with DPP-4i.

## INHALED CORTICOSTEROIDS AND HPA AXIS SUPPRESSION: HOW IMPORTANT IS IT AND HOW SHOULD IT BE MANAGED?

**Dr Kalpana Dash, Raipur**

Corticosteroids are very important in treating bronchoconstrictive lung disorders. However, inhaled corticosteroid (ICS) preparations play a central role in treating chronic obstructive pulmonary disease (COPD) and asthma, limiting the exposure to systemic steroid therapy and its long-term consequences.

More potent ICS therapy has significant absorption across the lungs, leading to hypothalamic-pituitary-adrenal (HPA) axis suppression, iatrogenic Cushing's syndrome, adrenal insufficiency, very rarely osteoporosis, growth failure in children and development of posterior subcapsular cataract. This is much higher in 'higher risk' patients exposed to high cumulative ICS doses, and in those treated with frequent oral corticosteroids or drugs which inhibit cytochrome P450 3A4, like ritonavir and antidepressant drugs.

There are different ICS available like beclomethasone dipropionate (BDP), budesonide, ciclesonide, fluticasone propionate and mometasone furoate.

They all have common mode of action by binding to glucocorticoid receptors. Early detection of adrenal suppression after ICS therapy is required and biochemical testing needs to be done to confirm the diagnosis, and careful patient education about the need for steroid supplementation at times of stress is an important part of management.

## DIAGNOSIS AND MANAGEMENT OF MALE HYPOGONADISM

**Prof Subhankar Chowdhury, Kolkata**

- Diagnosis of male hypogonadism is made by testing early morning fasting testosterone by reliable assay in appropriate clinical setting.
- Treatment options depend on etiology (primary/secondary); fertility concern; age of patient and safety issues.

- It is important to treat the primary/underlying cause.
- Primary hypogonadism requires testosterone therapy. Fertility options include TESE and ICSI, donor sperm and adoption.
- In secondary hypogonadism, gonadotropin therapy improves fertility.
- Testosterone therapy monitoring - Target testosterone: Mid-normal range for healthy young males; Serum testosterone and packed cell volume (PCV): 3-6 months post-initiation, then yearly; PCV >54% - stop therapy, till it decreases to <50%, evaluate for hypoxia and sleep apnea and reinitiate with a reduced dose; PSA: 3-12 months post-initiation if age >40 years. Δ PSA >1.4 ng/mL or absolute value >4 ng/mL warrants urology referral.
- Pubertal induction in boys with isolated hypogonadotropic hypogonadism (IHH) - Injection testosterone monthly; start with low-dose, with 6-monthly increments; Reach adult dose over 3-4 years; Adult dose - 200 mg/2 weekly or 100 mg/week.
- Testosterone replacement in hypogonadal males: Benefits >>> risks.

## MANAGEMENT OF GRAVES' ORBITOPATHY: AN UPDATE

**Dr Wilmar M Wiersinga, Netherlands**

- In a study conducted to construct a predictive score for the development or progression of Graves' orbitopathy (GO) in Graves' hyperthyroidism (GH), among patients without GO at diagnosis, 15% developed GO (13% mild, 2% moderate-to-severe) during subsequent treatment with ATD. Independent baseline determinants for the development of GO included clinical activity score, thyroid-stimulating hormone (TSH)-binding inhibitory immunoglobulins, duration of hyperthyroid symptoms and smoking.
- A recent study compared the efficacy and safety of add-on mycophenolate to methylprednisolone in comparison with methylprednisolone alone in patients with moderate-to-severe GO. While there were no significant differences in the rate of response at 12 weeks or rate of relapse at 24 and 36 weeks, post-hoc analysis suggested that addition of mycophenolate improved rate of response to therapy by 24 weeks in patients with active and moderate-to-severe GO (Kahaly et al. *Lancet Diab Endocrinol.* 2018;6(4):287-98).
- Selenium is known to improve mild GO and prevents deterioration of mild GO. Promising new therapies in active moderate-to-severe GO include rituximab, teprotumumab and tocilizumab. But, IV steroids remain the treatment of choice until RCTs comparing steroids with these novel agents show greater efficacy and better tolerability. It is too early to dismiss rituximab as a disease-modifying drug and too early to accept it as an alternative to IV methylprednisolone. Therefore, rituximab currently has a role in resistant cases, not responding to steroids.

## EVOLVING GLIPTIN – EVOGLIPTIN

**Dr Awadhesh K Singh, Kolkata**

- Evogliptin (DA-1229) is a piperazine derivative. It is a selective, potent and reversible inhibitor of DPP-4.
- The agent has been studied in a Phase II study and two Phase III studies in South Korea in T2DM patients.
- According to a recent study, evogliptin 5 mg monotherapy significantly decreased HbA1c and was well-tolerated in patients with T2DM inadequately controlled on diet and exercise.
- The results suggested that T2DM patients with modest hyperglycemia may be good candidates for evogliptin monotherapy.
- Evogliptin 5 mg added to metformin therapy has been found to improve glycemic control and was non-inferior to sitagliptin and well-tolerated in T2DM patients inadequately controlled by metformin alone. Evogliptin is a weight-neutral agent and has minimal potential for drug interactions. It can be used safely in patients with renal dysfunction.

## THYROID MICROCARCINOMAS – TO TREAT OR NOT

**Dr Bipin Kumar Sethi, Hyderabad**

Increasing surveillance has led to detection of many thyroid nodules that the patients would have lived (and died) happily with. Detection of a nodule should not lead to further work-up (FNAC) unless otherwise indicated. All lesions without the high risk characteristics can be offered the choice of observation, and if they are operated, could have the choice of less extensive surgeries. Active follow-up is the key to the plan of surveillance should the patient choose this path. Active surveillance does not mean no treatment. Treatment is delayed until the cancer shows significant progression.



*IJCP SUTRA 878: "Consuming plenty of fluid helps the kidneys clear sodium, urea and toxins from the body which, in turn, results in a "significantly lower risk" of developing chronic kidney disease."*

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# News and Views

## One in Four Health Care Facilities Lacks Basic Water Services

One in four health care facilities around the world lacks basic water services, impacting over 2 billion people, according to a new report by WHO and UNICEF Joint Monitoring Program for Water Supply, Sanitation and Hygiene (JMP).

The WHO/UNICEF JMP report, *WASH in Health Care Facilities*, is the first comprehensive global assessment of water, sanitation and hygiene (WASH) in health care facilities. It also finds that one in five health care facilities has no sanitation service, impacting 1.5 billion people. The report further reveals that many health centers lack basic facilities for hand hygiene and safe segregation and disposal of health care waste. These services are crucial to preventing infections, reducing the spread of antimicrobial resistance and providing quality care, particularly for safe childbirth… (*WHO, April 3, 2019*)

## FDA Proposes New Fluoride Standard for Bottled Water

The US Food and Drug Administration (FDA) is proposing a lower concentration level standard for fluoride in bottled water, yet some scientists and environmental groups believe that the proposed limit is still too high and poses a danger to human health.

If finalized, the new regulation will lower allowable levels of fluoride in domestically packaged and imported bottled water to 0.7 mg/L, a slight reduction from the current standard range of between 0.8 and 1.7 mg/L allowed by the FDA. The proposed standard would apply only to bottled water with added fluoride. It would not affect allowable levels of fluoride in bottled water that may contain fluoride from source water… (*CNN, April 2, 2019*)

## A New Fixed-dose Combination Inhaler for COPD

The US FDA has approved a fixed-dose combination of aclidinium bromide 400 μg (long-acting muscarinic antagonist [LAMA]) and formoterol fumarate 12 μg (long-acting beta-agonist [LABA]) for the maintenance treatment of chronic obstructive pulmonary disease (COPD). It is to be administered twice-daily via the breath-actuated inhaler.

