“Doctors are often accused of callousness of venality, and self infatuation, but they remind us that they have sacrificed the springtime of their lives, completely lost the precious years between their twenties and their thirties acquiring skills to benefit their fellow men.

Further more they have suffered deprivation, most of them have not had more than a dozen real nights of sleep in all this time many have Sacrificed their marriage and lost the unique opportunity to see their children grow.

So when they argue that the world owes them some compensation in the form of wealth, respect and social status, their demands are not entirely without cause.

Also, as the grim Statistics show, they often suffer worse than any patient for no one can repair a broken marriage or restore the children damaged by their Father’s ostensible neglect.

ERIC SEGAL, "The Doctor"
**Theme:** DIARRHOEA

**Past Editors**
- Prof. Mahendra Ch. Mishra
- Prof. Niranjan Tripathy
- Prof. Krupasindhu Panda
- Prof. Niranjan Rout
- Dr. Rekha Das

**Advisory Board**
- Prof. Prasanna Ku. Das, Cuttack
- Prof. Sidhartha Das, Cuttack
- Prof. Bidyut K. Das, Cuttack
- Dr. Sidharth N. Shah, Mumbai
- Dr. M. Abbas, Cuttack
- Prof. Sasaank R. Joshi, Mumbai
- Prof. Rohini Handa, New Delhi
- Dr. Kabi Pr. Mishra, BBSR
- Prof. Sukumar Mukherjee, Kolkata
- Prof. Pramod Mallick, Cuttack
- Prof. V. Mohan, Chennai
- Prof. Ramnath Mishra, Lucknow
- Prof. Gopal Ch. Kar, Cuttack
- Prof. Sanatan Rath, Cuttack
- Dr. B.B. Reewari, New Delhi
- Prof. J.P. Das, Cuttack
- Dr. Jitendra Singh, J & K
- Prof. P.C. Sahoo, Berhampur
- Prof. Ashok Das, Puducherry
- Prof. Sarita Bajaj, Allahabad
- Prof. K.M. Prasannakumar, Bangalore
- Prof. P.V. Rao, Hyderabad
- Prof. Annapurna Panda, Cuttack

**Editorial Board**
- Prof. P.C. Mohapatra, Cuttack
- Prof. C.B.K. Mohanty, Cuttack
- Prof. Jagannath Mohapatra, BBSR
- Prof. Shyama Kanungo, Cuttack
- Prof. S.P. Singh, Cuttack
- Prof. Maya Gantayet, Cuttack
- Dr. Sreejoy Patnaik, Cuttack
- Prof. Pravat Kumar Padhy, Cuttack
- Prof. Biswa N. Mohanty, Cuttack
- Prof. Indu Bhusan Kar, Cuttack
- Prof. Kashinath Padhiary, Birla
- Dr. Jayanta Rath, Cuttack
- Prof. Sarat Ku. Mohapatra, Cuttack
- Dr. Ananga M. Dwibedy, Cuttack
- Prof. D.C. Pattanaik, Cuttack
- Prof. L.K. Meher, Berhampur
- Prof. Datteswar Hota, Cuttack
- Prof. B.B. Mishra, Cuttack
- Prof. Nilamadhab Rath, Cuttack
- Prof. Abhaya Kar, Berhampur
- Prof. S.N. Panda, Cuttack
- Prof. Rabi Satpathy, Berhampur
- Prof. N.C. Padhy, Berhampur
- Prof. Umesh Chandra Patra, Cuttack
- Dr. Nageswar R. Subudhi, Berhampur

**Journal Committee**
- Prof. Manoj Ku. Mohapatra, Burla
- Prof. Susil K. Giri, Cuttack
- Prof. Niranjan Mohanty, Cuttack
- Prof. Surendra N. Senapati, Cuttack
- Dr. Chitta Prasad Das, Cuttack
- Prof. Biranchi N. Mohapatra, Birla
- Prof. Mrutyunjay Behera, Cuttack
- Prof. M.R. Patnaik, Berhampur
- Dr. P. Subasis Rao, Cuttack
- Dr. Ashok Singh, Sambalpur
- Dr. Braja Kishore Dash, Cuttack
- Dr. Prakash Ch. Panda, Sambalpur
- Prof. Satya N. Routray, Berhampur
- Dr. Saroj Kumar Sahu, BBSR
- Dr. Feroz Ali, Cuttack
- Dr. Saroj Kumar Sethi, Cuttack
- Dr. Sharada P. Swain, Cuttack
- Prof. K.M. Pathy, Berhampur
- Prof. Sarojini Sarangi, Cuttack
- Dr. Manoranjan Behera, Cuttack
- Prof. R.N. Sahoo, Cuttack
- Prof. Pramod Acharya, Bhubaneswar
- Prof. R.K. Jena, Cuttack

**Office Assistance:** Rabi N. Mishra, Atindra Mohapatra, Sudip Patelt, Deepak Mohanty, Subhransu Ku. Samal

**Editorial Correspondence**

**Dr. Jayanta K. Panda, Editor**
Asso. Professor, Medicine, SCB Medical College
Mob.: 9437028282, Email: drjayantpanda@gmail.com
IMA House, Medical Road, Ranihat, Cuttack - 753007, Orissa
Ph.: 0671-2413060, 2121125, Email: imaoorissa@gmail.com, Website: www.imaoorissa.com
Manuscript submission : Check List for Contributors

1. Letter of submission.
2. Copyright statement signed by all the authors.
3. Three copies of manuscript with copies of illustrations attached to each.
4. Title page.
   
   Title of manuscript.
   
   Full name(s) and affiliations of author(s); institution(s) and city(ies) from which work originated.
   
   Name, Address, Telephone, Fax numbers and e-mail address of corresponding author.
   
   Number of pages, number of figures and number of tables.
5. Structured abstract (objectives, methods, results, conclusion) along with title, and key words.
6. Article proper (double spaced on A/4 size paper).
7. Acknowledgements (separate sheet).
8. References (double spaced, separate sheets, Vancouver style).
9. Maximum number of references for Original articles - 20, Short articles-10,
   Case reports-6, Documentation-3, Correspondence-3.
10. Each table on separate sheet.
11. Figures/diagrams on separate sheet.
12. Photographs in envelope appropriately marked.
13. Legends on separate sheet.
14. Covering letter signed by all authors confirming that they have read and approved the contents and also confirming that the manuscript is not submitted or published elsewhere.
15. Statement regarding Ethics Committee Approval and informed consent from subjects.
16. CD with soft copy of the article.

– Hon Editor.
Editorial

DIARRHOEA : “Common to Occur, Difficult to Control”
Jayanta K. Panda

Secretary's Commentary

Diarrhoea : An Overview
Prasanna Ku Rathor

Invited Article

Gene Therapy : The Progress to Success
K.S. Panda, Sanjoy Panda

Theme Articles

A Practice Page on Childhood Diarrhoea
Prakash C. Panda, Smita K. Panda

Infectious Diarrhoea – An Overview
Nidhi Prasad, Gautam Patnaik, Nirupama Chayani

Diarrhoea in Elderly Patients in Long Term Care Facilities
G. Kumar, P.K. Rathor, K.P. Pattnaik, D.N. Moharana

Diarrhea in Immunocompromised Patients – An Overview
P. Das, J.K. Panda, K.P. Patnaik

Cryptosporidium Associated Diarrhea
Indrani Mohanty

Clostridium Difficile Associated Diarrhea
Susmita Sahu

Hiv & Diarrhoea
Sanjay Swain

Research Articles

Magnitude of Hepatitis A Virus Infection and its Clinical Course in Adults in a Tertiary Care Centre in Odisha

Study of Lipid Profile Abnormalities in CKD

Current Concept

Controversy in reducing Blood pressure in type 2 diabetes : post ACCORD scenario
D.R. Das, S.N. Routray, T.K. Mishra

Ultrasound - A New Weapon in the Anesthesiologist’s Armamentarium
N. Pani, S. Routray, R.K. Sarangi

Update Article

Corrosive injury of upper G.I. Tract
M.K. Panigrahi, H.S. Das
Basic Concept

Micro RNAs – an understanding
Srikrushna Mahapatra

Case Report

An unusual complication encountered in a spiral embedded tube.
A.Kumar, S. Nanda, H. Dalai

Spontaneous Adult Transmesentric Hernia
M.R. Sahoo, V. Bhaskar, A. Behera, R. Kaladagi

Cancer cervix presenting as pyoperitoneum
S. Panda, G. Kar

Primary Hyperparathyroidism with Complications
K.C. Mohapatra, J.K. Panda, A. Patnaik

Aggressive Angiomyxoma In Male: A Rare Case Report

Soft tissue coverage for heel defect where microvascular facility not available
P.K. Das, S. Samantara, S.P. Mishra

A Rare Case of Pulmonary AV Malformation
A. Behera, D. Bindhani

Nosocomial C. Meningosepticum Sepsis in A Diabetic Patient Treated for Retroperitoneal Hematoma
N. Prasad, G. Patnaik, G. Sarangi, A. Mohapatra, P. Das, D. Mahapatra, N. Chayani

Retroesophageal Right Subclavian Artery – An Anatomical Variation with Short Review
S. Sethy, C. Mahapatra, P.K. Chinara, C. Sarangi

Colocolic Intussusception due to an inflammatory fibroid polyp managed laparoscopically
M.R. Sahoo, M. Lopamudra, Anil Kumar T., J. Sarangi

Gastro Intestinal Stromal Tumour (GIST) of the Ampulla of Vater: Report of Two cases
D. Mohapatra, A.P. Dash, S. Panda, Md. Ibrarullah, P. Devi

In-vitro study of proliferation in short term cultured Umbilical Cord blood stem cells
S. Mantri, P.C. Mohapatra

Warfarin Embryopathy – To prevent or to treat?
P. Mishra, J.R. Panigrahy

Left Lung Hypoplasia with Right Aortic Arch
G. Pradhan, T. Mohanty, G. Panda, H.K. Sethy, J. Patnaik

Original Article

Use of Rubber Hair Bands for external Fixation using K Wire after release of Hand Contracture
A.P. Patnaik, S.P. Mishra

Pictorial CME

Rare Presentation of a Rare Disease: Tubercous Sclerosis

Letter to Editor

What should be the income of Doctors?
G. Sarangi

Practitioners Column

Prevalence of Diabetes and Hypertension in adults
Diarrhoea is one of the commonest presentation which is also a common cause of death in developing countries. Its varied possible aetiologies ranges from simple infective causes of dysentary by bacterial toxins like e.coli, shigella, salmonella & vibrio choleri; drugs like amoxycillin due to clostridium difficile; parasites or protozoas like amoeba, giadia; viruses like rota, adeno; mycobacteria like intestinal kochs; to chronic relapsing conditions like IBS, IBD, malabsorption or pancreatitis; to grave, horrifying diagnosis of septicemia, food poisoning by staphylococcus or botulism, HIV/AIDS & colonic malignancy.

It is really challenging for a physician to establish the exact aetiological diagnosis which may need simple tests like stool examination to culture & sensitivity, sigmoidoscopy with colorectal biopsy, small bowel barium X-rays & serology like serum gastrin, VIP, calcitonin, thyroxine & urinary hydroxyindolacetic acid & histamin & evaluation of fecal PH, lactose intolerance & magnesium ingestion.

Fluid & electrolyte replacement orally or by intravenous route is of central importance to all form of acute diarrhoea. In nonfebrile and nonbloody diarrhoea antimotility & antisecretory agents like loperamide and racicadrotil are useful adjuncts. Judicious use of antibiotics and antiparasitic drugs are crucial in timely control of symptoms. Management of chronic diarrhoea always depends on specific aetiology and controlled by curatives, supressives or empirical management.
Diarrhoea has been derived from the Greek word “diarrheo” meaning “flowing through” and is the condition of having three more loose/liquid bowel movements per day. It is a common cause of death in developing countries and the second most common cause of infant mortality globally.

In 2009, diarrhoea was estimated to have caused 1.1 million deaths in people aged 5 and over and 1.5 million deaths in children aged under 5 years.

The elderly are not equal risk of acquiring diarrhea, but compared to younger persons are more susceptible. In the elderly, the likelihood of diarrhea increases due to diminished physiological reserves, the burden of acute and chronic multisystem illnesses, undernutrition, general debility and cognitive impairment.

Many new microbial causes of diarrhea have been discovered during the past three decades. Research laboratories can now identify a microbial cause in over three quarters of children presenting at health facilities with diarrhea.

Many microbial deaths are caused by dehydration. An important development has been the discovery that dehydration from the acute diarrhea of any etiology and at any age, except when it is severe, can be safely and effectively treated in over 90% of cases by the simple method oral rehydration.

Diarrhoeal disease also represents an economic burden for the developing countries, reducing the health of its workforce. Fortunately simple and effective treatment measures are available that can markedly reduce diarrhea deaths, make hospitalizations unnecessary in most cases, and prevent the adverse effect of diarrhea on nutritional status. Practical preventive measures can also be taken that substantially reduce the incidence and severity of diarrhoeal episodes.

Prasanna Kumar Rathor
Gene Therapy: The Progress to Success
K.S. Panda¹, Sanjoy Panda²

Gene therapy is the transfer & expression of genetic material into a cell, tissue or organ for a therapeutic purpose.

**History**

1860: Mandel's discovery - in plants
1909: The Particle of inheritance - carried inside the cell "Gene"
1910: Rous sarcoma Virus (ras gene)
1914: Bover's Chromosomal abnormalities.
1915: Morgan - genes were born on chromosomes.
1944: Avery - genes were carried in DNA RNA is the working copy of the genetic blue print.
1950: DNA Rr-.JA Protein {Central dogma of molecular biology}
"Cancer "is not merely a lump in the body, it is a disease that migrates, evolves, invades organs, destroys tissues and resist drugs.
1988: Vogelstein - Genetic progression of cancer was a multistep process.
2000: "Hallmarks of Cancer" Weinberg & Hanahan
1. Self sufficiency in growth signals - Proto-oncogene's
2. Insensitivity to growth inhibiting signals - (Suppressor genes)
3. Evasion of Programmed cell death (apoptosis)
4. Limitless replicative potential Sustained angiogenesis
5. Tissue invasion & metastasis genetic mutations - ras,myc, Rb, neu so forth - unleashed the hallmark behavior of cancer cells. Cancer in short is not genetic in origin, it is genetic In entirety.

Medicine begins with storytelling. Patients tell stories to describe illness, doctors tell stories to understand it. Science tells its own story to explain diseases. This story of one cancer's genesis - of carcinogens causing mutations in internal genes, unleashing cascading pathways in cells that ten cycles through mutation, selection and survival - represents the most cogent outline we have of cancer's birth. Having wandered in the darkness for decades, scientists have finally reached a clearing in their understanding of cancer. Present task is to continue that journey towards a new therapeutic attack.

2003: Human Genome Project - completed common "colossal atlas of cancer" in 50 most cancers human genome contains 20 thousand genes.
2005: David Hunter - integration of traditional epidemiology molecular biology & cancer genetics will generate new knowledge for preventions
2006: Best Vogelstein's group at John Hopkin's thirteen thousand genes in eleven breast & colon cancers.

Vogelstein splayed out entire the human genome as if it were a piece of thread zigzagging across a square sheet of paper.

Every Patient cancer is unique because every genome is unique.

Number of mutations - Passive & active "every cancer cell possesses some set of driver and passenger mutations"

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Number of Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>50 to 80 genes</td>
</tr>
<tr>
<td>Colon Cancer</td>
<td>50 to 60</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>50 to 60</td>
</tr>
<tr>
<td>Brain Cancer</td>
<td>40 to 50</td>
</tr>
<tr>
<td>All</td>
<td>05 to 10</td>
</tr>
</tbody>
</table>

Genetically simple tumors (ie those carrying few mutations) might inherently be more susceptible to drugs, and thus intrinsically more curable.

¹Professor of Surgery
Surgical Oncologist, Director
Panda Curie Cancer Hospital, Cuttack - 753 001
Contact : 9861054177

²Asst. Professor ENT
AHRCC, Cuttack

© OMJ 2012
Pathway Disease:
The revolution in cancer research can be summed up in a single sentence: Cancer is in essence a genetic disease.
2007: Cancer is a "Pathway disease" Ras-Mek-Erk cascade? dysregulated "roughly there are 11 to 15 pathways, on an average 13.

How to regulate pathway:
Pessimistic view:
Will the oncologist need 13 independent drugs to attack 13 independent pathways to "normalize" a cancer cell? Given the slipperiness of cancer cells when a cell becomes resistant to one combination of 13 drugs, will we need as additional thirteen?

Optimistic view:
Attack on some of the core pathways may be particularly responsible to therapy-Viz-herceptin in breast cancer

Cellular biology of cancer:
Genetic anatomy genetic Physiology Therapeutics (Targeted therapies against genes)
Challenge - to determine which combinations of such drugs might inhibit cancer growth without killing normal cells.

James Watson - Co discover of DNA
We shall soon know all the genetic changes that underlie the major cancers that plague us. We already know most, if not all, of major pathways through which cancer inducing signals move through cells. Some 20-signals blocking drugs are now in clinical testing........ A few, such as Herceptin and Tarceva, have FDA approval and are in widespread use.
"Cancer" we have discovered is stitched into our genome. The discovering of the BRCA genes for breast cancer epitomizes the integration of cancer screening and cancer genetics.
"Cancer stem cell hypothesis" - John Dick act as the persistent reservoir of cancer generating & regarding cancer infinity. When chemotherapy kills the bulk of cancer cells, a small remnant population of these stem cells, thought to be intrinsically more resistant to death, regenerate and renew the cancer, thus precipitating the common relapses of cancer after chemotherapy. Cancer deaths can be presented before old age, if the terrifying game of treatment, resistance, recurrence and more treatment can be stretched out longer and longer, then it will transform the way we imagine this ancient illness.

"Death in old age is inevitable,
but Death before old age is not"

Members are requested to enroll more colleagues as members of IMA and join AMS and CGP in large nos for formation of local branches and extra academic activities.
Abstracts:

Diarrhoea is the second major under five killers. Acute watery diarrhoea constitutes 80% of cases. Dehydration and malnutrition are the common cause of mortality. The 5Ds of management are Dehydration, Drugs, Diet, Discussion and Difficult cases. HAF and ORS are cornerstone of Oral Replacement Therapy. Age appropriate diet should be encouraged. The only drugs proved to be helpful are Racecadotril and Zinc. Antibiotics are rarely helpful. Counseling is rewarding and should cover prevention and management skills at home.

Key words: Childhood Diarrhoea, ORT, ORS, Diarrhoea Mortality, Diarrhoea Treatment

Introduction:

Childhood diarrhea is still the second major killer in underfives across the world exclusive of neonatal causes9,11. Only recently has Pneumonia displaced it to the second slot thanks to ORS, the greatest life saving invention of the 20th century.

Acute diarrhoea in children are of three types. If it starts acutely and continues till 14 days it is termed ‘acute’. If it continues beyond 14 days it is known as ‘acute persistent diarrhoea’. When mixed with visible blood we call it ‘dysentery’. Most commonly (80%) it is of watery variety; dysentery and persistent types contribute 10% each.5,11

Major causes of acute watery diarrhea are viruses like Rota and toxin producing bacteria like ETEC (Enterotoxigenic E. coli). The presentation is acute, more prevalent in the early falls and winter affecting in late infancy till 2-3 yrs of age. Usually there is mild fever and persistent vomiting with a high purge rate often with perianal excoriation. Rarely is it rice water like when we should suspect cholera2.

Dysentery is caused by bacteria like shigella or salmonella typhimurium in almost all cases. Only in rarest of rare instances (1-2%) Entamoeba histolytica is the culprit.4

The diarrhea becomes persistent due to interplay of factors like persistence of infection (EAEC-Enteroadhesive E.coli) and dietary intolerance6. It often necessitates hospitalization with focus on a strict diet plan.

The major cause of mortality in diarrhea is dehydration (leading to acute kidney Injury, dyselectrolytemia, shock) and malnutrition(with its inherent complications)4,7. The cornerstone of management must address these two issues.

Chart 1. Dismal Practice Trends1,8

Making it simplistic and practical, the management may be discussed under headings of 5Ds i.e. D1-Dehydration, D2-Diet, D3-Drugs,D4-Difficult diarrhea and D5-Discussion.

D1: Dehydration (Prevention and Treatment):

The golden mantra of diarrhea management has been ‘Oral Replacement Therapy’ (ORT)8. There is loss of food, fluid and salts in the diarrhoeal stool and all these need to be replaced in toto. Replacement should start at home at the first loose stool as a preventive step not waiting till the features of dehydration to appear. The replacement fluid may be home available fluids(HAF) like salted rice water, salted...
dal water, sugar-salt-lemon sarbat, salted coconut water, salted watery curd and so on. But the items those should not be encouraged are fruit juices, tea, glucose drinks, only sugar water, soft drinks, energy drinks, protein drinks and so on. Food with plain water obviously is the best replacement fluid.

The golden tool for rehydration is ORS-oral rehydration salt. Recently the composition has been revised to match the electrolyte loss in common diarrhoeal stool and the new product is known as ‘low osmolar ORS’.

We can manage almost all cases of diarrhoeal dehydration with ORT only when the replacement starts early at home with a rational fluid with all efforts and caution. A breast fed child shall be offered ORS in between breastfeeds. Only one in a hundred cases ideally should be requiring intravenous fluid therapy.

D2: Diet (Age-Appropriate Diet):

Age old practice in diarrhea management has been ensuring bowel rest, withdrawal of the so called heavy foods and introduction of a strict therapeutic dietary regimen consisting of unusual, tasteless and non-nutritious foods. On the contrary, it is established beyond doubts that absorption of carbohydrates, fat and protein are retained as high as 80% during acute diarrhea and continued feeding favours early epithelial regeneration and recovery. Age appropriate foods must be ensured during acute diarrheal phase; the food should be more palatable and rich offered in small frequent feedings. A child under 6 months of age should continue breast feeding with ORS. A child after six months of age shall be offered age appropriate foods.

The problem of lactose intolerance in acute diarrhoea has been an overdiagnosis. Lactase enzyme located in the brush border of the gut is lost partially and transiently. But in selected cases only for a child totally dependent on milk, the daily consumption may be reduced by 20% for a few days only. It is better to encourage more solids and semisolids for a weaned baby and the milk intake automatically drops.

After recovery from acute diarrhoeal episode the child should be offered one extra feeding per day for the next 2 weeks to make up for the weight loss.

D3: Drugs (Rational Drug therapy):

The problem is that we prescribe more drugs than required in diarrhea; there is a problem of overtreatment.

Antibiotics should never be prescribed to children with diarrhoea unless there is evidence of a bacterial gut or systemic infection or the child is immunocompromised (more than 10 puscell/hpf in stool, dysentery, baby below 3 months of age, cases of severe malnutrition and so on). Aminoglycosides are the most misused parenteral drug; it is not effective even in cases of bacillary dysentery or diarrhea.

Metronidazole is the most misprescribed drug in diarrhea (indicated in 2%, but misused in 98%). The role of pro-prebiotics are established only in case of antibiotic associated diarrhoea. Stool-binders, antispasmodics, antimotility agents, enzymes, etc. are irrational.

Antisecretary drugs like Reccadotril carry some rationality for they control secretory diarrhoea caused by viruses and toxigenic bacteria.

Zinc is the new fudge word in childhood diarrhoea. Being an essential ingredient of most intracellular enzymes it helps in recovery and immune modulation. A 14 day therapy has been seen to reduce duration of diarrhea, reduce stool volume and reduce future episodes of diarrhea.

Table. 1. Common Drugs and Dosage in diarrhoea

D4: Difficult Diarrhoea

At times ‘diarrhoea mimickers’ lead to confusion and avoidable unnecessary aggressive treatment interventions imposed on the child. A breast fed baby may pass 10-20 small loose stools without any impact on weight gain or general wellbeing. Antibiotics when prescribed for common infections (usually respiratory)
to kids often induces diarrhea which ordinarily should not be treated with one more antibiotic.

Often diarrhea in a malnourished child poses a diagnostic and therapeutic challenge. Since common signs of dehydration like dry mucosa, sunken eyes, decreased skin turgor, altered mental status or absence of tears are not reliable, features like thirst, eyes recently more sunken, urine output and rapid thready pulse, hypotension are useful to assess the degree of dehydration in a malnourished child. The rehydration should be better by the oral route or through a nasogastric tube; intravenous fluids should generally be avoided and be reserved for cases of shock only. The fluid deficit may be replaced by a half normal saline slowly over a 12-24 hour period with a more frequent and stringent monitoring.

As such complications of diarrhoea like hyponatremia, hypernatemia, hypokalemia, acidosis, severe dehydration all need specialistic intervention for treatment. In mild, moderate or severe degree of dehydration the fluid deficit is calculated as 3, 6 and 9% of body weight in children above six years and 5, 10 and 15% in under six. The fluid deficit is replaced as an isotonic crystalloid solution like Normal saline or Ringer’s Lactate over a period of 6-8 hours. Nasogastric or intra-osseous routes are life saving in a health care set up where intravenous access is too difficult in a severely dehydrated kid.11

When a healthy kid from a well-off family and anxious overprotective parents offering too much of ORS presents with diarrhea with thirst, puffy eyes, poor urine output and intact skin turgor one should suspect hypernatremic dehydration. Obviously the kid needs to be in hospital and the management is not so easy.11

A child with puffy eyelids with anuria indicates Acute Renal Failure with fluid overload.

At times infection at an extra-enteral site (i.e. infection somewhere outside the gut) manifests as diarrhea; it is called ‘parenteral diarrhoea’. Cases of respiratory tract infection, urinary tract infection, skin infection, malaria or otitis media may cause diarrhea. Diagnosis and treatment of the original infection controls the diarrhea.11

D-5: Dialogue:

The key to success for a practitioner to manage a diarrhoea case rationally lies mostly on the art of counseling. The parents, family, neighbours, paramedics, colleagues and above all self-belief all come in the way of rationality.

The natural history of a viral diarrhea has to be explained to the parents. As a sign of improvement during acute diarrheal illness within 48hrs the child starts to play, the vomit stops, fever improves, urine output betters, child accepts food and weight loss ceases; the last thing to improve in the series is the stool volume and the stool frequency which may take as long as two weeks. Danger signs during diarrhea as explained to the mother are not the frequency or volume of stool passed, but lethargy, blood in stool, persistence of fever, persistence vomit, refusal to eat or drink and no urine for 4-5hrs among others. A good counseling should concentrate on ORT, ORS usage and diet pattern. A simple routine and microscopic stool test often convinces self and others that it is a self limiting diarrhea. Dialogue should also cover preventive interventions involving health education towards promotion of exclusive breast feeding till six months, healthy weaning, hand washing (before preparing food, before feeding the child, after toilet, after baby wash and after stool disposal), immunization (measles, Rota), vitamin A supplements, hygienic food and water and so on. References:


Epilogue:

Medical Science must seek answers to bottle necks in diarrhoea management. The taste of ORS, Zinc and Reccadotril must improve. Small ORS packs (for 200ml) should be in government supply. Pro/prebiotics should not be allowed to be sold in sachets mimicking ORS sachets. Commercial weaning foods should be banned. Rotavirus vaccine should find a place in national Immunisation schedule (cost!). Safe water should reach to every household. Advocacy must expand to encompass interventions towards rational diarrhea management as well as prevention.

References:

Physicians/ Surgeons interested in the field of HIV/AIDS may join Association of HIV Physicians of Odisha, Cuttack for updating, interactions and participation.

CONTACT

Dr Sanjaya Swain, Secretary
Mobile : 9437029089
E-mail : hivdrswainindia@yahoo.co.in
www.AHPOdisha.com

Physicians/Surgeons interested in the field of HIV/AIDS may join Association of HIV Physicians of Odisha, Cuttack for updating, interactions and participation.
Diarrhea is formally defined as an increase in daily stool weight above 200 gm. Typically, the patient may also describe an abnormal increase in stool liquidity and frequency. In layman’s language, it is described as the frequent passage of loose or watery stools. It is sometimes accompanied by abdominal cramps or fever. Diarrhoeal disease is the leading cause of childhood death and the second most common cause of death worldwide.

CAUSATIVE AGENTS

It may be caused by infection, allergy, or could be a sign of a serious disorder, such as IBD (inflammatory bowel disease), or Crohn’s disease. Infectious diarrhoea is the most common cause of diarrhoea worldwide and is responsible for more deaths than gastrointestinal cancers, peptic ulcer, or inflammatory bowel disease. There are vast numbers of bacteria, viruses, and parasites that can cause diarrhoeal disease. New enteropathogens continue to be discovered. The microorganisms listed in table 1 are the most clinically significant agents.

<table>
<thead>
<tr>
<th>Enteropathogen</th>
<th>Viruses</th>
<th>Parasites</th>
<th>Fungus</th>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rotaviruses</td>
<td>Entamoeba histolytica</td>
<td>Candida albicans</td>
<td>Vibrio (V.cholerae, V.parahemolyticus, other halophilic vibrios)</td>
</tr>
<tr>
<td></td>
<td>Norwalk virus</td>
<td>Giardia lamblia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adenovirus</td>
<td>Cryptosporidium parvum</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Astrovirus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcivirus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|                |                  |                            |                 |                                        |

Clinical Presentation:

Infectious diarrhoea presents clinically as one of three major clinical syndromes.

• Acute watery diarrhoea, which usually resolves within 5–10 days.
• Diarrhoea with blood (dysentery).
• Persistent diarrhoea with or without evidence of intestinal malabsorption; persistence is defined as diarrhoea that has continued for more than 14 days.

Pathophysiology:

Infectious diarrhoea occurs as a result of two major disturbances in normal intestinal physiology: These are:

• increased intestinal secretion of fluid and electrolytes, predominantly in the small intestine; and
• decreased absorption of fluid, electrolytes, and sometimes nutrients that can involve the small and large intestine.

Table 1 - Enteropathogen

1Post Graduate, 2Senior Resident, 3Professor & HOD
Department of Microbiology
SCB Medical College & Hospital, Cuttack
Contact: 9438591160, E-mail: dr.gautam.patnaik@gmail.com
© OMJ 2012
• **Increased intestinal secretion:**

Intestinal secretory processes can be activated by infection with bacteria and viruses. Secretory enterotoxins are the major cause of increased intestinal secretion in infective diarrhoea. Cholera toxin (CT) is the “prototype” enterotoxin and its mechanism of action has been extensively researched. It is the paradigm for enterotoxin mediated diarrhoea. CT causes secretion without any macro or microscopic damage to the enterocyte. Other secretory enterotoxins have also been well characterised and include the closely related *E. coli* heat labile toxin (LT) and the structurally distinct *E. coli* heat stable toxin (ST) (3). Since the discovery of these toxins, other prosecretory enterotoxins have been discovered. Other more recently discovered enterotoxins have not been well characterised.

It is now evident that secretory diarrhoea may be mediated by other mechanisms of secretion, as well as the classical enterocyte interaction. Multiple extracellular factors regulate epithelial ion transport—paracrine, immunological, neural, and endocrine factors. There is an extensive overlap and interplay between these systems and collectively these have been termed under a single super regulatory system i.e. PINES (paracrine-immuno-neuro-endocrine system). Secretory diarrhoea may be mediated by a variety of secretagogues, including prostaglandins, 5-hydroxytryptamine (5-HT), substance P, and vasoactive intestinal peptide (VIP). Neuronal pathways are involved in the amplification of the effects of enterotoxins (4).

CT has been shown to release 5-HT from enterochromaffin cells, which is thought to then activate the afferent limb of a neuronal reflex (5–6). The effector limb of the neuronal reflex is likely to complete the neuronal pathway by releasing the neurotransmitter VIP (5). This binds to specific receptors on the basolateral membrane and activates adenylate cyclase-cAMP intracellular secretory pathways. Interneurones propagate the secretory effects of CT distally in the small intestine.

The importance of 5-HT in mediating CT induced secretory diarrhoea has been confirmed by the use of 5-HT₂ and 5-HT₃ receptor antagonists, which decrease secretion in the rat and human intestine (6,7). Substance P antagonists also reduce CT induced fluid secretion in mammalian small intestine, suggesting that it may be a key neurotransmitter in the sensory afferent limb or interneurone of the neuronal reflex (8,9).

Hence CT affects the epithelium directly but also recruits other components in PINES, including enteric neurons, enterochromaffin cells, and multiple mediators to produce a complex secretory response. There may also be distant effects in the small intestine (9) and a reflex secretory response in the colon (10).

LT and ST also activate neural secretory reflexes but 5-HT does not appear to be involved in the secretory pathway of these toxins (11).

Rotavirus has been assumed to elicit diarrhoea by damaging absorptive cells but evidence is emerging that rotavirus intestinal infection can evoke fluid and electrolyte secretion by activation of the enteric nervous system (12).

• **Decreased intestinal absorption:**

The other major mechanism by which enteric pathogens cause diarrhoea is impaired intestinal absorption. This is usually accompanied by macroscopic and microscopic injury to the intestine (13).

Diarrhoea due to impaired intestinal absorption can be due to:

- impaired epithelial transport processes—that is, impaired fluid, electrolyte, and nutrient absorption in the small intestine;
- osmotic diarrhoea due to the appearance of incompletely absorbed nutrients in the colon; or
- impaired water and sodium reabsorption by the colon due to direct involvement of the colonic absorptive process. Intestinal absorption is also dependent on the duration of time allowed for digestion and contact with the epithelium, and therefore any alteration in small intestinal and whole gut transit times may result in impaired absorption.

**Epithelial injury in the small intestine and colon:**

It occurs in association with many enteropathogens—bacteria, parasites, and viruses. The nature of the injury can occur at many levels. It can range from:
• discrete damage to the microvillus membrane during the attachment of *E. coli* and *Cryptosporidium parvum*,

• mucosal inflammatory response to invasive pathogens—for example, *Shigella* spp, *Salmonella* spp, and *Entamoeba histolytica*, usually involving the release of cytolethal cytotoxins resulting in epithelial cell loss and ulceration.

Rotavirus, another invasive enteropathogen, directly invades the epithelial cells in the middle and upper portion of the villus, with rapid epithelial cell death and acute villous trophy.

**Invasive enteropathogens can produce diarrhoea by multiple mechanism** like

producing an acute inflammatory response within the mucosa, recruiting proinflammatory mediators such as prostaglandins and leukotrienes, resulting in both impaired intestinal absorption and initiation of a prosecretory state in the intestine.

Invasive enteropathogens also promote the synthesis and release of chemokines, such as interleukin (IL)-8, by intestinal epithelial cells. IL-8 is a known potent chemoattractant for polymorphonuclear leucocytes that enhance the inflammatory cascade and produce further mucosal and epithelial damage by release of reactive oxygen species.

Neutrophils also release 52-AMP, which is a potent secretagogue acting through the adenosine A2 receptor on the apical membrane of intestinal epithelial cells.(17)

In the clinical setting, these two pathophysiological disturbances—secretory diarrhoea, and secondly, impairment of epithelial transport processes with enteropathogenic invasion and epithelial cell injury—often coexist. *Shigella*, *salmonella*, and *campylobacter* produce a secretory diarrhoea in the small intestine in the early phase of the illness, most likely as a result of enterotoxin activity, but then invade the epithelium of the distal ileum and colon to produce an inflammatory ileocolitis. At this stage there will be epithelial cell loss and impaired absorption of fluid and electrolytes.(17)

**Specific Investigations :**

Specific investigation is not normally required in the majority with acute watery diarrhoea as this is usually self limiting, and resolves without specific treatment. Patients with bloody diarrhoea (dysentery) or persistent diarrhoea do require further investigation. The general approach is to start with the simplest, least invasive, “economically competitive” test, progressing in a hierarchical way to more invasive and expensive investigations.(17)

**Stool microscopy and culture :**

Stool microscopy and culture are the first line investigation. Three stool samples should be examined under the light microscope for parasites by an experienced observer, and then cultured for bacterial enteropathogens. Detection of parasites with standard microscopy is labour intensive and insensitive. Special stains are required to enhance detection of cysts and spores. But still microscopy is vital for the diagnosis of *Entamoeba histolytica*, *Giardia intestinalis*, *Cryptosporidium parvum*, and *Cyclospora cayetanensis*.

Newer antigen and toxin detection assays have been developed that increase the sensitivity of the examination for giardia and cryptosporidium. In addition, commercially available enzyme immunoassays are able to distinguish between *E. histolytica* and the non-pathogenic but microscopically indistinguishable *E. dispar* and *C. difficile* require confirmation by detection of toxin A in faeces by enzyme linked immunosorbent assay (ELISA). Faecal antigen ELISAs are also available for rotavirus.

For bacterial pathogen, specimen is cultured on selective media and incubated at 37°C for 24-48 hours. Identification of the isolate depends on colony morphology, biochemical reactions and slide agglutination test with antisera.(14)

**Serodiagnosis :**

Antibody testing is useful to confirm or support other tests in a limited number of infections. Specific serum antibodies are present in 80–90% of patients in invasive amoebiasis. Antibodies are useful in *Y enterocolitica*, but a result can take up to 10–14 days. ELISA kits are widely available for the diagnosis of strongyloides and schistosomiasis. They are often used as first line screening tests for these infections, especially in travellers returning from endemic areas.
• Abdominal imaging:

Plain abdominal radiograph is usually performed in those who are severely unwell with abdominal pain to exclude bowel perforation and for assessing the severity and extent of infectious colitis.

Transabdominal ultrasound can detect bowel wall thickening, enlarged lymph nodes, pneumatosis, abdominal tuberculosis, and complications such as amoebic liver abscesses\(^{(17)}\).

• Endoscopy:

Upper gastrointestinal endoscopy is useful in the investigation of patients with persistent diarrhoea, with or without clinical features of intestinal malabsorption. Severe villous atrophy in the second part of the duodenum can occur in infections due to small intestinal protozoa—giardia, cryptosporidium, cyclospora, and the microsporiida. Changes in villous morphology can be confirmed by duodenal biopsy, which may also reveal the presence of protozoal cysts or trophozoites. Duodenal fluid can also be aspirated during the procedure—this is particularly helpful for the detection of \textit{Giardia intestinalis} cysts and trophozoites and for the larvae of strongyloides.

Endoscopic examination of the colon and ileum are useful following negative stool culture and microscopy in the presence of dysentery or persistent symptoms. This may be helpful for distinguishing between infectious colitis and inflammatory bowel disease, but the pathological features are not very reliable in the acute setting. Discrete ulceration can occur in amoebiasis and colonic tuberculosis and there are few distinguishing features that reliably differentiate these infections from Crohn’s disease. Pseudomembranes in the colon are generally indicative of \textit{C difficile} infection but can be also found in ischaemic colitis. Colonic biopsies can detect \textit{E histolytica}, Cytomegalovirus, and the ova of \textit{Schistosoma} spp\(^{(17)}\).

