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Editorial

The Impact of New Technology in Health Research :

Medical Education, Bio-medical Research, and Continuing Professional Development

The Department of Health Research (DHR) was created in 2007 with the vision of promoting and coordinating basic, applied, clinical and operational research in areas related to medicine, health, bio-medicine and medical as well as para-professional education through development of infrastructure, human resource and skills in cutting-edge areas. At the same time, the Indian Council for Medical Research (ICMR) has its own network of large number of National Institutes and also a strong and vibrant culture of extramural research in medical colleges and other institutes. These institutions conducting innovative bio-medical research are likely to be further expanded in the future.

The strategies for health research in the 12th Five-Year Plan were proposed to be the following:

Address national health priorities: The key outcome of the efforts of DHR would be to generate intellectual capital, which may have a public health impact. DHR would, therefore, prioritize its research to find cost-effective solutions for health priorities and health system issues facing the country, namely:

1. Maternal and child nutrition, health and survival;
2. High fertility in parts of the country;
3. Low child sex ratio and discrimination against the girl child;
4. Prevention, early detection, treatment, rehabilitation to reduce burden of diseases-communicable, non-communicable (including mental/psychiatric illnesses) and injuries (especially road traffic related), congenital malformation and disorders of sex development;
5. Sustainable health financing aimed at reducing household's out-of-pocket expenditure;
6. Health Information Systems (HIS) covering universal vital registration, community based monitoring, disease surveillance and hospital based information systems for prevention, treatment and teaching;
7. Measures to address social determinants of health and inequity, particularly among marginalized populations;
8. Suggest and regularly update Standard Treatment Guidelines which are both necessary and cost-effective for wider adaptation;
9. Public Health systems and their strengthening; and
10. Health regulation, particularly on ethical issues in research.

Build Research Coordination Framework: Though DHR is the empowered Department on medical and health research, many organizations are engaged in research on related topics, namely the Ministry of Environment and Forest, Departments of Health and Family Welfare, AYUSH, AIDS control, Space, Science and Technology, Biotechnology, Agricultural Research; agencies like ICAR, DSIR, CSIR, NDMA, DRDO and the National Knowledge Network. DHR would play a lead role in research involving human health, bringing all the concerned organizations on one platform to facilitate mutual discussion, resource pooling and prioritization, and avoid duplication, to find innovative solutions to national priorities in a timely manner. Some of these issues will be highlighted in the next issue of the Annals on **'Research in Medical Education'***.

Use of Information and Communication Technology (ICT) in health can be broadly in four areas viz. Education, Research, Referral, and Management of Data. National Knowledge Network (NKN) connects approximate 1500 knowledge institutions in India. NKN was launched in March, 2010. As a network, NKN will continue for 10 years. NKN supports 1 Gbps (Giga Bits Per Second) connection today. NKN encompasses all engineering, science, medicine and agriculture institutions that are engaged in education and research. Using the principle of coherent synergy, NKN expects to provide an ambience in which researchers learn from each other and work on problems that are transdisciplinary in nature.

Health and Education:

When ICT is applied to medical education, it is possible to make high quality education available pan India seamlessly. NKN does just that. In fact, unified effort by practicing medical doctors, clinical and para-clinical researchers, medical research institutions, academies such as National Academy of Medical Sciences and a host of other such institutions from engineering and sciences (especially biosciences) can significantly enhance the effectiveness and reach of medical education.

National Centre for Information Technology (IT) and Telemedicine:

There is an urgent need to incorporate the power of modern computational systems into the biomedical programmes so as to enlarge the scope and reach of telemedicine both for enhancing the quality of health care as also for enlarging the reach of continuing professional development. With the availability of National Knowledge Network (NKN), tertiary care institutions as well as National Academy of Medical Sciences must be connected with a large number of professional institutions.

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* Volume 51 (1&2), January-June, 2015

The advancing knowledge, innovative and new technologies and skills can thus be widely disseminated.

Acknowledgement :

The views expressed in this Editorial are based on the report of the Working Group on Tertiary Care Institutions for the 12th Five-Year Plan (2012-17)*. These views reflect the collective wisdom as well as individual expertise of the Members of the Working Group. Their contributions are appreciated and acknowledged.

The impact of the information and communication technology on innovations in medical education, para-professional education, bio-medical research and cost-effective healthcare (Chapter no. 6)** are based on the major contributions of Dr. S.V. Raghavan, Scientific Secretary, Office of Principal Scientific Advisor to Government of India, New Delhi. This is gratefully acknowledged.

Chairman, Prof. J.S. Bajaj
***** Information and Communication Technology in Health Care in the Report of the Working Group on Tertiary Care Institutions, 12th Five-Year Plan (2012-17), Planning Commission, Government of India.***

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Improving child survival :Paediatric critical care training and education is the key

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SUMMARY

To reduce global under-five mortality by two-thirds by 2015 in low and middle-income countries and achieve that UN Millennium Development Goal 4, there is a need to strengthen health systems to provide good quality emergency and critical care services. This is one of the weakest area of the health system. Emergency triage and treatment has been developed for paediatric patients with promising results. Imparting training to health care providers in effective triage, fundamentals of critical care concentrating on ABC (airway, breathing, and circulation) and management of common medical emergencies can contribute substantially to child survival and improved quality of life without being resource intensive. Training increases short-term knowledge improves attitude and skills. Community education to administer simple emergency treatments at home and in village, and access the emergency care system is needed to bring down child mortality. Widespread use of radio and TV can be made to educate parents on early recognition, first-aid steps and care at health facility. All health care providers, be it Primary Health Center (PHC) workers, paramedics, nurses or doctors, should be trained in Basic Pediatric Emergency care, appropriate for their professional level. This, integrated with training in managing common medical emergencies, with appropriate guidelines, using simple emergency treatments such as suction and oro-pharyngeal airways to keep airways open, oxygen and bag-valve mask resuscitator for patients with breathing difficulty, pulse oximetery to treat hypoxemia and monitor oxygenation, oral rehydration solution, intravenous access and fluids for correction of dehydration and shock, antibiotics for pneumonia, sepsis and meningitis, emergency drugs such as diazepam etc. can be a successful way to organize critical care protocols in rural and small hospitals. Mothers and family members can be trained as care providers be it at home or in hospital to meet the resource deficit. Rather than attempting to create a system *de novo*, introducing effective triage and emergency treatments, and delivery system using established health care facilities is possible within the available resources. A framework for training commensurating with level of care and available facilities is outlined.

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DR. K.L. WIG ORATION delivered during NAMSCON 2013 at the All-India Institute of Medical Sciences, Jodhpur

Introduction

I thank the Academy for the honor and privilege to deliver an oration named after a great teacher, educationist and mentor, Padma Bhushan Dr K L Wig, in a city where I received my basic medical education. As a pediatrician with specialization in emergency and critical care, I have, for years, believed that critical care training and education can make a huge impact to health of our children. I am here today to convince you that we can bring down global under 5 mortality by imparting training and education in pediatric critical care to all the stake-holders in child health viz. families, school teachers, community leaders/health volunteers, primary level health workers, paramedical staff and physicians.

Global under-five mortality rate is to be reduced by two-thirds between 1990 and 2015 states the UN Millennium Development Goal 4 (1). There has been some progress, but under-five mortality 99% of which occurs in developing countries is not declining fast enough. No doubt, achieving this goal requires substantial strengthening of efforts to improve nutrition and hygiene, breastfeeding, immunization coverage and vitamin A supplementation as well as to improve maternal education and health. While these preventative measures are important, many children will still become ill and require treatment. Strengthening health systems and giving good quality health care is therefore vital in low-income countries. Emergency and critical care services are often one of the weakest parts of the health system and improving such care has the potential to significantly reduce mortality (2). Emergency triage and treatment has been developed for paediatric patients with promising results. Imparting training to health care providers in effective triage, fundamentals of critical care concentrating on ABC- airway, breathing, and circulation - and management of common medical emergencies can contribute substantially to the child survival and quality of life without being resource intensive.

What is critical and Emergency care?

The concept of emergency care envisages provision of immediate or urgent medical interventions- necessary to prevent death or disability. The purpose of emergency care is to stabilize patients who have a life- or limb-threatening injury or illness.

The emergency care provider should be able to distinguish a child in need of emergency or urgent care from a large numbers of less serious presentations. Studies have identified that children have higher mortality rates than adults in similar emergency situations because health care is accessed late. They are often malnourished and arrive with advanced disease severity, which lead to poor outcome.

Why Emergency Medical Care for children?

Burden of critical illness is

especially high in low-income countries (3). Most of the conditions causing death in children 'under 5' in low-income and middle income countries present with critical illness that can be successfully treated and deaths can be averted by prioritization and provision of simple, inexpensive emergency and critical care interventions. These include neonatal illnesses, pneumonia, diarrhoea, malaria, road-traffic accidents, and surgical emergencies. Every year pneumonia and diarrhea cause 1.4 and 0.8 million child deaths, respectively, worldwide. Malaria kills one million and there are as many as three million deaths in the neonatal period annually (4). HIV, road-traffic accidents, trauma, and burns also cause significant mortality (5). All it requires is a trained health functionary and a functioning health facility. Good quality emergency care can indeed be the first step in improving child survival.

Current state of Pediatric Emergency Services :

The availability and access to emergency services in India is far from satisfactory. Pediatric Emergency Care, which exists as a separate specialty in United States since 1970, is still in early stages of development in India. Further, 20 -60 % of all patients presenting to the emergency departments have urgent yet simple and uncomplicated problems that can be cared for quickly and efficiently. The situation can be improved, without much demand on resources, by training the available manpower in identification of a child in need of emergency or urgent care and management of common emergencies.

Access to Emergency and Critical Care:

Access to medical care for urgent or life-threatening conditions is a key expectation of community. Enhancing health systems responsiveness to people's expectations leads to improved utilization of services. In Sri Lanka, people expected to receive emergency care from the primary care system. They turned to primary care medical facilities for acute complaints or when a child seemed seriously ill (6). In rural Nepal, people used their health care centre more often for medical emergencies than for preventive services (7). *People expect and use primary health care in emergency.*

In India, 30% of emergency patients die before they reach a hospital. In many places it is difficult or dangerous to walk after dark and private transport is costly, so a guardian must wait until morning to start journey to hospital. A child may have been breathless or lying comatose or seizuring whole night before reaching the health care facility. It is not surprising that such children arrive moribund at the hospital. Cases referred from PHC's have to wait for hours on the road for an ambulance/transport. When a transport vehicle is available, it may start only when it is full, which makes logistic sense but delays emergency care.

Over 80% of accident victims do not achieve access to medical care within one

hour of the incident. Bystanders usually perform prehospital care, including patient transport. In a study at our centre in 2004, of 733 pediatric patients, two-third had travelled more than 100Km, 2% arrived dead (8). The situation has not improved much in 2012. Only 6.6 % referred patients arrived in ambulance; almost 50% travelled by bus, for a mean SD distance of 53.4 ± Kms shows a recently completed study of 900 arrivals to our Pediatric Emergency (unpublished data). In urban Guinea-Bissau, 20 of 124 acutely ill children died either on their way to hospital or while waiting in the reception area of an outpatient clinic (9).

There are no successful models for improving the overall provision of emergency medical care in developing countries. Prevailing models of emergency medical transport used in North America and Western Europe are costly and impractical for most LICs. *Severe resource constraints, the poor condition of roads or trails, and a lack of fuel may dictate the utilization of a wider range of option, including availability of basic emergency care at the door-step.*

Prehospital care: training of mothers as care provider :

Most emergencies start at home. But often because of family or cultural beliefs to seek traditional medication, high transport costs, and distance from health facilities delays in seeking medical care are common. Mothers may be unaware of danger signs of ill health in their children; simple instructions as to when to access a health facility if a child is ill or not improving can improve the access. Many of the benefits of pre-hospital emergency care could be realized by teaching parents about danger signs (fast breathing, inability to feed, fever, loose stools etc.) and community volunteers in simple triage and vital interventions such as establishing and maintaining a patent airway, controlling bleeding. *It requires the community to be aware of danger signs in sick and injured children and to have the ability and facility to react to them.*

In Mexico, training of mothers and first-level health care workers in the basic principles of triage- led to more prompt care seeking and significant reduction in child mortality: deaths attributed to respiratory and diarrhoeal illness by 43% and 39% respectively among children under 1 year of age and by 36% and 34% respectively in children <5 years (10). In Tigray, Ethiopia, mothers were taught to give antimalarials promptly in the home to their sick children and this was followed by a 40% reduction in under-five mortality (11).

Prehospital care: training of community volunteers as Health workers :

Community participation on emergency care is one of the weakest links in healthcare approaches in India. The community, through schools, community and religious centres can be made aware of danger signs in sick and injured children and be taught what to do when

they are found or when trauma occurs. Training a lay health worker in counting respiratory rate, heart rate, measuring temperature, use of oral rehydration solution and zinc for diarrhea, antibiotics for non severe and severe pneumonia is feasible, and it can reduce risk of death considerably. Training of lay people as community health workers have proved successful in managing simple ailments and advising parents when to go to a hospital for care. Essential clinical signs in sick children such as counting of respiratory rate and ability to drink can be easily taught to them. In rural India, the home-based management of neonatal sepsis halved mortality, and the evaluation of clinical signs showed that the presence of two of seven clinical signs were 100% sensitive and 92% specific in identifying neonatal deaths due to sepsis (12, 13). In South-East Asia and Africa, pneumonia case management at home by trained lay responders or paramedics resulted in a reduction of pneumonia mortality by 36% among infants and children under 5 (14).

In a 5 year (1997—2001) prospective study in Iraq and Cambodia, a pre-hospital trauma system was put in place in which first responders and local paramedics were taught simple danger signs and treatment protocols.135 local paramedics and 5200 lay First Responders were trained to provide trauma care in field. 1061 trauma victims with mean evacuation time 5.7 hours. The trauma mortality rate was reduced from pre-intervention level of 40% to 14.9% over the study period (95% CI 17.2 – 33.0%), and from 23.9% in 1997 to 8.8% in 2001 (15). Lay people trained in first aid can effectively respond to emergencies in a community with a high burden and low cost rural trauma systems could have a significant impact on trauma mortality in low income countries.

Poorly trained health staff, and poor access to drugs are barriers to good health service provision. Previous encounters with demoralized health staff is not conducive to rapid re-attendance. Mothers may not be encouraged to return for review and so tend to seek help from one health unit after another. This causes delay and fails to provide any continuity of care.

In a nutshell, the community and family empowerment, by building the capacity of the community in health promotion and emergency care, is needed. India has provided the evidences of the possible role of community participation in child survival through highly acclaimed Jamkhed Project and Gadchiroli model. However, it has not been utilized for policy making at a large scale. The country is at an advantage by having more than 700,000 ASHA workers to further build and strengthen the community participation and mobilization. The Village Health and Sanitation Committees (VHSCs), strong *Panchayati Raj* Institutions mechanism are the right fora, and the only need is for integrated efforts and strong political will (16).

Training at Primary Health Centre and first level referral facility :

In rural areas emergency medical care is expected and delivered from sub center to a primary health center to a community health center, and privately run small clinics and hospitals managed by general practitioners. All these health care providers must receive training in rapid assessment of severity of illness, to decide the treatment and referral. They should be able to triage, provide basic ABC care- oxygen, IV fluids, antibiotics, early referral, truama care. Training of health care providers (doctors and nurses) in a structured approach to emergency care, like the one used in most developed countries, is needed.

Training in Integrated Management of Childhood Illness (IMCI) can prepare health workers at primary healthcare units to assess, treat and refer children appropriately. Integrated management of Childhood illnesses (IMCI) developed by WHO, however, focuses on five major causes of death in childhood: diarrhea, pneumonia, malaria, measles, and malnutrition. It has been recognized that implementing IMCI guidelines implies referring up to 20% of the patients. It is these children who are severely ill and at the highest risk of death. However, many children in need of emergency/critical care do not reach the next level health facility. It is important to train PHC worker in recognition and management of time sensitive critical conditions viz. hypoxia due to respiratory illness, hypovolemia due to diarrhea or blood loss caused by injury, severe sepsis, and timely use of oxygen, fluids and antibiotics for these conditions. It may be integrated within framework or IMCI to save lives and transport costs.

Training increases short-term knowledge and improves attitude and skills. Short courses in emergency and critical care of either 20 hours or 2 weeks have had impressive effects. Training of staff in WHO's Emergency Triage Assessment And Treatment (ETAT) course which uses the same approach as other life support courses and has been validated against that in APLS has led to 50% reduction in patient mortality Malawi (17). Introducing pulse-oximeter for identification of hypoxia and monitoring the oxygen therapy, and training of health care providers in its use, reduced case fatality rates for pneumonia by 35% in Papua New Guinea (18).