## NIH Begins First-in-human Trial of a Universal Influenza Vaccine Candidate

The first clinical trial of an innovative universal influenza vaccine candidate is examining the vaccine's safety and tolerability as well as its ability to induce an immune response in healthy volunteers. Scientists at the National Institute of Allergy and Infectious Diseases (NIAIDs), part of the National Institutes of Health (NIH), developed the experimental vaccine, known as H1ssF_3928.

H1ssF_3928 is designed to teach the body to make protective immune responses against diverse influenza subtypes by focusing the immune system on a portion of the virus that varies relatively little from strain to strain… (*NIH*)

## Antiviral Treatment Prevents HCV Infection in Transplant Recipients from Infected Donors

In patients without hepatitis C virus (HCV) infection who received a heart or lung transplant from donors with hepatitis C viremia, treatment with an antiviral regimen for 4 weeks, initiated within a few hours after transplantation, prevented the establishment of HCV infection. These conclusions from the DONATE HCV Trial Team were published April 3, 2019 in the *New England Journal of Medicine*.

## USDA, EPA and FDA Recognize April as Winning on Reducing Food Waste Month

The US Department of Agriculture (USDA), the US Environmental Protection Agency (EPA) and the FDA kick off Winning on Reducing Food Waste Month by calling for greater collaboration with public, private and nonprofit partners as well as state and local officials to educate and engage consumers and stakeholders throughout the supply chain on the need to reduce food loss and waste…

## Dana-Farber Opens First Center Devoted to Lynch Syndrome

The Dana-Farber Cancer Institute in Boston, Massachusetts, has opened the Lynch Syndrome Center, with the goal of providing genetic counseling and testing to those at risk for the syndrome as well as delivering a new model of coordinated care. It is the first such center.



IJCP SUTRA 879: "Do not advocate "aggressive fluid loading", which can cause side effects."

Lynch syndrome remains a largely unknown genetic disease, and most carriers are either undiagnosed or are diagnosed only after they have developed cancer. It is an autosomal dominant genetic disorder that is associated with germline mutations in DNA mismatch repair genes. It increases the lifetime risk for colorectal cancer by up to 80%, for endometrial cancer, by up to 60%; the risks for cancers of the stomach, ovary, small bowel, hepatobiliary tract, urinary tract, brain, and skin…. (*Medscape*)

### CDC's Successful "Tips from Former Smokers" Campaign Returns this Month

New emotionally powerful ads kick off the 8th year of the CDC's "Tips from Former Smokers" campaign. The new ads share personal stories of Americans suffering from smoking-related illnesses—and the devastating impact of these illnesses on smokers' families.

One of the new ads features Susan Nimoy, the wife of Leonard Nimoy, the American actor best known for his role as Spock on Star Trek. Mr Nimoy quit smoking cigarettes after 37 years, but those years of smoking damaged his lungs. He suffered from COPD, as a result of smoking, until his death in 2015. Nimoy's desire to educate the public about the dangers of smoking will now live on as part of CDC's Tips campaign.

Beginning April 1, Tips ads will run for 27 weeks on national and cable television, online and in magazines… (*CDC*)

### Long-distance Commuting During Pregnancy Adversely Affects Health of the Baby

The first study on the effects of long commutes during pregnancy on infant health has shown that a 10-mile increase in travel distance raises the probability of low birth weight by 0.9 percentage points. A 10-mile increase in travel distance raises the probability of intrauterine growth restriction by 0.6 percentage points. These findings are published online in *Economics & Human Biology*.

### Monocytes may Predict Prognosis in Patients with Idiopathic Pulmonary Fibrosis

Increased monocyte count was associated with poorer outcomes in patients with idiopathic pulmonary fibrosis (IPF), according to a retrospective, multicenter analysis reported in *Lancet Respiratory Medicine*. Estimated CD14+ classical monocyte percentages above the mean were found to be associated with shorter transplant-free survival times in the analysis, while higher T-cell and B-cell percentages were not associated with shorter transplant-free survival times.

### FDA Approves Ambrisentan Generics for PAH

The US FDA has approved four generic versions of ambrisentan, an endothelin receptor antagonist indicated for treatment for pulmonary arterial hypertension (PAH).

### CDC Modifies its Travel Advisory for India on Zika Virus Disease

The CDC has modified its travel advisory for India on Zika virus disease on 27th March 2019. The status of India has now been changed from "ongoing outbreak" to "current or past transmission but no current outbreak."

In December 2018, CDC, USA had issued a travel health notice on Zika virus in India, which depicted that India has an ongoing outbreak of Zika virus disease in Rajasthan and its surrounding states. The advisory further cautioned pregnant women not to travel to areas with ongoing Zika outbreaks. Women planning pregnancy were also alerted on travel. Such an advisory could have serious implications on travel and trade in India.

Ministry of Health and Family Welfare, Govt. of India expressed serious concern over the whole issue. Prof. Balram Bhargava, Secretary, Department of Health Research and Director General, Indian Council of Medical Research (ICMR), wrote to CDC to withdraw or modify the travel advisory providing evidence of the contained outbreak in India. This communication provided data on human and vector surveillance for Zika virus disease in India … (*ICMR, April 2, 2019*)

### HC Refuses to Hear Plea on Generic Drugs

The Delhi High Court declined to entertain a petition seeking directions to the Centre and the Medical Council of India (MCI) to ensure that doctors prescribe generic medicines.

The plea by advocate Amit Sahni said that the MCI had on January 21, 2013, issued a circular addressed to the deans of all medical colleges, directors of all hospitals, presidents of all state medical councils, whereby the doctors practicing medicine were called upon to prescribe drugs with generic name as far as possible. But the authorities have failed to ensure that doctors write only generic medicines in their prescription despite clear statutory directions. Generic medicine works and provides the same clinical benefit as brand-name versions, and generic medicines cost 5% and 60% less than their branded counterparts.

Mr Sahni had argued that citizens belonging to the lower-middle class and economically backward section may not be in a position to approach the court due to lack of awareness, and would benefit from a court direction to doctors to prescribe generic medicines… (*The Hindu*)

### NPPA Approves Hike in Prices of Coronary Stents

Drug price regulator National Pharmaceutical Pricing Authority (NPPA) has approved hike in prices of cardiac stents by 4.2% in line with the wholesale price index (WPI) of the previous calendar year, as per an official statement.

As per the new prices notified by the NPPA, a bare metal stent (BMS) would now cost Rs. 8,261, while the drug-eluting stent (DES) will cost Rs. 30,080.

"After considering the WPI at 4.26% for the year 2018 over 2017, it has been decided to revise the ceiling prices of coronary stents with effect from April 1, 2019," the NPPA said in a statement.

The drug pricing authority had earlier revised the prices of stents in February last year. It had increased the prices of BMS from Rs. 7,400 to Rs. 7,660. On the other hand, it had reduced the price of DES to Rs. 27,890 from Rs. 30,180.

Providing a major relief to lakhs of cardiac patients, the government had for the first time cut prices of life-saving coronary stents by up to 85% in February 2017. BMS used to cost as much as Rs. 45,000 and DES Rs. 1.21 lakh prior to the imposition of the price cap in February 2017.

The NPPA also said in a separate statement that it has revised ceiling/retail prices of 871 formulations under Drugs (Price Control) Order, 2013.

### US Measles Cases at Second Highest Since Disease was Eliminated in 2000

A total of 387 individual cases of measles have been confirmed in 15 states from January 1 to March 28, according to the US CDC. This is the second-greatest number of cases reported in the United States since measles was declared eliminated in 2000, reported CNN. The highest number of reported cases since elimination was 667 in 2014. The states reporting cases are Arizona, California, Colorado, Connecticut, Georgia, Illinois, Kentucky, Michigan, Missouri, New Hampshire, New Jersey, New York, Oregon, Texas and Washington.

