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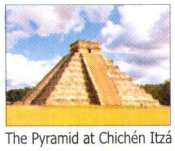
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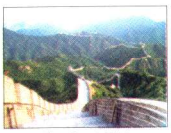
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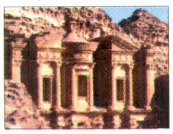
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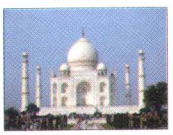
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Vertex

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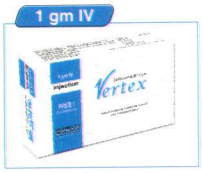


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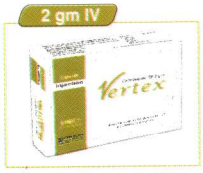


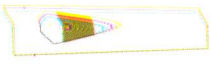

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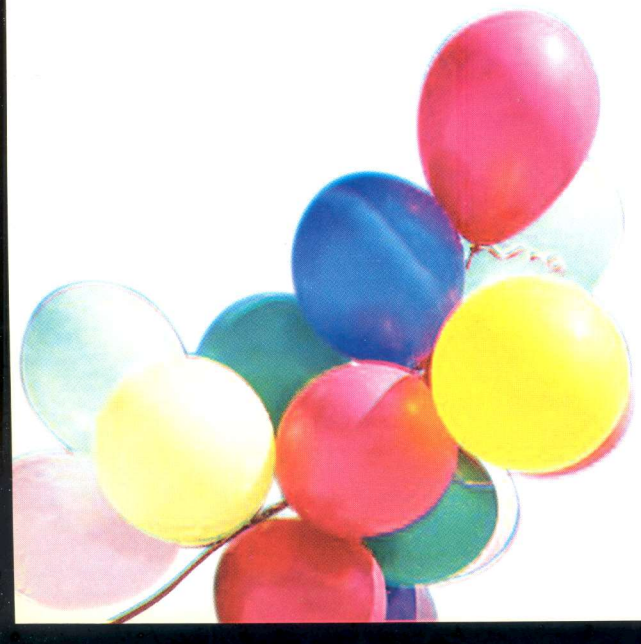

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# The ORION medical journal

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## Editor's Choice

### The ORION, ONLY, serving CME since 1998

The ORION is the ONLY medical journal among the national pharmaceuticals' publications that has been relentlessly serving the Continued Medical Education Program since 1998. This extraordinary achievement of The ORION is based on the spontaneous support of all readers who are persistently accompanied in every moment of nine years. This accomplishment will assure 'The Editorial', 'The Advisory' & 'The Review' boards members to expedite further development of the journal. With the volume of 28, The ORION crosses the national boundary and extent its interaction with the international authors. This achievement enriches the archive of the journal. This issue compiles one special article, three original articles, three review articles and an interesting case report.

Editorial of this volume "Burn and Plastic surgery unit in Bangladesh" (P-482) concentrates on burn incidence in Bangladesh and also narrates the history of establishing burn unit in Dhaka Medical College Hospital along with its recent available facilities.

The special article from Singapore East Shore Hospital on 'The cure of childhood cancers' (P-483) inoculates to understand the cancer biology and molecular genetics for improving the diagnostic accuracy in the treatment of childhood malignancies. It also shares the practical experiences of haematopoietic stem cell transplantation and improvement of supportive care to reduce the treatment related toxicities.

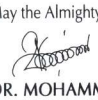
The first original article on `Factors influencing the weaning knowledge of mothers of under 5 children: A hospital based study' (P-487) exhibits the weaning knowledge of mothers based on their literacy, nutritional & economical status of their family. Followed by another one 'Evaluation of admitted case of convulsion in pediatric ward of a medical college' (P-490) evinces the causes of convulsion in children & the effectiveness of per rectal diazepam to control seizure. The third original article 'Pattern of eye diseases in a tertiary hospital in a suburban area: A retrospective study' (P-492) assesses the epidemiology & diseases pattern of 1750 ophthalmic patients admitted between 1st July, 2005 to 30th June 2006 in the International Medical College & Hospital.

The first review article from New Jersey Dental School, USA on "Orthognathic surgery on the partially edentulous patient" (P-495) narrates the disorders of skeletal malocclusion, that can't be corrected by orthodontics alone. Moreover, it identifies the differences in treatment and complications compared to surgery in dentate patients. Followed by the second one 'Insulin analogues' (P-497) recapitulates the historical achievements in the insulin therapy and critiques criteria, structure & therapeutic role various insulin analogues. The last review article on 'Prevention of in-stent stenosis: Drug-eluting stents create new hope in the PCI' (P-501) is focused the promising result of Drug-eluting stent in the field of antirestenosis research.

A case report on 'Amplatzer device closure of Patent Ductus Arteriosus (PDA) : A case report' (P-505) discusses the non-surgical closure of Patent Ductus Arteriosus by Amplatzer device and evidences it as a safe and effective interventional treatment for PDA.

Opinion and suggestion is highly encouraged for development of The ORION. It also makes available online at www.orion-group.net/journals for contributing the advancement of public health and medical research. For reproducing multiple copies of any of 'The ORION' articles, please e-mail: orionjournal@yahoo.com/ orionmsd@dhaka.net/ journal@orion-group.net & mention the article title, author's name, volume, page number, year of publication and mostly the purpose for reproducing.

May the Almighty bless all in the spirit of good health.



DR. MOHAMMAD ZAKIRUL KARIM
Chief Editor
The ORION medical journal

# Burn and Plastic surgery unit in Bangladesh

Sen SL[1]

The ORION 2007; 28: 482

Chemical (Acid) Burn is a social problem in our society. To cater for these victims, there is a special Burn unit in Dhaka Medical College Hospital. In addition, domestic burns, flame burns, electric burns are also very common in our country. Due to carelessness, a person may be crippled for whole life from severe Burn. Majority of these injured are from the poor community and cannot afford private treatment and rely on government hospitals.

## Burn incidence in Bangladesh

Throughout the country, an estimated 1% of the population suffers from different types of burns each year. The common causes of burns in Bangladesh are as follows:

A. *Flame burn:* 75% of incidences occur due to flame injuries -

i. Accidental:- this occurs mainly in the home during household work like cooking, particularly from gas leakage or burst stoves, and setting clothes alight. Women and children wearing "Shari" or "Orna" are the major victims.
ii. Trapped in a burning house.
iii. Using fire pots for warming in the winter, especially old people and children.
iv. Warming the lower part of the body after delivery specially women in remote village areas.
v. Homicidal and suicidal:- Pouring kerosene oil, diesel, gasoline or other inflammable liquids onto a human body and setting alight.

B. *Others:* About 20% burns are electric burns. The cause of electric burn is mainly accidental. The majority of such cases occur due to electric short circuits in garments factories or other small factories, congested markets and slum areas.

C. *Acid burn (chemical burn):* These are almost all homicidal cases except a very few reported cases of accident. Nitric acid, sulfuric acid and hydrochloric acid are the most common examples. This constitutes 5% of total burn cases.

## History

In 1972 after liberation, Prof. R. J. Garst came to Bangladesh to help the crippled freedom fighters. After commencing treatment, Prof. Garst realized that a Plastic surgeon was very much needed to help the injured freedom fighters. To fill this vacuum, he arranged to bring Dr. Pervez Bazliel, Plastic Surgeon from Ludiana, India to Shaheed Suhrawardy Hospital at Sher-E-Bangla Nagar, Dhaka in 1974. I joined in 1975 in Plastic Surgery at SSH. This was the beginning of the concept of plastic surgery in Bangladesh. However, following his sudden demise in 1978, there was acute shortage of trained plastic surgeons. So, I was deputed by the govt. for a Diploma training course for 9 months in Vienna, Austria. In 1986, Professor Shahidullah, the 1st Bangladeshi Plastic Surgeon joined Dhaka Medical College Hospital & I joined as Assistant Registrar and subsequently Dr. Sayed Shamsuddin Ahmed (acting Professor in Burn Unit) also joined Dhaka Medical College and Hospital.

Late Prof. Kabiruddin Ahmed, the then Head of Department, Surgery, DMCH had started a campaign along with Prof. Shahidullah for a separate Burn & Plastic Surgery unit at Dhaka Medical College Hospital. The 1st proposal for making a separate unit for Burn & Plastic Surgery in Dhaka Medical College Hospital was given by Prof. Dr. Md. Shahidullah in 1986.

In 2003, a separate unit for Burn patients was started with 50 beds and now this unit has extended to 100 beds for both Burn & Plastic Surgery patients. Within the existing facilities and limited manpower, the burn unit is trying to best serve the patients.

However, in the new unit, all modern facilities for burn patients are being planned. In addition there will be a teaching centre for plastic surgery and nationwide training in burn care.

Additionally, to render the health service facilities to the burn patients, we also conduct various charity programs within the unit. Accordingly, different voluntary organizations from UK, Italy, Australia, USA, & Japan are visiting the unit along with their Plastic Surgeons and Anaesthesiologists and performing free Plastic surgery in the burn unit of DMCH on the occasion.

We also conduct countrywide "Mobile Cleft Lip" program with support from Director General Health and Ministry of Health & Family Welfare, Govt. of Bangladesh. Doctors of Burn unit of DMCH go to the different Govt. District Hospitals & Upazilla Health complexes to perform Cleft Lip operation free of cost for the poor girls in the villages.

The Burn & Plastic Surgery unit mainly deals with acute burns and post burn complications along with other form of reconstructive surgery.

## Conclusion

The Burn and Plastic Surgery unit is the only government referral hospital for burn patients in the country. The unit gets patients from almost all districts of the country. About 73% of the patients who were admitted in the unit during a study report[1] conducted in 2004 were from Dhaka and nearby districts and the rest, 27% came from other parts of the country.

There should be the provision of training and sensitization of personal dealing with burn patients. Expert and specially trained doctors as well as paramedics should be given priority for working at very specialized burn hospital[2]. More care should be given for handling of burn cases. Moreover, we urgently need to open a small unit of Burn & Plastic surgery in every Medical College Hospital to cope with the overwhelming mass of patients in our country.

A prevention campaign[3] should also be launched immediately, involving the government, public health workers, health related NGOs, media and other concerned business organization like electric supply authority to reduce the incidence of burn accidents in the country. Along with treatment, the long-term goal of the project is to reduce the incidences of burns in the country.

1. Dr. Samanta Lal Sen, MBBS (Dhaka), DSS (Vienna)
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Continued from Vol.27

# The cure of childhood cancers

Lee AC[1]

The ORION 2007; 28: 483-486

**Abstract**

The success in the treatment of childhood cancer has been one of the most remarkable advances in modern medicine. Breakthroughs in the understanding of cancer biology and molecular genetics not only improve diagnostic accuracy, but also lead to the development of novel therapeutic agents. The success of haematopoietic stem cell transplantation from both related and unrelated donors provides a powerful rescue treatment for children with malignancies that are otherwise refractory to conventional chemotherapy. Improvements in supportive care including the treatment of infections and Tumour Lysis Syndrome reduce treatment-related toxicities and allow timely administration of cytotoxic chemotherapy. However, the most significant progress has been produced by collaborative studies organised by national and international oncology groups. To date, more than 70% of children with newly diagnosed malignancies are expected to be long-term survivors and better outcomes are expected in the near future.

**Keywords**

Bone marrow transplantation; cytogenetics; leukaemia; paediatric oncology

## Introduction

Cancers in children are uncommon diseases. Nevertheless, they are an important determinant of child health and one of the leading causes of deaths in children. Half a century ago, childhood cancers were practically incurable. Advances in medicine that took place in the last four decades have changed the outlook of childhood cancers completely. To date, more than 70% of children with newly diagnosed malignant diseases are expected to survive 10 years or more[1]. The changing prognosis has been the results of betterments in diagnostic capability, therapeutic armamentarium and supportive care, the themes of discussion in this article.

## Collaborative studies in childhood cancers

National collaborative groups such as the National Wilms Tumor Study group started to appear during the 1960s when paediatric oncologists realized that no single institution was able to study the clinical characteristics and therapeutic effects of childhood cancers because of their infrequent occurrence. Some of these collaborations have gradually merged to become trans-national organizations such as the Children's Oncology Group and international organizations such as the International Society of Pediatric Oncology. With these collaborative efforts, new ideas in cancer diagnostics and therapeutics can be studied systematically and tested in randomised manners. These have been translated into successive leaps in the survivals of most kinds of childhood cancers as listed in Table1[2-29].

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Table 1: Childhood cancers and published survival data from national or international collaborative studies.

| Types of cancers | Survival data | References |
|---|---|---|
| *Leukaemias:-* | | |
| Acute lymphoblastic leukaemia | 5-year EFS of 77.6-80.8% | 2-4 |
| Acute myeloid leukaemia | 5-year EFS of 46-57% | 5-7 |
| Chronic myeloid leukaemia | 3-year EFS of 61-78% for HSCT; 5-year PFS of 83% for Imatinib; 5-year PFS of 57% for Interferon | 8-11 |
| *Lymphomas:-* | | |
| Non-Hodgkin lymphoma | 5-year EFS 85-86% | 12, 13 |
| Hodgkin lymphoma | 10-year EFS 83-91% | 14, 15 |
| *Brain tumours:-* | | |
| Medulloblastoma | 5-year EFS 64.8% | 16 |
| Germ cell tumours | 3-year EFS 55.6-92% | 17, 18 |
| Astrocytomas | 10-year PFS > 60% for low-grade tumours | 19 |
| Neuroblastoma | 2-year EFS > 90% of early-staged; 4-year EFS of 9-30% for advanced | 20 |
| Wilms tumour | 5-year EFS 79.6-91% | 21, 22 |
| Germ cell tumours | 4-year EFS 76.2-90.9% | 23, 24 |
| Rhabdomyosarcoma | 3-year EFS 77% for non-metastatic | 25 |
| Osteosarcoma | 5-year EFS 62-65% | 26 |
| Ewing sarcoma/ primitive neuroectodermal tumour | 3-year EFS 75-82% for localized | 27 |
| Hepatoblastoma | 3-year EFS 89% for standard-risk | 28 |
| Retinoblastoma | 5-year EFS 98% | 29 |

## Risk-adapted therapeutics

While childhood cancers are classified into various histological types and each has to be managed differently, there are different biological subtypes of cancers even of the same histological diagnosis. These biological variations can be defined by clinical staging, laboratory features such as total leukocyte counts at diagnosis in leukaemias[30], histological subtypes as in Wilms tumours[31] and rhabdomyosarcomas[32], cytogenetics, molecular pathology and therapeutic responses[33]. Again, thanks to the efforts of the collaborative groups, cancer children can now be accurately stratified and given risk-adapted therapies to maximize their chance of cure and to minimize potential toxicities simultaneously.

### The importance of molecular studies

While cancers are traditionally diagnosed by examination of the cells or tissues under the microscope, often with the aid of immunohistochemical stains, diagnostic uncertainties are still common in the group of small, blue round cell tumours. Molecular genetic studies using fluorescence in-situ hybridisation (FISH) and/or the reverse transcriptase-polymerase chain reaction (RT-PCR) are valuable adjuncts for the evaluation of undifferentiated tumours such as the detection of t(11;22)(q24;q12) in Ewing sarcoma and t(9;22)(q22;q12) in myxoid chondrosarcoma[27].

In childhood leukaemias, molecular genetic studies have proven to be of prognostic importance (see Table 2)[6,30].

Table 2: Common molecular events in childhood leukaemia and their clinical significance.

| Genetic changes | Genes involved | | Significance |
|---|---|---|---|
| t(12;21) (p12;q22) | TEL | AML1 | Good prognostic marker in childhood acute lymphoblastic leukaemia |
| t(9;22) (q34;q11) | ABL | BCR | Adverse prognostic factors in childhood acute lymphoblastic leukaemia. Haematopoietic stem cell transplantation is may be indicated during first complete remission. |
| t(4;11) (q21;q23) | AF-4 | MLL | |
| t(15;17) (q22;q12) | PML | RARα | Molecular marker for acute promyelocytic leukaemia. Patients may be treated on a specific protocol different from the usual acute myeloid leukaemia reatment. |
| t(8;21) (q22;q22) | ETO | AML1 | Good prognostic markers. Haematopoietic stem cell transplantation may not be indicated during first complete remission. |
| inv(16) (p32;q22) | MYH 11 | CBF | |

For instance, the presence of t(15;17)(q22;q12) or the PML-RARα transcript, the marker for acute promyelocytic leukaemia, implies that the patient will respond better to an all-trans-retinoic acid and anthracycline-based chemotherapy protocol[34]. In addition, these molecular markers have been found to be useful to monitor the presence of minimal residual disease and may be able to select those patients who have a higher chance of relapse during or at the end of conventional treatment[35]. In patients with chronic myeloid leukaemia receiving treatment with imatinib mesylate, the clearance of cells bearing bcr-abl transcripts is an important determinant of the success of therapy[9].

### Haematopoietic Stem Cell Transplantation (HSCT)

Since the report of the first successful HSCT in 1968 in a child with immune deficiency syndrome, HSCT has evolved into an important treatment of both malignant and non-malignant disorders[36]. Allogeneic HSCT remains the only curative treatment for patients with chronic myeloid leukaemia and other blood dyscrasia in which only palliative chemotherapy is available. It is also the treatment of choice in paediatric patients with acute leukaemias in which a significant risk factor, for example, failure of induction treatment or presence of the Philadelphia chromosome, is present when the probability of treatment failure is high. High-dose chemotherapy followed by autologous haematopoietic stem cell rescue is now a standard treatment for children with advanced neuroblastoma. The expanding registries of unrelated marrow donors and umbilical cord blood worldwide coupled with improved techniques in HLA typing have facilitated transplantation by increasing the availability of alternative donors. All these have contributed to the ever-improving prognosis in paediatric oncology.

### Management of infectious complications

Besides disease refractoriness and recurrence, infectious complications are the leading cause of mortality and morbidity in children undergoing anticancer therapy[37]. Children are susceptible to infections because of the adverse effects of chemoradiotherapy on their skin and mucous membranes. The use of indwelling central venous catheters provides a common portal of entry for the bacteria from the skin flora. Neutropenia following myelosuppressive chemotherapy is an important factor underlying most of the invasive bacterial and fungal infections. Immunosuppressive therapy such as corticosteroids, an essential component in the treatment of lymphoid malignancies and graft-versus-host disease following HSCT, leads to an increased risk of viral and fungal infections. Nosocomial infections can be equally, if not more, hazardous because of the lack of infection control policy, isolation facilities and frequent construction works[38].