• Histology:

If colonic mucosal biopsies are taken within the first 24–72 hours, histological features may be indicative of infection, including mucosal oedema, straightening of the glands, and an acute inflammatory infiltrate\(^{(15,16)}\). After this stage it can very difficult to distinguish between infectious colitis and non-specific inflammatory bowel disease. Biopsies can reveal the pseudomembranes of \textit{C difficile} and the caseating granulomata of tuberculosis\(^{(17)}\).

Treatment:

There are four main approaches to the treatment of infectious diarrhoea.

• Supportive therapy—fluid and electrolyte replacement.

• Antidiarrhoeal symptomatic treatment to reduce stool frequency and any other symptoms such as abdominal pain.

• Antisecretory drug therapy aimed at reducing faecal losses.

• Specific therapy such as antimicrobial chemotherapy to reduce duration and severity of the illness.

Oral rehydration therapy (ORT) remains mainstay in the case management. The search for antisecretory drugs continues. Real progress have been made by the introduction of a new class of drugs, the enkephalinase inhibitors. Other new drugs are in the early phases of development. The role of antimicrobial agents in the management of infective diarrhoea continues to be clarified with the emergence of new agents and simplified treatment regimens. The place of probiotics in the treatment and prevention of infectious diarrhoea continues to be evaluated but studies to date suggest moderate efficacy\(^{(17)}\).

Conclusion:

Since diarrhoeal disease is the leading cause of childhood death and the second most common cause of death worldwide, knowledge about the causative agents, clinical presentation, pathophysiology and available modalities of laboratory diagnosis are essential so that the proper and timely treatment can be given to reduce the morbidity and mortality considerably.

References:


---

**APICON ODISHA 2013**

9th & 10th November, 2013

*Venue*: V.S.S. Medical College, Burla

*Scientific Programme by National & State Faculties*

*Contact Details:*

Prof. S.K. Mahapatra

*Organising Secretary, Dept. of Medicine*

V.S.S. Medical College, Burla

---

OMJ • Vol.33 • No.1 • 2013
Diarrhoea in Elderly Patients in Long Term Care Facilities

G. Kumar¹, P.K. Rathor², K.P. Pattnaik³, D.N. Moharana⁴

Introduction:

Diarrhoea is one of the most common gastrointestinal complaints, the 2nd most common cause of death worldwide, and one of the four most common infections in elderly people especially those in Long Term care facilities (LTCFs). Non-specific diarrhoea is the most common type of diarrhoea, however it is anticipated that an increase in the number of specific infectious causes of diarrhoea will be diagnosed with the development of newer diagnostic technique¹,².

Physiological protective mechanisms against invasion of pathogenic organisms e.g. gastric acidity, forward propulsive gut motility, and normal intestinal flora may be compromised in the elderly. This may be due to age related changes or a combination of co-morbid conditions and factors e.g. polypharmacy, decreased antibody formation and decreased helper T-cells and mucosal IgA.

Precise implications of immunosenessence on disease acquisition in the elderly are not very clear. However, it appears to increase their susceptibility to infectious diarrhoea as compared to younger population²,⁴,⁵,⁶. However, after acquiring a diarrhoeal disease, elderly patients tolerate it less well and suffer more frequent complications than their younger counterparts with the same disorder.

Infectious diarrhoea in LTCF residents may be associated with significant morbidity and mortality. Mortality from diarrhoea is much higher in older LTCF residents, especially in those older than 75 years.

About 1/3rd of all deaths due to diarrhoeal diseases occur in elderly residents in LTCFs, probably because of their lack of tolerance to resulting volume depletion with diarrhoea complications e.g. cardiovascular compromise and organ failure.

The hospitalisation rate due to diarrhoeal illness, duration of hospital stay, morbidity and mortality is significantly higher in older patients in comparison to patients younger than 50 years, being highest in those older than 75 years⁷,⁸.

Early recognition and prompt treatment of diarrhoeal disease are, therefore, essential in preventing serious complications of dehydration and electrolyte disturbance that may result in multiple organ system failure and death. The risk of exposure to pathogens that cause diarrhoea is enhanced in LTCF residents, because of shared bathroom and dining facilities, liberal social and physical mixing of residents, and suboptimal infection control measures.

Etiology of diarrhoea in Long-term care facility residents⁹,¹⁰,¹¹

<table>
<thead>
<tr>
<th>Non-infectious causes</th>
<th>Infectious causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses</strong></td>
<td></td>
</tr>
<tr>
<td>Norwalk agent</td>
<td>Dietary</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>Hyperosmolar formula</td>
</tr>
<tr>
<td>Rota virus</td>
<td>Lactose intolerance</td>
</tr>
<tr>
<td>Calicivirus</td>
<td>Fructose and sorbitol</td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td>Medications</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Antacids</td>
</tr>
<tr>
<td>C. perfringes</td>
<td>Laxatives</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Escherechia coli</td>
<td>Gut disorders</td>
</tr>
<tr>
<td>Listeria</td>
<td>Ischemic bowel disease</td>
</tr>
<tr>
<td>Salmonella</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Shigella</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td></td>
</tr>
<tr>
<td>Vibrio</td>
<td></td>
</tr>
</tbody>
</table>
Clinical manifestations:

Diarrhoea may occur sporadically in one or more residents or as an outbreak in multiple residents. The clinical spectrum of diarrhoea may vary from a few loose stools to a potentially life-threatening condition. Most patients in the general population suffering from diarrhoea may complain of one or more of the following symptoms:

- Crampy lower abdominal pain, anorexia, nausea, fever, malaise and watery or bloody diarrhoea.

However, elderly residents in LTCFs with diarrhoea may or may not complain of diarrhoea and thus the condition may escape prompt detection. Sometimes, complications resulting from dehydration, e.g. altered mental status, stroke, MI, and renal failure may prompt the discovery of diarrhoea. Infectious diarrhoea may or may not be accompanied by fever; occasionally, it may manifest as hypothermia.

Severe constipation and fecal impaction may manifest as overflow diarrhoea.

Clostridium difficile – associated pseudomembranous colitis, which usually is accompanied by low-grade fever and watery diarrhoea may sometimes occur with little or no diarrhoea and appear as an acute abdomen and, if unrecognized, may lead to unnecessary surgery, increased morbidity and even mortality.

Bloody diarrhoea or blood in stools – usually a sign of infection associated with inflammation, microbial invasion of mucosa, or tissue damage may occur in E.coli O157-H7, Yersenia, Shigella or Salmonella infections. This should be differentiated from non-infectious causes of diarrhoea e.g. Inflammatory bowel disease(IBD), diverticular bleeding or ischemic colitis.

An uncommon but clinically important scenario is when elderly persons with underlying inflammatory bowel disease (Ulcerative colitis/ Crohn’s disease) develop infectious diarrhoea. If the diarrhoea episode is mistakenly considered as an exacerbation of the underlying IBD and corticosteroids are administered, catastrophic complications e.g. Hyperinfection syndrome may develop, leading to significant morbidity and even death.

Diagnostic approach

History:

In the evaluation of infectious diarrhoea, non-infectious causes of diarrhoea must be considered in the differential diagnosis. LTCF residents often consume multiple medications which may cause diarrhoea.

Likewise, diarrhoea can be a manifestation of several systemic diseases, e.g. Type2 Diabetes Mellitus, Hyperthyroidism or such covert intestinal disorders e.g. IBD, Coeliac disease, Bacterial overgrowth and Ischemic bowel disease.

A careful symptom-specific history should be obtained from the patient. Thirst and decreased urination may be early symptoms of volume depletion, followed by lethargy and altered level of consciousness as dehydration progresses. Elderly patients may not volunteer information about diarrhoea. This reluctance may be due to embarrassment or lack of understanding.

Information about mode of onset of diarrhoea (sudden/ gradual), sporadic or outbreak in multiple patients, duration of symptoms, character of stools (watery, mucus, bloody) and associated symptoms (abdominal pain, nausea, vomiting, tenesmus, fever) is germane for the clinical diagnosis of diarrhoeal diseases.

In cases of diarrhoea due to food poisoning, the incubation period may give a clue to the culprit organism.

Antibiotic associated diarrhoea usually occurs 4-7 days after initiation of antibiotic therapy, although it may even occur > 1month after stopping the antibiotics.

Excessive ingestion of sorbitol-containing foods, e.g. grapes, sugar-free candies may result in diarrhoea as does milk or milk products ingestion in residents with lactose intolerance.

In patients receiving enteral feeding, the formulation of feeding solution and rate of administration should be carefully monitored, as rapid administration of hypertonic formulas may cause diarrhoea.
Table 1:

<table>
<thead>
<tr>
<th>DRUGS CAUSING DIARRHOEA IN ELDERLY PATIENTS</th>
<th>Antiarrhythmics: Quinidine, Procainamide, Digoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Medications</td>
<td>Antihypertensives: hydrochlorthiazide, Furosemide, ACE-i, ( \beta ) blockers, Methyldopa</td>
</tr>
<tr>
<td>GI Medications</td>
<td>Antacids: Mg(^2+) containing antacids, H(_2) receptor antagonists, Proton</td>
</tr>
<tr>
<td>Pulmonary medications</td>
<td>Pump inhibitors, Misoprostol. Theophylline</td>
</tr>
<tr>
<td>Cholesterol lowering agents</td>
<td>Gemfibrozil</td>
</tr>
<tr>
<td>Central nervous system medications</td>
<td>Lovastatin, Fluvastatin, Levodopa</td>
</tr>
<tr>
<td>Medication for infectious diseases</td>
<td>Lithium, Donepezil, Haloperidol, Carbamazepine, Selective serotonin re-uptake inhibitor (SSRI), Antibiotics: clindamycin, quinolones,</td>
</tr>
<tr>
<td>Anti-arthritic medications</td>
<td>macrolides, tetracyclines, cephalosporins, Antiviral: amantadine, IFN, acyclovir, ribavirin, Antiprotozoal: metronidazole, tinidazole, trimethoprim, sulfamethoxazole</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>NSAIDs (Non steroidal anti-inflammatory drugs), Colchicine</td>
</tr>
<tr>
<td>Lab tests:</td>
<td>Laxatives, lactulose, Oral hypoglycaemic agents, ticlopidine, bisphosphonates, chemotherapeutic agents, ethanol, herbal remedies</td>
</tr>
</tbody>
</table>

Lab tests are expensive and often unnecessary in most cases of self-limiting diarrhoeal illness. However, a CBC (complete blood count), serum chemistry, and urinanalysis (to exclude Urinary tract infection presenting as diarrhoea) should be obtained in patients with significant diarrhoea who appear ill or have rapid decline in function. After consideration of non-infectious causes of diarrhoea, stools should be examined for ova, parasites and fecal leukocytes/ fecal lactoferrin.

If the diagnosis is still unclear and patient is febrile, tachycardic or hypotensive, transfer to an acute unit should be considered for further evaluation and management\(^{21}\).
Management plan of Acute diarrhoea in LTCFs

Acute diarrhoea in elderly

Exclude fecal impaction

Evaluate severity, correct dehydration and electrolyte imbalance,
Look for evidence of systemic symptoms

No systemic symptoms

Observation

Persistent diarrhoea > 72 hours

Systemic symptoms present (i.e. fever, etc.)

Further work-up
CBC, serum electrolytes, stool, fecal WBCs, Lactoferrin

Parasite present

Specific anti-parasite therapy

If the diagnosis is still unclear, clinically deteriorating, persistent fever, tachycardia, hypotension, altered mental status

Consider transfer to acute care unit for further evaluation and management

Fecal WBC +’ve

C.difficile toxin assay (if recently hospitalized and treated with antibiotics)

Culture for enteric pathogens(salmonella, shigella)

Continue hydration and symptomatic therapy

Fecal WBC -’ve
Therapeutic intervention

A careful history and vigilant physical examination will guide the clinician in proper management of acute infectious diarrhoea. Most cases of infectious diarrhoea, especially those of viral etiology, are usually self limiting, and symptomatic supportive therapy with fluid and electrolyte replacement is all that is required.

Correction of the primary cause of diarrhoea, e.g. stopping/ replacing the culprit medication, change to isotonic tube feeding formulas and/or decreasing the rate of infusion and relief of fecal impaction may be important therapeutic manoeuvres.

Initial lab studies are more helpful to elucidate the degree of dehydration and electrolyte disorder, rather than to provide organism – specific diagnosis.

Principles of therapy are basically the same irrespective of exact etiology of diarrhoea and include adequate hydration and maintaining electrolyte balance.

Oral route should be used whenever possible. Oral fluids {water, juices, soups and Oral Rehydration Solution(ORS)} should be encouraged as tolerated. To facilitate early recovery, adequate calories should be provided to the extent tolerated. ORS as a primary therapy or as a supplemental therapy should be considered in all patients who do not have vomiting or altered level of consciousness.

All elderly patients with acute diarrhoea should be assessed frequently, to determine success or failure of ORS therapy and timely intravenous(i.v.) fluid replacement as needed.

If the patient shows signs of significant dehydration (poor skin turgor, dry skin, altered level of consciousness, >10% weight loss, hypotension, orthostasis) then i.v. administration of fluids and electrolyte solutions may be required and the patient may need a transfer to an acute care facility.

Particular care should be exercised in rapid i.v. replacement of fluids, as frail patients may have limited tolerance to fluid overload and can swiftly develop pulmonary edema and electrolyte imbalance due to underlying renal and cardiovascular disease.

In addition, empirical therapy with fluoroquinolones e.g. ciprofloxacin or pathogen specific antimicrobial therapy may be considered in patients who manifest evidence of systemic illness e.g. fever, leukocytosis and severe diarrhoea/dysentery, especially among those at high risk of complications particulary frail elderly, diabetics and immunocompromised.

References:

Diarrhea is defined as an increase in the frequency of defaecation and/or fluidity of the faeces. It is not only inconvenient, but also can be life-threatening if not adequately managed. If severe, it may manifest as faecal incontinence.

Diarrhea is defined as acute if duration of diarrhea is < 2 weeks, as persistent if duration is 2-4 weeks and if > 4 weeks duration, it is defined as chronic diarrhea (1).

Immunodeficiency is a state in which the immune system’s ability to fight infectious disease is compromised or entirely absent. A person who has an immunodeficiency of any kind is said to be immunocompromised. There are many conditions that can lead to an immunocompromised state e.g. acquired infections - such as HIV, malignancy, chronic diseases like diabetes, end stage renal disease and cirrhosis, medications - such as chemotherapy, steroids, immunosuppressive agents and physical state - such as pregnancy.

**HIV-Associated Diarrhea:**

During the course of their illness, > 50% of AIDS patients experience diarrhea. In up to 25% of all patients, it can be an important cause of morbidity and mortality (2).

**Etiology of diarrhea in HIV/AIDS:** Diarrhea in HIV/AIDS patients is commonly infective in origin. A large number of pathogens including bacteria, virus, mycobacteria and protozoa are responsible for secondary infections of the GI tract involving the small and/or large bowel (3). Classical pathogens are Cryptosporidia, Isospora belli, Microsporidia, Mycobacterium avium-intracellulare (MAI), Salmonella, Shigella and Campylobacter. Incidence of diarrhea due to Cytomegalovirus (CMV) is much less nowadays due to advance in HIV treatment.

In addition to diarrhea caused by specific secondary infections, HIV-infected patients may also experience a chronic diarrheal syndrome for which no pathogen other than HIV can be identified - a condition called AIDS enteropathy or HIV enteropathy, which is most likely a direct result of HIV infection in the GI tract.

In approaching an HIV/AIDS patient with diarrhea, it is important to consider three basic aims: detection of treatable causes, relief of symptoms, and the prevention of malabsorption.

As infection is the commonest cause of diarrhea in HIV/AIDS, the diagnosis should be made promptly to facilitate effective treatment. Inspite of the various pathogens which might be the cause of the symptoms, patients may present very similarly. A careful evaluation will help in assessing the severity, pinpointing the underlying cause, and making plan on how to manage.

**Initial evaluation of HIV-associated diarrhea:** A careful food history, drug history, travel, and associated symptoms (e.g. nausea, vomiting, fever and other systemic upset), diet (e.g. lactose) may provide some hints to the underlying cause.

Initially, the degree of immune deficiency should be evaluated; it is useful, as it is a common factor behind some major bacterial causes of diarrhea. A low CD4 count and previous history of opportunistic infections are indications of a poor immune status. Infection with Cryptosporidia, C. difficile, I. belli and Microsporidia occur in the presence of a low CD4 of often less than 100/ul.

The evaluation will also lead to the anatomical site of the pathology. Large volume or relatively infrequent or nocturnal diarrhea points to the small bowel involvement; whereas frequent small volume, bloody, bowel movements with lower abdominal pain,
urgency and rebound tenderness are features of large bowel problems.

**Determining the etiology of diarrhea:** After a good history and physical examination a provisional diagnosis can be made. Chronic diarrhea, low CD4 count of less than 200/ul, male homosexual and significant weight loss are factors deserving attention (4). Infective causes must be considered. Some additional hints of a bacterial etiology are as follows:

a. Salmonella infection may present with a variety of nonspecific symptoms including fever, anorexia, fatigue and malaise of several week’s duration; diarrhea is common but may be absent.

b. Campylobacter infection presents with crampy abdominal pain, fever and bloody diarrhea.

c. Presentation of Cryptosporidial infection range from a self-limited, intermittent diarrheal illness in early stage of HIV infection to a severe, life-threatening diarrhea in severely immunodeficient individuals. It is however not distinguishable clinically from Isospora and Microsporidia infection.

d. Infection with C. difficile is associated with antibiotic uses, notably clindamycin and penicillin.

e. In CMV infection, the virus typically produces a colitis that presents as diarrhea, abdominal pain, weight loss and anorexia. The diarrhea is usually nonbloody.

f. MAI is often associated with significant systemic upset including fever, weight loss and night sweat.

Although various viruses such as rotavirus, adenovirus, coronavirus, astrovirus and calcivirus have been implicated as causes of diarrhea in AIDS, most appear to be self-limiting and do not require treatment.

**Investigations:** As in non-HIV diarrhea, stool examinations including culture, examinations for ova, parasites and examination for Clostridium difficile toxin can be the most important investigation in determining the cause of the symptoms when infections are suspected.

Commonly three sets of stool studies are sent to the laboratory because the shedding of microorganisms is often episodic. Diagnosis of Salmonella infection is made by culture of blood and stool, stool examination in Campylobacter infection reveals presence of fecal leukocytes. Microsporidia can be identified in stool samples with the use of chromotrope-based stains by light microscopy, characteristic finding in Cryptosporidial diarrhea is the presence of oocysts that stain with acid-fast dyes, the cysts of Isospora appear in the stool as large, acid-fast structures that can be differentiated from those of Cryptosporidia on the basis of size, shape and number of sporocysts.

If stool examination gives inconclusive results, additional evaluation, including upper &/or lower endoscopy with biopsy is the next step. Approximately 50% of HIV infected patients in whom chronic diarrhea remains unexplained after multiple stool tests have a potential etiology identified by endoscopic examination (5). Specifically,

a. Patients with classic small bowel diarrhea should undergo upper gastrointestinal tract endoscopy, with biopsy from the distal duodenum or proximal jejunum.

b. If the history suggests colorectal problem, lower endoscopy is indicated.

c. C difficile can be difficulty to diagnose. A C. difficile toxin assay should be considered as part of the investigation for new-onset watery diarrhea, especially if there is associated fever, leukocytosis and cramp.

d. In CMV colitis, the diagnosis is achieved through endoscopic appearance of multiple mucosal ulcerations, and the demonstration of characteristic intranuclear and cytoplasmic inclusion bodies on biopsy.

The diagnosis of HIV enteropathy is made, where there are histopathological and functional abnormalities of the small bowel but absence of pathogen or malignancies after investigations. Antiretroviral therapy may lead to a resolution of the diarrhea.

If fever accompanies the diarrhea, blood culture, chest radiograph and urinalysis should also be performed.

If diarrhea persists for over 6 to 8 weeks, the diagnostic cycle should begin again, with stool tests and then endoscopic examination and biopsies.
Treatment of HIV associated diarrhea:

There are two forms of treatment, specific therapy for identified etiology, and general treatment to relieve symptoms. Highly active antiretroviral therapy (HAART) is another treatment option that works by improving the immunity.

Pathogen-specific therapy: Generally, most infective causes of diarrhea are amenable to treatment. Treatment responses can sometimes be one means of confirming the original diagnosis. Standard treatment regimen for common infective causes of diarrhea are: Metronidazole is the treatment for C. difficile.

*Box 7.1 Pathogen-specific treatment *

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter coli</td>
<td>Ceftriaxone 500 mg/kg IV every 12 hours for 14 days. If intolerant or unresponsive, use fosfomycin 99 mg/kg per day IV for 14 days</td>
</tr>
<tr>
<td>M. avium infection</td>
<td>Rifabutin 300 mg daily, plus ethambutol 400 mg PO every 12 hours, and clarithromycin 500 mg PO every 12 hours.</td>
</tr>
<tr>
<td>Salmonella/Shigella</td>
<td>Ciprofloxacin 900 mg PO every 12 hours for 14 days</td>
</tr>
<tr>
<td>enterocholera</td>
<td>Campylobacter coli</td>
</tr>
<tr>
<td>Cryptosporidiosis</td>
<td>Paromomycin 500 mg PO every 8 hours for 14 days. No proven effective therapy. Other possible treatment includes azithromycin and loperamide. Response generally poor for all treatment.</td>
</tr>
<tr>
<td>Microsporidiosis</td>
<td>Albendazole 400 mg PO every 12 hours for 14 days. No proven effective therapy. Response generally poor and relapse is common.</td>
</tr>
<tr>
<td>Isosporiasis</td>
<td>Tinidazol-praziquantosan 160 mg PO every 6 hours for 10 days, then twice daily for 21 days. Relapse common.</td>
</tr>
</tbody>
</table>

The most effective way to deal with cryptosporidiosis in patients with HIV infection is to restore the immune system by treating the HIV infection with HAART. Treatment with upto 2000 mg/d of Nitazoxanide is associated with improvement in symptoms or decrease in shedding of organisms in about half of patients of cryptosporidiosis.

Even if initial treatment is successful, relapse is common in case of CMV, MAI, cryptosporidiosis and microsporidia infections.

Supportive treatment: Symptomatic management is the mainstay of the treatment in diarrhea, in particular when no treatable cause can be identified. A non-narcotic, narcotic, or antisecretory drug can be used. Chronic diarrhea may lead to malnutrition, which can jeopardize the quality and length of life. The use of nutritional supplements, vitamin and mineral replacements is important.

Diarrhea In Malignancy:

In oncological patients, diarrhea can occur in several different situations. Possible etiologies could be either cancer treatment like chemotherapeutic agents, radiotherapy or decreased physical performance, graft versus host disease and infections or cancer itself. Radiation therapy that focuses on abdomen or pelvis, or that is given to whole body, can cause diarrhea. How severe the diarrhea is that depends on the radiation dose. If certain parts of the intestine is removed in order to remove the cancer, this might alter the intestines’ ability to absorb nutrients or fat and may result in diarrhea. Diarrhea can also be a complication of graft-versus-host disease if one received bone marrow stem cells from a donor. The stress and anxiety that one feel while fighting cancer also can cause diarrhea. Hormone-producing (neuroendocrine) tumors, including carcinoid syndrome and Zollinger-Ellison syndrome, Colon cancer, Lymphoma, Medullary carcinoma of the thyroid and Pancreatic cancer can cause diarrhea. Cancer treatment makes the patient more susceptible to various infections, which can cause diarrhea. In addition, the antibiotics that may be used to treat an infection can cause diarrhea. Chemotherapy-induced diarrhea (CID) is a common problem in patients with advanced cancer and has to be carefully differentiated from other causes of diarrhea. It can occur in 50–80% of patients, depending on the chemotherapy regimen (7, 8). Chemotherapeutic agents commonly causing diarrhea include 5-fluorouracil (5-FU), capecitabine and irinotecan (8, 9).

Careful analysis of the causative agent can lead to a more accurate management and early intervention may help to prevent severe complications that may be irreversible (10, 11).

Diagnosis of CID begins with a history to determine the severity according to the NCI CTC grades (National Cancer Institute Common Toxicity Criteria). The volume and duration of diarrhea should also be determined, and the history should include questions concerning foods or drugs that might play a contributory role.

Management:

Patient education is central to the management of chemotherapy-induced diarrhoea. Before starting...
chemotherapy with the potential to cause diarrhoea, patients must be informed of the potential and what action to take should they experience diarrhoea. They will require nutritional advice and support in order to achieve a satisfactory nutritional status. A low residue diet with high fluid intake should be advised. Bulking agents may be suggested for patients with a stoma.

The treatment of CID includes nonpharmacologic and pharmacologic interventions to control diarrhoea and careful serial evaluation to rule out significant volume depletion or comorbidities that may require specific intervention or hospitalization (8,12). Initial nonpharmacologic measures include avoidance of foods that would aggravate the diarrhoea and aggressive oral rehydration with fluids that contain water, salt, and sugar (13). These principles are similar to those used for infectious diarrhoea.

**Pharmacological measures**:

- In Grade 1 – 2 diarrhoea: Loperamide is prescribed 4mg initially, taking 2mg after each subsequent bowel movement, to a maximum of 8mg in 24 hours. In grade 3 or above and where the patient has a colostomy or ileostomy Loperamide can be prescribed to be taken on a regular basis until the diarrhoea is under control. Codeine phosphate can be prescribed instead of Loperamide or added to Loperamide when control is not achieved with Loperamide alone.
- Dose modification of cytotoxic drugs should be considered, if diarrhoea is severe, according to ASWCS chemotherapy protocols.

**Diarrhoea In Diabetes**:

Diabetic autonomic neuropathy (DAN) is a serious and common complication of long standing type 1& 2 diabetes mellitus. It may affect many organ systems throughout the body (e.g., gastrointestinal [GI], genitourinary, and cardiovascular). Nocturnal diarrhoea, alternating with constipation, is a feature of diabetes mellitus-related GI-autonomic neuropathy. Diagnostic approaches should rule out autonomic dysfunction and the well-known causes such as neoplasia. Current treatments for these complications of diabetes mellitus are inadequate. Improved glycaemic control should be a primary goal, as some aspects like neuropathy, gastric function may improve. Diabetic diarrhoea in the absence of bacterial overgrowth is treated symptomatically with Loperamide and may respond to Octreotide (50-75 µg 3 times daily, SC).

Diabetic subjects are also prone for infective (bacterial / viral) diarrhoeas especially in developing countries. Conventional WHO Oral Rehydration Solutions (ORS) or even Low Glucose Low Sodium ORS can be safely administered to diabetic patients with acute diarrhoea (without development of significant hyperglycaemia) and this may avoid unnecessary admission to hospital. The diabetic patients with acute diarrhoea may take their normal advised diet and continue their antidiabetic drugs during the episodes of diarrhoea (14). The antimicrobials during infective diarrhoea may depend on the local prevailing causative organisms and their culture sensitivity pattern. However empirical antimicrobial therapy is indicated in case of:

- Fever (oral temperature >101.3°F) together with either dysentery (grossly bloody stool) or those with leucocyte-lactoferrin- or hemoccult-positive stool: suggested antimicrobial therapy is Quinolone: Norfloxacin 400mg- / Ciprofloxacin 500mg- /Ofloxacin 300mg b.i.d for 3-5 days.
- Traveller’s diarrhoea: suggested antimicrobial therapy is Quinolone: Norfloxacin 400mg- / Ciprofloxacin 500mg- /Ofloxacin 300mg b.i.d for 1-5 days.
- Persistent diarrhoea (possible Giardia infection): Metronidazole 250 mg q.i.d for 7 days.

**References**:

1. Harrisson’s


Cryptosporidium Associated Diarrhea
Indrani Mohanty

Introduction:

*Cryptosporidium* is a protozoan pathogen of the Phylum Apicomplexa and causes a diarrheal illness called cryptosporidiosis. It affects the intestines of mammals and is typically an acute short-term infection. It spreads through the fecal-oral route, and often through contaminated water. The main symptom is self-limiting diarrhea in people with intact immune systems. In immunocompromised individuals, such as AIDS patients, the symptoms are particularly severe and often fatal. *Cryptosporidium* spp. are a major cause of diarrhea in developing countries mainly affecting children and HIV-infected individuals with low CD4 counts. Other susceptible populations studied include patients with malignancies and organ transplant recipients. Molecular tools have permitted speciation and genotyping, leading to more detailed epidemiological studies. Based on these methods, the common *Cryptosporidium* spp reported to affect both HIV-infected adults and children in India are *C. hominis* and *C. parvum*. There is no satisfactory treatment or vaccine available for cryptosporidiosis.

Fifteen years ago the only organism known to cause gastroenteritis in man was enteropathogenic bacteria. Cryptosporidia have been known to be pathogenic to animals since 1907, but the first human case was reported in 1976. Since then there have been a number of papers published on human cryptosporidiosis and there have been reports describing chronic life threatening diarrhea in immunocompromised patients. Recently there have been descriptions of self limiting gastroenteritis in immunocompetent adults and children.

*Cryptosporidium* spp:

Cryptosporidiosis in humans is mainly attributable to 2 of the 14 identified species – *C. hominis* and *C. parvum*. *C. hominis* is found almost exclusively in humans, whereas *C. parvum* is found in domestic livestock, wild animals as well as humans. Other *Cryptosporidium* spp reported to infect humans, mainly immunocompromised hosts, include *C. meleagris*, *C. felis*, *C. canis* and *C. muris*. Transmission occurs by direct person-to-person spread, ingestion of contaminated food or water, or contact with infected animals. The route of entry is by oral route. The high resistance of *Cryptosporidium* oocysts to disinfectants such as chlorine bleach enables them to survive for longer periods and still remain infective. Infection occurs following the ingestion of as few as 10 oocysts, as evidenced in studies on healthy adult volunteers. The life-cycle of *Cryptosporidium* spp. is completed within the small intestine and colon of the host. The developing stages are seen in the luminal surface of the intestinal epithelial cells, where it remains intracellular but extracytoplasmic. After ingestion of the oocysts there is release of motile sporozoites in the intestine which invade the epithelial cells. The parasite surface glycoproteins are involved in the invasion and attachment. From there they become trophozoites. Asexual (merogony) and sexual reproduction of the parasite occurs within the extracytoplasmic vacuole, resulting in merozoites that infect adjacent epithelial cells and the production of sporulated thin-walled and thick-walled oocysts. Thin-walled oocysts can excyst endogenously, resulting in autoinoculation, which along with repeated first generation merogony, helps to explain the mechanism of persistent infections in patients with AIDS. The spherical, thick-walled, environmentally hardy oocysts (3-6µm in diameter), shed in the fecal material of the infected host are immediately infectious, unlike other coccidian parasites, and hence can be transmitted from person to person.
Pathogenesis:

The parasite is located in the brush border of the epithelial cells of the small intestine. It does not invade beyond the mucosal layer of the intestine. The alteration in the intestinal structure and physiology that lead to the pathogenesis of cryptosporidiosis include:

- Rapid loss of the microvillus border,
- Shortening and fusion of the villi and
- Lengthing of the crypts

All these lead to malabsorption due to loss of membrane-bound digestive enzymes, decreased absorption, reduced glucose-NaCl absorption and increased chloride anion secretion. Pro-inflammatory cytokines specifically INF-α and INF-γ also contribute to the pathogenesis by increasing the production of prostaglandins, neural peptides and reactive nitrogen intermediates the epithelial barrier leading to a leaky and dysfunctional epithelium and alteration of solute transport leading to osmotic diarrhea. Diarrhea possibly occurs as a combination of secretory and malabsorptive process. Though the immune responses involved in mediating the resistance to infection to this parasite is not clearly understood, but immunodeficient animal models have shown involvement of CD4+ lymphocytes in the control of *C. parvum* infection.

Cryptosporidiosis in Children:

This protozoan pathogen is an important cause of diarrhea in children all over the world with a high associated morbidity and mortality. In seemingly normal children *Cryptosporidium* may cause mild gastroenteritis lasting up to two weeks, with 4-6 watery, mucoid, offensive stools a day. Abdominal pain may be prominent in older children. Vomiting, nausea, headache and fever are frequent. Rarely transient asymptomatic carrier stage may occur. Cryptosporidium is responsible for up to 7% of episodes of acute gastroenteritis in Western children. Cryptosporidiosis is more common with severe consequences in malnourished in comparison to well-nourished children in developing countries. In India *Cryptosporidium* spp positivity rates ranged from 1.1% to 18.9% in diarrheal stool samples, and 0% to 9.8% in asymptomatic cases. In a study on children with malabsorption, the parasite was seen in 14% cases. A community-based study from Vellore showed that the 2 most common species identified were *C. hominis*-81% and *C. parvum*-12%.

Cryptosporidiosis in HIV-infected:

Diarrhea is one of the most common presenting complaints in HIV-infected individuals. The infectious etiological agents include both opportunistic agents that consistently cause severe, chronic or frequent gastrointestinal disease and non-opportunistic agents that usually cause acute, treatable diarrheal illness. Several species of protozoan have been associated with acute and chronic diarrhea in HIV disease. The most commonly reported parasites include *C. parvum*, *Isospora belli*, *Microsporidium* spp., *Giardia intestinalis*, *Entamoeba histolytica* and *Cyclospora* spp. Besides these *Strongyloides stercoralis* can cause diarrhea and overwhelming infection in HIV patients. The result is progressively severe dehydration, electrolyte imbalance, malnutrition, wasting and eventual death. Cryptosporidiosis is a substantial threat to HIV-infected individuals. Patients can have chronic watery diarrhea that can last for > 2 months and shed oocysts in the stool during the entire period, resulting in severe dehydration, weight loss, anorexia, nausea, vomiting, fatigue and low-grade fever. Mortality rate for HIV-infected patients is based on CD4+ cell counts. In patients with CD4+ cell count >180 cells/cumm, there is recovery with supportive hospital care and medication. But in case of CD4+ cell count < 50 cells/cumm the condition is fatal and patient usually die within 3-6 months. In India, there have been reports from the mid-1990’s on the prevalence of symptomatic cryptosporidiosis in HIV-infected adults from different parts of the country, ranging from as low as 0.7% to as high as 81%. Antiretroviral therapy (ART) greatly influences the outcome of cryptosporidiosis both indirectly by immune restitution and increase in CD4+ cell counts and by direct effect of protease inhibitors on oocyst shedding, resulting in sustained therapeutic effect after follow up. However, despite the use of highly active retroviral therapy (HAART), HIV-infected patients can still present with coccidian diarrhea, which may be due to non-compliance with medications, resistance to drugs or decreased bioavailability of drugs. Owing to its sequestered location within the host cell, its ability to set up an auto-infective cycle in the host, innate antimicrobial resistance and wide host range, *Cryptosporidium* spp have better survival advantage over other enteric pathogens.
There are 4 clinical presentations in patients with AIDS –
1. No symptoms (in 4% cases)
2. Transient infection (in 29% cases) diarrhea lasts < 2 months
3. Chronic diarrhea (in 60% cases) diarrhea lasts for 2 months or more
4. Severe cholera-like (in 8% cases) patients excreting at least 2 liters watery stool per day with maximum up to 25 liters per day.

In the immunocompromised host Cryptosporidium spp is the most commonly isolated pathogen in the biliary tract in patients with AIDS cholangiopathy. A few studies have reported other sites of infection including the pancreas and lungs.

**Laboratory Diagnosis:**

Diagnosis of Cryptosporidiosis clinically is difficult as the condition mimics giardiasis, isosporiasis, cyclosporiasis and infections caused by other enteropathogens. The absence of pus cells, blood and Charcot-Leyden crystals rule out amoebiasis, isosporiasis and bacillary dysentery and may raise the possibility of cryptosporidiosis. The detection of Cryptosporidium is not undertaken routinely by most laboratories. There are many diagnostic tests for Cryptosporidiosis, which include microscopy, staining, detection of antigens and molecular methods. Faeces is the sample of choice and to increase the chance of finding the oocysts, multiple stool samples should be examined before declaring a stool specimen negative. Also, stool samples should be concentrated prior to microscopic examination to recover maximum number of oocysts. There are several techniques to concentrate the stool samples like modified formalin-ether concentration, modified zinc sulphate technique and Sheather’s sugars floatation procedure.

The microscopic examination of direct faecal smear by wet mount or stained smear preparations is adequate for demonstration of oocysts. Stool microscopy is useful in cases of non-acute illness, excreting small numbers of oocysts, evaluation contacts of infected individuals and in epidemiological surveys. In case of specimens containing moderate to high numbers of oocysts iodine wet mount preparation is used for screening. A large number of staining techniques are used like; Kinyoun’s modified acid fast technique, hot safranin-methylene blue stain and fluorescent staining. Kinyoun’s modified acid fast technique using cold carbol fuscin is a simple and effective method for detecting oocysts which appear as red stained oocysts against blue background. Direct fluorescent microscopy is the method of choice to detect oocysts in stool smears. This method is more sensitive and specific than other staining methods. Detecting antigens is yet another way to diagnose the disease. This can be done by immunofluorescence and ELISA.

Serodiagnosis by detecting circulating antibodies in the serum may be done after 6-8 weeks after onset of infection. PCR is another way to diagnose cryptosporidiosis and identify the different species.

Other diagnostic techniques are ultrasound, endoscopic retrograde cholangioscopy (ERCP) in biliary cryptosporidiosis - identification of oocysts in the bile by ERCP. Histologic examination of the small intestine is not required to confirm the diagnosis of cryptosporidiosis. The parasite is seen projecting from the brush border of the mucosal surface. Estimation of CD4+ lymphocyte counts helps to know the progression of the disease in patients infected with HIV.

**Treatment:**

Treatment is primarily supportive. Fluid replacement is the mainstay either orally or intravenously. A lactose free diet should be advised as tolerated. There is no reliable treatment for cryptosporidiosis. Certain agents such as spiramycin, nitazoxanide, paromomycin, rifaximin, azithromycin and immunotherapy are sometimes used but they usually have temporary effects. Although, nitazoxanide has been recently licensed for the treatment of cryptosporidiosis in children and immunocompetent individuals in most countries including India, there is still no effective treatment for cryptosporidiosis in patients with AIDS. Treatment with up to 2000mg/d of nitazoxanide is associated with improvement in symptoms or decrease in shedding of organism in half of the patients. Its overall role in the management of this condition remains unclear. There is also no vaccine available to prevent cryptosporidiosis in susceptible populations.
Conclusion:
Humans acquire infection on ingestion of food or drink contaminated with the fecal matter containing oocysts of Cryptosporidium spp. The reduction or elimination of oocysts from the environment forms the mainstay of control of cryptosporidiosis which is difficult. Care should be taken to avoid contamination of food and water with fecal oocysts to prevent transmission of infection to man, by measures including hand washing, use of gloves in hospital and improved personal hygiene.