The CDC says six outbreaks - defined as three or more cases - are ongoing in California (Santa Cruz and Butte County), New Jersey, New York (Rockland County and New York City) and Washington. These outbreaks are linked to travelers who brought measles back from other countries such as Israel, Ukraine and the Philippines, where large measles outbreaks are occurring… (*CNN, April 1, 2019*)

### Better Glycemic Control with Oral Semaglutide vs. Sitagliptin in PIONEER-3

Among adults with type 2 diabetes uncontrolled with metformin with or without sulfonylurea, oral semaglutide, 7 mg/day and 14 mg/day, compared with sitagliptin, resulted in significantly greater reductions in HbA1c over 26 weeks, according to findings from the randomized, double-blind controlled PIONEER-3 trial published online in *JAMA*.

### Noninvasive Brain Stimulation is a Feasible Alternative Treatment in Resistant Depression

Findings of a new systematic review and network meta-analysis published online in *BMJ* show nonsurgical brain stimulation is a viable alternative or add-on treatment for major depressive disorder in adults.

### Govt. Extends Deadline for Linking PAN with Aadhaar Till September 30

The government has extended the deadline for linking Permanent Account Number (PAN) with biometric ID Aadhaar by 6 months till September 30, an official statement said.

This is the sixth time the government has extended the deadline for individuals to link their PAN to Aadhaar.

In June last year, the government had said that PAN has to be linked with the biometric ID by March 31. "…. Now the cut-off date for intimating the Aadhaar number and linking PAN with Aadhaar is September 30, 2019, unless specifically exempted," the Central Board of Direct Taxes (CBDT) said in a statement. However, quoting of Aadhaar will be mandatory while filing income tax returns (ITRs) with effect from April 1, 2019… (*The Pioneer-PTI*)

### Testosterone Therapy can Help Men with Hypogonadism Lose Weight

Long-term testosterone therapy can help men with hypogonadism lose weight and maintain their weight loss, according to 10-year results from a study presented at ENDO 2019, the Endocrine Society's annual meeting in New Orleans, Louisiana. Over

10 years, the testosterone-treated men lost 20.3% of their baseline weight (50.5 lb; 22.9 kg); their waist circumference dropped by 12.5 cm (4.9 in). Body mass index (BMI) decreased by 7.3 kg/m$^2$, and the waist-to-height ratio decreased by 0.07. By contrast, the untreated men gained 3.9% of their baseline weight (3.2 kg; 7.1 lb), and their waist size increased by 4.6 cm (1.8 in). In this group, BMI increased by 0.9 kg/m$^2$ and waist-to-height ratio increased by 0.03.

### First Gene Therapy for β-thalassemia Gets the Go-ahead in Europe

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has recommended approval of the first gene therapy for transfusion-dependent β-thalassemia (TDT), a rare inherited blood condition that causes chronic severe anemia.

Autologous CD34+ cells encoding β A-T87Q-globin gene is for people 12 years and older with TDT who do not have a β0/β0 genotype, for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen-matched related HSC donor is not available.

### Climate change could Expose 1 Billion More People to Bug-borne Diseases

As the planet gets warmer, scientists say, diseases like Zika, chikungunya and dengue will continue spreading farther north. The authors of the new study, published in the journal *PLOS Neglected Tropical Diseases*, created a model that includes data on predicted temperature changes and the known range of the day-biting, disease-carrying mosquitoes *Aedes albopictus* and *Aedes aegypti*.

Europe will probably see some of the biggest increases in diseases from both of these species, the researchers say. The United States, East Asia, high-elevation parts of Central America, East Africa and Canada will also see large increases in risk for these diseases. The much warmer climates in Southeast Asia and West Africa will not be as suitable for the albopictus species… (*CNN*)

### Fewer Reproductive Years in Women Linked to an Increased Risk of Dementia

According to a new study published in the journal *Neurology*, women who start their period later, go through menopause earlier or have a hysterectomy may have a greater risk of developing dementia. Women who had their first menstrual cycle at age 16 or older had a 23% greater risk of dementia than women who had their first menstrual cycle at age 13. Women who went through natural menopause before age 47 had a 19% greater risk of dementia than women who went through menopause at age 47 or older.

### Omega-3 and Omega-6 fatty Acids may Play Opposite Roles in Childhood Asthma

Dietary intake of two fatty acids, omega-3 and omega-6, may have opposite effects on the severity of asthma in children and may also play opposite roles in modifying their response to indoor air pollution, according to new research published online in the *American Journal of Respiratory and Critical Care Medicine*. In the study, higher levels of omega-6 in the children's diet correlated with higher percentages of neutrophils in response to particulate pollution.

### A New Oral Treatment for Multiple Sclerosis

The US FDA approved cladribine tablets to treat relapsing forms of multiple sclerosis (MS) in adults, to include relapsing-remitting disease and active secondary progressive disease. The drug is not recommended for MS patients with clinically isolated syndrome. Because of its safety profile, the use of cladribine is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS.

### Beetroot, Nitrate Supplements could help Prevent Salt-induced Hypertension

Adding tiny amounts of beetroot or dietary nitrate to salty food products might help prevent high blood pressure (BP), according to a preliminary study of rats reported in the journal *Hypertension*. Both the juice and the nitrate supplement were more than 100 times more potent than potassium in protecting rats against salt-induced increases in BP.

### New UN Global Climate Report 'Another Strong Wake-up Call' Over Global Warming

The increasing number of natural disasters and dangers linked to climate change, highlighted in a major UN report represents "another strong wake-up call" to the world, which must be countered by finding sustainable solutions quickly, UN Secretary-General António Guterres has said. Speaking at the launch of the State of the Global Climate report by the World Meteorological Organization (WMO), Mr Guterres reiterated his call for action, underlining that the alarming conclusion that

climate change is accelerating, "proves what we have been saying: climate change is moving faster than our efforts to address it." (*UN*)

### Artesunate Now First-line Treatment for Severe Malaria in the US

CDC is issuing new guidance to clinicians for the treatment of severe malaria cases in the US. This change in treatment protocol is necessary because the only FDA-approved intravenous (IV) antimalarial drug in the US, quinidine, has been discontinued by the manufacturer and will no longer be available. As of April 2019, artesunate, the World Health Organization (WHO)-recommended first-line treatment of severe malaria, will become the first-line treatment for severe malaria in the US… (*CDC*)

### Diseases Cost the African Region $2.4 Trillion a Year, Says WHO

The WHO estimates that nearly 630 million years of healthy life were lost in 2015 due to the diseases afflicting the population across its 47 Member States in Africa, now amounting to a loss of more than 2.4 trillion international dollars ($) from the region's gross domestic product value annually.

Noncommunicable diseases have overtaken infectious diseases as the largest drain on productivity, accounting for 37% of the disease burden. Other culprits for lost healthy years are communicable and parasitic diseases; maternal, neonatal and nutrition-related conditions and injuries. Around 47%, or $ 796 billion, of this lost productivity value could be avoided in 2030 if the Sustainable Development Goals related to these health conditions are achieved, WHO found… (*WHO Africa*)

### HIV-positive Woman Donates Kidney to HIV-positive Recipient

An Atlanta woman became the first living HIV-positive kidney donor in the world when surgeons at Johns Hopkins Medicine in Baltimore transferred her organ to a recipient who is also HIV-positive, according to a statement from the medical center. Both the donor and the recipient, who wishes to remain anonymous, are doing well.

The 36-year-old public health consultant acquired HIV as a 6-week-old in 1983, when she received a blood transfusion in the years before blood banks began routine testing for the virus. HIV damages the immune system and interferes with the body's ability to fight the organisms that cause disease.

"She met the standard donor criteria: She was otherwise healthy without hypertension, without diabetes, so her only additional risk factor for kidney disease was HIV. And we had determined from our research that was an acceptable and small additional risk," said Dr. Christine Durand, Associate Professor of Medicine and Oncology and member of the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center and the HIV team specialist for Martinez's surgery… (*CNN*)

### FDA Approves Treatment for Patients with a Type of Inflammatory Arthritis

The US FDA has approved certolizumab pegol injection for treatment of adults with a certain type of inflammatory arthritis called nonradiographic axial spondyloarthritis (nr-axSpA), with objective signs of inflammation. This is the first time that the FDA has approved a treatment for nr-axSpA.