Much of the improvement in the outcomes of childhood cancer comes from a better understanding of the immunocompromised host and the microbiology in the field of paediatric cancers. Although the efficacy of prophylactic antimicrobials, with the exception of prophylaxis against pneumocystis jirovecii (formerly known as pneumocystis carinii) pneumonia, remains controversial, timely pre-emptive treatment of suspected infection in a child undergoing cytotoxic chemotherapy is of utmost importance in reducing treatment-related deaths[37]. The use of broadspectrum antibiotics with anti-pseudomonal activities under such circumstances is essential. Conventional amphotericin B deoxycholate remains an important drug against invasive fungal infections, but its clinical use is often limited by its toxicities, especially nephrotoxicities[39]. Newer formations such as liposomal amphotericin and innovative classes of compounds such as the triazoles and echinocandins have widened our capacity to handle mycosis in oncology practice[40].

Growth factors such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor produced by recombinant DNA technology have improved our success in the treatment of infectious complications by shortening the duration of neutropenia[41]. As a result, chemotherapeutic regimens can be given without undue delay, thus improving the control of the underlying malignancy.

### Tumour Lysis Syndrome

In children presenting with high-grade B-cell lymphomas and acute lymphoblastic leukaemia with hyperleukocytosis, tumour lysis syndrome is a notorious life-threatening complication. The metabolic derangements are characterized by

followed and taken into consideration with utmost importance[5]. Numerical data were obtained from records of the OPD and indoor register.

Several large epidemiological studies have determined that low socio economic status is related to increased disease morbidity and mortality[6]. So economic status were obtained by asking direct question to the patient & the patient guardian in case of children.

Questions were as follows-

a. Sources of income.
b. Monthly income & expenses.
c. Number of depended member of the family.
d. Number of members were incoming in the family.
e. Status of the dwelling like kacha, packa, and in slum areas or affluent areas.
f. Status of education.

Taking above history patient are economically divided in three groups, poor, middle class and affluent.

### Aim of study

1. To find out the annual attendance of ophthalmology department of this suburban industrial area.
2. To find out the diseases pattern of attendants in the ophthalmology unit of this tertiary hospital.
3. With the result, recommendations can be made to the hospital authority for improvement of this unit in respect of manpower and equipments.
4. With this study it can be found out how much helpful of a tertiary hospital in a suburban industrial areas. The study intends to evaluate the optimal outcomes for the patients in terms of visual function and quality of life[7].

### Results

1. Total number of patients: 1750 (n=1750).
2. OPD and indoor: OPD =1606 (91.77%), Indoor = 144 (8.23%).
3. Male and female: Male = 911 (52%) and Female = 848 (48%).
4. Age distribution: Table-II.
5. Economical status: Poor-1178 (67%), middle class - 449 (25.5%), Affluent-132 (7.5%).
6. Following data as per diseases pattern: Table-I.
7. Following tests were done almost in each or every patient-
   a. Snellen's chart test.
   b. Slit lamp examination.
   c. External examination of the eye by well illuminating torch.
   d. IOP measure by Schiotz Tonometer.
   e. Ophthalmoscopic examination.
   f. Retinoscopic examination.
8. Operative microscope, indirect ophthalmoscope were on processing of procurement.
9. Non availability of Yag laser, Fluorescent Angiogram, Perimetry.
10. One Medical Officer & one Assistant Registrar, one Registrar and one Associate Professor were involved.
11. From this study it is evident that at least one part time if not full time posterior segment surgeon is essential.

Table I: Individual diseases pattern (n=1750)

| Sl. No | Diagnosis | No of patient | Percentage |
|---|---|---|---|
| 1 | Conjunctivitis | 384 | 21.94 |
| 2 | Cataract | 161 | 9.20 |
| 3 | Refractive error | 266 | 15.20 |
| 4 | Headache | 194 | 11.09 |
| 5 | Dacryocystitis | 114 | 6.51 |
| 6 | Pterygium | 66 | 3.77 |
| 7 | Epiphora | 58 | 3.31 |
| 8 | Chalazion | 55 | 3.14 |
| 9 | Presbyopia | 66 | 3.77 |
| 10 | Traumatic injury* | 52 | 2.97 |
| 11 | Foreign body | 43 | 2.46 |
| 12 | Blepharitis | 56 | 3.20 |
| 13 | Corneal ulcer | 21 | 1.2 |
| 14 | Stye | 22 | 1.26 |
| 15 | Viral keratitis | 21 | 1.20 |
| 16 | Sub Conjunctival Hemorrhage | 17 | 0.97 |
| 17 | Episcleritis | 15 | 0.86 |
| 18 | Pinguecula | 10 | 0.57 |
| 19 | Pseudophakia | 14 | 0.80 |
| 20 | Cellulitis | 5 | 0.29 |
| 21 | Nightblindness** | 21 | 1.20 |
| 22 | Glaucoma | 34 | 1.94 |
| 23 | Uveitis | 15 | 0.86 |
| 24 | Squint | 12 | 0.69 |
| 25 | Lacrimal Abscess | 9 | 0.51 |
| 26 | Diabetic Retinopathy | 13 | 0.75 |
| 27 | Retinal Detachment | 6 | 0.34 |
| | Total | 1750 | 100.00% |

* Traumatic injury includes- Lime burn, acid burn etc.
** Nightblindness includes - Xerophthalmia, Retinitis pigmentosa etc.

Causes of blindness in India (NPCB-WHO survey 1986-1989) Glaucoma-1.70%[8]. Age related cataract, the world's leading cause of blindness[9]. Glaucoma is an optic neuropathy with characteristic appearances of the optic disc and specific pattern of visual field defects that is associated frequently but not invariably with raised IOP[10]. It accounts for 10% of all blindness in the world. In Bangladesh glaucoma is a major cause of blindness. According to the report Glaucoma Prevalence Survey 1993, conducted by Bangladesh Eye Care Society, the incidence of glaucoma was 2.8% in the population above 35 years of age. Glaucoma is the 3rd common cause of blindness after cataract and corneal disease in Bangladesh[11].

Table II: Age distribution of the patient (N=1750)

| Age pattern (years) | No of patient | Percentage |
|---|---|---|
| 0-9 | 174 | 10 |
| 10-19 | 286 | 16 |
| 20-29 | 444 | 25 |
| 30-39 | 279 | 16 |
| 40-49 | 282 | 16 |
| 50-59 | 142 | 8 |
| 60+ | 152 | 9 |

### Discussion

This is semi urban industrial area just outskirts of the capital city. It is evident from the analytical study that most of the patients are poor, age, sex, economic pattern are shown in the result sheet. As this area is semi urban industrial area, there is scope of further growth of industry with improvement of

economy and wealth pattern may be changed. Diseases pattern study could not be found in literature search out so this study could not be compared. But there are some common infectious diseases of eye, such as blepharitis, stye, chalazion (meibomian cyst), herpes zoster ophthalmicus, chronic dacryocystitis, simple acute conjunctivitis, purulent keratitis (ulceration of cornea), anterior uveitis, purulent conjunctivitis, ophthalmia neonatorum[12]. Herpes simplex virus keratitis (HSVK) is one of the main causes of infectious corneal opacification and infection-related visual loss[1] and is a leading indication for penetrating keratoplasty. The prevalence of HSVK in the United States is about 50,000 cases, which also includes 28,000 cases of reactivation; and an annual estimated incidence of 20,000 newly diagnosed cases per year. HSV is DNA virus with two serotypes, HSV-1and HSV-2 that belongs to the Herpes Virus family. HSV-1 is the more prevalent of the two and is primarily transmitted by a symptomatic shedding of virus through saliva. Local host factors are responsible for the frequency of recurrence of HSV-1and HSV-2 in the facial and genital area[13]. With this study it has been already recommended to the management authority for equipments and increase in manpower especially for ophthalmology department. After this study management has already procured operative microscope.

## Conclusion

On this study pattern of eye diseases in this suburban area, among them conjunctivitis, cataract, refractory error, headache, blepharitis and glaucoma were predominant. The patient diagnosed like diabetic retinopathy, retinal detachment, lime burn are referred to centers for proper treatment with right instrument and expertise.

This type of study is helpful to have idea about the epidemiology of any type of diseases in area served by the hospital. This helps in planning & management of a hospital.

Early detection of diseases such as cataract & glaucoma in this population will reduce the burden of blindness[14] in Bangladesh.

The area is already an industrial area with growth of garments industry and there is further scope of growth of this & other industry in this area, which may open further awareness for expansion & growth of the ophthalmological department.

## Acknowledgement

Authors express their gratitude to Professor A.S.Q.M. Sadeque & Ms Tahsin Akter Nowrin for permitting to take out the study.

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# Orthognathic surgery on the partially edentulous patient

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**Abstract**

Orthognathic surgery is the surgery to treat disorders of skeletal malocclusion, that can not be corrected by orthodontics alone. Specifically, orthognathic surgery treats significant open bite malocclusions, class 2 and class 3 malocclusions. Mandibular orthognathic surgery has been performed since the 19th century, while maxillary osteotomies were not routinely performed until the 20th century. Orthognathic surgery is typically performed on young adults, uncommonly performed on older patients or patients who are partially or completely edentulous. The focus of this article is to review orthognathic surgery on the partially/fully edentulous patient and to identify differences in treatment and complications compared to surgery in dentate patients.

## Introduction

Orthognathic surgery is mostly commonly performed on young adults with a full complement of teeth that have been orthodontically prepared prior to surgery. However, in some situations, the atypical orthognathic surgery patient may present with an old age or a patient that is partially or fully edentulous. These patients have the same basic desires as the typical orthognathic patient is to achieve as normal an occlusion as possible to treat the functional and aesthetics deficiencies that are associated with a skeletal malocclusion. As a major tertiary care university medical center for the State of New Jersey, our institution frequently treats these atypical patients. The goal of this paper is to share our experiences as well as pitfalls and recommendations for treating the partially edentulous orthognathic surgery patient.

The early orthognathic literature discusses treating the edentulous patient. Kazanjian, in 1951, reviewed his treatment of prognathism in four partially edentulous patients. His treatment included extraoral ramus osteotomies as well as utilizing splints attached to a head frame to ensure proper immobilization. In addition, intraosseous wiring was utilized[1]. In 1953, Van Alstine and Dingman described treating prognathism in the edentulous patient via an ostectomy of the body of the mandible secured by intraosseous wiring. Acrylic splints wired circumferentially were utilized to place the mandible into a favorable position[2]. In 1954, Caldwell and Letterman published the technique of the Extraoral Vertical Ramus Osteotomy to treat prognathism[3]. This was later modified by Hebert, Kent, and Hinds in 1970 to an intraoral vertical ramus osteotomy (IVRO), a technique commonly used by today's surgeons[4]. In addition, Obwegeser in 1952 started developing the sagittal split osteotomy to treat mandibular prognathism and retrognathia. What is most astounding about the development of the sagittal split is that Obwegeser notes the first 15 cases were done under local anesthesia in the dental chair[5]!

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## Discussion

The work up for the partially edentulous orthognathic surgery patient is no different from that patient with a full complement of teeth. A full extraoral evaluation, noting facial symmetry and proportions, as well as standard radiographic evaluation (panoramic and cephalometric films). Of note on the radiographs-evaluation of the bone quality and height is needed in the long-standing edentulous patient as bone atrophy may occur. This especially important in the patient planned for sagittal splits-an atrophic mandible may not be amenable to a favorable split; in the prognathic patient with an atrophic mandible, the IVRO may be a superior procedure. In addition, an edentulous maxilla may lead to an extremely atrophic anterior maxillary wall, creating a very fragile Le Fort 1 osteotomy. A thorough intraoral exam should be performed - evaluating the arches in relation to one another from transverse, anterior-posterior, and vertical dimensions. If the patient has an existing prosthesis, evaluation should be performed both with and without the dental prosthesis in the mouth, with attention paid to any changes in vertical dimension with and with out the prosthesis.

Once all the clinical and radiographic date has been collected, a standard surgical prediction tracing should be done as well to determine the required orthognathic movements and plan for the model surgery. The model surgery is performed in a standard fashion. Where the differences lie in the partially edentulous patient compared to the dentate patient is in the fabrication of the surgical splints. In most orthognathic surgeries, a surgical splint is an integral part of the surgery, guiding the surgeon to place the maxillofacial skeleton into the presurgically determined ideal position. In addition, tooth position and occlusion help guide the surgical movements. In the partially edentulous patient, these splints have even more of an importance, as there may not be teeth available to help guide the surgical movement of the maxilla and mandible. In our experience, fabricating splints to fit into the edentulous spaces has been useful in guiding the orthognathic surgery. In addition, to ensure appropriate maxillomandibular fixation (MMF), we have incorporated arch bars into splints in the edentulous areas (Figure 1a-1e)

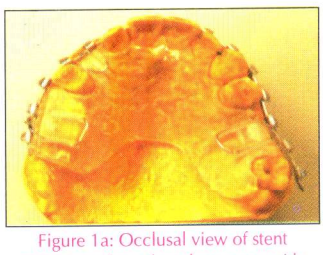

Figure 1a: Occlusal view of stent encompassing edentulous areas with arch bar attached

Figure 1b: Occlusal view of surgical splint in conjunction with stent

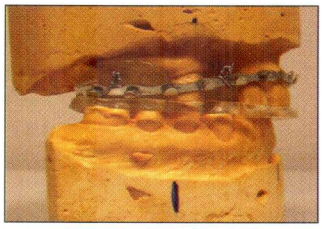

Figure 1c: Lateral view of splint/stent complex

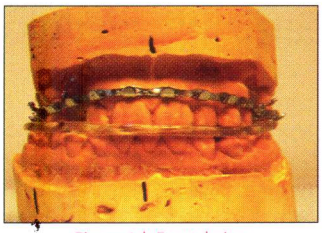

Figure 1d: Frontal view

Figure 1e: Lateral view of final surgical splint with arch bar attached

or utilized transosseous MMF screws to obtain adequate fixation (Figure 2). If the patient has an existing prosthesis, this is utilized as well as a guiding splint during surgery; an arch bar or MMF screws can be attached to the prosthesis to facilitate MMF.

The major surgical pitfall in treating partially edentulous patients is that there may be significant bone atrophy in the areas of missing dentition. As noted above, in the mandible this may lead to an unfavorable sagittal split or increase the risk of injury to the mandibular neurovascular bundle. In the maxilla, bone atrophy leads to an exceptionally thin anterior maxillary wall; if care is not taken, the process of completing the Lefort 1 osteotomy can result in fragmenting the anterior maxillary wall, making it difficult to secure rigid fixation or determine if the maxilla has moved into its planned position (Figure 3).

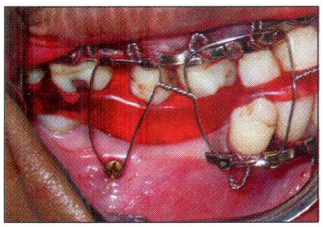

Figure 2: Transosseous Maxillomandibular fixation screw

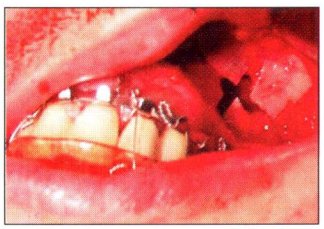

Figure 3: Fragmentation of the Lefort 1 osteotomy in an edentulous area of the maxilla

If this occurs, place the maxilla in its optimum surgically determined position, fixated it, and then bone graft to areas of bony defects. Often freeze-dried iliac crest will suffice, precluding the need for harvesting autogenous ileum. In addition, trying to minimize the amount of Periosteal stripping during surgery to maximize blood supply to the bone is preferred to ensure post surgical healing. Finally, as with any orthognathic procedure, ensuring that the bone segments are completely immobile once placed into their new position, and ensuring bone to bone contact are keys to avoiding relapse and facilitate optimal healing.

## Conclusion

Orthognathic surgery in the edentulous and partially edentulous requires some minor modifications compared to surgery on a patient with a complete dentition. Edentulism in the maxilla often leads to maxillary atrophy, requiring extra care when completing Lefort Osteotomies. Additionally, sagittal split osteotomies in edentulous mandibles have a higher incidence of bad splits, requiring extra care and attention. Finally utilizing splint to encompass the edentulous segment can be beneficial to placing the jaw in the ideal presurgically determined position.

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## Discussion

A considerable portion of mothers (41%) were either poor or medium weaning knowledge category. Several studies have reported low levels of awareness of mothers regarding appropriate breast feeding practices in Bangladesh[27-29]. These portions of mothers need to be educated and motivated about the usefulness and proper use weaning food by the concern agencies for the betterment of health status of the children.

Major cases (62) of high weaning knowledge category mothers were found in primary and secondary literacy level. But in poor weaning knowledge group, major cases were found among illiterate and primary literacy level mothers (106). Literacy level of the mothers had positive and statistically significant relationship with their weaning knowledge ($p=<0.001$). This means that educated mother had higher weaning knowledge than illiterate and less literate mother. Significantly more number of illiterate mothers exclusively breastfed their babies up to five months of age[30]. However, some studies also reported negative association between duration of breast feeding and education level of mothers due to might be their less awareness or less knowledge of breast feeding[30-32].

Higher numbers of normal and moderate nutritional status cases (66) were found in high weaning knowledge category mothers compared to poor weaning knowledge category mothers (30). But figure was opposite in case of severely malnourished cases might be due poor weaning knowledge of mothers. Wrong perception of mothers about weaning practices ultimately affects the nutritional status of the children. Wrong perception about giving extra water beside breast milk to met thirst a cause of low rate of exclusively breast feeding in urban slum of Dhaka city[22].

Poor weaning knowledge of the mothers was found highest (92) in low economic status category than high and medium economic status categories might be due to their lesser scope of having necessary information sources or financial inabilities. Mothers with low socio economic status had inaccurate perception on weaning practice as well as low purchasing ability that ultimately increased the malnutrition of children[22].

Poor weaning knowledge was found in high (56 and 48) in case of early and late weaning time categories compared to normal weaning time. This finding might be due to lack of awareness or knowledge about proper time of weaning. Time of weaning practice and weaning knowledge of the mother was differed significant ($p=<0.001$). This means that mothers with high weaning knowledge had higher rate of accurate weaning food supplementation. A study conducted in Peru indicated that early weaning practice was due to wrong perception of maternal health problems[33].