Pre-hospital Transport :

In a study at our centre in 2004, of 733 pediatric patients only 2% of patients were transported to the emergency department (ED) by ambulances, only 15% had emergency drugs and fluids during transport, 2% arrived dead (8). In 2012, the proportion that travelled by an Ambulance was 6.6% . Given the current scenario, any mode of transportation that gets a patient to a facility where definitive care is available, is acceptable. Motorized transport for moving patients to the nearest health care facility, using triage criteria to ensure efficient and timely utilization of existing resources is needed

at every level.

Ambulance drivers, as a minimum, should be taught basic first aid. National or regional guidelines for triage, patient delivery decisions, and prehospital treatment plans are needed. An efficient ambulance service manned by trained paramedics can make a significant contribution. With 1 team to 50000 people the response times could be as low as 4-6 min; (19) while with 1 team per 600000 people recorded an average response time of 30 minutes (20). Training paramedics in basic life-saving skills improves patients' outcome (20).

Access to Emergency Care in a Large City Hospitals: Clearing the Maze

Trouble is not yet over when a sick child arrives in a large hospital in a city despite all the barriers discussed above, be it a District Hospital, Medical College Hospital or a Corporate Chain Hospital. Fifty percent of deaths of children in hospital occur within 24 hours of admission. While some of these children are too ill to be saved, most have reversible disease that can respond to quick resuscitative therapies such as oxygen, fluids and antibiotics. But very often precious time is lost in locating the place and the personnel that will render emergency /critical care. There is often no separately identified emergency care area, and here I am not asking for a separate area for emergency care of children as needs of critically children differ from those of adults. Patients are first seen in outpatients or ward. Clinicians see the patients in the order they arrive. There is usually little prioritizing of patients and no formal triage system. Once a critically ill patient is identified, there can be delays in accessing emergency drugs and providing essential treatment. The critically ill are often admitted to general ward in first level hospitals or pediatric wards in a referral/district hospital. Most of the hospitals do not have an ICU. Essential clinical signs in sick children such as respiratory rate and ability to drink are frequently not sought or recorded. Established treatments and supportive therapies are not used and global strategies or national guidelines are not followed.

Plan an emergency receiving area :

Critically ill children need rapid identification, prioritization and urgent treatment, and where hospital systems don't provide this the result can be disastrous. The receiving area in a hospital should be planned: it should be accessible and well sign-posted; have a resuscitation room or area with emergency equipment at hand, and an area where the doctor examines and treat children. No doubt, there is a resource limitation; there is a severe lack of doctors, nurses, and other health staff (21). Too few health professionals have been trained, and many are subsequently lost to other jobs or to the 'brain drain' to richer countries (22). The quality of care, however, can be improved by ongoing training in critically care.

Triage and Resuscitation Training :

Triage is a brief clinical assessment that determines the time and sequence in which patients should be seen in the casualty or, if in the field, the speed of transport and choice of hospital destination. These decisions are based on a short evaluation of the patient's overall appearance, history of illness and/or injury, and an assessment vital signs and mental status within 30-60 seconds. Triaging gets priority over registration in Emergency. Children presenting in cardiopulmonary failure or arrest, shock or respiratory distress need to be identified and treated without delay. *Training the doctors and nurses through short courses, lasting one to one and half days, in a systematic approach to patient assessment, categorization of illness and treatment using clear guidelines can achieve these goals.* In a study from a large volume pediatric emergency department from Chennai central-peripheral temperature gap and respiratory failure requiring manual ventilation were found to be major risk factors for mortality in the children aged > l year. Among the post neonatal group, poor pulse volume and respiratory failure were strong risk factors (23). Given these observations, the clinical features of circulatory and respiratory failure at presentation as proposed in Pediatric Advanced Life Support (PALS), APLS and ETAT guidelines with some modification can be useful for triage decisions even in the under resourced emergency departments' of the developing countries. Further, the training in resuscitation priorities can focus on appropriate use of oxygen, bag mask ventilation, intravenous access, fluid boluses and timely administration of antibiotics Resuscitation training in developing countries is well received and viewed as valuable. Trauma and newborn resuscitation in developing countries has significantly reduced mortality, but similar data on patient survival after pediatric resuscitation are not available (24).

Basic Critical Care Training :

World Health Organization states that every hospital where surgery and anesthesia are performed should have an ICU, but only a handful of hospitals do so. There is a misconception that critical care has to be complicated and technologically sophisticated. Physicians and nurses are rarely trained in critical care and lack the knowledge and methods for caring for the critically ill. Working in such under resourced hospitals can lead to a sense of fatalism whereby very sick children are presumed to be beyond saving and left to take their chances. It is therefore important to have limited–resource intensive care unit offering treatment for time sensitive conditions such as severe sepsis and shock, upper and lower respiratory illness causing respiratory failure, severe dehydration and hypovalemia, suited to local needs, and establish appropriate training for all levels of personnel in critical and emergency care.

Table 1: Distribution of 43,800 patients attending pediatric emergency (PGIMER between 1990-2000, with respect to major diagnosis)

Major Illness	**No. of patients (percentage of total)**
Gastrointestinal	**10173(23.3%)**
Diarrhoea	7724
Intestinal obstruction	536
Acute liver failure	49
Others	1387
Respiratory	**10269(23.44%**
Upper respiratory infection (URI)	3183
Pneumonia	2695
Asthma	2302
Others	2089
Central Nervous System	**7038(16.07%)**
Seizures	3096
Meningitis (bacterial, aseptic)	1222
Encephalitis	669
Others	2051
Neonatal illnesses	**6830(15.59%)**
Suspected sepsis	1657
Jaundice	1577
Birth Asphyxia	951
Others	2645
Systemic infections	**2849(6.73%)**
Septicemia	1126
Malaria	822
Enteric Fever	493
Others	408
Cardiac	**2070 (4.9%)**
Acyanotic heart disease	960
Congenital cyanotic heart disease	863
Others	247
Hematological	**2034(4.8%)**
Renal	**1996(4.3%)**
Poisoning	**253 (0.58%)**

Adapted from – Reference no. (26)

Table 2: Important causes of morbidity in patients attending pediatric emergency service: comparison of a tertiary care hospital vs a community hospital

Type of Morbidity	Number of patients (%) seen at	
	Community Hospital Naraingarh (%)	Tertiary care hospital PGIMER (%)
Total	596	8301
GIT	249(41)	1713(21)
Diarrhea	228	1175
With no dehydration	151	823
With some dehydration	77	352
Hepatitis	3	96
Abdominal pain	11	129
ARI	108(18)	2003(24)
Pneumonia	87	494
URI	11	703
Asthma	4	468
Foreign body	Nil	53
Neonates	69(11)	1360(16)
Neonatal sepsis	65	408
Neonatal jaundice	4	402
CNS	35(6)	1374(17)
Seizures generalized	17	195
Febrile seizures	3	64
Focal Seizure	NA	325
Hematological	5(1)	223(3)
Sepsis	13(2)	80(1)
Fever without focus	60(10)	31(<1)
Poisoning	5(1)	184(2.3)

Adapted from Reference (7)

Planning the Training of Health care providers :

Periodic audit is essential to prioritize contents of training and allocation of resources. Knowledge of the spectrum of the diseases along with seasonal and temporal variations can help in planning the services and training suitable for given time and place. The spectrum of pediatric emergencies as seen in our hospital is given in the Table 1. In our experience, the comparative disease burden of pediatric emergencies in a

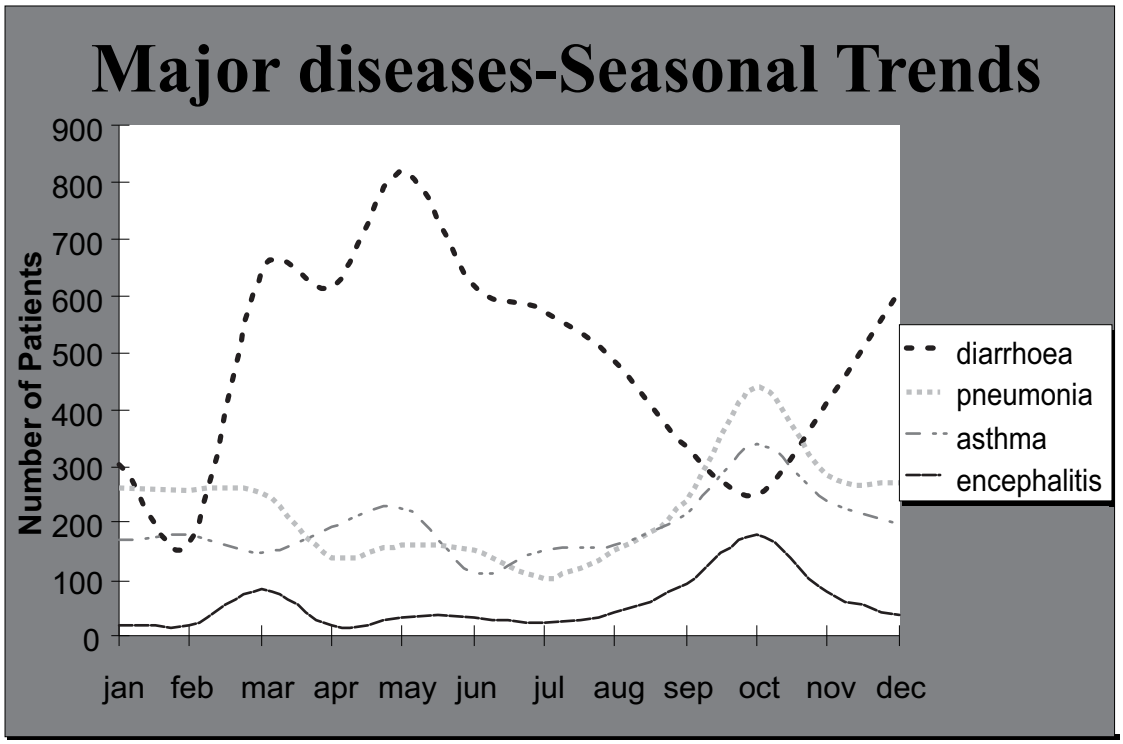

Figure 1: Seasonal variations in major emergencies presenting to Pediatric Emergency Service, PGIMER, 1995-2000, based on data of 45000 patients.

community vs. tertiary care hospital reveal that Diarrhea, Acute Respiratory infections and Neonatal illnesses, which included birth asphyxia, sepsis and prematurity, were the frequent causes of morbidity at both the places (Table 2) (8). The peak numbers of emergency visits in both the hospitals were reached in the monsoon months of July-August (25). Peak of respiratory illnesses was seen in winters and diarrhea in summers (figure 1) (26). About half (52.5%) of the patients were infants. Fever (29.5%), breathing difficulty (17.4%) and diarrhea (14.5%) were the most common presenting symptoms. Respiratory and gastrointestinal illnesses were the two commonest pediatric emergencies. About 2% (n-198) patients died within 24 hours of hospitalization; 42.3% deaths were in the age group of 0-28 days. Sepsis was the commonest diagnosis in patients who died (25). The allocation of resources and training priorities can be optimized according to the seasonal variation in disease frequency.

Planning the resuscitative measures and equipment required :

In a study of nearly 2000 children below 5 years brought to our Pediatric Emergency, 25% of the children required resuscitation in one form or other.

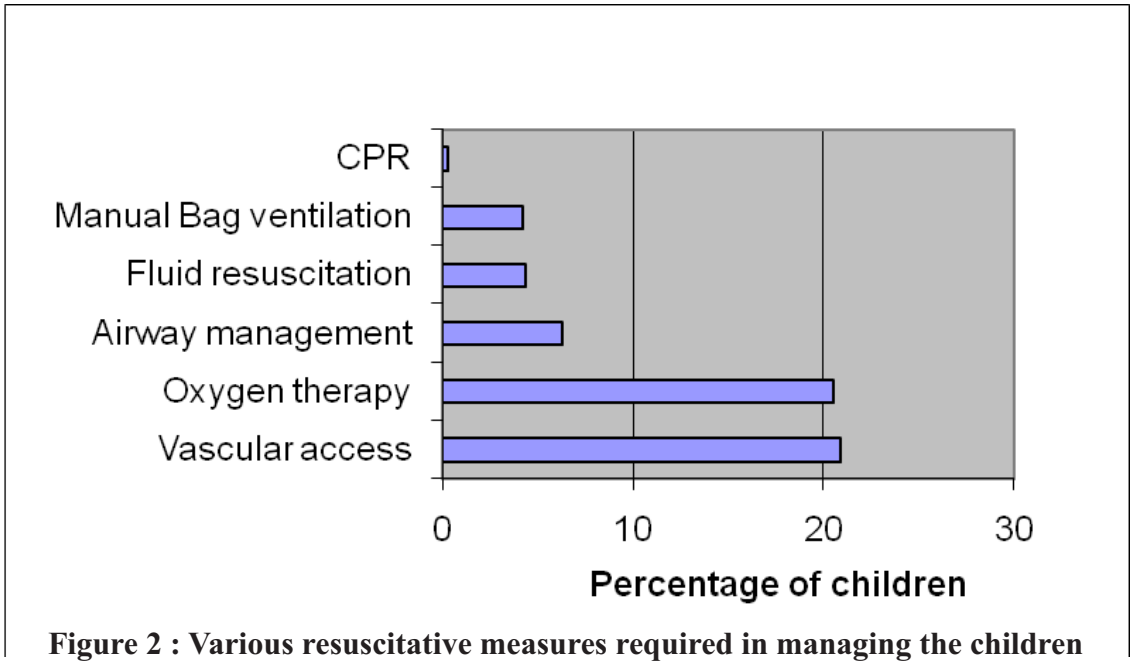

Figure 2 : Various resuscitative measures required in managing the children treated at Pediatric Emergency Unit, PGIMER, 2005-06.

Frequencies of various resuscitation measures in three different age groups are given in the Figure 2. The data implies that training in simple procedures like use of oxygen, airway management; manual bag ventilation, intravenous access and fluid administration are good enough for dealing with almost all the pediatric emergencies. These can be integrated in Pediatric Advanced Life Support training courses for primary care programmes to improve child survival.

Learning the ABCD :

In a qualitative study of 21 hospitals (13 district hospitals and 8 teaching hospitals) in seven developing countries, emergency treatment areas were mostly poorly organized and lacked essential supplies, families were routinely required to buy emergency drugs. Fourteen facilities (10 of 13 district hospitals) did not have an adequate triage system. Poor clinical assessments in 41% and potentially harmful delays occurred in 19% of children (27).

Paediatric emergency care is a relatively new discipline, only recognized as a separate entity in the 1980s. Traditional medical teaching has emphasized ward-based clinical skills. Little thought and less teaching has gone into healthcare delivery and the management of emergencies in which the diagnosis is not clear and treatment must be guided by the ABCD approach (Airway, Breathing, Circulation, Dehydration). There have been several appeals for emergency paediatric care in developing countries. The time has come

for paediatric emergency care to be recognized and established in health care system of developing countries. Emergency pediatricians should develop and deliver training courses for health staff and rapidly raise the standard of emergency care. They should provide the much-needed senior clinical supervision in the emergency department.

Pediatric Emergency Department in Tertiary Care Hospitals :

The emergency department (ED) should be located on the ground floor, with direct access from the main road with ample space for ambulances and parking. Though it should be physically separate from other areas in the hospital; it should be easily accessible from the intensive care unit (ICU), and all essential support services including radiology and blood bank. This will facilitate prompt care of the ill child in a facility close to an area where maximal resuscitation expertise is available. The emergency departments should always have a provision to cater to a major disaster involving many children'.

Our model of Pediatric Emergency is shown in figure 2. Clinical facilities include distinct areas for initial triage and resuscitation, Procedure/treatment area for both minor and major procedures, Monitoring and treatment area for the critically ill children and observation area for short stay. There is a separate area for the neonates and for children with diarrhea, as they constitute nearly 16% and 23% of our patients load. There is a separate isolation room for children with communicable diseases. Administrative and public areas include reception, space /room for the staff, ambulance driver and attendant. Public waiting areas have toilet facilities, water coolers, public telephones and facility for charging the mobile phones, snack bar, a vending machine and an ATM.

Personnel and training :

Staffing an emergency department has always been a challenge. Ideally pediatricians with skills, knowledge and commitment to care for critically ill children and nurses trained in resuscitation and emergency care should be present 24 hours per day, 7 days per week in large hospitals. In small emergency rooms providing a basic facility, a trained assistant or a resident can supplement the work of a pediatrician who is promptly available for supervision and provide directions to the staff.