### Study Shows Safety of Metformin in Psoriasis Patients with Diabetes Mellitus

Metformin can be prescribed for psoriasis patients with diabetes without safety concerns as reported in *The Journal of Clinical Endocrinology & Metabolism*. The metformin group and the non-metformin group did not significantly differ in the risk of all-cause mortality, severe psoriasis, psoriasis-related admission and any-cause re-admission.

### Participation in Sport can Improve Children's Learning and Skills Development

Participation in sport improves children's educational attainment and skills development including empowerment, leadership and self-esteem – contributing to their overall well-being and future prospects, according to new research "Getting into the Game: Understanding the Evidence for Child-Focused Sport for Development" released by the Barça Foundation and UNICEF.

"It's long been understood that sport promotes children's health and physical development, but now we have solid evidence to suggest that sport can have a powerful impact on their overall education and life skills development," said UNICEF Deputy Executive Director Charlotte Petri Gornitzka. "We must use this evidence to inspire investment in sports for children, especially the most vulnerable."

The new report features analyses from global research literature and data from more than 300 sports for



*IJCP SUTRA 883: "Stress can tense your muscles, and constant tension of this kind can cause back pain. Thus, it is important to find ways to reduce stress."*

development (S4D) programs in 100 countries. Other highlights from the report include:

- Successful sport for development initiatives involve multi-sectoral cooperation, such as the inclusion of education and social components.
- Coaches play a critical role in safeguarding children and mitigating possible negative influences.
- There is little evidence to suggest involvement in sport reduces a child's risk of abuse and exploitation. In fact, when not done well, there are indications that some sports can increase exposure to violence.
- Better evidence is needed for the monitoring of sport for development initiatives, including more research on effective implementation.
- More meaningful child participation in program design and evidence building is needed.

(*UNICEF*)

### Improving TB Patient Care in the Russian Federation with Video-observed Treatment

To help tuberculosis (TB) patients keep to their gruelling treatment regimens, WHO recommends that the intake of medicines is observed, in person, by a health care worker, to support the patient in taking the medication regularly. However, ensuring daily face-to-face contact at a health facility can be challenging for both patients and health service providers. Digital technologies, such as video-observed treatment (VOT) can help meet this challenge.

In 2016, the city of Tomsk in Siberia, Russian Federation, started supporting TB patients using VOT, which allowed patients to take TB drugs under the care of a nurse via video calling software on smart phones. Each patient signs an informed-consent form to begin VOT and agrees to be available for their daily session in a quiet room. Based on the agreed schedule, a health worker initiates the call. The health worker also advises the patient on the appropriate storage of medicines, which is an important aspect of treatment success.

The program started with 6 patients and has grown to 88. Following the example of Tomsk, VOT is now available in other regions of the country, including Tyumen, Voronezh, Vladimir, Ivanovo and Arkhangelsk Oblast.

This treatment approach is considered a step forward in making care more people-centred and is valued by patients and nurses alike. VOT has been shown to improve access to TB treatment, support regular intake of drugs and treatment adherence, decrease the risks of occurrence of drug resistance and the spread of infection, and improve the overall quality of life for patients… (*WHO Europe*)

### A New Oral Testosterone Capsule for Treatment of Men with Certain Forms of Hypogonadism

The US FDA approved testosterone undecanoate, an oral testosterone capsule to treat men with certain forms of hypogonadism. These men have low testosterone levels due to specific medical conditions, such as genetic disorders like Klinefelter syndrome or tumors that have damaged the pituitary gland. The drug should not be used to treat men with "age-related hypogonadism," in which testosterone levels decline due to aging, even if these men have symptoms that appear to be related to low testosterone.

### AAP Report Advises on Therapy Services for Children with Disabilities

An American Academy of Pediatrics (AAP) clinical report "Prescribing Physical, Occupational and Speech Therapy Services for Children with Disabilities" published online has described how health care providers can best connect the rising number of children who have disabilities with evidence-based therapy services in hospital, community, home and school settings. The report highlights the importance of coordinating care with therapists to help children gain or recover key skills.

### Eating Later in the Day may be Associated with Obesity

Eating later in the day may contribute to weight gain, according to a new study presented at ENDO 2019, the Endocrine Society's annual meeting in New Orleans, Louisiana. On average, participants consumed food throughout an 11-hour timeframe during the day and slept for about 7 hours a night. People who ate later in the day slept at a later time, but they slept for about the same amount of time as those who finished eating earlier. Later meal timing was associated with a higher BMI as well as greater body fat.

### Low-dose, Low-frequency PUVA Treatment Safe and Effective in Mycosis Fungoides

Low-dose, low-frequency oral psoralen-ultraviolet A (PUVA) treatment, followed by maintenance, was safe and effective and can be used to treat early-stage mycosis fungoides with extended disease-

free intervals as shown in a study reported in *JAMA Dermatology*.

### Govt. Notifies New Rules for Drugs and Clinical Trials

Aimed at promoting clinical research in the country, the Health Ministry notified New Drugs and Clinical Trials Rules, 2019 reducing the time for approving applications to 30 days for drugs manufactured in India and 90 days for those developed outside the country. The new rules will ensure patient safety, as they would be enlisted for trials with informed consent. The ethics committee will monitor the trials and decide on the amount of compensation in cases of adverse events, Drugs Controller General of India (DCGI), S Eswara Reddy said.

"In case of injury to clinical trial subject, medical management will be provided as long as required as per the opinion of the investigator or till such time it is established that the injury is not related to the clinical trial."Also, compensation in cases of death and permanent disability or other injury to a trial subject will be decided by the Drug Controller General," Reddy said.

These rules will apply to clinical trial, bio-availability or bio-equivalence study, new drugs and regulation of ethics committee relating to clinical trial and biomedical health research. "The aim is to promote clinical research in India, have predictable, transparent and effective regulations for such trials and also make faster accessibility of new drugs to Indian population," he said… (*ET Health-PTI*)

### Ebola Outbreak in Eastern Democratic Republic of Congo Tops 1,000 Cases

As of March 24, 2019, public health officials documented that the Ebola outbreak in eastern Democratic Republic of Congo (DRC) had surpassed 1,000 cases; the total number of confirmed and probable cases being 1009, including 625 deaths and 318 survivors. The outbreak is the largest in DRC's history and the second largest outbreak recorded of Ebola ever (after the 2014-2016 outbreak in West Africa).

"This is a disappointing milestone. This remains a highly complex Ebola outbreak with active transmission in 13 of the 21 affected health zones," said CDC Director Robert R Redfield, MD "Despite this, CDC will continue to work 24/7 with our partners in DRC, in DRC's neighboring countries, and around the world to prevent the spread of Ebola and bring this outbreak to an end."

### Cabo Verde Launches First "Solidarity Chain" in Africa with a Flash Mob Promoting Universal Health Coverage

Led by the Cabo Verde's Minister of Sports and the WHO Regional Director for Africa, hundreds of people held hands and stood side by side in an umbrella shape on Quebra Canela beach in Praia to show their solidarity for universal health coverage.

The flash mob was organized through word of mouth and social media and was the first in Africa of many similar global events leading up to World Health Day on 7 April, with the "solidarity chain" reflecting the 2019 themes of solidarity and equity … (*WHO Africa*)

### Walking Downhill after Meals Boosts Bone Health in Postmenopausal Women with Diabetes

Walking downhill after eating can reduce bone resorption, the process in which old bone is broken down and removed from the body, in postmenopausal women with diabetes, according to research presented at ENDO 2019, the annual meeting of the Endocrine Society, in New Orleans, Louisiana. Walking uphill does not have the same benefit, the study found. An easy way to walk downhill is to walk down stairs.