References:
Clostridium Difficile Associated Diarrhea
Susmita Sahu

Abstract:

C. difficile associated diarrhea (CDAD) is now considered to be one of the commonest causes of nosocomial diarrhea. Although the incidence and severity of CDAD have increased in the western world especially in health care settings; it still is under-recognized in India and Asia. Any episode of diarrhea with fever and leucocytosis in a patient on some antibiotics in hospitals is strong pointer towards presence of CDAD. Clinical suspicion is usually confirmed by ELISA based C. difficile toxin assays in the stool sample. The aim of therapy is to restore normal colonic microflora, resulting in the elimination of C. difficile. Majority of patients will require antibiotic therapy and, whenever possible, discontinuation of the predisposing antibiotics. Metronidazole and vancomycin are the mainstay of the treatment of CDAD, as both these agents are highly active against all strains of pathogenic C. difficile. Control of health care associated CDAD involves a range of primarily preventive measures including proper hand hygiene, use of personal protective equipment, environmental decontamination, isolation or cohort nursing and adequate treatment of CDAD cases.

Introduction:

Diarrhea is one of the most frequent side effects of antibiotic treatment. The symptoms may vary from slight abdominal discomfort to severe diarrhea and colitis. Clostridium difficile is a Gram-positive spore bearing anaerobic bacteria that causes diarrhea and colitis associated with antibiotics. The intestinal tract of normal people contains millions of bacteria referred as commensal flora that have a role in protecting the body from infection. Taking antibiotics can kill these commensal bacteria allowing C. difficile to multiply and release toxins that damage the intestinal epithelium causing different serious manifestations like colitis, Pseudomembranous colitis, toxic megacolon and perforation.

Clostridium difficile is the major aetiological agent of antibiotic associated diarrhoea and colitis. Hall and O’Toole (1) originally identified the organism as a component of normal colonic flora of newborn infants. C. difficile is commonly present in the stools of 5 per cent of healthy adults and in about 15-70 per cent of infants(2,3,4). The majority of hospitalized patients infected by C. difficile are asymptomatic carriers who serve as silent reservoirs for continued C. difficile contamination of the hospital environment. (5) It is a serious condition with mortality up to 25 per cent in frail elderly people (6) C. difficile is now recognized as the primary cause of hospital acquired colitis in patients who receive antibiotics, chemotherapeutics or other drugs that alter their normal flora.

Source of the infection:

It can be found on the surface of bedside tables, door knobs, counters, lavatories and sinks in the hospital. The organism can be spread between patients via contact with contaminated objects and/or the hands of health care workers.

Epidemiology

CDAD is under-recognized in India and Asia, due to lack of clinical suspicion, difficulty in culturing the organism and cost of toxin assay. Prevalence of CDAD is around 2 to 4% in patients without diarrhea and 7 to 30% in patients with diarrhea in different hospital based studies(7,8,9,10,11,12). When only adult population were investigated, the positivity for C. difficile toxin was 19.4% in the antibiotic receiving hospitalized patients (11) Gebhard et al reported that for 15% of the cases of nosocomial diarrhea was mainly due to C. difficile in 1999(12). Majority of C. difficile isolates
in India respond to metronidazole\textsuperscript{13,14}. Although there is a possibility that there may be emergence of resistant strains with severe disease manifestations in general practice.

Risk Factors:

The risk factors associated with \textit{C. difficile} associated diarrhoea are listed in Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
</tr>
<tr>
<td>Antimicrobial agents</td>
</tr>
<tr>
<td>Fluroquinolones</td>
</tr>
<tr>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Clindamycin</td>
</tr>
<tr>
<td>Macrolides</td>
</tr>
<tr>
<td>Antineoplastic therapy</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
</tr>
</tbody>
</table>

Pathogenesis:

Transmission of \textit{C. difficile} occurs both endogenously as in the carrier state and exogenously through nosocomial source \textsuperscript{(15)}. When an individual is exposed to \textit{C. difficile} or its spores, an initial disruption of the normal colonic bacterial flora occurs resulting in colonization of the organism through surface proteins \textsuperscript{(16)}. Damage to enterocytes due to \textit{C. difficile} toxins occur as soon as \textit{C. difficile} colonizes the intestine resulting in cytoskeletal changes and the release of fluids and inflammatory products \textsuperscript{(17)}. Pathogenic \textit{C. difficile} produces two high molecular weight potent toxins - A and B - which bind to specific receptors on the luminal aspect of the colonic epithelium resulting in various colonic manifestations\textsuperscript{(18)}.

Clinical manifestations: \textit{C. difficile} causes colonic as well as Extra colonic manifestations which are described in Table 2.

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colonic</strong></td>
</tr>
<tr>
<td>Asymptomatic carriers</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Colitis</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
</tr>
<tr>
<td>Fulminant colitis</td>
</tr>
<tr>
<td>Recurrent CDAD</td>
</tr>
</tbody>
</table>

Diagnosis:

Clinical information about the cause of diarrhea, underlying disease and antimicrobial therapy should be obtained by taking the history. Culture of stool samples and toxin assay are the two important methods followed for the diagnosis of CDAD. (Table 3)

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test used</strong></td>
</tr>
<tr>
<td>Culture</td>
</tr>
<tr>
<td>Tissue culture cytotoxin assay</td>
</tr>
<tr>
<td>Countercurrent immunolectrophoresis</td>
</tr>
<tr>
<td>Latex agglutination assay</td>
</tr>
<tr>
<td>Enzyme immunoassay</td>
</tr>
<tr>
<td>Rapid membrane test</td>
</tr>
<tr>
<td>Polymerase chain reaction</td>
</tr>
</tbody>
</table>

Treatment:

- The most important step in the treatment of \textit{C. difficile} is to stop the antibiotic which caused the infection to develop.
- Fluid replacement and treatment of electrolyte imbalance is very important.
- Antibiotic treatment: The drug of choice for seriously ill patients is oral vancomycin because it is not absorbed by the intestine. Oral metronidazole can be used instead of vancomycin and is favoured because it is less expensive. As
resistance to this antibiotic has seen in some isolates it used for patients with mild or moderate illness but not in case of critically ill patients.

- Probiotics like Lactobacilli spp or Saccharomyces boulardii can also be used to replace the pathogenic C.difficile flora.
- If the infection worsens surgery may be necessary to remove the infected colon. This is usually limited to the cases of life threatening illness.

**Prevention**:

It is uncommon for people who are not taking antibiotics to become infected with C.difícile. However it is still important to avoid spreading the bacteria. Prevention of C. difficile infection has two major components:

A) Prevention of spread of organism

B) Reduction in likelihood of clinical disease.

**A) Prevention of spread of organism**

It involves proper hand hygiene, use of personal protective equipment, environmental decontamination, isolation or cohort nursing and adequate treatment of CDAD cases. Protective disposable gloves and aprons should be used while handling body fluids and nursing CDAD patients. C. difficile spores can survive in the environment for months or years, and environmental contamination has been linked to the spread of C. difficile infection in healthcare settings. It is therefore recommended cleaning of rooms, bed spaces, commodes, toilets and bathrooms of infected patients with chlorine containing cleaning agents or vapourised hydrogen peroxide daily (as they inactivate C. difficile spores).

Isolation or cohorting of patients with CDAD have been successful in limiting transmission of C. difficile in hospitals. Early identification and treatment of CDAD cases prevent further spread of infection.

**B) Reduction in likelihood of clinical disease**

Antimicrobials should be prescribed according to local policies and guidelines for treatment and prophylaxis. Restrictions in the use of broad-spectrum antibiotics have shown to reduce the frequency of CDAD. Prospective observational cohort studies suggest that restricted use of clindamycin and third generation cephalosporins result in fewer cases of C. difficile infection

Besides antibiotics, use of proton pump inhibitors has been associated with C. difficile infection. Therefore, indiscriminate and unwarranted use of proton pump inhibitor(s) should be avoided specially in health care setting.

**Conclusion**:

The incidence of health care associated CDAD is on the rise with associated increased morbidity and mortality. C. difficile associated diseases are not commonly recognized in many health care settings. Vancomycin and metronidazole remain the mainstay of treatment for CDAD, but newer investigational therapies hold promise. Control of health care associated CDAD is reduced by taking proper preventive measures.

**Reference:**

8. Farrell RJ, LaMont JT. Pathogenesis and clinical manifestations of *Clostridium difficile* diarrhea and
Introduction:

Gastrointestinal infections are very common in patients with HIV infection or AIDS [1]. Diarrhoeal diseases are frequent clinical presentations of these infections. Human immunodeficiency virus (HIV) infection can weaken the immune system causing its inability to combat opportunistic infections. Managing the complexity of these opportunistic infections has created a challenge for healthcare professionals. Our knowledge on the aetiological agents causing opportunistic infections in immunocompromised hosts has increased over the last two decades. For most of the causes of diarrhoea, the clinical signs are non-specific, and the laboratory diagnostic workup is neither easy nor fast. This review provides data on aetiological approaches of common diarrhoeal diseases including viral, microbacterial, parasitic, fungal infections and HIV enteropathy; diagnostic evaluation; and prophylaxis & treatment of diarrhoea in HIV-infected patients. It will provide some insight to the practitioners who are in the practice of managing diarrhoea in such patients.

Incidence:

Prior to the use of highly active antiretroviral therapy (HAART) in the United States, chronic diarrhea (defined as more than 28 days of diarrhea) was responsible for 17 percent of the new acquired immunodeficiency syndrome (AIDS) diagnoses reported to the Centers for Disease Control and Prevention (CDC) [2]. In the developing world, HAART is not routinely available for HIV-infected individuals, and diarrheal disease remains highly endemic even for those without HIV [3]. Chronic diarrheal disease in adults in Africa has been used as a predictor of HIV-seropositivity [4]. HIV-infected children are more likely to die with diarrhea than children with diarrhea who are not infected with HIV [5]. In contrast, in resource-rich nations where HAART is widely available, the incidence of infectious causes of diarrhea in HIV-infected patients with low CD4 counts (<200 cells/mm3) has declined [6]. Reports indicate that diarrhoea occurs in 30-60 per cent of AIDS patients in developed countries and in about 90 per cent of AIDS patients in developing countries. The incidence and prevalence of infection with a particular enteric parasite in HIV/AIDS patients is likely to depend upon the endemicity of that particular parasite in the community. C. Parvum, I. Belli, and E. Histolytica have been reported as the most frequently identified organisms in HIV infected individuals with diarrhoea from India and other parts of the world.

Risk Factors:

There is a trend for a higher prevalence of persistent diarrhoea amongst heterosexuals than amongst men who reported sex with other men as their HIV risk factor (p = 0.08). Individuals with diarrhoea have significantly lower mean CD4 cell counts (p < 0.001), and it is observed that the presence of pigeons at home is predictive of histoplasma parasitic infections, upper abdominal pain is predictive of Giardia and that keeping ducks is predictive of Shigella. Enteric pathogens are identified in 21% of HIV-infected control subjects without diarrhoea and 55% of HIV-infected case subjects with diarrhoea.

Etiopathogenesis:

The precise cause of diarrhoea in people living with HIV(PLHIV) can not be determined in 65 per cent of patients, suggesting a need for comprehensive aetiological studies covering bacterial, fungal, viral and parasitic causes of diarrhoea among HIV infected patients in India.

Diarrhoea as a drug-related side-effect:

Diarrhoea can be caused by some anti-HIV drugs. With some drugs, diarrhoea goes away after the first few weeks or months of treatment, however...
for some people it becomes a permanent feature of living with the drug.

The severity of diarrhoea also varies. Severe diarrhoea, involving several trips to the toilet each day, large, uncontrollable liquid bowel movements, and feelings of weakness and dizziness as a result of the loss of fluids and electrolytes is experienced by about a quarter of people starting treatment with nelfinavir, which is now very rarely used and by a lower proportion of people starting saquinavir, fosamprenavir and lopinavir/ritonavir. These drugs are in a group (or drug class) called protease inhibitors. Less serious problems have been experienced by people taking other anti-HIV drugs in this class and in other classes.

Changes in diet have little effect on drug-related diarrhoea. However a variety of treatments are available to try to control diarrhoea caused by drugs. These include:

- **Loperamide**: This is available on prescription by a doctor or can be bought over the counter from chemists. Stronger anti-diarrhoea drugs can be prescribed in intractable cases.

- **Oat bran tablets**: These have been proved effective. They work by absorbing fluid, making stools larger and slowing the movement of stools through the intestines.

It is important that one should continue to eat and drink even if there is diarrhoea which is caused by your medication. Medication should not be stopped even if it causes diarrhoea. Instead, the problems can be discussed with the treating physician, who may be able to recommend treatments for the diarrhoea or, if necessary, may change the HAART regimen judiciously.

Medical causes:

Diarrhoea is very common among people with HIV, particularly those with a low CD4 count. Often no specific cause can be found, and in cases of mild diarrhoea the cause might be HIV itself. Another common cause is irritable bowel syndrome, when diarrhoea often alternates with constipation and is associated with bloating and wind. Rather than being caused by an infection it is likely that lifestyle issues, such as stress, are to be blamed. Diarrhoea can also be caused by bacterial infections, parasites and viruses, so if diarrhoea persists it is important to investigate the cause.

**Who Guidelines For Diarrhoea:**

The World Health Organisation's (WHO) 1991 guidelines for the management of persistent diarrhoea in HIV-positive patients in resource limited countries may need revision in some settings.

Current WHO guidelines recommend initial therapy with co-trimoxazole for the management of chronic diarrhoea in HIV-positive individuals. But in Indian set up most bacterial pathogens are found sensitive to ciprofloxacin. The inclusion of metronidazole as a first-line drug for patients unable to return to the clinic frequently or as a treatment for those who do not respond to fluoroquinolones should also be considered, in view of the relatively high frequency of giardiasis.

Numerous opportunistic infections occur in HIV infected patients, due to downregulation of the immune system. Gastrointestinal parasitic infection is a universally recognized problem in these patients. These infections largely present with diarrhoea leading to life threatening complications.

Almost half of the patients with CD4 count less than 200 cells/µl are having gastrointestinal parasitic infections and a majority of which are opportunistic parasites (37%). Among the opportunistic parasites, C. Parvum (54%) is the predominant pathogen. The prevalence of opportunistic parasites in patients with CD4 count 200-499 cells/µl is only 9 per cent.

**Pathogen susceptibility to antibiotics:**

Almost all studies on antimicrobial susceptibility testing reveal that only 24% of the pathogens isolated from patients with or without diarrhoea are susceptible to co-trimoxazole, including only 16% of *Shigella* species, 7% of *Aeromonas* species, 50% of *Campylobacter* species and 33% of *Salmonella* species. By contrast all but one species of *Shigella*, *Salmonella* and *Aeromonas* are susceptible to ciprofloxacin and all *Campylobacter* species are susceptible to doxycline and erythromycin.

To summarise the enteric pathogens responsible for diarrhoea in HIV infected persons and the laboratory tests to investigate the causes of diarrhoea in such cases may be precisely put in following tables:
Table 1: Enteric pathogens in AIDS defining Diarrhoea

<table>
<thead>
<tr>
<th>Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
</tr>
<tr>
<td>Cytomegalovirus, Astrovirus, Picorna virus, Corona Virus, Rota virus, Herpes virus, Adenovirus, Small round virus, HIV</td>
</tr>
<tr>
<td>Bacteria and Mycobacteria</td>
</tr>
<tr>
<td>Salmonella, Shigella, Campylobacter, Clostridium difficile, T. Pallidum, Spirochaetes, N. Gonorrhoeae, V. Cholera, Pseudomonas sp., Staphs aureus, Mycobacterium avium-complex(MAC), Mycobacterium TB</td>
</tr>
<tr>
<td>Parasites</td>
</tr>
<tr>
<td>Giardia lamblia, Entamoeba histolytica, Cryptosporidium, Microsporidia (Enterocytozoon bieneusi, Encephalocytozoon intestinalis), Cyclospora</td>
</tr>
</tbody>
</table>

Table 2: Laboratory tests used to investigate diarrhea in patients with AIDS

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool cultures</td>
<td>Salmonella, Shigella, Campylobacter</td>
</tr>
<tr>
<td>Toxin</td>
<td>Clostridium difficile</td>
</tr>
<tr>
<td>For ova &amp; cyst</td>
<td>Giardia lamblia, Entamoeba histolytica</td>
</tr>
<tr>
<td>Stool stains</td>
<td>Modified Kinyoun acid-fast (Cryptosporidium and Isospora belli)</td>
</tr>
<tr>
<td>Blood studies</td>
<td>CD4 cell count, Total leucocyte count &amp; DC, Creatinine, electrolytes,</td>
</tr>
<tr>
<td></td>
<td>LFT, Total albumine, Blood cultures(MAC)</td>
</tr>
<tr>
<td>Tissue &amp; fluids</td>
<td>Duodenal aspirate(Giardia lamblia, Microsporidia)</td>
</tr>
<tr>
<td></td>
<td>Biopsy: duodenum, jejunum, ileum, colon, rectum</td>
</tr>
<tr>
<td>Biopsy stains</td>
<td>Hematoxylin-eosin, Giemsa or methenamine silver(fungi), Methylenes</td>
</tr>
<tr>
<td></td>
<td>blue-azure II-basic fuchsin(Microsporidia), Fite(Mycobacteria), Immuno-</td>
</tr>
<tr>
<td></td>
<td>histochemical stains (Cytomegalovirus), In-situ hybridization(CMV),</td>
</tr>
<tr>
<td></td>
<td>DNA amplification(CMV), Electron microscopy (cryptosporidium, adenovirus),</td>
</tr>
<tr>
<td></td>
<td>Touch preparation</td>
</tr>
<tr>
<td>Culture of colonic mucosal biopsy</td>
<td>Cytomegalovirus, Herpes simplex virus, Bacteria</td>
</tr>
</tbody>
</table>

Conclusion:

Usually diarrhoea settles down after a few days in almost all cases. If it lasts longer, it is important to consult a physician so the cause can be investigated and an appropriate treatment implemented. Very often it gives an opportunity for the diagnosis of HIV seropositivity in an individual.

As diarrhoea may result in losing essential salts and water from the body, it is important to drink plenty of fluids or special rehydration drinks. Eating foods like bananas, potatoes, chicken and fish will help to replace potassium, levels of which are commonly lowered in people with severe diarrhoea. Pulses, oats, bananas, apples and pears have also been shown to be effective against diarrhoea. Charcoal tablets may also be helpful.

Coffee, raw vegetables and spicy food make diarrhoea worse, and may trigger nausea, which is often combined with diarrhoea. In many cases, avoiding
foods which are high in fat, or milk may help to alleviate the symptoms of diarrhoea.

Increasing or decreasing the fibre content of diet may help in cases of irritable bowel syndrome.

It is useful to consult a specialist HIV dietician, who can provide with advice on suitable dietary changes, how to avoid losing weight and how to get adequate nutrition during diarrhoea.

Diarrhoea can also cause soreness around the anus which can be treated with common over-the-counter local application remedies for piles.

So diarrhoea in anyone especially in persons with HIV infection should not be neglected and should be attended promptly and rationally for better prognosis. With judicious use of evidence based medicines in people living with HIV(PLHIV) and affected by diarrhoea may lead a qualitative life in this era of modern HAART.

References:
Magnitude of Hepatitis A Virus (HAV) Infection and its Clinical Course in Adults in a Tertiary Care Centre in Odisha

U.C. Patra¹, R.P. Sahu², M. Nayak³, C.R. Sarangee⁴, R.K. Panda⁵, A. Devi⁶

Summary:
In this prospective study two hundred and fifty four patients diagnosed to be having AVH were analyzed with reference to clinical profile and viral markers and statistical analysis was done. Isolated viral infection was documented in 102 (40.1%) patients where as more than one hepatotropic viruses caused AVH in 27(10.6%) patients. Non A-E Virus was the major case of sporadic AVH (40.1%), HBV & HEV were the etiological agent in 23.6% & 25.1% respectively. HAV was detected in 16.5% of the patients and the HCV was incriminated rarely as cause of sporadic AVH. The demographic, clinical and biochemical profile amongst isolated & mixed viral infection were found to be similar. However, HAV-AVH had significant prolonged course (p<0.001) and was found to have significantly higher number of patients pursuing a course of relapsing hepatitis. Moreover HAV infection amongst adults in the present study was found to cause severe liver disease in few cases.

Key Words:
HAV - Acute Viral Hepatitis
HAV-AVH - Hepatitis A virus induced AVH
HBV-AVH - Hepatitis B virus induced AVH
HEV-AVH - Hepatitis E virus induced AVH
HCV-AVH - Hepatitis C virus induced AVH

INTRODUCTION:
Viral Hepatitis, caused by hepatitis viruses A through E, is a major public health problem in India¹, since 1955, several epidemics of hepatitis have been reported²-⁸. Although hepatitis A Virus (HAV) and hepatitis E Virus (HEV) both enterically transmitted are highly endemic in India, HEV has been responsible for most of these epidemics²,8,10. In India, HEV infection is responsible for 30-70% of cases of acute sporadic hepatitis & the major cause of Acute Liver Failure (ALF)¹¹. Amongst children, HAV is the predominant cause of acute hepatitis and dual infection with HAV & HEV have been more frequently reported amongst children with ALF¹². There are no published data in Eastern India especially in the State of Odisha. Further our clinical impression indicates rise in frequency of HAV infection amongst adults causing severe and atypical form of hepatitis. In view of paucity of data on the aetiology and clinical profile of AVH due to different hepatotropic viruses, the present study was undertaken to prospectively evaluate.

1) The aetiology of AVH in a tertiary care referral center in Eastern India, especially in the State of Odisha.
2) The clinical course of the HAV induced acute hepatitis amongst adults and to compare the clinical course of AVH due to HAV, HBV, HEV and Mixed Infection.

Materials And Methods:
Patients
Acute Viral Hepatitis (AVH) was diagnosed if a patient presented with following clinical & biochemical characteristics -

a) Sudden onset of clinical symptoms characteristics of AVH such as prodrome followed by onset of overt icterus or biochemical evidence of hepatitis.
b) Alanine transaminase (ALT) elevation of more than 2.5 times normal documented at least twice during the first two weeks of presentation.

c) Absence of ingestion of known hepatotoxins such as alcohol, indigenous medicines and known hepatotoxic drugs.

d) Absence of history suggestive of previous liver disease.

**Inclusion Criteria**:

Consecutive patients diagnosed as AVH and attending the Hepatology department at SCBMCH, Cuttack Odisha, India from January 2010 to December 2011 were included in this study.

**Exclusion Criteria**

Patients in whom history is unreliable or alcoholic and patients in whom other diseases like congestive cardiac failure were excluded from the study.

**Methods**:

All patients had a detailed clinical evaluation followed by routine relevant investigations.

**Clinical Evaluation**:

A detailed history with special reference to etiology was taken. Also a complete general and systemic examination was done to look for tender hepatomegaly, splenomegaly and other signs of liver failure.

**Investigations**:

Various biochemical, hematological, serological, microbiological investigations were undertaken in each patient as an outpatient basis on the first visit and then at regular intervals (10 days to 2 weeks) till recovery.

**A) Biochemical**

- LFT-Serum bilirubin
- Serum transaminase (AST & ALT)
- Serum protein & albumin
- Prothrombin time
- Others—Blood urea, serum creatinine, blood glucose, serum electrolytes.

**B) Hematological**:

- CBC/ Peripheral smear / ESR / Coagulation profile / Malaria Parasite & Leptospira

**C) Serological**:

Serum was collected at the time of initial examination to establish the etiological diagnosis of AVH. The following test were done.

- Hepatitis B Surface Antigen (HBsAg)
- IgM Antibody to Hepatitis A Virus (IgM HAV)
- IgM Antibody to hepatitis E Virus (IgM HEV)
- IgM Antibody to hepatitis B Core antigen (IgM anti-HBc)
- Anti Hepatitis C virus antibody (Anti HCV)

Markers of autoimmune Hepatitis (ANA, SMA, Anti LKM) were performed only in a selected group of patients diagnosed as non A-E AVH with prolonged course.

- HBsAg, IgM anti HBC, IgM anti HAV and anti HEV tests were performed using commercial Elisa kits (Organon Teknika, Netherlands) according to manufacturers instruction.

**Criteria for etiological diagnosis of AVH**:

<table>
<thead>
<tr>
<th>Virus</th>
<th>Criteria</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV</td>
<td>AVH - IgM anti HAV +Ve</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>AVH - IgM anti HBc +Ve</td>
<td></td>
</tr>
<tr>
<td>HEV</td>
<td>AVH - IgM anti HEV +Ve</td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>AVH - anti HCV +Ve</td>
<td></td>
</tr>
<tr>
<td>Non A-Non-E</td>
<td>AVH - Absence of all above markers in the sera.</td>
<td></td>
</tr>
</tbody>
</table>

**D) Radiological Study**—Chest X-ray was done in few cases to look for associated lesion.

**FOLLOW-UP**:

Patients were followed up every 10 days to two weeks to evaluate their clinical and biochemical improvement.

Cholestatic hepatitis is used to refer to a clinical picture in which the course of the disease and the laboratory finding simulate those associated with mechanical obstruction of the bile ducts. It is also used to describe the characteristic set of histological findings in the liver.

Prolonged viral hepatitis refers to rare cases of viral hepatitis that are atypically lengthy, laboratory abnormalities persist and symptoms and physical findings continue for more than 16 weeks.

Relapsing hepatitis refers to an illness in which the patient who has apparently had complete recovery after an acute episode of viral hepatitis manifests a
recurrence of the original symptoms and finding on one or more occasions usually within six months of the original illness.

**Statics:**

Discrete variables amongst various etiologies of AVH were compared using Chi-square test continuous and rating variables were compared using L test, Wilcoxon ranksum test, and Mann Whitney’s test.

**Results:**

Two hundred and fifty four consecutive patients over the age of 15 years diagnosed as AVH attending the Hepatology department at SCB Medical College & Hospital, Cuttack, Odisha from January 2010 to December 2011 were included in the present study. Their mean age was 29.7 ± 12.4 with a male : female ratio of 1.8:1. All the patients had distinct prodrome, hepatic phase and convalescence. There were only 11 (4.3%) anicteric hepatitis and the remaining patients (n=243) had overt jaundice. There liver function profile has been depicted in Table-1. This depicted liver function profile indicated the value at the time of maximum level of serum bilirubin in individual patients.

The etiological distribution of AVH has been depicted in table 2. Isolated viral infection was documented in 102 (40.1) patients. Mixed acute viral infection was documented in 27 (10.6%) patients and super infection of one of the hepatotrophic viral infection over hepatitis B virus carrier was documented in 23(9.0%) of the patients. Non A-E viral hepatitis (patients without any of known hepatotrophic viral marker) was documented in 102 (40.1%) of the patients. Non A-E viral hepatitis (patients without any of known hepatotrophic viral marker) was documented in 102 (40.1%) of the patients and 22 (21.5%) of these non A-E patients were HBV carriers. The over all frequency of HAV, HBV, HCV and HEV amongst these patients was 42(16.5%), 60(23.6%), 13(5.1%) and 64(25.1%) respectively. Isolated HAV, HBV, HCV and HEV infection was documented in 28(11%), 43(16.9%) 1(0.3%) and 30(11.8%) patients respectively. Amongst 23(9.0%) patients of HBV carrier with super infection, HEV was super infecting agent in 16 patients.

Table 3 depicts the details of acute mixed viral infection (co-infection) amongst patients with AVH. The commonest form of acute mixed viral infection was due to Hepatitis B+E & Hepatitis A+E co-infection.

To detect the difference in clinical and biochemical dynamics amongst various etiological agent induced AVH, they were grouped into following six groups:

- **Group-I : Isolated HAV Infection (n=28)**
- **Group-II : Isolated HBV infection (n=43)**
- **Group-III : Isolated HEV Infection (n=30)**
- **Group-IV : HAV with HBV or HEV or HCV (n=11)**
- **Group-V : HBV with HEV & HCV (n=17)**
- **Group-VI : Non A-E AVH (n=102)**

(* Details of clinical & Biochemical information were available only in these number of patients.)

Isolated HCV infection was documented only in one patient and hence was not taken as separate Group. The remaining 12 patients with HCV Infection were associated with another viral infection which was included in either group IV & group V. Twenty two patients (87.5%) in group I, 34(79%) in Group-II, 24(80%) in group-III, 6(54.5%) in group IV, 10(58.82%) in group V and 78(76.4%) in group VI could be followed up till they had complete clinical & biochemical recovery.

Table 4 depicts the demographic profile of AVH amongst various etiological group. The frequency of blood transfusion and needle prick amongst HBV-A VH was significantly (P<0.05) higher than other group of AVH. The age and sex distribution however was similar amongst the groups.

Table 5 denotes the important clinical features amongst various group of AVH. However the types of prodrome, duration of prodrome, duration of icterus & degree of hepatomegaly were similar amongst the groups.

Table 6 outline the various liver function profile amongst the six groups of AVH. It is obvious that the mean ( SD) and ranges of the various liver functions were similar amongst the different groups of AVH.

HAV-A VH in comparison to other types of AVH had significantly prolonged course (table 7). About 68% of patients with HAV-A VH had icteric hepatitis more than 6 weeks where as only about 40% of AVH due to other etiologies had icteric hepatitis of more than 6 weeks.
Two peaks of ALT could be documented amongst about 14% of HAV-AVH (Table-7) where as similar phenomenon was rarely observed amongst AVH patients due to other etiologies. Severe prolongation of prothrombine time was not a usual feature in any types AVH. Only two of the 254 patients developed complication in the form of fulminant hepatitis. Both these patients belonged to HAV-AVH. One patient imported with conservative treatment and the other succumbed four (4) patients developed sub-acute hepatic failure (HBV-2, Non A-E -2). 

Table-1

<table>
<thead>
<tr>
<th>Liver Function Profile</th>
<th>± Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>S Bilirubin(mg/dl)</td>
<td>7.9 ± 8.6</td>
<td>0.3 - 41.9</td>
</tr>
<tr>
<td>ALT (iu/dl)</td>
<td>207.2 ± 389.9</td>
<td>100-2130</td>
</tr>
<tr>
<td>AST (iu/dl)</td>
<td>155.1 ± 277.2</td>
<td>80-1900</td>
</tr>
<tr>
<td>SAP (iu/dl)</td>
<td>333.3 ± 211.5</td>
<td>23-1360</td>
</tr>
<tr>
<td>T. Pr. (g/dl)</td>
<td>7.4 ± 0.9</td>
<td>4.4-11.8</td>
</tr>
<tr>
<td>S.Alb(g/dl)</td>
<td>3.8 ± 1.1</td>
<td>0.5-5.7</td>
</tr>
<tr>
<td>Proth. Time Prolongation</td>
<td>1.2 ± 2.9</td>
<td>0-24</td>
</tr>
</tbody>
</table>

Table-2

<table>
<thead>
<tr>
<th>Etiology of AVH n=254</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV</td>
</tr>
<tr>
<td>HBV</td>
</tr>
<tr>
<td>HEV</td>
</tr>
<tr>
<td>HCV</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

No viral marker 102(40.1%), (22 had only HBsAg)

Under each etiology few patients had been common viz. acute HAV+HEV infection has been included both under HAV with another viral infection and HEV with another viral infection. Mixed viral infection occurred in 27(10.6%) patients.
Table-5

Clinical feature among various etiological types of AVH

<table>
<thead>
<tr>
<th>Clinical Profile</th>
<th>HAV Alone (n=28)</th>
<th>HBV Alone (n=43)</th>
<th>HEV Alone (n=30)</th>
<th>HAV with other viruses (n=11)</th>
<th>HBV with other viruses (n=17)</th>
<th>Non A-E (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Types of prodrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>26</td>
<td>34</td>
<td>26</td>
<td>8</td>
<td>10</td>
<td>87</td>
</tr>
<tr>
<td>Anorexia &amp; Nausea</td>
<td>27</td>
<td>38</td>
<td>29</td>
<td>8</td>
<td>12</td>
<td>95</td>
</tr>
<tr>
<td>Abd. Pain</td>
<td>5</td>
<td>4</td>
<td>11</td>
<td>1</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Duration of prodromme (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Means ± SD</td>
<td>5.4 ± 3</td>
<td>6.2 ± 4.6</td>
<td>6.6 ± 8.2</td>
<td>4.6 ± 2.3</td>
<td>5.2 ± 4.4</td>
<td>7.5 ± 7.3</td>
</tr>
<tr>
<td>Range</td>
<td>1-14</td>
<td>1-22</td>
<td>2-24</td>
<td>1-7</td>
<td>1-17</td>
<td>1-36</td>
</tr>
<tr>
<td>Duration of icterus (Days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Means ± SD</td>
<td>39.2 ± 34</td>
<td>68.9 ± 42.4</td>
<td>44.3 ± 40.6</td>
<td>60.1 ± 60.2</td>
<td>60.9 ± 55.9</td>
<td>42.3 ± 36.9</td>
</tr>
<tr>
<td>Hepatomegaly (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Means ± SD</td>
<td>2.4 ± 1.2</td>
<td>2.2 ± 1.1</td>
<td>3.3 ± 1.7</td>
<td>2.5 ± 0.5</td>
<td>3.1 ± 1.5</td>
<td>2.5 ± 1.3</td>
</tr>
<tr>
<td>Range</td>
<td>0-5</td>
<td>0-6</td>
<td>0-7</td>
<td>0-3</td>
<td>0-5</td>
<td>0-8</td>
</tr>
</tbody>
</table>

None of the above parameters were significantly different from each other (P>0.1)
Table-6
Liver function profile amongst various etiological types of AVH

<table>
<thead>
<tr>
<th>Liver Function</th>
<th>HAV Alone (n=28)</th>
<th>HBV Alone (n=43)</th>
<th>HEV Alone (n=30)</th>
<th>HAV with other viruses (n=11)</th>
<th>HBV with other viruses (n=17)</th>
<th>Non A-E (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.bil (mg/dl)</td>
<td>Means ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.5 ± 7.4</td>
<td>12.6 ± 11.3</td>
<td>8.7 ± 8.2</td>
<td>4.1 ± 3.4</td>
<td>6.6 ± 3.1</td>
<td>6.1 ± 7.1</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.5-42</td>
<td>0.5-29.2</td>
<td>0.5-10.4</td>
<td>2.5-12.2</td>
<td>0.3-35.4</td>
</tr>
<tr>
<td>AST(iu/dl)</td>
<td>Means ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>322 ± 567.8</td>
<td>236 ± 417.2</td>
<td>126.8 ± 254.6</td>
<td>92.6 ± 45.1</td>
<td>111.4 ± 59.5</td>
<td>112.9 ± 172.3</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>80-1500</td>
<td>75-1900</td>
<td>70-1300</td>
<td>45-150</td>
<td>52-190</td>
</tr>
<tr>
<td>ALT (iu/dl)</td>
<td>Means ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>322 ± 567.8</td>
<td>298.6 ± 422.7</td>
<td>124.7 ± 232.9</td>
<td>217 ± 135.3</td>
<td>130 ± 69.9</td>
<td>173.8 ± 39.3</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>150-1680</td>
<td>120-1680</td>
<td>100-1184</td>
<td>110-450</td>
<td>60-300</td>
</tr>
<tr>
<td>Alk.phos (iu/dl)</td>
<td>Means ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>373.3 ± 231.5</td>
<td>325.8 ± 214.9</td>
<td>194.7 ± 125.8</td>
<td>362.7 ± 152.8</td>
<td>383.8 ± 311.6</td>
<td>329.9 ± 214.5</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>70-948</td>
<td>120-1240</td>
<td>120-600</td>
<td>189-540</td>
<td>120-1240</td>
</tr>
<tr>
<td>T.Protein(g/dl)</td>
<td>Means ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.5 ± 0.7</td>
<td>7.7 ± 0.8</td>
<td>7.3 ± 1.1</td>
<td>8.0 ± 0.6</td>
<td>6.9 ± 1.1</td>
<td>7.2 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>6.2-8.4</td>
<td>5.5-9.0</td>
<td>5.0-8.7</td>
<td>8</td>
<td>4.9-7.7</td>
</tr>
<tr>
<td>S.albumin(g/dl)</td>
<td>Means ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.1 ± 0.7</td>
<td>3.9 ± 0.8</td>
<td>3.8 ± 0.8</td>
<td>3.3 ± 0.6</td>
<td>3.6 ± 2.1</td>
<td>3.8 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>3.2-5.5</td>
<td>2.8-5.6</td>
<td>2.5-5.1</td>
<td>2.8-3.7</td>
<td>1.9-5.0</td>
</tr>
<tr>
<td>Pro-time prolongation over control (Second)</td>
<td>Means ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.6 ± 1.1</td>
<td>1.7 ± 3.7</td>
<td>0.4 ± 1.0</td>
<td>0.1 ± 0.3</td>
<td>0.6 ± 1.7</td>
<td>1.5 ± 3.3</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0-3</td>
<td>0-17</td>
<td>0-4</td>
<td>0-1</td>
<td>0-6</td>
</tr>
</tbody>
</table>

There was no significant difference between the groups.
Table-7

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HAV Alone (n=28)</th>
<th>HBV Alone (n=43)</th>
<th>HEV Alone (n=30)</th>
<th>HAV with other viruses (n=11)</th>
<th>HBV with other viruses (n=17)</th>
<th>Non A-E (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Icterus more Than 6 wks</td>
<td>19(60.7%)*</td>
<td>20(46.6%)</td>
<td>10(33.3%)</td>
<td>3(27.2%)</td>
<td>7(41.1%)</td>
<td>32(31.3%)</td>
</tr>
<tr>
<td>Two peaks of ALT</td>
<td>3+</td>
<td>1</td>
<td>0</td>
<td>2+</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Proth. Time Prolongation &gt;20 seconds</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

* P<0.001 (Significantly higher proportion of HAV-AVH had prolonged course of AVH than any other groups of AVH. The remaining group had similar number of patients with prolonged hepatic illness.

+ 5 (12.8%) patients out of total 39 patients with HAV infection had two peak ALT which was significantly higher (p=0.04) than similar events in any other group.

Discussion:

The present study revealed four important events regarding the etiology of AVH in one of the large tertiary care centre in Eastern India in the State of Odisha.

First the major etiological agents of sporadic AVH was found to be HBV (23.6%) as well as HEV (25.1%) and hepatitis C virus is an infrequent cause of sporadic AVH (Table-2). This is in sharp contrast to developed nations where HEV is unusual and HBV as well as HCV constitutes the major viral etiologies of sporadic AVH. In the present study none of our patients with sporadic HCV-AVH which can be termed as community acquired HCV-AVH had history of any identifiable parenteral exposure such as blood transfusion or needle prick. None of them were drug addicts, alcoholic and neither had multiple sex partners. The source of such HCV infection needs evaluation.