## Conclusion

Above findings indicate that a considerable portion of mothers (41%) were in either poor or medium weaning knowledge category. These portions of mothers need to be educated and motivated about the usefulness and proper use weaning food by the concern agencies for the betterment of health status of the children through increasing literacy level and involving them income generating activities for higher economic status.

## Acknowledgement

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# Evaluation of admitted cases of convulsion in pediatric ward of a medical college

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## Abstract

*Objective of the study:* To see the incidence, sex, age distribution, causes of convulsion and to see the effect of per rectal diazepam to control seizure in admitted children. *Study place*: Pediatric department of Community Based Medical College Hospital, Mymensingh. *Study type:* Retrospective study. *Study period:* January 2005 to December 2006. *Results:* Out of 1950 admitted cases 42 were admitted with convulsion, which means 2% of the total admission were due to convulsion. Age distribution of the study population 2 months to 12 years, with a mean age 2.3 years, male 71% & female 29%. Causes were febrile convulsion 38%, meningitis 17%, diarrhea with electrolyte imbalance 4.7%, bacillary dysentery with convulsion 4.7%, measles with convulsion 2.4%, encephalitis 4.7%, cerebral malaria 9.5%, epilepsy 4.7%, space occupying lesion 7%. Thirty nine cases responded to one dose of per rectal diazepam & rest three cases needed extra dose to control convulsion. *Conclusion:* This study reflect that per rectal diazepam is quite effective in controlling seizure attack.


## Introduction

Seizure is a serious common neurological condition in childhood[1]. Males suffer more, febrile convulsion is the commonest cause of convulsion, next to which is meningitis.

The most important point in seizure is to find out the cause of seizure and to exclude meningitis. If any doubt exist about the possibility of meningitis a lumber puncture to be done to examine CSF to exclude meningitis[2].

To evaluate the cause of seizure meticulous history taking, physical examination and laboratory examination are necessary. Lab examination may include CBC, MP, CSF, urine examination, serum electrolytes, EEG, CT scan etc[3].

The basic mechanism which underlie the generation of seizures are incompletely understood, but involves abnormalities at the cell membrane level and in neuronal circuits[4].

Convulsions in children is a common problem. There are many causes of convulsions like febrile convulsion, meningitis, hypoglycemia, diarrheal diseases, epilepsy, space occupying lesion, cerebral malaria etc.

Convulsion or seizure are synonyms. "A seizure or convulsion is a paroxysmal time limited change in motor activity and or behavior that result from abnormal electrical activity in the brain". Seizure are common in pediatric age group and occur in approximately in 10% of the children. Most seizure in children are provoked by somatic disorders originating outside the brain, such as high fever, infections, head trauma, syncope, toxins, hypoxia or cardiac arrhythmia[5].

Other events, such as breath holding spells, gastro esophageal reflux can cause events that simulate seizure. A few children also exhibit psychogenic seizure of psychiatric origin.

Epilepsy is considered to be present when two or more unprovoked seizure occur at an interval greater then 24 hours apart. Annual prevalence of Epilepsy lower then 0.5-0.8%. In general outlook of Epilepsy is good now a days[6].

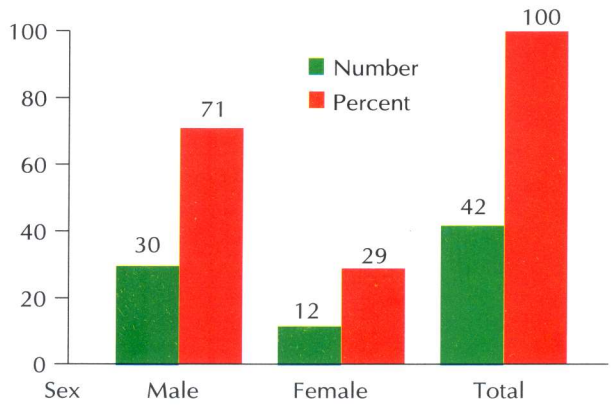
## Material & methods

It is a retrospective study, done in the department of pediatrics in Community Based Medical College Hospital, Mymensingh, during the period January 2005 to December 2005. Of the 42 cases we used per rectal diazepam in a dose of 0.5 mg/kg, seizure was controlled in all the case but in 3 cases per rectal diazepam were needed more then one time. Data were collected from records of the admitted patients & were analyzed with the help of Microsoft Excel program.

## Results

Out of 1950 admitted cases 42 were admitted with convulsion, which means 2% of the total admission were due to convulsion. Age 2 months to 12 years, Male 30 (71%) & female 12 (29%). Causes were febrile convulsion 16 (38%), meningitis 7 (17%), diarrhea with electrolyte imbalance 2 (4.7%), bacillary dysentery with convulsion 2 (4.7%), measles with convulsion 1 (2.4%), encephalitis 2 (4.7%), cerebral malaria 4 (9.5%), epilepsy 2 (4.7%), space occupying lesion 3 (7%).

From the result it is evident that 2% of the admission in pediatric ward were due to convulsion associated diseases. Most commonest cause of the convulsion found in our study is febrile convulsion & next commonest cause is meningitis.




Graph: Showing gender distribution of the study population


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Table: Showing causes of convulsions

| Diseases | Number | Percentage |
|---|---|---|
| Febrile convulsion | 16 | 38 |
| Meningitis | 7 | 17 |
| Cerebral malaria | 4 | 9.5 |
| Space occupying lesion | 3 | 7 |
| AWD with electrolyte imbalance | 2 | 4.7 |
| Cerebral palsy with convulsion | 2 | 4.7 |
| Dysentery with convulsion | 2 | 4.7 |
| Encephalitis | 2 | 4.7 |
| Seizure disorder | 2 | 4.7 |
| Measles with convulsion | 1 | 2.4 |
| Near drowning | 1 | 2.4 |

## Discussion

Admission with convulsion in pediatric ward is relatively common in our country. In our hospital it is 2% of the admission cases, so it is quite significant. If we consider the causes of convulsion in pediatric age group, list is quite long but febrile convulsion is the commonest cause. It is observed that 3% of all children suffer from febrile seizure and less then 3% may develop Epilepsy. It is believed that febrile convulsion occurs due to temporary impairment of the balance between the convulsant & anticonvulsant system of the brain. Probably the threshold level of the anticonvulsant system in these genetically predisposed children is comparatively lower & therefore, they react with convulsion due to rapid rise of temperature[7].

Febrile convulsions are treated by per rectal diazepam. Phenobarbiton & Sodium valproate are used for prophylaxis. Trial has been done with intermittent use of diazepam as prophylaxis, which reduces the recurrence rate of febrile convulsion in high risk children, provided that sufficient doses are given timely and adequately[8]. We all know that shigellosis can cause febrile convulsion and the cause of convulsion in shigellosis may be due to fever, severe dehydration, hypoglycemia, hyponatremia, or meningitis[9].

Sometimes we find diarrhea associated convulsion. Dehydration, electrolyte imbalance, specially hypo or hypernatremia may cause this convulsion. But high rise of temperature, with dysentery can also cause convulsion. HUS with hypertension can also cause seizure.

In 2nd May, WHO & UNICEF recommended reduced osmolarity fluid (ORS) to treat dehydration. ICDDRB tested the formula on a large number of patients. In the conclusion of their study they said, the risk of symptoms associated with hyponatremia in patients treated with reduced osmolarity ORS is minimal and did not increase with the change in formulation[10].

Various drugs are used to control seizure disorder. They need to be used for a long time often, so there may develop some side effects of the drug. In our country Phenobarbiton, Carbamazepin, Phenytoin sodium, Sodium valproate, Clonazepam, Diazepam are widely used. But Phenobarbiton is used very commonly for its cost and availability. But Phenobarbition is often blamed for its increased side effects in cognitive function.

Dhaka Shishu Hospital, Bangladesh did a study on the behavioral side effects of Phenobarbition & Carbamazepin in childhood epilepsy. In their study they concluded as such that, there was no excess in behavioral side effects with Phenobarbiton in children with epilepsy[11].

In seizure disorder, specially in status condition, Diazepam is very commonly used and can be used per rectally or IV and is found quite effective, but considered as invasive procedure. There are studies to compare the effect of intranasal Midazolam & Diazepam. Intranasal Midazolam is equally effective, safe- non invasive method of controlling seizure[12].

Seizure may have many causes, Intracranial aneurysm is one of the important cause of seizure but often missed. Pediatric aneurysm have male predominance, higher incidence of clinical features of mass effect or seizure[13].

## Conclusion

Convulsion in children is a common serious neurological problem. Febrile convulsion is the commonest cause of convulsion in children, followed by meningitis. Male predominates then female. Per rectal diazepam is quite effective in controlling seizure attack. Multicentered large sample national studies are needed for understanding of the selected topic.

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# Pattern of eye diseases in a tertiary hospital in a suburban area : A retrospective study

Murad MAU[1], ALAM MS[2], Miah AKMA[3], Akter MS[4], Kabir MH[5]

The ORION 2007; 28: 492-494


## Abstract

This is a retrospective study carried out in ophthalmology department of International Medical College & Hospital, Gushlia, Tongi, Gazipur for the period of one year from 1st July 2005 to 30th June 2006. Among one thousand seven hundred fifty (n=1750) human subject those who were attended to eye out patient department. This study was carried out to assess the epidemiology of ophthalmology patient served by International Medical College & Hospital (tertiary hospital) in a suburban industrial area. In this retrospective study, total sample size was 1750. Among them male were 52% and female were 48%. The conjunctivitis were 21.94%, cataract 9.2%, refractory error 15.2%, headache 11.09%, dacryocystitis 6.51% and blepharitis 3.2%.


## Introduction

Ophthalmology is one of the important speciality in Medicare services. Ophthalmology unfortunately lags behind in this field of quality of life assessment even though our discipline and the organ with which we deal have a major impact on quality of life. This includes a sense of well-being and other considerations, including whether people feel a burden to their families, have trouble getting up in the morning or performing daily duties[1]. It is a common problem in both rural & urban areas. Also equally spread over developed and under developed countries.

In the urban areas most of the patients can get medicare services in ophthalmology from attending the government hospital and private clinic. As the people in the city or commercial places are rich, educated and affluent. Frequency of disease manifestation varies from place to place[2]. So they can take the service either from government hospital or private clinic by their spending money.

In the suburban industrial area resident are mostly workers and they are very poorly paid in our country. Most of the people are poor, landless, day labourer and they cannot afford to pay medicare expenses available in the private sector. These poor people usually attend government and non-government charitable hospital and clinic where ophthalmologic medicare services are very insufficient and inadequate both in respect of equipment and manpower.


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This is a retrospective study and the data taken from a newly established private tertiary hospital situated in a suburban industrial area.

This study is conducted to find out the need of equipments and manpower in this newly established tertiary medicare hospital.

## Material and methods

One thousand seven hundred fifty (n=1750) cases were attended in both OPD & indoor of ophthalmology department of this tertiary hospital. All the cases were in OPD & in eye department in International Medical College Hospital from 1st July 2005 to 30th June 2006. Patient attending eye OPD get registration, they are examined by the Medical Officer or Assistant Register by taking history, clinical examination. An anterior segment examination with a torch light and loupe were carried out and the posterior segment was examined with a direct ophthalmoscope, initially without pupil dilatation[3]. Suspected cases like amblyopia, uveitis, cataract and squint etc were examined with pupil dilatation.

Figure 1: Uveitis

Figure 2 : Cataract

Von Graefe once said Amblyopia is a condition in which observer sees nothing in the eye and the patient very little the importance of amblyopia lies in the number of life years of blindness and the very little comparative cost requirement to detect, evaluate and manage it[4].

Following investigations like sac patency test, measurement of intraocular pressure by Schietz Tonometer, visual acuity test, biochemistry, serology, culture, biopsy, direct ophthalmoscopy, as per need of clinical diagnosis. Final opinions were given by the Associate Professor of ophthalmology working in the department. As per need cases were followed up on weekly basis up to 4 weeks. Few cases were admitted as per need of the condition of the patient.

Also a few cases were referred to other specialized ophthalmologic unit for better management, due to lack of specialized manpower and equipment in this hospital. The cases who failed to attend the follow up as per schedule were excluded from this study. Most of the cases were diagnosed by taking good history and physical examination. Majority of patients were very poor and could not afford to pay for any investigation. To establish the diagnosis and treatment some of cases were investigated without hospital fees. Surveillance and evaluation of the progress of the work at all levels were strictly

followed and taken into consideration with utmost importance[5]. Numerical data were obtained from records of the OPD and indoor register.

Several large epidemiological studies have determined that low socio economic status is related to increased disease morbidity and mortality[6]. So economic status were obtained by asking direct question to the patient & the patient guardian in case of children.

Questions were as follows-

a. Sources of income.
b. Monthly income & expenses.
c. Number of depended member of the family.
d. Number of members were incoming in the family.
e. Status of the dwelling like kacha, packa, and in slum areas or affluent areas.
f. Status of education.

Taking above history patient are economically divided in three groups, poor, middle class and affluent.

## Aim of study

1. To find out the annual attendance of ophthalmology department of this suburban industrial area.
2. To find out the diseases pattern of attendants in the ophthalmology unit of this tertiary hospital.
3. With the result, recommendations can be made to the hospital authority for improvement of this unit in respect of manpower and equipments.
4. With this study it can be found out how much helpful of a tertiary hospital in a suburban industrial areas. The study intends to evaluate the optimal outcomes for the patients in terms of visual function and quality of life[7].

## Results

1. Total number of patients: 1750 (n=1750).
2. OPD and indoor: OPD =1606 (91.77%), Indoor = 144 (8.23%).
3. Male and female: Male = 911 (52%) and Female = 848 (48%).
4. Age distribution: Table-II.
5. Economical status: Poor-1178 (67%), middle class - 449 (25.5%), Affluent-132 (7.5%).
6. Following data as per diseases pattern: Table-I.
7. Following tests were done almost in each or every patient-
   a. Snellen's chart test.
   b. Slit lamp examination.
   c. External examination of the eye by well illuminating torch.
   d. IOP measure by Schiotz Tonometer.
   e. Ophthalmoscopic examination.
   f. Retinoscopic examination.
8. Operative microscope, indirect ophthalmoscope were on processing of procurement.
9. Non availability of Yag laser, Fluorescent Angiogram, Perimetry.
10. One Medical Officer & one Assistant Registrar, one Registrar and one Associate Professor were involved.
11. From this study it is evident that at least one part time if not full time posterior segment surgeon is essential.

Table I: Individual diseases pattern (n=1750)

| Sl. No | Diagnosis | No of patient | Percentage |
|---|---|---|---|
| 1 | Conjunctivitis | 384 | 21.94 |
| 2 | Cataract | 161 | 9.20 |
| 3 | Refractive error | 266 | 15.20 |
| 4 | Headache | 194 | 11.09 |
| 5 | Dacryocystitis | 114 | 6.51 |
| 6 | Pterygium | 66 | 3.77 |
| 7 | Epiphora | 58 | 3.31 |
| 8 | Chalazion | 55 | 3.14 |
| 9 | Presbyopia | 66 | 3.77 |
| 10 | Traumatic injury* | 52 | 2.97 |
| 11 | Foreign body | 43 | 2.46 |
| 12 | Blepharitis | 56 | 3.20 |
| 13 | Corneal ulcer | 21 | 1.2 |
| 14 | Stye | 22 | 1.26 |
| 15 | Viral keratitis | 21 | 1.20 |
| 16 | Sub Conjunctival Hemorrhage | 17 | 0.97 |
| 17 | Episcleritis | 15 | 0.86 |
| 18 | Pinguecula | 10 | 0.57 |
| 19 | Pseudophakia | 14 | 0.80 |
| 20 | Cellulitis | 5 | 0.29 |
| 21 | Nightblindness** | 21 | 1.20 |
| 22 | Glaucoma | 34 | 1.94 |
| 23 | Uveitis | 15 | 0.86 |
| 24 | Squint | 12 | 0.69 |
| 25 | Lacrimal Abscess | 9 | 0.51 |
| 26 | Diabetic Retinopathy | 13 | 0.75 |
| 27 | Retinal Detachment | 6 | 0.34 |
| | Total | 1750 | 100.00% |

* Traumatic injury includes- Lime burn, acid burn etc.
** Nightblindness includes - Xerophthalmia, Retinitis pigmentosa etc.

Causes of blindness in India (NPCB-WHO survey 1986-1989) Glaucoma-1.70%[8]. Age related cataract, the world's leading cause of blindness[9]. Glaucoma is an optic neuropathy with characteristic appearances of the optic disc and specific pattern of visual field defects that is associated frequently but not invariably with raised IOP[10]. It accounts for 10% of all blindness in the world. In Bangladesh glaucoma is a major cause of blindness. According to the report Glaucoma Prevalence Survey 1993, conducted by Bangladesh Eye Care Society, the incidence of glaucoma was 2.8% in the population above 35 years of age. Glaucoma is the 3rd common cause of blindness after cataract and corneal disease in Bangladesh[11].

Table II: Age distribution of the patient (N=1750)

| Age pattern (years) | No of patient | Percentage |
|---|---|---|
| 0-9 | 174 | 10 |
| 10-19 | 286 | 16 |
| 20-29 | 444 | 25 |
| 30-39 | 279 | 16 |
| 40-49 | 282 | 16 |
| 50-59 | 142 | 8 |
| 60+ | 152 | 9 |

## Discussion

This is semi urban industrial area just outskirts of the capital city. It is evident from the analytical study that most of the patients are poor, age, sex, economic pattern are shown in the result sheet. As this area is semi urban industrial area, there is scope of further growth of industry with improvement of

economy and wealth pattern may be changed. Diseases pattern study could not be found in literature search out so this study could not be compared. But there are some common infectious diseases of eye, such as blepharitis, stye, chalazion (meibomian cyst), herpes zoster ophthalmicus, chronic dacryocystitis, simple acute conjunctivitis, purulent keratitis (ulceration of cornea), anterior uveitis, purulent conjunctivitis, ophthalmia neonatorum[12]. Herpes simplex virus keratitis (HSVK) is one of the main causes of infectious corneal opacification and infection-related visual loss[1] and is a leading indication for penetrating keratoplasty. The prevalence of HSVK in the United States is about 50,000 cases, which also includes 28,000 cases of reactivation; and an annual estimated incidence of 20,000 newly diagnosed cases per year. HSV is DNA virus with two serotypes, HSV-1and HSV-2 that belongs to the Herpes Virus family. HSV-1 is the more prevalent of the two and is primarily transmitted by a symptomatic shedding of virus through saliva. Local host factors are responsible for the frequency of recurrence of HSV-1and HSV-2 in the facial and genital area[13]. With this study it has been already recommended to the management authority for equipments and increase in manpower especially for ophthalmology department. After this study management has already procured operative microscope.