The training activities to improve the initial emergency management of severely ill children should receive substantial attention and resources so that the doctors and nurses are prepared to deliver the most updated standardized emergency management. Training courses such as the Pediatric Advanced Life Support (PALS) and nursing & paramedic pediatric emergency curricula can be adapted to local needs. National guidelines on setting up pediatric emergency care and life support courses have been developed by Indian Academy of Pediatrics for doctors and nurses & Basic Life Support training for lay people,

school teachers, high school students etc. Our endeavor is to train all the physicians and nurses involved directly in care of sick children in pediatric advanced life support course adapted and integrated for limited resources followed by recertification at regular intervals. In teaching institutions new resident doctors regularly replace the trained residents to provide 24-hour emergency coverage. Hence, ongoing training and teaching should be an inherent part of functioning emergency department. The management of common pediatric emergencies should follow set practices protocols determined prior to child attending the ED. These give a framework for junior and inexperienced physicians to practice safe and immediate care. Appropriate routines and protocols can result in better management of patients and more efficient use of resources (28, 29). Within this framework there should be supervision of experienced physicians to help and advice with difficult cases. As a general rule these protocols should be adhered to in the first instance and only varied by senior advice.

Conclusion :

We need to enhance healthcare professionals' education and training in pediatric critical care at all levels. We also need to define (and develop) minimal guidelines and "standards" for patient care and develop a pediatric data surveillance system, and standardization for facility recognition.

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Reducing the burden of neurological disorders in children in India- Mission Possible!

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SUMMARY

The burden of neurological disorders in children in India is enormous. Unlike that in developed countries, largely preventable conditions such as epilepsy, CNS infections, and neurodevelopmental disorders constitute over 80% of the burden. According to UN estimates there are ≈ 40 million disabled children in India. An estimated 5 million children in India suffer from epilepsy. Neurocysticercosis accounts for >60% of acquired epilepsy, 20% of our neurology OPD cases, and for > 1500 children seen annually in our clinic. Neurological illnesses constitute about a fourth of pediatric emergencies, and over a third of PICU admissions. CNS infections are responsible for 60% of non-traumatic coma and > 60% of refractory status epilepticus in hospital and for serious sequelae in ≈ 40% children. Cerebral malaria and tubercular meningitis cause significant neuromorbidity in many regions. Preventable birth asphyxia occurs in 0.51 million newborns per year and is a risk factor in >50% cases of cerebral palsy. Preventable causes of acquired cerebral palsy continue to be seen over 2 decades in ≈ 20% cases; of these CNS infections and kernicterus account for >60% and >35% of cases. In India 71 million people have iodine deficiency; 5.8% cases of mental retardation in North India are because of inborn errors of metabolism; upto 70% of visual and 50% of hearing disabilities are preventable.

Proven preventive strategies against most of these conditions exist. Over 75% of' meningitis can be prevented through universal immunization. Hib meningitis is almost eliminated from UK and USA after universal Hib immunization; in our hospital the

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overall burden of meningitis decreased by about 50% and that of Hib meningitis from 32% to almost nil after introduction of immunization. Japanese encephalitis (JE) has also been eliminated from Japan, Korea and China after vaccination; we too can stop devastating outbreaks of JE and reduce the annual burden of 8247 cases with vaccination. Neurocysticercosis and JE can be fully controlled with improved sanitation, animal husbandry and public education; consequently the incidence of epilepsy can be reduced. Mass human chemotherapy with niclosamide and praziquantel can reduce intestinal tapeworm by 90-95%. Vaccination and chemotherapy of pigs can reduce cysts by 99.9%. Birth asphyxia can be reduced by almost 50% with community based interventions. Iodine supplementation program has improved cognitive and developmental scores of babies. Newborn screening for metabolic disorders can reduce neuromorbidity and save about 10,800 lives annually.

Secondary prevention is equally important. Immediate appropriate antibiotic therapy significantly reduces mortality and morbidity of bacterial meningitis. Early cysticidal therapy increases resolution of neurocysticercosis lesions and reduces seizures. Therapeutic hypothermia has a relative risk reduction of 25% on mortality and neurodevelopmental disability in asphyxiated infants. Kernicterus can be eliminated with simple interventions. Acute shortage of pediatric neurologists in India necessitates training of medical officers and pediatricians at all levels to ensure early appropriate management of common neurological disorders in children.

The burden of neurological disorders in children in India is enormous with overall prevalence rate of 1-3% in children <5 years of age (1). In a population-based study from North India, the prevalence of major neurological disorders among children <10 years of age was 0.7% (2). Unlike those in developed countries, largely preventable conditions such as epilepsy, central nervous system (CNS) infections, and neurodevelopmental disorders constitute over 80% of the burden in childhood in developing countries (3).

A. Childhood Epilepsy :

An estimated 5 million children in India suffer from epilepsy. The prevalence of epilepsy in India is estimated between 5.4-22.2 per 1000 population (4, 5). Each year we see approximately 30,000 patients in our pediatric neurology outpatient department (OPD); epilepsy constitutes 85% of these. In our house-to-house survey of 3684 children in the age group 1-18 years, the incidence of epilepsy was 6.24 per 1000 population (5.48 urban, 6.99 rural) for Chandigarh (6). The treatment gap in India varies from 38-78% (7, 8); our study showed a treatment gap of 22% in Chandigarh inspite of relatively good health-care facilities and predominantly educated population (6). Extrapolating this to the total number of children with epilepsy,

approximately 1.1 million children do not get proper treatment inspite of being diagnosed with epilepsy. There are several acquired and preventable causes of epilepsy in addition to genetic causes in India such as infections and neurodevelopmental disorders such as Cerebral Palsy (CP) (9).

a) Infectious Causes :

(i) Neurocysticercosis

Neurocysticercosis is the commonest cause of acquired epilepsy in our country (9). NCC constitutes almost 30% of epilepsy cases seen in our OPD and causes >60% of partial seizures in children (10). Over 1500 cases with NCC are seen in our clinic annually. In our series of 500 children with NCC (11), we found that >90% presented with seizures-mostly (83.7%) partial seizures. Most (76%) children had single enhancing lesions on computed tomography (CT) (Table 1) (11).

Preventive Strategies :

Primary

NCC can be prevented by ensuring proper hygiene and sanitation, community interventions and enforcing strict animal husbandry and meat inspection procedures (12). Mass human chemotherapy with niclosamide and praziquantel can reduce intestinal tapeworms by 90-95%. Vaccination with newer effective vaccines such as TSOL18 and treatment with oxfendazole of pigs has been shown to reduce cysts by 99.9% (13, 14). An educational program of farmers in Kenya increased their awareness about limiting exposure to tapeworm eggs and about tethering their pigs (15).

Secondary

There was considerable controversy regarding treatment of enhancing lesions due to NCC with cysticidal therapy as these lesions were thought to represent degenerating lesions. Our placebo controlled study on 63 children showed that the use of Albendazole therapy was associated with a significantly faster and increased resolution of single lesions at 1 month (41% vs. 16.2%) (p 0.05) and after 3 months (64.5% vs. 37.5%) ($p<0.05$). Seizure recurrence after 4 weeks was less in the Albendazole treated group (31.3%) versus placebo group (12.9%) (Figure1) (16).

Subsequently other studies confirmed these findings and a recent Cochrane analysis concluded that cysticidal therapy was effective in increasing the resolution of lesions and in decreasing seizure recurrence (17). Based on this evidence the American Academy of Neurology recently recommended the use of cysticidal therapy for the treatment of enhancing lesions (18). However, the treatment involved administration of cysticidal therapy for 4 weeks and anti-epileptic therapy for two years. Our

Table 1: Signs and symptoms at presentation and CT findings in 500 children with NCC

Sign or symptom	**Number of cases (%) (N=500)**
Seizures	474 (94.8%)
Nausea/vomiting	157 (31.4%)
Headache	141 (28.2%)
Papilledema	33 (6.6%)
Motor neurodeficits	20 (4%)
Cranial nerve palsy	6 (1.2%)
Extraneural cyst	3 (0.6%)
Lesion characteristic on CT	**Number of cases (%) (N=500)**
Single	380 (76%)
Multiple	120 (24%)
Ring-enhancing	410 (82%)
Disc	59 (11.8%)
Edema	287 (57.4%)
Calcification	75 (15%)

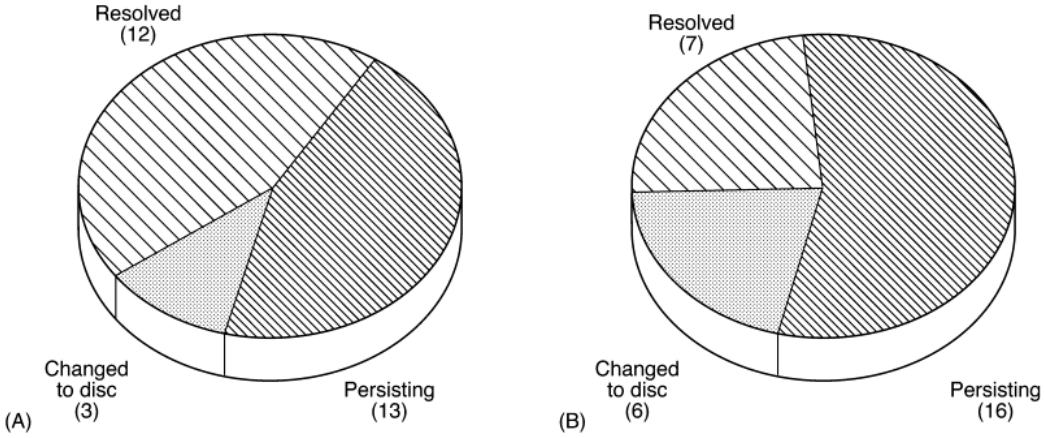

Figure 1: Comparison of single enhancing lesions on 1-month CT between (A) albendazole and (B) placebo

subsequent randomized study showed that 7-day therapy was as effective as 28-day therapy in children with single lesions (19). It is now our practice to use short-duration albendazole therapy in children with single lesions. Similarly in another randomized study, one year of antiepileptic therapy was found to be as effective as two years of antiepileptic therapy in children in whom the lesion had disappeared (20). Another study showed that the use of combination therapy with

praziquantel and albendazole may be better than either one alone (21), and that the use of steroids with albendazole is somewhat better than either alone (22). However larger trials are needed to establish these.

(ii) Other CNS Infections:

Acute symptomatic seizures occur in about one third of hospitalized cases of bacterial meningitis and late seizures (>72 hours) follow development of complications (23, 24). Meningitis is a common cause of febrile convulsive status epilepticus (25). Seizures are reported in 50-80% cases of Japanese encephalitis (26, 27), nearly 50% cases of tuberculous meningitis (28) and 22-50% cases of cerebral malaria (29). Prevention of these will be discussed later.

b) Neurodevelopmental Disorders and Disabilities :

Another important contributor to childhood epilepsy and intractable seizures is the presence of underlying developmental disorders and disabilities such as CP. In a study on 105 consecutive children (aged 1-14 years) with CP and active epilepsy and a retrospective cohort of 452 cases of CP, we found that 35.4% had epilepsy (30). The maximum incidence was seen in children with spastic hemiplegia (66%), followed by quadriplegia (42.6%) and diplegia (15.8%). Of the 105 children with active epilepsy, 38% had history of birth asphyxia. The mean age of onset of seizures was 18.9 months; 61% had seizure-onset in infancy. Generalized seizures were most common, followed by partial seizures, infantile spasms and myoclonic seizures. Social quotient values had a positive correlation with age of onset of seizures ($p<0.01$) and with better control of seizures ($p<0.01$) (30). Preventive strategies for these will be discussed later.

B CNS Infections :

a) Bacterial Meningitis :

Globally, 25,440 children <5 years of age were hospitalized with suspected meningitis in 2009 and from January-June 2010, 10,350 children <5 years of age with suspected meningitis were reported to the global Invasive Bacterial Disease-Vaccine Preventable Disease (VP-IBD) surveillance network; 51% from Africa and 21% from South East Asia (31). In children <5 years of age, the estimated incidence of H.Influenzae meningitis is 31 cases/1,00,00,00 (32), pneumococcal meningitis is 17 cases/100,00,00 (33), and that of meningococcal meningitis is 0.3-4 cases/100,000 populations in developed countries and 10-100/100,000 population in African counties (34). The prevalence of Hib meningitis was under-estimated in India as Hib is a fastidious organism to culture. In a PCR-based study, Hib could be detected in double the number of cases as were picked up on culture or latex-agglutination (35). In our hospital the incidence of Hib meningitis has remained

around 32-35% of the total meningitis cases. CNS infections were responsible for >60% cases of non-traumatic coma and constitute a huge burden in pediatric emergency and ICU (36); nearly 40% are left with serious sequelae (37, 38).

Preventive Strategies :

Primary

Over 75% of meningitis can be prevented through universal immunization. Vaccines against N. meningitidis, H. influenzae, and S. pneumoniae are currently available, but the protection afforded by each vaccine is specific to each bacterium and serogroups/serotypes. Routine use of polysaccharide-protein Hib conjugate vaccines has almost eliminated Hib meningitis/severe disease from developed countries. However in India, Hib meningitis still ranges from 1971-2433 cases/100,000 child-years of observation similar to western countries in pre-vaccination era (39).

Secondary

Immediate appropriate antibiotic therapy significantly reduces mortality and morbidity of bacterial meningitis. Use of shorter duration of ceftriaxone therapy (7 days versus 10 days) was equally effective in children over 3 months of age with uncomplicated meningitis (40). A recent large randomized double-blind study of 5 versus 10 days of ceftriaxone treatment conducted in six resource-poor

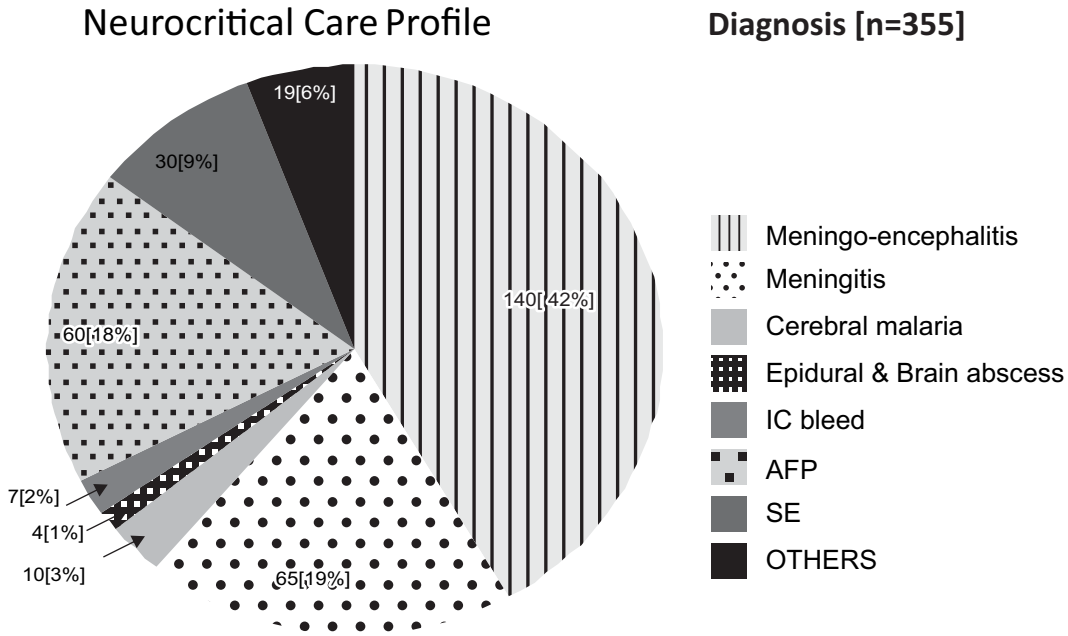

Figure 2: Neurocritical care profile of 355 children

countries found no significant difference in outcome of children (beyond the neonatal period) with uncomplicated bacterial meningitis due to Hib, pneumococci or meningococci, who were stable on day 5 of treatment (41).

In randomized controlled clinical trials, adjunctive therapy such as fluid restriction did not improve the outcome of acute meningitis in children (42). A Cochrane systematic review concluded that at least for settings with high mortality rates and where patients present late, evidence supports giving normal maintenance intravenous fluids rather than fluid restriction in the first 48 hours (43). CNS infections are responsible for >60% of refractory status-epilepticus (RSE) in hospital, which has a high mortality and morbidity. We found that intravenous diazepam infusion was effective in controlling seizures in RSE (44). However, due to the associated risk of hypotension and respiratory depression, diazepam infusion may be risky in places with no ventilators. Hence, we studied the efficacy and safety of intravenous sodium valproate and found it as effective as intravenous diazepam in controlling RSE, especially in resource limited settings (45).