Secondly, it was seen that about one tenth (10.6%) of our patients had serological evidence of acute infection due to more than one hepatotropic viruses. The commonest type of mixed infection encountered was due to hepatitis B+E and hepatitis A+E (Table-3). Such high frequency of mixed infection has not been reported previously from any part of the country and dual infection amongst sporadic AVH in developed nation is extremely rare and in English literature such reports are lacking. However despite having multiple hepatotropic viral infection, their demographic (Table-4), clinical (Table-5), liver function profile (Table-6) was similar to isolated viral infection. None of these multiple viral infected AVH developed severe acute hepatitis in the form of fulminant and subacute hepatic failure. This factor emphasizes that host factor possibly plays a major role in determining the severity of acute hepatic illness.

Third important fact noted in the present study was the frequency of HAV-AVH amongst adult (>15yrs). In the present study about 15% of the adults AVH were due to HAV. This fact assumes importance particularly in India because India is supposed to be endemic for HAV and by the age of 15 yrs 90% of population are reported to be protected against HAV due to sub-clinical exposure to HAV in childhood resulting in development of protective antibody against HAV in them.13

This observation indicate that in India, due to developmental progress certain population pockets are not exposed to sub-clinical HAV infection in childhood. Such observation also indicate the need to re-evaluate the seroepidemiology of HAV infection in population to identify the high risk group to develop HAV infection. Such information may influence vaccination strategy for HAV in this country. Further a recent report indicate that combined infection of HAV & HEV amongst children was responsible for 40% of fulminant hepatitis in this Country14. Both these studies may be indicating a serious problem due to Hepatitis A Virus that this country may face in the ensuing decade.

Fourthly the previous reports on sporadic AVH indicated non A, non B, as the etiological agent in about 60% of the patients. In the present study however non A-E Virus was found to be the cause in 40% of patient. Obviously this reduction in frequency of unidentified viral etiology of AVH is due to identification of HEV & HCV. Further it also indicates the possibility of existence of more than one non A-E viruses. In 1995 hepatitis G virus has been identified as the third major non A, non B virus, however its role in causation of acute sporadic AVH is yet to be evaluated. Recently it has been reported regarding the presence of HGV
in one patient in acute liver failure\textsuperscript{15}. Evaluation for presence of HGV among these sporadic non A-E patients may provide beneficial information.

The clinical and liver function profiles of isolated hepatotropic viral infection and acute mixed viral infection was found to be similar in the present study. However, patients with Hepatitis A virus infection were not infrequently found to have two peak ALT elevation. Recently in the Western country two forms of clinical course was described amongst patients with HAV infection viz. Cholestatic hepatitis and relapsing hepatitis (two peak ALT elevation) and here we have documented relapsing hepatitis amongst 15% of our HAV-AVH patients. The frequency of prolonged hepatitis amongst HAV patients was around 68% and this is significant as compared to other groups of AVH. Unlike Western report clinical course of adult HAV-AVH in the present study was relatively benign and severe form of hepatic illness was encountered in few cases only. We will like to conclude that non A-E followed by HBV & HEV are the major etiological agents of AVH at our centre. Despite endemicity of HAV in this country 15% of the adults AVH are due to HAV infection. More than one hepatotropic viral infection was encountered in about 10% of the patients. Fifteen percent of HAV-AVH had relapsing Hepatitis and 68% of HAV-AVH in adults demonstrate prolonged course. The demographic, clinical and liver function profile of isolated & mixed viral infection was similar.

REFERENCES :


Study of Lipid Profile Abnormalities in CKD
T.R. Behera¹, J. Sarangi², U.S. Mishra³, L.K. Meher¹, Tity P¹, A. Agarwal¹

Abstract:

Introduction: Cardiovascular disease is a major cause of morbidity and mortality among patients with chronic kidney disease. Lipid disorders are one of the known metabolic changes associated with chronic kidney disease (CKD). The prominent features of uremic dyslipidemia are an increase in plasma triglycerides and cholesterol in nearly all lipoproteins, and a reduction in high-density lipoprotein (HDL) cholesterol. The growing recognition that dyslipidemia is a major risk factor for coronary heart disease has prompted interest in the identification and management of abnormalities in plasma lipids and lipoproteins in CKD.

Objective: This study intends to assess the lipid profile abnormalities in chronic kidney disease and differences in lipid profile abnormalities between patients on haemodialysis and on conservative management.

Material and Method: 50 patients of chronic kidney disease (21 on haemodialysis and 29 on conservative management) and 30 age & sex matched controls were taken for study. Serum lipid profile estimation done and statistical calculation done using unpaired ‘t’ test & ‘p’ value.

Result: Serum triglycerides (176.3±46.1mg/dl Vs 119.5±32 mg/dl) and VLDL fraction (35.26 ± 9.2mg/dl Vs 23.9 ± 6.4 mg/dl) were significantly elevated in CKD patients compared to controls (p < 0.001). There was significant decrease in plasma HDL (36.9±6.0mg/dl Vs 49.1 ± 7.24 mg/dl) in CKD patients compared to controls (p < 0.001). There was no significant difference in total cholesterol (181±21.35 mg/dl Vs 179.9 ± 19.5 mg/dl) in CKD patients and Controls (p >0.05). On comparing lipid profiles in CKD patients on conservative management and Haemodialysis, there was significant increase in triglycerides (191.67±47.88 mg/dl vs 165.17±42.27mg/dl) and VLDL cholesterol (38.33±9.58mg/dl vs 33.03±8.45mg/dl) in haemodialysis group.

Conclusion: Uremic dyslipidemia is a specific metabolic abnormality. Excess triglycerides and VLDL fraction was observed in patients of CKD both on conservative management and haemodialysis. Further, reduced level of HDL cholesterol was also observed both in conservative and haemodialysis group of CKD patients. Because the lipid abnormalities observed in chronic kidney disease which accelerates the progression of the renal failure and predisposes to atherosclerosis, it is worth while detecting and treating hyperlipidemia in chronic kidney disease patients.

Key words: CKD, Haemodialysis, Lipid profile, Triglyceride, HDL, VLDL.
Introduction:

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive, irreversible decline in glomerular filtration rate (GFR).

Cardiovascular disease is a major cause of morbidity and mortality among patients with chronic kidney disease1,2,3. Majority of patients die from cardiovascular system complications. The growing recognition that dyslipidemia is a major risk factor for coronary heart disease has prompted interest in the identification and management of abnormalities in plasma lipids and lipoproteins in CKD.

In chronic kidney disease, the most prevalent lipid disorders are hypertriglyceridemia and decreased HDL concentration. LDL levels are usually normal or marginally increased4,5. Also there are reports available regarding accelerated atherosclerosis in chronic kidney disease due to altered lipid metabolism. In recent years, the levels of high-density lipoproteins have gained importance in view of the fact that increasing reports are available incriminating decreased HDL levels as one of risk factors for cardiovascular disease.

This study is intended to note the alteration of different lipoprotein fractions in chronic kidney disease patients and to note difference in lipid profile in chronic kidney disease patients on conservative management and haemodialysis.

Materials and Methods:

50 Cases of chronic kidney disease admitted in the medical wards of MKCG Medical college & Hospital from 2010 to 2012 were taken for study of whom 29 patients were on conservative management and 21 patients were on haemodialysis. 30 age & sex matched controls were also taken for study.

Inclusion criteria:

Patients of chronic kidney disease.

Diagnostic criteria for chronic kidney disease:

1. Clinical signs and symptoms of uremia
2. The presence of Chronic Kidney Disease was established based on presence of kidney damage and level of kidney function (GFR). Markers of kidney damage included abnormalities in the composition of blood (elevated blood urea, serum creatinine) or urine or abnormalities in imaging tests (Ultrasonographic evidence of bilateral shrunken kidney/ loss of corticomedullary differentiation.).

Exclusion Criteria:

1. Patients with diabetes mellitus
2. Patients with Ischemic heart disease
3. Patients who have undergone coronary artery bypass graft surgery
4. Patients on lipid lowering drugs
5. Patients with history of alcohol consumption and smoking
6. Patients with thyroid and liver disease.

All the selected patients were subjected to detailed history and complete physical examination and data collected was noted in a pre-designed proforma. The control group was formed by 30 healthy persons, which was age and sex matched to the study group.

Blood samples of patients were collected and sent for Hb%, serum urea, serum creatinine, s. Na+, s. K+, FBS estimation. Urine samples sent for presence of albumin. USG assessment of kidney size and corticomedullary echo texture done. Fasting blood samples collected and estimation of total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, VLDL cholesterol done by enzymatic method using autoanalyser. Normal values are of total cholesterol <200mg/dl, TG <150 mg/dl, HDL cholesterol > 40mg/dl, LDL cholesterol<100mg/dl.

Baseline characteristics as age and sex of the study participants were compared. Values of s. urea and creatinine, lipid profile among study group and controls were expressed in mean± SD(mg/dl). Student ‘t’ test was used to analyse differences in total ch, TG, HDL Ch, LDL Ch, VLDL Ch among patients and controls. Also among patients on conservative management and dialysis. P value of <0.05 was considered significant.

Observation:

Of the 50 patients in the study group, 31 patients were males(62%) and 19 patients were females(38%). Of the 30 patients in control group, 20(67%) were...
males and 10 (33%) were females. Decade wise age and sex distribution were depicted in table 1. The mean age for the total number of patients was 46.34. The mean age for male patients was 45.54. The mean age for female patients was 47.63 Male to female ratio in the study group was 1.6:1

Differences in serum urea and creatinine among cases and controls were depicted in table 2. Mean values for urea in controls and patients showed a considerable difference, which was found to be highly significant (P<0.0001). Creatinine levels in CKD patients were very high as compared to controls. This difference was statistically significant (P<0.0001).

Differences in lipid profile values among cases and controls were depicted in table 3. Total cholesterol value in controls and CKD patients are 179.9 ± 19.5 mg/dl Vs 181±21.35 mg/dl respectively (P>0.05). However this difference was not significant. Triglyceride values in cases and controls were 191.67±47.88 mg/dl vs 165.17±42.27 mg/dl respectively. Triglyceride values in patients of CKD were significantly high as compared to controls and this is statistically highly significant (P<0.0001). HDL values in chronic kidney disease patients are decreased compared to controls, i.e, 36.9±6.0 mg/dl Vs 49.1 ± 7.24 mg/dl respectively (P<0.0001). This was also statistically highly significant. Significant increase in VLDL were found in CKD patients as compared to controls, i.e, 35.26 ± 9.2 mg/dl Vs 23.9 ± 6.4 mg/dl respectively. This was statistically highly significant(P>0.5). There is significant reduction in HDL/TC ratio in patients as compared to controls, i.e, 0.206±0.036 vs 0.272±0.021 respectively. This was statistically highly significant (P<0.0001).

21 patients were on haemodialysis and 29 patients were on conservative management. Differences in lipid profile values among patients on conservative management and on haemodialysis were shown in table 4. Mean triglycerides in patients of CKD on conservative treatment and Haemodialysis group are 165.17±42.27 mg/dl vs 191.67±47.88 mg/dl respectively. This difference was statistically significant(P<0.05).

Table 1: Age and sex distribution among CKD patients

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Cases</th>
<th>Percentage</th>
<th>Male</th>
<th>Percentage</th>
<th>Female</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>100</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>21-30</td>
<td>9</td>
<td>18</td>
<td>6</td>
<td>66.6</td>
<td>3</td>
<td>33.3</td>
</tr>
<tr>
<td>31-40</td>
<td>8</td>
<td>16</td>
<td>7</td>
<td>87.5</td>
<td>1</td>
<td>12.5</td>
</tr>
<tr>
<td>41-50</td>
<td>11</td>
<td>22</td>
<td>6</td>
<td>54.5</td>
<td>5</td>
<td>45.5</td>
</tr>
<tr>
<td>51-60</td>
<td>11</td>
<td>22</td>
<td>4</td>
<td>36.3</td>
<td>7</td>
<td>63.7</td>
</tr>
<tr>
<td>61-70</td>
<td>8</td>
<td>16</td>
<td>6</td>
<td>75</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>&gt;70</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>50</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100</td>
<td>31</td>
<td>62</td>
<td>19</td>
<td>38</td>
</tr>
</tbody>
</table>

Table 2: Biochemical data in controls and CKD patients. (Mean?SD)mg/dl.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Serum urea</th>
<th>Serum creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n=30)</td>
<td>15.07 ± 3</td>
<td>0.68 ± 0.12</td>
</tr>
<tr>
<td>Cases (n=50)</td>
<td>117.1 ± 38.12</td>
<td>9.218 ± 2.79</td>
</tr>
<tr>
<td>Student’s t-test</td>
<td>14.5959</td>
<td>16.7095</td>
</tr>
<tr>
<td>Significance</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Student’s t-test (unpaired) P<0.0001-
Extremely statistically significant

Table 3: Biochemical (lipid profile) data in controls and CKD patients (Mean±SD)mg/dl.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Controls (n=30)</th>
<th>Cases (n=50)</th>
<th>t-value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>179.9±19.5</td>
<td>181.0±21.35</td>
<td>0.2303</td>
<td>0.8185 (N.S.)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>119.5±32</td>
<td>176.3±46.1</td>
<td>5.9377</td>
<td>&lt;0.0001 (H.S.)</td>
</tr>
<tr>
<td>HDL Ch</td>
<td>49.1±7.24</td>
<td>36.9±6.0</td>
<td>8.1414</td>
<td>&lt;0.0001 (H.S.)</td>
</tr>
<tr>
<td>LDL Ch</td>
<td>106.9±14.2</td>
<td>109.6±19.2</td>
<td>0.6677</td>
<td>0.5 (N.S.)</td>
</tr>
<tr>
<td>VLDL Ch</td>
<td>23.9±6.4</td>
<td>35.26±9.2</td>
<td>5.9477</td>
<td>&lt;0.0001 (H.S.)</td>
</tr>
<tr>
<td>HDL/TC</td>
<td>0.272±0.021</td>
<td>0.206±0.036</td>
<td>9.1380</td>
<td>&lt;0.0001 (H.S.)</td>
</tr>
</tbody>
</table>

*Students t-test (unpaired ) P< 0.001 highly significant NS- not significant P(>0.05)
Discussion:

The results of the study on the lipid disorders in patients with chronic kidney disease show that there are significant alterations in the lipid profiles of these patients as compared to controls.

In this study, triglycerides were markedly elevated compared to control group and it was statistically highly significant (P values <0.001). Attman P.O, Alaupovic P6 stated that hypertriglyceridemia is the most common plasma lipid abnormality in patients of chronic kidney disease.

There was decrease in HDL cholesterol seen in patients compared to controls, which was statistically significant (P<0.001). P.O.Attman et al found decrease in plasma HDL cholesterol concentration in patients with CKD. It was also reported that decreased HDL was associated with decrease in both the fractional catabolic rate and the total synthetic rate of ApoA1. The slow fractional catabolic rate of Apo A1 in patients with chronic kidney disease could be a primary event resulting from a decrease in synthesis or secretion of Apo A1.

John D Bagdade et Al7 demonstrated that patients of renal failure treated by chronic dialysis have lower HDL levels compared to controls.

There was marginal decrease of serum total cholesterol in chronic kidney disease patients compared to controls but this was not statistically significant P(>0.05). P.O. Attman et al in their study showed no significant change in levels of total cholesterol. Thomas Quasctining et al8 reported combined hyperlipidemia (elevated total cholesterol and triglycerides) in their study.

There is significant rise in VLDL levels in chronic kidney disease patients compared to controls (P<0.001). Gerald Appel et al9 also showed increase in very low density lipoproteins (VLDL).

There was marginal increase in LDL levels in patients as compared to controls which is not significant. In uremia, LDL lipoproteins are qualitatively altered. Marion Morena et al10 reported that there was increase in small, dense LDL subfractions in Hemodialysis patients. Hypertriglyceridemia observed in Hemodialysis patients results from a reduced lipolysis of TG-rich

Graph 1: Biochemical (lipid profile) data in Controls and Cases (Mean± SD)

Graph 2: Biochemical data (lipid profile) in chronic kidney disease patients on conservative management and haemodialysis.

Table 4:

<table>
<thead>
<tr>
<th>Groups</th>
<th>Conservative treatment n=29</th>
<th>Dialysis n=21</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>180.58±20.08</td>
<td>181.57±23.52</td>
<td>0.1601</td>
<td>0.8735 (N.S)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>165.17±42.27</td>
<td>191.67±47.88</td>
<td>3.95</td>
<td>0.04 (SIGNIFICANT)</td>
</tr>
<tr>
<td>HDLc</td>
<td>36.9±6.36</td>
<td>37±5.77</td>
<td>0.057</td>
<td>0.9548 (N.S)</td>
</tr>
<tr>
<td>LDLc</td>
<td>112.06±18.08</td>
<td>110.19±21.65</td>
<td>1.0593</td>
<td>0.2948 (N.S)</td>
</tr>
<tr>
<td>VLDLc</td>
<td>33.03±8.45</td>
<td>38.33±9.38</td>
<td>2.0694</td>
<td>0.04 (SIGNIFICANT)</td>
</tr>
<tr>
<td>HDL/TC</td>
<td>0.205±0.033</td>
<td>0.206±0.041</td>
<td>0.0955</td>
<td>0.9243 (N.S)</td>
</tr>
</tbody>
</table>
ORISSA MEDICAL JOURNAL

VLDL that leads to the accumulation of partially metabolized remnant lipoproteins (IDL and TG-rich LDL). This lipoprotein catabolism impairment is usually associated with reduced levels of HDL affecting reverse cholesterol transport. Such defect in atherogenic lipoprotein catabolism may predispose to the formation of small dense LDL particles, which appear to be more sensitive to ex vivo oxidation.

There was significant reduction in HDL/TC ratio in patients as compared to controls, this was statistically highly significant, (P<0.001).

There was significant increase in triglycerides in patients treated with hemodialysis compared to patients on conservative treatment (P<0.05). Increased serum triglyceride levels have been well documented by Alam et al. Morena Marion et al in their study on haemodialysis patients stated that haemodialysis patients are exposed to several atherogenic factors resulting from qualitative and functional lipid abnormalities, including triglyceride rich particles, increased susceptibility to LDL oxidation and impairment of HDL protective effects.

Present study on Lipid profile abnormalities in CKD was found to be well correlated with studies by previous investigators. In most of the studies, mean values of Triglycerides and VLDL were found to be elevated significantly as compared to controls and mean values of HDL were decreased.

CONCLUSION

There is significant increase in triglyceride and VLDL concentration and significant decrease in HDL cholesterol and HDL/Total Cholesterol ratio in patients with CKD as compared to controls. This may be the cause for increase in cardiovascular abnormalities in CKD patients.

Significant reduction in HDL and HDL/total cholesterol ratio are the important predictive indices for the risk of developing coronary artery disease in all group of patients with chronic kidney disease. This may be major contributory factor for enhanced atherogenesis in these patients.

Finally because the lipid abnormalities in chronic kidney disease accelerates the progression of the renal failure and predisposes to atherosclerosis, it is worth while detecting and treating hyperlipidemia in chronic kidney disease patients.

Bibliography:
10. Marion Morena, Jean-Paul Cristol, ,Marrie-Annette Carbonn eau, Bernard Descomps, Bernard Canaud et al. protective effects of high-density lipoprotein against oxidative stress are impaired in haemodialysis patients. nephrol dial transplant 2000;15:389-393
Controversy in reducing Blood pressure in type 2 diabetes : post ACCORD scenario
D.R. Das¹, S.N. Routray², T.K. Mishra³

Abstract:
Given the incremental CVD risk associated with hypertension in DM, and the clearly demonstrated graded association between magnitude of blood pressure reduction and CVD clinical risk reduction, patients with DM have been identified as a special population warranting more aggressive than usual blood pressure control, with targets for patients with DM of < 130/80 mmHg being endorsed by a number of professional guidelines.

More recently, results were reported from the NHLBI-sponsored Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, in which 4733 patients with type-2 diabetes at high cardiovascular risk were randomized to treatment to systolic blood pressure goals of < 120 mmHg versus < 140 mmHg. In a comparison of the more intensive versus less intensive arm, the point estimate of a 12% relative risk reduction in the primary composite endpoint of CV death, MI, and stroke failed to achieve statistical significance (HR=0.88; 95% CI, 0.73-1.06); more intensive control was associated with a significant 41% reduction in stroke (HR=0.59; 95% CI, 0.39-0.89). Hence the present target of <130/80 mmHg seems prudent, with no clear imperative to target more aggressive control.

Introduction
At a population level, an increasing proportion of all cardiovascular events is being attributed to the presence of diabetes.¹ and cardiovascular disease (CVD) is responsible for approximately half of all deaths in patients with type 2 diabetes.²³

Epidemiological studies have clearly shown a direct relationship between the levels of blood pressure and the complications of diabetes.⁴ The results of recent clinical trials examining the benefits of normalizing risk factor levels have been counter-intuitive and at times, disturbing.

Blood pressure
Epidemiological evidence from the general population suggests that cardiovascular risk starts to increase above a blood pressure of 115/75 mmHg and then it doubles for every 20mmHg rise in systolic pressure, and for every 10 mmHg rise in diastolic blood pressure.⁵

Here we present data to guide physicians regarding how low to go with blood pressure targets by examining diabetes trials that have randomized patients to different blood pressure targets.⁶⁻¹² We believe that these results are more likely to provide relevant information than extrapolating from the blood pressure levels achieved in trials that used alternative designs,¹³⁻²³ although these important trials have highlighted major clinical benefits, and have rightly influenced blood pressure guidelines, as reviewed recently.²⁴

Table-1 Selected clinical trials of blood pressure lowering in patients with type 2 diabetes, target levels and achieved risk factor levels and their associated outcomes.

Table-2 : Target levels of blood pressure in patients with type 2 diabetes according to current guidelines and position statements.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Target BP levels (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESC/EASD</td>
<td>130/80</td>
</tr>
<tr>
<td>European</td>
<td>130/80</td>
</tr>
<tr>
<td>IDF</td>
<td>130/80</td>
</tr>
<tr>
<td>JNC 7</td>
<td>130/80</td>
</tr>
<tr>
<td>ADA</td>
<td>130/80</td>
</tr>
<tr>
<td>AHA</td>
<td>130/80</td>
</tr>
<tr>
<td>JBS2</td>
<td>130/80</td>
</tr>
<tr>
<td>NICE</td>
<td>130-140/80</td>
</tr>
<tr>
<td>Canadian</td>
<td>130/80</td>
</tr>
</tbody>
</table>

Early trials

In the ‘pre-ACCORD era’ several important trials ignited the debate about blood pressure targets. The relationships of these targets, and achieved blood pressures with total mortality and the primary outcomes of these trials are presented in Table-1.

The United Kingdom Prospective Diabetes Study (UKPDS) blood pressure trial was the first major trial to randomize hypertensive patients with type 2 diabetes to conventional or to intense blood pressure targets.6,7 In this trial, ‘intensive’ blood pressure lowering was associated with major reductions in important clinical endpoints including a 32% reduction for diabetes related death; a 44% reduction in stroke; and a 37% reduction in microvascular endpoints—predominantly retinal photocoagulation.

The Hypertension Optimal Treatment (HOT) trial, which reported around the same time, randomized hypertensive patients to different diastolic blood pressure targets (table-1). A post-hoc diabetes subgroup analysis showed that major cardiovascular events were reduced by half, and cardiovascular death was reduced by two-thirds in the group randomized to the lowest vs. the highest blood pressure target.11

These early trials changed clinical practice, but now have limited clinical relevance because target blood pressures, and achieved levels, were well above those that are currently acceptable (Table-1). Trials published since these have shows less impressive additional benefits associated with lower blood pressure targets.

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial was the first to compare the benefits of normal blood pressure levels (target diastolic blood pressure 75 mmHg) with moderate blood pressure control (80-89 mmHg) on the progression of microvascular complications in patients with type 2 diabetes.8 After 5 years, intensive therapy did not reduce the risk for the primary outcome or for cardiovascular endpoints, but it was associated with lower total mortality (5.5 vs. 10.7%). This is the only early trial that achieved an on-treatment blood pressure of <130/80 mmHg in the intensive therapy group (Table-1).

ACCORD blood pressure trial

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial randomized patients with type 2 diabetes to a normal target systolic pressure target (<120 mmHg), or to standard therapy with the goal of reducing cardiovascular endpoints.12 The trial achieved an impressive blood pressure separation between the two groups, but this did not translate into a significant reduction in the primary outcome or the risk of death (Table 1). However, the annual rate of stroke was 39% lower in the intensive treatment group (p=0.01), which yielded an estimated number needed to treat (NNT) to prevent one stroke over 5 years of 89 patients.

The most obvious reason why the ACCORD blood pressure trial was negative for the primary endpoint is that targeting near normal levels of blood pressure has limited clinical benefit, with most of the benefits being achieved by targeting a level of <140 mmHg, as earlier trials have shown. However, cardiovascular event rates were much lower than expected, in part because patients with dyslipidaemia were recruited into the ACCORD lipid trial and higher-risk patients with renal impairment were excluded. This meant that the study was somewhat underpowered to detect difference between groups and therefore it was unable to exclude a 27% benefit for the primary endpoint.

Another possible explanation is that a u-shaped relationship exists between achieved blood pressure and coronary (but not cerebrovascular) risk such that the minimum coronary risk is achieved when the systolic pressure is reduced to somewhere between 120 and 130 mmHg.25 Previous trials have suggested that lowering blood pressures to <120/70 mmHg can cause harm.26-29 Although there was no suggestion that aggressive blood pressure lowering caused increased coronary risk in the ACCORD blood pressure trial, it is possible that the optimal blood pressure level was...
missed because of the wide separation of on-treatment systolic pressures in the intensive therapy group. Unfortunately, the cost of performing a trial to identify this optimal blood pressure level may be prohibitive and moreover, if this hypothesis was confirmed, then current blood pressure targets would probably remain unchanged (seen below).

Intensive blood pressure lowering was generally well tolerated, but there have been some concerns raised about potential harm associated with this intervention. Serious adverse events attributed to antihypertensive treatment that included hypotension, bradycardia, and hyperkalaemia, occurred in 3.3% of the intensively treated patients and in 1.3% in the standard therapy group (p<0.01).

The ACCORD blood pressure trial showed that intensive blood pressure lowering was associated with lower albumin excretion rates. There was no increase in the risk of end-stage renal disease or the need for dialysis, but there was a significant reduction in estimated glomerular filtration rate associated with intensive therapy. The long-term clinical impact of these changes in renal function is uncertain.

Current blood pressure guidelines in diabetes.

The main conclusion that can be drawn from the ACCORD blood pressure trial is that a systolic blood pressure target of < 120mmHg cannot be recommended for the majority of patients with type 2 diabetes. Current guidelines and position statements show a remarkable consistency in setting a target blood pressure level at 130/80 mmHg (Table 3). Based on current evidence, this is probably an appropriate blood pressure target for most patients. However a lower blood pressure target level might be justifiable in patients with a prior history of transient ischaemic attack or stroke, and in other high-risk groups such as South Asians. Further information refining the optimal individualized target blood pressure may come from post-hoc analyses of this trial.

How to lower blood pressure in patients with dysglycaemia

The clinical benefits of most classes of blood pressure-lowering medication have been demonstrated in trials involving patients with diabetes.

Some, but not all, data indicate that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) possess renoprotective benefits that are independent of their blood pressure-lowering effects. Here we highlight two recent trials that have provided additional information about the potential benefits of ACE inhibitors and ARBs in patients with diabetes or non-diabetic hyperglycaemia.

First, the Action in Diabetes and Vascular Disease Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial compared clinical outcomes associated with an ACE inhibitor-duretic combination (perindopril/indapamide) vs placebo in middle-aged, high-risk patients with diabetes, one-third of whom had established CVD. After 4.3 years, active therapy was associated with an average blood pressure lowering of 6/2 mmHg; a 9% reduction in the relative risk of macrovascular or microvascular complications (absolute risk reduction 1.3%); a 14% reductions in all-cause mortality; an 18% reduction in cardiovascular death; and a 21% reduction in total renal events. It is uncertain whether the observed clinical benefits can be explained simply by blood pressure lowering, or by ‘off-target’ effects of perindopril or indapamide. Pleotropic effects of perindopril seem unlikely because more than half the placebo-treated patients were taking perindopril by the time the trial concluded. The mechanism of benefit is important because the cost of this fixed dose combination may be prohibitive for large-scale clinical use despite claims of cost-effectiveness. Perhaps more importantly, this trial emphasizes the clinical benefits of achieving a systolic blood pressure of < 140 mmHg in high-risk patients with type 2 diabetes. Over 5 years, the NNT to prevent one death was ~79 patients, with greater absolute benefits in older patients and in those with chronic kidney disease.

Second, the blood pressure-lowering arm of the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAGIVATOR) trial assessed whether the ARB valsartan could reduce the risk of incident diabetes or CVD in high-risk patients with non-diabetic hyperglycaemia. During a 5-year follow-up, active therapy reduced incident diabetes by 14%, but failed to have any effect on CVD outcomes despite a blood pressure difference of 6/4 mmHg.
The reduction in diabetes risk was probably a real effect because other randomized and non-randomized studies have suggested a similar degree of benefit, although the mechanism is unknown.

The modest clinical benefit with valsartan (NNT~26 to prevent one case of diabetes) may have been limited by a high proportion of therapy crossovers, and the effects of a lifestyle intervention which was offered to all participants. Since the benefit of lifestyle intervention in preventing diabetes is much greater than that observed with valsartan, diet and physical activity will remain the cornerstone of diabetes prevention for most people. However, when choosing an antihypertensive agent, it is useful to know that valsartan has modest beneficial effects on diabetes risk when other agents may not.19

These recent data support the use of ACE inhibitors or ARBs as first-line anti-hypertensive agents in patients with dysglycaemia 40,41. However, in practice, this recommendation is somewhat arbitrary because most patients with hypertension and diabetes require more than one agent 12

CONCLUSION :

In a comparison of the more intensive versus less intensive arm of ACCORD trial, the point estimate of a12% relative risk reduction in the primary composite endpoint of CV death, MI, and stroke failed to achieve statistical significance (HR=0.88;95% CI,0.73-1.06); more intensive control was associated with a significant 41% reduction in stroke (HR=0.59;95% CI, 0.39-0.89). Of note, at the time of randomization, when clinical guidelines endorsed systolic blood pressure targets of <130/80 mmHg, the average blood pressure at study entry was 139/76 mmHg in this high-risk cohort. During the trial, the average blood pressure achieved in the < 120 mmHg arm was 119.3 mmHg. Contrasted with an average of 133.5 mmHg in the patients randomized to a target of < 140 mmHg requiring an average of 3.4 and 2.3 medications, respectively. Therefore, though the trial failed to prove the benefit of more intensive blood pressure control than contemporary targets, the blood pressure achieved in the less intensive group fell quite close to such targets, and in the context of favorable secondary outcomes with no prohibitive safety signals observed, the present target of <130/80 mmHg seems prudent, with no clear imperative to target more aggressive control.

References:


33. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT)/ JAMA 2002;288:2981-2997


Ultrasound - A New Weapon in the Anesthesiologist’s Armamentarium

N. Pani¹, S. Routray², R.K. Sarangi³

1Professor, 2Assistant Professor
3PG Student, Dept of Anaesthesiology
SCB Medical College, Cuttack

Contact : 9437004747
Submitted : 14.06.2012, Accepted : 15.07.2012
© OMJ 2012

Ultrasound technology is advancing at a rapid pace and the field of anaesthesiology is benefitting immensely. It is playing an increasing role in vascular access, regional anaesthesia for nerve blocks, as a transoesophageal echocardiography tool for cardiac imaging and viewing blood flows and can play a major role in the field of anaesthesiology, critical care & pain to perform with precision and reduce complications. It has special applications to assess the depth of epidural space in cases of difficult anatomy or in an otherwise high risk patient where interventional procedure is required.

The ultrasound technology has evolved leaps and bounds. Modern ultrasound machines are more compact & portable, with better resolution and enhanced tissue penetration making it a handy tool for identification and intervention.

The training in ultrasound techniques in near future will become part of the core training of every anaesthesiologists, just as laparoscopic work is for surgeons¹. Anaesthesiologists need to develop a thorough knowledge of sonoanatomy involved and acquire clear concepts for both ultrasound technology and skills to visualize various structures intended to be manipulated. A day is not far the ultrasound imaging may become an important component of anaesthesia machine¹.

The high cost of equipment is often the argument against ultrasound-guided techniques. A preliminary study by Sandhu et al² suggests that the cost of using ultrasound and nerve stimulator techniques is similar.

Patient satisfaction is another important measure of clinical outcome. To the patient, a nerve block deemed perfect by the anaesthesia provider may be viewed as disappointing by the patient if severe pain is experienced during block performance, particularly when the pain is aggravated in a fractured limb by muscle contraction during nerve stimulation. Ultrasound guided nerve blocks can be a relatively painless procedure when muscle contraction is avoided without nerve stimulation.

Another potential benefit of ultrasound-guided peripheral nerve block is a reduction in the incidence of systemic local anesthetic toxicity. The minimum effective dose of local anesthetic can be significantly reduced with the ultrasound technique³,⁴,⁵

Furthermore, ultrasound can differentiate an intravascular from an extravascular injection based on the pattern of local anesthetic spread.
Other advantages include direct visualization of non-neural structures, e.g., pleura and kidney, thus preventing accidental puncture during periclavicular blocks and psoas compartment block.

**Applied Physics of Medical Ultrasound**

A. Transducer position to image the sciatic nerve on the short axis in the popliteal fossa. B. The corresponding short-axis ultrasound image of the sciatic nerve. Note the characteristic circular appearance of the nerve. On the short axis, the anaesthesiologist has simultaneous anterior–posterior and lateral–medial perspectives of the nerve. C. If the probe position for the short-axis view is turned 90 degrees (clockwise or counterclockwise), the long-axis view of the same structure will be generated. D. The long-axis ultrasound image of the popliteal sciatic nerve. Note the characteristic tubular appearance. When imaging a nerve on the long axis, the operator loses the lateral–medial perspective. This can be disadvantageous when one is trying to identify needle location and the circumferential spread of local anesthetic around the nerve. L, local anesthetic. Image by –www.anaesthesiologynews.com

(The differences between imaging a structure on the short axis and imaging on the long axis. For this demonstration, the patient is in the prone position.)

**Applications of Ultrasound In Anaesthesia**

The applications of ultrasound in anaesthesia include

1. Ultrasound for vascular access
2. Ultrasound guided regional anaesthesia
3. Trans-esophageal echocardiography
4. In emergency medicine and critical care.
5. Newer applications
Ultrasound For Vascular Access:
ultrasound guided central venous cannulation

Two types of ultrasound guidance are described1:
a) two-dimensional (2-D) imaging ultrasound
guidance which provides a real-time image of
the anatomy.
b.) audio guided Doppler ultrasound guidance
which helps to localize the vein and differentiate
it from its companion artery. However it does
not give an idea about the depth of the vessel.

The literature failure rates for initial CVC
insertion with the traditional “landmark” method have
been reported to range between 10% and 35%6,7.

The risk of CVC insertion related complications
increases, depending upon1:
• Difficult anatomy: obesity, short neck, scarring
due to surgery or radiation
• Repeated catheterization: increased risk of
thrombus formation
• Coagulopathies
• Patients on mechanical ventilation

The advantages of ultrasound-guided central venous
catheterization include1:
• Identification of the vein
• Detection of variable anatomy
• Detection of intravascular thrombi
• Avoidance of inadvertent arterial puncture.
Puncture under usg guidance
( Image by - http://www.impaedcard.com)
A meta-analysis of 12 randomized controlled trials evaluating the effect of real-time ultrasound guidance using regular or Doppler ultrasound for CVC placement found a reduction in placement failure, decreased need for multiple attempts, and decreased complications, as compared to the standard landmark technique.7

Another meta-analysis of 7 trials comparing the use of 2-D ultrasound versus landmark method for central venous cannulation in adults showed that for IJV cannulation, 2-D ultrasound guidance was associated with reduced risks of failed catheter placements, catheter placement complications, failure on the first catheter placement attempt, and fewer attempts to achieve successful catheterization.8

Based on this meta-analysis, the NICE (National Institute for Clinical Excellence – NHS) has recommended that the use of two-dimensional (2-D) imaging ultrasound guidance should be considered in most clinical circumstances where CVC insertion is necessary9. The use of ultrasound for vascular access may be particularly helpful in haemodialysis patients who need wide bore access, present for repeated cannulation, may not be able to lie supine, and may have underlying coagulopathy or platelet dysfunction10.

Ultrasound can also be used as an alternative to X-ray to check for malposition of CVCs & Peripherally Inserted Central Venous Catheter and to rule out presence of thrombi, prior to recannulation10.

**Ultrasound for arterial cannulation**

Arterial cannulae are inserted for blood pressure monitoring and blood gas sampling.

**usg-guided arterial cannulation**
(Website for this image-ispub.com)
Studies comparing the use of ultrasound versus blind technique for radial artery cannulation found that ultrasound guidance decreases the number of attempts, and improves the overall success rate of cannulation11,12

**Ultrasound guided regional anaesthesia**

The features of any imaging technique used for regional anaesthesia should include13:
• Good resolution
• Safety - for both patient and operator – minimal exposure to radiation
• Offer real time guidance
• Portability
• Should not require additional personnel to operate

Among currently available imaging techniques, ultrasound fulfills these criteria.

A safe and successful ultrasound-guided nerve block requires 1) appropriate imaging and detection of the nerve to be blocked 2) experience in needle advancement in real time, and 3) visualization of local anesthetic spread around the target nerve. Ultrasound imaging for upper limb blocks is rather easier than lower limb blocks whereas neuraxial blockade is most challenging. The brachial plexus and peripheral nerves in the upper limb are superficial structures (within 3–4 cm) even in obese individuals.

Probe position for the interscalene brachial plexus.

The needle (indicated by the white triangles) is seen transgressing the middle scalene muscle with the tip located within the neural sheath between C6 and C7. AS, anterior scalene muscle; MS, middle scalene muscle. (Images by—usg guidance in peripheral regional anesthesia-lipincott Williams)

In routine anaesthetic practice, ultrasound can be used for:

1. Peripheral nerve plexus blocks
2. Central neuraxial blocks in children and in difficult anatomical situations in adults
3. In procedures for chronic pain

Peripheral nerve blocks

A successful regional block requires optimum distribution of local anaesthetic around nerve and plexus structures.

