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*Editorial*

# DIGITAL HEALTH TECHNOLOGIES : NEED OF THE HOUR

**JK Panda[1], SK Dhar[2]**

Digital health technologies—ranging from wearable sensors and portable diagnostic technologies to tele-medicine tools and mobile health care apps—have the potential to transform the health care delivery system by empowering consumers to play an active role in their care and define what services are important to them. They also can help health care providers, insurers, and others analyze a growing body of data to identify unmet needs and measure treatment outcomes to better tailor patient interventions.

Technology-enabled care delivery also may help constrain health care spending and can play a role in payment models that hold health care providers accountable for the quality and costs of care. There has been an influx of venture capital to support the development of tools, such as data-mining applications, that can be used by accountable care organizations and oth-ers working to improve the efficiency and effectiveness of their operations. Still, there are significant barriers to the development and adoption of effective digital health technologies. This report outlines these challenges and makes recommendations for overcoming them, with the explicit goal of encouraging clinicians, developers, and entrepreneurs to focus on the needs of patients with complex and costly medical and behavioral health conditions.

Such technologies will work toward achieving the vision of the triple aim: improving population health, improving care experiences, and reducing per capita costs of care. These include:

- Defining opportunities by focusing on the nation's greatest health and delivery system problems.
- Closing knowledge gaps among consumers, technology developers, entrepreneurs, health care executives, and investors through networking and learning events.
- Creating test beds in care settings to validate the impact of innovations on quality, outcomes, and costs as well as on clinical and consumer experiences.
- Enabling consumer-centered design and valuations of new technologies.
- Addressing barriers to uptake, including operational factors and challenges related to an evolving reimbursement and policy landscape.

Change is likely to come from a confluence of approaches that enable better communication, coordination, and more accessible and cost-effective modes of care. Given this, it is crucial that those seeking to improve care delivery—from developers, entrepreneurs, and investors to researchers, frontline clinicians, and consumers—work together to focus their efforts on areas of greatest opportunity.

**Reference :**

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1. Editor OPJ, Asso. Professor, PG Dept. of Medicine SCB Medical Cuttack
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*Original Article*

# CORRELATION OF C-REACTIVE PROTEIN LEVEL WITH CD4 CELL COUNT AND CLINICAL STAGING IN PLHA AND COMPARISON OF ITS VALUE WITH PRE AND POST ANTIRETROVIRAL THERAPY

**S. Mohanty[1], B. Parija[2], B. Sethy[3], S.N. Jena[4], N. Saif[1], T. Padhy[1]**

## Introduction

HIV infection/AIDS is a global pandemic, with cases reported from virtually every country. In 2014, an estimated 36.9 million individuals were living with HIV infection according to the Joint United Nations Programme on HIV/AIDS(UNAIDS).[1] The worldwide epidemic of Human Immunodefeciency Virus (HIV) is an international health problem of extraordinary scope and unprecedented urgency. AIDS has an adverse health outcome of profound importance for the individual, family and society.

The determination of CD4 count has become a standard measure of immunodeficiency in adults infected with HIV in resource rich areas where the burden of the pandemic is low.[2] Even though in the recommendation for public health approach 2010 revision by WHO suggests that all patients should have access to CD4 cell-count testing to optimize pre-ART care and ART management and HIV-RNA(viral-load) testing to confirm suspected treatment failure this has not come into routine practice especially in the resource limited settings due to its high economical burden.

The cost of routinely monitoring CD4 T-cell lymphocytes and HIV plasma viral load are prohibitively high for many resource-poor settings, and less-expensive assays may be useful in these situations to guide HIV care and treatment.[3] In India, a CD4 count and a HIV viral load cost approximately US $30 and $100 per blood sample, respectively. Meanwhile a CRP test approximately costs $2 per blood sample. Thus a CRP test is approximately one-fifteenth the cost of an HIV viral load.

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Higher CRP levels have been associated with lower CD4 cell counts and higher HIV RNA levels among HIV infected individuals,[4] but results from studies evaluating serum CRP as a predictor of mortality in resource-rich settings are conflicting. Studies have reported significant associations between increased CRP concentrations and faster time to AIDS and greater risk of mortality, but did not use clinically established CRP cut-off concentrations.

This study was taken up to find out the credibility of CRP level in disease progression in pre and post HAART therapy in PLHA.

## Aims and Objectives

- To study the level of CRP and CD4 cell count and staging of HIV in all newly diagnosed PLHA prior to starting HAART.
- To study level of CRP and CD4 cell count and staging of HIV patients 6 months post HAART.
- To establish a relationship between CRP level and CD4 cell count in HIV positive patients.

## Materials and Methods

It was a prospective study of two years conducted at the ART clinic, MKCG Medical College Hospital, Berhampur. More than 150 patients admitted in the hospital during the study period were examined for eligibility for enrolment in the study.

## Inclusion Criteria

- HIV patients admitted to department of general medicine MKCG Medical College and Hospital during the study period
- All patients above the age of 18 years who are HIV positive and attending the ART Centre.
- HIV positive patients who require HAART for the first time.

## Exclusion Criteria

- Patients who have been on ART earlier
- Patients below 18 years of age
- Patients on immunosuppressant therapy
- Patients who are critically ill or who have proven malignancy

Based on the above mentioned criteria 120 patients were enrolled in the study. All were ART naive. Out of these, 110 patients were followed up for 6 months (61 patients asymptomatic and 49 patients with some oppurtunistic infections)

**Methods**

The diagnosis of HIV infection was made by

- Detailed history and physical examination
- Routine laboratory investigations including HIV ELISA and Western blot

Venous samples were sent for CD4 count. At the same time, samples were sent for evaluation of CRP. CD4 count was obtained by flow cytometry by using BD FACS Calibur CD4 counter. CRP levels were obtained using immunoturbidometric assay on Hitachi 917 analyzer(Roche Diagnostics).

These patients were followed up and the parameters re evaluated after 6 months.

SPSS 21.0, GraphPad Prism and Microsoft Excel were used to analyze used to analyze the data. Linear regression was carried out. Pearson correlation coefficient was also reported. Chi square test and paired t test were done to establish correlation between CRP and oppurtunistic infections. The results are represented in numbers and percentages for categorical data and average and SD for continuous data in tables and figures. P value <0.05 was taken to be statistically significant.

**Observations**

Maximum number of patients (42.73%) are within the age group of 26 to 35 years followed by 36-45 age group (30.91%) whereas minimum number of patients were in the age group of 56-65 years.

Majority of patients were less educated (illiterate or primary educated). Most of the male patients were labourers (28.81%) followed by semiskilled workers (15.25%), entreprenuers(13.56%) and drivers(11.86%). Housewives (52.94%) constituted majority of the female patients in the study group followed by labourers(39.22%). Lowest representation was from the group of domestic servants, and farmers each constituting 2%. Most of the patients were married (81%), followed by widow/widower(13%), unmarried(5%) and divorcee(1%). Out of the 110 patients 104 were married and 50.96% of their spouses were positive for HIV. Among the married patients 52.88% have given a history of extramarital contact. 55% of the patients had some addiction most common being alcohol with tobacco chewing (29%). Majority of the patients were on TDF+LMV+EFV(79.09%) followed by ZDV+LMV+NVP(14.55%), ZDV+LMV+EFV(4.55%) and TDF+LMV+NVP (1.82%). Most of the patients were asymptomatic at presentation except for some fatigue(55.45%). Most common oppurtunistic infection was tuberculosis(55.10% of the oppurtunistic infections). Mean CD4 among the asymptomatic group was 338cells/cumm and CRP 1.26mg/dL. Mean CD4 in patients with oppurtunistic infection was 181cells/cumm and CRP 3.6 mg/dL. With treatment most of these patients were without any oppurtunistic infection by 6 months(91%).

Number of patients having CD4 count <200 at 0 month was 47 and it decreased to 17 after 6 months of treatment. Number of patients with CD4 count >350 at 0 month was 18 and it increased to 66 after 6 months.

Number of patients having CRP<1 at 0 month was 35 and it increased to 75 at followup. Similarly CRP >3 was found in 31 patients which decreased to 2 patients at follow up. The difference observed in CRP levels at the beginning and at follow up was found to be statistically significant.($p<0.0001$ , 95% CI was 1.095-1.700)

At the beginning of the study the mean CRP was 2.3mg/dl and the CD4 was 268cells/cumm. After 6 months mean CRP decreased to 0.9mg/dl where as mean CD4 increased to 425cells/cumm. At the beginning, the Pearson correlation coefficient r for CD4 and CRP was -0.4194($p<0.0001$). the linear regression coefficient (â) was -46.57; that is for each 1% increase in CRP there was 46% decrease in CD4 count. The model was capable of explaining 17.59%(coefficient of determination-adjusted $R^2$) of the variation. At 6 months it was observed that $R^2$=0.1938, the Pearson correlation coefficient r for CD4 and CRP was 0.4402($p<0.001$).

The linear regression coefficient (â) was -141.8; that is for each 1% increase in CRP there was a 141% decrease in CD4 count. The model was capable of explaining 19.38%(cofficient of determination-adjusted $R^2$) of the variation.

The decrease in CRP and incidence of oppurtunistic infections were also found have a correlation which is statistically significant ($p<0.006$).

**Discussion**

In our study, which included 110 patients, the baseline characteristics of the patients were comparable in terms of age, sex, marital status, economical status, extramarital contact, occupation and clinical presentation. The mean age of patients in our study was 33.5 years(ranging from 18-65 years). This is consistent with a study done by KV Ramana et al[5] in the year 2011 at Hyderabad(mean age 33 years). Among the patients, 84% had a CD4 count <350/cumm at the beginning. 68% of our patients showed a raised CRP i.e > 1 mg/dL and remaining had a normal CRP i.e. <1 mg/dL at 0 month. HIV being a state of chronic inflammation and increased incidence of oppurtunistic infection most of the patients in our study group had a raised baseline CRP. The mean CRP of 2.3 mg/dl decreased to 0.9mg/dl at the end of 6 months. Whereas the mean CD4 count increased from 268cells/cumm to 425cells/cumm by 6 months of treatment. The correlation between CD4 count and CRP at initial visit was evaluated and found to have significant negative correlation. The study showed that a cut off value of CRP of 1 mg/dl equals a CD4 count of 328cells/cumm. Conversely a CD4 level of 200 corresponds to a CRP level of 3.75 mg/dl in ART naive patients. When these patients were followed up for a period of 6 months with treatment it was found that the correlation persisted. Few studies have examined credibility of CRP as a predictor of AIDS, oppurtunistic infection or mortality in HIV infected patients. A cohort study done by Bryan Lau et al[5] in Baltimore, Washington DC in 2006 found that the CRP concentrations were inversely correlated with CD4 lymphocyte count ($r=-0.17$; $p<0.001$) and directly correlated with HIV RNA levels ($r=0.20;p<0.001$), findings similar to our study. Levels of CRP of more than 2.3 mg/dl were associated with a decreased time to the development of AIDS(relative time to AIDS, $0.36;p<0.001$) compared to individuals with CRP levels of 1.2 mg/dl or less. A cross sectional study done by Tahir A et al[6] in Maiduguri, Nigeria in 2013 found that a strong linear negative correlation between CRP and CD4 cell count in HIV infected patients as was observed in our study. The Pearson's product moment correlation coefficients (r) for the correlation between CRP and CD4 cell count were -0.596 ($p<0.001$). The diagnostic usefulness of the CRP measurement as a surrogate for CD4 cell count showed sensitivity, specificity and positive predictive values of 80.6%, 72.4% and 75.8% for HIV patients. Therefore, serum CRP level of >1 mg/dl in HIV infected patients, can be used to predict low CD4 cell counts in resource poor locations lacking the facility for measuring CD4 cell count. Similarly KV Ramana et al[5] in Hyderabad, India in 2013 found significant inverse relation between CRP and CD4 cell count ($r -0.341;p<0.001$) and predicted CD4 cell count <200 cells/cumm at a CRP level of 1.2mg/dl.

Nagesh YW et al[7] in Banglore, India in 2012, found that CRP and CD4 count exhibits significant negative correlation ($r = -0.2324,p<0.02$). A normal CRP indicated a CD4 level of 329cells/cumm and a CD4 count of 200cells/cumm equals to a CRP level of 9.24mg/dl. CRP was elevated in patients with oppurtunistic infection whereas CRP was normal in asymptomatic patients. PK Drain et al[8] in 2007 found that elevated CRP concentration was predictive of HIV disease progression and mortality, independent of anthropometric measurements, CD4 cell count, and plasma viral load. In addition, a high post-partum maternal CRP concentration was predictive of child mortality, but not HIV transmission. CRP is a simple and inexpensive test that can be used in many ways to develop clinical decision making tools in underserved resource poor settings during HAART therapy. The pattern of CD4 cell counts over time is more important than any single CD4 cell count value. CD4 cell count generally decreases as HIV progresses. Therefore it is more valuable to evaluate a series of CD4 cell counts than any single count. As the CD4 count is affected by the time of the day(lower in the morning), in acute illness, refrigeration of blood sample(increases CD4 cell counts) or with rough handling or contamination of blood sample, serial recording of CRP can give as equally stable reflection of progression of disease and development of AIDS in HIV positive patients.

## Conclusion

This study suggests physicians and auxiliary health care workers may readily be able to monitor patient after initiating ART without having concerns that ART use may affect the utility of CRP. It also provides new evidence that for patients on ART, CRP and other simple measures may be used in making clinical decisions, such as commencing prophylaxis for oppurtunistic infections, referral to a physician at a district hospital, and possibly even change in ART regimen depending on the level of care especially in resource limited setting like Odisha.

For specific populations (and specific clinical/ public health strategies), appropriate calibration with local (or applicable) data to obtain an optimal cut-off for CRP will be required in building the model and developing the predictive instrument in future.

Limitations of this study include the modest sample size and though the two groups- asymptomatic vs symptomatic were comparable, were not exactly the same to correlate between pre-ART and post-ART status. These findings suggest that rather than using CRP level due to concerns of diagnostic utility, further research is needed to define optimum cut-off values and should preferably be longitudinal with a much larger sample size. Region specific validation of CD4 and CRP changes on HAART are also needed.

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*Original Article*

# ASSOCIATION OF HUMAN PAPILLOMA VIRUS INFECTION WITH BACTERIAL VAGINOSIS, IN CASES AND CONTROLS : AN ONGOING STUDY AT AHRCC, CUTTACK

**P. Patnaik[1], B. Nayak[2], D. Soren[3], P. Patra[4]**

**Abstract :**

Bacterial vaginosis is one of the most prevalent causes of abnormal vaginal discharges, affecting women of reproductive age. This infestation is characterized by loss of indigenous lactobacillus predominant vaginal micro flora and a concurrent massive growth of anaerobic bacteria. The most common anaerobic organisms are Gardnerella vaginalis, Mobiluncus species, Prevotella, Mycoplasma and Atopobium species. BV increases the risk of upper genital tract infection and adverse outcomes of pregnancy. Association between BV and cervical HPV has been inconsistent among studies conducted so far. The objective of this particular research is to clarify and summarize the co-relationship of human HPV infection with BV: In cases and controls respectively.