## Conclusion

On this study pattern of eye diseases in this suburban area, among them conjunctivitis, cataract, refractory error, headache, blepharitis and glaucoma were predominant. The patient diagnosed like diabetic retinopathy, retinal detachment, lime burn are referred to centers for proper treatment with right instrument and expertise.

This type of study is helpful to have idea about the epidemiology of any type of diseases in area served by the hospital. This helps in planning & management of a hospital.

Early detection of diseases such as cataract & glaucoma in this population will reduce the burden of blindness[14] in Bangladesh.

The area is already an industrial area with growth of garments industry and there is further scope of growth of this & other industry in this area, which may open further awareness for expansion & growth of the ophthalmological department.

## Acknowledgement

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# Orthognathic surgery on the partially edentulous patient

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The ORION 2007; 28: 495-496


## Abstract

Orthognathic surgery is the surgery to treat disorders of skeletal malocclusion, that can not be corrected by orthodontics alone. Specifically, orthognathic surgery treats significant open bite malocclusions, class 2 and class 3 malocclusions. Mandibular orthognathic surgery has been performed since the 19th century, while maxillary osteotomies were not routinely performed until the 20th century. Orthognathic surgery is typically performed on young adults, uncommonly performed on older patients or patients who are partially or completely edentulous. The focus of this article is to review orthognathic surgery on the partially/fully edentulous patient and to identify differences in treatment and complications compared to surgery in dentate patients.


## Introduction

Orthognathic surgery is mostly commonly performed on young adults with a full complement of teeth that have been orthodontically prepared prior to surgery. However, in some situations, the atypical orthognathic surgery patient may present with an old age or a patient that is partially or fully edentulous. These patients have the same basic desires as the typical orthognathic patient is to achieve as normal an occlusion as possible to treat the functional and aesthetics deficiencies that are associated with a skeletal malocclusion. As a major tertiary care university medical center for the State of New Jersey, our institution frequently treats these atypical patients. The goal of this paper is to share our experiences as well as pitfalls and recommendations for treating the partially edentulous orthognathic surgery patient.

The early orthognathic literature discusses treating the edentulous patient. Kazanjian, in 1951, reviewed his treatment of prognathism in four partially edentulous patients. His treatment included extraoral ramus osteotomies as well as utilizing splints attached to a head frame to ensure proper immobilization. In addition, intraosseous wiring was utilized[1]. In 1953, Van Alstine and Dingman described treating prognathism in the edentulous patient via an ostectomy of the body of the mandible secured by intraosseous wiring. Acrylic splints wired circumferentially were utilized to place the mandible into a favorable position[2]. In 1954, Caldwell and Letterman published the technique of the Extraoral Vertical Ramus Osteotomy to treat prognathism[3]. This was later modified by Hebert, Kent, and Hinds in 1970 to an intraoral vertical ramus osteotomy (IVRO), a technique commonly used by today's surgeons[4]. In addition, Obwegeser in 1952 started developing the sagittal split osteotomy to treat mandibular prognathism and retrognathia. What is most astounding about the development of the sagittal split is that Obwegeser notes the first 15 cases were done under local anesthesia in the dental chair[5]!


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## Discussion

The work up for the partially edentulous orthognathic surgery patient is no different from that patient with a full complement of teeth. A full extraoral evaluation, noting facial symmetry and proportions, as well as standard radiographic evaluation (panoramic and cephalometric films). Of note on the radiographs-evaluation of the bone quality and height is needed in the long-standing edentulous patient as bone atrophy may occur. This especially important in the patient planned for sagittal splits-an atrophic mandible may not be amenable to a favorable split; in the prognathic patient with an atrophic mandible, the IVRO may be a superior procedure. In addition, an edentulous maxilla may lead to an extremely atrophic anterior maxillary wall, creating a very fragile Le Fort 1 osteotomy. A thorough intraoral exam should be performed - evaluating the arches in relation to one another from transverse, anterior-posterior, and vertical dimensions. If the patient has an existing prosthesis, evaluation should be performed both with and without the dental prosthesis in the mouth, with attention paid to any changes in vertical dimension with and with out the prosthesis.

Once all the clinical and radiographic date has been collected, a standard surgical prediction tracing should be done as well to determine the required orthognathic movements and plan for the model surgery. The model surgery is performed in a standard fashion. Where the differences lie in the partially edentulous patient compared to the dentate patient is in the fabrication of the surgical splints. In most orthognathic surgeries, a surgical splint is an integral part of the surgery, guiding the surgeon to place the maxillofacial skeleton into the presurgically determined ideal position. In addition, tooth position and occlusion help guide the surgical movements. In the partially edentulous patient, these splints have even more of an importance, as there may not be teeth available to help guide the surgical movement of the maxilla and mandible. In our experience, fabricating splints to fit into the edentulous spaces has been useful in guiding the orthognathic surgery. In addition, to ensure appropriate maxillomandibular fixation (MMF), we have incorporated arch bars into splints in the edentulous areas (Figure 1a-1e)

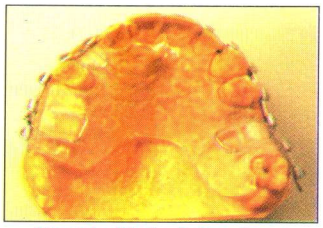

Figure 1a: Occlusal view of stent encompassing edentulous areas with arch bar attached

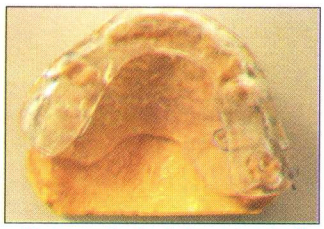

Figure 1b: Occlusal view of surgical splint in conjunction with stent

Figure 1c: Lateral view of splint/stent complex

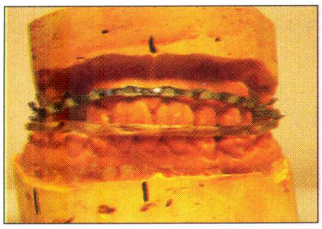

Figure 1d: Frontal view

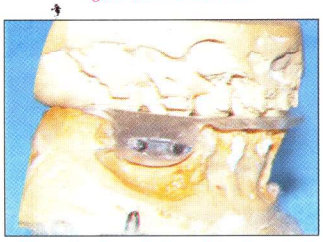

Figure 1e: Lateral view of final surgical splint with arch bar attached

or utilized transosseous MMF screws to obtain adequate fixation (Figure 2). If the patient has an existing prosthesis, this is utilized as well as a guiding splint during surgery; an arch bar or MMF screws can be attached to the prosthesis to facilitate MMF.

The major surgical pitfall in treating partially edentulous patients is that there may be significant bone atrophy in the areas of missing dentition. As noted above, in the mandible this may lead to an unfavorable sagittal split or increase the risk of injury to the mandibular neurovascular bundle. In the maxilla, bone atrophy leads to an exceptionally thin anterior maxillary wall; if care is not taken, the process of completing the Lefort 1 osteotomy can result in fragmenting the anterior maxillary wall, making it difficult to secure rigid fixation or determine if the maxilla has moved into its planned position (Figure 3).

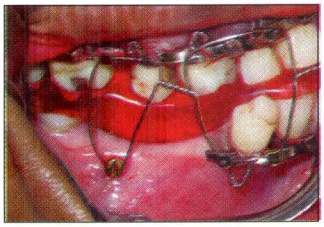

Figure 2: Transosseous Maxillomandibular fixation screw

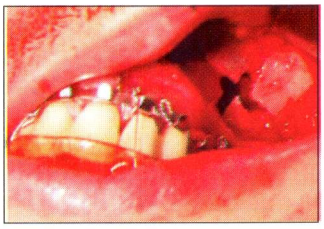

Figure 3: Fragmentation of the Lefort 1 osteotomy in an edentulous area of the maxilla

If this occurs, place the maxilla in its optimum surgically determined position, fixated it, and then bone graft to areas of bony defects. Often freeze-dried iliac crest will suffice, precluding the need for harvesting autogenous ileum. In addition, trying to minimize the amount of Periosteal stripping during surgery to maximize blood supply to the bone is preferred to ensure post surgical healing. Finally, as with any orthognathic procedure, ensuring that the bone segments are completely immobile once placed into their new position, and ensuring bone to bone contact are keys to avoiding relapse and facilitate optimal healing.

## Conclusion

Orthognathic surgery in the edentulous and partially edentulous requires some minor modifications compared to surgery on a patient with a complete dentition. Edentulism in the maxilla often leads to maxillary atrophy, requiring extra care when completing Lefort Osteotomies. Additionally, sagittal split osteotomies in edentulous mandibles have a higher incidence of bad splits, requiring extra care and attention. Finally utilizing splint to encompass the edentulous segment can be beneficial to placing the jaw in the ideal presurgically determined position.

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# Insulin analogues

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## Introduction

Diabetes mellitus is a very big challenge for our medical science. To overcome this problem we need newer generation of agents those can control glycaemic status nearer to physiology. In that case Insulin analogues will be the agents for improving glycaemic control.

The diabetic control and complication trail provided conclusive evidence that strict glycaemic control, reduced the incidence and progression of neuropathy, nephropathy and retinopathy.

The key to strict glycaemic control by the exogenous insulin lies in the delivery method that emulate physiological insulin secretion. Unfortunately conventional insulin preparation have limited pharmacokinetic profiles which make the goal of emulation impossible. On the other hand insulin analogues offer expanded pharmacokinetic profiles and the possibilites of regimens that closely mimic the physiology.

## Insulin analogues

Analogues are altered molecular version of a natural substance. They have been used in many therapies where hormone treatment is needed. The natural hormone is changed slightly, by rearranging the position of amino acid within the molecule (i.e.- It is something like changing the position of beads on a necklace). This new version of natural substance works basically the same way as original substance.

As there is slight difference of amino acid sequences between natural human insulin and insulin analogues, it would not be correct term to call the insulin analogue a type of human insulin. So, insulin analogue and insulin are two different terms.

## Historical achievement in insulin therapy

*1920- Discovery of insulin by Banting and Best.
*1922- The 14 year-old Leonard Thomson became the 1st patient to receive insulin.
*1923- Nobel prize in medicine was awarded to Banting and John McLeod.
*1930- Long acting protamine zinc insulin was developed.
*1950- Long acting insulin NPH was developed and insulin zinc (Lente) were introduced.
*1980- Development of pork insulin.
*1981- Introduction of recombinant human insulin.
*1984- Improvement in insulin delivery device and introduction of insulin delivery pen.
*1996- In July 1996 first recombinant DNA human insulin analogue, Lispro was approved.
*1999- Insulin analogue Aspart was introduced into market.

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Since then more insulin analogues have been introduced which provides new hope for controlling diabetic complications.

## Normal insulin secretion

In non diabetic persons insulin secretion has two basic components-

1) Basal &
2) Stimulated.

*1) Basal*

- Basal insulin is secreted continuously between meals and throughout the night at a rate of 0.5-1 u/h in adults.
- Basal insulin provides serum concentration of 5-15 microunit/ml.
- The low basal insulin reduces hepatic glucose production but allows sufficient glucose level for cerebral energy production. In diabetic patients treatment with intermediate acting and long acting insulin attempts to mimic the basal secretion.

*2) Stimulated*

- Stimulated secretion occurs normally in response to a meal resulting serum concentration of insulin 60 - 80 microunit/ml from just before to 30 minutes after meal.
- Concentration returns to normal level in 2-4 hours.

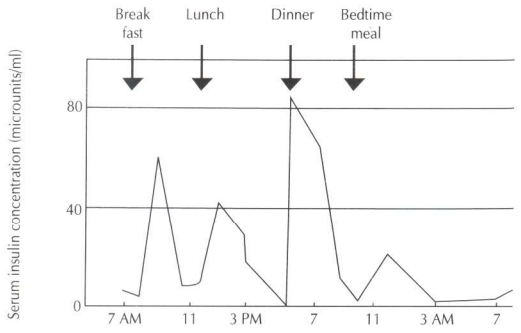


Figure 1: Normal insulin secretion. In the stimulated phase, serum insulin levels increase from within a few minutes before to 30 minutes after a meal. Return to basal level occurs within 2 hours.

## Indications of insulin therapy

1) Type-I DM.
2) Type-II DM with following conditions-
   i) Hyperglycemia despite of maximum dose of oral hypoglycemic agents.
   ii) Decompensation due to intercurrent events like infection, acute injury, stress.
   iii) Pregnancy.
   iv) Renal diseases.
   v) Surgery.
   vi) Severe hyperglycemia with or without ketonaemia or ketonuria.

### Therapeutic objectives of insulin therapy

- Correction of fasting and pre-prandial hyperglycemia (correcting the basal glucose metabolism).
- Minimization of the excessive post-prandial hyperglycemia.
- Prevention of hyperglycemia in between meals.
- To keep the Hb1c near normal.

### Disadvantages of conventional insulin therapy

*1) Disadvantages of regular/ soluble insulin*

- Regular insulin has a nature of self association and regular insulin is found in a self associated hexameric form.
- To be absorbed by the capillary the hexameric form must dissociate to dimer and then monomer.
- This dissociation process delays the onset of action from 0.5-1 hr, may not be peak for 4 hrs and duration of action of 8 hrs.
- So they should be taken 30 min before meal.
- As their duration of action is prolonged, it reaches peak concentration 2 hrs after injection (in many cases and depending on the dose it may peak 4-6 hrs after injection) when blood glucose level already may be low.

*2) Disadvantages of intermediate acting insulin (NPH & Lente)*

- Peak action is 4-10 hrs after injection.
- Effective duration of action 10-20 hrs .
- Their peak effect is a problem for using as a basal insulin.
- Their duration of action necessitates more than one daily injection.

*3) Disadvantages of long acting insulin (Ultralente)*

- Their duration of action is 16-20 hrs. So single injection is not enough.
- Their duration of action is variable.
- Their peak effect is difficult to predict.

### Pharmacokinetic actions of conventional Insulin at a glance

| Insulin type | Onset of action | Peak action | Effect of duration |
|---|---|---|---|
| Regular | 0.5-1 hr | 2-4 hrs | 3-8 hrs |
| NPH | 2-4 hrs | 4-10 hrs | 10-20 hrs |
| Lente | 3-4 hrs | 4-8 hrs | 10-20 hrs |
| Ultralente | 6-10 hrs | Dose dependent | 16-20 hrs |

### Types of insulin analogues

1. Rapid Acting
   - i) Lispro
   - ii) Aspart
   - iii) Glulisine
2. Long acting
   - i) Glargine
   - ii) Detemir

### Criteria for good rapid acting analogues

- The short acting analogues would have time action profile with an onset of action less than 30 mins.
- A duration of action less than 4 hrs.
- Similar effect in all patients.
- They should be non immunogenic.

### Lispro

*Structure:* Insulin Lispro was formulated on the premise that insulin like growth factor-1(IGF-1) which structurally similar to insulin, does not trend to self associate.

In the B chain of natural human insulin, Lysine lies in the B29 position and Proline in the B28 position. Lispro is produced by inverting position of two amino acids. That is in Lispro B chain, Lysine lays in B28 position & Proline lies in 29 positions.

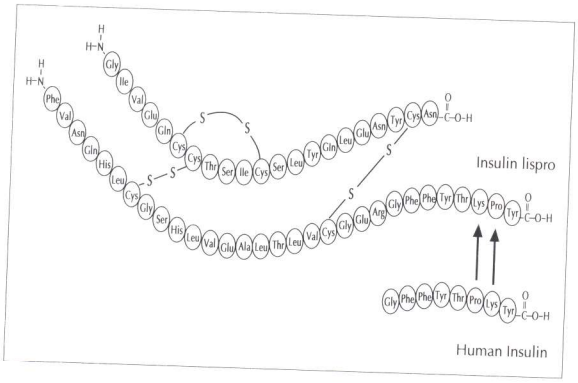


Figure 2: Structure of lispro

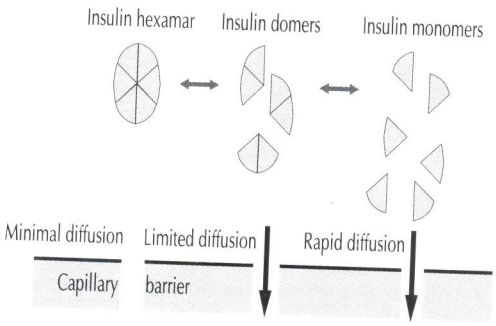


Figure 3: Regular insulin in Hexameric form. This form needs to become monomeric form for diffusion & absorption from subcutaneous or intramuscular area. But Lispro remains in monomeric form.

*Practical issue:* Because of this change in amino acid sequence Lispro has rapid onset of action in 15-30 min and peak action in 30-60 min and action last about 3-4 hrs.

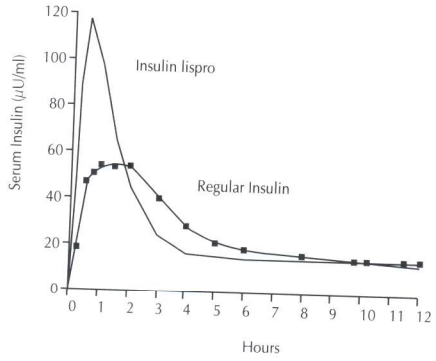


Figure 4: Rapid rise of serum level of lispro after administration in comparison to regular insulin

Lispro is non-immunogenic (In different studies it was observed that even before exposure to Lispro there is cross reactive antibodies but not Lispro specific antibody level. These antibodies decrease over time and have no clinical consequence).