Ultrasound imaging has the following advantages:

• Direct visualization of neural structures
• Direct visualization of related structures like blood vessels and tendons, which helps to identify nerves
• Guidance of the needle under real-time visualization
• Avoid complications like intravascular and intraneuronal injection
• Monitor the spread of local anaesthetic
• Allows repositioning of the needle after an initial injection to allow better delivery of local anaesthetic to areas that may not be completely blocked with a single dose
• Can be used in patients with poor twitch response to nerve stimulation

14,15,16,17
A number of clinical studies\textsuperscript{18} have examined block characteristics with ultrasound guidance at different anatomical locations. All studies found improved block characteristics, including reduced onset time and improved quality of block. The dose of local anaesthetic required was reduced\textsuperscript{19}. The incidence of paraesthesia was also decreased, which could minimize post-procedure neuropraxia. Complications like neurological damage and vessel puncture were avoided.

In fact, there is level Ib evidence (The hierarchy of medical evidence) to make a grade A (The hierarchy of design types with “A” representing randomized, controlled trials etc) recommendation that ultrasound guidance provides improvements in the onset and success of sensory block, a decrease in local anesthetic requirements, and decreased time to perform the lower extremity peripheral nerve blocks\textsuperscript{20}.

Central neuraxial blockade

Studies on the use of ultrasound for lumbar epidurals\textsuperscript{21} show good correlation between ultrasonographically measured data on the depth of the lumbar epidural space and direct measurement at the time of lumbar puncture. Studies indicate that ultrasonography should be used along loss of resistance techniques, to guide needle orientation, and to give an idea of the depth at which the ligamentum flavum should be encountered. Neuraxial imaging is technically challenging because the ultrasound beam do not penetrate bone to any great extent\textsuperscript{22}. The epidural space, dura, and the spinal cord are deep to the spine and hence are overshadowed by the shadows cast by the overlying bones. Beams can penetrate through the interlaminar space or the paramedian window in the adult lumbar space, but not in the thoracic level. Therefore, neuraxial images in adults are often of low resolution and more difficult to interpret. The spines of neonates and infants being not fully ossified allow such imaging. Ultrasound guidance is associated with significant reduction of the puncture attempts, reduction in the number of puncture levels, more precise application of the catheter, and improvement of analgesia quality and patient satisfaction. Ultrasound visibility has been shown to be higher in the paramedian as compared to the median plane. Ultrasound imaging has been shown to be superior to clinical palpation as a method of identifying lumbar intervertebral level\textsuperscript{22,23}

In one case series\textsuperscript{24}, ultrasound guidance was used to determine the least rotated vertebral body for epidural catheter insertion in patients undergoing scoliosis surgery. Ultrasound has also been used to identify landmarks prior to difficult lumbar subarachnoid puncture\textsuperscript{25,26}.
Ultrasound in paediatrics

Ultrasonography is particularly useful for neural blocks in children for the following reasons:

- Variability in anatomy according to age and constitution of the patient.
- Regional blocks are usually performed under anaesthesia or sedation - adverse effects may not be detected.
- Because of the superficial location of most neural structures in children, one can use higher frequency ultrasonic probes, with better resolution.
- Spinous interspaces and intervertebral foramina allow the ultrasonic beam to penetrate through, to visualize deeper structures.

Studies have shown that ultrasound provides information on the distance of skin-to-ligament flavum in neonates, infants and children. Hence, the risk of dural puncture is reduced and the spread of local anaesthetic can also be visualized.

Interventional Pain Management

The use of ultrasound has been shown to have 100% accuracy in locating the caudal space and guiding epidural needles for caudal injections for low back pain. Use of ultrasound for facet joint injections, lumbar sympathetic blocks, celiac plexus blocks, stellate ganglion blocks and identification of myofascial trigger points has also been described.

Ultrasound for trans-oesophageal echocardiography

TEE is used in anaesthesia to:
- Assess adequacy of repair and detect residual pathology or prosthetic valve dysfunction in patients undergoing surgery for valvular and congenital heart disease
- Diagnose ongoing ischemia by detecting fresh regional wall motion abnormalities in patients with ischemic heart disease

(The ME four-chamber image demonstrates the right atrium, right ventricle, left atrium, left ventricle, tricuspid valve, and mitral valve. Abbreviation: ME, midesophageal. - image by-prac usg in anesthesia for critical care and pain management)

- Assess left and right ventricular function, and volume status in patients with severe haemodynamic instability
- As a sensitive tool for early detection of pulmonary embolism, especially in patients undergoing neurosurgery in the sitting position
- Transesophageal stress echocardiography to detect coronary artery disease and viability.

Core Indications In Emergency medicine and Critical care

- Focused Assessment with Sonography in Trauma (FAST)
- Focused Aortic Scanning
- Focused Cardiac Scanning / Echo in Life Support
- Procedural Ultrasound
Pelvic (Early Pregnancy) Ultrasound
Detection of Pleural Disease
Shock Ultrasound

Other Indications for Use of Bedside Ultrasonography by the Intensivist
- Central line placement.
- Urinary bladder scan.
- Intra-aortic balloon counterpulsation.

Newer applications
Ultrasound has been used to visualize CSF leak in cases of post-dural puncture headache, and for the application of epidural blood patch under real time depiction\(^1\)\(^{21}\). Laryngeal ultrasound detects patients at risk of post-extubation stridor, by evaluating peri-cuff airflow\(^3\)\(^3\).

Ultrasound technology will continue to evolve, providing further improvements in portability, ubiquity, image processing, and display. Similar to the computer and telephone industry, ultrasound equipment will likely become smaller, highly mobile, potentially cordless, and available for use at the point of care anywhere at anytime.

To summarize
Advantages of Ultrasound include:-
- Increases success of nerve block
- Direct visualization of nerve & needle
- Avoid nerve damage
- Low volume of local anesthetic needed for nerve block
- Visualize the spread of local anaesthetic
- Soft tissue identification (including nerves)
- Blood vessels can be identified
- No exposure to ionizing radiation
- More readily available due to portability (Can be moved to patient exam room)
- Potentially cheaper (compared to CT, fluoroscopy), consider maintenance as well as initial costs
- Real-time injection
- Provides detailed knowledge of the anatomy
- Shows exact depth and angle for needle insertion
- Reduces the number of punctures
- Reduces the risk of complications
- Increases accuracy and success rate

References:
1. Ultrasound in anaesthesia P N Jain, Priya Ranganathan Indian Journal of Anaesthesia 2007;51 (3) : 176-183


20. Ultrasound and Review of Evidence for Lower Extremity Peripheral Nerve Blocks -Francis V. Salinas, MD, Regional Anesthesia and Pain Medicine & Volume 35, Number 2, Supplement 1, March-April 2010


Corrosive injury of upper G.I. Tract
M.K. Panigrahi¹, H.S. Das²

Introduction:
Corrosive injury to the upper gastrointestinal tract (UGIT) is an agonizing experience for both the patient and the treating physician. In the developed countries, corrosive injury to the gastrointestinal system as a consequence of either accidental ingestion or as a result of self-harm has become less. This could partly be attributed to the tighter legislation imposed by the government on detergents and other corrosive products and general public awareness. Though formulations of household cleansing agents have become safer in the recent times, corrosive injury still remains a common clinical problem in many countries, particularly India (1,2,3). While lye is the most frequently ingested caustic in the west (4), acid ingestion is a commoner cause of UGIT injury in India (1,2,3). Children account for more than 80% of accidental corrosive ingestion but ingestion in adult is more often of Suicidal intent and therefore tends to be more serious (5). The mortality rate is between 10% to 20% and rises to 78% in cases of attempted suicide (6).

Pathophysiology:
Corrosives can be acidic or alkaline in nature. Corrosive agents commonly ingested include strong alkalis like sodium hydroxide and potassium hydroxide and strong acids like sulfuric acid and hydrochloric acid. Most common corrosive agents used in our setup are dye used by weavers, battery acids, vinegar, toilet cleaner etc. The extent of injury depends on the nature of corrosive agent consumed (acid or alkali), its physical state, concentration and amount of the agent consumed, and duration of contact with the mucosa.

Alkaline substances produce more severe tissue injury by causing liquefactive necrosis which allows deeper penetration of the corrosive agent and further injury (7). Acids, on the other hand, produce coagulative necrosis resulting in formation of an eschar which protects against further damage (7). It has been generally believed that the acids predominantly injure the stomach and spare the esophagus because of rapid transit through the esophagus, its alkaline environment and relative resistance of esophageal mucosa to acids (1,5). However, several workers have reported esophageal injury after acid ingestion (2,3,5). Zargar et al. (3) reported that 88% of patients with acid ingestion had esophageal injury and 38% developed esophageal strictures; these figures are comparable to those observed with alkalis (8). Similarly gastric injury believed to be less common with alkalis, as these may be partly neutralized by acidic contents of the stomach. However, in one study, 93% of patients with alkali ingestion had evidence of gastric injury (8). For alkali, the critical pH is 12.5, though the titrable base content is also important, Lye, which has a pH of 12.5, is therefore a strong corrosive agent (9).

Concentration of the corrosive is also important. In animal studies, Krey (10) demonstrated that the depth of injury increased as the concentration of NaOH applied to an isolated esophagus was increased from 3.85% to 22.5%. The weakest solution caused damage only to the mucosa and submucosa while strong solutions caused transmural injuries and periesophageal reaction (10). Duration of mucosal exposure to the corrosive agent is another important determinant. Even weak caustics may produce significant injury if allowed to remain in contact with the mucosa for a long period of time (8).

Clinical Presentation:
Clinical features are variable and depend largely on the physical state, concentration and amount of the caustic ingested, it may be emphasized here that presence or absence of oropharyngeal involvement does not accurately predict the extent of esophageal or gastric injury (11).
Typically, the clinical course is triphasic, i.e. acute, latent and retractive phases (7). In the **acute phase**, the patient complains of pain in the oral cavity, retrosternal area or abdomen. Odynophagia and dysphagia are com-mon and gradually decrease over the next 3-5 days with decrease in mucosal edema and spasm. Aspiration of caustic material may lead to hoarseness, stridor and dyspnea necessitating urgent tracheostomy. Hematemesis may occur but is usually mild and self-limiting. Severe hematemesis occurring a few days after caustic ingestion suggests development of aortoesophageal fistula (12). Full thickness necrosis can produce perforation leading to mediastinitis, pleural effusion, empyema, or peritonitis (12).

Septicemic shock is a common cause of death. In the **latent phase**, there is transient decrease in symptoms like dysphagia, giving a false sense of improvement. The **retractive phase** is characterized by progressive fibrosis which gives rise to symptoms of esophageal or gastric outlet obstruction. Obstructive symptoms usually appear within 2-3 weeks of corrosive ingestion but may some-times be delayed for many months. About 10%-33% of patients with documented esophageal injury develop clinically apparent esophageal strictures (13). Strictures which appear- early, i.e. within 3-8 weeks of caustic injury, progress rapidly while those appearing more than 8 weeks after the injury have a slower progression (7).

**Diagnosis:**

The diagnosis is easy in most cases since history of corrosive ingestion is available. At times, however, for fear of medicolegal action, accurate history may not be forthcoming. Besides examination of mouth and pharynx which may provide important clues, endoscopic and radiologic examination of the UGI tract not only helps in making a diagnosis but also in assessing the extent and severity of injury and presence of complications, which is not possible on the basis of symptoms alone (11).

**Upper Gastrointestinal Endoscopy:**

Only 20%-40% of patients with caustic ingestion have identifiable esophageal injury and this may present without any oral involvement (14). Thus, endoscopy performed soon after corrosive ingestion is an excellent tool for assessment and staging of injury and tailoring the treatment accordingly. Patients with minimal or no injury to the esophagus and stomach can be discharged safely while those with severe injury need hospitalization. Endoscopic examination with a flexible pediatric endoscope should be done after hemodynamic stability is achieved. At times, edema and erythema may develop 12-24 hours after subtle injury and may be missed at endoscopy done at an earlier time (12). It is wise to withhold endoscopy in the subacute phase (5-15 days after caustic ingestion) because of higher chances of perforation. Esophageal burns due to corrosive ingestion have been divided into three grades (15). In first degree burns, there is mucosa erythema and edema; subsequently, the mucosa sloughs without any scar or stricture formation. Second degree burns include ulceration with necrotic tissue and white plaques that are less than circumferen-tial, while the third degree burns include circumferential involvement of the esophageal wall. A majority of strictures develop following severe and circumferential involvement (16). Zargar et al (17) have modified the classification of esophageal burns to help in better prog-nostic and therapeutic guidance. They divided Grade 2 injuries into Grade 2a (friability, hemorrhages, erosions, blisters, exudates and superficial ulcers) and Grade 2b (Grade 2a plus deep discrete or circumferential ulcers). Grade 3 injuries were classified into Grade 3a (Grade 2 plus scattered areas of necrosis) and Grade 3b (Grade 2 plus extensive necrosis). All patients with Grades 1 and 2a injuries recovered without sequelae while a majority of patients with Grade 2b (71%) and all survivors with Grade 3 injuries developed strictures. Most deaths also occurred in association with Grade 3 injuries.

**Radiological Evaluation:**

In the acute phase of corrosive injury, plain skigrams of the chest and abdomen may show evidence of esophageal or gastric perforation. Contrast studies with water soluble agents performed within two days may not give accurate information about esophageal and gastric involvement. In fact, information obtained may be misleading because of atonia or spasm. Later changes include blurring of mucosa, intramural pseudodiverticulosis, deep linear Ulcers with intramural dissection, retention and pocketing of contrast and intramural gas collection. The stomach
may show evidence of ulceration, bullae and pseudopolyps (18). Contrast studies are very useful for early detection of strictures. After about two weeks, signs of acute injury subside and barium examination may show development of esophageal or gastric strictures.

Complications:

Early complications

These include perforation, UGI bleeding, infection, septicemia, shock and death. Airway obstruction may occur within hours due to injury to the epiglottis or larynx. Aspiration may be followed by severe pneumonitis with opportunistic infections and adult respiratory distress syndrome. Perforation usually occurs a few days after ingestion because of progressive necrosis, and commonly present as slowly progressing mediastinitis (12). Early perforation (within hours) occurs after ingestion of large amount of a strong corrosive agent. Tracheoesophageal or bronchoesophageal fistulae may form. Shock is due to hypovolemia or sepsis. Most series report early mortality in the range of 1% to 4% (14). Mortality is generally lower in children.

Late Complications

Esophageal stricture: Stricture formation depends upon the depth of injury. Almost all survivors of Grade 3 injury will develop stricture while those with Grade 1 injury recover without sequelae (16,17). Development of a dense fibrous stricture lags about 4-6 weeks though dysphagia may appear earlier. Strictures may be long, tortuous, multiple and very tight. Barium contrast studies are the best method to demonstrate the presence, number, length and location of the stricture. These may also reveal associated gastric narrowing. A barium study should be obtained about 3 weeks after injury irrespective of the presence or absence of symptoms, and repeated as required. Eighty percent of strictures become apparent between 2 to 8 weeks after injury though some patients become symptomatic several months after initial injury (7).

Gastric cicatrization: Corrosive injury most often causes pyloric or antral stenosis, though other deformities like shortening and irregularity of lesser curvature and hour glass deformity of the stomach may also occur. Gastric outlet obstruction due to antral or pyloric stenosis is less common as compared to esophageal stricture. Symptoms of gastric obstruction usually appear within 5-6 weeks of injury but in some cases may at times become apparent after a few years. They may at times become apparent after esophageal stricture is dilated, enabling the patient to eat.

Malignant potential of corrosive:

Several reports and small series suggest an increased risk of squamous cell carcinoma of the esophagus following caustic injury (19). The risk is estimated to be about 1000-3000 fold higher as compared to the general population (19). History of corrosive ingestion is present in 1.4% to 26% of patients with esophageal carcinoma (19,20). These patients develop carcinoma a decade earlier than other patients with esophageal cancer. The average time interval between corrosive intake and development of carcinoma is about 40 years. The prognosis after resection is good with reports of 75% five-year survival. The factors which may account for such good prognosis include younger age of the patient, early diagnosis and limitation to the spread of carcinoma by the surrounding avascular scar tissue (20).

Unlike esophageal carcinoma there is no good evidence to support an increased risk of gastric cancer after caustic injury. There are few case reports of gastric cancer and squamous metaplasia in persons with history of caustic ingestion, but the etiological relationship is not well established (21).

Treatment:

Emergency Management

In the absence of perforation, treatment is largely symptomatic and aimed at prevention of early and late complications. Assessment of airway status is a very important part of the emergency management, since laryngeal injury with respiratory difficulty; proper airway should be immediately established by endotracheal intubation or tracheostomy.

Unlike many other poisonings, emesis should not be induced as it will again expose the esophagus, pharynx, buccal cavity and larynx to the corrosive material. Similar-ly, gastric lavage is also not of value because of the extreme rapidity with which tissue necrosis occurs after contact with the caustic substances. Further, gastric lavage may add to the
injury by producing heat and gasses as a result of neutralization of caustic materials. Use of nasogastric tube is not widely advocated but can be helpful in aspiration of gastric contents and determination of pH \((15)\). Intravenous fluids are given to correct hypovolemia, maintain nutrition and any acid-base imbalance. Broad-spectrum antibiotic may be needed to cover superimposed infection. Early surgery is needed for perforation of esophagus or stomach following ingestion of corrosives. Some workers advocate immediate surgical intervention if endoscopic finding suggest full thickness necrosis or gastric pH is alkaline \((15)\). Surgical approach usually consists of aggressive resection of necrotic tissue and tissue with doubtful viability, appropriate diversion and bypass, adequate drainage \((22)\).

**Prevention of Stricture**

Though many agents have shown promising results in animal studies human trials are lacking. Some of these agents are Heparin, collagenases, aminopropionitrile, N acetylcysteine, penicillamine and colchicines, Trapidil, Ebselen, hyperbaric oxygen therapy, Ketotifen, Resveratrol, Trimetazidine, 3 Amino benzamide. Various modalities used for prevention of stricture formation include steroids, antibiotics, esophageal stents, prophylactic bougienage and antifibrotic drugs.

Steroids: Although corticosteroids have been used by many workers to prevent the formation of corrosive esophageal strictures (CES) after caustic injury, their exact role remains uncertain. In a prospective controlled trial that included 60 children with acid or lye injuries, steroids (2 to 2.5 mg/kg/day of prednisolone for 3 weeks and then tapered over the next 2 – 3 weeks) proved to be of no value in preventing stricture formation \((16)\). It is possible that results of steroid treatment may be different in adults, or with longer duration of use. Further as the total number of children treated with steroid was relatively small analysis of their efficacy in different grades injuries was not possible. In a review of 13 publications of 361 patients, strictures were seen in 19% of those treated with steroids compared with 41% of those not treated with steroids \((23)\). However it is clear that steroid are not needed in grade 1 injury and are not useful in grade 3 injuries. Their efficacy in grade 2 injuries is doubtful and side effects significant, so use of steroids for prophylaxis against CES remain controversial.

Antibiotics: Antibiotics have not been shown to have any attenuating effect on scar formation either in animal or human studies. These are given only if evidence of infection is present or as an adjunct to steroid therapy \((12)\). However in one study, the combination therapy of steroid and antibiotics in Grade 2 and Grade 3 esophagitis decreased the frequency of stricture formation \((24)\).

Nutrition: Since oral feeding may cause further damage to the esophagus or stomach, intravenous hyperalimentation is recommended in the acute phase. Further, these patients not only suffer from dysphagia but also have high nutritional demands due to catabolic stress. Di Costanzo et al \((25)\) suggested that total parenteral nutrition (TPN) (40-50 Kcal/Kg body weight) may help in preventing stricture formation. None of their patients with Grade 2 and only 36% of those with Grade 3 injuries showed stricture formation receiving TPN.

Placement of Stents: A wide bore silicone tube stent placed across the injured area may theoretically prevent tissue contraction and formation of CES. Prophylactic placement of stents has been found useful for prevention of CES in children also \((26)\).

Prophylactic bougienage: The rationale for this is similar to that for stents placement. A large study showed no benefit from prophylactic bougienage \((27)\). On the contrary, it may cause further trauma.

In the absence of any definitive therapy to prevent stricture formation, the approach at present is essentially one of vigilant anticipation to detect stricture formation early.

**Summary :**

Corrosive injury to the UGI tract is a common problem and has a wide spectrum of presentation. Depth of the injury is most important factor which determines the outcome. Endoscopy done soon after corrosive ingestion is safe and is very helpful in assessing, the extent and severity of injury and in planning proper management of these patients. At present no therapy has been proven to be effective for prevention of stricture formation. Endoscopic dilatation seems to be the treatment of choice for management.
of most esophageal stricture with very good short and long term results. Removable plastic stents are also recently in use for those who require very frequent dilatation. Surgery should be considered only in few selected cases.

References:

Micro RNAs – an understanding
Srikrushna Mahapatra

Introduction:
Research in the last decade has revealed a new world of RNAs which subvert the formula of central dogma of molecular biology. The central dogma states that DNA produces RNA by a process of transcription and protein is synthesized from the information present in RNA by a process of translation. The newly recognized small RNAs do not code for proteins, but instead exercise control over the RNAs which do protein synthesis. These small RNAs are also called noncoding RNA (ncRNA). ncRNAs include rRNA, tRNA, small nuclear RNA, small nucleolar RNA, miRNA, and some lesser known RNAs like vault RNAs, Y RNAs, rasi RNA (repeat associated small interfering RNA), and piwi interacting RNA, some suggest rasiRNA to be the same as piwi RNA. Although many classes of small RNAs have emerged, various aspects of their origin, structure associated effector protein and biological roles have led to the general recognition of three major categories:

1. Short interfering RNA (siRNA)
2. micro RNA (miRNA)

It is viewed that miRNAs are endogenous and purposefully expressed products of an organism’s own genome, whereas siRNAs were thought to be primarily exogenous in origin, derived from virus or transposons as a mechanism of genome defense. Further, miRNAs appeared to be processed from stem loop precursors with incomplete double stranded character whereas siRNAs were found to be excised from long, fully complementary double stranded RNAs. One of the key differences between miRNA and most siRNAs is the precision of their ends. The other differences between the two commonly reckoned are i) miRNA with less stringent binding with target mRNA inhibits inhibition of translation and with complete complementarity digests target mRNA while siRNA exhibits stringent complementarity with target mRNA and only digests it. ii) usually miRNA is endogenous while siRNA is exogenous in origin although presently endo siRNA in yeasts are recognized. miRNAs have a highly exacting end whereas siRNAs tend to be more heterogenous in end composition. However, despite these differences, they exhibit a size similarity and sequence specific inhibitory effect which suggests their biogenesis and mechanism of action. These small RNAs effect gene silencing by a process which is called RNA interference. RNA interference (RNAi) is an evolutionarily conserved, sequence specific gene silencing mechanism that is induced by exposure to double strand RNA.

Germ stem cells undergo asymmetric divisions. Asymmetric division of these cells is controlled by a protein called PIWI (P-element induced wimpy testis) and this protein is only expressed in gonadal cells. This protein belongs to the Argonaute family of proteins which take part in gene silencing. A subset of ncRNAs associate with PIWI and are called piRNAs which maintain the integrity of the germline stem cell genome. The piRNAs are longer than siRNA/miRNA i.e. 26-32 nucleotides in length and they can be sense or antisense to the transcript they are targeting, while siRNA and miRNA are always antisense to their targets.

Among the small RNAs, miRNAs are the most phylogenetically conserved and function post-transcriptionally to regulate many physiological processes including embryonic development.

It has been known that only 2% of genome (DNA) codes for proteins and the rest is called junk...
DNA. This junk DNA was thought to be evolutions’ debris with no function. With the door of knowledge opening for non-coding RNAs, it is now realized that portion of this junk DNA is highly relevant in the regulation of gene expression. It is predicted that miRNAs account for 1-5% of the human genome and regulate at least 30% of protein coding genes. Till July 2010, 940 distinct miRNA genes have been identified in human genome. (5)

MicroRNA biogenesis:

The first miRNA lin-4 (abnormal cell LINEage) and its target mRNA lin-14 were discovered by Lee, Feinbaum and Ambros in Caenorhabditis Elegans in 1993. (6) They discovered that lin-4 did not code for a protein but instead produced a pair of short RNA transcripts which regulate the timing of larval development of C. Elegans by translational repression of lin-14 (lin-14 codes for a nuclear protein). Seven years later the second miRNA, let-7 (LEThal) was discovered. (7) The let-7 miRNA similar to lin-4 also regulated developmental timings of larval stages in C. Elegans. The era of miRNA research had begun! miRNAs are non-coding single-stranded RNAs (ssRNA) of usually ~22 nucleotides in length in their mature forms and are encoded by their own set of genes. (8) Genes for miRNA are an integral part of the cell genetic programme and many of them are evolutionarily conserved. They can be transcribed in clusters as polycistronic primary transcripts, or could be present at intergenic regions or could be present in exonic/intronic regions of protein coding and non-coding transcription units. (9) Generally, miRNAs are transcribed by RNA Polymerase II (which also transcribes mRNA), as primary transcript which may be several kilo bases long that are called pri-miRNA and bear hairpin structures. Pri-miRNA receive a 5’ cap and a poly A tail similar to mRNA. However, recent studies have shown that RNA polymerase III can also transcribe miRNA from dense human clusters interspersed among repetitive Alu elements. (10)

The processing of pri-miRNA occurs in the nucleus through the activity of a double stranded endonuclease RNase III called Drosha. Drosha associates with a double stranded RNA binding protein called DGCR 8 (Di George syndrome Critical Region gene 8) and several other proteins to form Drosha microprocessor complex. Drosha microprocessor complex cleaves the pri-miRNA near a hairpin base and release a ~70-90 nt hairpin shaped stem loop structure called pre-miRNA. (11) An alternative pathway also has been reported in mammals; this pathway generates new regulatory RNAs from intronic pri-miRNA precursors called mirtrons, using splicing mechanisms and the lariat debranching enzyme to bypass Drosha cleavage. (12) The subsequent export of pre-miRNAs into the cytoplasm is mediated by Exportin-5. Exportin -5 is a RAN-GTP dependent nuclear transport receptor. (9)

Pre-miRNA is processed in the cytoplasm by a double stranded RNase III enzyme called Dicer into ~22 nt. miRNA:miRNA duplex with 2 nt. overhanging at 3’ end. One strand of the mature miRNA is called the guide strand and the other strand is called passenger strand. Dicer is highly conserved throughout evolution and present in nearly all eukaryotic organisms. Dicer associates with TAR RNA binding protein (TRBP) and protein kinase R activating protein (PACT). These associations enhance Dicer stability and processing activity. (13) Some organisms contain Dicer isotypes that have distinct role e.g. in D. Melanogaster Dicer I is required for miRNA biogenesis and Dicer II functions in siRNA production. (14) Dicer is a multi domain protein located in the cytoplasm or the rough endoplasmic reticulum. It has a N-terminal ATPase/Helicase domain, DUF283 (domain of unknown function), PAZ (Piwi/Argonaute/Zwilli) domain, two RNase III nuclease domain (RNase IIIa & RNase IIIb) located at C-terminal end followed by a double strand RNA binding domain (ds-RBD). The PAZ domain, RNase III nuclease domain and ds-RBD are involved in binding and cleavage of dsRNA. (15)

Following Dicer cleavage the ~22 nt RNA duplex is loaded to an argonaute (Ago) protein complex so as to generate the effector complex-RISC (RNA induced silencing complex). Dicer, TRBP, and/or PACT and Ago proteins contribute to RISC assembly by forming a RISC loading complex called RLC in humans. It is proposed that the stable end of RNA duplex is bound to TRBP in RLC and the other end interacts with the Ago proteins. (16) The human genome contains eight Ago family proteins: Ago 1-4 and Piwi 1-4. Piwi 1-4 are needed for piRNA activity which occurs only in...
germ cells. While all of the Ago proteins have the ability to interact with miRNA and siRNA, Ago 2 is the only one with RNA cleavage (slicer) activity and is thought to play a crucial role in miRNA-mediated RNA silencing. (17) Removal of passenger strand of RNA from the RNA duplex is called slicer activity which is present in Ago-2 and absent in Ago 1,3 and 4 proteins in humans. An RNA helicase activity is also thought to mediate the unwinding and removal of the unselected strand of the miRNA duplex. (14)

In humans, there are eight classes of RISC complexes that are based on protein composition centered around Ago proteins. RISCs that load miRNA are designated microRNA containing ribonucleoprotein complex (miRNP). The mechanism of human miRNA RISC assembly is unclear and hypotheses are based on Drosophila model. Recent data suggests that RNA helicase A (RHA) also referred as DHX 9 is responsible for duplex RNA unwinding that is associated with RISC activation in humans. However, the process of passenger RNA strand cleavage is still unclear; it could be due to Ago 2 protein/Dicer or an unidentified cytoplasmic helicase. (18)
MicroRNA maturation and function:

The miRNA gene is transcribed to generate a primary microRNA (pri-miRNA) precursor molecule that undergoes nuclear cleavage to form a precursor microRNA (pre-miRNA). The pre-miRNA is cleaved in the cytoplasm to create a microRNA duplex (miRNA:miRNA*, passenger strand designated with asterisk) containing the mature miRNA. The duplex unwinds and the mature miRNA assembles into RISC. The miRNA base-pairs with target mRNA to direct gene silencing via mRNA cleavage or translation repression based on the level of complementarity between the miRNA and the mRNA target.

Nuclear component of microRNA biogenesis. (5)

Intergenic miRNAs are transcribed by RNA polymerase II or III generating a primary miRNA (pri-miRNA) molecule, which is processed into a precursor miRNA (pre-miRNA) by the microprocessor complex comprised of DGCR8 and Drosha. Pre-miRNAs are exported to the cytoplasm in a nucleocytoplasmic transporter containing Exportin 5 and Ran-GTP.

MiRNA within introns are transcribed as part of precursor mRNA (pre-mRNA) by RNA polymerase II. The miRNA sequence is excised from the pre-mRNA by spliceosomal components or the microprocessor to liberate a mirtron or a pre-miRNA that is exported. Alternatively, a primary miRNA (pri-miRNA) is released which undergoes microprocessor cleavage to generate pre-miRNA.
Cytoplasmic component of microRNA biogenesis: (5):

Pre-miRNA is cleaved by Dicer to generate miRNA duplex or by Ago2 to generate an Ago2-cleaved precursor miRNA“ (ac-pre-miRNA) that subsequently acts as a substrate for Dicer. The asterisk (*) near a protein symbolizes it is responsible for the cleavage event. The miRNA duplex liberates the mature miRNA to assemble into RISC loading complex comprised of Ago2, TRBP, PACT and Dicer. The mechanism of mature miRNA release is unclear. Possible mechanisms involving RNA Helicase A (RHA), Dicer cleavage, Ago2 cleavage and uncharacterized proteins have been illustrated.

Mechanism of gene silencing:

Activated RISC (this carries ssRNA) binds to target mRNA through Watson-Crick base pairing between guide strand and the 3’ UTR (untranslated region) of the target. Residues 2-8 at the 5’ end of the guide strand of miRNA is called ‘seed’ which is mainly responsible for target recognition. In animals, usually there is 100% base pairing in the seed but not in the whole miRNA—this results in imperfect RNA hybrid with characteristic bulges at sites where there is no complementarity. (17) It is widely accepted that miRNA bind to their target mRNA and negatively regulate their expression. A single miRNA can regulate several mRNA targets and conversely many miRNAs cooperatively can regulate one mRNA. (19)

There are two distinct silencing mechanisms by which miRNA down regulate target mRNA: a) Slicing, b) inhibition of translation.

a) Slicer mechanism:

Slicer activity refers to endonuclease cleavage of target mRNA by Ago2 which requires extensive base pairing between miRNA and mRNA. Cleavage products are degraded by bulk cellular mRNA degradation processes beginning with removal of poly A tail (deadenylation). Subsequently the mRNA is
degraded via exosome which is a multiprotein complex with 3'-5' exonuclease activity. Alternatively the 5' cap can also be removed first by enzyme DCP(DeCapping Protein) 1 and DCP 2, and then by 5'-3' degradation with exoribonuclease Xrn 1 p.(20)

By a slicer independent pathway, miRNA may also sequester the target mRNA to discrete cytoplasmic foci called P bodies(Processing bodies). P bodies are rich in GW 182, decapping enzymes, deadenylation enzymes, RNA helicases which help in mRNA decay. But there has been also controversies on the role of P bodies in miRNA mediated gene silencing.(21)

b) Inhibition of translation:

Inhibition of translation is effected through three mechanisms.(20)

1. miRNA inhibit initiation of translation at the 7' methyl GTP cap recognition step by displacing eIF 4E from the cap structure. This inhibits the formation of the preinitiation complex.

2. Ago 2 recruits eIF 6, a factor which is required for association of the large and small ribosomal units. Thus 80 S initiation complex formation during translation process is inhibited.

3. During translation, eIF 4E binds at the cap of mRNA at 5' end and cytoplasmic poly A binding protein(PABPC-1) binds to poly A tail at the 3' end. eIF 4 G connects to both eIF 4E and PABPC-1 giving a closed loop structure to mRNA that greatly facilitates translation. Ago 2 protein prevents this closed loop structure formation by an ill defined mechanism and also by a process of deadenylation and thus inhibit translation.

miRNA in development and disease:

MicroRNAs (miRNAs) regulate gene expression and play an important role in various cellular processes, including cell growth, differentiation, proliferation, and apoptosis. miRNA expressions occur in tissue restricted profiles and differential timings during development. Both patterns suggest that miRNA contribute to morphological development and organogenesis. Conditional depletion of Dicer in mice has shown that general loss of miRNA functions affect T cell development, limb formation and organ maturation. It has also been observed that Dicer deficient embryonic stem cells are defective in differentiation and do not form the three germ layers.

The miR 375 miRNA is specifically expressed in murine pancreatic islet cells, where it regulates myotrophin gene and thereby glucose stimulated insulin exocytosis. Muscle specific miR-1 regulates the balance between differentiation and proliferation of cardiomyocytes during heart development in mice. Over expression of miR-1 leads to proliferation defect and failure of ventricular myocytes to expand.(22)

In adult mammalian brains miR124 miRNA and miR128 miRNA are expressed at the highest levels in neurons, while miR26 miRNA and miR29 miRNA are more strongly expressed in astrocytes. miR-133b miRNA is expressed in midbrain dopaminergic neurons where it regulates the maturation and function of these neurons. It has been reported that miR-133b miRNA is deficient in midbrain tissue from patients with Parkinson's disease.(23)

The exact mechanism as to how miRNA promote human carcinogenesis is not known. However, studies indicate that some miRNA act as tumor suppressors and others act as oncogenes. Reduced expression of the former and excess expression of the latter could cause tumorigenesis. It has been demonstrated that more than 50% of miRNA genes are located at fragile sites and cancer associated genomic regions suggesting that miRNA might play a role in pathogenesis of human cancers.(24)

The miRNAs that are encoded let-7 family were the first group of oncomirs(oncomir-miRNA that are associated with cancer) shown to regulate expression of an oncogene specifically the Ras gene. Ras proteins are membrane associated GTPase signaling proteins that regulate cellular growth and differentiation. Excess Ras expression results in cellular transformation and cancer. let-7 controls Ras expression by 3' UTR mediated repression in human cells. It has been shown that let-7 expression is decreased and Ras expression is increased in squamous cell carcinoma of lungs.(25)

HMG 2A (High motility group AT-hook 2) is a non histone transcription factor which alters DNA confirmation to direct transcriptional activation of a variety of genes that influence cell growth. HMG 2A is undetectable in normal tissue, but highly expressed in embryonic tissue, lung cancer and uterine
leiomyomas. let-7 regulate HMG 2A by destabilizing its mRNA through 3’ UTR binding. Loss of let-7 control on HMG 2A promotes cell growth and proliferation. (26) It has also been proposed that let-7 inhibit numerous cell cycle regulators such as c-myc, CDK-6, cyclin D2 which suggests that let-7s play a much larger role in controlling cell proliferation and differentiation. (27)

The miR15/16 family of miRNA has four members that are putative tumour suppressors. All four members share a 9 nucleotide seed region that targets the 3’ UTR of the antiapoptotic protein Bel 2 for post transcriptional repression. The oncogenic Bel 2 protein is commonly overexpressed in hematopoetic malignancies and promote cell survival by evading apoptosis. Also in B cell Chronic lymphocytic leukemia deletion of miR 15/16-1 miRNA cluster is observed. (28)

miR 21 miRNA down regulates four tumour suppressor genes: mapsin, programmed cell death 4 (PDCD 4), tropomyosin 1 (TPM 1), and phosphatase and tensin homolog (PTEN). It is suggested that miR 21 binds to the 3’ UTR of the gene transcript and prevent their translation. miR 21 repression of these genes promotes cell transformation, tumor growth invasion and metastasis; thus miR 21 behaves as an oncogenic miRNA. (29)

The miR17-92 miRNA cluster is very complex. In humans it produces six mature miRNAs (miR17, miR18-a, miR19-a, miR19-6-1, miR20a, and miR92-1) from a polycistronic loci in chromosome 13. The miR17-92 is mostly thought of as an oncogene. High levels of miR 17-92 are observed in a variety of lymphomas, lung cancer, colon cancer, cancer of pancreas and prostate cancer. (30) However, the miR17-92 functional network is very complex and under intense research.