### AAP/AHA Policy Statement to Reduce Consumption of Sugary Drinks in Children

In a joint policy statement published in *Pediatrics*, the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) endorsed a suite of public health measures including excise taxes, limits on marketing to children, and financial incentives for purchasing healthier beverages designed to reduce kids' consumption of sugary drinks. As per authors, teens who drink more than 10% of their daily calories from added sugars are more likely to have abnormal cholesterol levels, including higher "bad" LDL (low-density lipoprotein) cholesterol, higher triglycerides and lower heart-protective HDL (high-density lipoprotein) cholesterol.

The AAP and AHA recommend:

- Local, state and national policymakers should consider raising the price of sugary drinks, such as via an excise tax, along with an accompanying educational campaign. Tax revenues should go in part toward reducing health and socioeconomic disparities.
- Federal and state governments should support efforts to decrease sugary drink marketing to children and teens.



*IJCP SUTRA 885: "If you maintain good eating habits, you not only will maintain a healthy weight, but you also will not put unnecessary stress on your body."*

- Healthy drinks such as water and milk should be the default beverages on children's menus and in vending machines, and federal nutrition assistance programs should ensure access to healthy food and beverages and discourage consumption of sugary drinks.
- Children, adolescents and their families should have ready access to credible nutrition information, including on nutrition labels, restaurant menus, and advertisements. Hospitals should serve as a model and establish policies to limit or discourage purchase of sugary drinks.

## Children Develop PTSD when they 'Overthink' Their Trauma

Children are more likely to suffer post-traumatic stress disorder (PTSD) if they think their reaction to traumatic events is not 'normal', according to a new research published in the *Journal of Child Psychology and Psychiatry*. Children begin down this route when they have trouble processing their trauma and perceive their symptoms as being a sign that something is seriously wrong.

## Avocados Recalled in Six US States Over Listeria Concerns

CNN reported on March 25, 2019 that California-grown avocados sold in bulk to retail stores in six states by the Henry Avocado Corporation are being recalled due to potential contamination with the bacterium *Listeria monocytogenes*, the company announced recently.

"Henry Avocado is issuing this voluntary recall out of an abundance of caution due to positive test results on environmental samples taken during a routine government inspection at its California packing facility," reads the company's statement. There have been no reported illnesses associated with the recall at this time.

Listeria bacteria is especially concerning in pregnant women because they can cause miscarriage, stillbirth, premature delivery or a life-threatening infection in a newborn.

Others at risk for listeria infection are the elderly and individuals with weakened immune systems. Symptoms of listeriosis include fever, muscle aches, headache, stiff neck, confusion and loss of balance. Patients may experience diarrhea or other gastrointestinal symptoms, as well as convulsions. It can be treated with antibiotics… (*CNN*)

## Health Ministry Commemorates World TB Day

The Ministry of Health and Family Welfare commemorated the World TB Day with a function to mark the occasion, and reiterated the commitment to eliminating TB in the country by 2025.

Ms Preeti Sudan, Health Secretary, presided over the function. She stressed on the importance of more sensitive and responsive doctors, paramedics, frontline health workers and community partners, while dealing with TB patients. The systems of care for TB patients should be patient-centric, and sympathetic to their well-being, she emphasized. She stated that India has been able to be free of Polio, Yaws, MNTE due to the sturdy health systems, especially at the primary health care levels. She stated that partnerships with all stakeholders hold the key to making India TB-free.

Various presentations made at the event highlighted the key changes introduced in the policy landscape of TB in the country.

- India is now closest ever to covering all TB cases with 21.5 lakh new TB patients notified in 2018. With the aim of universal access to free diagnostics and treatment services, path breaking policy changes have been introduced.
- Universal drug susceptibility testing has been rolled out, and shorter and newer treatment regimen has been expanded countrywide.
- India is moving towards an injection-free regimen.
- Private sector engagement has been elevated as one of the highest priorities with strengthened regulatory measures, collaborative incentives and scale up of successful Patient Provider Support Agency (PPSA) interventions, which led to a 35% increase in TB notification from the private sector. The Nikshay Poshan Yojana has benefited 15 lakh TB patients for nutrition support with Rs. 240 cores disbursed as DBT since April 2018.
- A comprehensive call centre (1XXX-XX-6666) for information, addressing grievance, patient linkages and provider relationship has been established. Institutional system of award for TB-free status has been introduced to generate federal competitiveness, motivate and to bring about proactive actions from States and Districts.
- As on date, 15 lakh patients have been initiated in the Fixed-dose Combination (FDC) regime.

(*PIB, Ministry of Health and Family Welfare*)

### Replacing Sitting Time with Physical Activity Associated with Lower Risk of Death

A new study from the American Cancer Society suggests that replacing modest amounts of sitting time with even light physical activity may have the potential to reduce the risk of premature death among less active adults. For those who get the least amount of physical activity, replacing a half hour of sitting time with physical activity was associated with up to a nearly 50% reduction in mortality. These findings are published in the *American Journal of Preventive Medicine*.

### Avelumab + Axitinib Improves Progression-free Survival for Advanced Renal-cell Carcinoma

Progression-free survival was significantly longer with avelumab + axitinib than with sunitinib among patients who received these agents as first-line treatment for advanced renal-cell carcinoma in a trial published in the *New England Journal of Medicine*.

### Paternal Smoking may Increase the Risk of Congenital Heart Defects in Children

Fathers-to-be who smoke may increase the risk of congenital heart defects in their offspring, according to a meta-analysis published in the *European Journal of Preventive Cardiology*. All types of parental smoking were associated with the risk of congenital heart defects, with an increase of 74% for men smoking, 124% for passive smoking in women, and 25% for women smoking, compared to no smoking exposure.

### Ovary Function is Preserved in Transgender Men at 1 Year of Testosterone Therapy

Transgender men preserve their fertility potential even after 1 year of treatment with the male hormone testosterone, according to a study presented at ENDO 2019, the Endocrine Society's annual meeting in New Orleans, Louisiana. Even with the expected increase in testosterone blood levels and decrease in estrogen at 1 year of therapy, anti-Mullerian hormone (AMH) levels remained in the normal range for fertility. AMH levels are used to assess the ovarian reserve.

### Uterine Fibroid Embolization as Effective as Myomectomy

Uterine fibroid embolization (UFE) effectively treats uterine fibroids with fewer post-procedure complications compared to myomectomy, according to new research presented at the Society of Interventional Radiology's 2019, Annual Scientific Meeting. After an average 7-year follow-up, women who underwent myomectomy had a higher rate of post-procedural complications, including a 2.9% rate of blood transfusion versus 1.1% rate for women who were treated using UFE.

### Bond Service after MBBS not Necessary for PG Admissions

MBBS students in government medical colleges (GMCs) will be eligible for admissions to post graduate (MD/MS) courses without completing the 1-year bond service, at least for the next 3 years starting 2019-20.

The Bombay High Court has ordered that students who have been admitted to MBBS course up to October 12, 2017, can seek admission to PG courses without fulfilling the requirement of 1-year compulsory bond after MBBS course. They will complete their bond service after the PG course. The HC has clarified that students who have taken admission to MBBS course after October 2017 would have to complete their bond service before seeking admissions to PG. However, such candidates will apply for PG only after completion of their 4-year MBBS course, which is not before 2021-22. So, effectively, bond service after MBBS will not be a necessary clause till then… (*ET Health*)

### Study Shows Significant Rise in Psychiatric ED Visits for Children and Young Adults

A study in the April 2019 issue of *Pediatrics* shows that there has been a significant increase in psychiatric emergency department (ED) visits for children and young adults. Overall psychiatric visits were found to have increased 28% among children and young adults, ages 6-24 years. The largest increases occurred among teens, young adults and non-white youths.