**Keywords :** Bacterial vaginosis, Human papilloma virus, anaerobic bacteria.

**Introduction :**

**Pathogenesis of BV :**

The search for a single organism to explain the pathogenesis of BV has been unrewarding although Gardnerella vaginalis is found in almost all women with BV, it s also present in 50% of healthy vaginal flora. Mobiluncus species, a highly motile curved bacillus is found only when BV is present, but in only 50% of cases of BV. Atopobium vaginae, is a gram positive anaerobe which like Gardnerella vaginalis, is found in the flora of over 95% of BV cases, but also occurs in the vagina of healthy women. Both Mobiluncus species and Atopobium vaginae have high level resistance to metronidazole, and have been implicated in treatment failures with this agent. Numerous other anaerobes, particularly Prevotella species, and various anaerobic Streptococci are common participants' in BV flora. Perhaps the most enlightening work on BV organisms was provided by Fredrick and Colleagues. Using nucleic acid amplification techniques for bacterial 16SrDNA, these investigators identified 9-17 anaerobic phylotypes(mean, 12.6) per vaginal sample from 27 women with BV and 58% were novel (previously uncultivated) organisms in such unfamiliar genera as Megasphaera and Sneathia. Moreover, 3 newly recognized species in the order Clostridiales were the most specific for BV. Liners, a non hydrogen peroxide producer was found commonly in the BV flora. A number of biochemical and micro-environmental changes have also been described in BV. Increased availability of the substrates ,raised in pH and loss of Lactobacillus species, where implicated for BV because the vagina of normal women were predominantly inhabited by Lactobacillus species that produced hydrogen peroxide which play an important role in suppressing the overgrowth of anaerobes either directly or by producing a hydrogen halide complex catalyzed by naturally occurring cervical peroxidase. Following the anaerobic bacteria overgrowth, there will be an elevated polyamine production by the anaerobes, enhanced by the decarboxylases which broke down the vaginal peptides into polyamines. These polyamines along with vaginal organic acid are cytotoxic to the vaginal cells, leading to the vaginal cells exfoliation manifesting as vaginal discharge which is malodorous and volatile due to its high amine content. Polyamines act to facilitate the transudation of vaginal fluid and exfoliation of epithelial cells, creating a copious discharge and elevated pH. Clue cells are formed when Gardnerella vaginalis present in high numbers. The normal vaginal epithelium is covered by a thin layer of mucin. In BV this presumed protective layer is replaced

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by a Gardnerella vaginalis specific biofilm.â defencin-1 and 2 mRNA and secretory leucocytes protease inhibitor concentrations are depleted in BV. Interleukins (IL 1 á, 1â) are increased, and levels of IL-8 are depressed. Increases in 70 kD heat shock protein, lytic enzymes, nitric oxide and endotoxin are found in the vagina in BV. In aggregate, these events deprive the vagina of normal protective mechanisms and increase destructive and inflammatory influences. (Cherpes et al 2008)

**Mechanism of HPV infection in the cervix :**

Innate and cell mediated immunity are important for control and resolution of HPV infections. HPV can suppress or hide from protective immune responses. In addition to very low levels of antigen expression the keratinocyte is an immunologically privileged site for replication. The L1 protein of HPV is the viral attachment protein and initiates replication by binding to $\alpha$6 integrins and heparin proteoglycans, the membranes of the lower basal keratinocytes and especially those of the transformation zone of the cervix on the cell surface. This is an area of immature epithelial cells that are especially hormone sensitive in women of reproductive age groups and thus are susceptible to infections and mutations. As basal cells differentiate and progress to the surface of the epithelium HPV DNA replicates and is transcribed and viral particles are assembled in the nucleus. Ultimately complete virions are released tightly associated with the remnants of the shed dead keratinocyte shell. Normal appearing epithelium may contain HPVDNA and the presence of residual DNA after the treatment of warts may lead to recurrent disease. In benign lesions caused by HPV, viral DNA is located extrachrosomally n the nuclei of infected cells however when HPV DNA is detected in high grade intraepithelial neoplasias and cancers, it is generally integrated. Integration oh HPV DNA may occur at preferential sites in host cell chromosomes and it specifically disrupts the E2 ORF. Interruption of E2 probably plays a role in the pathogenesis of malignant disease because expression of this ORF normally leads to down regulation of E6 and E7. E6 and E7 genes of the high risk HPV types are by themselves true oncogenes since when they transfect normal keratinocytes invtro, they can induce carcinogenesis: their products interact and inactivate tumor suppressor proteins, such as p53 and retinoblastoma protein with concomitant release of E2F transcription factor. As a consequence of the above, p16INK4A and telomerase expression is unregulated, cyclin inhibitors are inactivated and cyclins are activated and chromosomal instability and aeuploidy and apoptosis evasion occur. In warts or condylomata, viral replication is associated with proliferation of all epidermal layers except the basal layer. This leads to acanthosis, parakeratosis, hyperkeratosis and deepening of rete ridges, creating the typical papillomatus cytoarchitecture seen histologically. Some infected cells undergoes the characteristic transformation of koilocytosis. With histology, koilocytes are large usually polygonal, squamosal cells with a shrunken nucleus lodged inside a large cytoplasmic vacuole (Huh et al, 2009). Cytoplasmic keratohyalin inclusion bodies may also be observed. Excessive proliferation of the basal like cells with a high nuclear /cytoplasmic ratio, accompanied by a high number of mitoses, some abnormal s a feature of incipient and premalignant disease.

**Co-relation of BV with HPV infection and CIN**

The possible relationship between bacterial infection and cervical epithelial lesions has been proposed in the 1970s. Most of the studies have shown that bacterial vaginosis occurs significantly in patients with cervical precancerous changes or early cancer as opposed to women with normal cervixes. Barten found BV in 54% of women with cervical precancer or early cancer compared with 38% of controls. Neuer and Menton demonstrated Gardnerella vaginalis and Mycoplasma in 22% of 216 patients with cervical intraepithelial neoplasia (CIN) 1- 3 and in 5% of symptom free controls. In a retrospective re-examination by Dr. JensPlatz-Christensen of 6150 Papanicolau stained smears for clue cells, the relative risk of CIN III/ carcinoma in-situ if the women had BV was 5.0 with 95% confidence interval of 2.2- 11.6. CIN was found in 5% of these women with vaginosis as compared with 1.4% of the women without vaginosis. Morever when early stage CIN was excluded, second and third stage CIN occurred in 2.9% of the patients with bacterial vaginosis but only 0.4% of those without this infection. However this study did not include a control for the presence of HPV nor other STDs. Studies by Boyle(1998) and Guijon(1992) have shown

a higher incidence of dysplasia in women with BV. In a study Eltabbakh(1995) have found that 50% of women with cervical abnormalities at Pap smear test had a cervicovaginal infection, 28% of which were BV. However Peters et al in uncontrolled study of 280 women with dyskaryotic cervical smears, failed to confirm these findings. In all these studies smoking and sexual behaviour are possible confounding factors in establishing an etiological link. BV is associated with major changes in the vaginal environment. Because women with BV posssess a Lactobacillus-poor flora, their changes in the vaginal ecosystem may provide biological plausibility for an increased risk or reactivation of HPV infection.

Mucolytic enzymes, musinases including those which degrade terminal carbohydrate residues or those which disrupt the mucin apoprotein primary structure are produced by some bacteria associated with BV. Previous work has shown that the presence of glycosidases, including sialidase, is frequently associated with BV. Sialidases remove terminal sialic residues in various sialoglycocongugate carbohydrate chains and as the negative charge in these molecules is lost this may affect visco-elasticity in mucins or other binding properties associated with sialocongugates. This may partially explain the thin nature of the vaginal discharge frequently associated with this condition. Till date sialidase is the only enzyme with mucinase activity suggested as a virulence determinant of BV associated micro-organisms, Prevotella and Bacteroides spp. Intensive production of hydrolytic enzymes in BV might lead to diminished mucosal barrier protection through disruption of secreted mucus visco-elasticity and deglycosylation of the apical cell surface glycocalyx. In addition key enzymes produced in BV may degrade the mucosal barrier, mediate bacterial adhesion to host surfaces, and provide energy sources for the bacteria, thus enhancing bacterial colonization of the mucosa. Another hypothesis proposes that mucin-degrading enzymes are increased in vaginal fluid of women with BV. These enzymes, like sialidases play a role in degradation of the gel layer coating the cervical epithelium, causing micro-abrasions or alterations of epithelial cells. Such enzymes may promote virulence through destroying the protective mucosa barrier and hence increase susceptibility to cervical HPV infection by facilitating adherence, invasion and eventually incorporation of HPV oncogenes into the genome of cells of the transformation zone. Both nitrites and aminases, the elements for nitosamine synthesis are produced by the abnormal and predominant anaerobic vaginal flora of patients with BV. As abnormal microflora can also stimulate the release of cytokines, such as interleukin-1â, which has been suggested to be important in the development of cervical cancer. Pavic et al suggested that locally produced nitosamines may act synergistically with other etiological agents in the development of cervical neoplasia. Carcinogenic nitrosamines increase the probability of DNA damage and an altered cytokine profile may reduce immune systems ability to eliminate HPV infection. Thus the changes may create a condusive enviorenment for cancer development. In support of this, increased levels of IL-1á were seen in the cervical mucous of pregnant patients with BV. Furthermore, cervical mucous from these women with BV induced production of IL-6 from monocytic cells in-vitro. In another study a shift to TH2 cytokines was observed with increasing grades of cervical dysplasia. Therefore changes in the microbial flora, cytokine profile, or both may predispose to cervical dysplasia. (Pavicic et al 1984)

It has also been suggested that a raised vaginal pH may arrest squamous metaplasia in the post pubertal cervix and prolong the period in which the transformation zone is vulnerable to agents promoting dysplasis such as human HPV. Therefore, BV will interact with HPV infection with the cosequence of higher risk of developing cervical cancer among those with BV and HPV-infection than those with a mono-infection. However other infections for instance Candida was not associated with the development of CIN or cervical carcinoma. (Warner et al, 2003)

**Analyzing host immunity in patients with BV and CIN**

Patients especially with BV and CIN are known to exhibit raised levels of interleukins, IL-1, IL-6, IL-8, IL-10 and nitric oxide in both endocervical and vaginal secretions. Bacteria associated with BV produce minute amounts of lactic acid, while producing massive amounts of immunomodulatory products such as proteases, sialidases, succinate, and posses other inflammatory substances such as peptide-glycans, lipopolysaccharides etc. The above mentioned proinflamatory cytokines

produced in response to the above substances and components promote the growth of neoplastic cells both in vivo and invitro. The elevated levels of IL-6 and IL-8 may play a part in tumor angiogenesis and promoter of neoplastic growth. However such inflammatory events may also be promoted by certain factors such as personal hygiene and sexual activities and thus these two factors were also cofounders of cervical carcinoma(Morris et al, 2001) The purpose of establishing BV as the main driving factor for the activation of inflammatory cascades with sidewise development of cervical carcinoma remains elusive. The role of infectious agents such as BV in particular in up regulating integrin expression, should also be elucidated. It has been established that integrin expression was regulated by cytokines, such as transforming growth factors like TGFâ, the signaling pathway of which was hypothesized by microbial components acting through TLRs. On activation TGFâ will stimulate the expression of integrin which will play a role in cervical carcinoma pathogenesis by recruiting and phosphorylating focal adhesion kinase which in turn activates JNK with P13K phosphorylation. This will culminate in activation of protein kinase B/AKB, Rac and extracellular ERK. Since these events regulate the cell cycle up regulation of â6-integrin will promote tumorigenesis through perpetuating the proliferation and survival of cancer cells.

**Materials and Methods**

**Place of research :** This prospective study was funded by DST, Odisha, and was conducted in the Department of Gynecologic Oncology, AHRCC, Cuttack in collaboration with the Departments of Oand G, Microbiology, and Pathology SCBMCH, Cuttack along with the Virology Laboratory of RMRC,Bhubaneswar.

**Study Population :** Women aged between 19-49 years attending the gynecologic OPD of SCBMCH and AHRCC, Cuttack were included in the study and consent was obtained from the women who were included in the prospective study.

**Exclusion Criteria :** The following women were excluded in the study such as:

a) Unmarried women

b) Pregnant women

c) Vaginal bleeding at the time of clinical examination

d) Women who have undergone hysterectomy

Preparation of questionnaire: A research questionnaire was obtained from the participating women regarding their socioeconomic status, age of sexual debut, number of sexual partners during their life time, current contraception method, and history of STDs if any.

**Collection and Processing of Specimen:**

a) 3 high vaginal swabs were collected from each patient by sterile cotton tip swabs from posterior vaginal fornix, the swabs were dipped in 0.5ml normal saline and the characteristics of vaginal discharge such as color, nature, consistency, odor etc were recorded. The material from the cervix was collected using Ayres spatula around the external os including squamocolumnar junction by 360% rotation with minimum pressure and uniformly spread by rotator smear technique on a single glass slide permanently marked by a diamond pencil. The slide was then immersed in a fixing solution and was allowed to remain in the fixative for at least half an hour to ensure adequate fixation and then stained by Papanicolau technique and evaluated under Bethesda III system for specimen adequacy and general categorization. Additional endocervical cells were collected using a Dracon swab and was transferred into tubes containing PBS stored at 70% until further processing. Extraction of total DNA, was done using QI Amp DNA mini kit according to manufacturer's instructions.

b) pH of vaginal discharge was recorded at the OPD using standard pH indicator paper with a range of 2-10.5.

c) The amine test was performed by adding a few drops of 10% KOH solution directly over the soaked swab to detect if there was any emission of amine like odor.

d) Clinico-microbiological diagnosis of BV was made on the basis of presence of any of the 3 criteria as described by Amsel et al 1984 such as:

1) A grey homogenous fishy smelling vaginal discharge.

2) Vaginal pH e" 4.5.

3) Presence of clue cells in wet mount preparation of vaginal discharge.

4) The positive amine test in which a fishy odor is released after addition of 10% KOH of vaginal fluid.

e) The presence of clue cells was identified using Grams staining technique, and also for the identification of Gram negative or gram variable bacilli, budding yeast cells, polymorphs etc. A scoring of the vaginal flora pattern was done according to the scoring system of Nugent et al 1991.

f) The results of PAP smears were reported according to Bethesda III system (2001).

g) DNA extraction from cervicovaginal smear was done by manual extraction using QIAamp DNA Kits.

h) PCR amplification of the extracted DNA was performed using consensus degenerate primers(MY09 and MY11) derived from highly conserved L1 open reading frame of the HPV genome with an amplicon size of 450bp. The â globin gene was used as an internal control with an amplicon size of 268bp. PCR was performed in a final volume of 50µl. Each PCR mixture contained 10µl extracted DNA, 5µl of Qiagen PCR buffer, 1µl of dNTP mix, 7µl of 25mM magnesium chloride, 2µl each of forward and reverse primers, 0.5 U of Taq DNA polymerase and 22.5µl of distilled water. Each reaction was then amplified in a thermal cycler for a total of 35 cycles with an initial denaturation at 94%C for 5 minutes followed by 34 cycles of denaturation at 94%C for 30 seconds, annealing at 55%C for 30 seconds and extension at 72%C for 1 minute. A final extension step was done at 72%C for 5 minutes.

i) Agarose gel electrophoresis technique was employed, where the gel casting tray was rinsed and dried in 95% ethanol. The ends of the casting tray were taped. The level of the comb was adjusted so that it rested evenly with a few millimeters space between the teeth and the tray. 1.5% agarose gel was prepared using 5x TBE buffer. About 30ml agarose gel was poured into the casting tray and allowed to solidify for about 10 minutes. The comb and tape were subsequently removed. Aliquots of 15µl of the amplification products were resolved in 1.5% agarose gels, stained with ethidium bromide and separated by electrophoresis at 50V for 30-45 minutes till DNA fragments migrated. The gel was visualized by gel documentation system with inbuilt software. Negative and positive controls were included in each PCR reaction.