An association between higher miR-211 expression and most advanced nodal metastasis, vascular invasion, and poor prognosis has been demonstrated in OSCC. Furthermore, it has been seen that an expression ratio of upregulated miR-221 and downregulated miR-375 showed a high sensitivity and specificity for disease prediction, thus miR-221 and miR-375 should be evaluated as diagnostic biomarkers for prevention and treatment strategies for HNSCC. (31) Overexpression of miR-184 was found in tongue squamous cell carcinoma tissues and it has been detected that plasma miR-184 levels were significantly higher in tongue squamous cell carcinoma patients when compared with normal individuals, and the levels appeared to be reduced after surgical removal of the primary tumors. (31)

MiRNA regulation has also been implicated in virus-induced diseases. It is stated that cellular miRNA expression may confer host immunity against viral infections; and also, viruses may have evolved to utilize miRNA machinery for their replication advantage. The example of the former came from the study of retroviruses primate foamy virus (PFV) in the human embryonic kidney cell line 293T, which showed that human miR-32 inhibits PFV replication by impairing the translation of viral mRNAs bearing target sequences. (32)

Modified anti-miRNA oligonucleotides (AMOs) or Antagomirs are chemically engineered oligonucleotides which inhibit mRNA target binding through competitive miRNA binding. These are therapeutic trial agents for treatment of human disease based on the principle of antagonizing miRNA activity. Most informations on miRNA in humans have evolved using bioinformatic systems and computational analysis; all these require refinement and great accuracy. miRNA can have multiple targets which makes therapeutic use of Antagomirs very difficult and a full understanding of the functional mechanisms miRNAs are required to design appropriate antagonirs. (33)

Conclusion:

RNA interference due to siRNA has been studied in great detail because of the relative simplicity and reproducibility of the procedure and its potential therapeutic uses are under intense research. siRNA can be synthetically produced against target mRNA. However therapeutic uses of miRNA poses great challenge. The growth of research in the field of miRNA has been exponential in the last decade. Developments in Bioinformatics, microarray throughput computational analysis has greatly helped in the field of research. The miRNA network is extremely complex and much more knowledge is required to clarify many ambiguous informations also the roles of various miRNAs in human physiology. An advantage of using miRNAs for therapy is that they...
offer an alternative for targeting multiple gene networks controlled by a single miRNA. For the same reason, the use of miRNAs as therapeutic agents must be carefully designed to avoid unwanted off-target effects. Through miRNA therapy, treatment of cancer can be effected by either decreasing the activity of oncomirs or restoring the levels of miRNAs acting as tumor suppressors. The most fundamental challenge is identification of miRNA target recognition, as this information is necessary to understand which mRNA they regulate. The field of miRNA has a great potential to help understand development, differentiation of organs and development of miRNA based therapeutics.

The article is written for the educational benefit of UG, PG students and faculty not involved in pure basic sciences studies after a web search of available articles published in last 10 years.

Reference:


State executives/Branch secretary/presidents are requested to send short announcements (if any) to be published in next issue of OMJ to reach Editor/State HQ Office Before end of June, 2013.
An unusual complication encountered in a spiral embedded tube.

A.Kumar¹, S. Nanda¹, H. Dalai²

Abstract:
Spiral embedded tubes are ideal choice for endotracheal intubation in head and neck surgeries. Here a case is discussed presenting with somewhat relatively uncommon complication.

Key words:
Spiral embedded tube, Balloon/cuff malfunction.

Introduction:
A secure airway is always of paramount importance to an anaesthesiologist. It is of more significance in head and neck surgeries wherein easy and immediate access to the airway is not obtained. Spiral embedded tubes by its design resist bending, kinking and compression; hence advocated in such situations. However, respiratory obstruction upon using these tubes has been reported. Here a case is discussed where difficulty to ventilate was encountered with the use of a spiral embedded tube.

Case report:
A 35 year old female patient weighing 58 kg having a left sided goiter of size 10x8x8 cms was posted for hemi thyroidectomy. She was a known hypertensive being treated with amlodipine 5mg. On clinical examination her pulse was 82/min, regular, B.P 130/80, trachea was shifted to right, chest was clinically clear and no cardiac abnormality were detected. X ray neck revealed tracheal deviation to right, but no compression. Her routine investigation findings were within normal limits. FNAC suggested nodular goiter. General anesthesia with naso-tracheal intubation was planned and she was advised to continue with the anti hypertensive medication and was kept on overnight fasting.

On the day of surgery her pre operative pulse was 86/min, BP-130/90 mm Hg. After securing an IV line and with monitors (ECG, NIBP, SpO2) attached she was premedicated with inj. Glycopyrrolate 0.2mg I.V, Inj midazolam 1mg I.V, inj butorphanol 1mg IV. Preoxygenation with 100% oxygen for five minutes was followed by inj. vecuronium 6mg and inj. Propofol, 100mg. Nasotracheal intubation was performed under direct laryngoscopy with a well lubricated 34f latex flexo-metallic tube in a single attempt, position of the tube was confirmed and E.T. tube was secured, connected to Bain’s coaxial circuit. Cuff was inflated with 7ml of air, anesthesia was maintained with N2O:O2-60:40, with 0.5% Halothane. She was ventilated manually, muscle relaxation being provided through intermittent doses of inj. vecuronium. E.C.G lead 2, Pulse, Blood pressure, SpO2, was monitored continuously.

Midway between the surgery patient’s oxygen saturation suddenly started to fall with a resistance to bagging and no expansion of chest. Immediately she was put on 100% oxygen, SpO2 probe was checked. On auscultation there was no air entry on ventilation. Direct laryngoscopy revealed tube was inside trachea. No kinking of tube or circuit was detected. Attempts for suction of the lumen of the E.T. tube failed as the catheter could not be negotiated adequately through the tube. Patient’s oxygen saturation and pulse were gradually decreasing so it was decided to remove the tube and re-intubate. Unfortunately the cuff of the E.T. tube could not be deflated completely. So it was removed with a partially inflated cuff. PVC cuffed ETT (7.5mm) was placed orally under direct laryngoscopy without any difficulty. On ventilation there was adequate chest expansion with good air entry to all parts on auscultation. Patient’s pulse rate, oxygen saturation improved, N2O was re-administered in a 50: 50 ratio with oxygen. Inj. Frusemide 20mg, hydrocortisone 200mg, inj. deriphylline, were

¹Assistant Professor, ²Associate Professor Department of Anaesthesiology MKCG Medical College, Berhampur, Orissa, India.
Contact : 9437325563, E-mail : drhkdalai@gmail.com
Submitted : 15.05.2012, Accepted : 20.06.2012 © OMJ 2012
Fig. 1. Pic. showing the projection of the cuff in the syringe.

Fig. 2. Pic. from a different angle denotes the cuff encroachment.

Fig. 3. Pic. showing the frontal view with the deviation of the tube.

Fig. 4. Frontal view of the tube in syringe with some dye.

Fig. 5. Pic. shows the tube tip compressed against the syringe.
administered as there were some fine crepitation over both lung fields. Surgery was completed without any further complications. At the end of surgery residual muscle relaxation was reversed with inj.neostigmine 2.5mg and glycopyrrolate 0.5mg.iv. Recovery was uneventful, she was conscious, responding to verbal commands. Chest was clear, pulse was 98/min, BP 130/94, SpO2 100% in room air.

Discussion:

Examination of the used spiral embedded tube revealed no intraluminal obstruction; complete deflation of the cuff could be achieved after inflation. But there was a certain weakening of the cuff of the balloon at one point with over bulging of the cuff on that side. To simulate the endotracheal tube position inside the patient’s trachea the tube was placed in a PVC syringe piston and the cuff slowly inflated. The balloon of the cuff bulged at the weakened point and pushed the tip of the ET tube considerably to the opposite direction; this displacement was corrected by gradual deflation of the cuff. From this observation it was assumed that probably during the intra operative period the size of the pre-inflated cuff of the balloon might have increased further due to the administration of N2O, tilting the tip of the ET tube to impinge it against the wall of the trachea thereby blocking it. (1,2,3,4). This might have been compounded by the surgical manipulation and pressure exerted over the neck for hemostasis by the surgeon.

Similarly the incomplete deflation of the cuff may also be attributed to the change in the morphology of the cuff due to unequal expansion apart from this no other plausible cause could be inferred.

Respiratory obstruction with reused spiral embedded endotracheal tubes has been reported (3, 5, 6,7,8,9). Studies have shown that intra cuff pressure and volume of pre inflated air filled cuff do increase with the administration of N2O anaesthesia. (1,2,3,4,7). Studies have also shown that repeated sterilization and reuse of spiral embedded tubes can cause weakening of the cuff resulting in eccentric inflation and ballooning of the cuff over the tip of the tube and pushing the beveled end to the wall of the trachea(10,11). This later phenomenon helped by the increase of the cuff volume due to diffusion of N2O is suspected to have happened in this case. Time and again it has been observed that similar problems occur when re-sterilized or defective endotracheal tubes are used.

Conclusion:

Intubation with a fresh single use tube is always the safest way to avoid such complications. Filling the cuff with sterile saline when using N2O and intermittent monitoring of the cuff pressure may help in early detection of rise in cuff volume and pressure.

Whenever intra operative respiratory obstruction is encountered with spiral embedded tubes immediate exchange of the tube with a conventional tube is the most prudent and safest alternative.

References:

Spontaneous Adult Transmesentric Hernia

M.R. Sahoo¹, V. Bhaskar², A. Behera³, R. Kaladagi²

Abstract:

Internal hernia may be either congenital or acquired. Its incidence has been reported to 0.2-0.9% on autopsy¹. Internal hernias are rare cause of intestinal obstruction with a reported incidence of 0.5%-5.5%². The herniation may lead to variable degree of vascular compromise to the herniated bowel.

Transmesenteric is a extremely rare type of internal hernia. The reported incidence of transmesentric hernia constitutes around 5%-10% of all internal hernias. This type of herniation occurs when the intestine prolapses into an abnormal opening in the mesentery. Transmesenteric hernias are difficult to identify preoperatively, and often requires resection of the involved segment of bowel. We report a rare case of spontaneous transmesenteric herniation of jejunum through a large defect in the mesentery with severe congestion of the bowel but no gangrene in a 81 year female.

Case Report:

A 81 yr old female was admitted to SCB MEDICAL COLLEGE on 28th March, 2012 with complaints of pain abdomen- 3days and features of subacute intestinal obstruction not responding to conservative treatment at a peripheral hospital. On examination patient was conscious, cooperative. Vitals were stable. Abdomen was distended, guarding was present, but there was no rigidity or rebound tenderness. On percussion, a tympanic note present all over and bowel sound was sluggish.

X-ray revealed diffuse gas shadow. There was no air fluid level or gas under diaphragm.

Ultrasound abdomen and pelvis revealed mildly dilated small bowel loops with sluggish peristalsis. Minimal collection in the peritoneal cavity.

A provisional diagnosis of acute abdomen with small bowel obstruction was made and exploratory laparotomy done on emergency basis using a midline incision. On opening the peritoneal cavity small amount of serous fluid seen which was aspirated. Several loops of jejunum presented which was dusky red in appearance and edematous.(fig.1) Further exploration revealed around 50 cms of jejunum had herniated through a rent in the mesentery of the small bowel. The hernia was reduced without any difficulty and the mesenteric defect was identified as a circular defect around 10×8 cms lying fairly close to the DJ junction. The herniated bowel was quite viable. The defect was closed using PDS sutures. The recovery was uneventful and the patient discharged 10th post op day.

Discussion:

A transmesenteric hernia is a form of internal hernia. Internal hernia has been classified by STEINKE in 1932 as follows³:

A: Retroperitoneal
1. Paraduodenal
2. Paracecal
3. Intersigmoid
4. Foramen of winslow

B: Through Anomalous Opening
1. Mesentry of small bowel
2. Mesentry of transverse colon
3. Mesentry of sigmoid colon
4. Omentum
5. Broad ligament

Defects in the mesentry of small bowel may be congenital or acquired.

Congenital cases do not give any significant past history of trauma and a developmental origin of these defects is most probable⁴. An acquired defect may follow after operation, trauma, or inflammation. Post

¹Associate Professor, ²Senior Resident, ³Junior Resident
Department of Surgery
SCB Medical College, Cuttack
Contact : 9668656413, E-mail : ved2203@gmail.com
Submitted : 30.08.2012, Accepted : 26.09.2012
© OMJ 2012
Initial picture of dusky red bowel loops as seen on laparotomy. There were no gangrenous changes.

Internal herniation have well being described and the causes of which are now widely known. Stammer had described various types that can occur after gastrectomy and those complicating colostomy. Internal hernias, including strangulated hernias, have most recently been noted after the performance of operations for morbid obesity, especially Roux-en-Y gastric bypass. Antecolic position of the Roux limb was associated with a lower incidence of internal hernias leading to

obstruction in most early series. However, follow-up reports suggest that the incidence of late internal hernia may increase with an antecolic approach. The cases of inflammatory origin usually involves the ileo-caecal region.

Clinical Features:

A mesenteric defect with or without herniation of bowel through it may be symptomless, or symptoms may be minor so as to attract little or no attention. When obstruction or strangulation occurs, symptoms come with dramatic suddenness and usually proceed with great rapidity.

In early cases sudden, severe, colicky pain is the cardinal features. Vomiting occurs early, constipation is usually present and later on abdominal distension and other features of intestinal obstruction supervene. Gangrene occurs in over 50% of cases and is of early onset and rapid progression.

The radiographic findings are usually not specific and usually suggests features of intestinal obstruction

Treatment:

A correct pre op diagnosis is usually not possible and laparotomy is carried for intestinal obstruction. On opening the abdomen free fluid is usually present and if dark, blood stained or foul smelling suggests strangulation and gangrene. The affected bowel will have classical changes of a strangulated hollow viscus of various degrees. The definitive treatment consists of reducing the hernia and closure of the mesentric rent using absorbable sutures as done in this case. However in case of gangrene a resection and anastomosis may be required.

Summary:

This is a rare case very difficult to identify preoperatively and a possibility should be kept in mind if other common causes of obstruction are ruled out. So surgery should not be delayed for want of diagnosis.

The large spontaneous mesenteric defect seen after reduction of obstructed small bowel loop
References:


Members of IMA, Odisha who have not received their copy of “OMJ 2012” are requested to collect it from State HQ Office, Cuttack

Members of IMA, Odisha are requested to correct their contact details at State HQ Office, Cuttack
Cancer cervix presenting as pyoperitoneum

S. Panda¹, G. Kar²

Abstract:
An elderly postmenopausal multiparous lady presented with features of acute abdomen, with available gadgets she was diagnosed as a case of ilial perforation/ intestinal obstruction and subjected for emergency exploratory laparotomy where pyoperitoneum, omental adhesion to uterine fundus & right iliac fossa was found. There was a rent on fundus of uterus with necrotic margin. Pus culture & sensitivity, Appendectomy, biopsy from uterine rent & repair of uterus were taken. On 20th POD, gynecological referral was sent. From history & speculum examination, cancer cervix clinical stage IIB was made, which was confirmed by pap smear & biopsy.

Key words: pyoperitoneum, cancer cervix, pap smear

Introduction:
Cancer cervix is preventable, at least can be diagnosed at earlier stage by simple speculum examination due to its symptomatic presentation. It is interesting to note that a typical complaint of offensive vaginal discharge was not clinically analysed in the following case who was diagnosed as an acute surgical emergency and subjected for exploratory laparotomy. Pyoperitoneum due to perforated pyometra was the cause of peritonitis. She underwent a stormy post op period & recovery, incidentally diagnosed as a case of cancer cervix on 21st POD.

Spontaneous perforation of pyometra is a rare pathologic condition that presents as diffuse peritonitis mimicking gut perforation and cancer cervix could be a cause.

Case report
A 60 yr, postmenopausal, multipara, presented to ED of a tertiary care hospital on 2.11.10 complaining of pain abdomen for 3days, obtipation for 3days, fever for 2days, no urination for 18hrs and white discharge per vagina for 8days. General examination NAD. Her vitals were stable. Per abdomen examination reveals distention, tenderness in all quadrants, no rigidity or guarding, dullness over hypochondrium, e/o free fluid. Respiratory, cardiovascular and nervous systems were normal.

Investigations: Significant positive findings are: TLC, 28000/mm with 95% neutrophils. B.urea:64mg%, S.Creatinine: 2.2mg%. Imaging studies: plain X-ray abdomen in erect posture: multiple fluid levels, USG: bulky uterus with irregularity of endometrial lining, Moderate ascitis with omental thickening. U/S guided aspiration of peritoneal fluid study: exudative.

Management: A provisional diagnosis of ilial perforation? Adynamic Intestinal Obstruction was made & she was taken for emergency exploratory laparotomy with broad spectrum antibiotic coverage.

Operative finding: about 3L of foul smelling pus present in peritoneal cavity, small bowel loops adherent to each other by pyogenic membrane, distal portion of appendix sloughed off, two centimeters remaining, uterus & B/L adnexa normal but congested. Omentum adherent to uterine fundus & right iliac fossa. There was a rent on fundus of uterus with necrotic margin (Fig 1&2)


¹Associate professor, Dept. of Obstetrics & Gynaecology, Great Eastern Medical School, Ragolu, Srikakulam, 532484, A.P. India
²Ex Prof. & HOD, Dept. Of Obstetrics & Gynecology, MKCG Medical College & Hospital, Brahmapur, Odisha
Contact : 9861385003
Submitted : 23.07.2012, Accepted : 25.08.2012
© OMJ 2012
On day of surgery, she developed breathlessness & shifted to ICU for assisted positive pressure ventilation. Managed symptomatically. Serum electrolytes WNL, Urea: 64mg%, Creatinine: 2.1mg%. Pus Culture: coagulase +ve staphylococcus, sensitive antibiotics continued, omental biopsy : inflammatory.

On 5th POD repeat investigations showed serum electrolytes , RFT, LFT all WNL. On 7th POD peritoneal drains removed, she was shifted to ward, parenteral medication continued for 10days.

On 16/11/10, 13th POD, USG repeated, which showed B/L pleural effusion, minimal free fluid in peritoneal cavity involving interloop collection & paracolic gutter, mildly bulky uterus with minimal fluid in endometrial cavity. After 2days chest tubes from POD removed.

On 20th POD, a gynaec referral was made for no specific symptom. There was h/o foul smelling vaginal discharge for 8days at the time of admission. On examination the previous findings confirmed. Abdominal wound is healing. Per speculum : Cx replaced by an excavating, ulcerative growth, right side vaginal wall congested & bleeds to touch, pus coming through os high up from a tented vault. Cervical os could not be visualised. Per vaginum : induration of right fornix with involvement of medial 1/3rd of rt. Parametrium, cervix could not be felt. Uterine size could not be assessed due to indurated abdominal scar. No palpable node in POD. P/R : rectal mucosa free, pelvic side wall free.

A provisional diagnosis of cancer cervix clinical stage II ( B) with pyometra was made, same confirmed by PAP smear & biopsy from lesion showing squamous cell carcinoma (Fig 3). She was then referred to Mahatma Gandhi Cancer Institute for further management.

Follow-up: she received RT and continues to be symptom free.

Discussion:

Pyometra is collection of purulent fluid in the uterine cavity when its natural drainage is blocked [1]. It has an incidence of 0.1%-0.5% [3,5]. Cervical occlusion may be caused by malignant or benign tumors, radiation cervicitis, atrophic cervicitis, infection or congenital anomalies.[2]. Spontaneous perforation of the uterus is rare and thought to occur at a site of degenerative or necrotic change. Pyometra is a serious medical condition because of its association with malignant disease & the rare danger of spontaneous perforation with subsequent diffuse peritonitis that carries significant morbidity & mortality.[2]. So far some 28 cases have been reported in the literature since 1980,[6], which includes only 8 cases associated with cancer cervix.[2,7], our case being the ninth to be reported. A review of 8 cases of spontaneous uterine perforation in cervical cancer is summarized in table 1.

<table>
<thead>
<tr>
<th>Ref. no</th>
<th>age</th>
<th>Symptoms</th>
<th>Provisional diagnosis</th>
<th>Perforation site</th>
<th>Histology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>34</td>
<td>AP,PP GP,PP</td>
<td>Left cornal region</td>
<td>Squamous cell carcinoma</td>
<td>Drainage and PL</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>AP</td>
<td>GP</td>
<td>Squamous cell carcinoma</td>
<td>Drainage and PL</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>AP,F,V</td>
<td>GP</td>
<td>Adeno- carcinoma</td>
<td>Pigtail drainage</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>52</td>
<td>AP, DB, shock</td>
<td>PP</td>
<td>Squamous cell carcinoma</td>
<td>Subtotal hysterectomy</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>67</td>
<td>AP,DB</td>
<td>GP</td>
<td>Squamous cell carcinoma</td>
<td>Aspiration &amp; drainage</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>PM</td>
<td>AP</td>
<td>GP</td>
<td>Squamous cell carcinoma</td>
<td>TAH with BSO</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>60</td>
<td>AP, F</td>
<td>GP</td>
<td>Squamous cell carcinoma</td>
<td>TAH with BSO</td>
<td></td>
</tr>
<tr>
<td>Present case</td>
<td>60</td>
<td>AP, uremia</td>
<td>GP</td>
<td>Squamous cell carcinoma</td>
<td>Aspiration and drainage</td>
<td></td>
</tr>
</tbody>
</table>

AP: abdominal pain; BSO, bilateral salpingo-oophorectomy; F, fever; GB, genital bleeding; GP, generalized peritonitis; PL, peritoneal lavage; PP,
perforated pyometra; TAH, total abdominal hysterectomy; V, vomiting

All the patients presented with features of generalised peritonitis. Seven out of 8 cases are postmenopausal women. The most common perforation site was the uterine fundus and in only one case it was cornual region. Perforated pyometra was not the preoperative diagnosis in any of the cases.

Ultrasound scan is a poor diagnostic tool, some time Computed tomography also fails to give a preop diagnosis. However, a contrast enhanced abdomen pelvic CT in reformatted sagittal & coronal plane as well as T2-weighted MR imaging are the tools for correct diagnosis.

Perforated pyometra should be considered as a differential diagnosis from other causes of acute surgical abdomen especially in a postmenopausal woman. No symptom in a patient is trivial, therefore should be analysed in a proper perspective.

Acknowledgement:

Prof. Dr KPV Prasad Rao, MD, Prof. & Head, Dept of General Surgery, Maharajah’s Institute of Medical Science, A.P India.

Dr Sindhuma PG, O&G; Dr Satyavathi PG, General Surgery, Maharajah’s Institute of Medical sciences, Vizianagar, Andhra Pradesh, India

Prof Dr K Prasad Reddy, MD, Dept of Pathology, Maharajah’s Institute of Medical sciences, Vizianagar, Andhra Pradesh, India

References:

A 29-year-unmarried female was attended to our hospital for evaluation of fracture of right femur, low back ache and generalized body pain. History revealed a 1-year history of constipation, recurrent episodes of renal colic, pain in the both the ankle and knee, for which she has been treated by several physicians. Laboratory tests on admission showed hypercalcemia (serum calcium-11.7 mg/dL, serum calcium ionized-6.82mg/dl), hypophosphatemia (0.90 mg/dL), increase in intact-PTH level (1585.2 pg/mL) and an normal 1,25-dihydroxycholecalciferol level (39.45 pg/mL). Thyroid and kidney function tests were within normal limits. X-ray suggestive of fracture of right femur and resorption of bones. Tc 99m MDP scan revealed there is increased skeletal metabolism in the skull, right shoulder and right upper end of the femur. Ultrasound of abdomen suggestive of cholelithiasis and bilateral renal calculi. Neck ultrasound was suggestive of enlarged left inferior parathyroid gland. Tc 99m sestamibi parathyroid scintigraphy revealed, there is presence of adenoma/hyperplasia of the left upper parathyroid gland. On neck exploration left superior parathyroid was enlarged and excised and sent for HP study. The biopsy was parathyroid adenoma. Serum calcium level was normal in the immediate postoperative period, with PTH within normal limits (15.4 pg/mL, day 1 after surgery).

**Discussion:**

Clinical presentation of the primary hyperparathyroidism can be highly misleading, sometimes causing various clinical syndromes before it is diagnosed. Tc-99m sestamibi imaging techniques have played a important role in diagnosis and defining the preoperative localization in this case study. After parathyroidectomy, there is immediate postoperative normalization of hypercalcemia, and PTH level.

**Conclusion:**

Any patient complaining of musculoskeletal problems shall be advised for serum calcium and X-ray of long bones and skull. In clinical practice, hyperparathyroidism must be considered in the differential diagnosis of hypercalcemia.
USG neck showing left superior parathyroid hypertrophy

TC-99m-sestamibi parathyroid scintigraphy revealing presence of adenoma/hyperplasia of the left superior parathyroid gland

USG abdomen showing bilateral renal calculi

Tc 99m MDP scan revealing increased skeletal metabolism in the skull, right shoulder and right upper end of the femur.

Excision of left superior Parathyroid Gland

Barium enema showing dilatation of large gut.
Aggressive Angiomyxoma In Male: A Rare Case Report
D.R. Samanta¹, S.N. Senapati², S.K. Das³, K.R. Mohanty⁴, C. Bose⁵, Roopesh. K⁶

Abstract:
Aggressive angiomyxoma is a rare soft tissue neoplasm. It is mostly found in females of reproductive age group with a peak incidence in 4th decade of life. Out of 150 reported cases of aggressive angiomyxoma in literature so far, only 39 patients have been found amongst male. Here we report a case of aggressive angiomyxoma of pelvic retroperitoneum in male, due to its rarity and for documentation.

Key words- Angiomyxoma, Soft tissue neoplasm, Retroperitonealtumour.

Introduction:
Aggressive angiomyxoma is a benign nonmetastasing soft tissue tumor which was described initially by Steeper and Rosai in 1983¹. Out of 150 reported cases of aggressive angiomyxoma in literature so far, only 39 patients have been found amongst male. It commonly occurs in females, where the usual sites of presentation are perineum, vagina, vulva and inguinal region. The occurrence of aggressive angiomyxoma in male is rare and male to female ratio is 6.6:1. Sites of involvement in male are scrotum, spermatic cord, inguinal region and perineum, however presentation of aggressive angiomyxomas at pelvis is a rare entity². On immunohistochemistry most of the aggressive angiomyxomas are positive for Desmin, smooth muscle actin, Vimentin, Estrogen receptor and Progesterone receptor but S-100 is invariably negative.

Here we report a case of aggressive angiomyxoma at pelvic retro peritoneum in a male patient due to its rarity and to highlight our experience on management of such rare tumors.

Case Report:
A 42 year old male clinically presented with pain at lower abdomen and progressive swelling of lower abdomen of 5 months duration. On examination, there was mild facial puffiness, bilateral pedal edema, no peripheral lymphadenopathy. Clinical examination of the abdomen revealed an ill defined mass palpable in right lumbar and iliac region. The mass was firm, non tender and non-ballotable. Examination of other system did not reveal any abnormality. His complete blood count and biochemical profiles were within normal limit. CT evaluation of abdomen and pelvis revealed a large, lobulated heterogeneously enhancing mass of size 11X8.7X6.2 cm extending from pelvis upto the lower pole of right kidney. Right kidney was displaced superomedially (Fig 1). Skiagram of chest was normal.

The patient underwent complete excision of retroperitoneal tumor on 28.04.2011. Histopathology examination revealed that the tumor was composed of short spindled to oval cells with collagen production and high vascularity. Entrapment of skeletal muscle was found with predominant myxomatous stroma and sparse cellularity. There was no necrosis and mitotic figure (Fig 2). Patient was subjected for immunohistochemistry which revealed desmin was positive but negative for CD-117/C-kit, ER/PR and S100.

Based on the above finding the patient was diagnosed as a case of aggressive angiomyxoma of pelvic retro peritoneum.

As it is a benign nonmetastasing soft tissue tumor, complete excision was done and ER/PR was negative, the patient was advised for close observation. Till now the patient completed 16 months of follow-up and clinicoradiologically his disease is under control.

Discussion:
Aggressive angiomyxoma is a slow growing neoplasm with local infiltration, high rate of local...
Fig 1:- CT scan showing lobulated heterogeneously enhancing mass of size 11X8.7X6.2 cm extending from pelvis upto the right lumbar area.

Fig 2:- Microphotograph showing spindled to stellate shaped cell with numerous blood vessels both thin and thick walled in a myxoid background.

recurrence and absence of systemic metastasis. Diagnostic difficulty is due to its rarity and its recent introduction as a separate entity. In the latest WHO classification, aggressive angiomyxoma is now classified under “tumor of uncertain differentiation”. This tumor is having female sex predilection. Sites mostly identified are perineum, vagina, vulva, inguinal region. In the presence of vulvar mass, possibility of aggressive angiomyxoma should be kept in mind. In males angiomyxoma is rare with predilection for sites like scrotum, spermatic cord, inguinal region. It is rarely found in retro peritoneum. Our reported case is a male in his 4th decade of life with involvement of pelvic retro peritoneum which is presented here due to its rarity. The radiological diagnostic method is invariably a CT evaluation with contrast which highlights the remarkable vascular pattern. Our case was also diagnosed radiologically with CT evaluation of abdomen and pelvis which revealed contrast enhancement of pelvic retroperitoneal mass that displaced right kidney with appreciable perinephric fat stranding and remarkable vascular pattern. Biopsy is always mandatory to ensure the diagnosis. Histopathology of aggressive angiomyxoma reveals myxomatous stroma with the stellate and spindled cells with hyperchromatic small nuclei and small nucleoli. A prominent vascular pattern composed of dilated capillaries, venules and arteries often present. In our reported case, histopathological examination showed a predominantly myxomatous tumor and sparse cellular areas adjoining proliferated small and medium calibre muscular blood vessels. The neoplastic cells were also stellate and spindled. On immunohistochemistry, most aggressive angiomyxomas are positive for Desmin, SMA, vimentin, but negative for S-100. In the present case patient has desmin positive and S-100 negative which was suggestive of origin of myoblastic differentiation. CD117/C-kit was done to rule out stromal tumor. Based on a mass of 11X8.7X6.2 cm at pelvic retroperitoneum with presence of stellate to spindled cells, numerous thick and thin walled blood vessels in a myxomatous background and Desmin positivity, patient was diagnosed as a case of aggressive angiomyxoma. Such patient may express estrogen and progesterone receptor, however these receptors were not expressed in this case.

Surgery with adequate margin is the mainstay of treatment. The reported patient underwent complete excision of mass with adequate margin and without any leftover disease. When ER/PR is positive, hormonal treatment like Goserelin is advised, but when ER/PR is negative, there is no role of adjuvant hormone.
therapy. The patient of aggressive angiomyxoma should be subjected for external beam radiotherapy if there is any residual or left over disease to prevent subsequent local recurrence. In the reported case, ER/PR were negative and there was no residual disease. Hence the patient was kept under close observation to detect any local recurrence. Until now, the patient has completed recurrence free interval of 16 months without any clinicoradiological evidence of locoregional disease.

Conclusion:

Aggressive angiomyxoma is a rare slow growing neoplasm with potentiality for local infiltration. Histopathology and immunohistochemistry are two important diagnostic modalities of this entity. This entity is common in females and rare in males. Presentation at pelvic retro peritoneum among male is further uncommon.

Surgery with adequate margin is the mainstay of treatment. External beam radiotherapy is indicated if there is any residual disease and if ER/PR positive, hormone therapy should be included as adjuvant treatment. Here we report a case of aggressive angiomyxoma in male with involvement of pelvic retro peritoneum due to its rarity and highlighting the treatment outcome in this rare tumor.

References:

Soft tissue coverage for heel defect where microvascular facility not available

P.K. Das¹, S. Samantara², S.P. Mishra³

Introduction:
Coverage of the soft tissue defects of the limbs, especially the lower one third of leg and heel has been a difficult problem to tackle.

The steps of reconstructive ladder range from simple closure to micro vascular flaps.

Pedicle flap is an old concept in reconstructive surgery that utilizes the superficial and deep fascia and its definite vasculature for nourishment of flap.

Many questions still remain unanswered e.g.
1. What is the anatomical basis of these flaps?
2. What are the safe limits of the flap?
3. What structures are really essential for the survival of the flaps (Nerve and the peri/paraneural vasculature, the vein, deep fascia, perforators from the major arteries etc?)
4. Where should be the pivot point?

Materials and Methods:
A prospective study was done in the department of surgical oncology at A.H. Regional Cancer Centre, Cuttack, from June 2011 to July 2012. Total four number of cases of heel defect were selected. All were neoplastic ulcer/growth who would be needing radiotherapy subsequently. More over microvascular surgery facility was not available at the regional cancer centre.

Case 1: 50 year Hindu male presented with ulcerative growth right proximal heel since six months.

It was a cauliflower ulcerative growth with palpable inguinal nodes, however inguinal nodes were not clinically significant. The punch biopsy report was invasive squamous cell carcinoma. The patient was planned for a surgery of wide local excision with prophylactic ileo-inguinal node dissection.

Case no 1

Case no 2.

Case no 3

45 years Hindu male, known diabetic presented with nonhealing ulcer at left heel since four months, slough present around, margins were found inflamed and indurated. The biopsy was Invasive squamous cell carcinoma.

Case no 3

35 years Hindu male presented with growth at right heel with palpable inguinal nodes. It needed inguinal block dissection with

Case no 2.

Case no 3
Wide local excision of primary growth.
Case no 4.-

36 years Hindu tribal female presented with ulcerative growth at left proximal heel without palpable inguinal nodes.

All these four cases biopsy report were invasive squamous cell carcinoma and needed wide local excision with healthy margin and depth up to bone. Hence for the shake of reconstruction each needed good flap cover so that patient can walk and facilitate post operative radiation therapy. In this institution no operative microscope was available hence it was decided to follow delay procedure and with pedicle flap to cover the defect.

Principle followed- In the leg as we know tibial and peroneal perforators are present. Reverse sural flap usually outlined 10 cm below popliteal line. We delayed the territory above conventional sural flap. Then conventional sural flap was raised after five days and tried to cover the defect.

Pedicle was divided after three weeks.

Patients were allowed for weight bearing after six weeks.

Pe operative planning were done one day before surgery.

Planning in reverse were done so that defect would be covered.

Operative Technique:

The patients were operated under spinal anaesthesia. After excision of primary growth/ulcer. The flap was approached in prone position. A tourniquet were used in all cases. The dissection started in the most proximal part of the flap. The incision was deepened till the sub fascial plane. Lesser saphenous vein and sural nerve were ligated and divided. The deep fascia was anchored to the skin to avoid shearing of the flap. The bleeding in the divided sural neuro vascular bundle gave some idea of the blood supply to the flap. The flaps were dissected off the gastrocnemius, ligating the neuromuscular and musculocutaneous perforators encountered. Then flap were resutured to donor area and principle of delay followed.

After five days second stage procedure followed- The flaps were elevated till the pivot point, which were at least 5 cm above the tip of lateral malleolus. In the medial side, incision made close to tendoachilis. Vascularity checked. The flaps were now insetted into the defect.

The flap can be raised as islanded or as peninsular flap. In its peninsular form designing the flap in a teardrop fashion or tapering in the lower part, facilitated better arc of rotation. After marking the skin island, a decision was made regarding the width of the flap base, designed obliquely towards the lateral malleolus, to include maximum number of perforators in the pedicle. Division of the pedicle was done after three weeks. Patients were allowed for weight bearing after six weeks.

The pivot should remain at least 4-5 centimeters above the tip of lateral malleolus to include the most constant peroneal perforator in the inter-crural septum. The donor site was large in 50% of cases and was skin grafted.

A drain was kept under the flap in all cases. The leg was immobilized in plantar flexion with Plaster of Paris cast for two weeks.

The details of postoperative complication and management were recorded.
The following points regarding postoperative management (in days) were noted.- Primary dressing,. Drain removal,. Stitch removal,. Mobilisation/Ambulation,. Weight bearing allowed.

**Observation**

The average hospital stay was 16 days inclusive of the delay period

Partial flap necrosis occurred in one out of four cases which was managed by debridement and skin graft

Weight bearing was painless in all 4 cases.

Aesthetic appearance was acceptable in all 4 cases

**Discussions :**

**Free tissue transfer-HISTORY**

The origins of microvascular surgery can be traced back to Alexis Carrel in the early 1900s. His work illustrated reproducible methods of suturing vessels together with excellent patency rates. Modern microvascular techniques are credited to Jacobsen and Suarez who borrowed the use of the operating microscope from their otologic colleagues, in the 1950s.

Human tissue transfer was accomplished as early as 1957 when Som and Seidenberg reconstructed an esophagus with a free jejunal segment. Multiple reports of free fasciocutaneous flaps entered the literature in 1972, and in 1979 Taylor introduced the composite osteocutaneous groin flap. The late 1980s saw an explosion in free flap reconstruction of mandibular and soft tissue defects, and the use of osseointegrated implants was introduced. From the late 1980s until present, free tissue transfer techniques have become an accepted tool in the reconstruction of head and neck defects.

**PREOPERATIVE CONSIDERATIONS**

Because of the great technical demand involved in this technique, preoperative planning is a major undertaking that significantly impacts on the success of the procedure. Patient selection, anesthetic planning, donor site selection, and timing of the procedures are all additional concerns in the work-up of a patient who is already preparing to undergo a major head and neck procedure. The viability of the transferred tissue is generally attributed to the technical aspects of microvascular anastomosis; however, errors in patient selection, donor selection, flap-transfer timing, and the geometry of flap inset can all result in flap failure.
There are a number of patient factors that severely limit the likelihood of successful free tissue transfer. Age in and of itself may not be important; however, many serious systemic diseases are more often found in patients of advanced age. Severe cardiovascular disease and atherosclerosis may compromise flap vessels. Diabetes impairs wound healing and negatively affects vessel health. Connective tissue disorders may also compromise the cardiovascular system. Prior irradiation, diabetes (well-controlled), method of anastomosis, timing, vein graft, and specific arteries/veins are not felt to contribute to flap failure rate. The effects of nicotine on flap failure is controversial.

References:
2. Grabbes encyclopedia of flaps.
3. Mathese text books of plastic surgery.
A Rare Case of Pulmonary AV Malformation

A. Behera¹, D. Bindhani²

- 52 years female patient named Pramila Pradhan presented with progressive breathlessness with bluish discolouration of lips and nails of 3 months duration.
- Clinically patient had cyanosis and clubbing of fingers with spo2 was 82% with room air and signs improved with oxygenation
- Chest X-Ray shows lobulated mass of right lower lobe (RLL)
- CT scan of thorax demonstrates an intrapulmonary vascular malformation and their feeding vessels
- **Pulmonary angiogram shows there is a saccular aneurysm of right lower pulmonary artery with direct drainage to left atrium.**
- **Diagnosis of pulmonary A – V Malformation was done based on clinical features, typical features of chest X-ray & facilitated by CT scan and pulmonary angiogram**
- Treatment given surgical resection of right lower lobe with ligation of afferent and efferent vessels

**Figure1.** Photograph of the patient showing bluish discoloration of lips.

**Figure2.** X-ray chest showing lobulated masses and dilated feeding arteries and veins of Right lower lobe.

**Figure3.** CT scans showing the anatomy of PAVM and their feeding vessels.

¹Assistant Professor, Dept. of Pulmonary Medicine, KIMS, BBSR
²Consultant Intensivist, Pulmonologist, Aditya Care Hospital.
Submitted : 18.09.2012, Accepted : 15.10.2012
© OMJ 2012
Discussion

Pulmonary A – V malformation is very rarest complicated case for diagnosis and for surgical correction. PAVM are usually closely related to visceral pleura and 70 % cases occur in lower lobe. About 95% of PAVM derive their blood supply from branches of pulmonary artery and drained into pulmonary venous circulation. The most common complications are haemoptysis, hemothorax, TIA and CVA.