Intra-cranial Pressure (ICP) monitoring for initial 24-48 hours can be helpful in maintaining adequate cerebral blood flow and perfusion in critically-ill children with CNS infections with a Glasgow Coma Scale (GCS) score ≤8 or abnormal CT findings. Cerebral perfusion pressure (CPP) targeted therapy, aimed at maintaining CPP>50 mmHg is useful for monitoring ICP; a CPP <40 mmHg is associated with high mortality (46).

b) Viral encephalitis :

Japanese encephalitis (JE) is the single largest cause of acute epidemic encephalitis worldwide and is responsible for 68000 cases/year and 13,000-20,000 deaths/year in Asia (47). Case fatality rate is 30% with severe neurological disabilities in survivors (48). It is transmitted by Culex mosquito, with water birds serving as natural reservoirs and pigs as amplifying hosts. In the 2005 epidemic in just five months, 5,737 cases and 1,344 deaths were reported from seven districts of Uttar Pradesh (49). Herpes simplex encephalitis is the commonest cause of sporadic encephalitis and has a high mortality and morbidity if treatment is delayed. Recently other viruses such as Enterovirus, Chandipura virus and Nipah virus are also being reported from various parts of India (50).

Preventive Strategies :

Primary

Preventive strategies are based on three pillars including national acute encephalitis syndrome surveillance, vector control and vaccination. The live attenuated vaccine has been shown to provide >90% protection. A cost-effectiveness analysis for 14 countries estimated that from 2007 to 2021, 193,676 cases, 43,446 deaths, 77,470 cases with sequelae, 6,622,932 disability-adjusted

life years (DALYs), and US$19 million in acute hospitalization costs could be avoided by immunization with the live, attenuated SA 14-14-2 JE vaccine through campaigns and implementation of routine immunization programs (51). Hence JE vaccination is a very cost-effective intervention. Although steps have been taken by the government to have active encephalitis surveillance and the Indian Academy of Pediatrics has also provided guidelines for this purpose (52), we are still lagging behind in immunization. In 2006, the Government of India initiated a five-year strategy (2006-2011) of JE vaccination campaigns to immunize children and adolescents between 1 and 15 years of age in high-risk districts, followed by introduction of JE vaccine into the routine immunization program. However, we have not yet achieved this. Increased production of JE vaccine and mass immunization particularly in hyperendemic areas is essential to prevent/ control JE epidemics.

Secondary

Early stabilization of cases, control of raised ICP and seizures can prevent the secondary morbidity associated with acute encephalitis. Prompt treatment with acyclovir can significantly reduce mortality and morbidity of herpes encephalitis.

c) CNS Tuberculosis :

CNS tuberculosis (TB) contributes considerably towards childhood neurological burden (53). In 2011 the estimated prevalence of tuberculosis was 125 cases per million globally with 0.5 million cases and 64000 deaths among children. India alone accounts for 26% of global cases of tuberculosis (54). About 10% of patients who have tuberculosis develop CNS tuberculosis, hence the number of estimated cases of tubercular meningitis is huge and children are most affected. Estimated mortality due to tubercular meningitis in India is 1.5 cases per 100,000 populations. HIV co-infection is associated with higher complications and case fatality rate (54). In a prospective study on 139 children with TBM, we found that two thirds were <5 years of age and three fourths presented late in stage 2 or 3 of the disease. About 30% children died; of the survivors, about half were left with serious neurological sequelae (unpublished data). In an analysis of 350 children with CNS TB, the mortality was 24.6% and 56.1% were left with neurological sequelae (unpublished data).

Preventive Strategies :

Primary

Prevention of CNS tuberculosis is a huge challenge (55). In a landmark development, the Ministry of Health and Family Welfare, Government of India, has taken important steps to establish the compulsory notification of tuberculosis in the country. A government order to this effect was issued on 7 May 2012. Childhood disease can be prevented by vaccination and by giving prophylactic isoniazid to children exposed to infectious

adults. Several tuberculosis vaccine trials are being explored to find the most effective vaccine (56).

Secondary

CNS tuberculosis requires at least one year of antitubercular therapy; hence ensuring drug availability and compliance particularly in the low socio-economic strata is a big problem, but can be achieved through the National TB Control Program. A recent Cochrane systematic review and meta analysis of 7 randomized controlled trials involving 1140 participants (with 411 deaths) concluded that corticosteroids reduced the risk of death or disabling residual neurological deficit in HIV-negative children and adults with tubercular meningitis (57).

C. Neuro-developmental disorders :

According to WHO estimates, worldwide 15-20% of children have disabilities; 85% of which are in developing countries (58). According to UN estimates 10% of the population has disability and of all persons living with disability, 35.9% are children and young adults; hence there are ≈40 million disabled children in India. The Census of India has determined that persons with disabilities (including visual, hearing, speech, locomotor, and mental disabilities) constitute 2% of the total population (59). This translates to almost 3 million children with disability.

The prevalence rate of mental retardation is about 20 per 1000 in general population, while that of developmental delays is about 30 per 1000 in children up to the age of 14 years (60). In an ICMR Task Force study, the prevalence of disability among children <6 years of age was found to be 8.8, 6.5 and 12.6/thousand in Delhi, Jaipur and Lucknow respectively (61). Nearly 70% of disabled children had a single disability while 30% had multiple disabilities.

In another community-based study in children <2 years of age, the overall prevalence of neurological disorders was estimated to be 28/1000 children. Prevalence of epilepsy was 1.3/1000, vision and hearing impairment each 0.6/1000, motor impairment 11/1000, and general developmental delay 26/1000 children in <2-years age-group. Perinatal, neonatal difficulties were the leading cause followed by congenital disorders and post-neonatal brain infection (62). The recent INCLEN study from 5 different geographical areas of India in children 2-9 years of age estimated that the prevalence of all NDD in 2-5 yrs of age is 11% and in 6-9 yrs old children is 15% (63). Dedicated house-to-house surveys in 3 villages using the WHO Ten Questions Screen in children aged 2-9 years in rural Chandigarh revealed a disability prevalence of 1.6% (64).

The spectrum of CP in our country is very different from that in the West, with a significant proportion (≃50%) being associated with birth asphyxia. In a centre based study on 1000 children with CP, spastic quadripledgia was the commonest

(63%) type of CP. Acquired preventable causes were seen in 22% cases (65). Kernicterus was responsible for 21.6% of acquired CP. In another study of 1212 children from the same centre it was found that though spastic quadriplegia still is the commonest type of CP (51%), however there is a relative increase in the proportion of spastic diplegia possibly because of increased survival of pre-term babies. CP due to CNS infections occurs in 57-64% cases and that due to bilirubin-encephalopathy occurs in 30% (66).

Inborn errors of metabolism :

The estimation of inborn errors of metabolism in India is 1 in 2497 newborns. An expanded newborn screening program of around 18,300 newborns from various government hospitals in Andhra Pradesh during 2000 revealed a high prevalence of inborn errors of metabolism - 1 in every 1000 newborns (67). Screening study of 1,12,269 newborn babies for amino-acid disorders reported that tyrosinemia, maple syrup urine disease, phenylketonuria, hyperglycinemia, homocystinuria and alkaptonuria were among the major aminoacidopathies (68).

Preventive Strategies :

Primary

Childhood Disability

A large proportion of childhood disability can be prevented by good antenatal, perinatal and neonatal care, avoidance of consanguineous marriages, ensuring safe delivery and timely immunization and neonatal screening for metabolic disorders. Birth asphyxia can be reduced by almost 50% with community based interventions involving training of health workers in neonatal resuscitation (69).

Secondary prevention is equally important. Therapeutic moderate hypothermia after perinatal asphyxia results in improved neurocognitive outcomes in childhood (70). Kernicterus can be entirely eliminated with simple interventions such as preventing Rh-isoimmunizations and promptly instituting phototherapy and exchange transfusion when needed.

There is an acute shortage of not only pediatric neurologists but even adult neurologists in India. As per WHO report, the number of neurologists in South East Asia is 0.07 per 100,000 population (71). There is an urgent necessity of training of medical officers and pediatricians at all levels to ensure early appropriate management of common neurological disorders in children.

Conclusion :

To conclude therefore, a huge burden of neurological disorders in childhood is secondary to preventable causes. Childhood epilepsy, CNS infections and childhood disability are inextricably interlinked. Simple preventive measures such as mass immunization, health care and sanitation

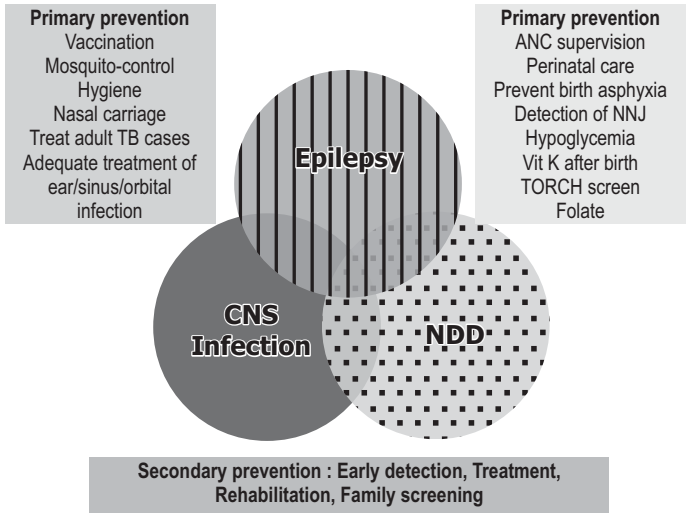

Figure 3: Proposed model for primary and secondary prevention of neurodisabilities in children due to CNS infections, epilepsy and Neurodevelopmental disorders (NDD)

can significantly reduce CNS infections and their associated epilepsy and disability. Antenatal care and safe institutional delivery can prevent almost half the case of cerebral palsy and mental retardation in our country and the associated epilepsy. Concerted efforts from the government, concerned professionals and the community can go a long way in reducing the burden of childhood neurological disorders (Figure 3).

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Nutrient : Women Need Most

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SUMMARY

The body needs calcium to maintain strong bones and to carry out many important functions. Osteoporosis, reflected only by a low bone mineral density (BMD), is increasingly becoming a major public health problem in Asian countries. Genetic factors along with environmental factors are responsible for substantial variation in bone density and bone mass. Women whose calcium intake is inadequate before the age of 20-25 and do not achieve their ideal peak bone mass, have a higher risk later on in life of developing osteoporosis, because calcium is drawn from the bones as a reserve. In pregnancy, very high circulatory concentrations of estrogens and progesterone alter the concentration of many substances including calcium in the maternal blood. There is an increased demand for calcium and inorganic phosphate for fetal development during pregnancy. All these factors which negatively affect bone mass consistently persist in premenopausal as well as postmenopausal period.

A high incidence of vitamin D deficiency in pregnant and non-pregnant women has been reported from developing countries including India. Vitamin D deficiency and hypocalcemia have been associated with a variety of pregnancy complications such as preeclampsia, gestational diabetes and prematurity.

It has been observed that daily intakes of energy (1563.4 ± 267.2 kcal), protein (48.7 ± 8.7 g) and calcium (543.7 ± 161.3 mg) were below the recommended dietary allowance of women. The major part of this dietary calcium came from plant sources, which are known

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to have low bioavailability. The diets were typically cereal-based with a very low intake of protective foods and animal protein. Insufficient intakes of calcium do not produce obvious symptoms in the short term because the body maintains calcium levels in the blood by taking it from bone. But in the long run, it causes osteopenia and increases the risks of osteoporosis and bone fractures.

Daily dietary energy, protein, and calcium intakes were correlated with BMD at the lumbar spine. Age, BMI, and physical activity were significant predictors for BMD at all sites. Dietary pattern coupled with higher education levels and greater physical activity favored bone health. There is need to change dietary pattern and habits by improving education and socio-economic level. Calcium and vitamin D supplementation, especially in second and third decade are the first-line strategy for the prevention of osteoporosis.

Calcium is the most abundant inorganic element in human body and makes up about 1.5% to 2% of the total body weight and 40% of the total body minerals. Approximately 99% is present in bones and teeth, 1% in blood & extracellular fluid. Calcium is essential to all vital functions and an intracellular messenger indispensable for all cell functions. Serum calcium is the most precisely controlled biological constant. Apart from maintaining the structure & functions of bone, calcium is essential for nerve impulse transmission and immune function. It regulates muscle contraction as well as blood pressure & also essential for blood clotting.

The regulation of plasma calcium depends on the interplay of three organs i.e. bone, kidney and intestines. The adaptive mechanisms involved in the maintenance of homeostasis during the periods of increased calcium demands involve greater intestinal calcium absorption, decreased urinary calcium losses and increased bone resorption. These adaptations are mediated by increased secretion of the various calcitropic hormones such as 1,25-dihydro-xyvitamin D3 (1, 25(OH)2 D3), parathormone, calcitonin and parathyroid hormone related peptide (PTHrP). In all of these adaptive mechanisms, vitamin D is involved directly or indirectly.

A key adaptive change i.e increased 1, 25 dihydroxyvitamin D production during pregnancy, leads to a marked increase in intestinal calcium absorption and as a consequence, hypercalciuria. This is an independent phenomenon, occurring as early as 12 weeks of gestation and may allow the maternal skeleton to store calcium in advance of peak fetal demands later in third trimester.

The concentration of calcium in plasma is closely maintained at between 8.5-11 mg/dl. To maintain these titres, if diet does not provide enough calcium,

then body steals it from the bones (1).

Usually low serum levels of calcium are not suspected clinically. Symptoms of hypocalcaemia therefore generally represent an extreme aberration in the homeostasis. Hypocalcaemia becomes symptomatic when its level falls below 5 mg/dL.

A recent study confirmed that serum ionic calcium levels remain normal during pregnancy (2). The decrease in total calcium level was because of hemodilution and hence decrease in albumin bound calcium fraction. True ionic hypocalcemia may occur in pregnant women with vitamin D deficiency.

Calcium Intake and Serum Calcium :

It has been demonstrated that 57.8% of consecutive non pregnant healthy young women (82/142), attending gynecological OPD with minor gynecological ailments, had hypocalcemia (serum calcium level below 8.5 mg/dL). However in none of them, the calcium levels were below 5 or resulted in symptoms pertaining to hypocalcemia. Serum calcium (mean±SD;mg/dL) was 7.5±0.9 and 9.3±0.6 in hypocalcemic and eucalcemic women respectively. There was no difference among the women with or without hypocalcemia with respect to their nutritional status or consumption of calories, protein or dietary calcium intake. Majority of women were well nourished signifying that malnutrition may not have been a determining factor (unpublished data).

Calcium Intake and Serum Calcium during pregnancy :

A total of 545 consecutive women in second trimester of pregnancy without any obstetric and medical risk factor attending the antenatal clinic were recruited (3). Nearly two thirds of women (66.4%) had hypocalcemia (362/545). None of the women had symptoms pertaining to hypocalcaemia. Daily intake of calcium was grossly inadequate in both the groups. Nearly half of the participants in both groups consumed less than 300 mg of calcium per day (Table 1). There was no correlation between daily calcium intake and the serum calcium levels (correlation coefficient: -0.8). Urinary calcium excretion was lower in women with hypocalcaemia versus those without hypocalcaemia but it did not reach significance (p value 0.08). On linear regression, serum calcium was not found to be dependent on any baseline variables included in this study. The pregnancy outcome was not significantly different in two groups (3).

Such a high incidence of hypocalcaemia has not been reported from a low income country like India. In a study by Ainy et al, 19% of 48 pregnant women had hypocalcaemia (i.e. serum calcium level below 8.5 mg/dL) (4). Bhalala et al has reported that 88% (37/42) mothers from Western India had serum calcium in normal range (8.1-10.5 mg/dL) and remaining 12% had serum calcium values from 7.1 to 7.7 mg/dL (5).