*Special considerations in using insulin lispro*

| Potential problems | Comments and possible solutions |
|---|---|
| Patient eats dinner late | Because of insulin lispro's shorter duration of action, hyperglycemia may occur because the time from lunch to dinner may be too long.<br><br>Consider adding a small dose of intermediate-acting (NPH) insulin at lunch to meet basal insulin requirements between meals. |
| Patient has snacks containing more than 5 g of carbohydrate | Consider adding an additional dose of insulin lispro; if the patient also eats dinner late in the evening, this additional dose of insulin lispro can replace lunchtime basal NPH insulin supplementation. |
| Patient is a slow eater or a grazer (i.e., eats small amounts of carbohydrates throughout the day rather than at three meals) | Because of the rapid onset of insulin lispro, this type of patient may not respond as well to insulin lispro as to regular human insulin. |
| Patient has unpredictable eating habits | Insulin lispro offers the patient flexibility, in that the administration of this insulin can be timed with meals. |
| Patient has type 2 diabetes and is receiving two injections of NPH/regular insulin each day | This patient could benefit from the substitution of insulin lispro for regular human insulin to decrease postprandial blood glucose excursions. |
| Patient exercises | The patient who uses insulin lispro can expect fewer episodes of hypoglycemia if the exercise is undertaken 2.0 to 2.5 hours after the injection of insulin lispro. |

*Therapeutic role of lispro*

Insulin lispro has been found to be a safe and effective treatment for diabetes mellitus. Improvement in glycemic control is demonstrated by a decreased postprandial blood glucose concentration, although the longtime clinical significance of this improvement is as yet unknown. Multinational clinical trials have shown no statistically significant difference between hemoglobin A1c levels in patients treated with insulin lispro and patients treated with regular human insulin. However, the use of insulin lispro in external insulin infusion pumps has been shown to produce a small, yet clinically significant (0.34 percent) reduction in hemoglobin A1c levels compared with the reduction achieved using regular human insulin. This improvement in hemoglobin A1c represents an approximately 20 percent reduction in the risk of retinopathy in patients with diabetes.

Near-normal glycemic control is necessary to prevent or delay the onset of complications in patients with type 1 or type 2 diabetes. Patients with type 2 diabetes who have not responded to oral glucose-lowering agents often require insulin therapy to achieve the glycemic goals set forth by the American Diabetes Association. One study in both type 1 and type 2 diabetics concluded that insulin lispro improves postprandial glycemic control without increasing the risk of hypoglycemia. Short- or long-term insulin therapy has been shown to be useful in type 2 diabetics in whom the rapid component of endogenous insulin secretion is missing. In these patients, insulin lispro is a physiologic therapy. Primary care physicians should consider including mealtime insulin lispro in insulin regimens. The disadvantages of insulin lispro therapy are the increased risk of hypoglycemia if meal ingestion or absorption (gastroparesis) is delayed and the increased overall cost of therapy. Nonetheless, a short-acting insulin analog such as insulin lispro should provide increased convenience and flexibility to patients who are currently receiving regular human insulin. Furthermore, the characteristics of insulin lispro may help patients achieve improved long-term glycemic control and may reduce the incidence of hypoglycemic episodes. Insulin analogs may be an important tool for helping patients with diabetes mellitus achieves their target glucose goals.

*Drug Interactions*

No studies have specifically evaluated drug interactions in diabetic patients who are receiving lispro insulin. Close monitoring of blood glucose levels is important when a drug regimen is changed in any patient with diabetes.

**Aspart**

*Structure:* In insulin aspart, proline is replaced by aspartic acid at position B28 in insulin molecule.

This change results in stay Aspart in monomeric form and thus helps in rapid absorption.

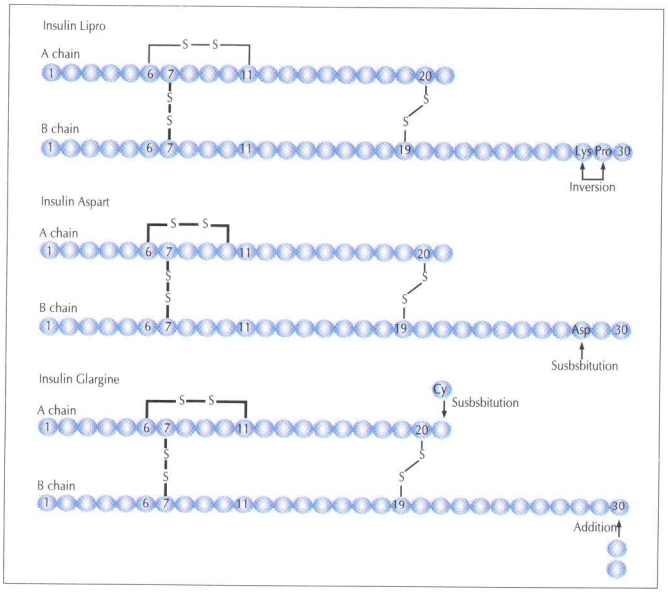


Figure 5: Structure of lispro, aspart, glargine

*Practical issue:* Onset of action within 30 min, peak action 30-60 min and action lasts for 4 hrs.

Although some preliminary comparisons of Aspart with Lispro have suggested that they are similar in action, other comparison suggested that there are some differences. So it is not recommended that Aspart and Lispro are interchangeable.

### Glulisine

*Structure:* Glulisine differs from human insulin in that the amino acid Asparagine at B3 position is replaced by Lysine and Lysine is replaced by Glutamic acid. It is still in clinical trial.

### Benefit of short acting analogues

- As their onset of action very rapid, they can be used just before and even after meal.
- As their duration of action is short, they are less likely to cause hypoglycemia in between meals. This is the key point of strict glycaemic control. They rapidly reduces the blood glucose level just after meal but are not cause hypoglycemia 4-6 hrs after meal.
- So, they can be used to those who wants more flexibilities in their meal times and those who suffers late midnight hypoglycemia.
- They improve HbA1c.

### Premixed insulin analogues

*Two premixed insulin analogue preparations are now available*

1) 75% Neutral Protamin Lispro + 25% Lispro
2) 70% Protamin Crystalline Aspart + 30% Aspart

### Basal/long acting insulin analogues

*Criteria for long acting insulin analogues*

1) An ideal insulin analogue should have peak less effect.
2) Should have long half life, so that one injection is enough.
3) Little inter-patient and intra-patient variability.

### Basal & long acting insulin analogues

*Two long acting analogues are available*

1) Glargine
2) Detemir

### Glargine

*Structure:* Glargine is produced by recombinant DNA technology through nonpathogenic E. Coli. The difference is only in structure from human insulin where Glargine has both the addition of two Arginine at C-terminus of B-chain and substitute of Glycine for Aspargenic acid at A21 position.

*Practical issue:* This change in structure makes Glargine soluble in pH of 4 but has relatively slow solubility when injected into neutral pH environment.

When Glargine is injected, micro precipitates forms and slowly insulin resolubilized and absorbed. This sequence of changes is predictable and provides a relatively constant level of insulin with no peak effect over a period of 24 hrs. So, single injection can maintain constant level for 24 hrs.

There is no difference in absorption rate of Glargine in different sites of the body. There is no evidence that Glargine accumulates in the body. Large number of trials have

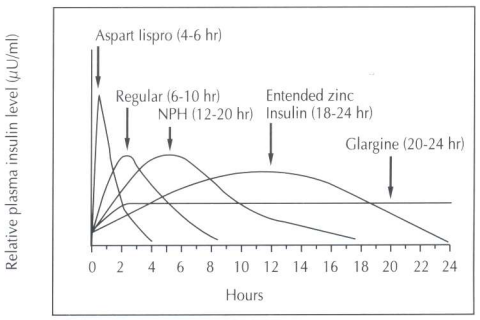


Figure 6: Different curves showing comparison of duration of action insulin analogues (Apart, Lispro, Glargine) & conventional insulin (Regular, NPH & Extended Zn insulin)

documented that Glargine can control glycaemic status more strictly then NPH, Lente or Ultralente but significantly reduces the nocturnal hypoglycemia. It significantly reduces HbA1c than other intermediate & long acting insulin.

### Detemir

- It is under trial.
- After injection, Detemir binds with the albumin through a fatty acid chain attached to Lysine at residue B29, which leads to a reduction in free Detemir level.
- The initial data suggested that Detemir has less variability in absorption than NPH.
- Data suggested it is less hypoglycemic.
- One study suggested that Detemir has some effect on hepatic glucose metabolism.

### Limitations of insulin analogues

- May cause hypoglycemia on overdose or if patient don't take adequate amount of food prior to injection.
- Insulin analogues are not recommended for I.V use.
- Rapid acting analogues are not recommended in diabetic gastroparesis.
- Insulin allergy, lipoatrophy and lipohypertrophy same as conventional insulin.
- Glargin requires OHA in Type-II & regular insulin in Type-I DM.

### Conclusion

Insulin treatment has always been as much an art as a science. Insulin analogues have met all the requirement for strict glycemic control also give the patient more flexibility in the timing of meal without the risk of hypoglycemia. Although these insulin analogues have much benefit over conventional insulin, the cost of these analogues is the main disadvantage for their use.

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# Prevention of in-stent stenosis : Drug-eluting stents create new hope in the PCI

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**Abstract**

The long term outcome of stent implantation is affected by a process called in-stent stenosis. Smooth muscle cell migration and proliferation in the intima produce neointimal hyperplasia, which is pathognomic of in-stent stenosis. Increased extracellular matrix form the bulk of the neointimal hyperplasia tissue. Emerging evidence of the role of inflammatory cytokines and suppressors of cytokine signalling make this an exciting and novel field of antirestenosis research. Several drugs have been used systemically and locally (Drug-eluting stents), to prevent proliferation and migration of smooth muscle cells. Drug-eluting stents have now become the medium for local drug delivery to the site of the lesion. Stents coated with any of several pharmacotherapeutic agents such as sirolimus and paclitaxel can be used. Initial result with Drug-eluting stent was promising.

**Keywords**

Drug-eluting stent, in-stent stenosis, percutaneous coronary intervention (PCI).

## Introduction

Over 1.5 million percutaneous coronary revascularisation procedures are performed annually world wide, most being intracoronary stenting. Despite enormous advances in devices, the major limitation of PCI is in-stent stenosis[1]. Although in-stent stenosis rates are 10-20% in selected patients, but rates are much higher, up to 59% in some high risk lesions[2,3,4].

The introduction of a metallic spring into the popliteal artery of an experimental animal by Charles Dotter[5] signalled the beginning of the stent era. However, the first human stent implantation, by Sigwart et al[6], in 1986, and it was only in 1994 that the US Food and Drug Administration approved the use of stents[2,3]. On average, stents appear to have a 10% lower rate of restenosis compared with angioplasty and the favuorable results due to stent usage have been reported in several studies[7]. The risk factors of restenosis include the method (stented or not), lesion location (the left anterior descending artery is found to be less susceptible to restenosis)[8], diabetes[9], residual stenosis, number of stents[10], the stent length[11], total occlusion and late total occlusion[12], and bifurcating or ostial lesions[13]. Experimental studies suggest that the process of cellular proliferation starts between the first few days and up to 2-3 weeks after stent implantation. In an attempt to further reduce the degree of restenosis, numerous adjunctive strategies, such as use of high pressure stent[14], use of specific materials and designs, prior debulking[15] and no pre-dilatation[16] have been tried.

Brachytherapy represents a potentially powerful way to prevent restenosis. The delivery of local radiation to the target site after angioplasty has now been shown to help reduce restenosis[17,18,19]. Brachytherapy is not universally accepted, due predominantly to late thrombosis and the logistics of administering radioactivity.

Several drugs have been used systemically and locally (Drug-eluting stents), to prevent proliferation and migration of smooth muscle cells. Drug-eluting stents have now become the medium for local drug delivery to the site of the lesion. Drug-eluting stents containing the immunosuppressive agent rapamycin and the antimitotic agent paclitaxel have shown encouraging reductions in in-stent stenosis[20,21].

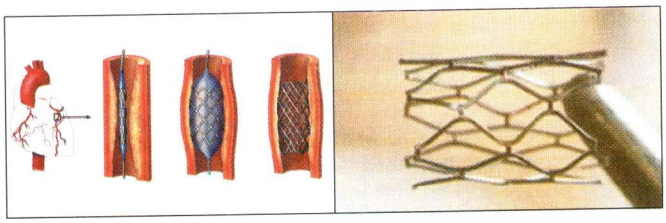

Figure: Coronary stent

## Definition and classification of in stent restenosis

In-stent stenosis can be defined clinically or angiographically. Clinically it is defined as the presentation of recurrent angina or objective evidence of myocardial ischaemia, whereas angiographic in-stent stenosis is the presence of >50% diameter stenosis in the stented segment[22]. Traditionally, in-stent stenosis has been classified based on the length of the lesion, as focal (<10 mm) or diffuse (>10 mm).

## In-stent stenosis: an epidemic

Currently, over 1.5 million percutaneous coronary intervention procedures are performed each year worldwide, and the rate doubles every 5 to 8 years[23]. Despite the steady and continuous advancement in the field of interventional cardiology, restenosis remains an important limitation of percutaneous coronary revascularization[24]. In the United States, about one quarter of the procedures are performed in lesions that were previously treated with PCI. Considering that more than 700,000 cases are performed in the United States annually, this translates to a cost of $ 3.5 billion/year for the treatment of restenosis. Because the number of procedures performed is increasing each year, the absolute number of patients affected by restenosis may continue to rise until definitive measures for the prevention and treatment of restenosis are discovered and implemented.

## Mechanisms of restenosis

Following angioplasty there is dissection of both the intima of the plaque and the vessel media, associated with an enlargement of the treated segment. Restenotic lesions develop over weeks to months. The vessel's response to coronary intervention is a complex process. Luminal narrowing can be considered as an expected but excessive healing response. In brief, restenosis following vascular injury is due to three

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interrelated processes, early elastic recoil and late remodeling, activation of hemocoagulative pathway and thrombus formation, and neointimal growth. The vessel may also remodel chronically in response to the mechanical arterial wall injury, resulting in an increase (positive remodeling) or decrease (negative remodeling) of the overall cross-sectional area, the so-called Glagov phenomenon.

### Reorganisation of thrombus

Fibrin and platelets are deposited on stent struts early after implantation. The association of fibrin and platelets with neointimal accumulation and extensive neovascularisation at in-stent stenosis sites suggests that organisation of mural thrombus promotes in-stent stenosis.

### Neointimal formation

Arterial injury induces vascular smooth muscle cell undergo either cell proliferation, migration or both, with subsequent synthesis of extracellular matrix and collagen, resulting in neointima formation. Neointimal formation is the major cause of in-stent stenosis. Neointima increases up to three months after the procedure, with little change to six months, and a gradual reduction between six months and three years.

### Cellular and molecular pathophysiology of restenosis

The complex mechanisms leading to in-stent stenosis can be divided into an "early" (days to weeks) and a "late" (weeks to months) phase. Endothelial injury produces some element of thrombus formation[25], and fibrin and platelet deposition at the site of injury provides the foundation for the inflammatory aggregate. There is increased leukocyte trafficking to the stent site and subsequent migration into the vessel wall[26], the predominant cells being monocyte derived macrophages[27]. Sustained production of adhesion molecules, cytokines, chemoattractants and growth factors lead to further leukocyte recruitment and infiltration. The weeks following injury lead into the late phase. The main event of the late phase is the phenotypic modification of medial smooth muscle cells followed by their migration and subsequent proliferation in the intima. Coordinated extracellular matrix synthesis by these smooth muscle cells is responsible for the increasing volume of intimal tissue, and the bulk of the new intimal hyperplasia is composed of extracellular matrix proteoglycans and collagens, with cellular elements making up only about 11%[28]. Thus, over the months subsequent to stent implantation, there is a shift towards greater extracellular matrix synthesis rather than smooth muscle cell proliferative activity[29,30].

### Treatment and prevention of in-stent stenosis

Brachytherapy and Drug-eluting stents are the modality of treatment for prevention of restenosis.

*Drug-eluting stents:* Drug-eluting stent has being developed to minimize in-stent restenosis.

*Rapamycin:* Rapamycin (sirolimus) possesses weak antibiotic activity, but is a potent modulator of immune function. Sirolimus is a natural macrocyclic lactone produced by Streptomyces hygroscopicus with potent antiproliferative, anti-inflammatory, and immunosuppressive effects[31]. The mammalian target of rapamycin (MTOR) is the phosphatidylinositol kinase (PIK) related kinase family that regulates protein translation, cell cycle progression, and cell proliferation. Rapamycin enters cells easily where it is bound to a specific intracellular receptor FKBP12-the rapamycin/FKBP12 complex is a highly specific inhibitor of mTOR.

Firstly, sirolimus is a potent inhibitor of vascular smooth muscle cells proliferation. Secondly, rapamycin reduces vascular smooth muscle cells migration. Thirdly, rapamycin is a potent inhibitor of cell size. Fourthly, rapamycin may have significant effects on cell matrix synthesis. Finally, rapamycin is an inhibitor of inflammation in vessels after injury. Both sirolimus (rapamycin) and tacrolimus inhibit T lymphocyte proliferation and activation, acting as both anti-inflammatory and immunosuppressant agents.

These biological properties mean that rapamycin eluting stents are potent inhibitors of in-stent stenosis[32,33,21] and low levels of restenosis are seen in upto 2-3 years. The result of 15 slow-release rapamycin-coated Bx VELOCITY stents has been reported by Reusing and colleagues[34]. At 6-month follow-up; no adverse cardiac events were reported, and no patients had angiographic restenosis. No in-stent or edge restenosis was observed. Randomized Study with the Sirolimus-Eluting VELOCITY Balloon Expandable Stent (RAVEL) trial[35] at 6-months follow-up showed restenosis rates (>50% diameter stenosis) among who received the drug-eluting device was reported as 0% compared with 26.2% in the group that received the uncoated stent. The Sirolimus-Coated Bx VELOCITY Balloon Expandable Stent (SIRIUS) trial with 1101 subjects with single de novo coronary artery lesions, showed the safety and efficacy of sirolimus-coated devices.

*Paclitaxel:* Another agent considered for local delivery for the prevention of restenosis is paclitaxel. Paclitaxel is a potent antiproliferative agent that inhibits the disassembly of microtubules. The stabilized microtubules are dysfunctional, and inhibits cell replication[36]. Micro-tubular stabilization also affects cell motility, shape and intracellular transport. Paclitaxel is highly lipophilic, which enables it to easily pass through cell membranes, resulting in a longlasting antiproliferative action. The European Evaluation of Paclitaxel Eluting Stent (ELUTES) trial examined the safety, efficacy and dosing of a paclitaxel-coated stent in patients implanted with paclitaxel coated V Flex Plus stents[37]. Paclitaxel-eluting V Flex Plus stents have also been shown to be effective for the prevention of recurrent in-stent restenosis. Asian Paclitaxel-Eluting Stent Clinical Trial (ASPECT)[38] shows at 6-month follow-up, a significant, dose-dependent reduction in binary restenosis rates. The TAXUS I study showed the feasibility and safety of low-dose paclitaxel-eluting stents (NIRx) used for the treatment of de novo and restenotic lesions[39]. TAXUS IV study represents the safety and efficacy of a moderate-release paclitaxel formulation, using an Express stent platform, on both de novo lesions and in-stent restenosis.