### Optimizer Implant Now Available for CRT-ineligible Heart Failure

The US FDA has approved another device therapy for patients with chronic moderate-to-severe heart failure, the Optimizer Smart System. The specified indication is for improving 6-minute walk distance, quality of life, and other aspects of functional status of patients with symptomatic heart failure in sinus rhythm despite optimal medical therapy.

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*IJCP SUTRA 887: "Know your eGFR = 140 - age × weight in kg/serum creatinine × 72 (×0.85 in women)."*

Indian Journal of Clinical Practice, Vol. 29, No. 11, April 2019

# The Science Behind Death, Life After Death and Samadhi

KK AGGARWAL

As per Chandogya Upanishad, death is not instantaneous but an active process. The five Karmendriyas are the first to stop functioning. They are elimination (payu or excretory organ), reproduction (upastha or sexual organs), movement (pada or feet or the locomotor organ), act of grasping (pani or the organ of action, the hands) and speech (Vak or the speech organ). As per the Upanishad, when these five Karmendriyas stop functioning, it is called "Vak vriti". They stop functioning in sequence and speech is the last function to go.

In medical science, the first question we ask is "Can the person speak?" If the answer to this is yes, the process of death has not started yet.

The next to go are the five sense organs called Jnanendriyas. They are smell (ghrana or nose), taste (rasana or tongue), vision (caksu or eyes), touch (tvak or skin) and ability to hear (srota or ears). The Jnanendriyas also stop functioning in sequence and the last to go is hearing.

The next question to be asked is "Can the person hear?"

Once the ability to hear has gone, the next to go is "Manas", which includes mind, intellect, memory and ego.

When both the Jnanendriyas and Manas stop functioning, the situation is called "Manovriti". In this phase, the person cannot speak, hear and think.

Once the Vak vriti and Manovriti have stopped functioning, the next to stop functioning are the five Pranas.

Prana vayu (the upward moving force of the chest region responsible for respiration), Apana Vayu (the downward moving energy of the sacral region connected with the functions of excretion and reproduction), Samana Vayu (the laterally moving energy helping in digestive functions), Udana Vayu (the energy that compresses and causes deglutition and separates physical body from astral) and finally the Vyana Vayu (the energy moving in circles in the entire body and responsible for circulatory system).

These 'Vayus' too cease functioning with the 'Vyana Vayu' being the last to cease. Once all five Vayus cease to function, this is called "Prana vriti".

Therefore, medically the third question to be asked "Is the patient breathing?" If yes, is the circulation on?

The above sequence also explains the difference between the "brainstem death" and "death". In brainstem death, the Prana Vayu ceases to function but other vayus continue to function.

Once the Prana stops functioning, the Prana vriti merges with Tej (Tejas or to lose control of temperature regulation) and these merge in Sat (Sath). With this, life comes to an end.

The "Sat" may be taken as a state when the consciousness or the life force leaves the body.

At any stage, before "Tejas" merges with "Sat" death is reversible; before Prana vriti by putting a person on ventilator and at Tejas by creating therapeutic hypothermia.

In Ayurveda, there are three terms called Prana, Tejas (Tejesvi Bhava) and Ojhas (Ojhasvi Bhava). These represent the life forces and are consistent with the above observations. The nearest equivalent to Tejas is control of metabolism and temperature regulation. Till the Tejas is under control, life force cannot cease to function.

If hypothermia develops, medically or naturally, Prana vriti cannot merge with the Tejas, the life force can be kept preserved for a long duration. A person can be revived later by bringing back the body to a normal temperature and with proper resuscitation. In modern medicine, this is called therapeutic hypothermia.

A person in whom the Karmendriyas, Jnanendriyas, Manas and Prana have stopped functioning and if put

Group Editor-in-Chief, IJCP Group

in a state of therapeutic hypothermia, the person can be revived later after re-warming and cardiopulmonary resuscitation (CPR). CPR is revival of Vyana Vayu, which in turn revives Prana Vayu and Udana Vayu, which has not yet left the body by merging into Tejas.

The above sequential process also can explain the "near death" experiences. They depend at which stage the person was revived.

For example, if a person is revived at a stage of Vak vriti, he or she may recall experiences related to the motor organs. If the person is revived at a stage of Manovriti, he or she may recall experiences of both motor and sensory organs as well as experiences related to mind, intellect, memory and ego and if the patient gets revived at the stage of Prana vriti, he or she may recall the near death experiences linked to motor organs, sensory organs and breathing.

The process of death therefore is Vak vriti merging into Manovriti, Manovriti merging into Prana vriti and Prana vriti taking the heat of the body (Tejas) and merging into "Sat" and the "Sat" merges into "Brahamand" in the atmosphere. [Chandogya Upanishad 6.15.1]

## Samadhi

Samadhi is a state of oneness in body, mind and the soul. The process of Samadhi also involves the above process starting with control of Karmendriyas, then Jnanendriyas, followed by control of the mind (manas), then the control of Prana and finally the control on metabolism (Tejas) and lowering of body temperature.

At this state, the life force can be preserved for a long period and the person can revive back even after months. Samadhi has been practiced by Rishi Munis in Vedic literature but in natural environments on the hills.

## Food is Brahman

Motor organs, sensory organs, Prana (the life force) are all formed by the food we consume.

When ghee and oil in the food gets digested, it gets divided into three parts: The "crude" part makes bone, the "middle part" makes bone marrow and the "subtle" part makes the Karmendriyas (Vak).

When the non-fat part of the food is digested, it too gets divided into three parts: The "crude" part make the feces; the "middle part" Manas and the "subtle" part Jnanendriyas.

When the liquid part of the food is digested, it also gets divided into three parts: The "crude" part gets converted into urine, the "middle" part into blood and "subtle" into Prana.

This explains the process of fasting. A person can live without air for 3 minutes, without water for 3 days and without food for 3 weeks. The first effect of fasting unto death is cessation of speech then hearing and then the Prana.

The above is true in non Samadhi state. In the state of Samadhi, your metabolism may be so slow that you may live longer without food. Even today many Jain Munis live without food for months.

## Life After Death

As per Upanishads, the 'Sat' or the life force called consciousness remains in the atmosphere. After a variable period of time it will fall on to the earth through the rain drops when (the RNA and DNA) gets taken up by the food grains. Therefore, the term "food is Brahman".

When the appropriate father and mother eat that food, the life force enters in the ova and the sperm and from there the new life begins (Soul never dies: Bhagavad Gita 2.20).

This process of new birth is just the reverse of the process of death. In the process of death, the first to go is Vak vriti or speech and in the process of birth the last to come is Vak or speech.

This explanation, though, is difficult to explain in terms of modern science.

## The Science of Karma

Karmas in Vedic knowledge are described in three terms: Sanchita Karma, Prarabdha Karma and Agami Karma.

Every action results in a reaction. Action and the resultant reaction together is called a Karma. The end result can be positive or negative, depending upon the resultant reaction.

As per Vedic literature, the net negative Karmas get accumulated and need to be neutralized either in this birth or in the next birth. At the time of death, all the resultant accumulated negative Karmas, which remain to be neutralized, constitute Sanchita Karmas.

If the Sanchita Karmas constitute a high burden, then some of them, as instalment, are constituted as Prarabdha Karmas, which need to be neutralized in the coming birth.

Therefore, when a person is born, he is born with predefined Prarabdha Karmas. These need to be neutralized and faced in this life, while the left over

Sanchita Karmas are to be faced in the subsequent birth unless some of them are neutralized in this birth by good positive Agami Karmas.

Agami Karmas are day-to-day Karmas of this birth. If the net result of positive and negative Agami Karma is positive, they can neutralize the Sanchita Karma that form the basis of Vedic saying and recommendation of keep doing the good job. It also resolves the myth that if one's destiny is predefined in terms of Prarabdha Karma, why should one do good deeds.

According to Buddhism, one is born to suffer as per the number of Prarabdha Karma at the time of birth. Buddhist philosophy says that suffering exists, there is a reason for that suffering and one can live and make modifications to enjoy that suffering.