Table 1- Baseline characteristics of the pregnant study women

Characteristics	Group A Women with hypcalcemia (n=362)	Group B Women without hypocalcemia (n=183)	P value
Age* (years)	21.8±2.4	22.0±2.7	0.26
Participants' education			
Illiterate	42(11.6%)	16(8.8%)	
Up to metric	220(60.9%)	108(59.3%)	0.43
12th standard	53(14.7%)	32(17.6%)	
graduate	41(11.4%)	20(10.9%)	
Postgraduate	5(1.4%)	6(3.3%)	
Husband education			
Illiterate	31(8.6%)	8(4.4%)	
Up to metric	216(59.8%)	104(57.1%)	0.13
12th standard	48(13.3%)	37(20.3%)	
graduate	58(16.1%)	28(15.4%)	
Postgraduate	8(2.2%)	5(2.8%)	
Monthly per capita income* (Indian rupees)	1338±159	1422±101	0.35
Less than 500	12(6.6%)	14(3.9%)	0.16
More than or equal to 500	171(93.4%)	348(96.1%)	
Height * (cm)	149±6.2	149±6.1	0.31
Weight* (Kg)	51.9±8.6	51.7±9.4	0.81
Body mass index (Kg/M^2)			
Underweight: <18.5	24(6.6%)	18(9.8%)	
Normal: 18.5-24.99	229(63.3%)	120(65.6%)	0.31
Overweight: 25-29.99	84(23.2%)	32(17.5%)	
obese ≥30	25(6.9%)	13(7.1%)	
Gestation* (weeks)	18.2±3.4	17.6±3.6	0.06
Hemoglobin* (g/dL)	10.8±1.4	10.7±1.5	0.31
≤6: severe	1 (0.3%)	0	0.14
7-10: mod	68 (18.8%)	49 (26.8%)	
10-<11 mild	83 (22.9%)	34 (18.6%)	
Daily calcium intake* (mg)	323±203	327±193	0.81
<300	172(47.5%)	85(46.5%)	0.74
300-599	138(38.1%)	76(41.5%)	
600-1199	51(14.0%)	21(11.5%)	
≥1200	1(0.3%)	1(0.6%)	
Serum calcium level* (mg/dL)	7.2±0.8	9.8±0.8	0.00
Urinary calcium excretion * (mg/24 hr)	125±69	136±62	0.08

Data expressed as *mean±SD or number (%)

The principal maternal adjustment during pregnancy is an increasing parathyroid hormone secretion which maintains the serum calcium concentration in the face of a falling albumin level, an expanding extracellular fluid volume, an increasing renal excretion, and placental calcium transfer. The placenta transports calcium ions actively, making the fetus hypercalcemic relative to its mother, which in turn stimulates calcitonin release and perhaps suppresses parathyroid hormone secretion by the fetus.

The dietary intake of calcium was very low in all the participants and nearly half of women consumed calcium less than 300 mg daily (3). Another study revealed daily dietary calcium intake range from 800 to 1500 mg besides supplemental calcium intake of 250-500 mg (5). There was no relationship between the daily intake of calcium and the occurrence of hypocalcaemia. It is most likely that faulty dietary habits or vitamin D deficiency are responsible for it. The major part of this dietary calcium came from plant sources, which are known to have low bioavailability. The inhibitors of calcium absorption such as phytates and oxalates are abundant in the vegetarian diet and retard the absorption of dietary calcium. Moreover, absorption of calcium could be hampered by vitamin D deficiency as it is the major factor influencing absorption of calcium from the gut. A study by Vupputuri *et al* revealed that 60% of healthy adults living in Delhi city had 25 hydroxy vitamin D values ≤9 ng/ml which is significantly lower than the recommended vitamin D levels (6). In a study by Ainy *et al*, 20% of women had vitamin D levels <10 ng/ml in first trimester (4).

Devine *et al* showed that the fractional absorption of calcium was significantly negatively correlated with years since menopause ($r = -0.15$; $P < 0.05$) (7). The foods rich in calcium such as milk and dry fruits are expensive and not available to this population. Therefore, age related falling absorptive power along with poor quality of diet aggravates the situation.

It was observed that high calcium intake combined with adequate protein intake based on a high ratio of vegetable to animal protein may be protective against osteoporosis (8). Protein-energy under nutrition is a risk factor for bone loss, osteoporosis, and fracture, and the elderly in particular are at risk for protein under nutrition (9). Low levels of serum albumin negatively affect transport of serum calcium. It has been observed that women with higher calcium and better dietary intakes from high-income groups have better bone densities (10). There are reports of high prevalence of suboptimal dietary calcium intake and 25(OH) D insufficiencies in South Indian populations (11) and North Indian healthy subjects (12, 13).

Calcium and Pregnancy Complication :

A very low prevalence of pre-

eclampsia had been reported from Ethiopia where the diet contained high levels of calcium. These observations were supported by other epidemiological and clinical studies and led to the hypothesis that an increase in calcium intake during pregnancy might reduce the incidence of high blood pressure and pre-eclampsia among women with low calcium intake. Low calcium intake may cause high blood pressure by stimulating the release of parathyroid hormone and/or renin, thereby increasing intracellular calcium in vascular smooth muscle and leading to vasoconstriction. Calcium supplementation is useful in pregnancy because it reduces parathyroid release and intracellular calcium, thereby reducing smooth muscle contractility and promoting vasodilatation. It reduces uterine smooth muscle contractility and prevents preterm labor and delivery. Calcium may also inhibit endothelial damage.

A total of 524 primigravida women with 12 to 25 weeks were randomly assigned into calcium (2 g of elemental calcium) and placebo group and followed-up until delivery (14). It was concluded that daily supplementation of 2 gram elemental calcium is associated with a reduction of 66.7% risk of pre-eclampsia and 44.9% risk of preterm delivery (Table 2, 3).

The greatest reduction in risk of preeclampsia after calcium supplementation was for women at high risk and those with low baseline dietary calcium intake (15,16). The study population (14) itself has low calcium intake (85.71-910.71 mg/day) compared with the recommended dietary allowances of 1000mg/day throughout pregnancy and lactation (17).

A Cochrane review of trials found that calcium supplementation during pregnancy is a safe and relatively inexpensive and cost effective means of reducing the risk of pre-eclampsia in women at increased risk and also in women from communities with low dietary calcium. It included 13 studies of good quality (involving 15,730 women) (18). One of these trials is from Northern India (14). The average risk of high blood pressure was reduced with calcium supplementation rather than placebo (12 trials, 15,470 women: risk ratio (RR) 0.65, 95%confidence interval (CI) 0.53 to 0.81). There was also a reduction in the average risk of pre-eclampsia associated with calcium supplementation (13 trials, 15,730 women: RR 0.45,95% CI 0.31 to 0.65). The effect was greatest for women with low baseline calcium intake (eight trials, 10,678 women: RR 0.36, 95% CI 0.20 to 0.65).

Calcium and Vitamin D during pregnancy :

Now, it is being observed that, not only dark-skinned but even Caucasian women tend to go into vitamin D deficiency during pregnancy. Studies have reported a prevalence that ranges from 18-84%, depending on the country of residence and local clothing customs. Global prevalence of vitamin D deficiency

Table 2: Baseline characteristics of pregnant subjects recruited and completed the study

Parameter	Subjects recruited in the Study			Subjects who completed the Study		
	Placebo (n= 262)	Calcium (n= 290)	p value	Placebo (n = 251)	Calcium (n= 273)	p value
Age (yrs)	21.94±2.51 (18-31)	21.81±2.52 (17-35)	0.538	21.91±2.47 (18-31)	21.83±2.51 (17-35)	0.725
Height (cm)	149.24±6.17 (130-165)	149.26±6.17 (130-166)	0.961	149.14±6.22 (130-165)	149.32±6.22 (130-162)	0.747
Weight (kg)	51.97±8.74 (36-91)	51.69±8.85 (35-87)	0.717	51.86±8.75 (36-91)	51.68±8.91 (36-87)	0.822
BMI (kg/m^2)	23.37±3.89 (15.79-42.69)	23.25±3.98 (15.61-37.65)	0.710	23.35±3.92 (15.79-42.69)	23.35±3.92 (15.79-42.69)	0.688
Dietary Calcium intake (mg/day)	313.04± 203.75 (85.71- 873.43)	314.92± 201.59 (85.71– 910.71)	0.913	312.84± 204.63 (85.71– 873.43)	314.83± 201.87 (85.71– 910.71)	0.911
Serum calcium (mg/dl) ‡	7.93±1.39 (5.1-11.9)	8.14±1.49 (5.1-11.9)	0.093	7.92±1.38 (5.1-11.9)	8.13±1.49 (5.1-11.9)	0.105
Urine calcium (mg/dl) §	128.43±67.79 (40.5-400)	130.21±65.82 (40.5-387)	0.754	129.84±68.34 (40.5-387)	131.80±66.55 (40.5-387)	0.805
Gestational age at recruitment (Weeks)	17.80±3.53 (12-25)	17.85±3.63 (12-25)	0.869	17.80±3.51 (12-25)	17.86±3.51 (12-25)	0.854
Haemoglobin (gm %)	10.76±1.48 (7-14)	10.76±1.43 (6-14)	0.976	10.76±1.48 (7-14)	10.76±1.42 (6-14)	0.974
Systolic BP at recruitment (mmHg)	113.16±8.47 (90-130)	113.23±8.23 (90-130)	0.925	113.15± 8.47 (90-130)	113.23± 8.17 (90-130)	0.913
Diastolic DBP at recruitment (mmHg)	74.25±6.45 (50-90)	73.92±6.56 (50-92)	0.552	74.23± 6.51 (50-88)	73.78± 6.65 (50-92)	0.442

Data are given as mean ±SD
†Range in parentheses
‡Normal range: 8.5-10.5 mg%
§ Normal range: 100-400 mg/24hrs

Table 3: Maternal and Neonatal outcome in the study population

	Placebo group (n= 251) n (%)	**Calcium group (n =273) n (%)**	**p value**
Maternal outcome measures			
Pre-eclampsia	30(12)	11(4.0)	**0.001***
Preterm delivery	32(12.7)	19(7.0)	**0.026***
Induction of labor	12(4.8)	10(3.7)	0.524
Caesarean delivery	27(10.8)	41(15)	0.147
Fetal distress in labor	5(2.0)	6(2.2)	0.870
Meconium in labor	5(2.0)	10(3.7)	0.249
Neonatal outcome measures			
Mean period of gestation at delivery ± SD, weeks	38.27 ± 2.04	38.59 ± 1.67	0.050
Period of gestation at delivery in weeks, n (%) < 32 32-36 37-40 >40	 4(1.6) 28(11.2) 204(81.3) 15(6.0)	 1(0.4) 18(6.6) 233(85.3) 21(7.7)	 0.112
Mean birth weight ± SD, gm	2685.35 ± 338.00	2696.27 ± 304.10	0.697
Birth weight in Kg, n (%) <2.0 2.0-2.5 2.5-4.0	 6(2.4) 65(25.9) 180(71.7)	 4(1.5) 60(22.0) 209(76.6)	 0.398
Small for gestational age, n (%)	21(8.4)	17(6.2)	0.346
Stillbirth, n (%)	5(2.0)	6(2.2)	0.618

* significant p value.

in pregnant women has been estimated to be 5-50% (19).

In one of our studies of 418 primigravida attending the antenatal clinic of Lok Nayak Hospital, New Delhi, the prevalence of vitamin D deficiency (serum levels of 25 hydroxy vitamin D < 32 ng/ml) was found to be 95.4% (399/418). Most of the pregnant women (61%, 255/418) had insufficient levels of 25 hydroxy vitamin D (10-32ng/ml) and 34.4% (144/418) had severe deficiency of vitamin D (serum 25 hydroxy vitamin D level <10ng/ml). The mean maternal serum calcium levels improves significantly with increase in maternal serum 25 hydroxy vitamin D levels ($p<0.001$). A positive correlation was found between maternal serum 25 hydroxy vitamin D and maternal serum calcium ($r=0.651$; $p=0.000$) (Unpublished data).

Adverse outcomes such as preeclampsia, low birth-weight, neonatal hypocalcemia, poor postnatal growth, bone fragility, and increased incidence of autoimmune diseases have been found to be associated with low vitamin D levels during pregnancy and infancy.

In a systematic review and meta-analysis, vitamin D insufficiency is found to be associated with an increased risk of gestational diabetes, pre-eclampsia, and small for gestational age infants. Pregnant women with low 25-hydroxy vitamin D levels had an increased risk of bacterial vaginosis and lower birth weight infants, but not delivery by caesarean section (20).

The serum 25-hydroxy vitamin D [25(OH) D] level is thought to reflect the vitamin D nutritional status accurately and has been used widely for this purpose. Sunlight exposure and dietary intake are the main determinants of serum 25 (OH) D levels.

Calcium Intake and Bone Mineral Density :

Osteoporosis is a silent disease reflected only by a low bone density. Osteoporosis is increasingly becoming a major public health problem in Asian countries, due mainly to the rapid aging of the population.

A cross-sectional study of 255 women (20-70 years) was conducted to find out the relation of dietary nutrients and bone mineral density (BMD) in North Indian women (21). The study subjects (participants) were healthy normal relatives of the patients being admitted in the obstetrical and gynecological wards of the hospital. The mean age, height, weight and body mass index (BMI) were 40.5 ± 12.6 years, 153.4 ± 4.9 cm, 57.3 ± 12.0 kg and 24.3 ± 4.8 kg/m2 respectively. The daily dietary intakes of the subjects were: energy, 1563.4 ± 267.2 kcal; protein, 48.7 ± 8.7 g; fat, 31.3 ± 9.3 g and calcium, 543.7 ± 161.3 mg. The diets were typically cereal-based with a very low intake of protective foods such as milk and milk products, flesh foods, fish, fruits and vegetables. Animal sources of protein were consumed irregularly. The daily intakes of energy, protein and calcium of postmenopausal women were

significantly lower than that of premenopausal women (1487.8±259.6 kcal, 46.4 ± 9.3 gm, 496.1± 169.3mg and 1608.9±262.0 kcal, 50.1± 8.1 gm, 572.5 ± 149.6 mg respectively; p <0.001). Baseline characteristics according to various age groups are shown in Table 4.

BMI, physical activity and educational level was positively correlated with BMD. The daily intakes of energy (1563.4 ± 267.2 kcal) and protein (48.7 ± 8.7 g) were below the recommended dietary allowance. Daily dietary total energy, protein and calcium intake had significant correlations with BMD lumbar spine. Serum calcium levels were found to have positive correlation with BMD femoral neck and Ward's triangle.Stepwise multiple linear regression analyses showed that age, BMI and physical activity were the significant predictors for BMD at all sites. In addition, energy intake was also a predictor for BMD at lumbar spine (21).

Genetic factors seem to account for substantial variation in bone density and bone mass and environmental factors also influence the quality and durability of bone (22, 23). The effect of environmental factors on bone is likely to vary across the lifespan and length of exposure to exercise, diet, alcohol, caffeine and smoking may have increasing impact in older women.

Indians from low-income groups subsist on diets that have inadequate calcium coupled with too few calories, proteins and micronutrients (24). The mean daily intakes of energy and protein were below the recommended dietary allowance (RDA) of 2225 kcal/day and 50 g/day respectively for these women (Table 4). The calcium intake of the participants was only low as compared to the RDA of 800–1,000 mg/day, which is accepted worldwide (25).

The premenopausal females were more osteopenic than postmenopausal females (26) but osteoporosis was more prevalent in postmenopausal females (Table 5). It represents that the factors which negatively affect bone mass consistently persisted in premenopaual as well as postmenopausal period. These factors combined with estrogen deficiency then made these women osteoporotic after the attainment of menopause. Osteoporosis not only affects elderly but young adults also. This is determined by ideal peak bone mass. The peak bone mass is usually achieved in thirties and than it declines (27). If a young adult does not achieve their ideal peak bone mass, they develop osteoporosis at much earlier age.