*7-hexanoyltaxol (QP2):* A more hydrophobic derivative of paclitaxel, 7-hexanoyltaxol (QP2), a taxane, has been tested on a unique stent delivery platform for the prevention of restenosis. The mechanism of activity is similar to that of paclitaxel, in that it inhibits microtubule formation by inhibiting microtubule depolymerization, thus interfering with the cell cycle. Study to compare restenosis rate between QueST and QuaDDS-QP2 (SCORE) shows unfavorable result.

*Actinomycin D:* Guidant has developed an actinomycin D-eluting stent, the MULTI-LINK TETRA D stent, for the prevention of restenosis. Actinomycin D is an antibiotic that

has been approved as an anticancer chemotherapeutic agent. It binds DNA, preventing cell division and protein production. Actinomycin D affected cells in all phases of the proliferation cycle. The Actinomycin Eluting Stent Improves outcomes by reducing neointimal hyper-plasia (ACTION) trial shows actinomycin Drug-eluting stents were not effective in preventing restenosis.

*Dexamethasone:* The Study of Anti-restenosis with BiodivYsio Matrix LO Dexamethasone Eluting Stent (STRIDE), objectives were to evaluate the safety and efficacy of the MATRIX LO stent with dexamethasone. Dexamethasone is a steroid (corticosteroid) anti-inflammatory drug that is used to inhibits the inflammatory response and reduce tissue injury resulting from trauma. Dexamethasone's mode of action targets many of the inflammation processess, including (1) the inhibition of cyclo-oxy-genase-2, which reduces prostaglandin synthesis (2) the inhibition of the transcription gene for phospholipase A2, which gives rise to the prostanoids, platelet-activating factor, and leukotrienes; and (3) the induction of the anti-inflammatory protein mediator lipo cortin-1. It is thought that the delivery of dexamethasone to the site of injury from a stent could prove beneficial in the inhibition of cytokines, leading to a reduction in the proliferation of inflammatory cells around the stent struts, with a resultant reduction in restenosis.

*Batimastat:* Batimastat, a broad-spectrum MMPI developed by British Biotech (Oxford, UK), is a low-molecular-weight peptide mimetic containing a hydroxamate group that chelates the zinc atom in the active site of the matrix metalloproteinase (MMP) and thereby inhibits the enzyme. Batimastat is a potent, but reversible, inhibitor of MMPs: collagenases, stromelysins, and gelatinases. Collectively, these enzymes can degrade all of the components of the extracellular matrix and induce cell migration and proliferation. The injury caused by the stent to the vessel wall and the resulting smooth muscle cell proliferation causes expression of several members of the MMP family, and batimastat can inhibit the cell migration and proliferation process. The BiodivYsio Batimastat SV Stent versus Balloon Angioplast for the Reduction of Restenosis in Small Coronary Arteries (BATMAN) (Americas) and Batimastat (BB-94) Antirestenosis Trial Utilizing the BiodivYsio Local Drug Therapy PC Stent (BRILLIANT) (European Union) programs were a series of clinical studies designed to evaluate the safety and efficacy of the batimastat-eluting BiodivYsio MATRIX stent. BATMAN I was a pilot safety trial recently completed in Latin America. BRILLIANT I show the batimastat BiodivYsio stent had no extra benefit .These results led to the suspension of recruitment into the 400-patient BRILLIANT II randomized trial.

*Biodegradable stent with pharmacologically active agents:* The development of a suitable biodegradable stent with pharmacologically active agents incorporated into the polymeric matrix has waned considerably in interest. To be effective, a drug-releasing biodegradable stent must be bio-compatible and not cause an inflammatory reaction, and the breakdown products must be nontoxic. Stent delivery must be reliable, the devices must have high radial strength, and stent degradation should occur in a reasonable time period (12 to 24 months). The ideal stent would deliver drugs locally that inhibit restenosis, in concentrations that are effective without inducing tissue injury. The Duke Biodegradable Stent 40 and the Igaki-Tamai bio-degradeable stent are capable of incorporating pharmacologically active agents.

*Sirolimus versus paclitaxel:* In the Kastrati et al 41 meta-analysis, all six trials were pooled to describe angiographic and clinical outcome for 3669 patients. At follow up there was no difference in mortality, death or MI and stent thrombosis in the sirolimus or paclitaxel treated patients. Although major safety measures were similar, angiographic results favoured sirolimus including target lesion revascularization and angiographic restenosis were less.

*Des versus brachytherapy:* The Sirolimus- Eluting Stent Versus Brachytherapy in Patients with Bare Metal In-Stent Restenosis (SISR) trial shows overall results indicate that use of SES is superior to brachytherapy for prevention of recurrent in stent restenosis[42].

*New non drug coated stents for restenosis:* Titanium nitride oxide stent coating has a superior biocompatibility to stainless steel, has been shown to reduce vascular inflammation and neointimal hyperplasia. Windecker et al[43] found this stent had a significantly lower late loss, binary restenosis, and neointimal volume compared with patients who received a non coated stent.

## Update in adjunctive pharmacologic therapy to limit restenosis

Oral medications to reduce restenosis may be benefit. In the multicenter Cilostazol for Restenosis Trial (CREST), shows cilostazol had significant reduction in angiographic restenosis at six months[44]. Benefit was also seen in subjects with diabetes and small vessels. Piogliatazone has antirestenotic properties. Marx et al[45] study shows without diabetes undergoing stent implantation, pioglitazone treatment had a significantly reduced neointimal volume within stented segment and lower binary restenosis rate compared with control patients. Troglitazone inhibited neo-intimal hyperplasia in a small human study[46]. Tranilast reduced in stent restenosis in a porcine model[47], but could not elicit similar results in a human study[48]. Valsartan[49] and some statins[50] have also been studied without any conclusive benefits.

## Potential toxicity

Drug-eluting stents are local drug delivery vehicles, ability to deliver high local concentrations of drugs whose systemic concentrations would lead to unacceptable side effects. Drug toxicity also depends upon the dose of drug on the stent, the elution profile, the amount of drug bound and retained in the vessel, and blood concentrations. Major concern with Drug-eluting stents relates to failure of complete vessel healing, with subsequent lack of re-endothelialisation and late thrombosis, and medial thinning with stent malapposition. Clinical studies with high dose paclitaxel casuses failure of re-endothelialisation and thinning of the media. Long term treatment with antiplatelet therapy may thus be required to prevent late occlusion. Taxanes may be beneficial as anti-angiogenesis in atherosclerosis, but may also underlie some incomplete healing.

## Conclusion

Although stents reduce the risk of restenosis compared with plain PTCA, the prevailing rates of in-stent stenosis are still unacceptably high. Theoretical "ideal" properties of an antirestenosis drug are lipophilic with good tissue retention, strong binding/slow elution from polymer, antiproliferative without inducing cell death, potent inhibitor of vascular smooth muscle cells but not endothelial cells, specific to

intimal smooth muscle cells, antimigration action on vascular smooth muscle cells, anti-inflammatory action and antiplatelet action. Rapamycin and paclitaxel affect a number of biological processes responsible for in-stent stenosis. Drug-eluting stent reduce in-stent stenosis almost zero. In-stent stenosis is a major challenge in interventional cardiology, Drug-eluting stent creates a new hope to prevent this challenge.

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# Insulin analogues

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## Introduction

Diabetes mellitus is a very big challenge for our medical science. To overcome this problem we need newer generation of agents those can control glycaemic status nearer to physiology. In that case Insulin analogues will be the agents for improving glycaemic control.

The diabetic control and complication trail provided conclusive evidence that strict glycaemic control, reduced the incidence and progression of neuropathy, nephropathy and retinopathy.

The key to strict glycaemic control by the exogenous insulin lies in the delivery method that emulate physiological insulin secretion. Unfortunately conventional insulin preparation have limited pharmacokinetic profiles which make the goal of emulation impossible. On the other hand insulin analogues offer expanded pharmacokinetic profiles and the possibilites of regimens that closely mimic the physiology.

## Insulin analogues

Analogues are altered molecular version of a natural substance. They have been used in many therapies where hormone treatment is needed. The natural hormone is changed slightly, by rearranging the position of amino acid within the molecule (i.e.- It is something like changing the position of beads on a necklace). This new version of natural substance works basically the same way as original substance.

As there is slight difference of amino acid sequences between natural human insulin and insulin analogues, it would not be correct term to call the insulin analogue a type of human insulin. So, insulin analogue and insulin are two different terms.

## Historical achievement in insulin therapy

*1920- Discovery of insulin by Banting and Best.
*1922- The 14 year-old Leonard Thomson became the 1st patient to receive insulin.
*1923- Nobel prize in medicine was awarded to Banting and John McLeod.
*1930- Long acting protamine zinc insulin was developed.
*1950- Long acting insulin NPH was developed and insulin zinc (Lente) were introduced.
*1980- Development of pork insulin.
*1981- Introduction of recombinant human insulin.
*1984- Improvement in insulin delivery device and introduction of insulin delivery pen.
*1996- In July 1996 first recombinant DNA human insulin analogue, Lispro was approved.
*1999- Insulin analogue Aspart was introduced into market.

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Since then more insulin analogues have been introduced which provides new hope for controlling diabetic complications.

## Normal insulin secretion

In non diabetic persons insulin secretion has two basic components-

1) Basal &
2) Stimulated.

*1) Basal*

- Basal insulin is secreted continuously between meals and throughout the night at a rate of 0.5-1 u/h in adults.
- Basal insulin provides serum concentration of 5-15 microunit/ml.
- The low basal insulin reduces hepatic glucose production but allows sufficient glucose level for cerebral energy production. In diabetic patients treatment with intermediate acting and long acting insulin attempts to mimic the basal secretion.

*2) Stimulated*

- Stimulated secretion occurs normally in response to a meal resulting serum concentration of insulin 60 - 80 microunit/ml from just before to 30 minutes after meal.
- Concentration returns to normal level in 2-4 hours.

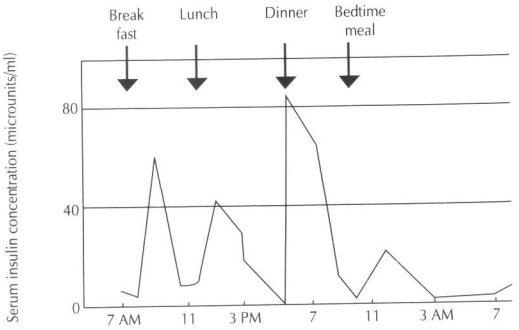


Figure 1: Normal insulin secretion. In the stimulated phase, serum insulin levels increase from within a few minutes before to 30 minutes after a meal. Return to basal level occurs within 2 hours.

## Indications of insulin therapy

1) Type-I DM.
2) Type-II DM with following conditions-
   i) Hyperglycemia despite of maximum dose of oral hypoglycemic agents.
   ii) Decompensation due to intercurrent events like infection, acute injury, stress.
   iii) Pregnancy.
   iv) Renal diseases.
   v) Surgery.
   vi) Severe hyperglycemia with or without ketonaemia or ketonuria.

### Therapeutic objectives of insulin therapy

- Correction of fasting and pre-prandial hyperglycemia (correcting the basal glucose metabolism).
- Minimization of the excessive post-prandial hyperglycemia.
- Prevention of hyperglycemia in between meals.
- To keep the Hb1c near normal.

### Disadvantages of conventional insulin therapy

*1) Disadvantages of regular/soluble insulin*

- Regular insulin has a nature of self association and regular insulin is found in a self associated hexameric form.
- To be absorbed by the capillary the hexameric form must dissociate to dimer and then monomer.
- This dissociation process delays the onset of action from 0.5-1 hr, may not be peak for 4 hrs and duration of action of 8 hrs.
- So they should be taken 30 min before meal.
- As their duration of action is prolonged, it reaches peak concentration 2 hrs after injection (in many cases and depending on the dose it may peak 4-6 hrs after injection) when blood glucose level already may be low.

*2) Disadvantages of intermediate acting insulin (NPH & Lente)*

- Peak action is 4-10 hrs after injection.
- Effective duration of action 10-20 hrs .
- Their peak effect is a problem for using as a basal insulin.
- Their duration of action necessitates more than one daily injection.

*3) Disadvantages of long acting insulin (Ultralente)*

- Their duration of action is 16-20 hrs. So single injection is not enough.
- Their duration of action is variable.
- Their peak effect is difficult to predict.

### Pharmacokinetic actions of conventional Insulin at a glance

| Insulin type | Onset of action | Peak action | Effect of duration |
|---|---|---|---|
| Regular | 0.5-1 hr | 2-4 hrs | 3-8 hrs |
| NPH | 2-4 hrs | 4-10 hrs | 10-20 hrs |
| Lente | 3-4 hrs | 4-8 hrs | 10-20 hrs |
| Ultralente | 6-10 hrs | Dose dependent | 16-20 hrs |

### Types of insulin analogues

**1. Rapid Acting**

i) Lispro
ii) Aspart
iii) Glulisine

**2. Long acting**

i) Glargine
ii) Detemir

### Criteria for good rapid acting analogues

- The short acting analogues would have time action profile with an onset of action less than 30 mins.
- A duration of action less than 4 hrs.
- Similar effect in all patients.
- They should be non immunogenic.

### Lispro

*Structure:* Insulin Lispro was formulated on the premise that insulin like growth factor-1(IGF-1) which structurally similar to insulin, does not trend to self associate.

In the B chain of natural human insulin, Lysine lies in the B29 position and Proline in the B28 position. Lispro is produced by inverting position of two amino acids. That is in Lispro B chain, Lysine lays in B28 position & Proline lies in 29 positions.

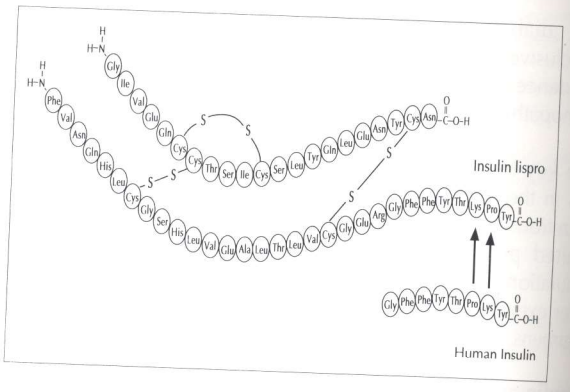


Figure 2: Structure of lispro

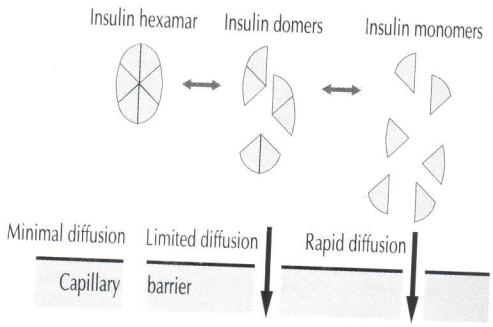


Figure 3: Regular insulin in Hexameric form. This form needs to become monomeric form for diffusion & absorption from subcutaneous or intramuscular area. But Lispro remains in monomeric form.

*Practical issue:* Because of this change in amino acid sequence Lispro has rapid onset of action in 15-30 min and peak action in 30-60 min and action last about 3-4 hrs.

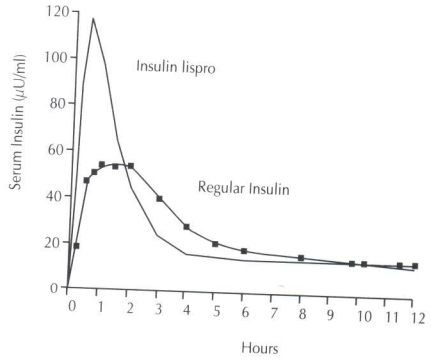


Figure 4: Rapid rise of serum level of lispro after administration in comparison to regular insulin

Lispro is non-immunogenic (In different studies it was observed that even before exposure to Lispro there is cross reactive antibodies but not Lispro specific antibody level. These antibodies decrease over time and have no clinical consequence).

*Special considerations in using insulin lispro*

| Potential problems | Comments and possible solutions |
|---|---|
| Patient eats dinner late | Because of insulin lispro's shorter duration of action, hyperglycemia may occur because the time from lunch to dinner may be too long.<br><br>Consider adding a small dose of intermediate-acting (NPH) insulin at lunch to meet basal insulin requirements between meals. |
| Patient has snacks containing more than 5 g of carbohydrate | Consider adding an additional dose of insulin lispro; if the patient also eats dinner late in the evening, this additional dose of insulin lispro can replace lunchtime basal NPH insulin supplementation. |
| Patient is a slow eater or a grazer (i.e., eats small amounts of carbohydrates throughout the day rather than at three meals) | Because of the rapid onset of insulin lispro, this type of patient may not respond as well to insulin lispro as to regular human insulin. |
| Patient has unpredictable eating habits | Insulin lispro offers the patient flexibility, in that the administration of this insulin can be timed with meals. |
| Patient has type 2 diabetes and is receiving two injections of NPH/regular insulin each day | This patient could benefit from the substitution of insulin lispro for regular human insulin to decrease postprandial blood glucose excursions. |
| Patient exercises | The patient who uses insulin lispro can expect fewer episodes of hypoglycemia if the exercise is undertaken 2.0 to 2.5 hours after the injection of insulin lispro. |

*Therapeutic role of lispro*

Insulin lispro has been found to be a safe and effective treatment for diabetes mellitus. Improvement in glycemic control is demonstrated by a decreased postprandial blood glucose concentration, although the longtime clinical significance of this improvement is as yet unknown. Multinational clinical trials have shown no statistically significant difference between hemoglobin A1c levels in patients treated with insulin lispro and patients treated with regular human insulin. However, the use of insulin lispro in external insulin infusion pumps has been shown to produce a small, yet clinically significant (0.34 percent) reduction in hemoglobin A1c levels compared with the reduction achieved using regular human insulin. This improvement in hemoglobin A1c represents an approximately 20 percent reduction in the risk of retinopathy in patients with diabetes.