**Results and Discussion**

In the present study a total of 368 vaginal/cervical samples were processed and the results were analyzed. Out of 368, 7.06% samples revealed the presence of Candida species and 2.44% samples had presence of Trichomonas vaginalis (Table 1). Hence those samples were excluded from further study. Following Amsels microbiological criteria and taking any three positive criteria into consideration, presence of BV could be assessed in 30.93% out of 333 women (Table2). By employing the widely accepted Gram stain scoring system of Nugent's et al, out of 333 women, 26.12% women were diagnosed with BV, 202 women had an intermediate score and 44 women had a normal score (Table 3). In the present study findings with overall presence of BV is 30.93 % (Table 4)which is in agreement with most of the studies carried so far that show different rates ranging from 17% - 37%. But higher rates of BV have been reported in some studies carried out in developing countries. In a study from Haryana BV was diagnosed in high percentages amongst rural women (Garg et al 2002). In the present study BV was found to be associated with older age groups. More than 75% of BV cases from the study varied between 25-45yesrs of age. (Table 5). This is in consistence with the study carried out by Madhavan et al 2008. However it has been established by previous research that the condition is more common amongst younger women, while others have found that the risk of BV increases with age. (Moncla et al, 1990). Table 6 shows the association between socio demographic profile of the study population and prevalence of BV. All women in the study were reportedly married, with 10 women living with another partner apart from their spouse, four were widowed and four divorced. Almost 26% of the women were illiterate and did not receive any schooling. 74.17% of the women in the study population were either housewives or domestic maids. In addition to running a household, 20.12% of women

worked as unskilled agricultural laborers and 5.7% of women reportedly were employed variously. None of the women in the study population were commercial sex workers. 60% of the target study cohort had made their sexual debut before 18 years of age. Condom use was almost 3% and reversible methods of contraception were rarely used.56.45% of the participants had undergone tubal ligation. None of the women taken into consideration used multiple contraceptive methods. Cigarette smoking, douching and drug use were not reported by any woman in the study population. The highest prevalence of BV in this study was reported in urban slums (38.83%), and urban middle class community (29.12%). Although our study does not have adequate information on partner's sexual behavior, studies suggest that the sexual habits and characteristics of the male partner may play a vital role in the development of BV.(Jones et al, 2007). There is however a limitation in our study. Since risk factors were self reported and it is possible that there may be under-reporting and misclassification of risk behaviors'. This study involved collection of sensitive sexual behaviors as well as information on women's sex partners so there is a possibility of measurement error that may lead to residual confounding effect obscuring the relationship between BV and risk factors.

Out of 103 cases of BV, the common symptom found was vaginal discharge in( 84.4%), followed by lower abdominal pain (63.10%)and pruritus (27.18%)(Table 7). A number of studies explored the association of vaginal discharge with vaginal infections. With regards to clinical manifestations of vaginal infections among symptomatic women, all these studies found a variable degree of association between complaints of vaginal discharge and vaginal infections.(Bornstein et al 2001). Clue cells in the wet mount were found to be significantly associated with BV as shown by its specificity(98.7%) and positive predictive value (78.27%)(Table 8). The findings on positive clue cells also support previous studies that found it to have the highest specificity of the individual clinical criteria for diagnosing BV. (Gutman et al 2005). The present study has shown that the incidence of CIN was significantly higher in cases than in controls. (X= 18.44, pd"0.0001)(Table 9) but the presence of BV was not associated with the severity of CIN(p=0.76)(Table 10) and as per the co-relationship between BV and HPV infection, this study revealed a somewhat positive correlation between these two very common conditions, with an overall estimated odds ratio of 7.63.(95% confidence interval : 4.2 – 13.7)(table11). These data are consistent with the results of four previous studies i.e.; 3 cross-sectional and 1 prospective that found an increased rate of HPV infection in women with BV.

However the question still remains whether BV and cervical HPV infection are simply related because there is a biological interaction between them or because both occur frequently in sexually active women. A positive co-relationship between BV and HPV might be explained by the fact that sexual risk behavior and promiscuity are found more often in women with BV than in comparison groups. A number of variables are contributing to the observed heterogeneity in previous studies. Various social habits and ethno-geographical risk factors may explain the wide BV prevalence range observed(3%- 47.2%). Technical biases such as collection of specimen, subjectivity, sensitivity, and specificity of diagnostic methods are also attributing to detected heterogeneity. Complete STD screening was not performed for the present study which may have confounding effects to a certain degree on the results of the present study as well. Thus further research in this field is imperative.

The present prospective study comprises evaluation of 368 vaginal/ cervical swab specimens collected from 368 women attending the gynaecology OPD of SCB & AHRCC Cuttack.

**TABLE: 1**

**Non-bacterial isolates obtained from vaginal swabs (n=368)**

| Pathogens | Total no. Vaginal swabs n=368 |
|---|---|
| Candida species | 26 (7.06%) |
| Trichomonas vaginalis | 9 (2.44%) |
| Others | 333 (90.48%) |

Out of the 368 numbers of vaginal swabs 26 were positive for Candida species and 9 revealed Trichinmonas vaginalis. Hence these women were excluded from further study.

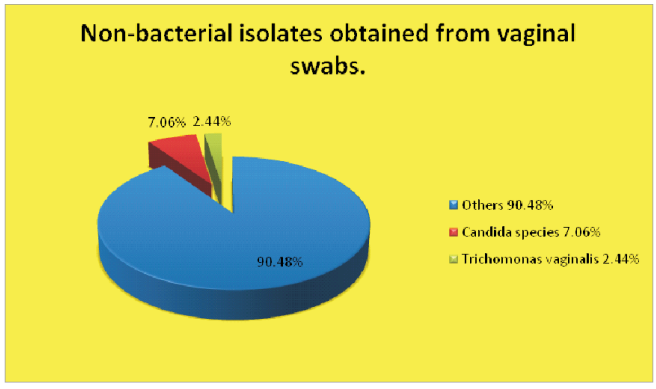
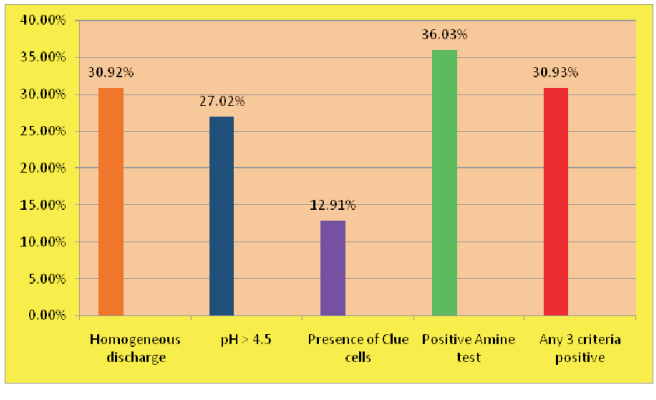



**TABLE:- 2**

**Bacterial vaginosis diagnosed by Amsel's criteria**

| Criteria | Total number of patients n=333 |
|---|---|
| Homogeneous discharge | 103 (30.93%) |
| pH > 4.5 | 90 (27.02%) |
| Presence of clue cells | 43 (12.91%) |
| Positive amine test | 120 (36.03%) |
| Any 3 criteria positive | 103 (30.93%) |

Taking into consideration any of 3 positive criteria 103 out of 333 women were diagnosed with bacterial vaginosis according to Amsel's criteria.




**Bacterial vaginosis diagnosed by Amsel's criteria**

**TABLE:- 3**

**Bacterial vaginosis diagnosed by Nugent's scoring**

| Scoring of bacterial flora | No. of patients n= 333 |
|---|---|
| 0 – 3 (normal score) | 44 (13.21%) |
| 4 – 6 (intermediate score) | 202 (60.66%) |
| 7 – 10 ( BV score) | 87 (26.12%) |

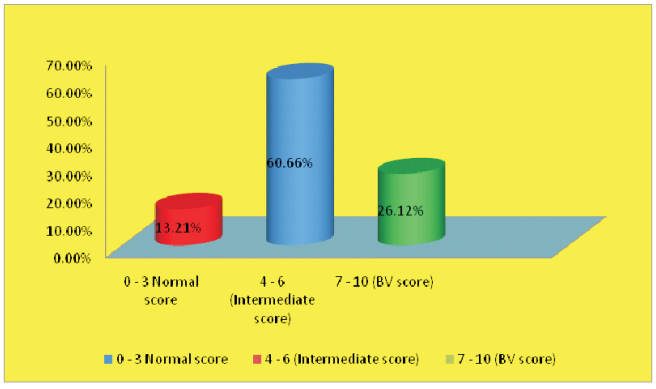



**TABLE:- 4**

**Prevalence of bacterial vaginosis in the present study according to Amsel's criteria**

| Total no. of women | n= 333 |
|---|---|
| Cases | 103 (30.9%) |
| Controls | 230 (69.10%) |

Taking Amsel's criteria into consideration prevalence of bacterial vaginosis was found to be 30.9% in our study which were considered as Cases and the rest 69.10% were considered as Controls.

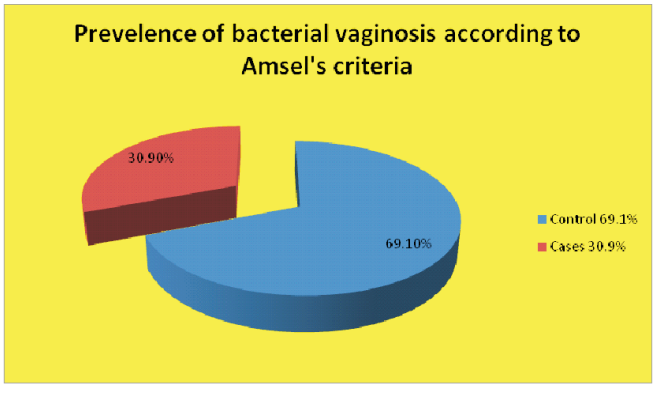



**TABLE:- 5**

**Age distribution in Bacterial Vaginosis**

| Age groups in years | BV (Amsel's criteria, n = 103) | BV (Nugent's score, n = 87) |
|---|---|---|
| < 25 | 18 (17.23%) | 13 (14.62%) |
| 25 - 40 | 78 (76.09%) | 65 (75.32%) |
| >40 | 7 (6.68%) | 9 (10.06%) |

Prevalence of BV was highest between 25 - 40 years of age group and minimum in >40 years age group by both Amsel's criteria and Nugent's scoring system.

Age distribution in Bacterial vaginosis.

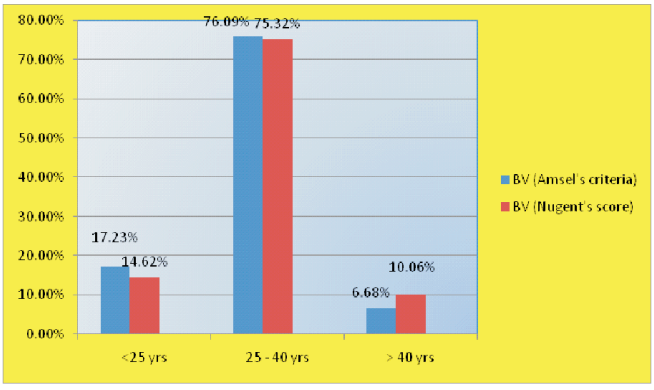



**TABLE:- 6**

**Co-relation between bacterial vaginosis and socio demographic and risk factors**

| Demographic data | Total n 333(%) |
|---|---|
| **Religion** | |
| Hindu | 229 (68.76 |
| Muslim | 96 (28.82) |
| Christian | 8 (2.42) |
| **Literacy** | |
| Literate | 246 (73.87 |
| Illiterate | 87 (26.12) |
| **Location** | |
| Urban Slum | 199 (59.75 |
| Urban middle class | 77 (23.12) |
| Rural | 57 (17.13) |
| **Age of 1st sexual contact** | |
| Before 18yrs | 200 (60.06 |
| After 18yrs | 133 (39.94 |
| **No. of sexual partners** | |

Out of the total 333 women included in the study 199 belonged to urban slums while 77 and 57 belonged to urban middle class and rural communities respectively. The majority of women included in the study were not working (74.17%) and most of them were Hindus, literate and non-smokers. Women with BV were on the average Hindus, house wives had their sexual debut before 18yrs of age and living with their partners for more than 10years and belonged to urban slums. There was no significant difference in other base line demographic characteristics between the 2 groups i.e. Cases and Controls.

**TABLE:- 7**

**Co-relation 0f symptoms with bacterial vaginosis**

| Laboratory diagnosis | Symptoms | |
|---|---|---|
| | Abnormal vaginal discharge (%) | Lower abdominal pain (%) |
| Cases (n=103) | 87 (84.4) | 65 (63.10) |
| Controls (n=230) | 16 (6.95) | 54 (23.47) |

Maximum number (84.4%) of cases presented with abnormal vaginal discharge followed by lower abdominal pain (63.1%) and Pruritus (27.18%). Among Controls, lower abdominal pain was the most predominant (23.47%) symptom.

**Co-relation of symptoms with bacterial vaginosis**

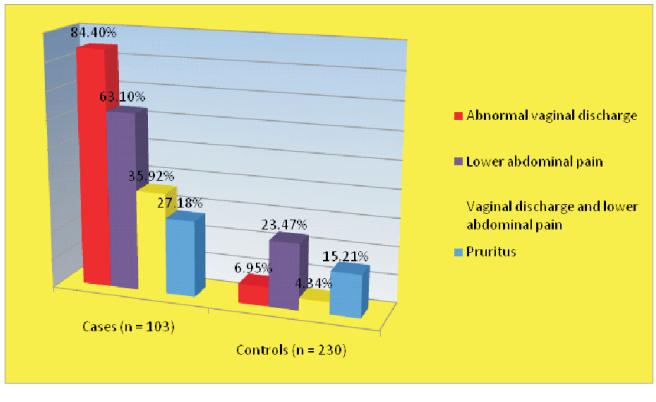



**TABLE:- 8**

**Statistical evaluation of clue cell and Amine test in diagnosis of BV.**

| Test | TP | FP | TN | FN | Sensitivity |
|---|---|---|---|---|---|
| Clue cell | 40 | 3 | 227 | 63 | 38.83% |
| Amine test | 85 | 35 | 195 | 18 | 82.52% |

TP: True positive, FP: False positive, TN: True negative, FN: False negative, PPV: Positive predictive value, NPV: negative predictive value

The sensitivity and specificity of clue cells was found to be 38.83% and 98.7% respectively whereas, Amine test had higher sensitivity (82.52%) but lower specificity (84.78%) but both the above criteria were significantly associated with BV.

**Statistical evaluation of Clue cell and Amine test in diagnosis of BV**

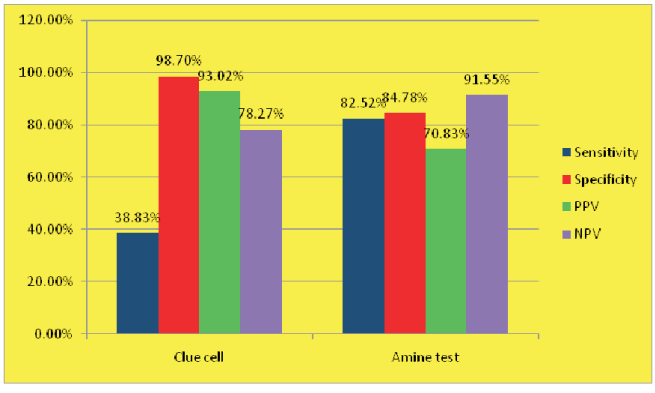



**TABLE:- 9**

**Co-relation between bacterial vaginosis with CIN and ASCUS**

| | ASCUS (%) | CIN Present (%) |
|---|---|---|
| Cases (n=103) | 12 (11.7) | 64 (62.1) |
| Control (n=230) | 14 (6.0) | 99 (43.0) |

Among 103 women with BV (Cases), CIN was diagnosed in 64 women and among the 230 women without BV (Controls), CIN was diagnosed in 99 women. The incidence of CIN was significantly higher in Cases (p<0001).