It was found that calcium intake is affected by various demographic factors like educational level, socioeconomic status. Approximately 71% of the subjects had less than 10 years of education and had lower intake of calcium (296.24mg/day). Total 85% of the subjects had their per capita income below 2000 Indian rupees and had lower intake of calcium (376.92mg/day). The mean calcium intake improves with the improvement of educational levels of the

Table 4: Baseline Characteristics, daily dietary intake and biochemical parameters* of study population

Age Group (years)	20-29	30-39	40-49	50-59	60-69	20-69
Number (%)	67 (26.3)	63 (24.7)	54 (21.2)	46 (18.0)	25 (9.8)	255 (100)
Age (Years)	25.51 ± 2.82	34.95± 2.62	43.87 ± 3.08	53.22 ± 2.48	63.72± 3.68	40.47 ± 12.64
Height (cm)	153.55± 5.26	153.49 ± 5.29	153.00± 4.91	154.13± 4.68	152.40±3.25	153.41 ± 4.92
Weight (kg)	56.52 ± 12.06	57.06± 11.47	60.89± 13.89	58.74± 10.31	49.44± 8.51	57.29 ± 12.05
BMI (kg/m^2)	23.94 ± 4.66	24.25± 4.35	25.98 ± 5.63	24.51± 4.07	21.22± 3.66	24.28 ± 4.76
Per capita income (INR)	4800.00 ± 3047.60	5058.73 ± 3523.77	3967.35 ± 4207.42	4634.91 ± 5162.09	3588.64 ± 4266.24	4539.05 ± 3977.91
Parity	1.21 ± 1.17	2.48 ±1.23	3.15 ± 1.65	3.78 ± 1.78	4.64 ± 2.32	2.73 ± 1.89
Energy (kilocalories/ day)	1636.00 ± 214.40	1660.22 ± 299.09	1447.76 ± 192.67	1488.39 ± 249.82	1512.20 ± 340.52	1563.36 ± 267.16
Dietary Protein (gm/day)	50.83± 9.47	50.15 ± 6.86	49.26 ± 9.09	46.82 ± 7.41	41.52 ± 8.56	48.70 ± 8.73
Dietary Calcium (mg/day)	577.85 ± 132.81	594.14 ±156.06	488.56 ± 145.35	523.46 ±168.60	481.56 ± 205.95	543.71 ± 161.31
Dietary Fat (gm/day)	31.75 ± 5.63	32.67 ± 6.71	29.70 ± 7.31	30.80 ± 7.56	30.60 ± 21.71	31.26 ± 9.28
Serum calcium (mg/dl)	8.42 ± 1.15	8.06 ± 1.16	8.43 ± 1.39	8.45 ± 1.37	8.54 ± 1.21	8.35 ± 1.26
Serum Phosphorus (mg/dl)	3.85 ± 0.56	3.96 ± 0.64	4.13 ± 0.83	4.06 ± 0.97	3.82 ± 0.59	3.97 ± 0.73
Serum albumin (g/L)	4.26 ± 0.70	4.35± 0.64	3.83 ± 0.67	4.09±0.69	4.54 ± 0.66	4.19 ± 0.70
Alkaline phosphatase (U/L)	173.43 ± 45.02	155.44 ± 41.64	171.93 ± 91.75	158.11 ± 46.55	155.80 ± 39.12	164.18 ±57.47

* Values are mean ± S.D. BMI = Body Mass Index, INR = Indian Rupees
Normal Range:
Serum calcium 8.0-11.0 mg%, Serum Phosphorus 2.7-4.5 mg%, Serum Alkaline phosphatase 95-226 U/L, Serum albumin 3-5 g/L

subjects and their husbands (subjects: p = 0.000, husband: p=0.000) (28). It has been observed that Indian women with low education level have low calcium intake (29).

There were significant differences across all educational groups with respect to weight, BMI, dietary intakes of energy, protein, calcium and BMD at the lumbar spine and Ward's triangle (Table 6). The protective role played by educational level could be due to other overall determinants, such as a better health status and nutrition, a more positive attitude to taking drugs or preventive measures, and a more efficient use of health care resources. In a complex manner, under nutrition might affect the positive relationship between occupational activities and bone parameters (30). With improved educational level and per capita income, the population have better living condition and then better nutritional intake.

Table 5: Prevalence of osteopenia and osteoporosis in all participants. Data are presented as percentages with osteopenia (> -2.5 SD to < 1.5 SD below young adult BMD) and osteoporosis (< 2.5 SD below young adult BMD)

Age (Number)	20-29 years (67)	30-39years (63)	40-49years (54)	50-59years (46)	60-69 years (25)	20-69 years (255)
Lumbar Spine (L2-L4):						
Osteopenia	32.8%	19.0%	35.2%	21.7%	24.0%	27.0%
Osteoporosis	4.5%	0%	18.5%	17.4%	60.0%	14.1%
Femur Neck:						
Osteopenia	31.3%	39.7%	38.9%	34.8%	8.0%	33.3%
Osteoporosis	4.5%	0%	11.1%	4.3%	56.0%	9.8%
Femoral Ward's triangle:						
Osteopenia	31.3%	42.9%	33.3%	32.6%	8.0%	32.5%
Osteoporosis	0%	3.2%	18.5%	6.5%	60.0%	11.8%

Conclusion :

Assessment of dietary intake revealed that the daily intake of pregnant subjects comprises of the local vegetables regularly and few dairy products. There is an urgent need for measures to improve the nutritional status, dietary calcium intake and thus the bone health of women. It can be achieved largely by improving dietary pattern and habits and by improving education and socio-economic level. There are evidences suggesting that Vitamin D supplementation should also be recommended. These steps along with awareness towards bone health especially in second and third decade will go a long way to improve morbidity of osteoporosis.

Annexure

Dietary evaluation of all the participants was done by the following method (21). The dietary evaluation of all the subjects was done by using the 24-hour recall method (11). All the subjects were asked for everything they consumed in the last 3 days including 2 consecutive working days and one holiday. Time of the day, food, quantity, and recipes of composites dishes were recorded. The self-prepared standardized portion sized models in terms of households measures (cups, glasses, spoons, bowls, etc.) were used to accurately quantify the intake of both raw and cooked food items. Portion sizes were quantitated by the participants to which standard weights were assigned. Completeness, creditability of the reported number of servings and consistency in reported consumption frequencies were checked. The validity and repeatability of the dietary assessment was rechecked at random over the period of the study. For analyses, food consumption data were converted into energy and nutrients. The intakes of total

Table 6: Daily dietary intakes and BMD of participants by educational levels

Variables *	No education (n = 85)	Less than 10 years (n = 102)	10 to 12 years (n = 30)	More than 12 years (n = 38)	P value
Energy (kcal)	1485.4 ± 311.7	1607.6 ± 233.5	1636.2 ± 295.6	1661.5 ± 168.6	0.006**
Protein (g)	45.7 ± 7.9	50.2 ± 7.8	50.9 ± 12.5	49.5 ± 7.8	0.002**
Fat (g)	29.3 ± 13.2	31.8 ± 6.1	32.3 ± 7.7	33.3 ± 5.6	0.103
Calcium (mg)	497.5 ± 174.2	557.4 ± 146.5	583.3 ± 172.9	578.9 ± 140.5	0.009**
BMD at Lumbar spine (g/cm^2)	0.996 ± 0.210	1.152 ± 0.187	1.192 ± 0.186	1.198 ± 0.185	0.0001**
BMD at Femur neck (g/cm^2)	0.885 ± 0.208	0.933 ± 0.152	0.966 ± 0.163	0.968 ± 0.184	0.092
BMD at Ward's triangle (g/cm^2)	0.752 ± 0.257	0.811± 0.205	0.817 ± 0.184	0.876 ± 0.225	0.036**

* =Values are mean ± S.D
** = Significant P value
BMD = Bone mineral density

energy, calcium, fat and protein were calculated with the use of food composition table, detailing the nutritive value of Indian foods, developed by Indian Council of Medical Research (31). The daily amount of total calories, calcium, fat and protein consumed by the subjects, were calculated by taking the mean value of the 3 days for each foodstuff.

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Medical Education: A Re-evaluation of Current Problems and Possible Way Ahead

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SUMMARY

In this article the author analyzes the contemporary issues of medical education. He puts forth the plausible solutions focussing on four core issues namely- Objectivity in assessment, quality in high stake entrance examination, question banking and faculty development. Several of these issues are linked with quality of the faculty. These issues can be resolved with gradual, consistent and substantial efforts by administration, faculty and students. The author proposes that in the residency program, there should be structured course covering pedagogic skills, scientific research tools and professionalism. So far as the strategy for curriculum reforms is concerned, the issue has been taken up by Medical Council of India under 'Curriculum Implementation Support Program'. It includes four components- foundation course, early clinical exposure, integrated teaching and skills training. There should be institutionalized system for curriculum and assessment reforms. There is a need to develop a policy to strengthen our selection procedure/entrance exams. In order to improve the standards of medical education we must have functional Medical Education Units in each medical college.

Key words: Medical Education, Objective assessment, Entrance exam, Question banking, curriculum reforms

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Medical education has always been a challenge for academicians. It is not very easy to incorporate changes in the system according to contemporary needs. Under the aegis of the Medical Council of India (MCI) regulations, Regional Training Centres (RTCs) and Medical Education Units (MEUs) have been set up across the country. These Medical Education Units face their own problems to deal with various issues. In fact, this article re-evaluates the contemporary issues in the light of current status. The author also puts forth the plausible solutions. It is not possible to address all the issue related to medical education. Therefore, the author has taken up those issues where he has contributed to the development of medical education. The article focuses on the following issues:

1. Objectivity in assessment
2. Quality in high stake entrance examination and question banking
3. Faculty development and capacity building
4. Vision for Medical Education

1. Objectivity in assessment :

Objectivity in Assessment is an essential component of medical education. In order to maintain this objectivity it is very important to understand the dynamics of curriculum and its relation to assessment.

Contemporary societal needs actually shape the Curriculum. For example malnutrition, infection and water borne diseases occupy special significance in our UG curriculum. A curriculum determines how the learning objectives of syllabus will be framed and executed. Teaching influences the learning in a conventional set up. Learning is always assessed in the examination. What has surprised medical educationists is the fact that assessment drives learning (1). Therefore, a student focuses on what is actually being assessed in an examination. In such a scenario a part of curriculum and societal needs fall apart from the teaching-learning process. It has been observed that learning is also influenced by a hidden curriculum. The hidden curriculum is not taught but learned and emulated by students. What the students emulate influences to a great extent the health care delivery system of our society. This serves as important variable in teaching learning process.

There are several ways in which assessment may be improved. The formative assessment which is conducted periodically at short intervals can be improved by structuring the contents of assessment in detail. After each formative assessment a detailed explanatory feedback should be provided to each student, possibly soon after the assessment. It is advisable that a model answer should be provided to the students. For effective and objective summative assessment a teacher should be very clear about his role- a role like a judge. In general, the quality of any assessment is improved by proper structuring, blue printing, adequate coverage of contents, paying attention to validity and keeping a track of reliability.

Objective Structured Clinical Examination (OSCE) and Objective Structured Practical Examination (OSPE) have been used to enhance the objectivity in assessment for last three decades. OSPE is pre-clinical version of OSCE since pedagogically both are same. According to Harden and Gleeson (1979) "The clinical competence to be tested is broken down into various components …. Each components is assessed in turn and is the objective of one of the stations in the examination…..At procedure station, the student's skill is assessed. The examiner uses a check list to record the performance……" (2). It is noteworthy to mention here that we started OSPE at AIIMS in early 80s for the first time in the country, soon after the introduction of OSCE by Harden and Gleeson in 1979 in Dundee. Since then OSPE has passed through different evolutionary phases in terms of its research, development, application and creating a system for usage of OSPE.

Nayar et al (1986) have reported that OSPE score on two consecutive occasions showed consistency. A significant correlation coefficient of 0.81 has been reported (3). Soon after this study we investigated students' attitude towards OSPE since OSPE was naive to our system at AIIMS. In our study, the students reported that it is a valid examination. It is a reliable method of conducting the practical examination. It facilitates the learning process for the students. It is more challenging and stressful than the conventional practical exam. The students further opined that it assesses an entirely different set of skills as compared to the conventional practical examination. **Figure 1** shows students' attitude towards OSPE as measured on Osgood's differential scale. On the whole OSPE has high acceptability by students (4).

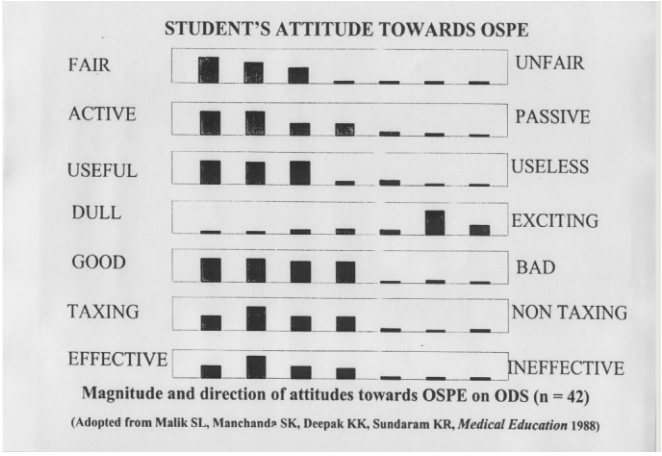

Figure 1. Student's attitude towards Objective Structured Practical Examination (OSPE) as measured on Osgood's differential scale (ODS) scale. (Data reproduced from article published in Medical Education in 1988, with permission) (4)

Figure 2 depicts a typical lay out for OSPE examination. In OSPE several practical task based questions are prepared that can actually be performed and answered in short duration i.e. 4-5 minutes. During the OSPE examination the skill learned are actually demonstrated by the students. The tasks which seek demonstration of psychomotor skills are called *procedure stations*. One example of procedure station to assess skills of recording blood pressure in humans is given in **Table 1**. The other types of stations which assess cognitive skills like interpretation of graphs, calculation of values and knowledge related to psychomotor skills are called *question stations*. In formative internal assessment we use 12-16 OSPEs in department of Physiology at AIIMS. In final summative assessment a total number of 25 to 30 OSPE stations which require about 120 minutes are arranged.

In the department of Physiology at AIIMS we have more than 500 OSPEs, generated out of a self sustaining system to create OSPEs. Figure 3 flowchart provides the detailed steps involved in preparation of OSPE questions and checklists. We implemented the administrative measures to improve objectivity in the professional examination at the level of institute. This was done by doing a situation analysis of objective practices like OSPE/OSCE and structured viva-voce examination across all UG and PG professional examinations and initiating administrative steps to implement appropriate measures.

The system of OSCE and OSPE brought revolution in assessment process. As the OSCE/OSPE are composed of several quantifiable units of information, the item analysis can be easily performed. Therefore, it is easy to compute the reliability. About 25-30 OSCEs (requires

Table 1: Q. Record the blood pressure of the subject provided
Check list for the examiner for observing and scoring the recording the blood pressure

Sl No.	Component of task performed	Score	
		Yes	No
1	Deflation of cuff	(.2)	(0)
2	Tying the cuff	(.4)	(0)
3	Identifies the site of auscultation	(.2)	(0)
4	Raises pressure up to 200 mmHg	(.4)	(0)
5	Releases pressure slowly	(.4)	(0)
6	Correct recording	(.4)	(0)
Total score		(2)	(0)

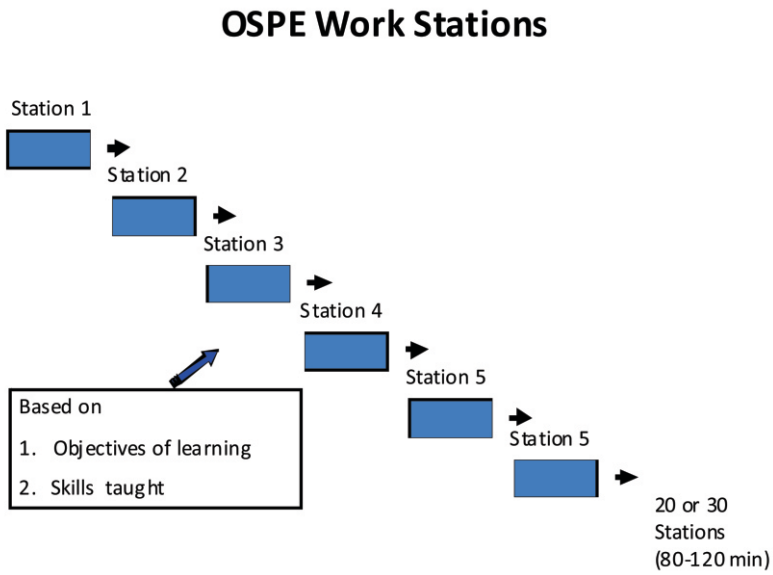

Figure 2. A typical lay out for Objective Structured Practical Examination (OSPE) examination. In final summative assessment a total number of 25 to 30 OSPE stations are arranged.

about 120 min of exam) would normally carry the acceptable reliability from pedagogical point of view. The OSCE/OSPE has brought objectivity, transparency and assurance of wide coverage of contents. The face validity of OSPE has been reported to be high by the students (4).

OSPE has certainly influenced the teaching-learning process in medical education. It has been reported that it

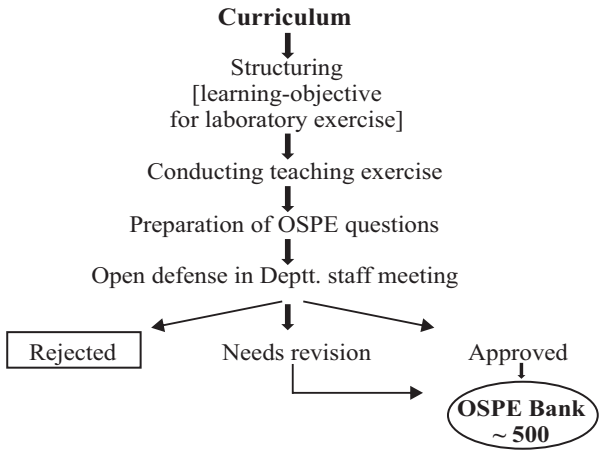

Figure 3. A system for preparation, editing and pre-validation of Objective Structured Practical Examination (OSPE) questions and checklists. Adapted from: Deepak, 1993 (5).

increases seriousness at study and improves attendance of students. After the introduction of OSPE the teachers have become more conscious of their own performance. OSPE also helps in giving a structured feedback. Therefore, OSPE has emerged as a successful instrument for practical examination in terms of objectively, reliability, practicability and validity (4, 6).