The purpose of life, therefore, should be to live our Agami Karma in such a way that they not only neutralize our Prarabdha Karma, but also the Sanchita Karma.

According to Bhagavad Gita, whatever you think throughout your life, will be your thinking at the time of death and whatever is the thinking at the time of your death, will be the type of womb you will get in the next birth (Bhagavad Gita 8.6, 8.7).

As per Prasna Upanishad (Mantra 10), whatever are one's thoughts (at the time of death) that thought remains with the outgoing Prana. Prana coupled with Udana and Atman, leads to whatever world has been conceived (in the last thoughts).

Prana joined with fire (Udana), together with the soul, leads to whatever world has been fashioned by thought.

The thinking at the time of death decides, which Karmas will form the instalment of Prarabdha Karma. Therefore, thoughts at the time of death decide the destiny of birth in the next generations.

So, as per Bhagavad Gita, one should be in a positive state of mind at the time of death. If spontaneous positive thinking is not possible, then every effort should be made to convert negative into positive thinking.

According to Bhagavad Gita, the best time to die is Uttarayana, before full moon in the day light or in an atmosphere of Yagna. The bad time to die is Dakshinayana, before Amavasya, in the night or in the dark.

To convert bad into good timing, the process of death should take place at home, in a lighted environment (artificial Dias, in the vicinity of Vedic hymns) in the company of positive thinking people. In that situation, the chosen Prarabdha Karmas out of the Sanchita Karmas will be positive and the life force with positive aura will enter into the womb of parents who are positive. In this way, even if you are born to suffer, you will suffer and yet not suffer.

*Note: The views written are my personal views and interpretations based on my literature search and knowledge acquired after interaction with many spiritual Gurus over the last many decades.*

■■■■

### London Gets World's First 24-hour Air Pollution Charge Zone

London is the first city in the world to implement a 24-hour, 7-day a week Ultra Low Emission Zone (ULEZ), inside which vehicles will have to meet tough emissions standards or face a charge, reported CNN.

The introduction of the zone aims to reduce toxic air pollution and protect public health, according to a press release from the office of Sadiq Khan, Mayor of London.

Under new rules introduced April 8, polluting vehicles will be discouraged from entering the ULEZ thanks to a daily charge of £12.50 (around $16) for some cars, vans and motorbikes and £100 ($130) for trucks, buses and coaches. The zone will cover the same area as the existing Congestion Charge - collected from drivers in the city center - until 2021, when it will be expanded to cover the area between the major orbital roads known as the North and South Circular… (*CNN*)

### Polluted Air Cuts Short Life Expectancy by 20 Months

The life expectancy of a child born today could be reduced by an average of 20 months due to health damage caused by air pollution. In South Asia, where air pollution levels are the highest, the life expectancy for children born in countries like Pakistan and Bangladesh falls by more than 30 months, according to the annual State of Global Air report, published by the Health Effects Institute, a US-based nonprofit research group, online… (*Medscape*)

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# No Regrets About Today

If I knew it would be the last time that I'd see you fall asleep, I would tuck you in more tightly, and pray the Lord, your soul to keep.

If I knew it would be the last time that I see you walk out the door, I would give you a hug and kiss, and call you back for one more.

If I knew it would be the last time I'd hear your voice lifted up in praise, I would video tape each word, so I could play them back day after day.

If I knew it would be the last time, I could spare an extra minute or two to stop and say "I love you," instead of assuming you would KNOW I do.

If I knew it would be the last time, I would be there to share your day, well I'm sure you'll have so many more, so I can let just this one slip away.

For surely there's always tomorrow to make up for an oversight, and we always get a second chance to make everything right.

There will always be another day to say our "I love you," And certainly there's another chance to say our "Anything I can do?"

But just in case I might be wrong, and today is all I get, I'd like to say how much I love you and I hope we never forget.

Tomorrow is not promised to anyone, young or old alike, And today may be the last chance you get to hold your loved one tight...

So if you're waiting for tomorrow, why not do it today? For if tomorrow never comes, you'll surely regret the day.

That you didn't take that extra time for a smile, a hug, or a kiss and you were too busy to grant someone, what turned out to be their one last wish.

So hold your loved ones close today, whisper in their ear, Tell them how much you love them and that you'll always hold them dear.

Take time to say "I'm sorry," "please forgive me," "thank you" or "it's okay." And if tomorrow never comes, you'll have no regrets about today. She has been there, and done that.

■■■■

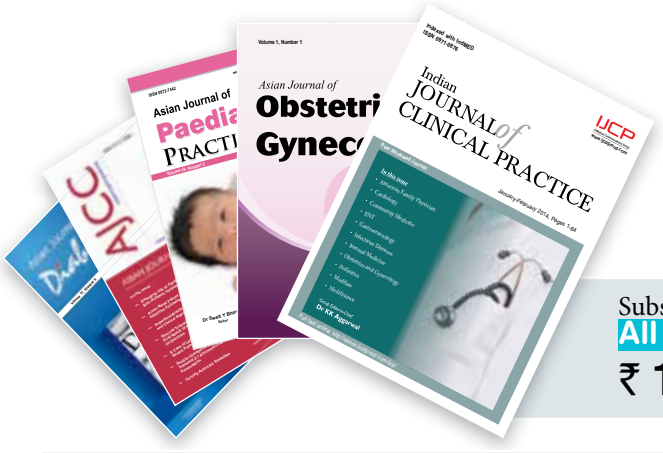
### Physicians may Overprescribe Antibiotics to Children During Telemedicine Visits

Children are more likely to be overprescribed antibiotics for colds, sinus infections and sore throats during telemedicine visits (52%) than during in-person visits to primary care providers (31%) or urgent care facilities (42%), suggests a study published April 8, 2019 in *Pediatrics*.

### ICMR National Ethical Guidelines for Biomedical and Health Research Now Becomes Mandatory

Indian Council of Medical Research's (ICMR) National Ethical Guidelines for Biomedical Research has become mandatory and needs to be adhered to for all biomedical research in the country as per the New Drugs and Clinical Trials Rules 2019 released recently by Ministry of Health and Family Welfare, Government of India. This will be effective after 180 days from the date of publication of Gazette.

- Any institution or organization which intends to conduct biomedical and health research shall be required to have an Ethics Committee (EC) which has been constituted, functions and maintains records in accordance to ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017. ECs shall review the research before initiation and oversee throughout the duration of the research.
- The EC shall be required to register with the Authority and the registration would remain valid for a period of five years from the date of its issue, unless suspended or cancelled by the authority. The ICMR National Ethical Guidelines will guide the ethical requirements for all institution that are engaged in such research whether it is medical colleges, research institutions, universities, public or private funded institutions, non-governmental organization or others (*ICMR Press release*)



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# Lighter Side of Medicine

HUMOR

## TOP SECRET COMMUNICATIONS CENTER

When my son was in the Air Force, my wife and I visited quite often. On our first visit, we were allowed inside this top secret Communications Center, but everything in sight was covered up so we could look around everywhere — Heck, even the toilet paper in the Men's room was disguised.

Anyway, at the exit, there's a sign above the door, which reads: "You have been exposed to Top Secret Material. Please destroy yourself before leaving the building."

## NEW DISEASE

A recent college graduate took a new job in a hilly Eastern city and began commuting each day to work through a tiring array of tunnels, bridges and traffic jams. Thinking it would make the trip more bearable, he invited several coworkers to share the ride. However, the commute actually got more stressful, especially the trips through the tunnels. He consulted the company doctor.

"Doc," the frustrated commuter complained, "I'm fine on the bridges, in the traffic, in the day and at night, and even when Joe forgets to bathe all week. But now, when I get in the tunnels with those four other guys crowded into the car, I get anxious and dizzy, and I feel like I'm going to explode."

Without further analysis, the doctor announced he had diagnosed the ailment. "What is it, Doc? Am I going insane?"