**Co-relation of bacterial vaginosis with CIN and ASCUS**

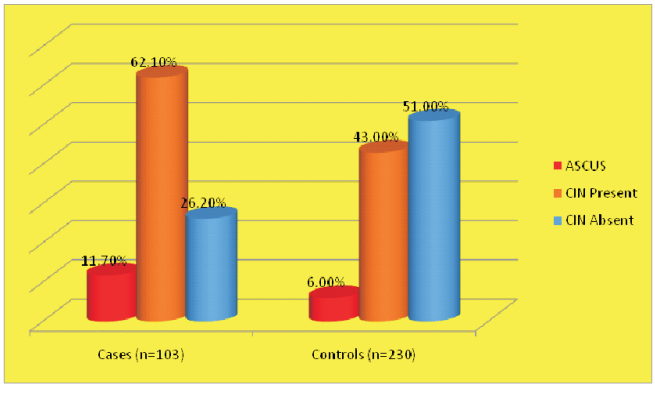


**TABLE:- 10**

**Co-relation between bacterial vaginosis and severity of CIN**

| CIN | Cases (n=103) | Controls (n=230) |
|---|---|---|
| Lowe grade | 25 (39.06%) | 41 (41.41%) |
| High grade | 39 (60.04%) | 58 (58.59%) |
| Total | 64 (100%) | 99 (100%) |

When CIN patients were sub-divided into low grade CIN 1 group and high grade CIN II/III groups, lower grade was present in 40.49% women and high grade was present in 59.51% women, 39.06% no. of Cases had low grade CIN and 60.04% No. of Cases had high grade CIN, and the presence of BV was not associated with the severity of CIN p=0.76.

**Co-relation of bacterial vaginosis and severity of CIN**

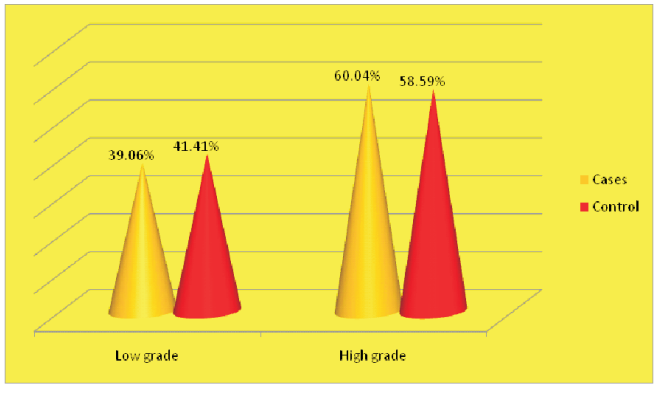



**TABLE:- 11**

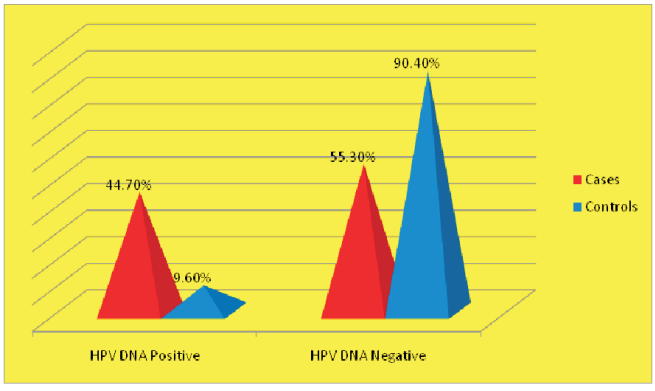
**Co-relation of BV with HPV infection**

| HPV Status | Cases (n=103) | Control (n=203) |
|---|---|---|
| HPV DNA positive | 44.7% | 9.6% |
| HPV DNA negative | 55.3% | 90.4% |

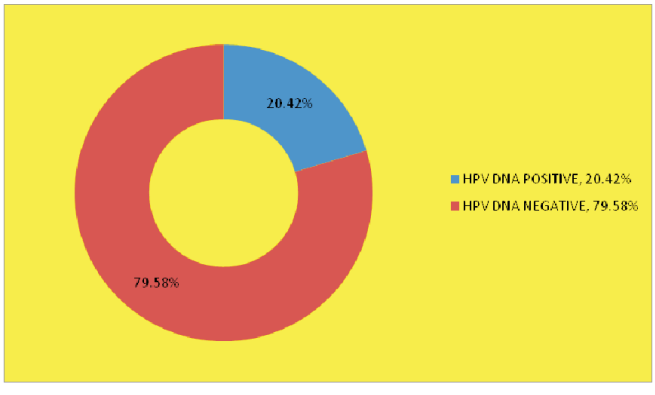
(Odds ration = 7.63; 95% Confidential interval 4.2 - 13.7)

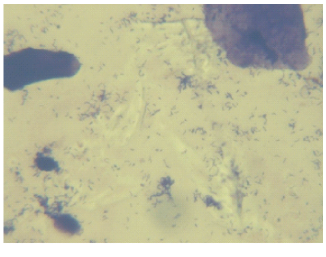
Among the total 333 no. of women 20.42% were positive for HPV DNA, HPV DNA was present in 44.7% of Cases and in 9.6% of Controls. There may be a significant co-relation between BV and HPV infection (p=0.05).

**Co-relation of bacterial vaginosis with HPV infection**

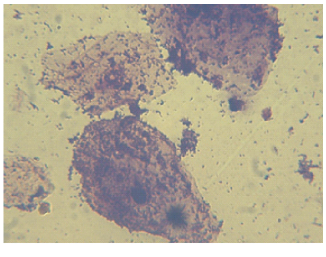



**Prevalence of HPV infection in the study.**

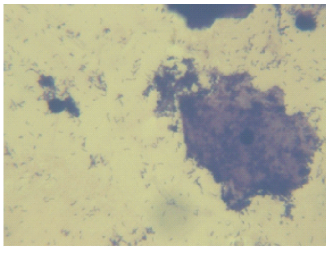


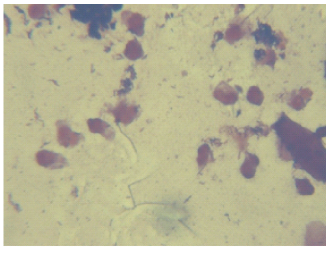
(a) Clue cells



(b) Clue cells with Gardnerella



(c) Clue cells with Mobiluncus



(d) Pus cells

**Summary and Conclusion**

The present study entitled "Association of Human Papilloma Virus infection with Bacterial Vaginosis, in Cases and Controls: An Ongoing Study at AHRCC, Cuttack" was funded by DST, Odisha, and was conducted in the Department of Gynecologic Oncology, AHRCC, Cuttack in collaboration with the Departments of Oand G, Microbiology, and Pathology SCBMCH, Cuttack along with the Virology Laboratory of RMRC,Bhubaneswar , with an objective to ascertain the following:

a) The prevalence of BV among the study population.

b) To determine the association of BV with development of CIN and acquisition of HPV infection.

A total of high vaginal/ cervical swabs were evaluated. 7.06% were positive for Candida species and 9 revealed Trichomonas vaginalis. Hence these women were excluded from further study. The HVS were subjected to pH determination, Amine test, and Clue cell detection. All cervical swabs were also subjected to PAP smear and HPV DNA testing by conventional PCR method .Following the clinical microbiological criteria of Amsel et al, BV was diagnosed in 30.93% out of the total 333 women. Interpretation of Gram staining scoring by Nugent's method revealed 26.12% to be positive for BV, 13.21%had normal score and 60.66% had an intermediate score. Taking Amsels criteria into consideration prevalence of BV was found to be 30.9% in our study which were considered as cases and the rest 69.10% were considered as controls. Maximum numbers of BV cases were from patients who complained of abnormal vaginal discharge (84.4%) and were detected in the age group of 25-40yrs (76.09%). Clue cells were found in 12.91% out of the total samples. The sensitivity and specificity of clue cell detection in relation to diagnosis of BV was 38.83% and 98.7% respectively. The positive and negative predictive values were 93.02% and 78.27% respectively. Clue cell detection was significantly associated with diagnosis of BV (p?0.05). With respect to diagnosis of BV the Amine test had a sensitivity of 82.52% and a specificity of 84.78%. Positive predictive value of the test was found to be 70.83% and it was also significantly associated with BV.

The highest prevalence of BV was seen in urban slums(30.83%) followed by rural community( 32.03%) and urban middle class community (29.12%). In this specific study more Hindu women had BV in comparison to women belonging to other religions. Other known socio-demographic factors such as douching and smoking were not associated with BV in the study population. Among 103 women with BV (cases), CIN was diagnosed in 64 women and in 230 women without BV (controls), CIN was diagnosed in 99 women. The incidence of CIN was significantly higher in cases (p?0.0001), however the presence of BV was not associated with the severity of CIN (p=0.76).Among the total 333 women, 68 were positive for HPV DNA. HPV DNA was present in 46 cases and in 22 controls. Thus there appears to be a link between BV and HPV infection. Thus the present study suggests of a somewhat significant association between BV, presence of CIN and cervical HPV infection.

However cervical screening remains of course a major preventive focus for the cancer control program. If BV is a risk factor for cervical HPV infection, it's but natural that screening guidelines must adapt and implement a sensitive tool like HPV DNA testing in primary screening of BV positive women instead of cytological testing. If a longitudinal prospective study shows a cause effect model then it is clear that greater attention needs to be given to BV in the global fight against HPV infection and women with BV should be considered as a priority group for prophylactic vaccination. Regular follow-up of these patients should be considered. Restoring the vaginal micro flora should in that case be a promising answer to the high prevalence of HPV infections. Randomized clinical trials to effect of BV control measures on HPV acquisition may be worth considering. At present suitable vaccines targeting HPV types 16 and 18 accounting for 70% of cervical cancers worldwide opened up new avenues in prevention of this important public health problem. In addition the need to evaluate the potential of BV treatment to prevent HPV acquisition and transmission a better understanding of risk factors and determinants of recurrence is required.

Considering that these conditions are very common among women worldwide, further research in this field is imperative. More data from prospective

studies are needed to accurately evaluate temporal sequence of acquisition of both conditions in any attempt to determine a causal relationship and to identify specific subpopulations with a stronger association between BV and HPV.

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*Case Report*

# A RARE PRESENTATION OF HAEMORRAGE IN TO THE CORPUS CALLOSUM

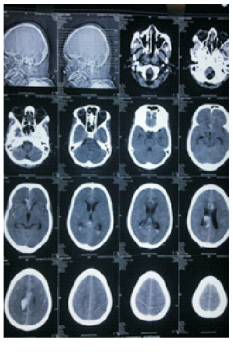
**M. Meher[1], S. Behera[3], S. Mohapatra[1], S.S. patnaik[2], R. Mohanty[4]**

## INTRODUCTION

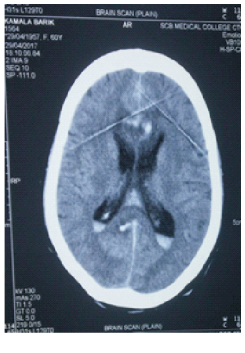
Intracerebral haemorrhage (ICH) accounts for around 10% of all cerebrovascular events . Among ICH the mortality rate is around 34.6% . Hypertension, rupture of aneurysm,coagulopathy, sympathomimetic drugs (cocaine, amphetamine) and cerebral amyloid angiopathy cause the majority of the haemorrhage. Hypertensive ICH usually results from spontaneous rupture of small penetrating artery deep in the brain. Common sites of hypertensive ICH are putamen thalamus, cerebellum,pons. Here we present a rare presentation of haemorrhage in to the corpus callosum.

## CASE REPORT

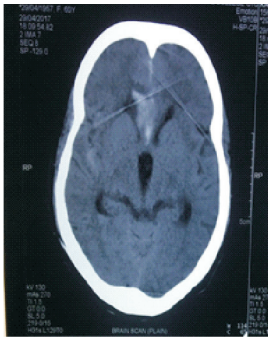
A 60 year old female known hypertensive for the last 5 years, presented with sudden onset altered sensorium with vomiting without history of convulsion followed by low grade fever for 1 day. On examination She was disoriented and febrile. Blood pressure was 170/90 mm of hg. Pulse rate was 96/min, regular. CNS examination revealed she was delirious, aphasic, cranial nerve are intact, normal power in both upper limb and lower limb, brisk deep tendon reflex in both upper limb and lower limb, loss of superficial reflex, and bilateral plantar extensor. Her CBC, LFT, RFT, RBS, electrolytes, coagulation profile were within normal limit. HDL=30 mg/dl , LDL=226mg/dl , TGs=186mg/dl. Blood slide and immune chromatography test for malaria parasite was negative. Urine routine and microscopic examination was normal. ECG showing the features of left ventricular hypertrophy. NCCT scan of brain showed haemorrhage in to the corpus callosum involving genu and body of corpus callosum extending in to the lateral ventricle, third ventricle,fourth ventricle and subarachnoid space (figure-1, figure-2, figure-3). Patient was managed with injection mannitol,injection ceftriaxone, injection pantoprazole. In day 3 of admission, patient sensorium improved and discharged on 8th day.



**(Figure-1)**



**(Figure-1)**



**(Figure-1)**

## DISSCUSSION

Corpus callosum consists of 5 parts from anterior to posterior-Rostrum, genu, body, isthmus, splenium. Main vascular supply of rostrum and genu are sub callosal and medial callosal arteries, branches of anterior

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communicating artery. Body is supplied by pericallosal branches of anterior cerebral artery which is a branch of internal carotid artery. Isthmus and splenium is supplied by posterior pericallosal artery, branch of posterior cerebral artery, which is a branch of basilar artery.

A number of lesions including aneurysm of the pericallosal artery, arteriovenous malformation, hypertension, intracranial infections, and intracranial tumours have been implicated as the cause of haemorrhage in to the corpus callosum. The blood can pass through the lamina terminalis in to the ventricle and thus appearing on the ventral as well as dorsal aspects of corpus callosum.

The prognosis depends upon the size of haematoma and underlying pathology . patients with smaller haemorrhage without any underlying pathology can recover with conservative management.

## CONCLUSION

Till date only 7 cases of corpus callosal haemorrhage are reported worldwide and national data shows only 2 case report of corpus callosal haemorrhage. That depicts the rarity of our case of ICH into corpus callosum with intraventricular and subarachnoid space extension. Patient recovered with conservative management.

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*Case Report*

# A TYPICAL PRESENTATION OF AN UNCOMMON DISEASE

**S. Mohapatra[1], S. Behera[3], M. Meher[1], S.S. Patnaik[2], R. Mohanty[4]**


## ABSTRACT

A 55 yr old female presented with dizziness and headache with splenomegaly. Laboratory investigation were suggestive of leucocytosis, erythrocytosis and thrombocytosis. JAK2 mutation was found to be positive and, she was diagnosed as a case of Polycythaemia Vera


## INTRODUCTION

PolycythaemiaVera is a chronic, progressive, and ultimately fatal disease in which is characterised by an excess production of the formed elements of the blood by a hyperplastic bone marrow. The marrow hyperplasia is not secondary to any known stimulus. With sensitive tests, around 95-99 percent of patients with polycythaemiavera have a JAK2 mutation[1].It occurs in about 2.5 cases in 1,00,000 patients.[2]

## CASE REPORT

A 55yr old female presented with the chief complaints of dizziness,headache,blurred vision, decreased hearing for 15 days. She had no history of fever, altered sensorium, convulsion or vomiting. She was a hypertensive on medication. On examination, she was conscious, cooperative with congested conjunctiva and plethoric hands. PR-92/min, BP 142/80 mm of Hg with mild splenomegaly.Rinnes test showed AC>BC, Webers was not lateralised Absolute bone conduction and Schwabachs test revealed decreased hearing in both ears. All other system examination was normal.

Investigations revealed a haemoglobin of 18.5gm%, PCV 55.8%, TLC 24,300/mm3 with 82% lymphocytes.TRBC 9.03*$10^6$, TPC 6,29,000/mm3. Blood Sugar, RFT, LFT and Lipid profile were within normal limits. Urine examination was normal.

Chest Xray was normal, USG revealed splenomegaly.

Since the patient complained of decreased hearing in both the ears, an audiometry was done which showed bilateral sensorineural hearing loss. The patient also had persistent dizziness, a CT scan was planned, it revealed an infarct in centrum ovale.

With this picture in mind, a diagnosis of polycythemiavera was suspected and thus the need was felt to assess the Serum EPO levels and JAK2 gene mutation.Serum EPO levels were 3.35(4.3-28.5). JAK2 gene mutation was detected.