2. Quality in high stake entrance examination and question banking :

Conducting an entrance test is a challenging task. Howsoever robust and strong a system may be, some elements may find loopholes in it. It is a worldwide phenomenon and our country is not an exception.

The problems of conducting an entrance examination are three fold: paucity of MCQs (quantity deficit), poor quality MCQs (quality deficit) and operational issues (procedural deficit). These factors impose big challenges in conducting a perfect entrance test. However, there are the ways to control these problems. So far as the paucity of questions is concerned the author in the capacity of Sub-Dean (Exams) at AIIMS created a system for yielding high quantity of MCQs. Instead of entrusting the preparation of MCQs to the heads of the Departments, the MCQs were actually collected directly from the faculty members. By using this method even if one faculty gives 12 Questions a year, one can comfortably collect 3000 good quality items after rejecting 50% at pre-validation level from 500 faculty members (7). Even in a medical college (having faculty of 150 members) it is not difficult to collect good items by creating an ongoing system. Like any examination work, a small token of remuneration for it is always helpful.

To improve the quality of MCQs one needs to initiate faculty development program. It is known that the quality of a question is directly related to academic excellence and pedagogic skills of the faculty. An item review (pre-validation, judgemental analysis) by a group of faculty always helps to improve the quality of an item (8). The next point refers to operational issue. The operational issue is how to generate and maintain a question bank. In our education system several question banks are available with various stake holders. Students maintain their personal banks. There are community banks in students' hostels. Considering the commercial interests, several books on MCQs and web based question banks are also available. Some web-based resources are freely available in public domain and some are available by paying a cost. MCQ banks do exist at institutional level, national and international level. They are called item banks (9,10).

It is a moot question, ideally how many items a bank should have. For medical sciences while preparing a question bank one should pay attention to a large number of learning objectives. There are 21 medical subjects taught at undergraduate level. To assess 21 medical subjects effectively, each subject may

have 2000-3000 items. It gives nearly 40,000 items which may cover the entire UG syllabus. If we calculate the number of items, we reach the same figure of nearly 40,000 items in accordance with system/organ based curriculum (integrated curriculum). In author's opinion this figure approximates the critical number of questions. There is a possibility to collect this number of questions in an item bank. This opens two avenues- first, by pooling resources, one can generate question bank with critical number of questions. Secondly, if a question bank is having critical number of questions, it may be made available in open domain (Open Question Bank). Pedagogically speaking, if a student can answer successfully the desired number of questions presented randomly, he can be declared successful. The concept of 'open question banking' is new. It can be successfully maintained and operated by using computational technology. Question paper can be given to students either by 'random question generation' or by 'criterion based manual selection'. From the question bank the reasoning and recall items can be mixed to generate a question paper. Therefore, the selection of question may be based on certain pre-defined criteria. After each examination if the questions are returned back to the bank, item analysis and appropriate editing of question is a must. Item analysis is the analysis of the responses of the students appeared in the examination. This analysis is also called 'post-validation' of items or psychometric analysis.

An attempt of cheating in an examination is a social evil. How aptly the Honourable Judge at Bombay High Court expressed his opinion with reference to a leakage of exam paper: “The bad element may be small in number, but they are active” (11). Over the years the methods used in cheating attempts have undergone a gradual change. Advanced communication technology has influenced these methods a lot. Accordingly, the methods to detect leakage and catch the culprit have also advanced. For example in the latest attempts to leak the question paper students have used miniaturised hardware to capture the image and used latest cordless communication technology (12). There is an urgent need to nullify such attempts by using high end technology like mobile jamming or advance ones. In order to prevent such attempts, not only we have to change process of our examination, but we need to explore psycho-social interventions as well. There is a serious need to do documentation of such events and develop a research evidence base for a sound strategy for prevention.

3. Faculty development and capacity building :

Before I re-evaluate the current issues in medical education it will be worthwhile to look at the continuing problems. The continuing problems of medical education include too much of rote learning, inadequate and non uniform clinical exposure, and deficient assessment practices. The newer

problems are related to commercialization of medical education. This problem is an off shoot of change in the mind set of stake holders namely corporate sector, students and faculty. Several of these problems can be solved by having a robust system for faculty development.

India is a big country. There are more than 335 recognized medical colleges in our country. To arrange the faculty development programme to all the faculty at continuous intervals is a mammoth task. To impart training on a regular basis Medical Council of India has established 17 regional training centres (13). If one questions whether all faculty may be trained at RTC level, the answer would be negative. If we take an average of 150 faculty members in each medical college, the total number of faculty would be about 50,500. If we divide them into the batches consisting of 25 faculty members each, the total No. of batches would be more than 2000 batches. If the present RTCs start training these batches, each RTC needs to train 120 batches. If one RTC trains 4 batches every month (one batch every week), it will take two years to complete one rotation. For several reasons, this option is not feasible. Therefore, MCI has evolved a cascade approach to impart training in medical education. In this approach RTCs are entrusted with the responsibility of educating staff at MEUs. The MEUs are supposed to train the entire faculty of a college. Still there are the following problems with this model:

1. Inadequate number of RTCs,
2. Poorly structured MEUs and
3. Lack of logistic resources at MEUs.

Therefore, besides reinforcing the existing cascade system of faculty development, there is need to have parallel support system integrated with cascade system of MCI. There are two suggestions: first, AIIMS, Delhi and upcoming six AIIMS may participate in a nationwide faculty development program. Secondly, scientific bodies and associations also develop a regular CMEs in medical education. There is a need for policy development for these issues at appropriate level. The distance learning modules, using vast capacity of National Knowledge Network (NKN) will certainly be useful for faculty development programs. The efforts of Foundation for Advancement of International Medical Education and Research (FAIMER) in creating the expert database in our country is commendable (14).

4. Vision for Medical Education :

The challenges and problems mentioned in forgoing discussion can be met with gradual, consistent and substantial efforts by administration, faculty and students. Keeping these views in mind MCI has been in the process of bringing sporadic changes in past. It had been a partial success, until MCI decided to bring out a vision document last year. This is called 'Vision Document 2015'(15). This year several rounds of meetings were held to develop a strategy to bring out the long lasting changes.

There are the following main changes/reforms that were proposed in the vision document.

1. Reforms in Entrance test: With the implementation of National Eligibility and Entrance Test (NEET), the concept of single entrance test is a reality now (MCI: Vision 2015) (15).
2. Curricular reforms.
3. Faculty development programs.

The present discussion focuses on curriculum reforms. The strategy for curriculum reforms has been defined by MCI as "Curriculum Implementation Support Program" as CISP. The CISP includes four components- foundation course, early clinical exposure (clinical relevance of pre-clinical teaching), integrated teaching and skills training. The aim of foundation course is to impart formal training in soft skills such as communication, language, group dynamic skills, leadership skills etc. Early clinical exposure has been planned to provide clinical relevance to pre-clinical teaching. In this program the students in preclinical years are exposed to clinical scenarios which help them to understand the significance of basic sciences. The integrated teaching occupies main role in CISP. The integrated teaching aims at integrating contents across basic and clinical sciences in a horizontal and vertical manner. It will result in meaningful and contextual learning, and presumably, it will avoid redundancy and duplication. Our experience over 2 decades and recently held symposium on Problem Based Learning (PBL) points towards the fact that Integrated curriculum is more suitable to Indian conditions than typical problem based curriculum. There have been several cases of failure of PBL in Asian countries (16). For uniform clinical skills training we require the help of computation technology and bio-medical engineering. Through advent of technology it is possible to use computer simulation, haptics and mannequins to provide adequate opportunities for skills training for medical students. These simulation models, besides helping in skills training, can also help in providing opportunity for research. The case in point is that the author developed a blood pressure simulation model as teaching aid (17), which was later used by students in a research project supported by National Aeronautical Space Administration (NASA, USA) (18).

Our country, under the aegis of National Knowledge Network (NKN) has developed a large knowledge network by connecting more than 850 institutions/organizations/colleges (19). More than 150 of them connected organizations belong to medical colleges/institutions. A very high band width connectivity is available with them. It will be of tremendous use in sharing medical knowledge both in real time and in offline mode. The onus of developing material to be used for such networking lies with individuals and individual medical colleges. Through such network synchronized didactic lectures can be shared, consequently creating a virtual classroom. One can develop virtual skill

lab which can be used by students across the country. Since the national knowledge network has immense capacity to store data, it may help to create medical research data base and virtual medical museum as suggested by Dr. SV Raghavan (19).

At AIIMS we have KL Wig Centre for Medical Education and Technology (CMET) which also serves to expand medical education and technology not only for AIIMS but for South East Asian region. Besides its main role of conducting faculty development programs it provides various media related services to the faculty. These services include designing and printing of posters for conference purpose, developing high quality clinical videos and photography, digitization and documentation of medical images. AIIMS has realized its responsibility towards training other staff in the hospital as well. Residents and tutors are pillars of any medical institution. They are future teachers. Realizing this fact, we conduct regular workshops and symposium for them. Other hospital staff members also need training to work more effectively in the health care system. We conduct workshops for them also. The model was followed by many others institution. CMET is also engaged in research to create evidence based medical education. Our future plan is to use high end technology for imparting uniform clinical exposure and teaching (20).

Medical education has tremendous scope for growth and development. In our set up when the residents join the department they are not familiar with pedagogic skills, scientific research tools and professionalism. Thus, I suggest that they should have some structured course/credit hours inbuilt in the residency program. There is a need to develop a policy to strengthen our selection procedure/ entrance exams. There should be institutionalized system for curricular and assessment reforms. In order to improve the standards of medical education we must have strong Medical Education Units with trained manpower in each medical college. These units should be networked using NKN support.

In summary, India has large base for advancing medical education. We represent about 14 % medical institutions of the world and about 37 % in Asia (13, 14). Undoubtedly, ours is the largest medical college network. Therefore, we have an opportunity to take a leadership role in medical education. The efforts of MCI in streamlining the regulating protocols are laudable. Our Government's initiative for starting 6 new AIIMS like institutions is a commendable effort. Some AIIMS like institutions have already started functioning and the rest are ready to start. These institutions may help in imparting faculty development program to several other medical institutions.

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Towards Early Diagnosis and Assessment of Cancer: Role of MRI and in-vivo MR Spectroscopy (MRS)

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SUMMARY

Cancer is a major disease that affects men and women, worldwide, while breast cancer is the leading cause of cancer related deaths in women. Early diagnosis is essential for timely initiation of treatment which would improve the quality and overall survival of patients. Last two decades has seen development of non-invasive MRI methods like contrast MRI, diffusion and perfusion MRI for breast cancer diagnosis. MRI is useful for preoperative staging; follow response to therapy, and to detect local recurrences; however it has poor specificity in differentiating benign from malignant lesions, even with the use of contrast agents. Both diffusion MRI and *in vivo* MR spectroscopy (MRS) have shown great potential to increase the specificity of MRI. This article presents a review of the results obtained from our Institute on the potential of various MRI and MRS methods in the early diagnosis and assessment of tumor response of breast cancer patients.

Key Words **:** Magnetic resonance imaging (MRI); *in vivo* proton (^{1}H) magnetic resonance spectroscopy (MRS); breast cancer; diagnosis; assessment; tumor response.

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INTRODUCTION

Cancer affects men and women of all ages, race and class. There is an alarming raise in the incidences of various cancers and considering its progressive nature, early diagnosis and treatment is essential for improving the survival and the quality of life of patients. Despite the availability of large number of investigational methods like biochemical and imaging modalities, the diagnosis of cancer is challenging. Various diagnostic methods are used routinely like X-ray, mammography, ultrasound, computed tomography, magnetic resonance imaging (MRI) and positron emission tomography for diagnosis. However, the 'gold standard' is still the histopathological evaluation of biopsied tissues. Further prognosis and survival rates vary widely depending on the cancer type, staging and treatment regimens given to the patient. Thus, accurate diagnosis of cancer at an early stage would be of immense use to clinicians for timely intervention and for initiation of appropriate treatment that would improve the quality and the overall survival rate of patients.

During the past two decades, extensive research has been directed towards the development of non-invasive imaging methods that are highly sensitive, specific and cost effective to improve the diagnosis. In this direction various MR imaging methods like dynamic contrast enhanced MRI (DCEMRI), diffusion MRI (DWI) and perfusion MRI have been evaluated at various centers. The MR images that are produced using a powerful MRI scanner are the spatial display of the distribution of hydrogen nuclei (protons) present in body tissues. The advantages of MRI include high-resolution anatomical images in multiple planes with high soft-tissue contrast resolution and the use of non-ionizing radiation. In addition to structural characterization, real time brain functions, blood flow etc. can also be measured using MRI. The sensitivity of detection of cancer with MRI is high; however it has poor specificity in differentiating benign from malignant lesions even with the use of contrast agents. In view of this, the addition of *in vivo* MR spectroscopy (MRS) has been shown to improve the specificity (1). *In vivo* MRS allows non-invasive detection of the biochemical composition of the tissues and provides information on both the biochemical and the physiological processes of malignant transformation. Further, the method facilitates obtaining biochemical or metabolic information from a well-defined region of interest (ROI) or volume element (voxel). Since both MRI and MRS are non-invasive methods, they are also useful for repeated monitoring or guiding treatment of cancer and the tumor response to treatments (2-5). MRS can be performed with a large number of nuclei; however most *in vivo* studies are performed using the nuclei hydrogen (^{1}H) and phosphorus (^{31}P) due to their high natural abundance in tissues. However, the focus of this oration article is to review the application of various MRI and *in vivo* proton (^{1}H) MRS methods in the study of breast cancer in Indian population carried out in our Institute over the last two decades for

early diagnosis as well as their role in monitoring the tumor response of patients undergoing therapy.

Incidence of breast cancer :

In India, breast cancer it is the second leading cause of death among females and the age-adjusted incidence is 28.6/100,000 with more cases detected in Delhi and Mumbai (6). A recent report by the Indian Council of Medical Research predict the number of breast cancer cases in India would rise to 106,124 in 2015 and to about 123,634 in 2020 (2). It has become a disease of major socio-economic importance due to high morbidity and mortality and hence diagnosis and treatment are recognized as priorities in research. The survival rates in developed countries are high while in the developing countries the survival rates are much lower. Thus, early detection using appropriate techniques along with better treatment options is necessary to improve the clinical outcome and to reduce the mortality.

Diagnosis of breast cancer :

Physical examination, mammography, ultrasound and fine needle aspiration cytology or core biopsy are routine methods used for the diagnosis of breast lesions. The primary screening technique for detection of breast cancer however, is mammography but it has limitations in identifying lesions in dense breast or micro-calcification. Ultrasonography is used for diagnosis of cyst, mammographically occult lesions and in screening young women with dense breast. Both mammography and ultrasonography have low specificity leading to unnecessary biopsies with associated complications such as hemorrhage, pain and complications related to anesthesia.

Magnetic resonance imaging (MRI) :

Recently, considerable interest is focused on the evaluation of various MRI methods in the characterization of breast lesions in view of the limitations of mammography, ultrasonography and other techniques (7-13). MRI has been used as complimentary modality for preoperative evaluation of lesion size, staging of cancer, to monitor the response to therapy, and to detect local recurrences. In addition, it plays an important role in studying the integrity of breast implants and delineates breast cancer around or behind the implant.

Several studies showed that the sensitivity and specificity of MRI for detection of cancer can be significantly increased with the use of paramagnetic contrast agents through DCEMRI (7-13). In DCEMRI, tumor angiogenesis is the basis of contrast enhancement and rapid imaging is used to detect the differential enhancement between malignant tumor and normal breast parenchyma. Imaging at high spatial resolution enables tumor characterization based on size, shape, margins and the internal features observed. In DCEMRI, two sets of T1-weighted images are acquired; one before and one after contrast administration with

identical parameters, and the differences in contrast enhancement is calculated. However, most DCEMRI studies report poor specificity (ranging from 20% to 100%) (14-16). DCEMRI is very useful for the detection of multi-focal, multi-centric disease, preoperative evaluation and for accurate staging. Additionally, MRI is used in the screening of high-risk women (9, 17-20) and has the sensitivity in the range of 95-100% for the early detection of breast cancer (21).