Near-normal glycemic control is necessary to prevent or delay the onset of complications in patients with type 1 or type 2 diabetes. Patients with type 2 diabetes who have not responded to oral glucose-lowering agents often require insulin therapy to achieve the glycemic goals set forth by the American Diabetes Association. One study in both type 1 and type 2 diabetics concluded that insulin lispro improves postprandial glycemic control without increasing the risk of hypoglycemia. Short- or long-term insulin therapy has been shown to be useful in type 2 diabetics in whom the rapid component of endogenous insulin secretion is missing. In these patients, insulin lispro is a physiologic therapy. Primary care physicians should consider including mealtime insulin lispro in insulin regimens. The disadvantages of insulin lispro therapy are the increased risk of hypoglycemia if meal ingestion or absorption (gastroparesis) is delayed and the increased overall cost of therapy. Nonetheless, a short-acting insulin analog such as insulin lispro should provide increased convenience and flexibility to patients who are currently receiving regular human insulin. Furthermore, the characteristics of insulin lispro may help patients achieve improved long-term glycemic control and may reduce the incidence of hypoglycemic episodes. Insulin analogs may be an important tool for helping patients with diabetes mellitus achieves their target glucose goals.

*Drug Interactions*

No studies have specifically evaluated drug interactions in diabetic patients who are receiving lispro insulin. Close monitoring of blood glucose levels is important when a drug regimen is changed in any patient with diabetes.

**Aspart**

*Structure:* In insulin aspart, proline is replaced by aspartic acid at position B28 in insulin molecule.

This change results in stay Aspart in monomeric form and thus helps in rapid absorption.

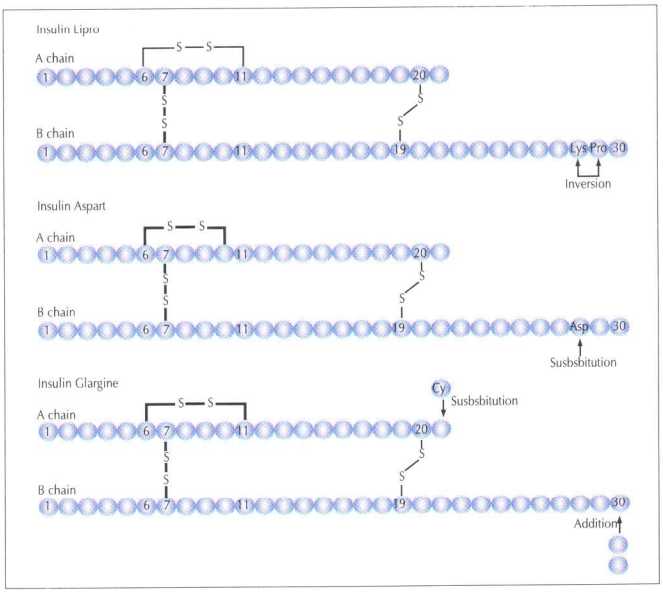


Figure 5: Structure of lispro, aspart, glargine

*Practical issue:* Onset of action within 30 min, peak action 30-60 min and action lasts for 4 hrs.

Although some preliminary comparisons of Aspart with Lispro have suggested that they are similar in action, other comparison suggested that there are some differences. So it is not recommended that Aspart and Lispro are interchangeable.

### Glulisine

*Structure:* Glulisine differs from human insulin in that the amino acid Asparagine at B3 position is replaced by Lysine and Lysine is replaced by Glutamic acid. It is still in clinical trial.

### Benefit of short acting analogues

- As their onset of action very rapid, they can be used just before and even after meal.
- As their duration of action is short, they are less likely to cause hypoglycemia in between meals. This is the key point of strict glycaemic control. They rapidly reduces the blood glucose level just after meal but are not cause hypoglycemia 4-6 hrs after meal.
- So, they can be used to those who wants more flexibilities in their meal times and those who suffers late midnight hypoglycemia.
- They improve HbA1c.

### Premixed insulin analogues

*Two premixed insulin analogue preparations are now available*

1) 75% Neutral Protamin Lispro + 25% Lispro
2) 70% Protamin Crystalline Aspart + 30% Aspart

### Basal/long acting insulin analogues

*Criteria for long acting insulin analogues*

1) An ideal insulin analogue should have peak less effect.
2) Should have long half life, so that one injection is enough.
3) Little inter-patient and intra-patient variability.

### Basal & long acting insulin analogues

*Two long acting analogues are available*

1) Glargine
2) Detemir

### Glargine

*Structure:* Glargine is produced by recombinant DNA technology through nonpathogenic E. Coli. The difference is only in structure from human insulin where Glargine has both the addition of two Arginine at C-terminus of B-chain and substitute of Glycine for Aspargenic acid at A21 position.

*Practical issue:* This change in structure makes Glargine soluble in pH of 4 but has relatively slow solubility when injected into neutral pH environment.

When Glargine is injected, micro precipitates forms and slowly insulin resolubilized and absorbed. This sequence of changes is predictable and provides a relatively constant level of insulin with no peak effect over a period of 24 hrs. So, single injection can maintain constant level for 24 hrs.

There is no difference in absorption rate of Glargine in different sites of the body. There is no evidence that Glargine accumulates in the body. Large number of trials have

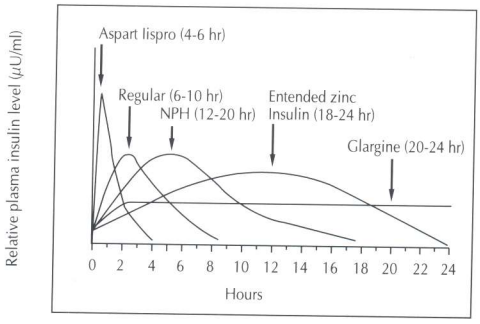


Figure 6: Different curves showing comparison of duration of action insulin analogues (Apart, Lispro, Glargine) & conventional insulin (Regular, NPH & Extended Zn insulin)

documented that Glargine can control glycaemic status more strictly then NPH, Lente or Ultralente but significantly reduces the nocturnal hypoglycemia. It significantly reduces HbA1c than other intermediate & long acting insulin.

### Detemir

- It is under trial.
- After injection, Detemir binds with the albumin through a fatty acid chain attached to Lysine at residue B29, which leads to a reduction in free Detemir level.
- The initial data suggested that Detemir has less variability in absorption than NPH.
- Data suggested it is less hypoglycemic.
- One study suggested that Detemir has some effect on hepatic glucose metabolism.

### Limitations of insulin analogues

- May cause hypoglycemia on overdose or if patient don't take adequate amount of food prior to injection.
- Insulin analogues are not recommended for I.V use.
- Rapid acting analogues are not recommended in diabetic gastroparesis.
- Insulin allergy, lipoatrophy and lipohypertrophy same as conventional insulin.
- Glargin requires OHA in Type-II & regular insulin in Type-I DM.

### Conclusion

Insulin treatment has always been as much an art as a science. Insulin analogues have met all the requirement for strict glycemic control also give the patient more flexibility in the timing of meal without the risk of hypoglycemia. Although these insulin analogues have much benefit over conventional insulin, the cost of these analogues is the main disadvantage for their use.

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# MSD NEWS

Medical Services Department (MSD) of ORION Laboratories Limited successfully arranged significant number of Round Table Meeting, Scientific Seminar in different venues of all over Bangladesh during April 2007 to July 2007.

## Scientific Seminar

**Oral & Maxillofacial Surgery Department, BSMMU:** A scientific seminar was arranged by Oral & Maxillofacial Surgery Department of BSMMU on "Orthognathic Surgery" on 2nd June 2007 at the Samad Seminar Room, BSMMU. Professor Dr. Motiur Rahman Molla, Chairman, Oral & Maxillofacial Surgery Department, chaired the seminar. Dr. Shahid Aziz, Assistant Professor, Oral & Maxillofacial Surgery Department, Newjersy Medical University, USA & Director, Centre for Dentofacial Deformities, University of Medicine & Dentistry, Newjersy, USA was the keynote speaker. About 100 doctors attended the seminar.


**Surgery Department, BSMMU:** Surgery department, BSMMU arranged a Scientific Seminar on "Anterior resection for carcinoma rectum" on 18th April 2007 at the classroom of surgery department of BSMMU. Dr. Zafarullah Khan, Assistant professor, surgery department, chaired the seminar and Professor Dr. Atai Rabbi, Chairman; surgery department was the chief guest. Dr. Saiful Islam Khan was the keynote speaker. About 135 doctors attended the seminar.

## Round Table Meeting (RTM)

### Dhaka

**Adhunik Sadar Hospital, Manikgonj:** Adhunik Sadar Hospital, Manikgonj arranged a RTM on "Role of ceftriaxone to treat various infections" on 27th June 2007 at the auditorim of Civil Surgeon Office, Manikgonj. Dr. Jamal Uddin Bhuian, Civil Surgeon, chaired the meeting. About 25 doctors attended the session.

**Medicine unit, Central Hospital:** A RTM was arranged by the doctors of medicine unit of Central Hospital on "Role of ceftriaxone to treat various infections" at the doctors room on 23rd May 2007. About 20 doctors attended the meeting.

**SHIMANTIK, UPHCP, Khilgaon:** SHIMANTIK arranged a RTM on "UTI in pregnancy" on 5th June 2007 at the seminar room. Dr. Md. Mizanur Rahman, Project Manager, chaired the meeting. About 15 doctors attended the meeting.

**HCDP, Savar:** On 6th June 2007 HCDP, Savar arranged a RTM on "Indapamide as a first step antihypertensive drug" at the seminar room. Dr. Md. Aminul Haque, Centre Director was the chairperson. About 10 doctors attended the meeting.

**Day Care Unit, Dhaka Shishu Hospital:** A RTM was arranged by day care unit on "Role of ceftriaxone to treat various infections" at Cheer's Restaurant, Dhanmondi on 1st July 2007. Dr. P. K. Das, Junior Consultant chaired the session. About 30 doctors enjoyed the meeting.

**Araihazar UHC, Narayangonj:** On 30th June 2007 Araihazar UHC arranged a RTM on "Role of ceftriaxone to treat various infections" at the seminar room of Araihazar UHC. Dr. Md. Feroz Ahmed Khan, UH & FPO, chaired the meeting & Dr. Abdul Halim Bhuiya, RMO was present there as a special guest. About 20 doctors attended the session.

**International Medical College, Tongi:** A RTM was arranged by the doctors of Intenational Medical College, Tongi on "Role of ceftriaxone to treat various infections" at the Seashell Chinese Restaurant, Uttara on 19th June 2007. About 15 doctors attended the meeting.

**Casualty Department, DMCH:** Casualty department of DMCH arranged a RTM on "Management of mass casualty" on 16th July 2007 at the clinical conference room. Dr. Hashem Bhuyan, Associate Professor, Dept. of casualty chaired the meeting. Dr. Roksana Parveen, HMO was the keynote speaker. About 80 doctors attended the session.

### Sylhet

**HEED Bangladesh, Moulvibazar:** On 22nd March 2007 HEED Bangladesh arranged a RTM on "Antiulcerant drugs" at conference hall. Mr. A. K. M. Aminul Haque, Program Manager chaired the meeting and Dr. Usheng Chowdhory, SMO was the chief guest. About 35 doctors attended the session.

**Sylhet Metropolitan Hospital:** A RTM was arranged by the doctors of Sylhet Metropolitan Hospital on "Omeprazole as an antiulcerant" at the conference room, SMH on 19th April 2007. Dr. Md. Jalal Uddin, SMO was the chairperson and Dr. Harunur Rashid, Director was present as chief guest. About 20 doctors attended the session.

**CCU, JRRMCH:** A RTM was arranged by CCU, JRRMCH on "Role of ceftriaxone to treat various infections" at the classroom on 10th May 2007. Prof. Dr. Arun Kumar Sarma, Head of the department chaired the session. About 25 doctors attended the meeting.

**Orthopaedic Department, JRRMCH:** Orthopaedic department, JRRMCH arranged a RTM on "Role of ceftriaxone to treat various infections" at the academic corner on 9th May 2007. Prof. Dr. Cyrus Sakiba, Head of the Department of Orthopaedics, chaired the session. About 35 doctors attended the meeting.

**Gynae unit-I, JRRMCH:** A RTM was arranged by Gynae unit-I, JRRMCH, Sylhet on "Role of ceftriaxone to treat various infections" at the academic corner on 7th May 2007. Prof. Dr. M A Sabur, Head of the Dept. was the chairperson. About 20 doctors enjoyed the meeting.

**Gynae unit-II, JRRMCH:** Gynae unit-II, JRRMCH arranged a RTM on "Role of ceftriaxone to treat various infections" at the academic corner on 8th May 2007. Dr. Afroza Begum Sheela, Associate Prof. chaired the session. About 25 doctors attended the meeting.

**Medicine unit-I, II & III & Phychiatry, JRRMCH:** A RTM was arranged by Medicine unit-I, II and III, & Phychiatry JRRMCH, Sylhet on "Role of ceftriaxone to treat various infections" at the lecture gallery on 12th May 2007. Prof. Dr. Azizur Rahman was the chairperson. About 60 doctors enjoyed the meeting.


**Surgery unit-I & III, JRRMCH:** A RTM was arranged by the doctors of surgery unit-I and III, Sylhet on "Role of ceftriaxone to treat varios infections" at the lecture gallery on 14th May 2007. Prof. Dr. Wasey was the chairperson. About 40 doctors attended the session.

**Paediatrics unit, JRRMCH:** A RTM was arranged by the doctors of Paediatrics on "Role of Zinc in children" at the class room on 13th May 2007. Dr. Sayed Safi Ahmed Muraz, Head of Paediatirics was the chairperson. About 40 doctors attended the session.

**Surgery unit-II, JRRMCH:** Surgery unit-II arranged a RTM on "Role of ceftriaxone to treat various infections" at the classroom on 14th May 2007. Dr. Fazlul Islam, RS, chaired the meeting. About 30 doctors attended the meeting.

**OPD-I, JRRMCH:** A RTM on "Role of ceftriaxone to treat various infections" was arranged by OPD-I, JRRMCH at the hall room on 5th May 2007. Dr. Kausar Ahmed, RMO, was the chairperson. About 25 doctors attended the session.

**OPD-II, JRRMCH:** A RTM on "Role of ceftriaxone to treat various infections" was arranged by OPD-II, at the hall room on 6th May 2007. Dr. Fazlul Islam, RS was the chairperson. About 30 doctors attended the meeting.

**Sunamganj:** A RTM was arranged at Tahira Communiry Centre by the GP doctors of Sunamganj, on "Role of ceftriaxone to treat various infections" on 1st May 2007. About 60 GP doctors enjoyed the session.

**Surgery unit-I, SOMCH:** On 19th May 2007 a RTM was arranged by surgery unit-I, at the classroom. Dr. Faruk Ahmed, Assistant Registrar, was the chief guest. About 65 doctors attended the session.

**Surgery unit-II, SOMCH:** On 20th May 2007 a RTM was arranged by surgery unit-II, at the classroom. Dr. Abdul Ahad, IMO, was the chief guest. About 75 doctors attended the meeting.

**Surgery unit-III & Neurosurgery ward, SOMCH:** A RTM on "Role of ceftriaxone to treat various infections" was arranged by surgery unit-III & Neursurgery ward on 30th May 2007 at the classroom. Dr. Partho Sarothi Mozumder chaired the session. About 60 doctors attended the meeting.

**Surgery unit-IV, SOMCH:** Surgery unit-IV, arranged a RTM on "Role of ceftriaxone to treat various infections" at the classroom on 21st May 2007. Dr. Forhat, Assistant Registrar, was the chief guest. About 50 doctors attended the session.


*The rest of the MSD news at page - 508*

# Medi News

## Simple method detects cervical cancer

A cheap method to detect cervical cancer using vinegar, cotton gauze and a bright light could save millions of women in the developing world, experts reported Friday. The study, published in The Lancet medical journal, found a simple visual screening test to look for the early signs of cervical cancer reduced the numbers of cases by a quarter. "This is a landmark study," said Dr. Harshad Sanghvi, medical director at JHPIEGO, an international health organization affiliated with Johns Hopkins University that has worked on preventing cervical cancer in poor countries. Cervical cancer is largely preventable. It causes about 250,000 deaths every year and is the second-most common cancer in women. Nearly 80 percent of those women are in the developing world. The visual screening test is done by a nurse or trained health care worker who washes a woman's cervix with vinegar and gauze using a speculum to hold it open. After one minute, any pre-cancerous lesions turn very white and can be seen with the naked eye under a halogen lamp. Researchers from the International Agency for Research on Cancer in France and their colleagues from Tamil Nadu in India used the technique to screen 49,311 women in Dindigul district, India, from 2000 to 2003. When pre-cancerous lesions were found, health care workers gave immediate treatment to destroy the abnormal cervical tissue. Another 30,958 women received standard care. They were told to watch for signs and symptoms of cervical cancer and encouraged to visit health care facilities where screening was available. There were 167 cases and 83 cervical cancer deaths in the women who received the screening, compared with 158 cases and 92 deaths in those who didn't. That represents 25 percent less cervical cancer and a 35 percent lower death rate among those screened. Previous research has shown visual screening is almost as effective in catching cancer as Pap smears, a more expensive technique used in the West, which involves scraping cells from the cervix to be examined under a microscope in a laboratory. "This is the final proof that with an extremely simple test, we can have a dramatic impact on cervical cancer rates," Sanghvi said. Experts think that the simple, inexpensive technique could be rolled out across the developing world relatively easily.

www.fobes.com/Health

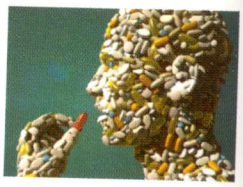
## Teens' stress levels linked to acne severity

The largest study ever conducted on acne and stress reveals that teenagers who were under high levels of stress were 23% more likely to have increased acne severity. "Acne significantly affects physical and psychosocial well-being, so it is important to understand the interplay between the factors that exacerbate acne," said Gil Yosipovitch, MD, lead author and a professor of dermatology. "Our study suggests a significant association between stress and severity of acne." While psychological stress had been identified among many factors that can worsen acne. The current study looked at whether levels of sebum, increase in times of stress and are related to acne severity. Hormone levels, sebum production and bacteria are all known to play major roles in acne. The study involved secondary school students in Singapore with a mean age of 14.9 years. The students' self-reported stress levels and acne severity were measured at two different times - just before mid-year exams and during summer break Ninety-two percent of the girls and 95% of the boys reported having acne. The researchers suspected that stress increases the quantity of sebum, which leads to increased acne severity. The researchers did find that students reporting high stress were 23% more likely to have increased severity of pimples. "Our research suggests that acne severity associated with stress may result from factors others than sebum quantity," said Yosipovitch. "It's possible that inflammation may be involved."