## DISCUSSION

Polycythemiavera usually presents very insidiously. Patients may be asymptomatic or may have vague symptoms. Hence, they do mostly do not seek consultation with the physician or are only diagnosed with the onset of severe symptoms.PV occurs in all age groups, although the incidence increases with age, and the disease is more common in men than women.[3]The major causes of morbidity and mortality associated with PV are as follows:

- Thrombosis has been reported in 15-60% of patients, depending on the control of their disease. Pulmonary emboli, renal vein or artery thrombosis, mesenteric vascular thromboses, or peripheral arterial emboli have been reported.[3]
- Haemorrhagic complications occur in 15-35% of patients and lead to death in 6-30% of these patients. [3]
- Peptic ulcer disease is reported to be associated with PV at a 3- to 5-fold higher rate than that of the general population due to increased histamine serum levels. [3]

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- Myelofibrosis and pancytopenia occur in 3-10% of patients, usually late in the disease, which is considered the spent phase of PV. [3]
- Acute leukemia or a myelodysplastic syndrome develops in 1.5% of patients treated with phlebotomy alone. [3]

The incidence of polycythemiavera in India has not been documented. It is mostly an uncommon diagnosis in our set up, with a low prevalence and incidence. For the diagnosis of polycythemiavera a definite set of criteria have been proposed. WHO diagnostic criteria for polycthemiavera includes

**Major criteria**

Haemoglobin >18.5mg/dl(men);.16.5gm/dl (women)

Presence of JAK@V617F or JAK@ exon 12 mutation

**Minor criteria**

Bone marrow trilineage proliferation

Sub normal erythropoietin levels

Endogenous erythroid colony growth

PV diagnosis requires meeting either both major criteria and one minor criterion **or** the first major criterion and second minor criteria

Our patient in this case fulfilled both the major criteria long with subnormal levels of erythropoetin. Hence the diagnosis is confirmed in this case.

Among the various complications of the disease, the patient had an infarct in the centrum ovale which was largely asymptomatic.

The patient was treated with hydroxyurea and phlebotomy was done as per recommendations.

## CONCLUSION

Polycythemiavera is largely asymptomatic and since its true incidence and prevalence in our set up is not known, it is important to recognise cases early and treat them appropriately. Early treatment can prevent most of the morbidity and mortality associated with the disease and enable the patient to lead a fairly normal life.

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*Review Article*

# COMMON ERRORS IN THE MANAGEMENT OF THYROID DISEASES

**I. Mishra[1], A.K. Choudhry[2], B.K.Mohanty[3], A.K.Baliarsinha[3]**

Thyroid diseases include one of the most common endocrine disorders in clinical practice affecting all the age groups. Thyroid disorder can manifest with features of hypothyroidism, hyperthyroidism or as thyroid nodule .Though the clinical features many overlap, yet specific conditions need different modes of management.(3)Though classically symptoms are easily recognised subtle signs may evade clinical detection if suspicion is not high.

## THYROID DISEASES IN INFANCY & CHILDREN

Thyroid hormones play an important role in the growth, development & maturation in pediatric age. Congenital thyroid disease usually manifest in early infancy and at times may be detected at later half of infancy(1). It can broadly be classified into hypothyroid or hyperthyroid disorders.

## CONGENITAL HYPOTHYROIDISM

It can be primary or secondary (at the level of hypothalamus or pituitary where other anterior pituitary hormone deficiency may be present).Usually they manifest with features of poor feeding, hypothermia, lethargy, constipation, prolonged physiological jaundice, abdominal distension, umbilical hernia, dry & mottled skin,macroglossia.hoarse cry and myxedematous appearance of face (2). Neonatals creening test is very helpful in detecting CH patients.After confirming the clinicaldiagnosis by clinical features &biochemical investigations treatment with levothyroxine needs to be started at earliest.It should be started at a dose of 10-15mcg/kg/day. The tablets should be crushed & given in water or breast milk with spoon but it should never be added to a bottle of milk or formula that the infant can not empty. Soy formula &colic drops containing simethicone, tend to decrease the absorbtion of levothyroxine&hence must be avoided.On the basis of rapid growth rates of infants, it seems reasonable to asses the thyroid function at intervals of not more than 3months in the first year& then 6 monthly from age 1 to 3 yrs. After 3 yrs there is no irreversible effect of under treatmenton brainfunction, hence yearly assesment are probably sufficient(2).

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## HYPERTHYROIDISM IN INFANCY

Neonatal hyperthyroidism is rare and is nearly always associated with maternal Graves disease(GD).This occurs due to transplacental transfer of maternal TRabs. Depending upon the serum TRab concentration, the thyrotoxicosis features usually manifest for 3 to 4 weeks after birth.They manifest with features of prematurity, acceleration of skeletal maturation, microcephaly, enlarged ventricles, frontal bossing, triangular facies, irrit ability, fever, diarrhoea, bounding pulse &sometimes congestive cardiac failure.

Treatment should be started with MMI(methimazole)-0.25-1mg/kg/day & needs to be given eight to twelve hrly.PTU(propyl thiouracil) is not used as first line treatment in children due to its adverse effects. Beta blockers like propranolol at 2mg/kg is used in severelly ill infants. Low dose of Lugols iodine &SSKI(saturated solution of potassium iodide)may be tried. A trial of glucocorticoids may be used in sick infants with thyrotoxicosis(2)

## HYPOTHYROID DISORDERS IN CHILDREN

They usually manifest with feautures of growth, maturational& pubertal disorder, depending upon the time of thyroid insult during the growth phase. Other clinical features of adult hypothyroidism may also be present. The levothyroxine dose needs to be modified depending upon the age group as growing children need

a higher dose of thyroxine in comparision to adults(1). The doses as per the ages are:Early infancy-(10-15ug/kg/day), late infancy-(7-10ug/kg/day),1-3yr-(4-6ug/kg/day), 3-10yr-(3-5ug/kg/day), 10-16yr-(2-4ug/kg/day)

## HYPERTHYROID DISORDERS IN CHILDREN

Most common cause of hyperthyroidism in children& adolescent is Graves disease(GD).Toxic adenoma & toxic MNG though rare but have also been reported.

Clinical presentation include goitre, tachycardia, hypertension, exophthalmus, tremors, increase appetite, weight loss, heat in tolerance, fatigue etc. The childhood hyperthyroid disorders usually present with features of delayed growth &maturation.They may also manifest with features of attention deficit hyperactive disorders(2). ATD(anti thyroid drugs) are the first line modality of treatment .They need a longer duration of treatment with ATD & are associated with more chances of relapse. RAA (radio iodine ablation) is preffered in children more than 18yrs of age. Recommended dose of MMI (methimazole) is 0.25-1mg/kg/day given once or twice daily. PTU is also effective given at a dose of 5-10mg/kg/day thrice daily.MMI is preffered over PTU because of once daily dosing,better compliance and less side effects.Surgery can be opted for those presenting with markedly enlarged thyroid, severe ophthalmopathy or those who donot have remission during ATD therapy. Operation of choice is neartotal thyroidectomy where less than 4 gm of thyroid tissue is left behind.(1,2)

## THYROID DISORDER IN PREGNANCY

The prevelance of hypothyroidism is 5/1000 & hyperthyroidism is 3/1000 women in India. Pregnancy is associated with various changes in thyroid homeostasis which alters the interpretation of thyroid function test in pregnancy.(3).Principal findings include elevation of total T4, total T3 ,suppression of TSH & increase in thyroid bonding globulin.

**Hypothyroid disorder** – Due to various changes in thyroid physiology in pregnancy the reference limits of TSH values are adjusted as per trimesters beyond which medical intervention is needed.(4)The target TSH as per trimester include; 1$^{st}$trimester -TSH (0.25-2.5 Miu/l), 2$^{nd}$trimester -TSH (0.3-3.0 Miu/l), 3$^{rd}$trimester -TSH (0.3-3.5 Miu/l).

All overt hypothyroid pregnant women must be treated with a minimum startingdose of 50mcg/day or at 1.6mcg/kg/day of levothyroxine.In a known hypothyroid taking levothyroxine increase the dose by 30% in the first antenatal visit. Subclinical hypothyroid (TSH>2.5MIU/L) with TPO ab positivity must also be treated.TSH should be monitored in every 6 weeks & the dose should be titrated till term.After delivery one should return to the prepregnancy dose & breast feedig can be continued even if the mother is on levothyroxine therapy.

### Hyperthyroiddisorders

It may include a variety of disorder ranging from Graves disease (GD), gestational thyrotoxicosis, hyperemesis gravidarum, toxic adenomas, MNG with toxicosis etc. Hence TRab measurement may be done to confirm the diagnosis of GD and asses the risk of feto-maternal transfer. (3,5)

Pregnant women with established GD on therapy should be switched over to PTU in the first trimester (with a dose equivalent of 20:1 of MMI) due to less risk of teratogenicity to fetus. In the second and third trimester MMI can be safely continued throughout pregnancy(at 10-20mg/day). TRab titres should be estimated at 22-24wks of pregnancy to determine the risk of transfer of TRab to the fetus & predict onset of neonatal hyperthyroidism.After completion of pregnancy, patient may be continue to take MMI.Ifsurgery is planned it should be undertaken in second trimester of pregnancy Breast feeding may be continued if requirement of MMI is less than 20mg/day and is contraindicated if the required dose is more.

Ideally then women of childbearing age with GDshould be advised to undergo radio iodine ablation& should plan to conceive after 6months to avoid teratogenic risk to fetus.If surgery is planned it should be undertaken in second trimester of pregnancy.

## POSTPARTUM THYROIDTIS

Women with sub clinical hypothyroidism and raised TPO titres if not treated initially may manifest with features of thyrotoxicosis at around 12-14 weeks postpartum.Though the course of illness is transient in nature it may confuse with that of GD. Hence TRab estimation must be done to confirm the diagnosis as the treatment modalities vary. In post partum thyroiditis in the toxic phase only symptomatic treatment with

beta blockers is needed.Patients should be followed up regularly as most of them develop permanent hypothyroidism by 20- 22 wks.(4)

## THYROID DISORDERSIN ELDERLY

Hypothyroid disorder – Elderly require low dose of levothyroxine ( less by upto 20%) especially those with coronary artery disease. Dosing can be started at 12.5ugm/day with gradual increment two weekly untilTSH is normalized.(4)

Hyperthyroid disorder-Elderly with hyperthyroidism may not manifest with classic features of thyrotoxicosis but may present as apathetic thyrotoxicosis. They present with atrial fibrillation or congestive cardiac failure. Hence elderly with biochemical findings of hyperthyroidism but absent clinical features of thyrotoxicosis must be carefully monitored and antithyroid drugs shouldbe started if required.(4)

## SUBCLINICAL THYROID DISORDERS

Subclinical hypothyroidism – This clinical entity presents biochemical picture of normal T3, T4 hormones but TSH values above the upper limit of reference range. Patients with this group of disorder need to be monitored and individualized for treatment with levothyroxine. Some indications for which treatment may be considered include; high TPO titres, pregnancy, dyslipidemia, women with dysfunctioning uterine bleeding & elderly

Sub-clinical hypothyroidism associated with dyslipidemia especially in age group of less than 50 years needs to be treated as it decreases the coronary artery disease risk.Treatment with levothyroxine with intermittent monitoring of thyroid function tests must be done.(3)

Sub –clinical hyperthyroidism-This clinical entity presents with normal thyroid hormone levels but, suppressed TSH values below the lower limit of the reference range.Sub-clinical hyperthyroidism must be suspected in cases of recovery from sick euthyroid disease, sub acute thyroiditis & hashitoxicosis. Patients should ideally undergo estimation of thyroid auto antibodies or radioimaging studies (Tc99m scan) for confirmation of diagnosis. Symptomatic treatment with watchful observation should be done if GD is ruled out.(3). However definitive treatment may be required if worsening of rhythm disorders,heart failure or osteoporosis is found.

## SPECIAL CONDITIONS NEEDING LEVOTHYROXINE DOSE MODIFICATIONS

Certain clinical entities need higher doses of levothyroxine for maintainence of normal thyroid profile and meeting the daily requirements(3). These include: pregnancy & malabsorbtion disorders, various drugs that interfere with levothyroxine absorption-cholestyramine, sucralfate, aluminiumhydroxide, calcium carbonate & ferrous sulphate. During that increase cytP450 enzyme activity neccesiting higher dose of levothyroxine include Carbamazepine, Estrogen, Phenytoin & Amiodarone

In conclusion, thyroid disorder have a wide spectrum of manifestations varying from neonatal period to elderly. Hence adequate knowledge of various clinical manifestations, diagnostic procedures and treatment modalities will help us minimising the common errors in management of thyroid disorders.

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*Review Article*

# HEART FAILURE : REDEFINED

**S. Mohapatra**

## INTRODUCTION:

Heart failure is an important healthcare issue. Repeated hospital admissions and that to for a prolonged period are big issues as well as the financial burden it causes. Heart failure is not a complete diagnosis in itself; it requires characterisation of the syndrome in terms of severity, the underlying cardiac disease, its aetiology and adjustment of the body to the pump dysfunction.

The definition of heart failure has evolved over the years. There is no universally accepted gold standard based on objective test. Various definitions have been used based on epidemiological studies, clinical trials and various clinical studies. This has made the task very difficult ***(1,2)***. Heart failure has been defined as a syndrome that develops as a result of cardiac disease and is recognised clinically by a constellation of symptoms and signs produced by a complex circulatory and neuro hormonal responses to cardiac dysfunction***(3).*** Although almost accurate this definition is of no use in epidemiological study. Another definition depicts that heart failure is a clinical syndrome that develops when the heart cannot make an adequate cardiac output or can do so at an expense of an elevated filling pressure. The term congestive cardiac failure is no longer used as pulmonary congestion though common is not universally present***.(4)***

### Current Definition and Classification

Heart failure is a clinical syndrome characterised by typical symptoms like breathlessness, ankle swelling and fatigue and may be accompanied by signs like elevated jugular venous pressure, crepitations in the lungs and peripheral pitting oedema caused by structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intra cardiac pressure at rest or under stress.

The current definition restricts itself to stages when clinical symptoms appear or apparent. Before these clinical symptoms or signs are apparent, patients can present with asymptomatic structural or functional cardiac abnormalities (systolic or diastolic left ventricular dysfunction) which are precursors of HF. Most studies are based on systolic heart failure where left ventricular ejection fraction is less than 40%, i.e. 35-40%. In some patients heart failure occurs in the presence of good left ventricular ejection fraction. This condition has been termed as 'Heart failure with preserved systolic function' or 'Diastolic heart failure***(5).*** *Vasan et al* made it very simple with objective evidence based on 2DEcho findings in the presence of symptoms of heart failure with normal systolic function when left ventricular ejection fraction is 50% or more ***(6).*** This definition has been endorsed by American College of Cardiology and American Heart Association Task force on practice guidelines ***(7).*** Data from case by case expert review in population based studies in the United Kingdom conducted by authors suggest that preserved systolic function is found in a proportion of 10-15% in new cases of heart failure ***(8,9).***

**Demonstration of an underlying cardiac cause is central to the diagnosis of heart failure. Heart failure as mentioned above comprises of 3 groups,**

1) Heart failure with normal LVEF(HFpEF)
2) Heart failure with reduced ejection fraction (HFrEF)
3) Patients with LVEF in the range of 40-49% (HFmrEF)

This group represents a grey area between GP1 and GP2.

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**TABLE - 1**

| Type of HF | HF v EF | H |
|---|---|---|
| CRITERIA | Symptoms + Signs LVEF<40% | Sympt LVE |
| | | 1.Elev of Nat peptic 2.At le additi of a)Rele struct diseas /or LA b)Dias dysfur |

Note : Signs may not be present in early stage of HF especially in HFpEF and patients treated with diuretics.