In recent times various researchers have also exploited the differences in various biophysical, biochemical and physiological characteristics of various breast tissue types using DWI (to study water diffusion), perfusion weighted imaging (to study vascularity) and MRS (to identifying biochemical markers). Studies using DWI have shown potential in differentiating malignant, benign and normal breast tissues (22, 23) as well as in monitoring the treatment response (24-27). Recently we studied about 203 subjects and among them 141 were infiltrating ductal carcinoma (IDC) patients, 34 were benign breast pathology and 28 were normal volunteers who did not have any breast abnormalities (28). Our data showed that the mean ADC of malignant lesion was significantly lower (1.03 ± 0.18) compared to benign (1.63 ± 0.28) and normal (1.80 ± 0.12) breast tissues. We used ROC analysis to determine the cut-off values of mean ADC among malignant, benign and normal breast tissues. Accordingly, a cut-off value of 1.18 ($x10^{-3}$ mm^2/s) was obtained to differentiate malignant from benign diseases. Similarly, a cut-off value of 1.42 ($x10^{-3}$ mm^2/s) was obtained for the differentiation of malignant and normal breast tissues. Similarly, a cut-off value of 1.62 ($x10^{-3}$ mm^2/s) was obtained to differentiate benign from normal breast tissues. These data indicated that ADC of breast cancer patients was significantly lower compared to benign patients and controls. The lower ADC values seen in malignant breast tissues reflects the underlying histological pattern of densely packed randomly organized tumor cells that inhibit effective motion of water molecules, thus restricting the diffusion and hence a lower ADC value. These results clearly indicated the diagnostic potential of DWI in characterizing the breast lesions.

Proton (^{1}H) MR spectroscopy :

The ^{1}H MR spectrum of breast tissue is not rich with many metabolites in comparison to the spectrum from brain (29, 30). The normal breast tissue without water suppression is dominated by lipid (at 1.33 ppm due to methylene [-(CH_2)n-] protons) and water (at 4.7 ppm) resonances (see **Fig. 1**) and showed

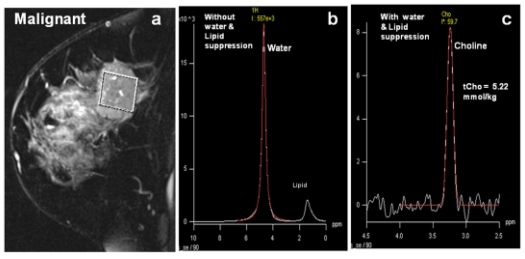

Figure 1.(a) T2-weigted sagittal image of a normal volunteer showing the voxel from which the ^{1}H MR spectrum shown in (b) was obtained without water and lipid suppression..

variation due to physiology, heterogeneity and hormonal variation during various phases of menstrual cycle (31). A change in the lipid composition of the normal breast parenchyma throughout the menstrual cycle has also been reported (32). We recently showed that within the normal breast and depending on the location of the VOI, due to the amount and distribution of adipose and fibro-glandular tissues, the ^{1}H MR spectral characteristics and the water-to-fat (W-F) ratio value vary considerably (31). Also, the W-F value of the para-areolar region is strongly influenced during the menstrual cycle with increase in the water content during menstruation and a gradual decrease, thereafter. The malignant breast tissues showed high water content with low contribution from lipids (see Fig. 2a & b) and thus a high W-F ratio compared to the normal breast tissues (33-35). Many studies have shown that W-F ratio can be used as a biomarker for diagnosis as well as to monitor the progression of cancer (34, 36). However, there are some limitations of using W-F ratio in diagnosis since substantial overlap of W-F values between benign and malignant breast tissues are also reported (33, 34-36).

Figure 2c is the water suppressed ^{1}H MR spectrum from a malignant breast tissue of a patient suffering from infiltrating ductal carcinoma showing clearly a peak at 3.2 ppm that correspond to several choline containing compounds (tCho) like phosphocholine, glycerophosphocholine, and free choline (1). The high level of tCho in tumor cells is attributed to the proliferative activity and

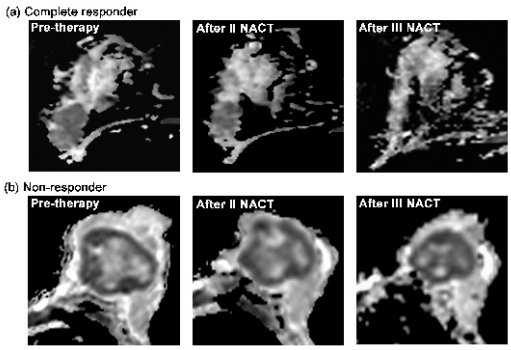

Figure 2.(a) T2-weigted sagittal image of a locally advanced breast cancer patient showing the voxel from which the ^{1}H MR spectrum shown in (b) was obtained without water and lipid suppression, while (c) shows the ^{1}H MR spectrum obtained with both water and lipid suppression.

increased membrane synthesis (37). Further, both increased synthesis by choline kinase and catabolic activity by specific phospholipase may also be responsible for high level of tCho in tumors (38).

A sensitivity of 83% and a specificity of 85%, respectively was reported when combined analysis of the MRS data available on breast cancer patients were carried out by Katz Brull *et al*. (39). With the addition of more data, Bartella *et al* showed an increase in both the sensitivity and the specificity of MRS as 87% (40). The potential application of using multi-voxel MRS to assess multiple lesions in a single study in breast cancer patients have also been reported (41-44). The advantages include distinguishing lesion borders and infiltration into the surrounding tissues.

Interestingly, several groups have

also reported the presence of tCho in normal, benign and in normal breast tissue of lactating women (45, 46). Thus, it is essential to accurately quantify the concentration of tCho instead of using the qualitative assessment of its presence or the absence for the differentiation of various breast tissue types. The two widely used approaches are: (a) semi-quantitative method of estimating tCho by calculating the signal-to-noise ratio (SNR), and (b) determination of the absolute concentration of tCho. The absolute concentration of tCho can be determined using both the external and internal water referencing methods (47, 48).

Studies from the literature showed a wide range of tCho concentrations in breast cancer patients and the reported values are in the range of 0 to 21.2 mmol/kg (47-55). These studies used water as an internal reference. Such a wide variation in tCho may be due to the heterogeneous nature or other molecular features of breast cancer. It is difficult to detect tCho in diffusive enhancement type cancers because of the intermingling of tumor cells with the adipose tissues (56).

Recently our group evaluated the potential of quantitative MR imaging and ^{1}H MRS in characterizing malignant, benign and normal breast tissues in a large cohort of women (57). The tCho concentration was found to be significantly higher in early breast cancer patients compared to LABC patients. Further, there was no association of tCho concentration with human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER) and progesterone receptor (PR) status of malignant breast cancer patients. Our results also revealed that tCho concentration was not related to the tumor volume, age and menstrual status of patients. The lack of expression of ER, PR and HER2 are described as triple-negative (TN) breast cancer, while triple-positive (TP) patients have the expression of all the three ER, PR and HER 2. In our study when all three molecular markers were taken into account (i.e, TN, non-TN and TP groups), significant differences in the tCho concentration and the age were observed. Our results indicated that TN patients were younger in age and had lower tCho concentration compared to non-TN and TP patients. In view of the data from large cohort of women were available, we also worked out a cut-off value for tCho concentrations for the differentiation of malignant, benign and normal breast tissues. Larger tumor volumes were seen in LABC patients of various stages compared to early breast cancer patients. ER- patients showed larger tumor volumes than in ER+ patients which are suggestive of aggressive tumor behavior combined with higher angiogenesis in ER- patients. These results demonstrated the molecular heterogeneity of breast lesions and its relation with the tumor volume and tCho concentration (57). Further, our group and several others have shown that addition of MR spectroscopy to MRI increases the specificity of diagnosis with the detection of high levels of choline-containing compounds in malignant breast tissues (58-60).

Therapy monitoring :

As indicated earlier, both MRI and *in vivo* MRS have rapidly evolved not only as sensitive tools for diagnosis but also as a tool for therapy monitoring in cancer research. For patients with advanced stage of the disease or LABC, neoadjuvant chemotherapy (NACT) is the standard treatment option, which is followed by surgery and post-operative therapies (61,62). The advantages of NACT include reduction in the tumor size, option of breast conservation surgery and inhibition of distant metastases (61,63-65) and its drawbacks include toxicity and variation in response of individual patients. Thus, it is necessary to identify the non-responders from responders so that non-responders may be offered alternate line of treatment. Hence, early and accurate assessment of tumor response to treatment is essential for patient management.

Normally, the tumor response to therapy in a clinical setting is assessed by physical examination of the palpable change in the tumor size. Also, techniques like mammography and ultrasonography are used for the evaluation of treatment response but are not accurate in differentiating chemotherapy-induced fibrosis and the residual tumor (61, 66-68). In this regard, MRI was shown to be useful for measuring the residual disease by measurement of the tumor size, both prior to and after the therapy (69, 70). Additionally, the use of DCEMRI has been reported to be more effective for estimation of the residual disease following chemotherapy (71-74). DCEMRI also has limitations like antiangiogenic treatment that may lead to decreased contrast uptake and the residual disease may be missed in diffused tumors due to partial volume averaging. It is reported that in comparison to histology, MRI underestimates the amount of residual tumor, especially in tumors that respond well to chemotherapy (75). The measurement of changes in the tumor size is the basis for assessment of the tumor response in most imaging methods, which is evident only at the late stage of therapy.

In this context, the utility of DWI and *in vivo* MRS have been explored especially in evaluating the early response of breast cancers to therapy. Recently, we evaluated the role of apparent diffusion coefficient (ADC) of tumors measured using DWI to predict the early response (see Fig. 3) compared with the anatomical

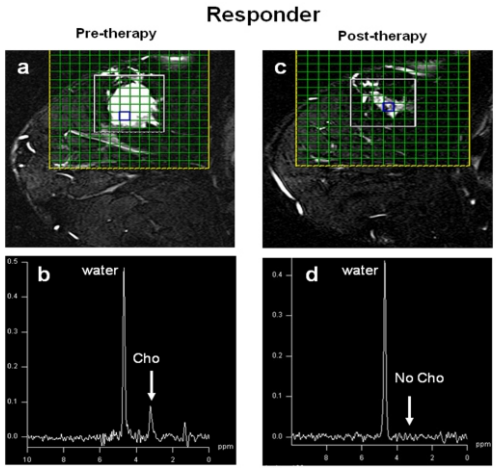

Figure 3. Representative ADC map of a breast cancer patient acquired prior to therapy and after II and III NACT: (a) complete responder, and (b) non-responder. [Reprinted from reference 27 with permission from John Wiley & Sons]

parameters like tumor volume and tumor diameter (27, 76). Our data on 56 patients showed that the specificity of differentiating responders from non-responders after III NACT was found to be 100% for ADC compared to volume and diameter (27). These results suggest the potential of DWI as an important tool in clinical imaging to predict the therapeutic response of cancer patients undergoing chemotherapy. Further, an interesting observation that emerged from our work was that the clinical responders showed significant change in tumor ADC as early as after I NACT. Whereas changes in structural parameters like tumor diameter and volume were evident only after II NACT (27).

A survey of the breast MR literature revealed that during the past decade, there is increasing interest in the use of ^{1}H MRS methods for monitoring the therapeutic response of breast cancer patients (50, 77). As discussed earlier, *in vivo* MRS provides biochemical information of tumor metabolism which is clinically valuable in the diagnosis as well as in the assessment of tumor response to therapy. Our laboratory and other centers have used proton ^{1}H MRS to complement breast MRI studies to improve the specificity of diagnosis and therapy monitoring. The malignant breast tissues have elevated W-F ratio and high levels of tCho and thus any effect of therapy can be expected to manifest as changes in their levels (36, 45). In responders, our sequential ^{1}H MRS data showed significantly reduced W-F ratio and tCho levels compared to that obtained prior to therapy during the course of therapy. These changes occur along with the reduction of the primary tumor size compared to the pre-therapy value. While in non-responders the decrease was insignificant (36, 45). Further study carried out in our laboratory showed that tCho peak was either reduced or absent in responders after III and/or VI NACT (45).

Recently we also evaluated the potential of SNR of tCho resonance and the tumor volume in the assessment of tumor response of patients undergoing NACT by sequential MR spectroscopic imaging (MRSI) and conventional MRI (78, 79). The MR response was compared with the clinical response. In responders, the pre-therapy tCho SNR was high which reduced after III NACT (see **Fig. 4**) with corresponding reduction of tumor

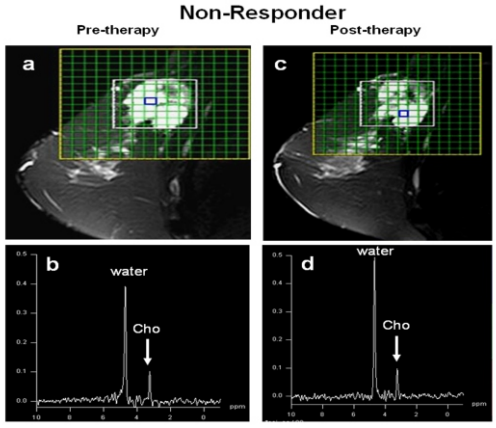

Figure 4. (a) Sagittal fat suppressed T2-weighted image of a LABC patient obtained prior to therapy who is a responder with the MRSI grid. (b) Spectrum obtained from a voxel shown in (a) with tCho resonance peak. (c) T2-weighted MR image of the same patient obtained after III NACT. (d) Spectrum obtained from a voxel highlighted in (c) that showed no tCho resonance peak. (Reprinted from reference 79 with permission from John Wiley & Sons].

volume. Non-responders showed no statistically significant changes in tCho SNR (see **Fig. 5**) and the tumor volume (78, 79). The changes in the tCho concent-

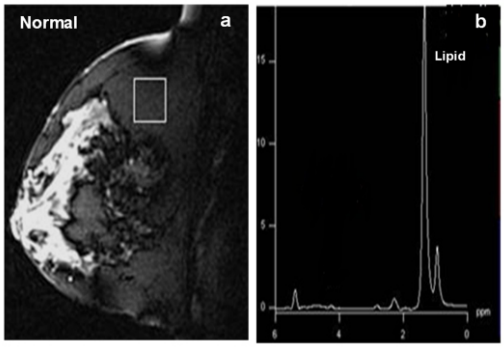

Figure 5. (a) Sagittal fat suppressed T2-weighted image of a LABC patient obtained prior to therapy who is a non-responder with the MRSI grid. (b) Spectrum obtained from a voxel highlighted in (a) showing tCho signal. (c) Post-therapy T2-weighted sagittal fat suppressed image of the same patient after III NACT. (d) Spectrum obtained from a voxel highlighted in (c) showing tCho signal. [Reprinted from reference 79 with permission from John Wiley & Sons].

-ration within 24 hours of administering chemotherapy that correlated positively to lesion size changes has also been reported by Meisamy et al (80). Further, we also reported changes in the absolute concentration tCho in predicting the tumor response of breast cancer patients undergoing NACT (81). The pre-therapy concentration of tCho showed significant reduction as early as after I NACT in responders compared to non-responders. Further reduction was observed after II and III NACT.

Summary :

The last two decades has seen the tremendous growth of various MRI methods as an important imaging tool in cancer management especially in breast cancer with a high sensitivity, high spatial resolution and 3D imaging capability. This is because MR is noninvasive; it avoids ionizing radiation and has the ability to generate high-resolution images. Additionally, through MRS it provides biochemical information at the molecular level. Dynamic contrast MRI shows high sensitivity for breast cancer detection, but with variable specificity. Both routine and DCEMRI are useful adjunct for mammography and ultrasonography. They are useful and have a distinct role in pre-operative staging, assessment of multifocal and multicentric disease, as well as chest wall involvement. Another advantage of various MRI methods is the ability of bilateral breast imaging at the same sitting, which is useful in detecting cancer of the contralateral breast.

Moreover, the advanced methods such as diffusion and perfusion MRI techniques and MR spectroscopy showed great potential for breast lesion characterization and have shown promise to increase the current level of specificity. DWI has the ability for evaluating the cellular changes while the vascular changes using DCEMRI in the same imaging session as MRS. Also, the development of various MRS procedures with water and lipid suppression and editing techniques has enabled obtaining non-invasive biopsy information. The

important feature of *in vivo* MRS is the ability to measure endogenous metabolites noninvasively as well as changes in tissue metabolism. Further, MR spectroscopy is also useful for monitoring therapeutic response of tumors, measuring the distribution, pharmacodynamic and pharmacokinetics of drugs *in vivo*. More studies are required to improve the sensitivity and specificity of *in vivo* MRS for several disease patterns particularly for small lesions before it is incorporated in clinical practice. For example in breast cancer, MRS acts as a complementary tool to histology, mammogram and other accepted techniques.

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