References:

Nosocomial C. Meningosepticum Sepsis in A Diabetic Patient Treated for Retroperitoneal Hematoma

N. Prasad, G. Patnaik, G. Sarangi, A. Mohapatra, P. Das, D. Mahapatra, N. Chayani

Introduction:

*Chryseobacterium meningosepticum*, formerly k/a *Flavobacterium meningosepticum* or CDC II-a, a gram-negative rod, is widely distributed in nature and acts as a potential source of infection to premature and newborn infants and also to immunocompromised adults. The organism is usually multiresistant to antibiotics, typically prescribed for treating gram-negative bacterial infections, including extended-spectrum ß-lactam agents and aminoglycosides, and thus causes clinical concern.

Objective:

Here we describe a case of nosocomially acquired *Chryseobacterium meningosepticum* sepsis associated with host immunocompromised status i.e. diabetes and prolonged hospitalization.

A 57-year-old diabetic man after a roadside accident with unstable vital signs was admitted to a trauma hospital. The provisional diagnosis of retroperitoneal hematoma was made. Debridement of the retroperitoneal hematoma under antibiotic cover and sugar control was done. But he developed high grade fever and breathlessness after 12 days of hospitalization. Subsequently he was referred to SCB Medical College, Cuttack. Samples were sent for routine Laboratory tests. Blood sample was sent for culture & sensitivity. Chest X-ray as well as a CT scan of the brain, chest and abdomen were done. Ceftriaxone was started empirically.

Routine Laboratory tests showed signs of infection with deteriorating liver and kidney function tests include white blood cell count - 22 x 10⁹/liter (84% granulocytes, 9% lymphocytes, and 7% monocytes), hemoglobin level - 7.9 g/dl, Platelet count - 116 x 10⁹/liter, Glutamyl transpeptidase level - 215 IU/liter, ALT- 80 IU/liter, AST- 60 IU/liter, alkaline phosphatase level - 169 IU/liter. Serum creatinine- 2.4 mg/dl and blood urea nitrogen -30 mg/dl. All of the remaining biochemical laboratory tests were unremarkable. Blood sugar was also under control on medication. Chest X ray as well as a CT scan of the brain, chest and abdomen showed no evidence of infection. Urine culture was negative, however, blood culture obtained through a peripheral venous site was positive. Bacterial growth was detected within 24 to 48 hr of aerobic incubation at 37°C. Sheep blood agar showed smooth, circular, non-diffusible, yellow pigmented colonies while non-diffusible yellow pigmented colonies were seen on nutrient agar. Similarly MacConkey agar showed nonlactose fermenter with nondiffusible yellow pigmentiation. Gram staining and motility testing showed Gram negative bacilli which was non motile. Biochemically it was catalase positive, oxidase positive, nitrate non-reducing. OF Glucose-oxidative, Indole positive and urease negative. From the above biochemical characters the bacteria was identified to be C. meningosepticum.

Antibiotic susceptibility testing by Kirby bauer disc diffusion method was done and the organism was found to be susceptible to levofloxacin, piperacillin/tazobactam, trimethoprim/sulfamethoxazole and resistant to ceftriaxone, amikacin, ampicillin/sulbactam imipenem, cefepime and azithromycin. Then, ceftriaxone was stopped and the patient was successfully treated with piperacillin-tazobactam (4.5 g every 8 h intravenously) for 10 days. The fever resolved 4 days later. There was no evidence of relapse during the next month.

Discussion:

The genus *Chryseobacterium* includes six species that were previously designated members of the genus *Flavobacterium* (1). *Chryseobacterium*
meningosepticum is the most pathogenic member of the genus, and was first reported by Elizabeth O. King in 1959. While she was studying unclassified bacteria associated with meningitis in infants, he named the organism recovered as Flavobacterium ("the yellow bacillus") meningosepticum ("associated with meningitis and sepsis"). In 1994, it was reclassified in the genus Chryseobacterium and was named as Chryseobacterium meningosepticum (2,3,4). It is a nonfermentative, nonmotile, slender; slightly curved with catalase-positive, oxidase-positive, and indole-positive saprophytic gram-negative bacillus. It is widely distributed in nature and so its role in the pathogenicity of community-acquired infections is reasonable in immunocompromised patients (5,6,7). It causes disease predominantly in premature newborns and infants. Meningitis and bacteremia are the most common clinical presentations. In the hospital environment. It can exist in water systems and wet surfaces and so it can be a potential nosocomial pathogen also. Positive identification of the organism enables prompt treatment and increases the chances of recovery.

**Conclusion:**

Colonization of patients through contaminated medical devices has been documented and Chryseobacterium meningosepticum can be a potential nosocomial pathogen and should be included in the list of suspected nosocomial infections, especially in patients with immunocompromised status. Administration of appropriate antibiotics, strict adherence to hand washing and routine screening of hospital water samples can prevent outbreaks with this bacteria.

**References:**


Retroesophageal Right Subclavian Artery – An Anatomical Variation with Short Review
S. Sethy, C. Mahapatra, P.K. Chinara, C. Sarangi

The subclavian arteries can vary on their origin, course or length. One of the most common anatomical variations is the right subclavian artery originating as the last branch of the aortic arch. This artery is known as a Retroesophageal Right Subclavian Artery (RRESA) or “lusory artery”.

We report a case of a rare anatomical anomaly of the Retroesophageal Right Subclavian Artery (RRSA) in a young female cadaver during routine dissection in the Department of Anatomy, SCB Medical College, Cuttack. The present study describes this RRSA and discusses the possible embryonic development of these branching pattern and their clinical and surgical significances and implications.

Key words: retroesophageal right subclavian artery, arteria lusoria, aortic arch

Introduction :
In about 80% of individuals 3 branches arise from the aortic arch: the brachiocephalic trunk, the left common carotid artery, and the left subclavian artery [1]. Adachi first described this branching pattern as type A [2]. Another 11% of reported cases exhibit Adachi’s type B pattern, which consists of a common trunk for the left common carotid artery and the brachiocephalic artery. This branching results in only 2 trunks originating from the aortic arch. The third most common pattern, type C, is characterised by the vertebral artery originating proximally to the left subclavian artery as a 4th branch of the aortic arch. The remaining 1% of cases is composed of numerous other aortic arch branching pattern variations [3]. We report a case in which the right subclavian artery arises as the distal branch of aortic arch and follows a retroesophageal course.

Case Report :
During the routine dissection in a young female cadaver in the Department of Anatomy, SCB Medical College, Cuttack, the right retroesophageal subclavian artery (RRSA) anomaly was recognised, and the patient’s aorta (along with the proximal parts of its branches and its associated thoracic viscera) was removed en bloc from the body. The specimen was then cleaned, dissected to expose silent features and photographed.

The young female did not possess any abnormalities apart from the anomalous right subclavian artery, which originated from the descending aortic arch as the last branch. It crossed the oesophagus and the trachea in a posterior position to reach the right upper limb. The aortic arch appeared to be normally located above the heart and was of normal length and width. Furthermore, it gave rise to 4 branches. From right to left these were as follows: the right common carotid, the left common carotid and the left subclavian and right subclavian arteries. The right subclavian artery coursed posterior to the trachea and oesophagus, thus allowing it to be more accurately described as a retroesophageal right subclavian artery (RRSA-arteria lusoria) (Photo. 1, 2, 3). Consequently, the brachiocephalic trunk was absent.
ORISSA MEDICAL JOURNAL

Photo 2 & 3- View of the dissected right retroesophageal subclavian artery (RRSA) posterior to oesophagus (after dissecting out the heart & three proximal branches)

The left subclavian artery (LSA) has a normal origin while the RRSA originates distal and posterior from the aortic arch. LRLN indicates the Left Recurrent Laryngeal Nerve. RC = Right common carotid artery, LC = Left common carotid artery, E = Esophagus and T = Trachea, DTA = Descending Thoracic Aorta.

As Photo 2, 3 reveal, the RRSA located distally on the aortic arch exhibited the largest diameter of the 4 branches, and arose slightly posterior to the midline of the aorta. The left subclavian artery was slightly anterior to the aortic midline of the aorta and 1 cm proximal to the RRSA. The first branch of the aortic arch was the right common carotid artery. There were no noticeable abnormalities or differences in the heart or the remaining thoracic organs. The trachea and oesophagus were positioned normally. All abdominal viscera were normally located without any malformation or disease. Surprisingly, the right recurrent laryngeal nerve did not recur. Instead, anomalous right inferior laryngeal nerves arose from the cervical portion of the vagus nerve at the level of the upper pole of the thyroid lobe, turning transversely by a very short course towards the larynx and running a nearly horizontal course to their point of entrance into the larynx. The left recurrent laryngeal nerve, on the other hand, looped typically around the aortic arch, and the cardiac branches of both vagus nerves entered the cardiac plexus normally.

Discussion:

The origin of the RRSA as the last branch of the aortic arch is a congenital aortic arch anomaly, with a reported prevalence of 0.4–2% [4,5]. The earliest reported description of this anomaly was published by Hunald in 1735 [6]. The clinical syndrome of RRSA was found to be associated with dysphagia, thus termed “dysphagia lusoria” by Bayford in 1787 [7]. In 1823 Stedman [8] described the entire anatomical picture associated with RRSA. Since Hunald, Bayford and Stedman’s work there have been a number of case reports describing different origins of RRSA, although these descriptions lack clinical correlations as well as possible embryological explanations. Therefore, in order to highlight the clinical significance of RRSA, we have, to a certain degree, extended our description into the field of embryology.

Initially 6 pairs of aortic arches extending from ventral to dorsal aortae develop in 1st month of embryonic life. 5th arches are transitory and disappear early. 1st pair of arches disappears except a part for maxillary artery and 2nd pair mostly regresses except its dorsal part which forms stapedial artery. Nutrition of developing upper limb bud is maintained by development of the 7th intersegmental artery which sprouts outwards from each dorsal aorta distal to attachment 6th aortic arch. 3 changes are observed culminating in development of adult pattern of blood vessels. 1) Portion of dorsal aorta between 3rd and 4th arches disappear on each side. 2) Ventral portion of right 6th aortic arch forms right pulmonary artery, whereas its dorsal part regresses. Ventral part of left 6th aortic arch forms the left pulmonary artery but its dorsal part persists in fetal life as ductus arteriosus. 3) Portion of right dorsal aorta caudal to origin of right 7th intersegmental artery disappears and regression extends up to fusion of 2nd dorsal aortae. On both side 3rd aortic arches persists as Common carotid artery. Right 4th aortic arch a part of right dorsal aorta caudal to ductus caroticus and right 7th intersegmental artery form together Right Subclavian artery [9,10,11].

The right limb of aortic sac which is connected with 3rd and 4th aortic arches persists as Brachiocephalic Trunk. On the left, the definitive Arch of Aorta is developed from - Aortic sac-proximal to
brachiocephalic trunk, Left limb of aortic sac-part of arch between brachiocephalic trunk and left common carotid artery, Left 4th aortic arch-part of arch between left common carotid and left subclavian artery, Left dorsal aorta-form distal part of arch of aorta. Left 7th intersegmental artery develops into left subclavian artery.

Regression of dorsal part of right 6th aortic arch causes the right recurrent laryngeal nerve to hook around the caudal surface of right subclavian artery. Persistence of dorsal part of left 6th aortic arch allows the left recurrent laryngeal nerve to loop upwards dorsal to ligamentum arteriosum around the caudal surface of arch of aorta. A Retroesophageal Right Subclavian Artery occurs when right 4th aortic arch and right dorsal aorta disappear cranial to right 7th intersegmental artery. As a result RRSA develops from right 7th intersegmental artery and distal part of right dorsal aorta [9, 10, 11]. As development proceeds, differential growth shifts the origin of the RRSA cranially until it comes to lie close to origin of left subclavian artery. With the shortening of aorta between left common carotid and left subclavian artery, origin of RRSA finally settles just below that of left subclavian artery. Since its stem is derived from right dorsal aorta, it must cross the midline behind the esophagus and trachea to reach the right upper arm. In this condition the right recurrent laryngeal nerve passes directly to larynx and does not undergo a recurrent course due to degeneration of dorsal part of 6th aortic arch and entire right 4th aortic arch-as non recurrent laryngeal nerve.

The RRSA however, is closely associated with the inferior laryngeal nerve. Many authors [12, 13, 14, 15, 16, 17] have postulated that in almost all the cases of RRSA the inferior laryngeal nerve will be also affected.

The clinical symptoms of RRSA vary from patient to patient, but the most common are listed below. In adults RRSA produces a vascular ring known as Kommerell’s diverticulum. The majority of patients are usually asymptomatic, but can present with significant trachea-esophageal compression causing dysphagia [18, 19]. In elderly patients, an RRSA occasionally becomes tortuous and ecstatic resulting in oesophageal or tracheal compression, for which surgery is indicated if the symptoms are severe [20, 21]. Furthermore, many authors have reported that the RRSA has been found to be present along with patent ductus arteriosus, aortic coarctation and aneurysmal formation [2, 19, 21, 22].

The RRSA is also clinically important to the angiographer who uses the right axillary, brachial or radial approach to the ascending thoracic aorta [23, 24]. The presence of a RRSA is suspected in cases in which catheterisation of the ascending aorta proves difficult. Using the right radial approach, access to the ascending aorta is usually easy, as the brachiocephalic trunk is the first branch of the aortic arch permitting direct access to the ascending aorta. Thus, in the presence of RRSA angiography could be very challenging [25].

Finally, the inferior right recurrent laryngeal nerve is an asymptomatic variation-anomaly, which can be an important obstacle and be seriously damaged during cervicotomy, thyroid and parathyroid surgery. In such cases the right recurrent laryngeal nerve is a classic risk [25, 26, 27]. The importance of the diagnosis of a RRSA and/or inferior right recurrent laryngeal nerve differs to whether the patient is a child or an adult. This is of particular importance when the diagnosis concerns an asymptomatic neural anomaly [13, 14, 15, 16, 17] discovered by dissection or a vascular anomaly whose symptoms are very variable [19, 17].

Conclusions:

The anatomic and morphologic variations of the aortic arch and its branches are significant for diagnostic and surgical procedures in the thorax and neck. If a RRSA is diagnosed during aortic arch repair, corrective surgery should be considered. Intensive care patients should be screened before long term placement of naso-gastic tube, in order to avoid fistulization and fatal hemorrhage.

RRSA in association with the inferior right recurrent laryngeal nerve can be potential risk factors that lead to surgical intervention. Both can also be present in a patient asymptomatically. In order to provide adequate care for patients, knowledge of the exact anatomical and clinical implications of RRSA and the inferior right recurrent laryngeal nerve is crucial.
Acknowledgements:

The study was conducted at the Department of Anatomy, SCB Medical College, Cuttack, Odisha, India.

Reference:


Abstract:

A 45 year old man presented with sudden onset of abdominal pain and diarrhoea with mucoid discharge. USG and CT scan diagnosed it as a case of colocolic intussusception. Laparoscopically by a 4 port approach right hemicolectomy and ileo-transverse anastomosis done by a linear cutter and stapler. Gross specimen showed bowel within bowel appearance. Histopathology report revealed it to be an inflammatory fibroid polyp.

Key message: Intussusception is rare in adults. Colocolic intussusception is the rarest form of intussusception. In our case, an inflammatory fibroid polyp is the lead point which has lead to a colocolic intussusception.

Keywords: Intussusception, Colocolic, Leadpoint, Inflammatory fibroid polyp

Introduction:

Intussusception is the invagination of one segment of the intestine into another. It is common in children but rare in adults. Only 5% to 10% of intussusceptions occur in adults. It is of 4 types-enteroenteric, ileocolic, ileocecal, colocolic. Colocolic intussusceptions is the rarest form. Colocolic intussusceptions in adults is mainly caused due to a malignant lesion. It is very rarely due to a benign cause.

Intussusceptions in adults can be further classified on the basis of whether there is a lead point or not. Intussusceptions without a lead point are usually transient.

An inflammatory fibroid polyp is an uncommon polypoidal lesion of the gastrointestinal tract. It commonly occurs in the stomach followed by the small bowel, manifesting as gastrointestinal bleeding or simple mechanical obstruction. An inflammatory fibroid polyp manifesting as an intussusceptions in the colon is very very unusual.

In this case report, we present an unusual case of colocolic intussusception due to an inflammatory fibroid polyp as the lead point.

Till now no case reports have been published on this topic.

Case Report:

We present a case of a 45 years old patient who presented with lower abdominal pain and diarrhoea with mucoid discharge for a period of 2 months. Clinical and per abdominal examination revealed no abnormality except for moderate degree of pallor. Hb level was 5.8, serum protein and albumin were reduced. Rest all routine investigations were within normal limits. USG of abdomen and pelvis showed colocolic intussusception. CT scan of the abdomen and pelvis showed the bowel within bowel configuration of the ascending colon suggestive of colocolic intussusceptions. Barium enema showed obstructive pathology with defect in the ascending colon. Colonoscopy revealed a mass lesion in the ascending
colon, occluding the lumen and hence the scope could not be negotiated beyond the mass lesion. The patient underwent a diagnostic laparoscopy, thecolocolic intussusception was identified. Laparoscopically, by a 4-port approach, righthemicolectomy was done. Ileo-transverse anastomosis was done by bringing the bowel loops out by a small incision. The anastomosis was carried out by a linear cutter and stapler. The cut open specimen showed a pedunculated polypoidal lesion at the leading edge of the intussusception. Histopathology showed a polypoidal lesion suggestive of an inflammatory fibroid polyp. There was no evidence of malignancy. The postoperative period was uneventful. The patient is now kept on a follow up regimen.

Discussion:

Intussusception is very rare in adults & old age. The supposed etiology for colocolic intussusceptions in this age group is usually due to an underlying malignancy. Benign intussusceptions are more common in the small bowel. Malignant lesions causing large bowel intussusceptions include primary tumours (adenocarcinomas, lymphomas) and metastatic tumours. Benign tumours include lipomas and adenomatous polyps. Idiopathic intussusceptions without a lead point occur in 10% of cases.

Intussusception is the telescoping of a bowel loop (intussusceptions) with its mesenteric folds into the lumen of a contiguous portion of bowel (intussuscipiens). The mass in the bowel acts as an irritant and provokes abnormal peristaltic movement which leads to the invagination of one segment over the adjacent bowel segment. The exact mechanism of for an intussusceptions without a lead point is not known, but this condition may be attributed to dysrhythmic contractions.
An intussusceptions may present with crampy abdominal pain, nausea, vomiting and subsequent constipation and diarrhea. It is usually diagnosed by barium enema, colonoscopy, ultrasound or by a CT scan. Ultrasound imaging of this condition shows a “doughnut shape” on a transverse section and a “bull’s eye” configuration on longitudinal section. A “pseudokidney sign” is also a typical finding in USG.

An intussusception has a pathognomonic appearance on CT Scan. It appears as a complex soft tissue mass consisting of an outer intussusceptum and the central intussusceptum. There is an eccentric area of fat density within the mass which represents the intussuscepted mesentry fat containing the mesenteric vessels within it. The intussusceptum appears as a “sausage” shaped mass when the CT beam is parallel to the longitudinal axis and as a “target” mass when the beam is perpendicular to the longitudinal axis. The appearance of an intussusceptions is quite but the exact characteristic on CT but the exact etiology cannot be well established. The etiology can be known only after correct histopathological examination.

References:
5. Colocolic intussusception - Leo S Figiel and Steven J Figiel. Digestive Diseases and Sciences Volume8, Number12, 1017-1028,1963.
Gastro Intestinal Stromal Tumour (GIST) of the Ampulla of Vater: Report of Two cases

D. Mohapatra¹, A.P. Dash², S. Panda², Md. Ibrarullah³, P. Devi⁴

Abstract:
Gastrointestinal stromal tumor (GIST) of the ampulla of Vater is extremely rare. A literature search yielded only 10 such reported cases till date. We present two cases of ampullary GIST, one benign and another malignant. The benign tumor presented with massive hematemesis and melena. The malignant tumor presented with obstructive jaundice. Both cases were successfully resected.

Key words: GIST, Periampullary tumor, hematemesis

Introduction:
Gastrointestinal stromal tumor (GIST) was first reported in 1983 by Mazur and Clark to describe nonepithelial tumors of the gastrointestinal (GI) tract that lacked the ultra structural features of smooth muscle cells as well as the immunohistochemical characteristics of Schwann cells. GIST represent only 0.2-3% of GI malignancies having an estimated incidence of 10-20/million. Stomach (40-60%) is the most common location of GIST followed by small intestine (30-40%), colo-rectum (10-15%) and duodenum (3-5%). Involvement of the ampulla of Vater is extremely uncommon. The available publications on this entity are in the form of anecdotal case reports only. We report two patients with ampullary GIST that was managed by us.

Case 1:
A 45-year-old-female was admitted with hematemesis and melena for two days. She had a similar attack 45 days back for which she was transfused four units of blood. Upper GI endoscopy during the present admission showed fresh blood in stomach & duodenum. On side-viewing endoscopy, the ampulla of Vater appeared bulky with an ulcer on its surface (Fig. 1). Biopsy of the ulcer was inconclusive. Her hemoglobin was 5gm/dl. Other hematological and biochemical parameters were within normal range. During present hospitalization she had another episode of bleeding necessitating an emergency laparotomy. The ampulla felt nodular from outside. Rest of the abdominal viscera appeared normal. The patient was subjected to pylorus preserving pancreaticoduodenectomy (PPPD). The resected specimen showed a nodular and ulcerated ampulla with a visible vessel at its center (Fig. 2).

Fig. 1: Side viewing endoscopy showing an ulcerated ampullary tumor.

Fig. 2: Resected pancreaticoduodenectomy specimen showing ulcerated and nodular ampullary mass. Note the visible vessel i.e. the bleeding point (arrow).
The patient made an uneventful recovery except for a pancreatic anastomotic leak that was managed conservatively. Histopathology of the tumor was consistent with benign ampullary GIST (mitotic figure of 5/50 HPF). Immunohistochemical study of the tumor was positive for CD 34, c-kit and SMA negative for Desmin and S-100. The patient remained healthy at follow up of 18 months.

**Case 2:**

A 52-year-old-male was admitted with complains of painless, progressive jaundice, and anemia of one and half month duration. His blood investigations revealed Hb of 7.8 gm/dl, serum total and direct bilirubin of 6.3 gm/dl and 5 gm/dl respectively. Serum alkaline phosphate was 1800 mg/dl, SGOT -37 mg/dl and SGPT- 46 mg/dl. Upper GI endoscopy showed an ampullary tumor and biopsy was inconclusive. Ultrasonography (USG) showed distended gall bladder, dilated intrahepatic biliary radicles (IHBR) and dilated (1 cm) common bile duct (CBD) with an abrupt cut off at the distal end. Contrast enhanced CT scan of abdomen showed a hyperdense 4 x 3 cm periampullary lesion with dilatation of CBD and IHBR. A clinical diagnosis of periampullary carcinoma was made and the patient was subjected to PPPD. In post-operative period the patient had prolonged gastric ileus that was managed conservatively. Histopathology of the tumor was consistent with malignant GIST (Fig. 3) with a mitosis count of 20/50 HPF.

**Fig 3:** Histology (H&E staining, 40x magnification) confirming malignant GIST in the second patient.

The cut margin of specimen and lymph nodes were free of tumor. The patient was discharged on the 25th postoperative day. In a follow-up of 30 months, he has remained disease free and in good health.

**Discussion:**

GIST is thought to arise from the interstitial cells of Cajal (ICC), a component of the intestinal autonomic nervous system. In 1998, Hirota and colleagues demonstrated gain-of-function mutations of the KIT proto-oncogene in the vast majority of GISTs. GIST are now identified by the near universal expression of the CD117 antigen (95%) and is characteristic of most GIST. Expression of CD-34 has been reported in 60-80% of GIST’s. Approximately 7% of GIST has gain-of-function mutations in the PDGFRA tyrosine kinase receptor.

After extensive review of literature and online search, we could find only 10 reported cases of the GIST of ampulla of Vater. The tumor is commonly encountered in the fifth and sixth decades of life without any preference for sex, race or ethnicity. Ampullary GIST may present with weight loss, nausea, melena, anemia and jaundice. Though GIST almost never metastasizes to regional lymph nodes; there has been one documented case of ampullary GIST presenting with multiple liver and lymph node metastasis. Tumors giving rise to metastases are generally more than 5 cm.
in diameter and have a high mitotic index (>10 mitoses/HPF). However, up to 20% of small GIST (<5 cm) can also exhibit metastatic behavior. The recognition that all GIST have some malignant potential, has now led to their classification as either low, intermediate, or high-risk based upon tumor size and mitotic count.

A preoperative diagnosis of GIST may affect the mode of treatment offered to the patient. This has ranged from local resection (3 patients) to Whipple’s procedure (6 patients), one patient died due to metastasis before any surgery was undertaken. An accurate preoperative diagnosis, however, may be extremely challenging. The reason being- (i) presenting as a mass in the ampullary region it mimics periampullary carcinoma, (ii) Preoperative endoscopic ultrasound, though has been reported to be highly successful in both documentation and biopsy confirmation, it is still not readily available or expertise may not be present everywhere. One of the cases reported here underwent pancreaticoduodenectomy with a preoperative clinical diagnosis of ampullary carcinoma. The second patient underwent an emergency resection for massive bleeding before biopsy confirmation could be obtained. Use of Imatinib in duodenal GIST preoperatively to control bleed has been reported but it is still very early to speculate its use in ampullary GIST. Given all considerations, pancreaticoduodenectomy is probably an appropriate mode of treatment for ampullary GIST.

References:
In-vitro study of proliferation in short term cultured Umbilical Cord blood stem cells

S. Mantri¹, P.C. Mohapatra²

Abstract:

Increased cell dose of both haematopoietic as well as mesenchymal stem cells of Umbilical Cord Blood (UCB) is now becoming a prime challenge for better engraftment after transplantation. Based on this concept, we tried to establish a short term culture protocol for stem cells, derived from 10-12mlof UCB & studied their proliferation rate. After the collection and separation of stem cells or mono nuclear cells (MNCs) from the whole blood, the cells were harvested in the growth media. On the 3rd day of the primary culture, the floating nonadherent fraction of cultured MNCs were removed & harvested in the culture media specific for HSC growth. After one week of culture of adherent & nonadherent fraction of UCB stem cells separately, very few number of fibroblasts were observed in adherent fraction of only 3% of total collected UCB samples, while expansion of nonadherent cells was not significant. Hence, our study concluded with the poor outcome of the proliferation as observed in both fraction of UCB stem cells.

KEY WORDS: Non-adherent cells, Haematopoietic stem cells, Adherent cells, Mesenchymal stem cells

Introduction:

To date, the Umbilical Cord Blood (UCB) stem cells have drawn the attention of clinical researchers as the potent candidate for stem cell based therapies because of the presence of both haematopoietic as well as mesenchymal stem cells. During the last three decades Hematopoietic stem cells (HSC) transplantation has become a well established treatment for hematologic malignancies and non-malignant disorders. HSCs tend to differentiate when they proliferate, hence in-vitro expansion of HSC for increased cell dose with the preservation of stemness, is required for better clinical outcome of autologous and allogeneic HSC transplantation. The nonadherent fraction of cultured UCB stem cells are haematopoietic in nature while adherent fibroblastic cells shows the mesenchymal stem cell characteristics.

Mesenchymal stem cells (MSCs) support the engraftment of hematopoietic stem cells (HSCs) (2,3). MSCs was also observed to support the long term HSC maintenance and engraftment of cord blood derived HSCs in NOD/SCID mice in some of the lab investigations (4). The most preferable source of MSC is the bone marrow (BM), in comparison to the UCB but its easy accessibility for collection (5,6) and primitive nature of MSCs (7,8,9) making UCB as the alternative source of choice. Furthermore, several groups demonstrated that UCB MSC can be harvested for a longer period with high proliferative capacity as compared to MSC derived from other sources (10,11). It can be obtained by a less invasive method, without any harm to mother & newborn. UCB cells provide no ethical controversies for basic studies and clinical applications (12, 13).

In our investigation, we tried to establish a short term culture condition for both of the Adherent and non adherence stem cells separately & study their rate of proliferation.

Methodology: We prepared Citrate-Phosphate-Dextrose (CPD) anticoagulant for the collection of UCB sample as shelf life of whole blood in CPD was 28days.

Anticoagulant Preparation (For 1000ml):

- Citric acid ———— 3.27gms
- Trisodium citrate ———— 26.3 gms
- Sodium Dihydrogen Phosphate—— 2.51 gms
- Dextrose ———— 25.5 gms

¹PhD scholar, Department of Bio-chemistry,
²Professor, Bio-Chemistry, Dean & Principal
S.C.B. Medical College, Cuttack.
Email: santonam_mantri@rediffmail.com
Mobile no.9937455646
Submitted : 12.12.2012, Accepted : 04.01.2013
© OMJ 2012
For 10ml of blood sample collection, we used sterile collection tubes containing 1.4ml of CPD anticoagulant.

Collection, Processing of the human UCB Sample:-

Collection of small volume of about 10-12ml of UCB in a sterile sample collection tubes containing anticoagulant Citrate-Phosphate-Dextrose(CPD) was carried out, with the approved (by institutional ethical committee) informed consent of the mothers, from the cords of the full term deliveries (gestation week:37-40). The eligible participants were above 20 years of age with no indication of Septicemia, any other Hematological infections or complications and negative for VDRL, human immunodeficiency, hepatitis B, hepatitis C viruses. The processing time was within 7 hours of collection without any sign of haemolysis or coagulation. The whole blood sample was diluted with Phosphate Buffered Saline (PBS-A) in 1:1 ratio. UCB stem cells or Mononuclear Cells (MNCs) or mono nuclear fractions(mnf) were recovered from the interface obtained by density gradient centrifugation (1.077g/ml Histopaque, Sigma). Then the collected MNCs were washed twice with PBS-A and the number of MNCs was measured by cell counting through Haemocytometer.

The above study was carried out in the Department of Biochemistry, S.C.B. Medical College, Cuttack. The study participants were chosen carefully from the Department of Obstetrics & Gynecology, S.C.B. Medical College, Cuttack.

Culture of UCB MNCs:-The UCB MNCs were set in culture at a cell concentration of 1 ×10^5 in Dulbecco’s Modified Eagle’s Medium (DMEM, PAN-BIOTECH, Germany) along with 10% Fetal Bovine Serum(FBS,PAN-BIOTECH, Germany), and 1% penicillin, streptomycin antibiotics(Himedia, India) in 6-well culture plates. Cell cultures were done at 37°C in a humidified atmosphere of 95% air and 5% CO2. The medium was replaced by fresh one after 48 hours. The non-adherent cells of the harvested MNCs were removed from the adherent layer and cultured separately. The culture was fed twice a week.

The non-adherent fraction of cells (HSCs) of primary culture, after removal was separately set in culture with Iscove’s Modified Dulbecco’s Medium with L-glutamine (IMDM,PAN- BIOTECH,Germany) containing 10% FBS,1% penicillin, streptomycin antibiotics with Seeding density of 1×10^6. After 7th day, the media with nonadherent cultured cells were centrifuged at 1500rpm for 5minutes, then the cells were washed with PBS-A and counted in Haemocytometer.

While the retained small number of adherent fraction of primary culture was harvested in DMEM-Low Glucose (DMEM-LG, PAN-BIOTECH), 2mmol/1L-glutamine, 10% FBS, 1% penicillin, and streptomycin antibiotics for 7days, in order to increase the number of cells. On 7th day, the cells were trypsinized with using 0.25% Trypsin/EDTA (Himedia, India) & washed twice with PBS-A for their counting.

Cell expansion and Viability were assessed by direct cell count by Trypan Blue Exclusion method using Haemocytometer.

Results :

We started this investigation with 10-12 ml of cord blood, in which the total number of stem cells or MNCs after processing was 1.7×10^8.

When the UCB MNCs were set in primary culture, three layers of cells were observed on the 3rd day.

The upper non-adherent fraction was observed to be consisted of two layers i.e. middle and the uppermost layer. In the middle layer, small round cells loosely attached to the lowermost adherent layer. They

![Fig-1 The non-adherent cells loosely attached to the adherent fibroblastic cells.](image-url)
can be easily separated after giving small stress to the culture (Fig-1). The uppermost layer consisted of a large number of small rounded floating cells.

The bigger flat sized cells like macrophages & sometimes spindle shaped or narrow thin strand like fibroblasts were observed to be firmly attached to the bottom layer of culture plate (Fig-2).

After setting up separate culture conditions for both of non-adherent and adherent layer of cells for a week, the mean (SD) fold expansion was evaluated as 0.61±0.05 for non-adherent cells. These cells did not attain confluence as observed after 7th day of their harvest (Fig-3).

The number of left over adherent cells was few which neither showed increased rate of expansion on further cultivation nor attained confluence after 7th day of culture under growth media containing DMEM-LG. In most of cases, cells did not show any fibroblastic morphology.

Fig-2 The big flat macrophages and spindle shaped fibroblasts as observed in adherent fraction of UCB stem cells.

After setting up separate culture conditions for both of non-adherent and adherent layer of cells for a week, the mean (SD) fold expansion was evaluated as 0.61±0.05 for non-adherent cells. These cells did not attain confluence as observed after 7th day of their harvest (Fig-3).

The number of left over adherent cells was few which neither showed increased rate of expansion on further cultivation nor attained confluence after 7th day of culture under growth media containing DMEM-LG. In most of cases, cells did not show any fibroblastic morphology.

Fig-3 The culture of non-adherent cells showing non- confluence.

The maximum 10- 12 numbers of cells with fibroblastic appearance was found in adherent fraction, after 7th day of culture in 3% of total collected UCB (Fig-4).

Fig-4 illustrating very few numbers of fibroblasts as observed in adherent cell culture.

Fig-5 A small group of adherent cells with fibroblastic morphology.
Sometimes fibroblastic cells occur in small group of 6-7 cells (Fig-5).

**Discussion:**

Our lab investigation reported that the non-adherent haematopoietic stem cells did not show significant *in-vitro* proliferation. Supplementation of the culture medium with haematopoietic growth promoting cytokines may be the best defined medium for HSC expansion as suggested by other reports (14,15).

This *in-vitro* study on UCB derived MSCs, observed their very low frequency in 10-12 ml of UCB, in few samples while in majority, there was complete absence of fibroblastic cells during the harvest of adherent fraction. The above observation supports some of the reports suggested by other investigators (16,11,6,17,18).

**Conclusion :**

In our experimental study, we have established the short-term culture methodology for cord blood stem cells, but failed to increase the number of harvested cells significantly for the attainment of confluence in both of its adherent & non-adherent fraction. Further investigation is required for the efficient isolation & long term proliferation of UCB stem cells.

**References :**


Warfarin Embryopathy – To prevent or to treat?

P. Mishra¹, J.R. Panigrahy²

Review of Literature

Warfarin is an oral anticoagulant that inhibits synthesis of vitamin K–dependent clotting factors (II, VII, IX, and X) and the anticoagulant proteins C and S.¹ Rats given very high doses (100 mg/kg) of warfarin have had offspring with marked maxillonasal hypoplasia and skeletal abnormalities, including abnormal calcium bridges in the epiphysial cartilages of the vertebrae and long bones.²

Several case series and case reports of human use of warfarin during pregnancy have been published. These reports (which range in size from one to 418 subjects) show a clear association between warfarin therapy and embryopathy. The exact risk of fetal damage from warfarin therapy during pregnancy is difficult to determine because most of the available studies are small and anecdotal.

Several reports have indicated, however, that using warfarin between 6 and 12 weeks’ gestation is associated with “fetal warfarin syndrome,” which is most commonly manifested by nasal hypoplasia, stippled epiphyses, limb deformities, and respiratory distress. Use of warfarin during the second and third trimesters has been associated sporadically with central nervous system abnormalities, including mental retardation, microcephaly, optic atrophy, and blindness.³-⁶

Other fetal abnormalities reported with maternal warfarin use include absent or non-functioning kidneys, anal dysplasia, deafness, seizures, Dandy-Walker syndrome, and focal cerebellar atrophy.³⁴⁵ Use of warfarin throughout pregnancy has been associated with hemorrhagic complications, premature births, spontaneous abortions, stillbirths, and death.⁴⁵, ¹⁰-¹⁵

One study⁸ reported on 418 cases of warfarin exposure from conception to 38 weeks after birth. About 16% of all pregnancies ended in spontaneous abortions or stillbirths, and another 15% resulted in babies with abnormalities at birth. The abnormalities included skeletal malformations (eg, stippling of cervical vertebrae, sacrum, and femurs; kyphoscoliosis; and nasal hypoplasia) bilateral optic atrophy leading to blindness, deafness, focal cerebral atrophy, respiratory distress, and seizures. Doses of warfarin ranged from 2.5 to 12.5 mg/d.

Salazar and colleagues reported on 128 babies exposed to warfarin therapy from 0 to 38 weeks’ gestation. About 8% of the 38 live-born infants displayed teratogenic effects of warfarin at birth, including nasal hypoplasia, choanal stenosis, and stippled epiphyses. When compared with 68 pregnancies where women’s warfarin therapy had been replaced with 1 g of acetylsalicylic acid and 400 mg of dipyridamole daily at the onset of pregnancy, it was clear that the rate of spontaneous abortions was significantly higher in the warfarin group (28% vs 10%). The rate of neonatal deaths was also higher in the warfarin group (2.3% vs 0). The rate of stillbirths was approximately 7% in both groups. Warfarin dose was adjusted for a target prothrombin time of 2 to 2.5 times control in most women.¹¹

Ayhan et al¹² reported on 64 pregnancies: 47 were exposed to warfarin, 11 were exposed to heparin, and 6 were not exposed to anticoagulation drugs. In 20 pregnancies, warfarin was discontinued after 36 weeks’ gestation. Fetal wastage occurred in 25 (53%) pregnancies exposed to warfarin, four (36%) exposed to heparin, and only one (17%) with no exposure to anticoagulation drugs. Two (4%) babies were born with warfarin-related malformations, manifested by a single kidney, digit deformities, and cleft lip and palate. There were nineteen (40%) spontaneous abortions and four (9%) stillbirths with warfarin, but only one (9%)
spontaneous abortion and no stillbirths with heparin. Warfarin doses were not reported in this study.

Vitali et al\textsuperscript{13} reported on 98 pregnancies exposed to warfarin since conception. Warfarin was replaced with heparin in six cases 3 weeks before delivery, was discontinued in six women before term, and was maintained in 13 women throughout the whole pregnancy. There were 37 spontaneous abortions (38\%) and 13 voluntary terminations (13\%). Of the 47 live births, two (4\%) had warfarin-associated malformations at birth, manifested by occipital bone abnormalities, nasal hypoplasia, severe choanal stenosis, and cleft palate. One baby died from respiratory insufficiency 4 hours after delivery, and four (9\%) babies were born with hemorrhagic complications secondary to warfarin therapy. Warfarin doses were not specified in this study.