BNP B type natriuretic peptide >35pg and/or NTPro BNP (N terminal Pro BNP) > 125pg/ml

**CLASSIFICATION OF HEART FAILURE**

**Congestive heart failure** : Similar to the definition of heart failure but with features of circulatory congestion like jugular venous distension, pulmonary rales, peripheral oedema and ascites.

**Non cardiac circulatory failure** : Clinically indistinguishable from congestive heart failure but there is no structural heart disease. Examples are acute renal failure and high output heart failure.

**Systolic heart failure** : A clinical syndrome with classic symptoms of breathlessness, fatigue and exercise intolerance. Usually heart is large, chambers are dilated and there is impaired systolic function.

**Diastolic heart failure** : LVEF (Left ventricular ejection fraction) is normal at rest. Features of HF present on exertion and heart is normal or small. There may be LV hypertrophy and impaired filling of heart caused by LV stiffness. Systemic hypertension, mitral regurgitation may be present. This condition may co exist with systolic heart failure during exercise.

**Right sided heart failure** : A clinical syndrome consisting with tissue congestion, jugular venous distension, peripheral oedema, enlarged liver and ascites. Usually RV systolic function is impaired and tricuspid regurgitation may be present. Conditions causing this syndrome are pulmonary disease with pulmonary artery hypertension, severe hypoxia, right ventricular MI and congenital anomalies of the heart. Commonest cause is severe left sided heart failure.

**Left sided heart failure** : A clinical syndrome where there is pulmonary oedema and no other systemic congestion.

**Acute heart failure** : Previously synonymous with acute pulmonary oedema but now this terminology includes new onset heart failure and worsening heart failure on the background on chronic heart failure.

**DIAGNOSIS :**

Symptoms and signs, particular at the early stage of HF are so non-specific and indiscrete that it may not help to discriminate between HF and other problems. Difficulty arises in obese and elderly patients with COPD. Younger patients with HF often have a different aetiology and clinical presentation and outcome compared to older patients.

**TABLE - 2**

| **SYMPTOMS** | **SIGNS** |
|---|---|
| **Typical** | **More** |
| Breathlessness, Orthopnea PND, Reduced exercise tolerance fatigue, tiredness longer time to recover post-exercise<br>Ankle swelling | Elevat (with Displa |
| **Less Typical** | **Less S** |
| Nocturnal cough, wheezing bloated feeling, loss of appetite, confusion, depression, palpritation dizziness syncope, Bendopnea | Weigh tissue Cardia pulmc effusi pulse respir cold pulse |

Patients presenting in out patients' departments for the first time should be evaluated on the basis of patients' prior medical history, physical examination and resting ECG. Normal elements will exclude Heart failure and possible other cause should be sought. If one element is abnormal then plasma natriuretic peptide (NP) should be measured. If NPs are above the exclusion threshold or NPs level cannot be assessed then Echocardiography is indicated. It may be emphasized that use of estimation of NPs is recommended to rule out HF but not to establish the diagnosis. In conditions like old age, atrial fibrillation, renal failure and obesity NPs are abnormally high.

**Diagnosis algorithm for Diagnosis of HF of non acute onset**

**Patients with suspected HF (non acute onset)**

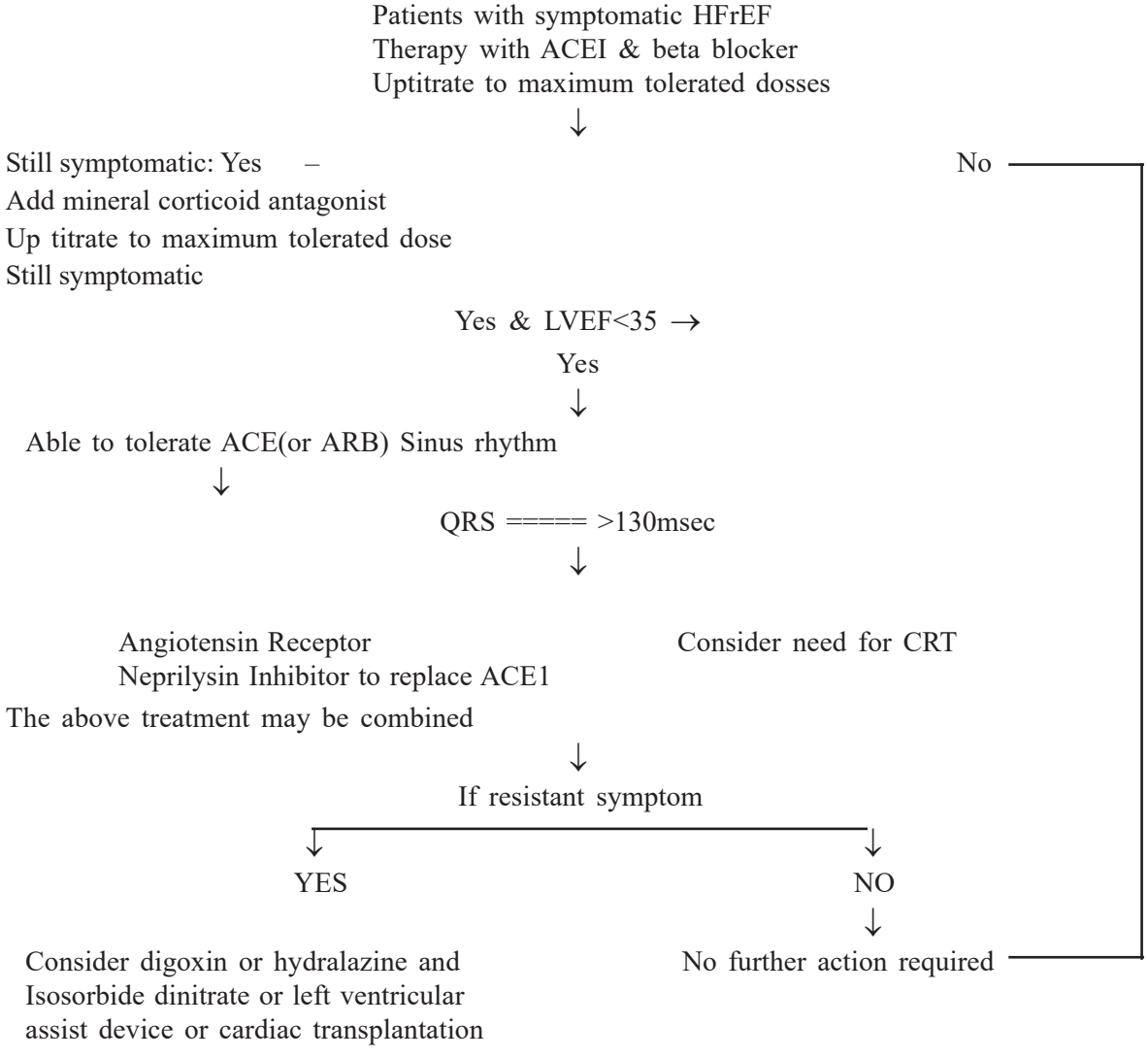
Assessment of probability

1. Clinical history: History of CAD
   (MI, CABG, Angioplasty)
   History of arterial hypertension
   Exposure to cardio toxic drugs/radiation
   Use of diuretics
   Orthopnoea/ PND
2. Physical examination
   Rales, bilateral ankle oedema
   Heart murmur, Raised JVP
   Laterally displaced apex beat.
3. ECG : Any abnormality

| | |
|---|---|
| > I Present | All Absent |
| Natriuretic peptides | HF unlikely |
| NT Pro BNP>125pg/ml | Consider other diagnosis |
| BNP>35pg/ml YES | NO Consider other diagnosis |
| Echocardiography Normal | HF unlikely Consider other diagnosis |

If abnormal Determine Aetiology & Start treatment

**Therapeutic Algorithm for patients of heart failure with reduced ejection traction (HFrEF)**



## ACUTE HEART FAILURE

Acute heart failure refers to a rapid onset or worsening of symptoms and/or signs of heart failure. It is an urgent situation requiring immediate evaluation and appropriate treatment and invariably need for hospitalisation. AHF may occur for the first time (de novo) or more frequently as an acute decompensation of chronic HF. This may be caused by acute decompensation of pre-existing primary cardiac condition or precipitated by extrinsic factors like infections, uncontrolled hypertension, rhythm disturbances or non-adherence to drugs or diets. Acute myocardial dysfunction (Ischemic, inflammatory or toxic), acute valve insufficiency or pericardial tamponade are the commonest cardiac causes of acute heart failure.

**TABLE 3**

Factors triggering Acute Heart failure

Acute coronary syndrome

AMI with (AF, VT) VF does not give time for delayed treatment

Accelerated hypertension

Infections: Pneumonia, infective endocarditic, sepsis

Non adherence to diet or drugs

Drugs and alcohol (Recreational drugs, NSAIDS, corticosteroids, negative ionotropic substances, chemotherapeutics.

Exacerbation of COPD, pulmonary embolism, surgery and peri operative complications, Metabolic/ Hormonal derangements (thyroid disorders, DKA, adrenal dysfunction, pregnancy and peripartum cardiomypathy)

Mechanical: Free wall rupture, acute VSD, acute MR, aortic dissection, trauma, acute native and prosthetic valve dysfunction.

There are several classification of acute heart failure. But, based on bedside physical examination in order to detect the presence of clinical symptoms or signs of congestion

(wet vrs dry: present vrs absent) and/or peripheral hypo perfusion (cold vrs warm : Present or absent).

This classification is helpful in guiding therapy and prognostic information.

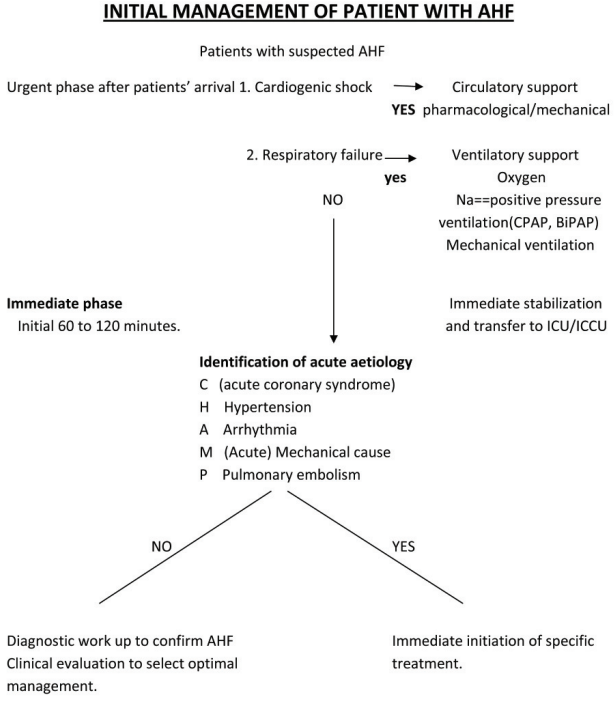
**TABLE**

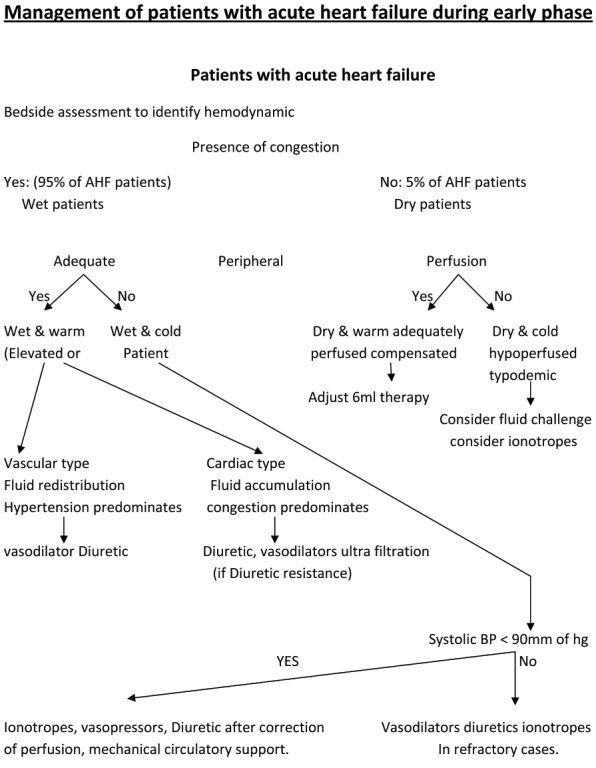
Clinical profile of patients with Acute Heart Failure

| Congestion Present | Congestion Absent |
|---|---|
| Pulmonary congestion<br>Orthopnoea/ PND<br>Peripheral Oedema<br>Jugular venous dilatation<br>Congested liver<br>Gut congestion, ascites<br>hepato<br>jugular reflux | NONE |

| Hypo perfusion present | Hypo perfusion Absent |
|---|---|
| Cold sweating in extremeties oliguria, mental confusion dizziness, and narrow pulse pressure<br>Cold Dry – Cold wet | Warm dry Warm wet |

Hypo perfusion and hypotension are not synonymous but often hypo perfusion is accompanied by hypotension.






## CONCLUSION

Heart failure affects 2-4% of the population of India. While the life span of Indians increasing by years this number is going to rise. Hence, to scrutinise the whole population with probable heart failure, it is essential we depend upon evidence which are objective and robust. With availability of 2DEcho and biochemical estimation of natrieuretic peptides heart failure diagnosis has become evidence based and can be diagnosed much before definite signs of heart failure appear. Many heart ailments and complications as well as aggravation of pre-existing heart disease may be prevented or at least delayed. Treatment of co morbid conditions like hypertension, obesity, diabetes, dyslipidaemia, cessation of smoking and early intervention in coronary artery disease will delay the onset of heart failure. Younger generation physicians will be benefitted by the modern diagnostics tools for diagnosis and this would be beneficial for therapeutic / interventional management of heart failure.

**Abstract:**

Heart failure is an important health issue more so in the elderly population. It poses a big issue in the hospitals and also a big financial burden on the national economy. There have been changes in the definition, diagnosis and management from time to time. In today's context there should be robust evidence while establishing diagnosis vis-a-vis management. Many co morbid conditions aggravate pre-existing cardiac abnormality as well as conditions like infections, DKA, stress, omission of drugs and discontinuation diet control may contribute to deterioration in hithereto stable cardiac condition. Hence, to keep up with the ongoing changes and availability of diagnostic tools and therapeutic modalities, one should open up his mind to adapt to the newer ideas and knowledge.

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*Review Article*

# PROLACTINOMAS : DIAGNOSIS AND TREATMENT

**S.R. Behera[1], D.K. Dash[1], A.K. Choudhury[2], A.K. Baliarsinha[3]**

## Introduction

Prolactinomas are benign neoplasms accounting for 40% of all pituitary tumors. Most prolactinomas are intrasellar and rarelyincrease in size. In some cases, prolactinomas invade surroundingstructures (invasive extensions) and exceptionally they maymetastasize to systemic organs. Prolactinomas consist of lactotrophs that secrete excess prolactin (PRL) to varying degrees, resulting in hyperprolactinemia. Lactotroph secretion of PRL is enhanced by estrogen and inhibited by dopamine (DA). DA is synthesized by hypothalamic neurons and transported to the pituitary via portal vessels. Prolactinomas can be classified as microadenomas (<10 mmdiameter) or macroadenomas (>10 mm diameter). PRLs physiologic role is to stimulate lactation but it also has secondary effects on gonadal function. The clinical features of hyperpro lactinemia result from secondary effects of PRL on the gonads and differ in both men and women.