Swedish Medical Journal

## Diabetes drugs 'double risk of heart failure'

Up to 10,000 patients in Britain may be at risk of heart failure because they take drugs for diabetes. UK and US researchers have found two of the world's top selling oral medications for diabetes double the risk of heart failure. The discovery in a study published yesterday is a major blow for sufferers from type 2 diabetes - there at least two million in the UK. The drugs are known as glitazones, and Actos. They sensitise the body to insulin and lower blood sugar levels and were hailed as a major advance against the disease when they were launched. But researchers who analysed existing studies and case reports covering more than 78,000 patients, estimated that one in every 50 patients treated with the drugs over 26 months would suffer heart failure as a result. An estimated 500,000 patients in the UK are taking the drugs, implying that 10,000 patients could be at risk. The study, published in Diabetes Care, follows a report in May linking glitazones with a 43 per cent increased risk of a heart attack. That study, published in the New England Journal of Medicine, led to a collapse in prescriptions for glitazones like Avandia. The drugs are not recommended for people suffering from, or at risk of, heart failure. But the new study, carried out by experts at the University of East Anglia (UEA) and Wake Forest University in North Carolina, suggests an increased risk even for those who have never suffered heart failure. Yoon Loke, a clinical pharmacologist at UEA, who led the study, said the findings meant the drugs "could have caused thousands of additional cases of heart failure, creating a substantial burden on hard-pressed NHS services". He added: "Most patients did not have heart failure prior to starting on treatment with these drugs. There doesn't seem to be a group of patients who are safe from these side effects. I think Nice should re-evaluate its decision to recommend these drugs." One of the causes leading to heart failure was too much fluid on the lungs. "We think this is one of the main mechanisms in this case," he said. The manufacturing company said the risk of heart failure with the medicines was "well recognised and clearly identified in prescribing information to doctors in the UK." It added it was well known that glitazones could cause fluid retention that could lead to heart failure and was "clearly stated".



New England Journal of Medicine

## Yogurt drink settles stomach after antibiotics

A yogurt drink containing "good" bacteria helped patients avoid the diarrhea caused by antibiotics, British researchers reported on Friday. People who drank Actimel, made by French food group Danone, were able to leave the hospital sooner, the researchers said in the British Medical Journal. None of the patients given yogurt drink developed diarrhea caused by Clostridium difficile, compared to 17 percent of people who drank a similar-looking milkshake, they found. One in every 250 hospital deaths involves C. difficile as a contributory or main factor, the researchers said. This particular bacteria is often resistant to antibiotic treatment and can make patients seriously ill. Between 5 percent and 25 percent of patients treated with antibiotics develop diarrhea, in part because the drugs kill some of the bacteria normally resident in the intestines. Many doctors recommend eating yogurt to replace some of these beneficial bacteria, and drinks are now sold commercially that claim to do the job even better. They studied 135 middle-aged and elderly patients who agreed to drink yogurt drink or a similar-looking milkshake twice a day during treatment and for a week afterwards. Only 12 percent of the patients who drank yogurt drink had diarrhea, compared to 34 percent of those who got the milkshake.

British Medical Journal

## Modern life 'causes major stress'

Modern life is causing "major stress" and sleepless nights, according to the results of two surveys. More than half of 1,001 people surveyed by life assurance firm CPP said worries about identity theft, terrorism and health risks kept them awake at night. Climate change and house prices were also found to make people anxious. A survey of 1,700 people by Travelodge found 3% of adults get the recommended amount of sleep, with stress cited as the main cause of a restless night. Results from the CPP poll suggests people feel more worried about a range of issues than they did five years ago. The number one worry was identity theft, followed closely by rising house prices, climate change, NHS cutbacks. Older people seemed to be more laid back than their younger counterparts with just 9% of people aged over 54 admitting to being deeply concerned about social and global problems compared with 15% of 18 to 34-year-olds. Among the younger respondents to the survey, rising house prices and climbing onto the property ladder was the biggest worry. Dr David Lewis, a cognitive neuropsychologist at The Mind Lab, said many of the things raised as concerns were outside of people's control. "The results of this survey, confirm that high levels of anxiety are prevalent in modern society. People feel themselves to be helpless. Societal anxieties have risen sharply in the last five years and the trend

looks set to continue." He added that when people felt under a lot of pressure it lead to sleepless nights which in turn made them less able to cope with events the next day. The second survey carried out by Travelodge found very few adults get the recommended eight hours sleep a night. The main reasons listed were stress and long working hours. More than half said lack of sleep made them feel physically run down and reduced their concentration.

www.bbc.com/Health

## Scents during sleep improve some memory

Researchers say a familiar smell in the bedroom while sleeping may improve memory -- if it's the right stage of sleep and memory. In the study, being published Friday in the journal Science, it worked only for some kinds of memories and during one stage of sleep, which means it's not the answer for people hunting a quick memory boost. German scientists using medical students for the study had them play a computer version of a common memory game. They turned over pairs of cards to find each one's match. Some played in a rose-scented room. Later that night, while they were in a deep stage of sleep known as slow-wave sleep, researchers gave them another whiff of roses. The next day, the rose-scented sleepers remembered the locations of those cards better than people who didn't get a whiff, answering correctly 97 percent of the time compared with 86 percent. People exposed to the odor during the lighter dream stage of sleep known as REM sleep saw no memory boost. With the card game, the odor reactivated the day's new memories of object placement, allowing a now-resting brain to consolidate them, the researchers wrote. But because different parts of the brain are involved with different types of memory, the odor didn't play a role with the more numerical finger-tapping test.

Journal Science

## Seniors safer on the road than young bloods!

Researchers at the Rand Institute for Civil Justice have found that young drivers between 15 and 24 years old are three times as likely to cause car accidents as people over the age of 65. The researchers say seniors make up 15 percent of drivers but were responsible for only 7 percent of the 330,000 fatal two-car crashes in the past 25 years, while drivers up to age 24 represented 13 percent of drivers, but caused 43 percent of the accidents across the United States. The research suggests that relatively few older drivers need to be legally prohibited from driving so they pose a relatively small risk to traffic safety overall. The researchers believe efforts to reduce accidents would be better focused on younger drivers, who drive more frequently and are riskier when they do so.

www.cnn.com/Health

## Vitamin C 'does not stop colds'

Taking a daily supplement of vitamin C will not protect most people from common colds, scientists say. A review of 30 studies, involving 11,350 people, also found doses of at least 200mg per day did little to reduce the length or severity of colds. Although they found it could reduce the duration of colds by up to 8% in adults and 13.6% in children, as most people only have two or three colds every year, this benefit is only very small. "It doesn't make sense to take vitamin C 365 days a year to lessen the chance of catching a cold." However, they say it may be justified in those exposed to severe cold or physical stresses, where vitamin C doses reduced the risk of getting a cold by half. Furthermore, they say there is "tantalising" evidence from one study that very large doses of vitamin C taken at the beginning of a cold might have a useful effect. In the 1970s, Nobel Prize-winning chemist Linus Pauling encouraged people to take 1,000mg of vitamin C daily to ward off colds. But since then the effects of the vitamin on colds has remained controversial. The current recommended daily allowance of vitamin C is just 60mg, and an optimum amount would be 200mg every day. Most people could easily obtain this amount through eating five portions of fruit and vegetables every day. Furthermore, eating too much vitamin C means it cannot be absorbed and so is removed from the body.

Cochrane Library, Australia

## Coffee linked to reduced liver cancer risk

A new study by scientists in Europe concluded that coffee drinking is linked to a reduced risk of primary liver cancer. Liver cancer is the fifth most common cancer and the third largest cause of death from cancer in the world, after lung and stomach cancer. According to the World Health Organization (WHO) liver cancer kills over 660,000 people globally every year. In this latest study, Bravi and colleagues carried out a meta analysis of published scientific literature on the relation between coffee drinking and risk of hepatocellular carcinoma (HCC), which accounts for 90 per cent of liver cancers. A meta analysis is a way of pooling the data from several studies looking at the same relationship between variables to find out if they are saying something consistent. The authors only included studies with quantitative information on coffee consumption and HCC incidence, and retrieved ten altogether covering a total of 2,260 cases of HCC. Six of them were case controlled studies from southern Europe and Japan (1,551 cases) and four of them were cohort studies from Japan (709 cases). They found that among coffee drinkers overall, there was a 41 per cent reduction in risk of HCC compared to those who never drank coffee. The reduced risk of HCC among coffee drinkers was also evident for people in Japan, who drink less coffee than people in southern Europe. For low or moderate coffee drinkers the reduced risk of HCC was smaller (30 per cent) and for high coffee drinkers the risk reduction was higher (55 per cent). Overall they found that an increase of 1 cup of coffee per day was linked to a reduced HCC risk of between 23 and 25 per cent.

Journal of the American Association

## Diesel pollution 'clogs arteries'

Diesel fumes appear to combine with artery-clogging fats to raise the risk of heart disease, research suggests. Scientists found the two acts in concert to switch on genes that cause potentially dangerous inflammation of the blood vessels. They hope their work will lead to a simple blood test enabling doctors to evaluate the impact of air pollution on a person's health. Lead researcher Dr André Nel, an expert in nanomedicine, said the impact of diesel particles and cholesterol fats combined was much greater than the impact of each in isolation. He said: "Their combination creates a dangerous synergy that wreaks cardiovascular havoc far beyond what's caused by the diesel or cholesterol alone." The researchers focused on the interaction between diesel exhaust particles and fatty acids found in low-density lipoprotein (LDL) cholesterol - the "bad" type of cholesterol that leads to artery blockage. Both are sources of molecules called free radicals which cause cell and tissue damage, and can trigger the inflammation that leads to artery disease. The researchers combined the pollutants and fats and cultured them with cells taken from the inner lining of human blood vessels. A few hours later, they extracted DNA from the cells for genetic analysis. They showed that the genes that promote cellular inflammation had been activated. Next, they exposed mice with high cholesterol to the diesel particles, and saw that some of the same genes were activated in the animals' tissue. Dr Nel said: "Exactly how air pollutants cause cardiovascular injury is poorly understood. But we do know that these particles are coated with chemicals that damage tissue and cause inflammation of the nose and lungs. "Vascular inflammation in turn leads to cholesterol deposits and clogged arteries, which can give rise to blood clots that trigger heart attack or stroke."

Journal Genome Biology

## Too many antibiotics prescribed for sinus infections

US scientists researching treatments for sinus infections suggest that antibiotics are over-prescribed to treat the condition. And they are concerned this could be increasing the drug resistance and virulence of infectious bacteria. According to the study, antibiotics were prescribed for 82 per cent of acute sinus infections and nearly 70 per cent of chronic sinus infections. This is surprising because most sinus infections are caused by viruses, and antibiotics only kill bacteria. In 69.95% of visits for chronic sinusitis at least one antibiotic was prescribed.

Archives of Otolaryngology

pep Corner

# Zinc...

## ...supplementation in acute diarrhea is acceptable; not interfere with ORS and decreases antibiotic/antidiarrheal use.


Abstract

*Objective:* Assess the impact of zinc supplementation with locally developed culturally specific educational statements (messages) on oral rehydration solution (ORS) and antibiotics or antidiarrheal use in children with acute watery diarrhea as well as to assess adherence and side effects of zinc. *Methods:* This was a randomized effectiveness trial conducted in outpatient health facilities of six sites in five countries, namely, Fortaleza (Brazil), Addis Adaba (Ethiopia), Cairo (Egypt), Lucknow and Nagpur (India), and Manila (Philippines). Participants were 2,002 children aged 2 to 59 months. Intervention was zinc (20 mg orally, once daily for 14 days) with ORS (zinc group) compared with ORS alone (control group). Primary outcomes were ORS use on day 3 to 5; adherence to zinc; and any use of an antibacterial/antidiarrheal up to day 14. *Results:* One thousand ten and 992 children enrolled in zinc and control groups, respectively. Loss to follow-up on days 3 to 5 and 15 to 17 was 1.2% and 2.8% in the zinc group and 0.8% and 1.7% in the control group. In five of six sites, ORS use in cases with continued diarrhea on days 3 to 5 was the same in the two groups or higher in zinc group. Overall adherence to zinc supplementation was 83.8% (95% confidence interval [CI] 81-86). There was no difference in vomiting by group. In consideration of the six countries overall, less antibiotic/antidiarrheal use occurred in the zinc group (absolute difference, 3.8% [95% CI 1.7-5.9]). *Conclusions:* In the management of acute watery diarrhea, zinc plus ORS along with culturally appropriate, site-specific messages in local language does not affect overall ORS use generally and decreases antibiotic/antidiarrheal use; children had good adherence without side effects.


Oral rehydration solution (ORS) has been successfully used around the world and has been responsible for reduction in diarrheal deaths in the last 2 decades. In spite of the success of ORS in prevention of dehydration, there is still a demand for medicines that will reduce the duration and severity of diarrhea. Consequently, many cases are treated with antibiotics and other drugs. Zinc has been shown to be efficacious in reducing the duration of diarrhea and associated mortality. In Bangladesh, the provision of zinc supplements for use during diarrhea by a village-based worker who also gave ORS increased the use of ORS and decreased the use of antibiotics and other drugs. It is critical to ensure in other settings that any promotion of zinc for treatment of diarrheal disease does not interfere with the use of ORS; in addition, it would be desirable to reduce the use of drugs for diarrheal disease. Therefore, we conducted this study with the hypothesis that zinc supplementation during acute watery diarrhea will not affect use of ORS, that it will reduce the use of antimicrobial and antidiarrheal drugs, and that zinc supplements will be accepted for treatment.

This study was conducted after institutional ethical clearances had been obtained in outpatient health facilities of Fortaleza (Brazil), Addis Adaba (Ethiopia), Cairo (Egypt), Lucknow and Nagpur (India), and Manila (Philippines). All children aged 2 to 59 months presenting to the study centers with diarrhea, defined as three or more loose or watery motions per day, and of less than 7 days' duration, were invited to participate. This was an effectiveness trial. Therefore, there were no other interventions that may have affected outcomes through the project activities. While subjects randomized to both the groups received instructions for the use of ORS, those randomized to the zinc group also received zinc tablets along with counseling and site-specific, culturally appropriate messages for zinc usage. Zinc was supplied as dispersible 10-mg tablets. Duration of zinc supplementation was 14 days. Ethiopia and Lucknow, India gave two zinc tablets, whereas the other sites gave one zinc tablet once per day because there were concerns about adherence to intake of two tablets per day by small children by care providers. Parents were instructed to dissolve zinc tablets in 5 mL clean water. In Philippines, Egypt, and Nagpur, India, they were also given instructions for dissolving it in breast milk and in the Philippines for dissolving in ORS as an option.

There were 1,010 and 992 children in the zinc and control groups. Loss to follow-up on days 3 to 5 and 15 to 17 were 1.2% and 2.8% and 0.8% and 1.7% in zinc and control groups, respectively. Overall adherence was 83.8% (cluster [day] effect adjusted 95% CI, 81-86) and was greater than 75% at all sites. At first follow-up, on days 3 to 5, 22.3% (n = 225) of children in the zinc group versus 26.2% (n = 260) in the control group still had diarrhea (P = 0.04). In those who had diarrhea on days 3 to 5, overall ORS use was 85.3% (n = 192) and 86.1% (n = 224) in zinc and control groups, respectively (absolute difference 0.8% [95% CI: 0.5 + 7.1]). In five of six sites, ORS use was the same in the two groups or tended to be higher in the zinc group. However, in Brazil, the use of ORS in those randomized to the zinc group was 68.8% versus 89.2% in the control group. In considering all the six sites, any antimicrobial/antidiarrheal drug use was lower in the zinc group compared with the control group (4.1% vs. 7.9%; absolute difference 3.8% [95% CI: 1.6 to 6.0]). During the study duration, there were 137 children who went to seek care in other facilities, 41 (4%) in the zinc group and 96 (9.7%) in the control group (absolute difference 5.7%, 95% CI 3.5-7.9%; P < 0.001). Home visits were made for follow-up for 1,033 children, of which 479 (47.0%) were in the zinc and 554 (55.8%) in the control group. Adherence was slightly lower in infants below 1 year of age, in malnourished children (WHZ score below -1 SD), and in centers where two tablets per day had been used (Ethiopia and Lucknow); these subgroup differences were approximately 2%, but none was statistically significant. Rates of ORS use on day 3 and of antimicrobial/antidiarrheal use up to days 3 to 5 and 13 to 15 did not vary significantly by subgroup.

This randomized, open-label effectiveness trial was conducted at six sites in five developing countries. There was excellent adherence to zinc supplementation during and for a short period after diarrhea and no difference in vomiting between the groups on days 3 to 5. Study found that 15% fewer (P = 0.04) children in the zinc group than the control group had continuation of diarrhea to days 3 to 5, which is consistent with the shortening of duration of diarrhea with zinc found in many placebo-controlled trials. There were 37.9% fewer clinical failures by days 3 to 5 in children randomized to the zinc group compared with the control group, but the difference was not statistically significant (P = 0.09).The primary hypothesis in this study was that supplementation with zinc along with ORS would not affect the use of ORS, and this was true overall and in five of six sites. The reasons for the lower ORS use in the zinc-treated children in Brazil are not known, and further formative research is needed in this site to determine how to promote zinc so that it does not detract from ORS use.

The impact of the use of zinc on the purchase and use of antimicrobial and antidiarrheal drugs is of great interest in that these drugs are unnecessary and can be costly and hazardous. These findings of a reduced rate of drug use in the zinc group are similar to the community trial from Bangladesh, except that in our trial, the frequency of drug use was relatively low, probably because of the exclusion of children taking such drugs from the study and counseling against drug use in both zinc and control groups. The current trial was performed in low and middle-income settings with a high prevalence of diarrhea. This extends the evidence for safety and benefit of zinc used along with ORT for the management of diarrhea and includes countries without prior trial experience similar to those participating in this study. After this multicenter trial was begun, WHO and UNICEF issued new guidelines for management of diarrhea, including the recommendation that zinc supplements be given in all episodes along with fluid replacement and continued feeding.


Journal of Pediatric Gastroenterology and Nutrition. 2006(March);42(2):300-305

pep

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- Pneumonia
- Mental disturbances
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