Vitale et al\textsuperscript{14} reported on 58 exposures to warfarin throughout pregnancy until 38 weeks’ gestation. Although 31 (53\%) babies were reported normal at birth, 27 (47\%) had fetal complications: 22 (38\%) spontaneous abortions, one (1.7\%) stillbirth, two (3\%) warfarin embryopathies, one (1.7\%) ventricular septal defect, and one (1.7\%) growth retardation. Warfarin doses in this study were adjusted for a target international normalized ratio (INR) of 2.5 to 3.5. When stratified according to dose, 22 (81\%) complications occurred after exposure to doses >5 mg/d. The study concluded there was a close association between warfarin dose and fetal complications.

One study looked at 114 exposures to warfarin during pregnancy.\textsuperscript{15} While 50 women took warfarin throughout pregnancy, the remaining 64 women received subcutaneous heparin during the first trimester and warfarin during the second and third trimesters. All the women’s warfarin therapy was replaced by heparin 2 to 4 weeks before labour. Spontaneous abortions occurred in 22\% of cases exposed to either warfarin or heparin, and stillbirths occurred in 9\% of cases exposed to warfarin and 11\% of cases exposed to heparin. No embryopathies were reported among the live births.

The review\textsuperscript{16} recommends that women receiving long-term oral anticoagulation have warfarin replaced with unfractionated or low molecular weight heparin when they become pregnant. There have, however, been case reports of unfractionated heparin being associated with adverse pregnancy outcomes, such as fetal loss and maternal thrombocytopenia, hemorrhage, and osteoporosis.\textsuperscript{14} Needless to say, the women in these studies were often sick, and their complications could have been caused by underlying illness. A study of 108 women who received low molecular weight heparin for thromboprophylaxis\textsuperscript{17} showed no increase above baseline for fetal deaths or malformations.

Bony C - Another case of warfarin embryopathy in mother treated with acenocoumarol showed chondrodysplasia punctata with telebrachydactyly, facial dysmorphism with nasal hypoplasia, cataract, and bilateral pyleuroreteral junction syndrome (Arch Pediatr. 2002)

Sathienkijkanchai A - A patient of WE developed difficulty breathing in the first few hours after birth from severe nasal hypoplasia, also had short limbs, brachydactyly, nail hypoplasia, and calcifications in the epiphyseal regions of humeri, femora and vertebrae radiographically, eventually died of respiratory failure at 6 months of age. (J Med Assoc Thai. 2005)

Khan AO - Optic nerve dysfunction in a child following low-dose maternal warfarin exposure (Ophthalmic Genet. 2007)

Raghav S - Neurological sequelae of intrauterine warfarin exposure (J Clin Neurosci. 2007)

The literature suggests a strong association between maternal warfarin use and fetal adverse effects.

CASE 1. B/o Poonam :

Single, Term, Male, Small for Gestational Age(SGA), LBW, asymmetric IUGR, Emergency LSCS(CPD in labour), Resp. Distress, Upper airway obstruction and Warfarin embryopathy.

7 months boy with frequent nasal obstruction relieved by normal saline nose drops, otherwise normal.

Fig. 1- Depressed Nasal Bridge
CASE 2. B/o Sarita:

Born on 14.08.09, had depressed nasal bridge & chondrodysplasia punctata in calcaneum bones of both ankles.

Fig.2 Stippled calcaneum right side

Fig.3 Stippled calcaneum left side

Fig.4. Skeletal survey of b/o Sarita showing stippled epiphyses.

B/O SUMAN

Born to 22yrs G3P0A2 mother with RHD(Rheumatic Heart Disease) since 2004, post double (Mitral & Aortic) valve replacement (Dec.2006), visited OPD at 8wks3days amenorrhea, Urinary pregnancy test-positive, USG:-single intrauterine gestational sac, cardiac activity present, crown rump length~8weeks.Spontaneous conception. Patient was admitted for heparin switch over. Got heparin & other cardiac drugs except warfarin. Folic acid also added. Early scan at 12 wks + anomaly scan at 18 wks showed no anomalies & was discharged at 12wks 3day with switch over to warfarin 5mg OD. T2-advised triple screen: she didn’t do it. Anomaly scan at 18 wks-no congenital anomaly. Received inj TT two doses, iron & calcium prophylaxis. Rest course-uneventful.T3-developed acute hydramnios at 31 weeks. Abdominal girth-38 inches,normal oral glucose tolerance test (OGTT) 3D/4D USG -absent nasal bone, AFI-31,no other anomaly, leaking pv at 33wks4days (06/08/09) for which labor was augmented.

Fig 5. Fetal ultra sound of Suman

Fig. 6. Fetal ultra sound of Suman

Fig 7- Photo b/o Suman

Fig 8- Depressed nasal bridge, Flat upturned nose, absent nasal bones

Fig9 Camptodactyly

Fig 10. Shortened fingers

GA-33 weeks, Male baby born by outlet forceps assisted vaginal delivery, 1542 gm, LBW, AGA, had sagging nose, absent nasal bone & difficulty in respiration. APGAR-6/8

X-ray spine shows stippling of bodies, characteristic of warfarin embryopathy.
Clinical course

D-1 - Respiratory failure, SIMV, minimal settings,
D-2 & D- 10 Extubation failure, Fibreoptic Nasal
endoscopy, D-11 Tracheostomy, D-15—Successful
extubation, on full feeds, O2 by hood.

Conclusion :

No method of anticoagulation during pregnancy is entirely free of risk

Warfarin throughout pregnancy is associated with lowest risk of valve thrombosis but increased risk of embryopathy

Detailed ultrasonography in patients on warfarin is warranted

Warfarin therapy should be avoided during pregnancy. If warfarin therapy is essential, it should be avoided at least during the first trimester (because of teratogenicity) and from about 2 to 4 weeks before delivery to reduce risk of hemorrhagic complications.

Unfractionated heparin or low molecular weight heparin could be substituted when appropriate because these agents do not cross the placenta and are considered the anticoagulant drugs of choice during pregnancy.

References :

INTRODUCTION:
Pulmonary hypoplasia is a rare bronchopulmonary foregut anomaly in which the gross morphology of lung is essentially unremarkable but there is decrease in number or size of airways, vessels and alveoli(1). Though one of the important causes of death in newborns and infants, Pulmonary hypoplasia is rare in adults(4). Boyden, in 1955, has classified the degree of pulmonary underdevelopment into three groups as pulmonary agenesis, pulmonary aplasia and pulmonary hypoplasia. The incidence of unilateral pulmonary agenesis has been estimated approximately one in 15,000 live births or between 0.0034% and 0.0097%. In 70% of cases, the left lung is absent (2). The incidence of primary hypoplasia has been estimated to be 1 to 2 per 12,000 births with no gender predilection. The accompanying congenital anomalies include cardiac lesions (Tetralogy of Fallot), bronchogenic cysts, central nervous system involvement (anencephaly, hydroencephaly), diaphragmatic hernias, skeletal anomalies, Klippel Feil syndrome and Down syndrome (1). A case of left sided pulmonary hypoplasia with rare association of right aortic arch (incidence 0.5%) is described here.

CASE REPORT

A 30 year-old female was admitted in the Department of Pulmonary Medicine, S.C.B. Medical College, Cuttack with chief complaints of breathlessness increasing on exertion and left sided dull aching chest pain since 5 months. There was no significant past history and co-morbidities. She is a housewife, married since last 12 years with no issues.

General physical examination was non-contributory, vitals were stable. Examination of respiratory system revealed decreased movement of left hemithorax, trachea shifted to left, apexbeat shifted to left (left 5th intercostal space on mid-clavicular line). Percussion note was dull over left hemithorax. On auscultation, air entry was poor on left side with crepitations present over left lung base.

Investigations: Hb-12 gm%, TLC- 9900/cmm, DC- N70, L26, E04
All other blood parameters were within normal limits. Sputum for AFB was negative. No lower respiratory tract organism was isolated from bacterial culture.

Spirometry: FEV1-pre: 45% pred, post: 40% pred, % change = -12%
FVC-pre: 48% pred, post: 56% pred, % change = 12%
FEV1/FVC-pre: 58.8, post: 48

Chest X-Ray: small left lung with trachea and heart shifted to left.

Figure 1: CXR showing small left lung with shifting of trachea & heart to left

HRCT & CECT Thorax: HYPOPLASTIC LEFT LUNG with minimal honeycombing changes in
posterior basal segment, Minimal herniation of anterior part of Right lung, Elevation of left hemidiaphragm. Aortic arch in right side branching into rt subclavian, rt common carotid and lt brachiocephalic trunk suggestive of RIGHT AORTIC ARCH WITH MIRROR IMAGE BRANCHING, Descending aorta present on the right side.

CT Thorax Angio: Right aortic arch with left brachiocephalic trunk and right descending aorta, LEFT PULMONARY ARTERY GROSSLY NARROWED; lumen could not be delineated properly.

2D ECHO: Normal study.

Bronchoscopy: Normal study.

Evaluation for Infertility: Thyroid function test normal, USG Abdomen Pelvis normal

Semen analysis of husband: volume 1ml, consistency less viscid. Total sperm count 82 millions/ml, actively motile 60%, non motile 20%

DISCUSSION

Development of bronchial tree takes place at about 26th-31st day of intrauterine life. Monal divided mal-development of lung into four groups; Group 1: no bifurcation of trachea, Group 2: only rudimentary main bronchus, Group 3: incomplete development after division of main bronchus, Group 4: incomplete development of subsegmental bronchi and small segment of the corresponding lobe.

Boyden (1955) classified mal-development into 3 categories; 1) AGENESIS- the entire lung, bronchus and its pulmonary vessels are absent, 2) APLASIA- the lung and pulmonary artery are absent, but there is a rudimentary bronchus coming off the trachea, 3) HYPOPLASIA- hypoplastic bronchus with hypoplastic lung parenchyma.

According to etiological factors Lung Hypoplasia is classified as a) Primary-no obvious cause for hypoplasia. b) Secondary-variable fetal and maternal abnormalities in 60% of cases. Some of the causes are

1.) Intrathoracic: Congenital diaphragmatic hernia (MC), Agenesis of diaphragm, Extralobar sequestration, Mediastinal mass (teratoma), Decreased pulmonary vascular perfusion, Congenital cardiovascular anomaly-TOF, Unilateral absence of pulmonary artery.

2.) Extrathoracic: Oligohydramnios and its causes, Potter sequence- fetal renal anomalies, Premature rupture of membranes, Skeletal dysplasias causing narrow fetal thorax, Achondrogenesis, Osteogenesis imperfecta.

In this case there is gross narrowing of the left pulmonary artery.

Frequency of Right Aortic arch is 0.5% in normal population. It is the 2nd most common cause of vascular ring after double aortic arch. Three common anomalies of right aortic arch are:

1) RAA with aberrant left subclavian artery
2) RAA with MIRROR IMAGE BRANCHING
3) RAA with isolated left subclavian artery
Right aortic arch with mirror image branching is commonly associated with congenital heart diseases like TOF, VSD, Truncus arteriosus. The present case has RAA with mirror image branching, but there is no associated cardiac anomaly.

CONCLUSION:

Hypoplasia or agenesis of lung or its lobes must be considered in the differential diagnosis in the case of an opaque hemithorax. It is important to investigate the coexistence of this anomaly. Asymptomatic cases do not require any treatment if there are no additional anomalies. These cases carry high-risk in any surgery because of low respiratory reserve.

REFERENCES:

5. Dr Maxime St-Amant and Dr Yuranga Weerakkody, Pulmonary Hypoplasia
6. CT & MRI of the whole body-HAAGA, 5th edition
Use of Rubber Hair Bands for external Fixation using K Wire after release of Hand Contracture

S.P. Mishra¹, R. Das², A.P. Patnaik³

AIM: The main aim of this study is to evaluate how hair rubber bands are being used for stable fixation of external fixators using K wires after the release of contractures of fingers and hand. The fingers can be kept apart & joint position maintained for adequate time in desired position for healing process to continue satisfactorily.(7)

METHODS: Study was done in the Department of Plastic & Reconstructive Surgery, SCB Medical College & Hospital Cuttack & at different private hospitals during the period 2008 to 2011. The contractures are released by incision or excision of scar tissue, true defect recreated, fingers and joints are kept in(4) desired position using K wires as fixators. The position is maintained by interwooving of K wires with the help of rubber bands. The entire procedure was carried out under regional block.

RESULTS: After release of contracture & after fixing with K wire, the position maintained with rubber band. It is seen position is maintained up to 21 days. It is easy to manipulate when necessary. Easy in dreshing change. Effect is equivalent with use of Alfa clamp.

CONCLUSION: use of K wire for stable external fixation(5) of K wire is effective, cheap method that is evaluable with minimum complications and can be used for longer period in comparision to standard and conventional method used for stable fixation of released contractures.

INTRODUCTION: Friction is the force acting against the relative motion of solid surface against each other. Classic rules sliding friction were discovered by Leo Nardo da Vinci (1452-1519). Coefficient of friction depends on the materials used; for e.g. Ice on steel has low coefficient of friction where as rubber on steel has coefficient of force nearly one. Keeping the above principle of Physics in mind the innovative study was done.(1). In our institute – SCB Medical college & Hospital & other private hospitals.

MATERIALS METHOD & PROCEEDURES: The study was conducted in the Department of Plastic & Reconstructive Surgery of SCB Medical College Hospital & private hospital Patients of Post Burn and Post Traumatic Contracture of fingers, web spaces & hand were selected. Preoperative evaluation & surgical planning was done. All the selected patients underwent release of contracture(6,7) by excision of scar tissue, re-creation of true defects & residual wound cover was done either by skin graft or flaps. The position of fingers, joints and web spaces are maintained by multiple intramedullary K wire fixation. These external fixator K-wires were stably maintained(2) by interwooving with hair rubber bands either in single plane or multiple planes.

Wide 1st webspace maintained
Table -1 shows how use of hair rubber band is cost effective in each unit of patient.  
(Only direct cost to the patient calculated however indirect cost is not included )

Table-2

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Rubber band</th>
<th>Alpha/Beta clamp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position maintained-</td>
<td>Maintained</td>
<td>Plastercast</td>
</tr>
<tr>
<td>Manipulation-</td>
<td>Easy</td>
<td>Maintained</td>
</tr>
<tr>
<td>(in between)</td>
<td></td>
<td>Not easy</td>
</tr>
<tr>
<td>Extra instruments-</td>
<td>Not necessary</td>
<td>Necessary</td>
</tr>
<tr>
<td>Dressing change-</td>
<td>Easy</td>
<td>Not easy</td>
</tr>
<tr>
<td>Multiplaner fixation-</td>
<td>Can be done</td>
<td>Extra maneuver</td>
</tr>
</tbody>
</table>

DISCUSSION

K wires can be fixed by other methods like alpha & beta clamps, other sources of external fixators lives universal clamps(Ao type)2.5m/3.5m size, Schanzpin(2.5),with connecting rods, finger-distracters,(Ref 4) plaster cast & hand splint, of aluminum or thermo acrylic material type. However these fixators are costly. Some are to be prepared preoperatively, has short term use, per-operative manipulation is cumbersome. But in our method the hair rubber bands are easily available, cheap(Tab-1) durable & no extra instruments are required for its application. The advantages are easy per-operative/post-operative manipulation done for desired positioning which sustained and maintained for long time has least damage to adjacent tissue, allows easy post-operative dressing change and evaluations. More over it is noticed that the joint position can be modified as per requirement by simply bending the K wires to different planes and positions.(1) We have no complications in any of the patients & the final results are quite satisfactory.(Tab2)

RESULTS : As the fingers were properly kept apart, the web spaces properly maintained, wrist Joint, MP Joint, PIP & DIP Joints also kept in desired position for graft or flap to settle well and prevent springing back effect.(3)

Table-1

<table>
<thead>
<tr>
<th>Name of fixator</th>
<th>Price Rs per piece</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha clamp</td>
<td>100.00</td>
</tr>
<tr>
<td>Beta clamp</td>
<td>100.00</td>
</tr>
<tr>
<td>Schanzh pin (2-5mm)</td>
<td>120.00</td>
</tr>
<tr>
<td>Schanzh pin (3.5mm)</td>
<td>150.00</td>
</tr>
<tr>
<td>Connecting Rod</td>
<td>150.00</td>
</tr>
<tr>
<td>Finger Distracter</td>
<td>750.00</td>
</tr>
<tr>
<td>Plaster cast</td>
<td>75.00</td>
</tr>
<tr>
<td>Hand Splint(Aluminum)</td>
<td>250.00</td>
</tr>
<tr>
<td>K wire one pc</td>
<td>60.00</td>
</tr>
<tr>
<td>Hair Rubber band (25pc)</td>
<td><strong>05.00</strong></td>
</tr>
</tbody>
</table>

References :
Rare Presentation of a Rare Disease: Tuberous Sclerosis

P.C. Patra¹, B.P. Behera¹, A.K. Sahu², J.K. Panda³, P.K. Rathor³, N. Dhal³, J.M. Nayak⁴

ABSTRACT

In this case report a 35 year lady presented with severe anaemia with congestive cardiac failure but found to have adenoma sebaceum, shagreen patches, sub-ependymal calcification and giant cell astrocytoma and was found to be a case of Tuberous Sclerosis.

Key words: adenoma sebaceum, shagreen patches, sub-ependymal calcification, giant cell astrocytoma, Tuberous Sclerosis.

INTRODUCTION

Tuberous Sclerosis is an autosomal dominant disorder. There occurs uncontrolled proliferation in numerous tissues, including the kidneys, skin, central nervous system, and heart. The kidneys are affected in 80% of patients. Patients have seizures, mental retardation, adenoma sebaceum (facial angiofibromas), shagreen patches, hypomelanotic macules, periungual fibromas, renal angiomyolipomas and cardiac rhabdomyomas.

CASE REPORT

A 35 year lady from Kendrapada got admitted to the Dept of Medicine, SCB MCH, Cuttack with breathlessness on exertion for 2 months and swelling of both the legs and face for 2 months. There was no history of similar episodes in the past, she was not a diabetic or hypertensive or a known case of heart disease.

On examination she was found to have severe pallor, bilateral pitting pedal edema, raised JVP. She was tachypneic (RR= 36/min). There was a no. of skin angiofibromas (adenoma sebaceum) which mimicked skin tags or acne vulgaris in her face. So we subsequently searched for and found Shagreen patches in her left flank, left side of her back and gluteal region also. She had cataract in her left eye which was congenital.

On systemic examination she was found to have her liver 5cm enlarged, moderate ascites. So she was provisionally diagnosed as severe anaemia in congestive cardiac failure with Tuberous sclerosis. But surprisingly she had neither any history of seizure in the past nor was she mentally retarded. Any of her family members also did not have any similar history.

On investigation she had Hb of 3gm%, TLC 8200/cumm (N-58%E-39%L-1%M-3%), RBS- 99gm/dL, serum urea-25mg/dL, creatinine- 0.8mg/dL, Na⁺-134mEq/L, K⁺-4.4 mEq/L, serum bilirubin(T)-1.3mg/dL, (D)-0.7mg/dL, AST- 70U/L, ALT- 32U/L, ALP-283U/L, total protein- 6.3gm/dL, albumin- 3.3gm/dL, peripheral smear comment- moderate hypochromasia

¹PG student, ²Senior resident,
³Asst. Professor, ⁴Assoc. Professor
PG Department of Medicine
SCB Medical College, Cuttack
Submitted : 5.02.2013, Accepted : 10.02.2013
© OMJ 2012
with mild anisocytosis, microcytosis of RBCs. USG of abdomen and pelvis showed hepatosplenomegaly, chronic medical renal disease, moderate ascites, minimal right pleural effusion. 2D echocardiography showed concentric LVH, diastolic dysfunction, mild MR, mild PAH with TR. CT scan of brain showed multiple sub-ependymal calcified nodules with sub-ependymal giant cell astrocytoma, suggestive of TUBEROUS SCLEROSIS.

TUBEROUS SCLEROSIS (BOURNEVILLE’S DISEASE/ EPILOIA) 1

This is an autosomal dominant disorder with an incidence of approximately 1 in 5000 to 10,000 live births. It is caused by mutations in either the TSC1 gene, which maps to chromosome 9q34, and encodes a protein termed hamartin or mutations in the TSC2 gene, which maps to chromosome 16p13.3 and encodes the tuberin protein. Hamartin forms a complex with tuberin, which is thought to negatively regulate cell growth and proliferation through inhibition of mammalian target of rapamycin (mTOR). The presence of either mutation produces uncontrolled proliferation in numerous tissues, including the kidneys, skin, central nervous system, and heart. Patients with tuberous sclerosis have seizures, mental retardation, adenoma sebaceum (facial angiofibromas), shagreen patch, hypomelanotic macules, periangual fibromas, renal angiomyolipomas, and cardiac rhabdomyomas. These patients have an increased incidence of subependymal nodules, cortical tubers, and subependymal giant cell astrocytomas (SEGA). Patients frequently require anticonvulsants for seizures. SEGAs often do not need treatment but occasionally require surgical resection. There is emerging evidence that mTOR inhibitors may have activity in SEGAs.

The kidneys are affected in 80% of patients. Renal TS occurs in three forms: renal angiomyolipomas, renal cysts, and renal cell carcinoma. Angiomyolipomas

Multiple sub-ependymal calcified nodules (arrow heads) and sub-ependymal giant cell astrocytoma (arrows)
are the most common renal abnormality. They occur bilaterally, are often multiple, and are usually asymptomatic; however, they may cause spontaneous bleeding, flank pain, hematuria, and life-threatening retroperitoneal hemorrhage. Large lesions, >4 cm, are more likely to be symptomatic and may require transcatheter arterial embolization or surgical excision. Cysts are usually asymptomatic and are not evident on imaging studies until adulthood. Rarely, cysts may be large and numerous, sometimes leading to ESRD and producing a clinical scenario that can be confused with ADPKD, especially if there are few other systemic manifestations of TS. Multicentric renal cell carcinomas occur with increased frequency in TS. Patients with TS should be screened for renal involvement at initial diagnosis with ultrasonography or CT. Those with cysts or angiomyolipomas require regular imaging to monitor for the development of renal cell carcinoma.

Diagnostic criteria for Tuberous sclerosis. 3,4

Major features
1. Renal angiomyolipoma (a)
2. Facial angiofibroma or forehead plaques
3. Non-traumatic ungula or periungual fibroma
4. Hypomelanotic macules (three or more)
5. Shagreen patch (connective tissue nevus)
6. Multiple renal nodular hamartomas
7. Cortical tuber (b)
8. Subependymal nodules
9. Subependymal giant cell astrocytoma
10. Cardiac rhabdomyoma, single or multiple
11. Lymphangioleiomyomatosis (a)

Minor features
1. Multiple renal cysts (c)
2. Non-renal hamartoma (c)
3. Hamartomatous renal polyps (c)
4. Retinal achromic patch
5. Cerebral white matter radial migration tracts (a, d)
6. Bone cysts (d)
7. Gingival fibromas
8. ‘Confetti’ skin lesions
9. Multiple, randomly distributed dental enamel pits

Diagnostic categories
Definite tuberous sclerosis complex
Two major features or one major plus two minor features

Probable tuberous sclerosis complex
One major plus one minor feature

Possible tuberous sclerosis complex
One major feature or two or more minor features

a) If both renal angiomyolipoma and lymphangioleiomyomatosis are present, other tuberous sclerosis complex features should be present before a definite diagnosis
b) Coexistent cerebral cortical dysplasia and white matter migration tracts should be counted as one instead of two features
c) Histological confirmation is suggested
d) Radiological confirmation is sufficient

References
What should be the income of Doctors?
G. Sarangi

Probably this could not have been a topic in a democratic country like India but for the fact that there is no homogenesity in distribution of the doctors and their charges for professional exercise which varies to a large extent from place to place. A doctor in a metropoly, a doctor in the small town or a doctor engaged in primary care charges differently for the same job undertaken. Even when the unskilled labourers and masses over the country are set to equalize their income, doctors in no way seems to think of the same.

The Variables

The two most striking variables that confronts inequality are the Government sector and the private sector. Doctors in the government sector are most poorly paid professionals in comparison to other countries of the world. But the country could curb down the inequality in inter disciplines. A Cardio thoracic surgeon, a Pediatricians, a Physician or to that extent a primary care doctor gets pay in accordance with their ability and seniority. Though payment is poor yet the inter disciplinary variation is not great leading to dissatisfaction of many in the lucrative departments and overall satisfaction in primary care doctors. Doctors in the private sector operating their own hospitals, are the better ones, some of whose income is comparable with the much developed countries like USA and Australia.

Causes of Inequality

In 1970s Dr. David Morley pointed out openly the basic cause of inequality. If you are operating upon a case of inguinal hernia what payment is expected. At a sophisticated hospital in a metropoly with the patient earning few lacks a month and covered by insurance in accordance’s with his pay needs satisfaction as well as minimal traumatic surgery with the best hands available around. Where as the same operation performed upon an unskilled worker at a small village hospital who is not covered by insurance is going to pay a minimal fraction of what the former could afford. Accordingly the payment to the doctors involved in such procedures will vary drastically. Therefore place, person and modernization in equipments becomes a far valid point than other considerations.

How much (The quantity)

The other day one of my doctor friends was asked, “As to how much should a doctor earn or how much should he be paid”. His reply was simple. For maintenance of a good life as much needed should be paid to a doctor. Though his description of good life may not be what other doctor friends believe but the conception may not vary very widely as it is existing today.

250 years ago a pioneering economist Mr. Adam Smith summarized at the prevailing time when he wrote, “We trust our health to physicians. Such confidence could not safely be reposed in people of a very mean or low condition. Their reward must be such, therefore, as may give them that rank in the society which so important a trust requires.” (An inquiry into the Nature and the causes of the wealth of nations; 1976)

Payment and Responsibility - A mismatched duo.

The responsibility of life and death is clearly reposed on doctors. The social wellbeing and economically stable functioning life is also a denominator of their practice. The society has to pay them sufficiently which in turn will attract the most brilliants to the profession. In India probably the answer is in negative. Of late the software business attracted young people to the extent of the creams running for engineering. Management and Administration are the other two which provides enough money, respect and satisfaction. The very denial of the community for better payment and life style culminates in lack of responsibility and accountability of doctors for human life. The dictum becomes “treat as much with what ever little available to make a total acceptable sum”, which culminated in lack of good service. According
to Joseph White an exponent in international healthcare system, “Doctors should be among the best paid people in the society because we give them a great deal of responsibility.”

Some economist advocate to keep doctors remuneration beyond 2 standard deviation of the payment given to the workers of a country. This clearly keeps them within the 2.5% high receiving bracket. This may be taken as a working principle for the Government but for many outside Government Institutions or corporates, who derive their remuneration from the public, no guideline is available. The preposition could be to pay them that much which will enable them for a good life in the area they are practicing to keep them within the affluent people economically above the 3 standard deviation (3SD) level. That makes a better life style adopted and granted to 15 per 10,000 people or even little more, above the poverty line.

**Issues of Life and Death Responsibility:**

This is an area of emotional concern. Scandinavian countries and countries like USA with high per capital income and cent percent literacy do have a high level of health consciousness. Their expenditure in health is in multiple of what India could afford with half its population below the poverty line. Day to day necessities is to be complied first. Health and education occupied the second place. The individual and national loss each death contributes in the two settings is dissimilar. Therefore doctors who handle the responsibility of death are not highly paid for it neither there is a lot of accountability. Even the courts view doctor’s negligence with soft corner to the profession. Recent trend of fixing more responsibility without increasing the remuneration and reducing work load produces chaos in the entire profession.

**Qualitative care, Better outcome, Proportionate Earning** –

After the corporate sector took up health, better services are provided than the Government sector. Free market economy also stimulated the growth of such organizations. For quality care one has to pay a good quantity. The assurance and feeling of better outcome has lead people who can pay to resort to the better hospitals and better trained doctors. As a result doctors in corporate sector gets more in comparison to the expectation of primary care doctors. This encouraged many to go for higher education and there is an “Intra National Brain Pooling” in contrast to what is known as “Brain Drain” 40 to 50 years back.

**Inter Disciplinary Inequalities** –

The erratic development with options handed over to the public to choose resulted in unequal distribution of payment. In 70s surgeons, pediatricians and physicians were too blessed than others. Obstetrics and Gynecology took up for a long time. Now the trend got reversed to Radiology, Ortho and the subspecialties. As there is no check and balances on performance and payment, it will be difficult to guide the entire situation even in days to come. The number of primary care doctors will gradually dwindle away. The reduction of primary healthcare will adversely affect the functioning of our healthcare system an health will not be cost effective. Odisha provides a solid testimony with most of the New PHC to cater for 20,000 populations being devoiced of a primary care physician.

**Money is not everything** -

Experts agree that money is important but not all. If the life style issue of a primary care doctor can be addressed to a better set, it may attract youngsters to take up the challenge. Doctors work for cash (money), kind and respect. Doctors over here get a meager income is well acceptable. It also can not be denied that a good accommodation, education for their children and safety in the working place is never assured for a person doing duty or on call for 24/7, without any authority. The very inherent respect for a doctor is gradually becoming a myth and got replaced by corporate or institutional names. These circumstances lead to severe breach in responsibility and accountability in part of the Doctors to serve to the ailing community.

Elevation of the moral of these silent workers will be a sacred duty of the community of whose action they are the direct beneficiaries. Modesty prevents most of these intellectuals to elaborate their sense of deprivation as they see most of the people around them are deprived. They have forgotten to look to the ivory towers because their countrymen are striving to change the hamlets to an asbestos shed. They believe and act as a part of the timing millions in the dusk and dawn expecting for the good days to come.
Prevalence of Diabetes and Hypertension in adults


Introduction:

Diabetes and Blood Pressure are the most common chronic diseases in the society and are responsible for majority of morbidities in the elderly population. Indian Medical Association Keonjhar branch decided to measure the prevalence of Diabetes and Hypertension among the >40 years age population during the health awareness program that was conducted on 26th November 2012 at Keonjhar.

Materials and Methods: The subjects were the people who came for the health awareness programs and aged more than 40. Those with previous h/o Diabetes and BP and already taking drugs, were excluded from the study. The Blood Pressure was measured by Sphygmomanometer and Stethoscope by qualified MBBS Doctors. Random Blood Sugar was estimated by Glucometer by a trained Laboratory Technician. Height and weight of the persons were recorded and BMI was calculated using the BMI chart. Persons with Blood Pressure Systolic >140 and Diastolic >90 were checked again after 30 min and if abnormal after that also then recorded as abnormal. Random Blood sugar > 150 mg/dl was taken as abnormal.

Results:

Results are summarised in the table given below

<table>
<thead>
<tr>
<th>Age</th>
<th>Age41-50</th>
<th>Age 51-60</th>
<th>Age 61-70</th>
<th>Age 71-80</th>
<th>Age &gt;81</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Females</td>
<td>84</td>
<td>55</td>
<td>102</td>
<td>42</td>
<td>53</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>372</td>
<td></td>
</tr>
<tr>
<td>BMI &lt;25</td>
<td>57</td>
<td>28</td>
<td>62</td>
<td>32</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>231</td>
<td></td>
</tr>
<tr>
<td>BMI&gt;25</td>
<td>21</td>
<td>24</td>
<td>37</td>
<td>11</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>BMI&gt;30</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>RBS&gt;150</td>
<td>12</td>
<td>3</td>
<td>25</td>
<td>9</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>High BP</td>
<td>17</td>
<td>13</td>
<td>28</td>
<td>15</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>130</td>
<td></td>
</tr>
</tbody>
</table>

Discussions: We observe from the table that BMI was beyond the normal limits in 140 persons out of 372 (36.6%). 92 persons (24.7%) had abnormal blood sugar levels and 130 (34.9%) persons had high Blood Pressure.
Many studies from India have reported prevalence of diabetes to be about 9% among population above 40 years of age. Prevalence of Hypertension is reported to be between 10 to 30% in adult population.

Our findings of Prevalence of diabetes and Hypertension to be 24.7% and 34.9% are quite high and are may be due to selection bias, as our population may not be true representative of general population of the society. The people who came to our study perhaps were at greater risk already as reflected in their BMI. 36.6% people had BMI >25 and thus were overweight.

Our study has other two major limitations also. First, the Blood Sugar was estimated by Glucometer and not by standard colorimetric tests. Second, the population size was small.

The study how ever throws light on the two important lifestyle disorders and perhaps indicates the increasing trend in the society. The finding of more overweight persons in the population (with increased BMI) perhaps tells the story as well. Lifestyles have changed and are changing rapidly and may be the changes are responsible for increased prevalence of Diabetes and Hypertension in the society. More studies of large scale and with better design are needed to ascertain the true prevalence of these, which are required to formulate strategy to fight against these two lifestyle disorders.

References:
PROPOSED CONVENTION CENTRE OF IMA ODISHA STATE BRANCH

IMA needs your co-operation and patronage

Members and Benevolent Doners are invited to be a part of this dream project

For further information please contact:

- State President, Mob: 9437012255
- State Secretary, Mob: 9437066627
- State Finance Secretary, Mob: 9437020333
- State Joint Secretary, Mob: 9437020050
- State Head Quarter, Mob: 8763349498
With Best Compliments from:

MICRO LABS LIMITED
27, Race Course Road, Bangalore - 560001

Telrose
A Promise to Protect

Hypotab

Melmet - 500/1000 SR
Metformin 500 mg / 1000 mg extended release tablets

Diapride
Glimepiride 1 mg / 2 mg + 4 mg tablets

Triptide
Glimepiride 1 mg / 2 mg + Metformin 500 mg SR + Pioglitazone 15 mg tablets

Dibizide-M
Gliclazide 5 mg + Metformin 500 mg tablets

PREGATOR
Pregabalin 75 mg + Methylcobalamin 1500 mcg + Alpha Lipoic Acid 200 mg + Pyridoxine 3 mg + Folic Acid 1.5 mg capsules
With Best Compliments from:

MODMED Medtech Pvt Ltd

The makers of

[Image with logos and contact details]
With Best Compliments from:
With Best Compliments from:
With Best Compliments from:
<table>
<thead>
<tr>
<th>Title</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1</td>
<td>Description of Figure 1</td>
</tr>
<tr>
<td>Figure 2</td>
<td>Description of Figure 2</td>
</tr>
<tr>
<td>Figure 3</td>
<td>Description of Figure 3</td>
</tr>
<tr>
<td>Figure 4</td>
<td>Description of Figure 4</td>
</tr>
</tbody>
</table>

*Please note: The table and diagram are placeholder text representations.*

---

135
With Best Compliments from:

ZUVENTUS HEALTHCARE LTD
Makers of

**AUGPEN** tab. 625mg/1gm  
(Amoxycillin+Clavulanic Acid)

**TROXIP-OD**  
(Troxipide 300mg ER tab)

**BEVON-CD caps**  
(Antioxidants+Multiminerals)

**VITANOVA-SG/Sachets**  
(Cholecalciferol 6000 IU)

**RABIFAST-XL caps**  
(Rabeprazole 20mg+ Levo sulpiride 75mg SR)

**ESLO-Tel 2.5/5 tabs**  
(S-Amlodipene 2.5/5 + Telmisartan 40)

**TIBROLIN tabs**  
(Trypsin 48 mg+ Bromelain 90mg+Rutoside 100mg)

**C-TAX-O 200**  
(Cefixime 200 mg)

**RETUNE - LS tab**  
(Levo sulpiride 25 mg)

**GUTCLEAR-IG/SYR100, 200ml**  
(Lactitol 10mg+ Isapgula 3.5gm/10mg/15ml)
With Best Compliments from:

GERMAN REMEDIES

**In the Management of PEI due to**

- Chronic Pancreatitis
- Gastrointestinal Surgeries
- Diabetes Mellitus
- Alcoholic Pancreatitis

**In DYSPEPSIA due to**

- Medication
- Alcohol
- Untimely food
- Stress
- GERD

**In management of GERD associated with DYSPEPSIA**

Clebopro

The New Age prokinetic
With best compliments from:

Makers of:

RiteOcef CV
(Cefixime 200mg & Clavulanic acid 125mg Tablets)

Montral
(Montelukast 10mg + Levocetirizine 5mg Tablets)

Faronac
(Faropenem 200 mg Tablets)

Combined to excel

Broad Spectrum Oral Penem
In Asthma:
FORMONIDE
(Formoterol + Budesonide)
100 200 400 (Inhaler & Respicaps)
The Single Inhaler Therapy

In Allergic Rhinitis:
FLUTICONE - FT
(Fluticasone Furoate 27.5 mcg Nasal Spray)
Fluticasone at its best

For Enhanced Enzymatic Action:
FORENZA 325
(Cefpodosine 200 mg + Clavulanic Acid 125 mg)
Resists the Resistance
With Best Compliments from:

WALLACE LIFE STYLE

VOLABAY 0.2M
(Voglibose 0.2mg+Metformin 500mg SR Tablets)

WALAPHAGE 850
(Metformin 850mg Tablets)

VOLABAY 0.2/0.3
(Voglibose 0.2mg/0.3mg Tablets)

WALAPHAGE 500
(Metformin 500mg Tablets)

WALAPHAGE GP 1/GP 2
(Metformin 500mg SR Tablets+
Glimipiride 1 / 2 mg Tablets)

WALAPHAGE 850
(Metformin 500mg+Gliclazide 80 mg Tablets)

WALFORMIN
(Metformin 500mg Tablets)

WALAPHAGE SR 500/SR 1000
(Metformin 500mg / 1000mg SR Tablets)

DEFZA 30/24/6/1
(Deflazocort 30/24/6/1 mg Tablets)
Subscription information
Orissa Medical Journal is published bi-annually and circulated amongst members. Price of each issue is ₹ 1,000/- (One Thousand only). The annual subscription is ₹ 1,500/- (One Thousand and Five Hundred only). The journal is despatched within India by surface mail.

Copyright and Photocopying
No part of this publication may be reproduced, or transmitted in any form or by any means, electronic or mechanical, including photocopy without written permission from the Hon. Editor.

Edited, Printed & Published by
Dr. Jayanta K. Panda
for the Indian Medical Association
Odisha State Branch
IMA House, Ranihat, Cuttack-753007, Orissa
Ph : 0671-2413060, 2121125
Email : imiorissa@gmail.com
Website : www.imaodisha.com

The Editor disclaims any responsibility or liability for statements made and opinion expressed by authors or claims made by advertisers.

Advertorial enquiry
Dr. Jayanta K. Panda, Hon Editor, OMJ
SCB Medical College
IMA House, Ranihat, Cuttack-753007, Orissa

Printed at
Graphic Art Offset Press, Nuapatna, Cuttack-1.
Notes