## Clinical features

Normal PRL levels in men and women are 20 and 25 ìg/l, respectively.Excess PRL may lead to infertility and gonadal dysfunction.The gonadal dysfunction is mediated by an interruptionin the secretion of gonadotropin-releasing hormone, luteinizinghormone and follicle-stimulating hormone as well as the interruption of gonadal steroidogenesis. If the prolactinoma is large, compression of other pituitary cells may cause hypopituitarism.Neurologic symptoms – most often headaches and visualcomplaints – are also noticed with large tumors as they are able to compress the optic chiasm and invade structures of the skullbase such as the cavernous sinus. There is a close correlation with tumor size and serum PRL levels and as such, macroadenomas generally result in serum PRL levels greater than 250 ìg/l [1]. Hyperprolactinemia in men often manifests as infertility, impotence and decreased libido [8]. Prolactinomas in women most often present as microadenomas. In premenopausal women, the most common symptoms of hyperprolactinemia are infertility and amenorrhea. Galactorrhoea occurs in approximately 80% of women with prolactinomas. Postmenopausal women, like men, often do not present with these typical symptoms but rather of symptoms of mass effect and larger tumors. Both males and females may develop reduced spinal bone mineral density with chronic hyperprolactinemia due to the inhibitory effects of PRL on sex steroids.

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## Clinical approach

The diagnosis of a prolactinoma requires endocrinological findings of hyperprolactinemia and radiographic evidence of a pituitary adenoma. Recent Endocrine Society clinical practice guidelines recommend using a single measurement of serum PRL to establish hyperprolactinemia as long as the sample was obtained without excessive venipunture stress [2]. Causes of hyperprolactinemia other than a prolactinoma must also be ruled out. Other large sellar or parasellar masses, brain trauma and hypothalamic damage may result in hyperprolactinemia either by impairment of hypothalamic DA production or transport. Hypophysitis mayalso cause hyperprolactinemia. Generally, such causes will rarely result in serum PRL levels greater than 150 ìg/l.Many drugs are able to cause hyperprolactinemia by antagonizing DA receptors or impairing DA delivery to the portal vessels. Some of these pharmacological agents include metoclopramide, risperidone, domperidone and verapamil. In general, medication-induced hyperprolactinemia rarely results inserum PRL levels greater than 100 ìg/l[3]. Patients with primary hypothyroidism may develop mild

hyperprolactinemia. It is thought that this is brought about by increased synthesis or sensitivity to hypothalamic thyrotropin releasing hormone that can stimulate pituitary lactotroph cells, although the actual mechanism is still unknown [4]. Chronicrenal failure and liver disease may result in mild hyperprolactinemia due to decreased clearance. During pregnancy, estrogen from the placenta stimulates PRL synthesis and raises PRL levels approximately tenfold compared with normal values[2]. When all causes of hyperprolactinemia have been ruled out,the diagnosis of idiopathic hyperprolactinemia can be considered. However, some of these patients may have microprolactinomas that are too small to be recognized radiographically which may appear at a later follow-up. Therefore, secondary causes of hyperprolactinemia can beruled out with a careful history, physical examination, routine biochemistry for liver and renal function, pregnancy test and TSH levels. If a patient is known to be taking a drug that can induce hyperprolactinemia, then withdrawal for 72 h or alternative drugs should be sought if safe and feasible [2]. Discontinuation of an antipsychotic medication should always be carried out after consulting the patient's physician. One should also be aware of the 'hook effect' and macroprolactin when analyzing serum PRL levels. The hook effect occurs when serum PRL is exceptionally high, such as in the case of a giant prolactinoma. The high PRL results in antibody saturation during immunoradiometric as say leading to apparently low PRL results. Serial dilutions help in eliminating this artifactin measurement and should be requested routinely in patients with large pituitary masses [5]. Macroprolactin is a complex of PRL with an IgG antibody that leads to decreased clearance and pseudo-hyperprolactinemia. Size exclusion chromatography, or more often polyethylene glycol precipitation, can confirm a macroprolactinemia[5]. After excluding secondary causes of hyperprolactinemia and PRL measurement artifacts, a gadolinium-enhanced MRI of the sella should be performed. It is important to note that a normal MRI does not rule out a microadenoma, and that a positive MRI with hyperprolactinemia is not definitively diagnostic of aprolactinoma, as any sellar mass compressing the pituitary stalkmay result in hyperprolactinemia. Confirmation of a prolactinoma can be obtained with pathology or by treating the patient with medication and obtaining serial PRL and imaging assessments. If both serum PRL normalize and the tumor shrinks substantially, then the diagnosis of a prolactinoma is confirmed. If serum PRL normalize but the tumor size remain stable, this confirms the diagnosis of a pituitary adenoma other than prolactinoma. If serum PRL and tumor size remain unchanged after medication, then the diagnosis of a resistant prolactinomais indicated [5].

**Management**

All patients with macroadenoma and many patients with microprolactinomas require treatment. In all patients the goal of treatment is to restore gonadal function but with microprolactinomas reducing tumor size and inhibiting tumor growth are also important. Premenopausal women with normal menstruation and postmenopausal women without bothersome galactorrhoea or mass effects do not need to be actively treated, but should have serum PRL and imaging monitored to watch for tumor growth.

**Medical therapy**

DA agonists such as bromocriptine or cabergoline are the first-line treatment approach in prolactinomas as they have been shown to effectively normalize PRL levels and reduce tumor volume irrespective of tumor size [6]. DA agonists work by binding the G-protein coupled lactotroph D2 receptors resulting in involution of the endoplasmic reticulum and Golgiapparatus, and therefore, tumor shrinkage [7]. DA binding to lactotroph D2 receptors also inhibits PRL release. Bromocriptine therapy is started at a dose of 0.625 mg daily for the first week, and is then increased by 1.25 mg weekly until PRL levels normalize. Doses that exceed 7.5 mg daily are rarely required [6]. Cabergoline treatment is started at 0.5 mg weekly and the dosage is increased monthly until PRL levels normalize [7]. Pergolidemesylate, a previously US FDA-approved treatment for Parkinson's disease and quinagolide, a selective D2 receptoragonist that is an approved treatment for prolactinomas in Europe, are also possible DA agonists but their use is limited. Several studies have shown that cabergoline is a well-tolerated agent and comparisons with bromocriptine show that cabergoline is superior in normalizing PRL levels and reducing tumor volume [7, 8]. The use of cabergoline during pregnancy has been shown to be safe, but the number of pregnancies studied is limited. If value is

placed on the reversal of hypogonadism, then cabergoline is considered the gold standard DA agonist [2].However, if value is based on cost and effects during pregnancy, then bromocriptine therapy should be considered given that it isless expensive and it is safe to use during pregnancy [2]. Despite the effectiveness of these drugs, some patients are intolerant at therapeutic doses and some do not respond attherapeutic levels or higher. Such patients are considered to be DA resistant. The mechanism of resistance seems to be mediated by a decreased number of D2 receptors without a decreased affinity for DA agonists, and an altered signal transduction mechanism [10. There have also been reports of the development of DA resistance after gonadotrophinre placement [11].In resistant patients, treatment options include switching DA agonists, increasing DA agonist dosage beyond convention and surgery and/or radiotherapy.

Until recently, bromocriptine was considered the gold-standard treatment for prolactinomas. Up to 85% of patients resistant to bromocriptine and quinagolide could obtain normal PRL levels after switching to cabergoline [12]. Therefore, it is recommended that patients who were started on bromocriptine and who are resistant switch to cabergoline prior to attempting surgical intervention. Levels of cabergoline may be continuously raised, irrespective of tumor size, as long as there is caution used to avoid adverse reactions and that the increased doses continue to provide therapeutic benefit. There are some reports indicating that cabergoline use may result in cardiac valve damage, but it seems that this is only the case in extremely high doses of cabergoline that is not necessary in the treatment of prolactinomas [13].

**Surgical & Radiation therapy**

When medical therapy proves ineffective and when the tumor is operable, trans-sphenoidal surgery is a good option. Are view of 50 surgical series showed that 75% of microadenomas and 34% of macroadenomas achieved normal PRL levels after surgery; recurrence rate for both micro- and macro-adenomas after 1 year was 20% [14]. Microprolactinomas and macroprolactinomas confined to the sella, have a higher chance of remission after surgery. Unfortunately, the invasiveness and complexity of giant prolactinomas makes a surgical approach anunlikely candidate for a cure. With macroprolactinomas, the aim of the surgery is often to reduce neurologic symptoms associated with optic and cerebral compression [15]. Radiation therapy is often reserved as a final therapeutic option for tumor shrinkage. Conventional fractionated radiotherapy results in reduced PRL levels in approximately 25% of patients. It can be associated with hypopituitarism, rarely stroke and development of a second tumor. In medically and surgically refractory patients, Gamma knife radiosurgery resulted in PRL normalizationin 26% of patients at 24.5 months follow-up [16]. Gammaknife radiosurgery is limited to well-defined tumors smaller than 3 cm that are a minimum of 3 mm away from the optic apparatus. In patients with recurrent, invasive prolactinoma and prolactinoma carcinomas with low *O*-6-methylguanine-DNA methyltransferase (MGMT) staining, temozolomide therapy can be used as a successful therapeutic agent [17]. Temozolomide therapy has even reduced tumor volume and normalized PRL levels in a resistant macroprolactinoma suggesting a possible role for temozolomide in resistant prolactinomas. The number of cycles of treatment necessary to determine efficacy has not yet been determined, although three cycles has been suggested as sufficient [17].

**Treatment & fertility**

In women who desire fertility, bromocriptine is the primary therapeutic agent. It is important to note that fertility can be restored immediately with DA agonists, and so the use of mechanical contraception is advised. In microprolactinomas,the risk of tumor expansion during pregnancy is low and therefore DA agonist therapy can be stopped as soon as pregnancyis confirmed to limit the exposure to the fetus [2]. Given the 30% chance of tumor expansion in macropro lactinomas during pregnancy, it is advised that conception be planned after PRL levels have normalized and tumor volumes have reduced significantly in females [2].In pregnant patients who stop therapy and develop symptomsof mass effect, an MRI without gadolinium should be ordered and DA therapy should be re-instituted if there is significant tumor growth. Surgery during pregnancy is potentially dangerous for mothers and fetuses and should remain a last resort. Also, it is important for women wishing to breast feed to stop DA therapy so that milk production is not impaired and to prevent excess DA in the breast milk.

### DA agonist withdrawal

Recent studies provide evidence for the possibility of DA agonist withdrawal and remission of hyperprolactinemia. The indications for withdrawal vary according to size. Given the little growth potential for microprolactinomas, DA therapy may be withdrawn after normalization of PRL and tapering is not necessary [18]. Patients with macroadenomas who have achieved normal PRL levels and have no evidence of a tumoron MRI may withdraw DA therapy after tapering. All patients should have PRL levels closely monitored for a minimum of 1 year after withdrawal given that remission rates are highest 1 year after withdrawal [2].

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*Current Concept*

# ROLE OF SHORT MESSAGE SERVICE (SMS) IN DIABETES

**Surg. Capt. S. Dutta**

**Introduction:**

Mobile technology is the technology used for cellular communication(1). A standard mobile device has evolved from a simple two-way pager to a mobile phone, GPS navigation device, an embedded web browser and instant messaging client, and a handheld game console. mHealthis an abbreviation for mobile health, a term used for the practice of medicine and public health supported by mobile devices(2). mHealth applications include the use of mobile devices in collecting community and clinical health data, delivery of healthcare information to practitioners, researchers, and patients, real-time monitoring of patient vital signs, and direct provision of care (via mobile telemedicine). With the advent of Smartphones, everyone today is talking about Internet on mobiles, 3G/4G speeds, mobile applications and social media. However, Short Message Service (SMS), a traditional SMS on mobile, even today is pretty much one of the frequently used feature for communication, especially in developing countries like India.

The number of mobile phone users globally is 688 million(3). In India the total mobile subscriber base has reached 1003.49 million in Oct 2015 with 902.26 million active subscribers. Urban India has a total of 578.11 million, while rural India has a total of 425.38 million mobile subscribers (4).In April 2016, the total users are 1034 million(5). An average Indian sends 29 SMS per month(6). mHealth, SMS in particular is a very important tool to aid in betterment of health conditions especially chronic disease like Diabetes and would impact in a very big way in a country like India owing to its huge number of users of mobile technology and huge diabetic patient population of 105 million (69.2 million diagnosed and 36 million undiagnosed)(7).

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Many studies and systematic reviews support the effectiveness of mobile technology to influencing lifestyle and providing health education especially for chronicd is ease like DM (8;9). Over the past decade, self-management education or supportby mobile-based applications has been launched to target theblood glucose and HbA1C levels control in patients with Diabetes (10). SMS is part of mobile-based interventions that has bridged an effective communication channel to endeavor behavioral change, enhance disease-specific knowledge, and subsequently improve health outcomes in the field of preventive medicine and chronic disease self-management. A structured literature review of available meta-analyses related to SMS, addressing various aspects in diabetes management including patient attendance at outpatient clinics, adherence to treatment, glycemic control, cost effectiveness and patient satisfaction have been provided here. Only recent literature reviews, meta-analyses or RCTs (wherever necessary) have been included to avoid overlapping of the studies.

**Role of SMS in Outpatient attendance:**

SMS intervention improved attendance at outpatient clinics and enabled routine exchange of patient information in a meta-analysis conducted by Lynn et al which included 77 studies(11). In this analysis seven studies combinedweb-based diabetes management program with SMS and were associated with significantly decreased HbA1c levels for the intervention group after implementation.

**Role of SMS in Glycemic control:**

A meta-analysis by Saffariet al including 10 studies with a total of 960 Type 2 Diabetes Mellitus (T2DM) patients suggested that self-management education through SMS has a considerable effect on glycemic control (nearlya 50% reduction in HbA1c compared to control group) in T2DM(12) (Fig.1). It has also shown that age, sample size, diabetes duration,

period of intervention, level of HbA1c and type of intervention may have implications regarding effectiveness of such educations. Another meta-analysis by Carukshi et al (overlap of few studies with Safari et al is to be noted) showed, in 13 out of 15 trials where datawere available, there was a difference in HbA1c of - 0.53% (95% CI -0.59% to -0.47%) between intervention groups compared to usual care(13) (Fig.2). Further research using other mobile applications and other tele-health educational methods on patients with other diseases is recommended. Including homogenous studies with greater sample sizes in future studies may also improve the generaliz ability of findings.

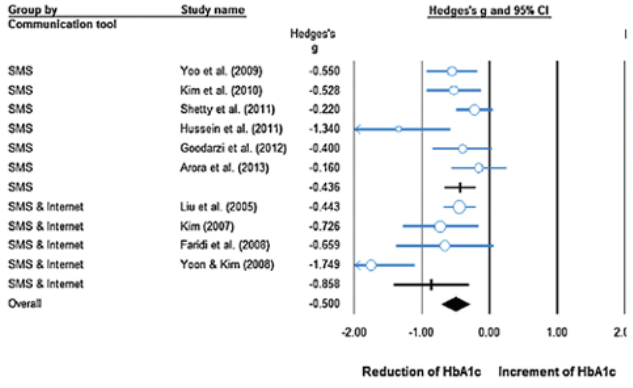


**Fig.1. Effect of SMS based interventions on HbA1c. (Saffari et al)**

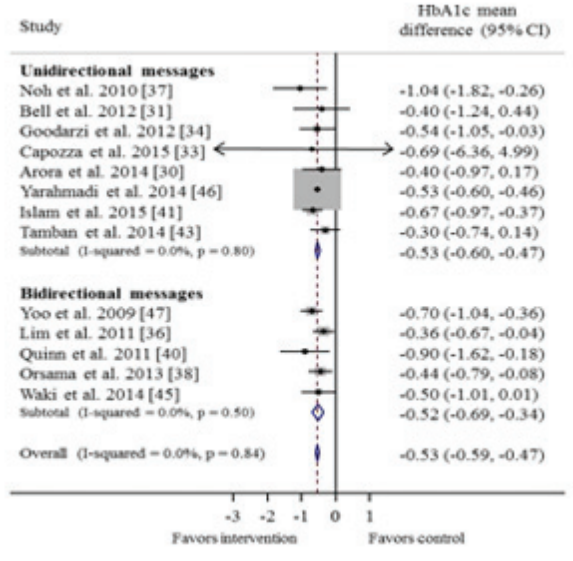


**Fig.2. Effect of SMS based interventions on HbA1c. (Carukshi et al)**

**Role of SMS in Medication adherence:**

Farmer et al assessed the impact of SMSbased intervention to support medication adherence in patients with T2DM and found a small but statistically significant effect sizes for improvement in adherence(14) (Fig.3). Although interventions based on SMS and monitoring may appear promising to improve medication adherence in patients with T2DM at low cost,good evidence is still scarce and more high-quality theory based research is needed (15;16).