"No, no, no, my boy. You have something that is becoming more and more common." "Tell me! What is it?"

"You have what is known as Carpal tunnel syndrome."

## MISSING HOMEWORK

After teaching high school for nearly 20 years, I thought I'd heard every possible excuse for missing homework until one parent sent me this note: "Please excuse Lori for not having her algebra homework. The cat had kittens on it last night."

## SALES PRACTICE

The out-of-work newlywed took a temporary job as a vacuum cleaner salesman to make ends meet. After 3 days of intensive training, the sales manager told him to go home and practice his pitch on his wife.

The next morning, the manager asked the novice how he made out.

"Well," the man began, "I did what you said, and after I finished, I asked her if she would buy the vacuum cleaner from me. She said 'Yes.' Then I asked her 'Why?' She replied, 'Because I love you.'"

## WHAT IT MEANS

Five-year old Becky answered the door when the Census taker came by.

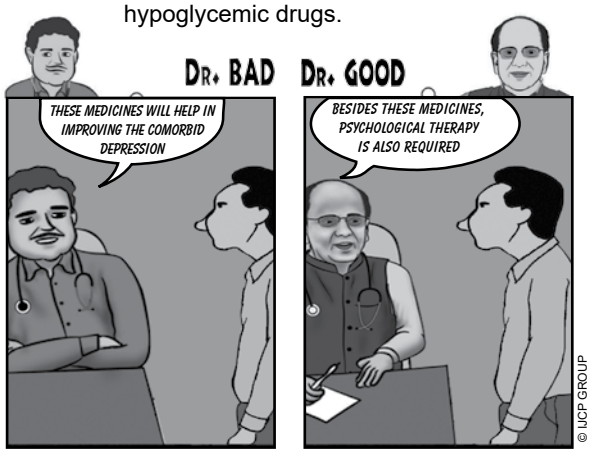
She told the Census taker that her daddy was a doctor and wasn't home, because he was performing an appendectomy.

"My," said the census taker, "that sure is a big word for such a little girl. Do you know what it means?"

"Sure! Fifteen hundred bucks and that doesn't even include the anesthesiologist!"

## Dr. Good and Dr. Bad

**SITUATION:** A man with type 2 diabetes and comorbid depression was advised to take oral hypoglycemic drugs.




**LESSON:** According to a meta-analysis, psychosocial intervention appears to be an effective approach and offers additional benefits for patients with type 2 diabetes and depression.

*Neuropsychiatr Dis Treat. 2017;13:2681-90.*

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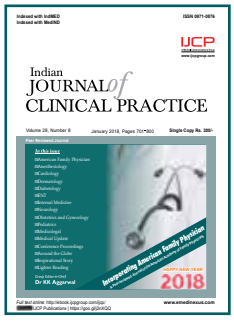

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**Dr KK Aggarwal**
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# Information for Authors

Manuscripts should be prepared in accordance with the 'Uniform requirements for manuscripts submitted to biomedical journals' compiled by the International Committee of Medical Journal Editors (Ann. Intern. Med. 1992;96: 766-767).

Indian Journal of Clinical Practice strongly disapproves of the submission of the same articles simultaneously to different journals for consideration as well as duplicate publication and will decline to accept fresh manuscripts submitted by authors who have done so.

The boxed checklist will help authors in preparing their manuscript according to our requirements. Improperly prepared manuscripts may be returned to the author without review. The checklist should accompany each manuscript.

Authors may provide on the checklist, the names and addresses of experts from Asia and from other parts of the World who, in the authors' opinion, are best qualified to review the paper.

## Covering letter

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- Principal/Senior author must sign the covering letter indicating full responsibility for the paper submitted, preferably with signatures of all the authors.
- Articles must be accompanied by a declaration by all authors stating that the article has not been published in any other Journal/Book. Authors should mentioned complete designation and departments, etc. on the manuscript.

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- All pages should be numbered consecutively beginning with the title page.

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Should contain the title, short title, names of all the authors (without degrees or diplomas), names and full location of the departments and institutions where the work was performed, name of the corresponding authors, acknowledgment of financial support and abbreviations used.

- The title should be of no more than 80 characters and should represent the major theme of the manuscript. A subtitle can be added if necessary.
- A short title of not more than 50 characters (including inter-word spaces) for use as a running head should be included.
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## Summary

- The summary of not more than 200 words. It must convey the essential features of the paper.
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## Introduction

- The introduction should state why the study was carried out and what were its specific aims/objectives.

## Methods

- These should be described in sufficient detail to permit evaluation and duplication of the work by others.
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- Method of allocating the subjects into different groups.
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## Results

- These should be concise and include only the tables and figures necessary to enhance the understanding of the text.

## Discussion

– This should consist of a review of the literature and relate the major findings of the article to other publications on the subject. The particular relevance of the results to healthcare in India should be stressed, e.g., practicality and cost.

## References

These should conform to the Vancouver style. References should be numbered in the order in which they appear in the texts and these numbers should be inserted above the lines on each occasion the author is cited (Sinha[12] confirmed other reports[13,14]...). References cited only in tables or in legends to figures should be numbered in the text of the particular table or illustration. Include among the references papers accepted but not yet published; designate the journal and add 'in press' (in parentheses). Information from manuscripts submitted but not yet accepted should be cited in the text as 'unpublished observations' (in parentheses). At the end of the article the full list of references should include the names of all authors if there are fewer than seven or if there are more, the first six followed by et al., the full title of the journal article or book chapters; the title of journals abbreviated according to the style of the Index Medicus and the first and final page numbers of the article or chapter. The authors should check that the references are accurate. If they are not this may result in the rejection of an otherwise adequate contribution.
Examples of common forms of references are:

### Articles

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.

### Articles in Books

Strong MS. Recurrent respiratory papillomatosis. In: Scott Brown's Otolaryngology. Paediatric Otolaryngology Evans JNG (Ed.), Butterworths, London 1987;6:466-470.

## Tables

– These should be typed double spaced on separate sheets with the table number (in Roman Arabic numerals) and title above the table and explanatory notes below the table.

## Legends

– These should be typed double spaces on a separate sheet and figure numbers (in Arabic numerals) corresponding with the order in which the figures are presented in the text.

– The legend must include enough information to permit interpretation of the figure without reference to the text.

## Figures

– Two complete sets of glossy prints of high quality should be submitted. The labelling must be clear and neat.

– All photomicrographs should indicate the magnification of the print.

– Special features should be indicated by arrows or letters which contrast with the background.

– The back of each illustration should bear the first author's last name, figure number and an arrow indicating the top. This should be written lightly in pencil only. Please do not use a hard pencil, ball point or felt pen.

– Color illustrations will be accepted if they make a contribution to the understanding of the article.

– Do not use clips/staples on photographs and artwork.

– Illustrations must be drawn neatly by an artist and photographs must be sent on glossy paper. No captions should be written directly on the photographs or illustration. Legends to all photographs and illustrations should be typed on a separate sheet of paper. All illustrations and figures must be referred to in the text and abbreviated as "Fig.".

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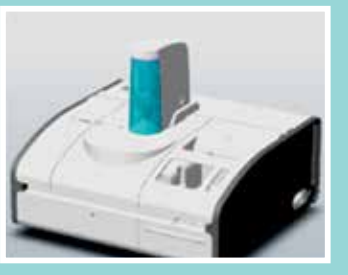

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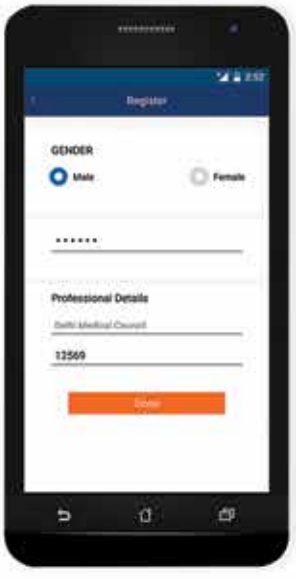


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