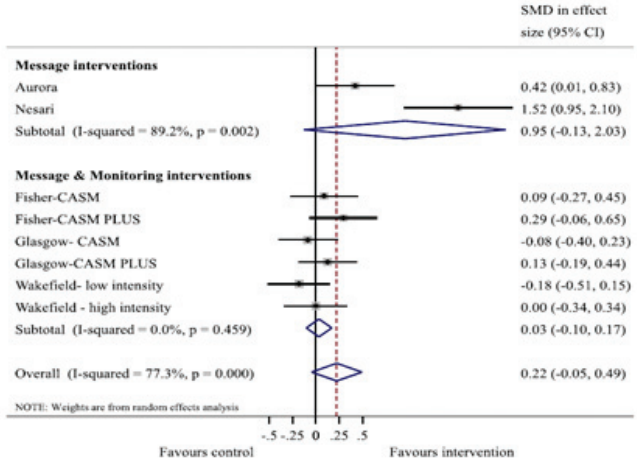


**Fig.3. Effect of SMS based intervention on medication adherence (Farmer et al)**

**Role of SMS in Insulin dose titration:**

Mobile Insulin Titration Intervention (MITI), a pilot study using SMS and phone calls showed that greater proportion of patients reached their optimal insulin glargine dose than patients in the usual care arm (88% vs 37%, P<.001). MITI is an effective way to help low socio economic state patients reach their optimal insulin glargine dose, as it is cost saving in terms of time for patients, who are able to have their insulin titrated without multiple clinic appointments(17).

**Cost effectiveness of SMS based intervention for Diabetes:**

Wong et al simulated the costs and effectiveness outcomes of the SMS intervention and usual clinical practice showed that the SMS intervention was a low-cost and effective program for T2DM prevention in subjects with impaired glucose tolerance, resulting in cost-saving to health service provider regardless of 2-year trial and 50-year lifetime periods. Within the two-

year trial period, the SMS intervention managed to reduce 5.05% onset of diabetes, resulting in saving $118.39 per subject over two years.In the lifetime model, the SMS intervention dominated the control by gainingan additional 0.071 QALY and saving $1020.35 per person(18).

**Patient satisfaction with SMS based intervention for Diabetes:**

Samantha et al evaluated patient satisfaction and perceptions regarding the modern health technological devices, including SMS reminder systems in patients with diabetes. The meta-analysis included 32 studies and found that feedback from patients was positive regarding almost all devices and did not differ by intervention type or outcome measure. Majority of the participants reported high satisfaction, indicated a desire to continue usingand would also recommend to others (19).

**Impact in different situations:**

Automated messaging service may have fostered a feeling of support by mimicking personalized messages that would normally besent by humans and making participants feel connected withthe system (20). A web-based program sending automatic SMS reminders will be more effective rather than manual texting(13). Effects of a single media approach such as SMS only versus a multimedia approach such as the concurrent use of SMS and the internet suggests that applying several media to convey health messages is a more successful intervention. Interventions conducted in low- and middle-income countries showed agreater impact than those conducted in high-income countries(13).

**Conclusion:**

SMS is a great mHealth tool for managing diabetes and especially in countries like India where the number of mobile users as well as the number of patients with diabetes is huge. SMS based programs can be used for improving outcomes in terms of glycemic control, self-care management, patient education and cost effectiveness,among patients with diabetes and canbe implemented wherever feasible. More studies needed to study the impact in various resources settings and different patient profiles.

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*Update Article*

# WILL GLOBAL LONGITUDINAL STRAIN REPLACE EJECTION FRACTION

**B. Mishra**


## Abstract

Echocardiography is the procedure of choice for assessment of cardiac structure and function. Estimation of left ventricular systolic function expressed as ejection fraction (EF) is the most frequently measured parameter. For several years EF remained the most important prognostic indicator in almost all kind of cardiac disorder. Methods of estimation EF has evolved from M-Mode to 2D to 3D with several refinements in technology. However, these volumetric indices have inherent limitations and measurement errors. Assessment of myocardial fibre deformation has recently become accepted as a reliable technique in assessing LV systolic , diastolic and regional function. Speckle-tracking imaging, the most accepted mode in routine clinical practice is based on frame-to-frame tracking of acoustic markers (speckles) obtained from gray-scale echocardiographic images. Out of all deformation parameters global longitudinal strain (GLS) is shown to be a robust marker of LV systolic function even before EF is actually reduced. Several studies have proven its superiority than EF as a prognostic indicator. As measurement of GLS will be practised widely and data accumulates, GLS has the potential of replacing EF in future.


**Key words:** Systolic Function, Ejection Fraction, Global Longitudinal Strain, Heart failure

## Ejection Fraction (EF): The Time-Honoured Parameter

Echocardiography (Echo) plays the most crucial role in determination of cardiac structural anomaly, functional impairment and therapeutic decision in all types of heart diseases. Because of its non-invasive nature, relatively low cost, ease of access, minimal patient discomfort, ability to perform at bedside and absence of patient risk, echo has emerged as the method of choice for diagnosis and follow-up of all kind of cardiac anomalies.[1] There are several echocardiographic markers or surrogates of left ventricular LV systolic function (Table-1), but Ejection Fraction (EF) is the most frequently measured parameter for determining LV systolic function. EF is expressed from LV end-diastolic volume (EDV) and end-systolic

| M-Mode | 2-D | Doppler | 2D+Doppler |
|---|---|---|---|
| Ejection Fraction | Ejection Fraction | Myocardial Performance Index | Stroke Volume |
| Fractional Shortening | Regional Wall Motion | MR Dp/Dt | |
| Velocity of Circumferential Fiber Shortening | | | |
| Mitral Annular Plane Systolic Excurtion | | | |
| E-Point Septal Separation | | | |

Table 1, Common Echocardiographic Surrogates of Left ventricular Systolic Function

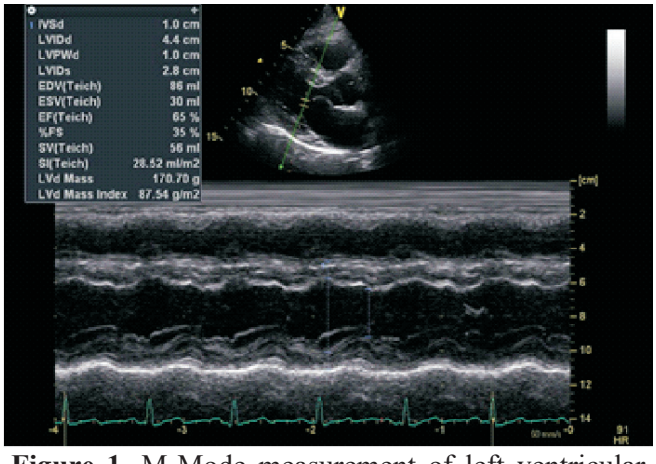


**Figure 1**. M-Mode measurement of left ventricular Ejection Fraction, systolic and diastolic dimensions are obtained along the cursor in a single line from which volumes are calculated to obtain the Ejection fraction.

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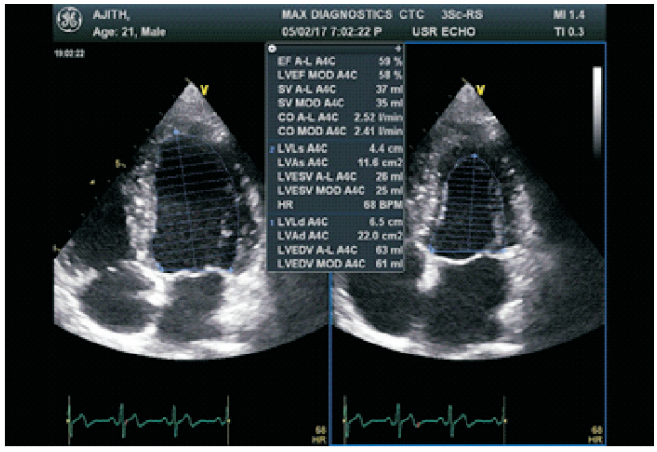


**Figure 2**. Measurement of left ventricular Ejection Fraction by 2D Echo, systolic and diastolic endocardial borders are traced from which volumes are calculated as a summation of disks (Simpson's rule) to obtain the Ejection fraction.

volume (EDV) with the formula (EDV – ESV).100/ EDV. Although EF can be measured by nuclear techniques, MRI or recent generation CT scans; 2-Dimensional echocardiography (2-D Echo) continues to be the most frequent method in clinical practice, though the gold standard for EF is MRI. Earlier determination of EF by M-Mode Echo (**Figure 1**) is no more recommended due to its inherent methods of presumption of different geometric shapes of the ventricle from the minor axis of LV. Presumptions of geometric shapes makes this method inaccurate in pathologically remodelled LVs, in presence of regional wall motion abnormalities and aneurysms. Current guidelines recommend global EF to be measured by 2D Echo by biplane disc summation method of Simpson's rule (**Figure 2**). It has done away with many drawbacks of M-mode techniques.[2]

**Limitations of EF**

EF is most commonly estimated by 2D echo. It is widely used in clinical practice. LV EF is the most important prognostic marker in almost all kind of heart diseases and has been established as a predictor of mortality.[3] However, 2D measurement of LV EF depends on factors such as image quality, tracing of the endocardium, and geometric assumptions. 2D Echo measurement of EF requires manual tracing of the endocardial borders. Inherent limitation of image acquisition, foreshortening, inadequate delineation of endocardial border makes the results highly variable which can be as high as 14%.[4] Recent developments like automatic enodocardial border detection, use of harmonics, contrast agents and 3-D Echo has increased the accuracy but limited by its cost and unavailability in a wide scale.[5]

In view of these limitations and time consuming methods, visual assessment of EF also known as 'eye balling' is the most commonly adopted method in most of the echocardiographic laboratories throughout the world. An experienced echocardiographer can near accurately predict the EF by seeing 2-D images in multiple views. Visual estimation of EF although accepted by many clinician for treatment decision, it is not a recommended method as because it is highly subjective, operator dependent and is rarely reproducible accurately. It has high intra and inter-observer variability.[6]

**Deformation/Strain Imaging: The Novel Marker of Systolic Function**

Limitations of EF led to research for a better method of determination of LV systolic function. M-Mode and 2-D Echo methods of measuring EF is basically dependent on calculation of LV volume by different methods. Development of tissue Doppler based imaging (TDI) made possible to measure deformation of different parts of myocardium. In the heart, the myocardial fibres have three directions longitudinal, circumferential and transmural. In systole, myocardial muscle shortens in the longitudinal, and circumferential dimensions and thickens in transmural direction. Because different myocardial fibers have different velocities and directions so the myocardium will change its shape during contraction which is known as deformity and measured by Strain and Strain Rate. The strain (å) is the rate by which the deformation occurs and derived from Lagrangian formula å = (L ˇ ô˘$%ô˘˘ Lo)/Lo where Lo is baseline length and L is the instantaneous length at the time of measurement. As it is a ratio, it is unitless, where as Strain Rate ( Ý) is calculated as change in velocity between 2 points (V1 and V2) divided by the distance L, Ý = (V1 - ô˘$%ô˘˘ V2)/L. positive strain means elongation, whereas negative strain is shortening. It represents the percentage change in myocardial fiber length from its original dimension. However, tethering and translational motion, difficulty

in ultrasound beam orientation remained major drawbacks in TDI based strain/deformation imaging.

Ongoing research and development made possible emergence of a novel technique that is 2D speckle tracking imaging (2DSTE) as a better and easier to do method for assessing LV systolic function.[7] It has overcome many drawbacks of TDI based deformation imaging. 2DSTE is based on measurement of the displacement of speckles on the 2-D Echo images. Speckles are natural acoustic markers in grey scale ultrasound images that form interference patterns within myocardial tissue. These patterns are quite stable over the short period of time between two consecutive frames, and the 2D displacement for each point in the myocardium is found by automatic search for similar patterns in the two frames, inbuilt software automatically calculates the strain and strain rate.[8] Strains are calculated from each LV segment in circumferential, longitudinal, or radial directions.[9] Most laboratories record LV strain in the long axis and use global longitudinal strain (GLS) calculated as the average from all segments, as a measure of global LV function (**Figure 3)**. Images for GLS are made in standard apical two, three-, and four-chamber views and aortic valve closure (AVC) is used for timing of end-systole.[10]

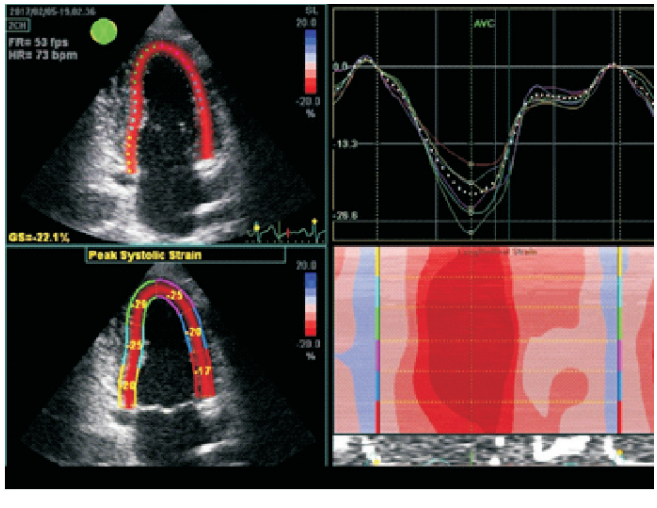


**Figure 3**. Longitudinal Strain obtained in apical 2-chamber view. Upper panel depicts strain in different segment coded in different colour, AVC is aortic valve closure. Lower panel left image shows strain values in different segments, average strain from different segments is the global longitudinal strain, right image shows colour coded strain in anatomical M-mode depiction.

## GLS: A Better Marker of Systolic Function than EF

GLS reflects the longitudinal contraction of the myocardium and its accuracy has been validated against tagged magnetic resonance imaging (MRI)[11]. This method is less operator dependent, more reproducible than EF, easily measured and more reproducable.[12] Several studies have shown the usefulness of 2DSTE derived GLS as a replacement of or an addition to LV EF for the prediction of outcome in different clinical settings. [13–15] Evidence of the predictive power of GLS and its superiority over conventional echocardiographic function parameters is growing. An increasing number of studies have suggested that GLS is superior to EF as a measure of LV function and as predictor of mortality and cardiac events.[16] In a number of cardiac disorders, the ability of GLS obtained by 2DSTE to predict cardiovascular outcome may be superior to LVEF.[17] In the general population and in patients with heart failure, GLS was shown to be a superior predictor of cardiac events and all-cause mortality compared to EF [18, 19]. More recently, GLS was found to be a robust prognostic marker following myocardial infarction[20] and cardiac surgery[21]. GLS has also been shown as superior predictor of adverse events in patients with cardiomyopathy[22] , aortic stenosis[23] and in heart failure with reduced EF[24]. Reduction of GLS before EF is reduced makes it a tool for very early evaluation of LV function particularly in those receiving cancer chemotherapy.[25]

## Conclusion

The amount of evidence of the superiority of GLS over conventional EF is growing. As our understanding of the mechanism of the similarities and the differences between GLS and other parameters such as LVEF is increases, its application may increase widely. Further development of strain imaging including 3D strain will result in better standardization and more clinical use. Further automation of the technique will definitely do away with operator dependency and improve its diagnostic power. As strain imaging is able to identify LV systolic dysfunction earlier than conventional methods, this has the potential for pre-clinical diagnosis and a role in heart failure prophylaxis and primary prevention.

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